Management of adrenal incidentalomas - a European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors

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Abstract

By definition, an adrenal incidentaloma is an asymptomatic adrenal mass detected on imaging not performed for suspected adrenal disease. In most cases, adrenal incidentalomas are non-functioning adrenocortical adenomas, but may also represent conditions requiring therapeutic intervention including adrenocortical carcinoma, pheochromocytoma, hormone-producing adenoma or metastasis. The purpose of this guideline is to provide clinicians with best possible evidence-based recommendations for clinical management of patients with adrenal incidentalomas based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system.

We predefined four main clinical questions crucial for the management of adrenal incidentaloma patients, addressing these four with systematic literature searches: A) How to assess risk of malignancy?; B) How to define and manage low level autonomous cortisol secretion, the so-called "subclinical" Cushing syndrome?; C) Who should have surgical treatment and how should it be performed?; D) What follow-up is indicated if the adrenal incidentaloma is not surgically removed?

Selected Recommendations: 1) At the time of initial detection of an adrenal mass establishing whether the mass is benign or malignant is an important aim to avoid cumbersome and expensive follow-up imaging in those with benign disease. 2) To exclude cortisol excess a 1-mg overnight dexamethasone suppression test should be performed (applying a cutoff value of serum cortisol ≤ 50 nmol/l (1.8 µg/dl)). 3) For patients without clinical signs of overt Cushing's syndrome but serum cortisol levels post 1mg dexamethasone > 138 nmol/l (> 5 µg/dl) we propose the term 'autonomous cortisol secretion'. 4) All patients with '(possible) autonomous cortisol' secretion should be screened for hypertension and type 2 diabetes mellitus, to ensure these are appropriately treated. 5) Surgical treatment should be considered in an individualized approach in patients with 'autonomous cortisol secretion' who also have comorbidities that are potentially related to cortisol excess. 6) In principle, the appropriateness of surgical intervention should be guided by the likelihood of malignancy, the presence and degree of hormone excess, age, general health and patient preference. 7) Surgery is not usually indicated in patients with an asymptomatic, non-functioning unilateral adrenal mass and obvious benign features on imaging studies. We provide guidance on which surgical approach should be considered for adrenal masses with radiological findings suspicious of malignancy. Furthermore, we offer recommendations for the follow-up of patients with adrenal incidentaloma who do not undergo adrenal surgery, for those with bilateral incidentalomas, for patients with extra-adrenal malignancy and adrenal masses, and for young and elderly patients with adrenal incidentalomas.

1. Summary of Recommendations[*]

1.1   General remarks

R.1.1   We recommend that patients with adrenal incidentalomas are discussed in a multidisciplinary expert team meeting, if at least one of the following criteria is met:

- Imaging is not consistent with a benign lesion.

- There is evidence of hormone excess (including "autonomous cortisol secretion").

- Evidence of significant tumor growth during follow-up imaging.

- Adrenal surgery is considered.

1.2   Assessment of the risk of malignancy

R.2.1   We recommend aiming to establish if an adrenal mass is benign or malignant at the time of initial detection.

R.2.2   We recommend that all adrenal incidentalomas undergo an imaging procedure to determine if the mass is homogeneous and lipid-rich and therefore benign (XOOO). For this purpose, we primarily recommend the use of non-contrast CT (XOOO).

R.2.3   We suggest that if the non-contrast CT is consistent with a benign adrenal mass (Hounsfield units ≤ 10) that is homogeneous and smaller than 4 cm no further imaging is required (XOOO).

R.2.4   If the adrenal mass is indeterminate on non-contrast CT and the results of the hormonal work-up do not indicate significant hormone excess, three options should be considered by a multidisciplinary team acknowledging the patient's clinical context: immediate additional imaging with another modality, interval imaging in 6 to 12 months (non-contrast CT or MRI), or surgery without further delay.

R.2.5   We recommend against the use of an adrenal biopsy in the diagnostic work-up of patients with adrenal masses unless there is a history of extra-adrenal malignancy and additional criteria are fulfilled (see R6.3.5).

1.3   Assessment for hormone excess

R.3.1   We recommend that every patient with an adrenal incidentaloma should undergo careful assessment including clinical examination for symptoms and signs of adrenal hormone excess.

R.3.2   We recommend that all patients with adrenal incidentalomas undergo a 1-mg overnight dexamethasone suppression test to exclude cortisol excess (XXOO).

R.3.3   We suggest interpretation of the results of the 1-mg overnight dexamethasone test as a continuous rather than categorical (yes/no) variable (XOOO). However, we

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[*] The recommendations are worded as *recommend* (strong recommendation) and *suggest* (weak recommendation). The quality of evidence behind the recommendations is classified as low very low (⊕○○○), low (⊕⊕○○), moderate (⊕⊕⊕○) and strong (⊕⊕⊕⊕). See further Section 3.4.

105   recommend using serum cortisol levels post dexamethasone ≤ 50 nmol/l (≤ 1.8 µg/dl)
106   as a diagnostic criterion for the exclusion of autonomous cortisol secretion (XXOO).

107 R.3.4 We suggest that post dexamethasone serum cortisol levels between 51 and 138
108   nmol/l (1.9 - 5.0 µg/dl) should be considered as evidence of 'possible autonomous
109   cortisol secretion' and cortisol levels post dexamethasone > 138 nmol/l (> 5.0 µg/dl)
110   should be taken as evidence of 'autonomous cortisol secretion'. Additional
111   biochemical tests to confirm cortisol secretory autonomy and assess the degree of
112   cortisol secretion might be required. However, for the clinical management the
113   presence of potentially cortisol-related comorbidities and age of the patient are of
114   major importance.

115 R.3.5 We recommend against considering 'autonomous cortisol secretion' as a condition
116   with a high risk for the development of overt Cushing's syndrome (XXOO).

117 R.3.6 We recommend screening patients with 'possible autonomous cortisol secretion' or
118   'autonomous cortisol secretion' for hypertension and type 2 diabetes mellitus (XOOO)
119   and suggest offering appropriate treatment of these conditions.

120 R.3.7 We suggest screening patients with 'autonomous cortisol secretion' for asymptomatic
121   vertebral fractures (XOOO) and to consider appropriate treatment of these conditions
122   (XOOO).

123 R.3.8 We suggest an individualized approach to consider patients with 'autonomous cortisol
124   secretion' due to a benign adrenal adenoma and comorbidities potentially related to
125   cortisol excess for adrenal surgery (XOOO). Age, degree of cortisol excess, general
126   health, comorbidities and patient's preference should be taken into account. In all
127   patients considered for surgery, ACTH-independency of cortisol excess should be
128   confirmed.

129 R.3.9 We recommend excluding pheochromocytoma by measurement of plasma free
130   metanephrines or urinary fractionated metanephrines.

131 R.3.10 In patients with concomitant hypertension or unexplained hypokalemia, we
132   recommend the use of the aldosterone / renin ratio to exclude primary aldosteronism.

133 R.3.11 We suggest measurement of sex hormones and steroid precursors in patients with
134   clinical or imaging features suggestive of adrenocortical carcinoma.

135 **1.4   Surgical treatment**

136 R.4.1 We recommend adrenalectomy as the standard of care for unilateral adrenal tumors
137   with clinically significant hormone excess.

138 R.4.2 We recommend against performing surgery in patients with an asymptomatic, non-
139   functioning unilateral adrenal mass and obvious benign features on imaging studies
140   (XOOO).

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141 R.4.3 We suggest performing laparoscopic adrenalectomy in patients with unilateral adrenal
142   masses with radiological findings suspicious of malignancy and a diameter ≤ 6 cm,
143   but without evidence of local invasion (XOOO).

144 R.4.4 We recommend performing open adrenalectomy for unilateral adrenal masses with
145   radiological findings suspicious of malignancy and signs of local invasion (XOOO).

146 R.4.5 We suggest an individualized approach in patients that do not fall in one of the above-
147   mentioned categories (XOOO).

148 R.4.6 We recommend perioperative glucocorticoid treatment at major surgical stress doses
149   as recommended by guidelines, in all patients undergoing surgery for an adrenal
150   tumor where there is evidence of '(possible) autonomous cortisol secretion', i.e. who
151   do not suppress to <50 nmol/L after 1mg dexamethasone overnight.

152 **1.5   Follow-up of patients not undergoing adrenal surgery after initial**
153   **assessment**

154 R.5.1 We suggest against further imaging for follow-up in patients with an adrenal mass <
155   4cm with clear benign features on imaging studies (XOOO).

156 R.5.2 In patients with an indeterminate adrenal mass (by imaging) opting not to undergo
157   adrenalectomy following initial assessment, we suggest a repeat non-contrast CT or
158   MRI after 6-12 months to exclude significant growth (XOOO). We suggest surgical
159   resection if the lesion enlarges by more than 20% (in addition to at least a 5 mm
160   increase in maximum diameter) during this period. If there is growth of the lesion
161   below this threshold, additional imaging after 6-12 months should be performed.

162 R.5.3 We suggest against repeated hormonal work-up in patients with a normal hormonal
163   work-up at initial evaluation unless new clinical signs of endocrine activity appear or
164   there is worsening of comorbidities (e.g. hypertension and type 2 diabetes) (XOOO).

165 R.5.4 In patients with 'autonomous cortisol secretion' without signs of overt Cushing's
166   syndrome, we suggest annual clinical re-assessment for cortisol excess comorbidities
167   potentially related to cortisol excess (XOOO). Based on the outcome of this
168   evaluation the potential benefit of surgery should be considered.

169 **1.6   Special circumstances**

170 **1.6.1 Patients with bilateral adrenal incidentalomas**

171 R.6.1.1 We recommend that for patients with bilateral adrenal masses each adrenal lesion is
172   assessed at the time of initial detection according to the same imaging protocol as
173   for unilateral adrenal masses to establish if either or both masses are benign or
174   malignant.

175 R.6.1.2 We recommend that all patients with bilateral adrenal incidentalomas should
176   undergo clinical and hormonal assessment identical to that in patients with unilateral

177   adrenal incidentaloma. The same applies for the assessment of comorbidities that
178   might be related to autonomous cortisol secretion. In addition, 17-
179   hydroxyprogesterone should be measured to exclude congenital adrenal
180   hyperplasia, and testing for adrenal insufficiency should be considered, if suspected
181   on clinical grounds or if imaging suggests bilateral infiltrative disease or
182   hemorrhages.

183   R.6.1.3   We suggest that for patients with bilateral incidentaloma the same recommendations
184   regarding the indication for surgery and follow-up are used as for patients with
185   unilateral adrenal incidentalomas.

186   R.6.1.4   We suggest that in patients with bilateral adrenal masses bilateral adrenalectomy is
187   not performed for ACTH-independent 'autonomous cortisol secretion' without clinical
188   signs of overt Cushing's syndrome. In selected patients, a unilateral adrenalectomy
189   of the dominant lesion might be considered using an individualized approach
190   considering age, degree of cortisol excess, general condition, comorbidities and
191   patient preference.

192   **1.6.2   Adrenal incidentalomas in young or elderly patients**

193   R.6.2.1   We recommend urgent assessment of an adrenal mass in children, adolescents,
194   pregnant women and adults < 40 years of age because of a higher likelihood of
195   malignancy.

196   R.6.2.2   We suggest the use of MRI rather than CT in children, adolescents, pregnant
197   women and adults < 40 years of age if dedicated adrenal imaging is required.

198   R.6.2.3   We recommend that the management of patients with poor general health and a
199   high degree of frailty be kept in proportion to potential clinical gain.

200   **1.6.3 Patients with a newly diagnosed adrenal mass and a history of extra-**
201   **adrenal malignancy**

202   R.6.3.1   We recommend measurement of plasma or urinary metanephrines to exclude
203   pheochromocytoma in patients with extra-adrenal malignancy with an indeterminate
204   mass, even if the adrenal mass is likely to be a metastasis. We suggest additional
205   hormonal work-up based on an individualized approach.

206   R.6.3.2   We suggest that in patients with a history of extra-adrenal malignancy FDG-PET/CT,
207   performed as part of investigations for the underlying malignancy, can replace other
208   adrenal imaging techniques.

209   R.6.3.3   We recommend that in patients with a history of extra-adrenal malignancy adrenal
210   lesions characterized as benign (see also R.2.3) by non-contrast CT require no
211   further specific adrenal imaging follow-up.

212   R.6.3.4 For indeterminate lesions in patients with a history of extra-adrenal malignancy, we
213   recommend imaging follow-up assessing the potential growth of the lesion at the
214   same interval as imaging for the primary malignancy. Alternatively, FDG-PET/CT,
215   surgical resection or a biopsy (see also R.6.3.5) can be considered.

216   R.6.3.5 We suggest performing a biopsy of an adrenal mass only if all of the following
217   criteria are fulfilled: (i) the lesion is hormonally inactive (in particular, a
218   pheochromocytoma has been excluded), (ii) the lesion has not been conclusively
219   characterized as benign by imaging, and (iii) management would be altered by
220   knowledge of the histology.

221   R.6.3.6 We recommend assessment of residual adrenal function in patients with large
222   bilateral adrenal metastases.

2. Adrenal Incidentaloma – Clinical presentation and terminology

2.1 Definition, etiology and epidemiology of adrenal incidentalomas

An adrenal incidentaloma is an adrenal mass detected on imaging not performed for suspected adrenal disease. By this strict definition, the imaging study is not done for symptoms related to adrenal hormone excess (e.g. pheochromocytoma, Cushing's or Conn's syndrome) or an otherwise suspected adrenal mass, but rather for the evaluation of symptoms that are not obviously related to an adrenal problem, such as abdominal or back pain or kidney stones. Similarly, screening imaging in patients with a hereditary syndrome leading to adrenal tumors is outside the definition of an adrenal incidentaloma. In addition, adrenal masses discovered on an imaging study performed during tumor evaluation for extra-adrenal malignancies ("tumor staging" or follow-up) do not meet the strict definition of adrenal incidentaloma. However, as this is a clinically frequent scenario, we will address this in a specific chapter (see 5.6.4).

Previous recommendations and reviews (1-13) have not considered adrenal incidentalomas smaller than 1 cm. Although this cut-off is obviously somewhat arbitrary, we agree with this approach and would perform additional diagnostic work-up only in lesions ≥ 1cm unless clinical signs and symptoms suggestive of adrenal hormone excess are present.

The etiology of adrenal incidentalomas varies and includes benign and malignant lesions derived from the adrenal cortex, the medulla or of extra-adrenal origin. The reported frequency varies, depending on the context of the study and inclusion size criteria (see Table 1). Some authors conclude, however, that the prevalence of malignant and functional lesions is likely to be overestimated (3), mainly because the prevalence of malignancy in surgical series is usually higher than in series including all patients presenting with an adrenal mass. There is, however, clear evidence that the vast majority of adrenal incidentalomas are benign adrenocortical adenomas.

The incidence and prevalence of adrenal incidentalomas can only be extrapolated from imaging or autopsy studies. Autopsy studies suggest a prevalence of clinically unapparent adrenal masses of around 2% (range 1.0-8.7%), which increases with age (5-7). Radiological studies report a frequency of around 3% in the age of 50 years, which increases up to 10% in the elderly (2, 5-7, 14-16). In childhood, adrenal incidentalomas are extremely rare.

254   ## 2.2. Remarks on terminology

255   As already discussed above, the term 'adrenal incidentaloma' can be defined by very
256   restrictive criteria, but is sometimes used in a much broader sense, referring to any adrenal
257   mass. Therefore, in the guideline we frequently speak of adrenal masses or lesions.

258   Another term, which is widely used in the literature in the context of adrenal incidentaloma, is
259   'subclinical Cushing's syndrome' (19). This term aims to define patients with biochemical
260   evidence of cortisol excess, but without the so-called "specific" clinical signs of Cushing's
261   syndrome (mainly the lack of catabolic features, like myopathy and skin fragility). There is,
262   however, clear evidence that patients with clinically unapparent cortisol excess very rarely
263   develop Cushing's syndrome (1, 2, 20-25) and that this condition is different from overt
264   Cushing's syndrome, which is clearly associated with severe morbidity and elevated mortality
265   (26-30). Nevertheless, there is some evidence that this low-grade autonomous cortisol
266   excess might be associated with certain comorbidities (see Table 2). Thus, the panel
267   unanimously decided to avoid the term "subclinical Cushing's syndrome" and to use instead
268   the term "'autonomous cortisol secretion'" in the context of an adrenal incidentaloma
269   throughout the guideline text (for the exact definition see chapter 5.3).

270   Although the term "laparoscopic adrenalectomy" is actually reserved for operations that use a
271   transperitoneal approach and should be distinguished from the term retroperitoneoscopic
272   adrenalectomy, this never gained general acceptance. Therefore, in this guideline we use the
273   term "laparoscopic adrenalectomy" to refer to minimally invasive approaches including
274   retroperitoneoscopic surgery.

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277   ## 2.3. Short overview on adrenal imaging

278   For the differentiation of malignant from benign adrenal tumors, there are three main imaging
279   techniques in current use: computed tomography (CT), magnetic resonance imaging (MRI),
280   and positron emission tomography with ^{18}F-2-deoxy-D-glucose (mostly combined with CT;
281   FDG-PET/CT). CT and MRI are techniques mainly aiming to identify benign lesions,
282   therefore representing tools designed for the exclusion of adrenal malignancy (47-50).
283   Conversely, FDG-PET/CT is mainly used for the detection of malignant disease (51-53).

284   CT has a high spatial and quantitative contrast resolution, which allows assessment of tissue
285   density by measuring X-ray absorption of tissues. This allows calculation of tissue
286   attenuation or tissue density values, which are measured in Hounsfield units (HU) and
287   quantify X-ray absorption of tissues compared to water, which is conventionally allocated a
288   HU value of 0. For **non-contrast (or 'unenhanced') CT**, HU of ≤ 10 is the most widely used
289   threshold attenuation value for the diagnosis of a lipid-rich, benign adrenal adenoma (54).
290   However, on non-contrast CT, some 30% of benign adenomas have an attenuation value

291   of > 10 HU and are considered lipid-poor, overlapping in density with malignant lesions and
292   pheochromocytomas (55-57).

293   **Contrast-enhanced washout CT** utilizes the unique perfusion pattern of adenomas.
294   Adenomas take up intravenous CT contrast rapidly, but also have a rapid loss of contrast - a
295   phenomenon termed 'contrast enhancement washout'. It is assumed that malignant adrenal
296   lesions usually enhance rapidly but demonstrate a slower washout of contrast medium. This
297   washout phenomenon can be quantified by 'contrast washout values', which involve lesion
298   attenuation measurements at specific time points acquired in a dedicated adrenal CT: prior to
299   injection of contrast medium (HU_{nativ}), at 60 seconds following injection of contrast medium
300   (HU_{max}) and then at 10 or 15 minutes after contrast injection. This allows calculation of the
301   relative contrast enhancement washout ($=100x(HU_{max}-HU_{10/15min})/HU_{max}$) and absolute
302   contrast enhancement washout ($=100x(HU_{max}-HU_{10/15min})/(HU_{max}-HU_{nativ})$). A relative
303   washout > 40% and an absolute washout > 60% is assumed to suggest that an adrenal
304   lesion is benign (56, 58-60).

305   **MRI** is a non-ionising radiation based imaging modality utilizing weak radio wave signals
306   emitted by body tissues when the body is placed in a strong magnetic field and radio
307   frequency pulses are applied. The advantages of MRI over CT are its lack of radiation
308   exposure, lack of iodine-based contrast media and its superior tissue contrast resolution. For
309   the differentiation of benign and malignant adrenal masses the MRI technique of **chemical-**
310   **shift imaging** is most commonly used (60-65). Chemical shift imaging relies on the fact that,
311   within magnetic fields, protons in water vibrate at a slightly different frequency than protons in
312   lipid. As a result, water and fat protons oscillate in and out of phase with respect to one
313   another. By selecting appropriate sequencing parameters, separate images can be
314   generated with water and fat protons oscillating in-phase or out-of-phase to each other.
315   Adrenal adenomas with a high content of intracellular lipid usually lose signal intensity on
316   out-of-phase images compared to in-phase images, whereas malignant lesions and
317   pheochromocytomas (but also lipid-poor adrenal adenomas) that all lack intracellular lipid
318   remain unchanged (58, 65, 66). Simple visual assessment of signal intensity loss is
319   diagnostic in most cases but quantitative methods may be useful in less clear cut cases.
320   Quantitative analysis can be made using the adrenal-to-spleen signal ratio and the signal
321   intensity index. MR signal intensity units are arbitrary units, unlike CT, and therefore are
322   subject to numerous technical variations.

323   **[18]F-FDG-PET** is a nuclear medicine modality that provides quantitative tomographic images
324   after intravenous injection of a beta-radiation emitting radiotracer (18-Fluorine) used to label
325   2-deoxy-D-glucose rendering Fluoro-deoxyglucose (^{18}F-FDG). Both glucose and
326   deoxyglucose enter cells via cell glucose transporters and undergo phosphorylation but while
327   glucose undergoes further enzymatic breakdown, deoxyglucose becomes trapped in

328   intracellular compartments. Cancer cells have an increased requirement for glucose and,

329   therefore, take up more glucose and deoxyglucose than normal cells (67). However, ^{18}F-FDG

330   is not a specific marker for cancer cells but a marker only for increased glucose metabolism

331   thus uptake can also be increased in cells with an increased energy requirement due to

332   conditions other than cancer. Quantitative measurement of ^{18}F concentrations within tissues

333   provides the most commonly used clinical measurement index, standard uptake value (SUV),

334   which compares the intensity of uptake of ^{18}F in the adrenal lesion to the average uptake of

335   whole body. SUV values have been utilized to differentiate between benign from malignant

336   adrenal lesions. FDG-PET has a high sensitivity for detection of metabolic changes but its

337   spatial resolution for anatomical localization is poor. The solution is a hardware fusion

338   between PET and CT (PET/CT) allowing simultaneous acquisition of PET and CT data. In

339   clinical practice this involves injecting patients with ^{18}F-FDG tracers at least one hour prior to

340   the start of combined PET/CT. Once post processing is complete, PET and CT data can be

341   viewed separately, side-by-side or as a fused images (68).

342   Other potentially emerging imaging techniques (e.g. metomidate-based adrenal imaging) are

343   not yet clinically widely available and, therefore, will not be discussed in this guideline.

344

345   **2.4. Remarks on the difficulties with hormonal testing**

346   Hormone assessment is crucial in the context of the work-up for an adrenal incidentaloma.

347   However, there are several pitfalls that have to be considered (e.g. daily rhythm, sex-/ age-

348   dependency, limitations of assays, drug interactions). Furthermore, normal ranges vary

349   substantially, depending on the method used, so it is essential to interpret test results in the

350   context of the appropriate reference range. Due to space restrictions we refer to other

351   guidelines that have addressed these issues in more detail (69, 70).

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354   **3. Methods**

355   **3.1. Guideline working group**

356   This guideline was developed by *The European Society of Endocrinology* (ESE) in

357   collaboration with the *European Network for the Study of Adrenal Tumours* (ENSAT),

358   supported by CBO (Dutch Institute for health care improvement). The chairs of the working

359   group Martin Fassnacht (clinical) and Olaf Dekkers (methodology) were appointed by the

360   ESE Clinical Committee. The other members were suggested by the chairs and approved by

361   the Clinical Committee of ESE: endocrinologists (Wiebke Arlt (UK), Irina Bancos (USA), John

362   Newell-Price (UK), Antoine Tabarin (France), Massimo Terzolo (Italy), Stylianos Tsagarakis

363   (Greece), a radiologist (Anju Sahdev (UK), and an endocrine surgeon (Henning Dralle

364   (Germany)). Irina Bancos served as representative of *The Endocrine Society USA*. The
365   working group had three in-person meetings (December 2013, October 2014, and June
366   2015) and communicated by phone and email. Consensus was reached upon discussion;
367   minority positions were taken into account in the rationale behind recommendations. Prior to
368   the process, all participants completed conflict of interest forms.

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371   **3.2 Target group**
372   This guideline was developed for healthcare providers of patients with adrenal
373   incidentalomas *ie,* endocrinologists, radiologists, surgeons, and specialists in internal
374   medicine. However, general practitioners might also find the guideline useful, as might our
375   patients. In addition, the guideline document can serve as guidance for patient information
376   leaflets. A draft of the guideline was reviewed by four experts in the field (see
377   "Acknowledgment' section) and has been submitted for comments by ESE and ENSAT
378   members. All comments and suggestions were then discussed and implemented as
379   appropriate by the panel.

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382   **3.3 Aims**
383   The overall purpose of this guideline is to provide clinicians with practical guidance for the
384   management of patients with adrenal incidentalomas.

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387   **3.4 Summary of methods used for guideline development**
388   The methods used have been described in more detail previously (71). In short, the guideline
389   used GRADE (Grading of Recommendations Assessment, Development and Evaluation) as
390   a methodological base. The first step was to define clinical question(s) (see section 3.5), the
391   second being a systematic literature search (see Section 3.6). After including relevant
392   articles, we 1), estimated an average effect for specific outcomes (if possible), and 2), rated
393   the quality of the evidence. The quality of evidence behind the recommendations is classified
394   as very low ($\oplus$OOO), low ($\oplus\oplus$OO), moderate ($\oplus\oplus\oplus$O) and strong ($\oplus\oplus\oplus\oplus$). Evidence tables
395   are provided in the Appendix.
396   For the recommendations we took into account: 1) quality of the evidence, 2) balance of
397   desirable and undesirable outcomes, 3) values and preferences (patient preferences, goals
398   for health, costs, management inconvenience, feasibility of implementation, etc). (72, 73).
399   The recommendations are worded as *recommend* (strong recommendation) and *suggest*

ESE and ENSAT guideline on adrenal incidentaloma

400 (weak recommendation). Formal evidence syntheses were performed and graded only for
401 recommendations addressing our initial questions. Additional recommendations based on
402 good practice were not graded (74). Recommendations were derived from majority
403 consensus of the guideline development committee, but if members had substantive
404 disagreements, this is acknowledged in the manuscript. For transparency, all
405 recommendations provided are accompanied by text explaining why specific
406 recommendations were made.

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409 **3.5.   Clinical question, eligibility criteria and endpoint definition**
410 At the beginning of the guideline development process, the panel agreed on the four most
411 important clinical questions in the management of patients with adrenal incidentalomas
412 (Table 3), for which a detailed literature search was subsequently performed.

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415 **3.6 Description of search and selection of literature**
416 A literature search in electronic medical databases was performed for all four clinical
417 questions separately. Of note, the approach for clinical question 1 (assessment of the risk of
418 malignancy) differed as the search, study selection and also the evidence synthesis was
419 performed in the context of a formal systematic review and meta-analysis published
420 separately from the current guideline. For all four clinical questions details of the yield of the
421 search are shown in Table 3. In summary, we included 37 studies for clinical question 1 (with
422 18 fulfilling the criteria for inclusion in the meta-analysis), twelve studies for clinical question
423 2a (biochemical profile in adrenal incidentaloma), four studies for clinical question 2b
424 (therapeutic approach in mild glucocorticoid excess), nine studies for clinical question 3
425 (surgery) and ten studies plus one relevant systematic review for clinical question 4 (follow-
426 up).

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428

429 **4. Summary and conclusions from systematic literature reviews**

430

431 4.1   Assessment of the risk of malignancy (Question 1)

432 4.1.1   Assessment of the risk of malignancy by imaging (Question 1a)

433 The following paragraph represents a summary of a recent meta-analysis on the use of
434 imaging for differentiating benign from malignant adrenal incidentalomas carried out with
435 involvement of some of the guideline panel members (75). Studies were considered all

436 studies of CT, MRI or FDG-PET in adults eligible if: 1) included patients underwent imaging
437 for any indications other than investigation of suspected adrenal mass; 2) index imaging test
438 characteristics were reported; 3) at least 50% of patients had an optimal reference standard:
439 histological diagnosis in malignant masses and availability of histology or imaging follow up
440 of any duration in the case of benign adrenal masses. Exclusion criteria are summarized in
441 Table 3. The review looked separately at patients with true adrenal incidentaloma and
442 patients with adrenal mass and a history of extra-adrenal malignancy.

443 We identified 37 studies for inclusion in the systematic review (49, 52, 61, 77-110), with only
444 18 of them fulfilling the criteria for inclusion in the actual meta-analysis (61, 77-93). No
445 randomized studies comparing imaging tests were identified. Risk of bias ranged from low to
446 high, with the majority having unclear or high risk of bias (mainly due to unclear population
447 selection, retrospective selection of the diagnostic threshold and inadequate reference
448 standards with resulting concerns of the applicability of results).

449 Five commonly used diagnostic thresholds were studied: (1) tumor density >10HU on non-
450 contrast CT; (2) CT with delayed contrast media washout: absolute percentage washout
451 and/or relative percentage washout at any washout percentage % or delay time on enhanced
452 CT; (3) MRI chemical shift analysis: loss of signal intensity between in and out of phase
453 images (including both qualitative and quantitative estimates of signal loss); and, for FDG-
454 PET or PET-CT, (4) the maximum standardized uptake value (SUVmax), and (5) the ratio of
455 SUVmax in the adrenal gland compared to the liver (adrenal liver ratio).

456 The 37 studies included were generally small with a median sample size of 45 (range 12 to
457 181). Of the 18 studies included in the formal meta-analysis, 7 addressed purely incidental
458 adrenal masses and 11 studies focused on patients with known extra-adrenal malignancy.

459 Limited data (two studies with 102 true incidentalomas) suggest that CT density >10 HU has
460 a high sensitivity for detection of adrenal malignancy (100%, 95% confidence interval 91-
461 100%); meaning that adrenal masses with a density of ≤10 HU are unlikely to be malignant.
462 In patients with a history of extra-adrenal malignancy five studies evaluating the >10 HU cut-
463 off as indicative of malignancy showed high sensitivity (93%) for detection of malignancy but
464 variable specificity; this means that 7% of adrenal metastases were found to have a tumor
465 density of ≤10 HU.

466 Disappointingly, all other estimates of test performance are based on small numbers of
467 studies with very few patients and accompanying wide 95% confidence intervals, indicating
468 much uncertainty in test performance for all other imaging markers. For true adrenal
469 incidentalomas, two of three MRI studies reported slightly lower sensitivity and specificity
470 than CT for measures of adrenal-liver and adrenal-spleen ratios and loss of signal intensity.
471 The performance of PET for adrenal liver ratio and SUVmax measures in the two included
472 studies was not clearly better than CT. In patients with a history of extra-adrenal malignancy,

14

473   only one study reported on CT contrast-enhanced washout tests, which showed very low

474   sensitivity (16%). Four of the five studies of MRI used 1.5 Tesla machines and reported high

475   sensitivity (89%-99%) for measures of adrenal-liver, adrenal-spleen, adrenal-muscle ratios

476   and loss of signal intensity. Specificity varied (60%-93%) but was high for most MRI

477   measures. The performance of PET was similar to MRI for ALR and max SUV measures.

478   Although more studies had evaluated CT, MRI and PET in the pathway for follow-up of

479   known extra-adrenal malignancy than for incidentally discovered adrenal lesions, estimates

480   of test performance are still based on too small numbers of studies to be able to discern

481   whether any test performs adequately or better than alternative tests from the available data.

482

483   4.1.2 Value of an adrenal biopsy (Question 1b)

484   The following paragraph represents a summary of a recent systematic review carried out with

485   involvement of some of the guideline panel members on published experience with adrenal

486   biopsy and its outcomes (76). Inclusion criteria and definition of reference standard differed

487   from the imaging meta-analysis mainly in population selection criteria (as adrenal biopsy is

488   not indicated in incidentaloma population but rather in patients at high risk for malignancy)

489   and in reference standard (where we accepted imaging and clinical follow up in addition to

490   histopathology as most metastases would not undergo adrenalectomy). We identified 32

491   studies (88, 111-138) with a total of 2174 patients which reported at least one outcome of

492   interest (complication rate, non-diagnostic rate, diagnostic accuracy parameters). Of these,

493   only 8 studies(88, 124, 125, 128-131, 138) were included for the diagnostic accuracy

494   analysis, reasons for exclusion being lack of any or optimal reference standard for at least

495   50% patients (n=20) and more than 30% patients with non-adenomas in benign cohort (n=4).

496   Included studies were assessed to be at a moderate risk for bias, most limitations relating to

497   patient selection, assessment of outcome and adequacy of follow up of the study population.

498   Studies had diverse population inclusion criteria, reference standards and biopsy techniques.

499   Pathology of adrenal lesion was reported only for 1600/2207 cases. Out of these 819 were

500   malignant (703 metastases, 67 ACCs, 49 other malignancies or not specified), 690 were

501   benign and 91 were various other non-malignant lesions (36 pheochromocytomas, 29

502   granulomas, 16 other). Pooled non-diagnostic rate derived from 30 studies (2030 adrenal

503   biopsy procedures) was 8.6% (CI 6.1%-11%; I2 = 84%, p<0.001). Pooled overall

504   complication rate derived from studies (1356 biopsies) was 2.4% (CI 1.5%-3.3%; I2 = 21%,

505   p=0.175), though likely under-represented due to differences in both assessment and

506   reporting of complication as well as retrospective nature of the studies. The diagnostic

507   performance of adrenal biopsy was calculated using the data from the 8 studies (323 adrenal

508   biopsy procedures) meeting pre-established eligibility criteria. Performance of adrenal biopsy

509   in the diagnosis of malignancy overall was: sensitivity 87% (CI95% of 78-93%), specificity

510   100% (CI95% of 76-100%), positive likelihood ratio of 229 (CI95% of 2.9-18145) and

511   negative likelihood ratio of 0.13 (CI95% of 0.07-0.23). Performance was lower (and with even

512   wide 95%CIs) for ACC: sensitivity 70% (CI95% of 42-88%), specificity 98% (CI95% of 86-

513   100%), positive likelihood ratio of 100.43 (CI95% of 8-1245) and negative likelihood ratio of

514   30.9 (CI95% of 4.16-229).

515

516

517   4.2   Assessment of autonomous cortisol secretion in adrenal incidentalomas

518   4.2.1 Assessment of autonomous cortisol secretion in relation to clinical outcomes

519   (Question 2a, Appendices I and II)

520   Studies were eligible for inclusion independent of the criteria used to define autonomous

521   cortisol secretion. Three different hormonal profiles were distinguished to describe

522   autonomous cortisol secretion associated with adrenal adenomas; Profile 1: serum cortisol >

523   50 nmol/l (>1.8 µg/dl) after 1-mg, 2-mg, or 8-mg overnight dexamethasone suppression

524   tests, or 2-day low dose dexamethasone test, and one of the following additional endocrine

525   alterations: increased 24-h urinary free cortisol (UFC), low plasma ACTH, elevated midnight

526   serum or salivary cortisol; Profile 2: serum cortisol > 83nmol/l (>3.0 µg/dl) after 1-mg

527   overnight dexamethasone test and one additional endocrine alteration (same as above);

528   Profile 3: cortisol > 138 nmol/l (>5 µg/dl) after 1-mg overnight dexamethasone test as sole

529   criterion. The defined profiles do not fit completely with the specific criteria used in all of the

530   studies included. Virtually all diagnostic algorithms are, however, variations of these profiles.

531

532   In total, twelve studies were included: seven cross-sectional studies (38, 42, 43, 45, 139-141)

533   and five cohort studies (40, 46, 142-144). In eight studies, a comparison was made between

534   patients with elevated (group 1) or normal (group 2) cortisol levels after a 1-mg

535   dexamethasone test. Two studies used the biochemical profile 1 and four studies used the

536   biochemical profile 2 with a variation since the post-dexamethasone serum cortisol cutoff

537   was not a mandatory criterion. Three studies identified 3 subgroups of patients (38, 142,

538   143), normal, intermediate and frankly altered cortisol suppression corresponding to cortisol

539   levels after 1-mg dexamethasone of < 50 nmol/l (< 1.8 µg/dl), between 50 to 138 nmol/l (1.8

540   µg/dl - 5.0 µg/dl), and > 138 nmol/l (> 5.0 µg/dl), respectively.

541   In the cross-sectional studies, the risk of bias is estimated as high, given the inability to

542   assess causality and the potential for residual confounding factors, and these issues hamper

543   the ability to make firm conclusions from these studies. Differences in diagnostic protocols,

544   definitions of outcome, and duration of follow-up were associated with considerable

545   heterogeneity between and within studies.

546

Outcome measures

Change in biochemical profile

In three studies with a median follow-up of 3, 6.9, and 7.5 years no patient progressed to overt Cushing's syndrome during follow-up (40, 143, 144).

551

Change in metabolic and cardiovascular profile

The risk of type 2 diabetes was higher in patients with impaired cortisol suppression after 1-mg dexamethasone test and increased further during follow-up (38, 143, 144). Also, the risk of hypertension was higher in patients with impaired cortisol suppression and increased further with follow-up (38, 140, 144, 145). A smaller study did not confirm the increase in diabetes and hypertension with time (40).

558

Major cardiovascular incidents

In two cohort studies (143, 144), the incidence of cardiovascular events was higher in patients with altered cortisol suppression.

562

Mortality

Two studies reported on mortality (142, 143) and found an increased mortality risk in patients with higher cortisol levels after 1-mg dexamethasone. However, the results were adjusted for other prognostic factors only in the first study, and effect estimates were uncertain due to low number of events.

568

Risk of vertebral fractures

Four studies reported a higher prevalence of vertebral fractures (38, 42, 43, 45) in patients with impaired cortisol suppression. In a cohort study (46), the incidence of new vertebral fractures was higher in patients with impaired cortisol suppression. However, most of the detected vertebral fractures were minor and of uncertain clinical impact.

574

575

4.2.2. Surgery vs. conservative management in patients with autonomous cortisol secretion (Question 2b, Appendices III and IV)

For question 2b, four studies were included in which surgery was compared to a conservative approach: one randomized controlled trial and three observational studies. The randomized trial (146) reported on patients with autonomous cortisol secretion who underwent surgery (n=23) or were treated by a conservative approach (n=22). The mean

17

582   follow up was 7.7 years and the results were only a qualitative description of changes in
583   hypertension, diabetes mellitus or dyslipidemia.

584   Tsuiki et al. included patients with autonomous cortisol secretion and compared a group
585   treated by surgery (n=10) and a group treated conservatively (n=10) (147). Follow up was 7-
586   19 months. The second cohort study included 41 patients with autonomous cortisol secretion
587   (25 treated by surgery and 16 conservatively treated) (44). Outcome measures included:
588   proportion of patients with steady, improved, or worsened blood pressure, fasting glucose or
589   LDL cholesterol. In the third study by Iacobone et al, 372 patients with autonomous cortisol
590   secretion (20 treated by surgery and 15 conservatively treated) (148). Outcomes were blood
591   pressure, glucose and cholesterol.

592   The quality of evidence from these studies is low to very low, mainly due to confounding
593   factors. Only one study was randomized, and none of the studies reported blinded outcome
594   assessment. Most studies were also downgraded for imprecision, due to low number of
595   events. Differences in diagnostic protocols, definitions of outcome, and duration of follow-up
596   were associated with considerable heterogeneity between and within studies.

597
598

599   ***Outcome measures***

600

601   *Change in metabolic and cardiovascular profile in patients with autonomous cortisol*
602   *secretion*

603   In the randomized trial, 25% of patients with type 2 diabetes mellitus had normalized
604   glycemic control after surgery (146), compared to none in the conservative group. The cohort
605   studies (44, 147, 148) reported an improvement in glucose levels in 10-48% of patients after
606   surgery. In the conservatively treated groups, none of the patients improved.

607   The cohort studies (44, 147, 148) reported an improvement in hypertension and dyslipidemia
608   in some patients after surgery. In the conservatively managed group, none of the patients
609   improved.

610

611   *Risk of vertebral fractures*

612   None of the included studies reported on the risk of vertebral fractures.

613

614   *Major cardiovascular incidents and mortality*

615   None of the included studies reported on the risk of major cardiovascular events or mortality.

616
617

618   4.3   Surgical approach: open vs. minimally-invasive adrenalectomy (Question 3,
619   Appendices V and VI)

620   As adrenocortical carcinoma is the main threat for an adverse outcome in patients with
621   adrenal incidentaloma undergoing surgery, we focused our efforts with regards to surgery on
622   the management of adrenocortical carcinoma. Nine cohort studies on the surgical treatment
623   of patients with non-metastatic adrenocortical carcinoma were included (149-157). Three
624   studies reported on the patients in whom complete resection of the tumor was achieved (151,
625   153, 157).

626

627   The quality of evidence from these observational studies is very low, mainly because patient
628   groups were not comparable at baseline with regard to important prognostic characteristics,
629   such tumor stage or size. Tumor stage was, on average, lower in patients with laparoscopic
630   surgery as compared to open surgery. In few studies (149, 156), treatment effects were
631   adjusted for differences in tumor stage. Mostly, however, only uncorrected estimates of
632   recurrence-free and overall survival were reported. Moreover, most studies had imprecise
633   effect estimates.

634

635   ***Outcome measures***
636   *Perioperative mortality and morbidity*
637   One study reported on perioperative mortality (149). In this study, none of the 152 patients
638   died perioperatively. Three studies reported on intraoperative or postoperative complications
639   (152, 153, 156). Major postoperative complications (Clavien-classification score 3-5)
640   occurred more often in open surgeries compared to laparoscopic surgeries (RR 1.7, 95% CI
641   0.5-6.2) but these estimates are imprecise due to low numbers of events.

642

643

644   *Completeness of resection*
645   In five studies the completeness of resection was reported (149, 150, 152, 154, 156). The
646   pooled estimate of these five studies indicated no clear difference in complete resection
647   between surgical approaches (RR 0.8 (95% CI 0.6 to 1.1)). The results of these studies were
648   inconsistent, leading to much uncertainty regarding this conclusion.

649

650   *Recurrence-free and overall survival*
651   Eight studies reported on recurrence after surgery, but differed in the presentation of these
652   data. These studies also provided data on overall or disease-specific survival (149-153, 155-
653   157). There is no compelling evidence that one of the approaches (laparoscopic or open
654   adrenalectomy) is superior with regard to time to recurrence and/or survival in patients with

19

655 adrenocortical carcinoma, provided that rupture of tumor capsule is excluded. However, the
656 studies have significant limitations, inconsistencies and imprecision precluding reliance on
657 this conclusion.

658

659 *Pain / patient satisfaction*
660 None of the studies reported on pain or patient satisfaction.

661

662 4.4   Natural course of apparently benign adrenal incidentaloma (risk of malignancy
663 or development of hormone excess) (Question 4, Appendix VII and VIII)
664 A systematic review of fourteen studies assessing the natural course of 1410 patients with
665 apparently benign, non-functioning adrenal incidentalomas (3) and ten additional cohort
666 studies were included (40, 44, 46, 144, 145, 158-166). The systematic review included
667 studies reporting the follow up of adrenal incidentaloma patients, published between 1980
668 and 2008, including publications that reported more than 20 patients, and in which the
669 majority were referred to an endocrinologist (excluding oncology series). The additional ten
670 studies, published between 2005 and 2014, included 1131 incidentaloma patients with
671 apparently benign non-functioning tumors or with autonomous cortisol secretion.

672

673 The quality of evidence from these studies was judged moderate or low. Selection criteria
674 were often not reported, the duration of follow-up was heterogeneous across studies
675 (medians ranging from 19 to 90 months) and the completeness of follow-up was difficult to
676 assess. Information on the protocol of biochemical or radiological re-evaluation was not
677 always provided and standardized. In addition, criteria for hormonal excess were
678 heterogeneous across studies.

679

680 ***Outcome measures***
681 *Malignancy*
682 The estimated pooled risk for developing malignancy in the systematic review was 0.2%
683 (95%CI 0.0 to 0.4) (3). In two cohort studies, one case of malignancy was found: one patient
684 with adrenal non-Hodgkin lymphoma and one patient with renal cancer metastasis. In the
685 first case, the imaging characteristics of the adrenal incidentaloma at the first evaluation were
686 not consistent with benign characteristics and the lymphoma may have been misdiagnosed
687 initially (22). The second case had a history of renal cell carcinoma and it is unclear whether
688 the adrenal mass was found incidentally or during the follow-up for cancer (167). No case of
689 malignancy was reported in the other 904 patients included in the cohort studies. Importantly,
690 no malignant transformation of a presumably benign incidentaloma was reported.

691

692   *Development of clinically overt hormone excess*

693   The risk of developing overt Cushing' syndrome in patients without clinical signs of Cushing's

694   syndrome at the time of initial assessment ranged in the individual studies from 0% to 4%,

695   whereas the risk of developing autonomous cortisol secretion in the absence of clinically

696   overt Cushing's syndrome was low, with a pooled estimate form a systematic review of 0.3%

697   (3). The risk of developing an aldosterone-producing adenoma in the individual studies

698   ranged from 0% to 2%.The risk of developing a pheochromocytoma ranged from 0% to 2%

699   but it is unclear whether an accurate initial imaging and biochemical screening was

700   performed.

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5.   Recommendations, Rationale for the Recommendations

5.1. General remarks

The main part of this guideline addresses the management of patients who fulfill the definition of adrenal incidentaloma (section 2.1). In addition, we discuss specific situations separately: bilateral adrenal masses (5.6.1), patients who are young or elderly and frail (5.6.2), and adrenal masses detected during evaluation for extra-adrenal malignancy (5.6.3).

R.1.1   We recommend that patients with adrenal incidentalomas are discussed in a multidisciplinary expert team meeting, if at least one of the following criteria is met (Figure 1):

- **Imaging is not consistent with a benign lesion.**
- **There is evidence of hormone excess (including 'autonomous cortisol secretion').**
- **Evidence of significant tumor growth during follow-up imaging.**
- **Adrenal surgery is considered.**

Reasoning:

Although we believe that the ideal would be for all patients with adrenal incidentalomas to be managed by an expert multidisciplinary team, in many health care settings this is an unrealistic aspiration. Despite lack of compelling evidence, we aimed at identifying subgroups of patients that would be most likely to benefit from multidisciplinary team discussion, and that these discussions occur quickly for patients that meet the criteria above. The core multidisciplinary team should consist of at least a radiologist, an endocrinologist, and a surgeon, all with significant experience in adrenal tumors. Furthermore, this team should have access to anesthetists and an endocrine pathologist, who are experienced in adrenal tumors. Although it is beyond the scope of this guideline, the use of a standardized pathology report is highly recommended.

There is sufficient evidence that higher surgical volume correlates with better outcome, however, for the time being no specific numbers of operations per year that result in this favorable outcome can be recommended (150, 168-170).

5.2. Assessment of the risk of malignancy

R.2.1 We recommend aiming to establish if an adrenal mass is benign or malignant at the time of initial detection.

<u>Reasoning</u>

It is critical to know if an adrenal mass is malignant or benign as clinical management is dependent on establishing this fact, regardless of whether the mass is functioning or not. Malignant lesions may need urgent surgical intervention and other therapies, and delay may cause harm.

R.2.2 We recommend that all adrenal incidentalomas undergo an imaging procedure to determine if the mass is homogeneous and lipid-rich and therefore benign (XOOO). For this purpose, we primarily recommend the use of non-contrast CT (XOOO)

R.2.3 We suggest that if the non-contrast CT is consistent with a benign adrenal mass (Hounsfield units ≤ 10) that is homogeneous and smaller than 4 cm no further imaging is required (XOOO).

<u>Reasoning</u>

In patients with no known extra-adrenal malignancy adrenal incidentalomas are likely to be benign. The non-contrast CT value is reflective of tissue density. Benign lesions including lipid rich adenoma, myelolipoma, fluid-filled homogenous cysts, and other soft tissue tumors (ganglioneuromas, some schwanomas) have low CT density ≤ 10 HU. Based on the systematic review and meta-analysis (75), in patients presenting without known malignancy a non-contrast CT with HU of ≤10 was only found in those with benign disease, whereas in patients with extra-adrenal malignancy 7% of cases with non-contrast HU ≤10 turned out to be malignant.

Similar to CT, the results of MRI with chemical shift imaging are based on the lipid content of masses (171, 172). Unlike CT (or FDG-PET) MRI has the advantage of avoiding ionizing radiation and its attendant risks to the patient. However, the quantitative assessment of loss in signal intensity is not well standardized between the different studies and, therefore, evidence base for performance of MRI in the diagnosis of malignancy is insufficient to make strong recommendations. Moreover, the interpretation of the images might be more dependent on the experience of the radiologist than for CT assessment. In addition, the meta-analysis was not able to determine the diagnostic value of MRI due to the low number and quality of eligible studies.

768   In conclusion, the panel felt - despite the limited evidence - confident about the negative

769   predictive value of non-contrast CT to recommend that additional imaging was not necessary

770   when benign characteristics were found in an adrenal mass < 4 cm, especially as additional

771   imaging may also risk false positive results and significant psychological and financial burden

772   for patients and the health system, respectively. We acknowledge that the cutoff of 4 cm is

773   not based on good evidence from clinical studies, but the panel felt it is necessary to provide

774   clear guidance based on clinical experience.

775   MRI with chemical shift has an even poorer evidence base with regard to its diagnostic value

776   in excluding malignancy and therefore should be first choice only where a CT is less

777   desirable (e.g. pregnancy, children). However, if an MRI with chemical shift is already

778   performed and the results are unambiguous, a multidisciplinary expert team might judge this

779   as sufficient for an individual patient.

780

781

782   **R.2.4 If the adrenal mass is indeterminate on non-contrast CT and the results of the**

783   **hormonal work-up do not indicate significant hormone excess, there are three**

784   **options that should be considered by a multidisciplinary team acknowledging**

785   **the patient's clinical context: immediate additional imaging with another**

786   **modality, interval imaging in 6 to 12 months (non-contrast CT or MRI), or**

787   **surgery without further delay.**

788

789   <u>Reasoning</u>

790   Evidence of targeted evaluation for "second or third-line" imaging in patients with

791   indeterminate adrenal mass is very poor (see section 4.1 and (75) for details). However, the

792   panel considered it important to provide some guidance for daily clinical practice (Table 4),

793   although consensus was not reached other than agreeing that such discussions needed to

794   be individualized and should take place within a multidisciplinary team meeting.

795   The advantages and limitations of MRI with chemical shift are already discussed at R 2.3.

796   Contrast washout CT has very limited and low quality evidence from studies (75). CT

797   washout is widely available but there is huge variability in the protocols applied and therefore

798   poor comparability between studies and centers; in addition, the meta-analysis could only

799   identify a single eligible study reporting CT washout study results, carried out in patients

800   without a history of extra-adrenal malignancy.

801   FDG-PET/CT has the advantage that the risk of false negative results (namely missing a

802   malignant adrenal tumor) is quite low, and this refers mainly to a few subtypes of extra-

803   adrenal malignancies with low uptake (173-176). This procedure is, however, more

804   expensive, not always easily available, and has the disadvantage that several benign adrenal

805   tumors (e.g. functional adenomas or benign pheochromocytoma) may be FDG-positive (177,
806   178).

807

808   Whilst the panel was in favor of attempts to fully characterize the adrenal mass on imaging,
809   due to the limitations summarized above, it considered that in patients with indeterminate
810   results on non-contrast CT further imaging by one of the modalities detailed above should be
811   arranged. Due to the lack of evidence and studies reporting direct comparison the panel was
812   not able to clearly judge one method over another. Alternatively, in patients without a strong
813   suspicion of malignancy and older patients, follow-up imaging 6-12 months after the initial
814   scan could be undertaken. The rationale for a follow-up scan at 6-12 months is based on the
815   principle that either primary adrenal malignancies or adrenal metastases are likely to
816   increase in size over this time period; lack of growth may be taken as an indicator of benign
817   disease in radiologically indeterminate lesions. The exact timing of this imaging should be
818   individualized. However, especially in cases with a low likelihood of a malignant tumor the
819   panel favors a time interval of 12 months. There are no published size or volume cut-offs
820   commonly agreed or with evidence base to support that they indicate growth suggestive of
821   malignancy; the expert panel agreed that an increase in > 20% of the largest tumor diameter
822   together with an at least 5 mm increase in this diameter should be considered as suspicious.

823

824

825   **R.2.5 We recommend against the use of an adrenal biopsy in the diagnostic work-up**
826   **of patients with adrenal masses unless there is a history of extra-adrenal**
827   **malignancy (see R6.3.5).**

828

829   <u>Reasoning</u>
830   Adrenal biopsy has a limited role in evaluation of adrenal masses – mainly in diagnosis of
831   extra/adrenal malignancy, lymphoma, infiltrative or infectious process. Even in such
832   situations, adrenal biopsy should only be performed by an experienced radiologist and when
833   it is required to guide further care. We particularly recommend against an adrenal biopsy if
834   an adrenal mass is likely to be an adrenocortical carcinoma, because a biopsy of such a
835   tumor runs the risk of tumor dissemination precluding an R0 resection (although this risk
836   seems to be low (179)). The only exception might be if a formal confirmation of the diagnosis
837   is needed in an inoperable tumor to inform oncological management or as part of a clinical
838   trial.

25

839   ## 5.3. Assessment for hormone excess

840

841   **R.3.1 We recommend that every patient with an adrenal incidentaloma should**
842   **undergo careful assessment including clinical examination for symptoms and**
843   **signs of adrenal hormone excess.**

844

845   Reasoning

846   All patients should undergo a careful evaluation with detailed history and physical
847   examination since a second round evaluation may detect clues of overt hormone excess that
848   were overlooked initially. For the clinical assessment and subsequent diagnostic procedures
849   for Cushing's syndrome, primary aldosteronism, and pheochromocytoma, we refer to
850   guidelines of other societies (69, 70, 180).

851   Rapidly developing hirsutism or virilization is a clinical indicator for an androgen-producing
852   tumor, and should be addressed by measuring testosterone and androgen precursors,
853   whereas recent onset of gynecomastia should trigger measurement of estradiol (181-184)
854   (see also R.3.10).

855

856

857   **R.3.2 We recommend that all patients with adrenal incidentalomas undergo a 1-mg**
858   **overnight dexamethasone suppression test to exclude cortisol excess (XXOO).**

859   **R.3.3 We suggest interpretation of the results of the 1-mg overnight dexamethasone**
860   **test as a continuous rather than categorical (yes/no) variable (XOOO). However,**
861   **we recommend using serum cortisol levels post dexamethasone ≤ 50 nmol/l (≤**
862   **1.8 µg/dl) as a diagnostic criterion for the exclusion of autonomous cortisol**
863   **secretion (XXOO).**

864   **R.3.4 We suggest that post dexamethasone serum cortisol levels between 51 and 138**
865   **nmol/l (1.9 - 5.0 µg/dl) should be considered as evidence of 'possible**
866   **autonomous cortisol secretion' and cortisol levels post dexamethasone > 138**
867   **nmol/l (> 5.0 µg/dl) should be taken as evidence of 'autonomous cortisol**
868   **secretion'. Additional biochemical tests to confirm cortisol secretory autonomy**
869   **and assess the degree of cortisol secretion might be required (Figure 2).**
870   **However, for the clinical management the presence of potentially cortisol-**
871   **related comorbidities (Table 2) and age of the patient are of major importance**
872   **(Figure 2).**

873

874   Reasoning

875   A variety of diagnostic algorithms have been used to exclude cortisol excess or to define so-
876   called 'subclinical hypercortisolism', but in the literature there are no head to head
877   comparisons between tests to assess their diagnostic performance (see section 4.2.1).
878   However, the panel recommends the use of the 1-mg overnight dexamethasone test based
879   on pathophysiological reasoning, simplicity, and the fact that the test was incorporated in the
880   diagnostic algorithms of most studies. It is important to consider drugs or conditions that
881   interfere with this test (see Appendix Table A9). In published guidelines and reviews variable
882   thresholds have been recommended (5, 8-10). Several studies have used post
883   dexamethasone serum cortisol values between 50 and 138 nmol/l (1.8 - 5.0 µg/dl) and/or
884   required further tests to secure the diagnosis of 'autonomous cortisol secretion'. However, in
885   none of these additional tests was the performance convincing enough to ultimately establish
886   diagnostic criteria.

887   The panel appreciated that this ongoing debate reflects a biological continuum with no clear
888   separation between non-functioning adenomas and functioning adenomas associated with
889   some degree of cortisol excess. However, a value of ≤ 50 nmol/l (≤ 1.8 µg/dl) may be
890   regarded as normal, excluding cortisol excess. This cut-off is supported by studies
891   demonstrating that patients with post dexamethasone cortisol values > 50 nmol/l (> 1.8 µg/dl)
892   have an increased morbidity or mortality (142, 143). Since the probability of clinically relevant
893   cortisol excess increases the higher the post-dexamethasone serum cortisol value and that
894   the principle of dexamethasone testing is based on pharmacological suppression of ACTH
895   secretion, we propose the following terminology be used on biochemical grounds. For
896   patients without overt Cushing's syndrome and a serum cortisol post dexamethasone
897   between 51 and 138 nmol/l we propose the term 'possible autonomous cortisol secretion'
898   and for higher values the term "autonomous cortisol secretion". However, for the clinical
899   management, the presence of potentially related comorbidities (Table 2) and age of the
900   patient are of major relevance (Figure 2).

901   The majority of panel members (but not all) preferred additional biochemical tests to confirm
902   cortisol secretory autonomy and assess the degree of cortisol secretion. However, we
903   acknowledge that use of several tests may be associated with an increased likelihood of at
904   least one being a false positive result Nevertheless, we suggest measurement of basal
905   morning plasma ACTH and to repeat the dexamethasone test after 3-12 months in all
906   patients with 'possible autonomous cortisol secretion' and comorbidities. In patients with
907   'autonomous cortisol secretion' we suggest the additional measurement of 24-h urinary free
908   cortisol and/or late-night salivary cortisol (although few studies suggest a poor performance
909   of this parameter in patients with incidentaloma). Following the concept that cortisol secretion
910   in patients with 'autonomous cortisol secretion' is independent of ACTH, a higher dose of
911   dexamethasone (e.g. 3mg, 2x2mg, or 8mg) might also be reasonable as additional test.

912   However, the published literature is too limited and controversial to make a clear statement

913   on these tests.

914

915

916   **R.3.5 We recommend against considering 'autonomous cortisol secretion' as a**

917   **condition with a high risk for the development of overt Cushing's syndrome**

918   **(XXOO).**

919

920   Reasoning

921   Studies reporting on follow-up of patients with adrenal incidentalomas have uniformly found a

922   very low percentage (< 1%) of patients with 'autonomous cortisol secretion' progressing to

923   overt Cushing's syndrome (1-3, 20-25).

924

925

926   **R.3.6 We recommend screening patients with 'possible autonomous cortisol**

927   **secretion' or 'autonomous cortisol secretion' for hypertension and type 2**

928   **diabetes mellitus (XOOO) and suggest offering appropriate treatment of these**

929   **conditions.**

930

931   Reasoning

932   Studies from different research groups have consistently demonstrated an association

933   between cortisol excess and hypertension and hyperglycemia (23, 31-39). The association

934   with dyslipidemia is less proven, although biologically plausible. There is also evidence that

935   patients with cortisol excess are at increased risk of cardiovascular events and excess

936   mortality (142, 143).

937   Therefore, the panel recommended screening for these conditions, which are well known

938   independent cardiovascular risk factors and which may be driven by cortisol excess, and to

939   treat them according to current guidelines.

940

941

942   **R.3.7 We suggest screening patients with 'autonomous cortisol secretion' for**

943   **asymptomatic vertebral fractures (XOOO) and to consider appropriate**

944   **treatment of these conditions (XOOO).**

945

946   Reasoning

947   Several studies, although mainly from a single research group, have demonstrated an

948   association between autonomous cortisol secretion and an increased risk of vertebral

949   fractures (41-46). Although most of the fractures are asymptomatic, the panel suggests

950   screening patients with 'autonomous cortisol secretion' for vertebral fractures at least once at

951   the time of diagnosis. This may be done by re-evaluating the available images (if a CT was

952   performed) or by plain X-ray. The panel did not reach consensus on recommending

953   assessment of bone mineral density by dual-energy x-ray absorptiometry (DXA). If

954   osteoporosis is present, active treatment should be considered. If there is no other likely

955   explanation for the osteoporosis, removal of the adrenal adenoma might be considered (see

956   R3.8).

957

958

959   **R.3.8   We suggest an individualized approach in patients with 'autonomous cortisol**

960   **secretion' due to a benign adrenal adenoma and comorbidities potentially**

961   **related to cortisol excess for adrenal surgery (XOOO). Age, degree of cortisol**

962   **excess, general health, comorbidities and patient's preference should be taken**

963   **into account. In all patients considered for surgery, ACTH-independency of**

964   **cortisol excess should be confirmed.**

965

966   <u>Reasoning</u>

967   Due to the limitations of current literature, especially the lack of high-quality randomized

968   trials, the panel could not reach consensus on the exact indication for surgery for

969   'autonomous cortisol secretion'. The panel appreciated that there is some evidence of

970   improvement of hypertension, hyperglycemia and dyslipidemia with surgery but this is based

971   on low quality data. However, no data are available on clinically relevant endpoints (e.g.

972   mortality or major cardiovascular events). Thus, the decision to undertake surgery should be

973   individualized taking into account factors that are linked to surgical outcome, such as

974   patient's age, duration and evolution of comorbidities and their degree of control, and

975   presence and extent of end organ damage. Because it is not possible to be sure that surgical

976   intervention will normalize or improve the clinical phenotype of an individual patient, there

977   was no complete agreement within the panel with regard to the optimal management of

978   these patients. Approaches varied between two ends of the spectrum. Overall, the group

979   agreed that there is an indication of surgery in a patient with post dexamethasone cortisol >

980   138 nmol/l (> 5 µg/dl) and the presence of at least two comorbidities potentially related to

981   cortisol excess (e.g. type 2 diabetes, hypertension, obesity, osteoporosis), of which at least

982   one is poorly controlled by medical measures. Conversely, there is no reason for surgery,

983   when serum cortisol post dexamethasone is < 138 nmol/l (< 5 µg/dl) and no comorbidities

984   are present. However, some panel members favor a more proactive approach, for example

985   considering surgical intervention, especially in younger patients with 'possible autonomous

986   cortisol' secretion and less comorbidities potentially related to cortisol excess, even if
987   controlled by medical therapy.

988   However, there was consensus that when surgery is considered due to 'autonomous cortisol
989   secretion', ACTH-independency has to be proven by a suppressed or low basal morning
990   plasma ACTH. If not, other reasons of cortisol excess have to be considered.

991
992

993   **R.3.9   We recommend excluding pheochromocytoma by measurement of plasma free**
994   **metanephrines or urinary fractionated metanephrines.**

995

996   Reasoning:

997   For details we refer to the most recent guidelines of other societies (e.g. (70)). Of note, there
998   are clinically silent pheochromocytomas (185-187) that might lead to hemodynamic instability
999   during surgical excision (188). Thus, metanephrines should be measured in normotensive
1000 patients and the diagnosis of pheochromocytoma should be considered in patients with
1001 borderline values of metanephrines and indeterminate imaging features on CT.

1002 In adrenal lesions with imaging criteria of an adenoma the likelihood of a pheochromocytoma
1003 is extremely low (189, 190). Thus, it seems to be reasonable to avoid measuring
1004 metanephrines in patients with clear evidence of an adrenal adenoma, but definitive data in
1005 this area are lacking.

1006
1007

1008 **R.3.10 In patients with concomitant hypertension or unexplained hypokalemia, we**
1009 **recommend the use of the aldosterone / renin ratio to exclude primary**
1010 **aldosteronism.**

1011

1012 Reasoning:

1013 For details we refer to the most recent guidelines of other societies (e.g. (180)).

1014
1015

1016 **R.3.11 We suggest measurement of sex hormones and steroid precursors in patients**
1017 **with imaging or clinical features suggestive of adrenocortical carcinoma.**

1018

1019 Reasoning:

1020 Adrenocortical carcinoma is associated in more than half of cases with elevated sex
1021 hormones and steroid precursors (183, 184, 191, 192). The panel does not recommend
1022 measurement of these hormones in patients with adrenal incidentalomas on a routine basis,

ESE and ENSAT guideline on adrenal incidentaloma

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but in cases with indeterminate adrenal mass by imaging or clinical signs for androgen excess, significantly increased sex hormones or precursors might clearly point towards adrenocortical carcinoma. Thus, measurement of serum DHEA-S, androstenedione, 17-hydroxyprogesterone as well as testosterone in women and estradiol in men and postmenopausal women can prove the adrenocortical nature of the adrenal mass. However, the panel acknowledges that the published evidence for this suggestion is very low (192, 193). A very promising new tool to discriminate benign from malignant adrenocortical tumors appears the analysis of a comprehensive urinary steroid profile measured by GC-MS or LC-MS (193, 194).

5.4. Surgical treatment

R.4.1 We recommend adrenalectomy as the standard of care for unilateral adrenal tumors with clinically significant hormone excess.

Reasoning:

As covered by several other guidelines, there is consensus that adrenal tumors leading to clinically significant hormone excess (e.g. primary aldosteronism, Cushing syndrome or pheochromocytoma) should be surgically removed (30, 70, 180). The guideline group is convinced that for these tumors the same rules regarding the surgical approach should apply as for endocrine inactive tumors (see below). There are no substantiated reasons why the surgical approach for hormone-producing tumors should differ from that in endocrine inactive tumors (R4.3-5).

R.4.2 We recommend against performing surgery in patients with an asymptomatic, non-functioning unilateral adrenal mass and obvious benign features on imaging studies (XOOO).

Reasoning:

Most adrenal incidentalomas are non-functioning benign lesions (e.g. adenomas, myelolipomas) that do not cause harm. Therefore, there is broad consensus that the majority of these adrenal masses do not require surgery. The guideline group defined two criteria that need to be fulfilled to allow characterization of a unilateral adrenal lesion as not harmful: (i)

1059   imaging criteria indicating a benign lesion (see section 5.2, Table 4) (ii) no relevant endocrine

1060   activity (see section 5.3).

1061   There was considerable discussion by the group if a certain cutoff of size should be a factor

1062   to consider surgery. There was consensus that a tumor with a diameter of ≤ 4 cm with benign

1063   imaging features does not require surgery, accepting that this size cutoff is arbitrary.

1064   However, due to the paucity of follow-up data on the natural history of large apparently

1065   benign adrenal incidentalomas the panel was divided on the approach to the management of

1066   patients with larger lesions. One approach is to rely on imaging criteria only to determine if a

1067   lesion is benign irrespective of size. Alternatively, because of clinician or patient uncertainty

1068   about the increasing incidence of malignancy the larger is size, surgery may be considered in

1069   larger lesions (e.g. > 4 cm) even if imaging characteristics suggest a benign nature of the

1070   mass, allowing for an individualized approach. We voted against a certain cutoff which

1071   indicates that surgery has to be performed. However, we acknowledge that with a larger

1072   tumor size patients and clinicians might feel increasingly uncomfortable, but again an

1073   individualized approach was deemed most appropriate.

1074

1075

1076   **R.4.3 We suggest performing laparoscopic adrenalectomy in patients with unilateral**

1077   **adrenal masses with radiological findings suspicious of malignancy and a**

1078   **diameter ≤ 6 cm, but without evidence of local invasion (XOOO).**

1079   **R.4.4 We recommend performing open adrenalectomy for unilateral adrenal masses**

1080   **with radiological findings suspicious of malignancy and signs of local invasion**

1081   **(XOOO).**

1082   **R.4.5 We suggest an individualized approach in patients that do not fall in one of the**

1083   **above mentioned categories (XOOO).**

1084

1085   _Reasoning:_

       The main threat of a unilateral adrenal mass, which is suspected to be malignant, is

1086   adrenocortical carcinoma. For adrenocortical carcinoma without metastases, surgery is the

1087   most important single therapeutic measure. Thus, the high expertise of the surgeon is of

1088   major importance. Although we cannot provide a specific number of required operations per

1089   year, we have no doubts that surgical volume correlates with better outcome. As summarized

1090   above (section 4.1.3) there are nine cohort studies on surgery for localized adrenocortical

1091   carcinoma comparing laparoscopic versus open adrenalectomy, each with more than ten

1092   patients per group (149-157), but these studies are, however, hampered by methodological

1093   flaws, and importantly none was randomized. Nevertheless, based on these data and the

1094   clinical experience of the guideline group members, it was judged that laparoscopic

1095

1096   adrenalectomy may be justified for tumors with radiological signs of malignancy but only
1097   where there was no evidence of local invasion. For this approach the group arbitrarily chose
1098   a cut-off size for the adrenal tumor of ≤ 6 cm, because for this size it is believed that
1099   laparoscopic adrenalectomy is feasible without rupture of tumor capsule (a major risk factor
1100   for recurrence), and is beneficial for the patient (e.g. less pain, shorter hospital stay).
1101   However, with increasing tumor size risk of tumor capsule rupture may increase. If during
1102   surgery there is a risk of tumor capsule rupture, conversion to open procedure should be
1103   performed. We acknowledge that the cutoff of 6 cm for laparoscopic vs. open adrenalectomy
1104   is not based on good evidence from clinical studies, and we recognize that laparoscopic
1105   adrenalectomy for tumors < 6 cm is common practice in most centers. However, this cutoff
1106   by no means indicates that every tumor smaller than 6 cm has to undergo laparoscopic
1107   adrenalectomy and every tumor larger than 6 cm open adrenalectomy. We are convinced
1108   that in many cases an individualized decision process is required to find the best surgical
1109   approach for a given patient. This is also true for all patients that do not fall in one of the
1110   categories described in R.4.2 - 4.4.
1111
1112   There are no sufficiently powered studies published on the approach to patients with stage III
1113   adrenocortical carcinoma (local invasion, lymph nodes metastases, or tumor thrombus in the
1114   renal vein or vena cava). However, the guideline group unanimously voted for open
1115   adrenalectomy as standard procedure for this stage of disease.
1116
1117
1118   **R.4.6 We recommend perioperative glucocorticoid treatment at major surgical stress**
1119   **doses, as recommended by guidelines, in all patients undergoing surgery for**
1120   **an adrenal tumor where there is evidence of 'possible autonomous cortisol**
1121   **secretion' or 'autonomous cortisol secretion'.**
1122
1123   _Reasoning:_
1124   Autonomous cortisol secretion may lead to adrenal insufficiency after removal of the adrenal
1125   source of cortisol (even in patients with incompletely suppressed ACTH (195)). Therefore,
1126   the group unanimously recommends intra- and post-operative glucocorticoid replacement,
1127   preferably by hydrocortisone in patients with an adrenal tumor and evidence for '(possible)
1128   autonomous cortisol secretion' (post dexamethasone cortisol > 50 nmol/l (> 1.8 µg/dl)) even
1129   if there are no clinical sign of cortisol excess. This should follow the suggestions for major
1130   stress dose replacement as per a recent international guideline (196). Postoperatively, the
1131   glucocorticoid dose should be tapered individually by a physician experienced in this clinical
1132   scenario.

1133
5.5 Follow-up of patients not undergoing adrenal surgery after initial assessment

1136

R.5.1   **We suggest against further imaging during follow-up in patients with an adrenal mass < 4cm with clear benign features on imaging studies (XOOO).**

1139

Reasoning

Amongst more than 2300 patients included in published follow-up studies (3, 9) there is no report of occurrence of adrenal malignancy in adrenal incidentalomas displaying typical features of adrenocortical adenomas at initial imaging studies. Therefore, the panel does not support repeating imaging investigations if the initial work-up is unequivocally consistent with a benign lesion. However, many patients with adrenal incidentalomas > 4 cm in diameter have undergone adrenalectomy in the past and the literature on follow-up of non-operated large adrenal incidentalomas is scarce. Thus, and similar to the discussion on the surgical treatment (R.4.2), some panel members argued that one follow-up imaging (non-contrast CT or MRI) after 6-12 months might be considered in lesions > 4 cm.

1150

1151

R.5.2   **In patients with an indeterminate adrenal mass (by imaging), opting not to undergo adrenalectomy following initial assessment, we suggest a repeat non-contrast CT or MRI after 6-12 months to exclude significant growth (XOOO). We suggest surgical resection if the lesion enlarges by more than 20% (in addition to at least a 5 mm increase in maximum diameter) during this period. If there is growth of the lesion below this threshold, additional imaging again after 6-12 months might be performed.**

1159

Reasoning

Contrary to benign adrenal tumors that may exhibit a slow growth tendency with time, malignant adrenal lesions (mostly adrenocortical carcinoma and metastases) are almost invariably characterized by a rapid growth within months (184, 191, 192). Consequently, the panel recommends performing follow-up imaging studies in adrenal incidentaloma, in which the benign nature cannot be established with certainty at initial evaluation, in order to recognize early a rapidly growing mass. Many clinicians would opt for surgical removal if the mass is of larger size and cannot be determined as benign with certainty.

Lack of growth of an adrenal mass over a period of 6-12 months makes a malignant mass highly unlikely while surgery is recommended if significant rapid growth is observed. There is

1170   no generally accepted definition of significant growth of an adrenal tumor. However, the

1171   panel proposes an adaptation of the RECIST 1.1 criteria (197). These criteria, which are

1172   used in most oncological trials, define progress by an increase of 20% of the largest

1173   diameter. Although RECIST 1.1 criteria are not validated for the differentiation between

1174   benign and malignant adrenal tumors, the 20% cut-off together with an absolute increase of

1175   at least 5 mm in diameter may serve as warning for significant growth and reconsideration

1176   then given for surgical excision.

1177   The panel is aware that there are exceptional cases of malignant adrenal tumor without

1178   significant growth for several years (198, 199). However, this can be considered a very rare

1179   exception and does not justify following all patients with an adrenal mass with repeated

1180   imaging over years. However, in case there is some measurable growth (10-20%) that does

1181   not qualify for the above-mentioned criteria, additional follow-up imaging should be

1182   considered.

1183

1184

1185   **R.5.3   We suggest against repeated hormonal work-up in patients with a normal**

1186   **hormonal work-up at initial evaluation unless new clinical signs of endocrine**

1187   **activity appear or there is worsening of comorbidities (e.g. hypertension and**

1188   **type 2 diabetes) (XOOO).**

1189

1190   Reasoning

1191   The pooled risk of developing clinically relevant hormonal excess (e.g. primary

1192   aldosteronism, Cushing's syndrome and pheochromocytoma) is below 0.3% in patients with

1193   initial hormonal work-up consistent with a non-functioning lesion (3, 9).

1194   Development of 'autonomous cortisol secretion' without signs of overt Cushing's syndrome is

1195   the most frequently reported event during the follow-up and may occur in 8 to 14% of

1196   patients with non-functioning adrenal incidentalomas. Owing to the risk of false positive

1197   results (200) the panel does not recommend systematic follow-up hormonal investigations in

1198   patients with non-functioning adrenal incidentalomas at initial evaluation (ie cortisol ≤ 50

1199   nmol/l (≤ 1.8 µg/dl) post 1-mg overnight dexamethasone test).

1200

1201

1202   **R.5.4   In patients with 'autonomous cortisol secretion' without signs of overt**

1203   **Cushing's syndrome (see Figure 2), we suggest annual clinical re-assessment**

1204   **for cortisol excess and comorbidities potentially related to cortisol excess**

1205   **(XOOO). Based on the outcome of this evaluation the potential benefit of**

1206   **surgery should be considered.**

1207

1208   <u>Reasoning</u>

1209   As discussed above, it is extremely rare that patients will develop overt Cushing's syndrome

1210   during follow-up. However, as elaborated in section 5.3, the panel considers 'autonomous

1211   cortisol secretion' as a condition associated with several comorbidities (Table 2). Therefore,

1212   the panel recommends annual clinical follow-up in patients with 'autonomous cortisol

1213   secretion' and in patients with both 'possible autonomous cortisol secretion' and potentially

1214   associated comorbidities, in whom an initial decision against surgery was made (Figure 2).

1215   Clinical follow-up should include evaluation of potentially cortisol excess-related

1216   comorbidities. The presence or worsening of these conditions should prompt hormonal re-

1217   evaluation at any time during follow-up. Appropriate symptomatic treatment and

1218   reconsideration of surgical removal of the adrenal mass is recommended, in line with the

1219   observed changes in the clinical and hormonal status of the patient.

1220   In the absence of evidence, we suggest that follow-up by an endocrinologist beyond 2-4

1221   years is not needed in patients with no relevant change during this time.

1222

1223

1224

1225   ## 5.6. Special circumstances

1226

1227   ### 5.6.1 Patients with bilateral adrenal incidentalomas

1228   **R.6.1.1 We recommend that for patients with bilateral adrenal masses each adrenal**

1229   **lesion is assessed at the time of initial detection according to the same**

1230   **imaging protocol as for unilateral adrenal masses to establish if either or both**

1231   **lesions are benign or malignant.**

1232

1233   <u>Reasoning:</u>

1234   In most cases bilateral adrenal masses represent benign bilateral adrenocortical disease:

1235   either bilateral adenomas, macronodular hyperplasia, or distinct bilateral nodules with normal

1236   or atrophic cortex intervening. The possibility of metastases (especially in patients with

1237   known malignancy), adrenal lymphoma or bilateral pheochromocytomas should also be

1238   considered. Moreover, bilateral adrenal masses may represent co-occurrence of different

1239   entities, such as adenoma, pheochromocytoma, cyst, myelolipoma, adrenocortical

1240   carcinoma, etc. Therefore the best approach is to separately characterize each lesion

1241   following the recommendations in R.2.2 and R.2.3.

1242

1243

1244   **R.6.1.2 We recommend that all patients with bilateral adrenal incidentalomas should**
1245   **undergo clinical and hormonal assessment identical to that in patients with**
1246   **unilateral adrenal incidentaloma. The same applies for the assessment of**
1247   **comorbidities that might be related to 'autonomous cortisol secretion' (Table**
1248   **2). In addition, 17-hydroxyprogesterone should be measured to exclude**
1249   **congenital adrenal hyperplasia, and testing for adrenal insufficiency should**
1250   **be considered if suspected on clinical grounds or if imaging suggests**
1251   **bilateral infiltrative disease or hemorrhages.**

1252

1253   Reasoning:

1254   Hormonal excess in patients with bilateral adrenal masses may originate either from one of
1255   the lesions or bilaterally. Cushing's syndrome, primary aldosteronism, and
1256   pheochromocytoma(s) may all be encountered. For the clinical assessment of these entities
1257   we refer to guidelines of other societies (69, 70, 180). As for unilateral lesions, subtle
1258   autonomous cortisol secretion is the most common secretory abnormality and, therefore,
1259   requires a full assessment of related comorbidities. Occasionally, bilateral adrenal
1260   enlargement is due to congenital adrenal hyperplasia and therefore the additional
1261   measurement of 17-hydroxyprogesterone should be performed (201). However, the
1262   measurement of 17-hydroxyprogesterone to identify the most common cause of congenital
1263   adrenal hyperplasia, 21-hydroxylase deficiency, as the cause of bilateral adrenal hyperplasia
1264   should be interpreted with caution. In some cases increased levels of 17-
1265   hydroxyprogesterone may represent increased secretion of steroid precursors from the
1266   lesion(s) (202) especially in malignant tumors or in bilateral macronodular adrenal
1267   hyperplasia. In these cases low/suppressed ACTH levels may argue against congenital
1268   adrenal hyperplasia. Bilateral adrenal enlargement due to metastatic disease rarely causes
1269   adrenal insufficiency (for details see R.6.3.6).

1270

1271

1272   **R.6.1.3 We suggest that for patients with bilateral incidentaloma the same**
1273   **recommendations regarding the indication of surgery and follow-up are used**
1274   **as for patients with unilateral adrenal incidentalomas.**

1275

1276   Reasoning:

1277   'Autonomous cortisol secretion' is more frequently encountered in patients with bilateral
1278   adrenal incidentalomas, compared to those with unilateral lesions, but there is no published
1279   evidence that they should be managed differently. However, in the few cases, in whom

1280 bilateral surgery is potentially indicated (e.g. bilateral pheochromocytomas), one can

1281 consider adrenal-sparing surgery (203).

1282

1283

1284 **R.6.1.4 We suggest that in patients with bilateral adrenal masses bilateral**

1285   **adrenalectomy is not performed for 'autonomous cortisol secretion' without**

1286   **clinical signs of overt Cushing's syndrome. In selected patients a unilateral**

1287   **adrenalectomy of the dominant lesion might be considered using an**

1288   **individualized approach considering age, degree of cortisol excess, general**

1289   **condition, comorbidities and patient preference.**

1290

1291 Reasoning:

1292 Surgery is a complex decision for patients with bilateral adrenal incidentalomas. This is

1293 because, in the absence of clinical signs of overt Cushing's syndrome, the clinical situation

1294 may not be severe enough to prompt surgical management. Moreover, bilateral

1295 adrenalectomy is associated with higher morbidity compared to unilateral surgery, the patient

1296 is dependent lifelong on adrenal replacement therapy and at risk for life-threatening adrenal

1297 crisis. In addition, glucocorticoid replacement is frequently sub-optimal and cannot mimic the

1298 diurnal profile of endogenous cortisol, and may result in persisting exposure to subtle cortisol

1299 excess. In bilateral macronodular adrenal hyperplasia there is limited evidence of beneficial

1300 effects of unilateral adrenalectomy (204, 205). In most published studies excision of the

1301 largest lesion was performed, based on observations that the size of the adrenal lesion

1302 correlates with the degree of cortisol excess (204). Adrenal venous sampling may aid in the

1303 lateralization of cortisol excess but the data are very weak (206). Due to the limited available

1304 evidence, an individualized approach, considering age, degree of cortisol excess, general

1305 condition, comorbidity status and patient's preference is suggested. However, when bilateral

1306 surgery is potentially indicated, cortical sparing adrenalectomy might be considered (207).

1307 In cases of bilateral macronodular hyperplasia, especially in younger patients or those with

1308 relevant family history, family screening with 1 mg dexamethasone test can be considered.

1309 A number of patients will have evidence of the presence of aberrant receptors, but routine

1310 assessment by the complex testing (27, 208-214) that is needed to establish the presence of

1311 these receptors is hard to justify based on the fact that in the majority of patients long-term

1312 management will not be based on knowledge of receptor activity, and therefore we suggest

1313 that these tests should be confined to clinical studies.

1314

1315

1316 **5.6.2 Adrenal incidentalomas in young or elderly patients**

1317 **R.6.2.1 We recommend urgent assessment of an adrenal mass in children,**
1318 **adolescents, pregnant women and adults < 40 years of age because of a**
1319 **higher likelihood of malignancy.**
1320 **R.6.2.2 We suggest the use of MRI rather than CT in children, adolescents, pregnant**
1321 **women and adults < 40 years of age if dedicated adrenal imaging is required.**
1322 **R.6.2.3 We recommend that the management of patients with poor general health and**
1323 **a high degree of frailty be kept in proportion to potential clinical gain.**

1324

1325 <u>Reasoning</u>

1326 The incidence of adrenal incidentaloma shows clear variation with age, with the majority of
1327 patients presenting in the 5th to 7th decade of life. Overall incidence of adrenal incidentaloma
1328 in a population undergoing routine imaging not related to suspected adrenal disease is
1329 reported as 1-4 % (15, 72, 74, 215). While 10 % or more of individuals older than 70 years
1330 harbor an adrenal mass detectable upon imaging or autopsy, adrenal nodules in individuals <
1331 40 years are much less prevalent and are a rarity in children and young adults.
1332 Consequently, work-up in young patients including pregnant women has to be pursued with
1333 urgency as the risk of malignancy in this cohort is much higher. Conversely, a smaller
1334 adrenal incidentaloma in an elderly patient can be assumed to have a very low pre-test
1335 probability of malignancy. Thus work-up in elderly patients only needs to be expedited if
1336 there are clear signs of suspicion of malignancy and the extent of imaging work-up should be
1337 kept in proportion to the clinical performance status of the individual and the expected clinical
1338 gain of further work-up in an affected patient.
1339 As radiation safety is even more important in the young patient, we suggest MRI as the
1340 preferred imaging technique. However, adapted low-dose unenhanced CT protocols can
1341 limited radiation exposure and can be considered as an alternative (especially if the
1342 availability of MRI is limited).

1343

1344

1345 *5.6.3* **Patients with a newly diagnosed adrenal mass and a history of extra-**
1346 **adrenal malignancy (Figure 4)**

1347

1348 General remarks:

1349 In principle, for adrenal masses in patients with known extra-adrenal malignancy the same
1350 recommendations apply as described above. However, in this situation it is particularly
1351 important to consider the different pre-test probabilities and the life expectancy of the patient.
1352 In patients with underlying extra-adrenal malignancy and an indeterminate adrenal mass,
1353 studies revealed a high rate of malignancy, up to 70%. Although age specific subgroup

1354   analysis is not available, it can be assumed that older patients have a higher likelihood of co-
1355   existent benign adenomas. Conversely younger patients with an underlying malignancy are
1356   more likely to have a metastasis.

1357

1358

1359   **R.6.3.1 We recommend measurement of plasma or urinary metanephrines to exclude**
1360   **pheochromocytoma in patients with extra-adrenal malignancy with an**
1361   **indeterminate mass, even if the adrenal mass is likely to be a metastasis. We**
1362   **suggest additional hormonal work-up based on an individualized approach.**

1363

1364   Reasoning
1365   Pheochromocytomas are almost impossible to distinguish from metastasis by conventional
1366   imaging (including FDG-PET/CT). Furthermore, pheochromocytomas can lead to life-
1367   threatening complications, especially in the context of medical interventions (surgery,
1368   biopsies etc.) (70, 216, 217). Additional hormonal work-up should depend on the stage of the
1369   extra-adrenal malignancy and life expectancy. Evidence of adrenal hormone excess
1370   indicating that the mass is a primary adrenal lesion can influence management of the extra-
1371   adrenal malignancy.

1372

1373   **R.6.3.2 We suggest that in patients with a history of extra-adrenal malignancy FDG-**
1374   **PET/CT, performed as part of investigations for the underlying malignancy,**
1375   **can replace other adrenal imaging techniques.**

1376

1377   *Reasoning:*
1378 ^{18}FDG-PETCT may add additional value in the assessment of an indeterminate adrenal
1379   mass, however, the evidence base is insufficient to make strong recommendations (75). Both
1380   qualitative and quantitative interpretations of ^{18}FDG-PETCT imaging have been studied, but
1381   these vary considerably. An adrenal lesion / liver ratio of 1.53-1.8 were investigated in
1382   patients with history of extra-adrenal malignancy (2 studies (92, 93), 117 lesions) and found
1383   to have sensitivity of 82% (95%CI 41-97%) and specificity of 96% (95%CI 76-99%) to detect
1384   malignant disease.

1385

1386

1387   **R.6.3.3 We recommend that in patients with a history of extra-adrenal malignancy**
1388   **adrenal lesions characterized as benign by non-contrast CT require no further**
1389   **specific adrenal imaging follow-up.**

1390

1391   *Reasoning*

1392   See details R2.2-4. However, we acknowledge that the currently available data suggest a

1393   false negative rate of 7% in this population.

1394

1395

1396   **R.6.3.4 For indeterminate lesions in patients with a history of extra-adrenal**

1397   **malignancy, we recommend imaging follow-up assessing the potential growth**

1398   **of the lesion at the same interval as imaging for the primary malignancy.**

1399   **Alternatively, FDG-PET/CT, surgical resection or a biopsy (see also R.6.3.5)**

1400   **can be considered.**

1401

1402   *Reasoning:*

1403   In many patients with advanced extra-adrenal malignancy (e.g. with multiple metastases) the

1404   knowledge of the origin of the adrenal mass will not alter the clinical management of the

1405   patient. If, however, clinical management would be altered by the demonstration that the

1406   adrenal lesion is a metastasis, then every effort should be made to allow this discrimination.

1407   If the adrenal mass is potentially the only metastasis and if resection of this metastasis

1408   seems to be reasonable from an oncological point of view, then surgery should be

1409   considered. Regarding biopsy, we recommend applying the criteria provided in R.6.3.5.

1410

1411

1412   **R.6.3.5 We suggest performing a biopsy of an adrenal mass only if all of the following**

1413   **criteria are fulfilled: (i) the lesion is hormonally inactive (in particular, a**

1414   **pheochromocytoma has been excluded), (ii) the lesion has not been**

1415   **conclusively characterized as benign by imaging, and (iii) management would**

1416   **be altered by knowledge of the histology.**

1417

1418   *Reasoning:*

1419   Adrenal biopsy may present with a significant non-diagnostic rate and a potential for

1420   complications (76). Biopsy is only recommended for masses not characterized as benign on

1421   cross-sectional imaging and where a biopsy result would affect clinical treatment decisions.

1422   In patients with no other obvious metastatic lesions and when surgical removal of the lesion

1423   is an option, FDG-PET/CT should be considered in order to exclude metastases outside the

1424   adrenal that were not visualized by CT or MRI. Adrenal biopsy presents with lower diagnostic

1425   performance for ACC and therefore is not recommended in this setting (76).

1426

1427

1428   **R.6.3.6 We recommend assessment of residual adrenal function in patients with large**
1429   **bilateral metastases.**

1430

1431   <u>Reasoning</u>

1432   In rare cases, bilateral adrenal metastases can lead to adrenal insufficiency. Thus, in all

1433   patients with potentially bilateral metastases, adrenal insufficiency should be considered and

1434   clinically evaluated. If adrenal insufficiency seems to be possible, we recommend first to

1435   measure a morning serum cortisol and plasma ACTH. In case of adrenal insufficiency,

1436   plasma ACTH is clearly elevated in parallel to low cortisol. In uncertain cases, a synacthen

1437   test should be performed (196).

1438   If only one adrenal metastasis is present, adrenal insufficiency is extremely unlikely and we

1439   recommend no specific assessment of adrenal reserve.

1440

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1441   **6. Future directions and recommended research**

1442

1443   The NIH conference on the management of the clinically unapparent adrenal mass in 2002

1444   formulated several research questions for future studies (5). Although some of these issues

1445   have been addressed, only few questions have been conclusively answered. From the

1446   current perspective we see need for clinical trials in all four areas particularly addressed in

1447   the guideline (see section 3.5). Given that most recommendations in this guideline are based

1448   on weak evidence, there is clearly room for studies aiming to improve the evidence base of

1449   management of adrenal incidentalomas.

1450   Among many important research questions, we selected five as particularly important. All of

1451   them can only be answered in a collaborative interdisciplinary manner.

1452   1) Large, cohort study in patients with an adrenal mass > 2 cm to investigate the most

1453   suitable imaging methods to determine if an adrenal mass is benign or not. It will be crucial to

1454   establish a definitive diagnosis either by histopathology or by long-term follow-up (> 2 years).

1455   2) Large, long-term study to define whether or not 'autonomous cortisol secretion' is

1456   associated with increased mortality and other hard clinical endpoints (e.g. myocardial

1457   infarction or stroke). Such a study will also provide evidence for a suitable biochemical

1458   definition of 'autonomous cortisol secretion'.

1459   3) Randomized trial on the potential benefit of surgery in patients with "autonomous cortisol

1460   secretion". To make such a trial feasible it is probably wise to define a surrogate endpoint

1461   (e.g. hypertension or type 2 diabetes) that can be well controlled (including standardized

1462   treatment regimens) throughout the study. A similar trial could evaluate the value of drugs

1463   targeting the cortisol excess.

1464   4) Prospective study (laparoscopic vs. open surgery) in patients with potentially malignant

1465   adrenal mass (<10 cm) without pre-operative evidence of local invasion and metastases to

1466   learn which surgical approach is the most suitable one for this patient cohort.

1467   5) We propose a long-term study with annual biochemical work-up of patients with adrenal

1468   incidentalomas to clarify if such a long-term hormonal assessment is justified. This study

1469   should also help to define the true incidence of relevant diseases like adrenocortical

1470   carcinoma and pheochromocytoma among incidentalomas.

1471

1472   Several other research questions deserve future research. Of particular importance seems to

1473   us the establishment of biomarkers to determine non-invasively the origin of the adrenal

1474   mass (adrenal cortex, medulla, extra-adrenal) and whether or not the mass is malignant.

1475   Currently, urine steroid metabolomics for non-invasive and radiation free detection of a

1476   malignant 'steroid fingerprint' in adrenocortical carcinoma patients (193) and the combination

1477   of functional imaging methods (e.g. metomidate-based imaging and FDG-PET/CT) are the

1478   most promising tools that should be further investigated. Similarly, for patients with

1479   'autonomous cortisol secretion' new methods to stratify on an individual basis to intervention

1480   (or observation) are needed.

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Declaration of interest

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Table 1: Adrenal incidentalomas - frequency of the different underlying tumor
types (adapted according (9))

Tumor entity	Median (%)	Range (%)
Series including all patients with an adrenal mass*		
Adenoma	80	33-96
Non-functioning	75	71-84
Autonomously cortisol-secreting	12	1.0-29
Aldosterone-secreting	2.5	1.6-3.3
Pheochromocytoma	7.0	1.5-14
Adrenocortical carcinoma	8.0	1.2-11
Metastasis	5.0	0-18
Surgical series**		
Adenoma	55	49-69
Non-functioning	69	52-75
Cortisol-secreting	10	1.0-15
Aldosterone-secreting	6.0	2.0-7.0
Pheochromocytoma	10	11-23
Adrenocortical carcinoma	11	1.2-12
Myelolipoma	8.0	7.0-15
Cyst	5.0	4.0-22
Ganglioneuroma	4.0	0-8.0
Metastasis	7.0	0-21

1499

1500 * Data from references: (2, 6, 14)
1501 ** Data from references: (2, 3, 6, 7, 10, 14, 17, 18)
1502 Due to the nature of these studies a selection bias is very probable (the populations studied not
1503 reflecting a random sample of all patients with an adrenal incidentalomas) and most likely leads to an
1504 overestimation of the frequency of some tumor entities.
1505
1506
1507

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1508 **Table 2: Comorbidities possibly associated with adrenal incidentalomas with**
1509 **'autonomous cortisol secretion'**

Comorbidities	Reference
Hypertension	(23, 31-36)
Glucose intolerance / type 2 diabetes mellitus	(23, 31-39)
Obesity	(23, 31-33)
Dyslipidemia	(23, 31, 32, 36, 40)
Osteoporosis	(35, 38, 41-46)

1510

1511

1512 **Table 3: Overview of the key clinical questions and predefined outcome parameters**

Clinical Question	Predefined selection criteria and key outcome parameters[1]	Metrics of the literature search
Question 1a) What is the most accurate diagnostic imaging procedure to determine whether an adrenal mass is benign in patients with unilateral or bilateral adrenal mass(es) on imaging with or without history of other malignant lesions?	• Original studies on imaging in patients with incidentally discovered adrenal mass(es), including those undergoing staging for known extra-adrenal malignancy. • Diagnostic intervention: CT (non-contrast, contrast-enhanced, washout), MRI, FDG PET(CT) • Reference standard: at least 50% of population had imaging-guided follow-up of any duration (for benign adrenal tumors), or histology after surgery or biopsy (for benign or malignant adrenal tumors) • Reporting 2x2 contingency table data or at least two indices of diagnostic accuracy (sensitivity, specificity, negative or positive predictive value) and disease prevalence.	• 5496 abstracts[2] • 525 potentially relevant articles • 37 studies included in systematic review, 18 in meta-analysis • Major reasons for exclusion of articles were lack of test accuracy data, inadequate or unclear reference standard and ineligible populations. Other reasons for exclusion data collection pre-1990, sample size <10, < 50% histology in malignant group, >30% pheochromocytomas in malignant group, >10% pheochromocytomas in benign group, no differentiation of children versus adults
Question 1b) What is the diagnostic accuracy of adrenal biopsy?	• Original studies on patients with adrenal masses undergoing an adrenal biopsy procedure • Outcomes: non-diagnostic rate, diagnostic accuracy data, complication rate • For studies included in the diagnostic accuracy analysis: 1) Reference standard: at least 50% of population either histology from adrenalectomy or autopsy, imaging follow up 3-12 months or clinical follow up of 2 years and 2) Reporting 2x2 contingency table data or at least two indices of diagnostic accuracy (sensitivity, specificity, negative or positive predictive value) and disease prevalence.	• 175 abstracts[3] • 80 potentially relevant articles • 32 studies included in systematic review of at least one outcome. • Diagnostic accuracy data included from 8 studies • Major reasons for exclusion overall were: no outcomes of interest, fewer than 10 patients, abstract only, patient overlap. • Major exclusions from diagnostic accuracy analysis were: suboptimal reference standard and >30% non-adenomas

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Question 2a)

Are certain biochemical profiles (see 4.2.1) associated with an increased cardiovascular, metabolic and fracture risk in patients with adrenal mass(es), in whom endocrine work-up for glucocorticoid excess was performed?

Question 2b)

Should surgery or a conservative/medical approach be recommended in patients with adrenal mass(es) and with defined biochemistry and cardiovascular, metabolic and fracture risk potentially indicative of mild glucocorticoid excess?

- Original studies on patients with adrenal mass(es), in which endocrine work-up for glucocorticoid excess was performed. Studies independently of their respective definition of 'autonomous cortisol secretion' were eligible.
- Comparison between patients based on biochemical profiles (including post-dexamethasone serum cortisol level) (question 2a)
- Comparison between surgery and conservative approach (question 2b)
- Reporting at least one of the crucial outcome: major cardiovascular events or mortality, vertebral fractures, metabolic profile, cardiovascular profile

Question 2a:
- 201 abstracts
- 23 potentially relevant articles
- 12 studies included

Question 2b
- 152 abstracts
- 18 potentially relevant articles
- 4 studies included
- Excluded articles were not relevant for outcome parameters (n=17), no relevant design (n=4), overlapping populations (n=2), position paper (n=1), poorly defined patient cohort (n=1)

Question 3)

Should laparoscopic (=minimally-invasive) or open surgery be used for patients with non-metastastic adrenal masses suspected to be malignant?

- Original studies on adults with suspected non-metastatic adrenocortical carcinoma
- Comparison between laparoscopic versus open surgery
- Reporting at least one of the crucial outcomes: perioperative morbidity and mortality; completeness of resection; recurrence-free and overall survival; pain or patient satisfaction
- Publications with less than 10 patients per study arm were excluded.

- 377 abstracts
- 13 potentially relevant articles
- 3 excluded due to samples size < 10 patients per arm, 1 excluded as review
- 9 studies included

Question 4)

What is the optimal follow-up in patients with an apparently benign adrenal incidentaloma in order to detect malignant transformation and/or development of overt hormone excess?

- Original studies on patients with an adrenal mass without hormone excess and no clear evidence of malignant adrenal tumor at time of primary diagnosis
- Reporting at least one of the following outcomes: malignancy in the adrenal (any kind); development of clinically relevant overt hormone excess (Cushing's syndrome,

- 133 abstracts
- 19 potentially relevant articles
- 9 excluded due to overlapping population (n=3), not relevant to question (n=3), not available in full-text (n=2), unclear methods (n=1)
- Included:

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pheochromocytoma, primary hyperaldosteronism)	• 1 systematic review of 14 studies • 10 additional cohort studies

1513

1514   [1] *For each question we searched separately for systematic reviews between 2000 and February 2014 in NHS Economic Evaluation Database (NHSEED),*
1515   *Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effects. This revealed no relevant systematic review. Then, we*
1516   *searched for original articles in Medline published between 2000 and July 2014 (Question 3), October 2014 (Question 4), November 2014 (Question 2), and*
1517   *August 2015 (Question 1).*
1518   [2] *Summary of separately published meta-analysis (75).*
1519   [3] *Summary of separately published meta-analysis (76)*
1520

1521
1522

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1523   **Table 4: Imaging criteria suggesting a benign adrenal mass[1]**

Non-contrast CT	≤ 10 HU
MRI - chemical shift[2]	Loss of signal intensity on out-phase imaging consistent with lipid-rich adenoma
CT with delayed contrast media washout[2, 3]	Absolute washout > 60% Relative washout > 40%
18F-FDG-PET[2]	Absence of FDG uptake or uptake less than the liver[4]

1524
1525   [1] these criteria apply only for masses with homogenous appearance, or masses that have other clear
1526   characteristics consistent with benign disease, e.g. myelolipoma. A homogeneous mass is defined as a lesion
1527   with uniform density or signal intensity throughout. The measurements/region of interest (ROI) should include at
1528   least 75% of a lesion without contamination by tissues outside the adrenal lesion. Inhomogeneous lesions
1529   should not be subjected to MRI or washout CT for further characterization.
1530   [2] Evidence is weak for MRI, CT with contrast washout, and FDG-PET and no comparative studies on "second line
1531   imaging" are available. Thus, in this guideline we clearly recommend non-contrast CT as imaging procedure of
1532   choice.
1533   [3] There is no clear evidence about the best time interval. We recommend 10 or 15 min.
1534   [4] Certain metastasis (e.g. from kidney cancer or low grade lymphoma) may be FDG negative
1535
1536

Figure Legends

Figure 1: Flow-chart on the management of patients with adrenal incidentalomas (overview)

[1] For patients with history of extra-adrenal malignancy, see special section 5.6.4
[2] only in patients with concomitant hypertension and /or hypokalemia
[3] only in patients with clinical or imaging features suggestive of adrenocortical carcinoma

Figure 2: Assessment and management of 'autonomous cortisol secretion' in patients with adrenal incidentalomas

[1] The majority of but not all panel members preferred additional biochemical tests to better judge the degree of cortisol secretion. In patients with comorbidities, we suggest to measure plasma ACTH and to repeat the dexamethasone test in 3-12 months.
[2] We suggest additional biochemical tests to better judge the degree of cortisol secretion: plasma ACTH, 24-h urinary free cortisol, (and/or late-night salivary cortisol), and repetition of the dexamethasone test in 3-12 months.
[3] See Table 2 for potentially cortisol-related comorbidities.
[4] Choice for surgery should always be individualized.
[5] Need of follow-up by an endocrinologist for 2-4 years

Figure 3: Flow-chart on the management of adrenal masses considered for surgery

[1] 'autonomous cortisol secretion' is not automatically judged as clinically relevant (see section 5.3 for details).
[2] in tumors with benign radiological features and a tumor size > 4 cm, surgery might also be individually considered (see text)

Figure 4: Evaluation of patients with adrenal mass and known extra-adrenal malignancy

[1] Always take life expectancy in consideration.
[2] If there is hormone excess, treat individualized.
[3] FDG-PET/CT should be considered to exclude other metastatic deposits in patients with no other obvious metastatic lesions for whom surgical removal of the lesion is an option.

53

1573   **Supplementary Data**

1574   **Tables Appendices 1-8: Description of analyzed studies and Results of the**

1575   **GRADE analyses**

1576

1577   **Table Appendix 9: Selected drugs that may interfere with results of the**

1578   **dexamethasone test**

1579

1580   **Table Appendix 10: Reviewers comments and responses by the authors**

1581

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Figure 1

Figure 2

Figure 2

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Figure 4
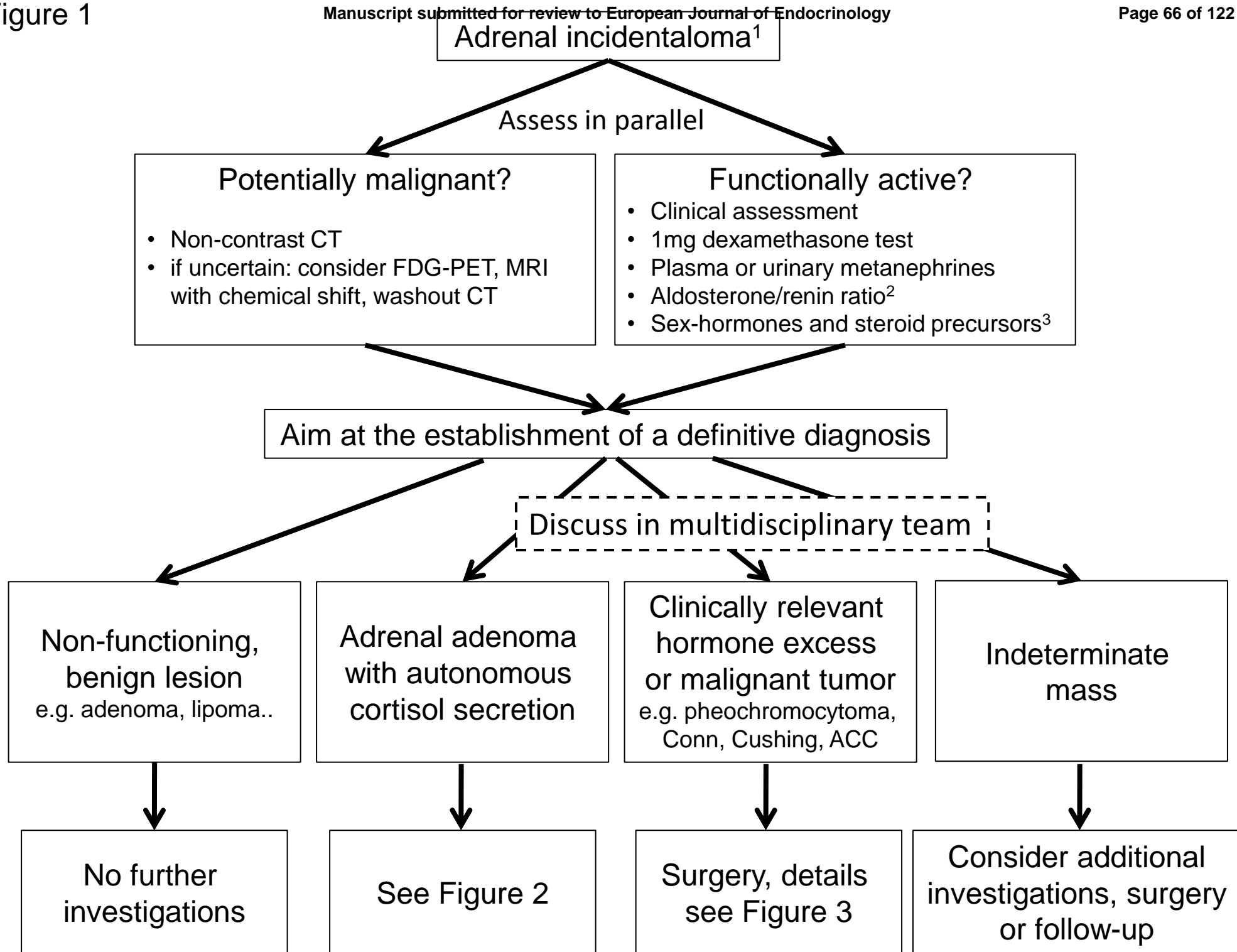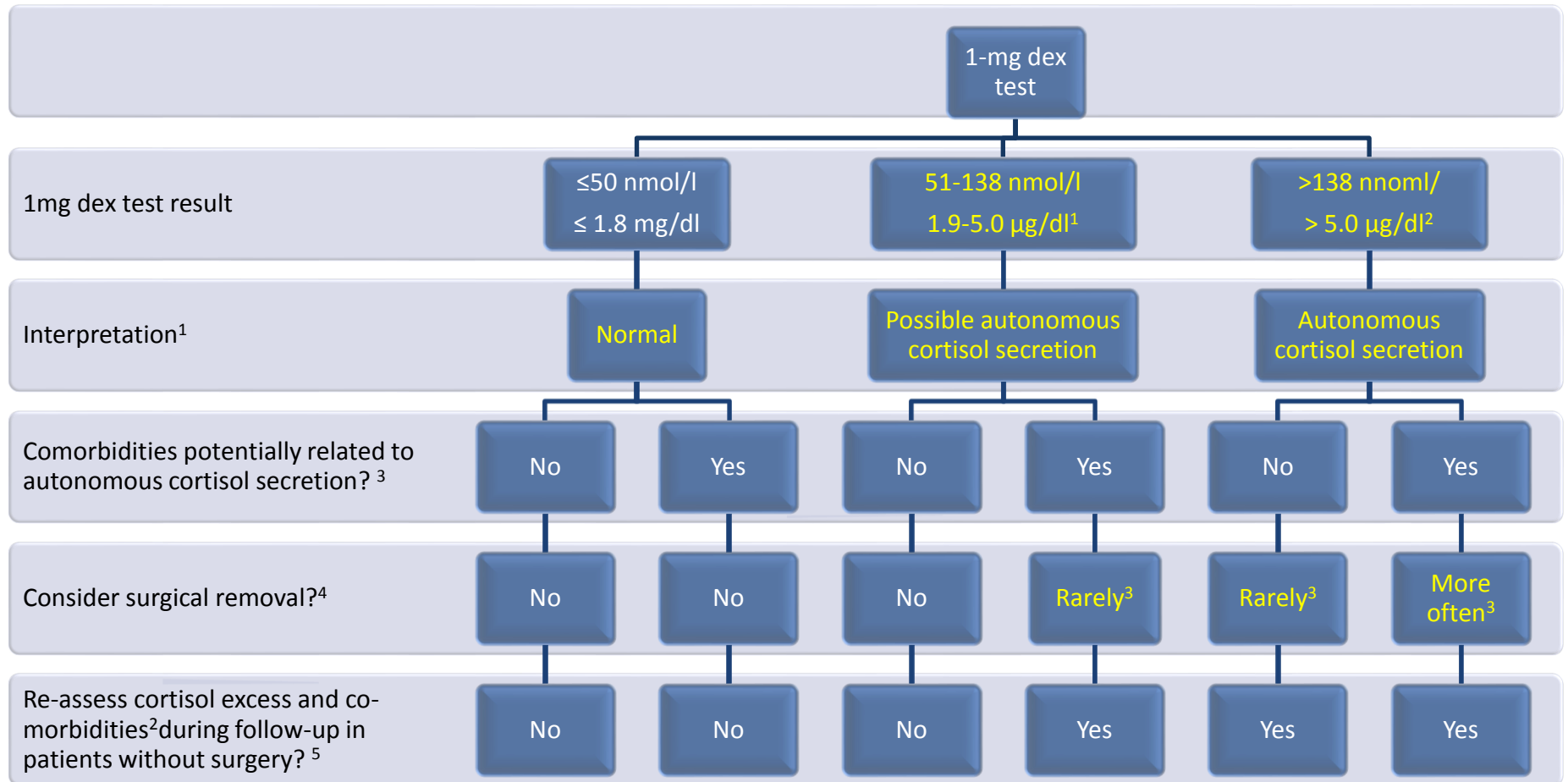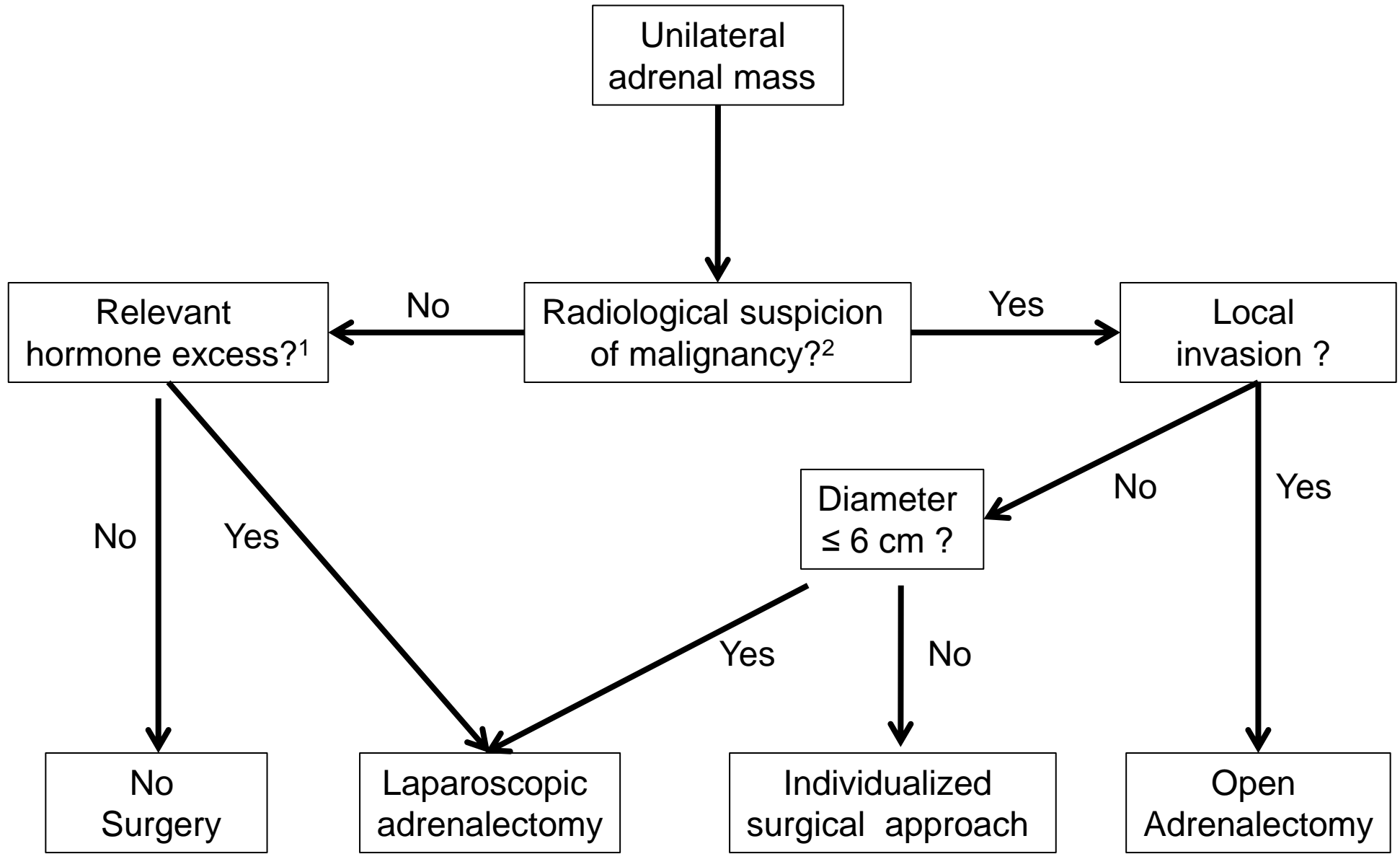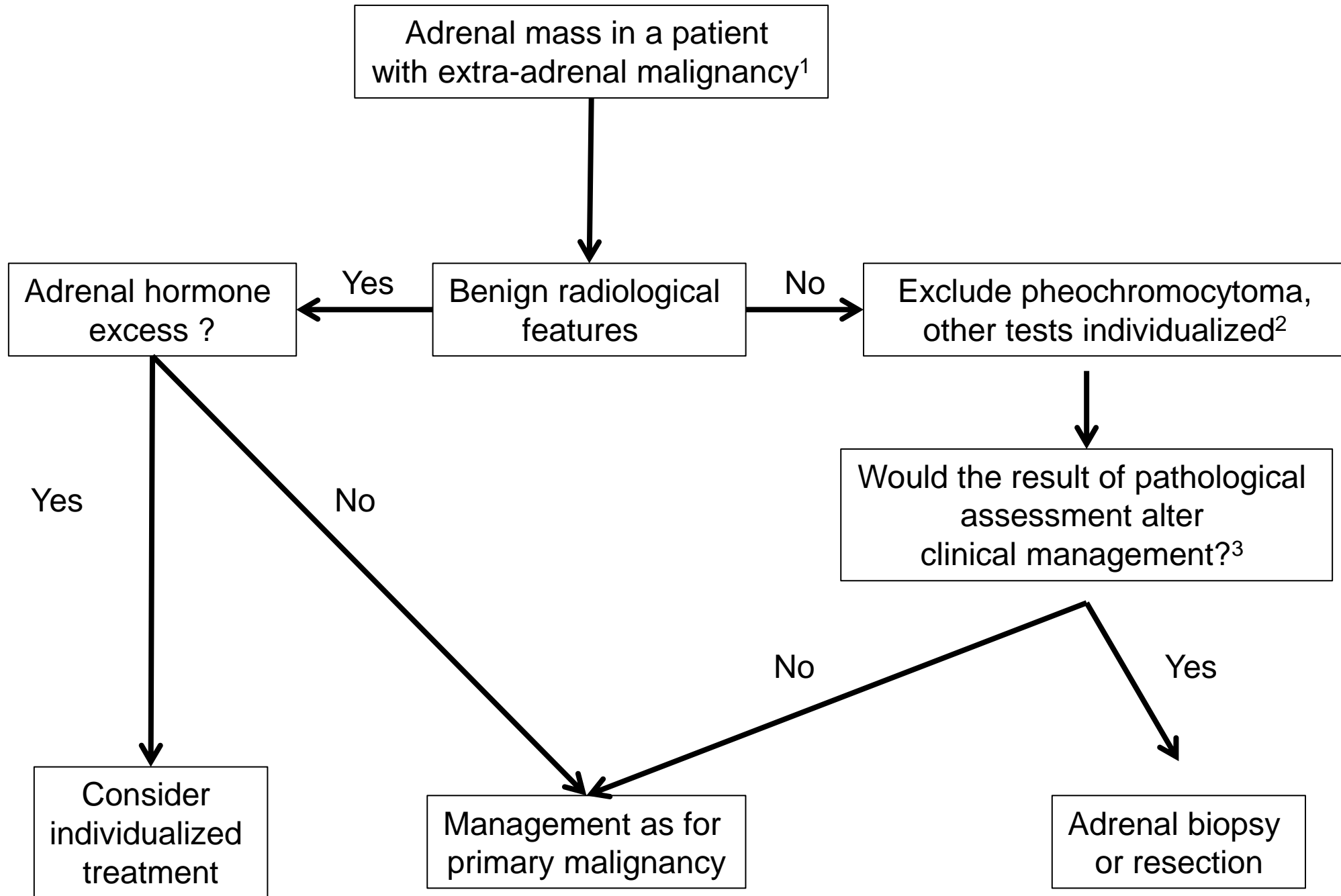
Supplementary data to Fassnacht et al., Management of adrenal incidentalomas - a European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors

Appendix I

Question 2A: cardiovascular, metabolic and fracture risk compared between subgroups adrenal incidentaloma patients (by biochemical profile)

Description of included studies

Reference [1], study design	Study population and study period	Subgroups according to biochemical profile [2] (sample sizes)	Follow-up	Outcomes	Number of events per subgroup (%)	Effect (95%CI)	Remarks
Cross-sectional studies							
Androulakis et al; Journal Clinical Endocrinology and Metabolism 2014 Cross-sectional study	Adrenal incidentaloma patients between 2008 and 2011; exclusion: DMII, hypertension, hyperlipidemia, history of malignancy, medication affecting any of the outcomes, and pheochromocytoma.	1. Normal N = 34 (LDDST < 1.09 µg/dL) 2. Abnormal N = 26 (LDDST > 1.09 µg/dL)	Not applicable	Impaired glucose tolerance (OGTT)	1. 6/34 (18 %) 2. 5/26 (19 %)	Risk ratio (unadjusted) 1.09 (0.37 to 3.18)	Assessment of prevalent disease Cut-off based on mean + 2SD values of control group
Chiodini et al; Journal Clinical Endocrinology and Metabolism 2004 Cross sectional study	Female adrenal incidentaloma patients from 1997 to 2002; exclusion: treatments affecting bone or diseases interfering with bone metabolism.	Premenopausal 1. Normal N =14 2. Abnormal (profile 2) N = 7 Postmenopausal 1. Normal = 35 2. Abnormal (profile 2) N = 14	Not applicable	Prevalence of fractures	Premenopausal 1. 1/14 (7%) 2. 3/7 (43%) Postmenopausal 1. 15/35 (43%) 2. 11/14 (79%)	OR (age adjusted) 5.8 (1.6 to 20.6)	Assessment of prevalent disease
Chiodini et al; Journal Clinical Endocrinology and Metabolism 2009 Cross sectional study	Patients with adrenal incidentaloma; enrolled between 1997 and 2008; exclusion criteria: (i) hypogonadism and diseases known to affect bone metabolism; (ii) administration of drugs influencing bone and cortisol metabolism; (iii) signs or symptoms specific of cortisol excess	1. Normal N = 202 2. Abnormal (profile 2) N = 85	Not applicable	Prevalence of vertebral fractures	1. N = 44/202 (21.8%) 2. N = 60/85 (70.6)	OR (adjusted for age, BMI, testosterone, BMD) 7.3 (3.9 to 13.4)	Assessment of prevalent disease

Reference [1], study design	Study population and study period	Subgroups according to biochemical profile [2] (sample sizes)	Follow-up	Outcomes	Number of events per subgroup (%)	Effect (95%CI)	Remarks
Di Dalmazi et al; European Journal Endocrinology 2012, Cross-sectional study	Adrenal incidentaloma patients between 2000 to 2010. Excluded: suspicion of malignancy, myelolipoma, ganglioneuroma, pheochromocytoma; history of steroid use, Cushing's syndrome; hyperaldosteronism; oral contraceptives and hormone replacement therapy.	1. Normal N = 203 2. Abnormal (profile 1 1.8 - 5 µg/dl) N = 126 3. Abnormal (profile 3 = >5 µg/dl) N = 19	Not applicable	Fractures	1. 5/203 (2.5%) 2. 4/126 (3.2%) 3. 3/19 (15.8%)	OR[3] 1.1 (0.3 to 4.4) 6.5 (1.3 to 33)	Assessment of prevalent disease
				Hypertension	1. 146/203 (73%) 2. 101/126 (80%) 3. 18/19 (94%)	Not reported	
				T2DM	1. 31/203 (15%) 2. 31/126 (25%) 3. 8/19 (42%)	OR[3] 1.7 (0.94 to 3.1) 3.4 (1.2 to 10.0)	
				Stroke	1. 1/203 (0.5%) 2. 5/126 (4%) 3. 1/19 (5%)	Not reported	
				Coronary heart disease	1. 6/203 (3%) 2. 15/126 (12%) 3. 5/19 (26%)	OR[3] 4.1 (1.5 to 11.4) 6.1 (1.4 to 26.5)	
Eller-Vainchier et al; JBMR 2012 Cross-sectional study	Patients with adrenal incidentaloma; exclusion criteria: (i) hypogonadism and diseases known to affect bone metabolism; (ii) administration of drugs influencing bone and cortisol metabolism; (iii) signs or symptoms specific of cortisol excess Study period 2010-2011	1. Normal N = 68 3. Abnormal (profile 2) N = 34	Follow-up in 40 patients; however relation fracture risk and cortisol not assessed	Vertebral fractures	1. 31/68 (46%) 2. 28/34 (82%)	Relative risk (unadjusted) 1.81 (1.34 to 2.45)	Assessment of prevalent disease No adjusted risk estimates provided
Olsen et al; Endocrine 2012 Cross-sectional study	Adrenal incidentaloma patients diagnosed 2005–2007	1. Normal N = 105 2. Abnormal (profile 1 1.8 - 5 µg/dl) N = 30 3. Abnormal (profile 3 = >5 µg/dl) N = 10	Not applicable	Hypertension	1. 68/105 (65%) 2. 24/30 (80%) 3. 9/10 (90%)	Relative risk (unadjusted) 1.24 (0.98-1.55) 1.39 (1.08-1.78)	Assessment of prevalent disease No adjusted risk estimates provided
Vassilatou et al; European Journal of Endocrinology 2014 Cross-sectional study	Adrenal incidentaloma patients between 2002 and 2012. Exclusion: overt Cushing's syndrome; corticosteroid use; malignancy; primary hyperaldosteronism, and pheochromocytoma	1. Normal N = 232 2. Abnormal (profile 1): N = 66	Not applicable	Hypertension	1. 141/232 (61%) 2. 47/66 (71.%)	Risk ratio (unadjusted) 1.17 (0.97-1.41)	Assessment of prevalent disease No adjusted risk estimates provided
				T2DM	1. 48/232 (21%) 2. 18/66 (27%)	Risk ratio (unadjusted) 1.32 (0.82-2.10)	
Cohort studies							
Debono et al; Journal Clinical Endocrinology and	Adrenal incidentaloma patients between 2005 and 2013; Exclusion: pheochromocytoma,	1. Normal N = 95 (< 1.8 µg/dl) 2. Abnormal	Mean 4.2 years	Mortality risk and mortality rate	1. 1/95 (1%) 2. 12/92 (13%) 3. 5/19 (26%)	Hazard ratio[4] 12.0 (1.6-92.6) 22.0 (2.6-188.3)	Adjusted time-to-event analysis not possible due to limited number events

Reference [1], study design	Study population and study period	Subgroups according to biochemical profile [2] (sample sizes)	Follow-up	Outcomes	Number of events per subgroup (%)	Effect (95%CI)	Remarks
Metabolism 2014 Cohort study	primary hyperaldosteronism, suspicion of adrenal malignancy and glucocorticoid treatment	(profile 1 1.8 - 5 µg/dl) N = 92 3. Abnormal (profile 3 = >5 µg/dl) N = 19					
Di Dalmazi et al; Lancet Diabetes and Endocrinonolgy 2014 Cohort study	Adrenal incidentaloma patients from1995 to 2010. Exclusion: suspected malignant disease; pheochromocytoma, primary hyperaldosteronism, overt Cushing; corticosteroid use	1. Normal N = 129 2. Abnormal (profile 1 1.8 - 5 µg/dl) N = 59 3. Abnormal (profile 3 = >5 µg/dl) N = 10	Mean 7.5 yrs (26 months- 5 yrs)	Cardiovascular events		Univariable analysis: mean cortisol DST (10 nmol/ L increase) HR=1.04 (0.93 to 1.16)	No comparison between baseline defined subgroups
				Mortality		Multivariable: mean cortisol DST (10 nmol/ L increase) HR=1.10 (1.01 to 1.19) (adjusted for age and myocardial infarction)	
Giordano et al; European Journal of Endocrinology 2010 Cohort study	Adrenal incidentaloma patients; excluded: overt endocrine disease or CT/MRI malignant features	1. Normal N = 102 2. Abnormal (profile 1) N = 16	1-10 years, median 3 years	Incident T2DM	1. 3/102 (3%) 2. 0/16 (0%)	Risk ratio not estimable	
				Incident dyslipidemia	1. 3/102 (3%) 2. 0/16 (0%)	Risk ratio not estimable	
				Incident hypertension	1. 0/102 (0%) 2. 0/16 (0%)	Risk ratio not estimable	
Morelli et al; JBMR 2011 Cohort study	Adrenal incidentaloma patients; enrollment period 2005-2007. Exclusion: hypogonadism, diseases and drugs known to affect bone metabolism, corticosteroid use	1. Normal N=76 2. Abnormal (profile 2) N=27	24 months	Incident vertebral fractures	1. 10/76 (13%) 2. 13/27 (48%)	OR 12.3 (4.1 to 36.5)[3]	Outcome assessment blinded All patients received vitamin D
Morelli et al; Journal Clinical Endocrinology and Metabolism 2014 Cohort study	Adrenal incidentaloma patients included between 1996 and 2012. Exclusion: overt hypercortisolism, psychiatric diseases, alcoholism, corticosteroids, history of malignancy, pheochromocytoma, primary hyperaldosteronism	1. Normal N=167 2. Abnormal (profile 2) N = 39	Mean 83 months, range 60–186	Worsened glycaemic control	1. 39/167 (23%) 2. 12/39 (30%)	Odds ratio (unadjusted) 1.5 (0.7 to 3.1)	Patients with > 5 year follow-up enrolled Outcome assessment not blinded * Risks based on incident cases, with exclusion of prevalent disease at baseline.
				Worsened blood pressure control	1. 52/167 (31%) 2. 18/39 (46%)	Odds ratio (unadjusted) 1.9 (0.9-3.8)	
				* Incident cardiovascular events	1. 11/164 (7%) 2. 4/35 (11%)	Odds ratio [3] 2.7 (1.0-7.1)	

[1] See for full bibliographical details main paper

[2] Biochemical profiles to define autonomous cortisol secretion:

1. Cortisol after dexamethasone suppression >1.8 mcg/dl (50 nmol/l) (1-mg overnight dexamethasone suppression test, 2-mg or 8-mg overnight dexamethasone suppression test, 2-days low dose dexamethasone suppression test -LDDST) and ONE additional endocrine alteration among the following ones: increased 24-h urinary free cortisol (UFC), low ACTH, elevated midnight serum or salivary cortisol.

2. Cortisol after 1-mg dexamethasone suppression test >3.0 mcg/dl (83 nmol/l) and ONE additional endocrine alteration (same as above).

3. Cortisol after 1mg dexamethasone > 5 mcg/dl (138 nmol/l) as sole criterion.

[3] Adjusted for confounding variables

[4] Univariate findings; multivariable modeling limited by small number of events, "tentative models including covariates confirmed univariate findings"

Appendix II

Question 2A: cardiovascular, metabolic and fracture risk compared between subgroups AI patients (by biochemical profile)

GRADE table

		Quality assessment				Effect estimates per study (95% confidence intervals)[1]	Pooled effect estimate (95% confidence interval)	Quality
Studies [2]	Design	Risk of bias	Inconsistency	Indirectness	Imprecision			
Glucose regulation								
Androulakis 2014 Di Dalmazi 2012 Giordano 2010 Morelli 2014 Vassilatou 2014	3 cross-sectional studies, 2 cohort studies	Potential (residual) confounding	No serious inconsistency	Serious indirectness (different definitions of exposure and outcome)	Serious (imprecise estimates)	Androulakis (Impaired glucose tolerance) Risk ratio (unadjusted) 1.09 (0.37 - 3.18)	No pooled estimate due to heterogeneity in design and analysis and indirectness	⊕◯◯◯ **VERY LOW**
						Di Dalmazi (prevalent diabetes) Odds ratio (adjusted) 1.7 (0.94 - 3.1) 3.4 (1.2 - 10.0)		
						Gioradano (incident diabetes) 3/102 (3%) vs 0/16 (0%)		
						Morelli (worsened glycaemic control) Odds ratio (unadjusted) 1.5 (0.7 - 3.1)		
						Vassilatou (prevalent diabetes) Risk ratio (unadjusted) 1.32 (0.82-2.10)		

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[1] Comparing groups with autonomous cortisol secretion to non-secreting patients. See for details the description of included studies
[2] For full bibliographical details: see main paper

Blood pressure regulation								
Di Dalmazi 2012 Olsen 2012 Giordano 2010 Morelli 2014 Vassilatou 2014	3 cross-sectional studies, 2 cohort studies	Potential (residual) confounding	No serious inconsistency	Serious indirectness (different definitions of exposure and outcome)	Serious (imprecise estimates)	Di Dalmazi (prevalent hypertension) Risk ratio (unadjusted) 1.1 (1.0-1.3) 1.3 (1.1-1.5)[3]	No pooled estimate due to heterogeneity in design and analysis and indirectness	
						Giordano (Incident hypertension) 0/102 (0%) vs 0/16 (0%)		
						Morelli (worsened blood pressure control) Odds ratio (unadjusted) 1.9 (0.9-3.8)		
						Olsen (prevalent hypertension) 1.24 (0.98-1.55) 1.39 (1.08-1.78)		
						Vassilatou (prevalent hypertension) Risk ratio (unadjusted) 1.17 (0.97-1.41)		
Fractures								
Chiodini 2004 Chiodini 2009 Di Dalmazi 2012 Ellen-Vainchier 2012 Morelli 2011	4 cross-sectional studies, 1 cohort studies	Potential (residual) confounding	No serious inconsistency	Serious indirectness (different definitions of exposure and outcome)	Serious (imprecise estimates)	Chiodini (prevalent fractures) Odds ratio (adjusted) 7.3 (3.9 - 13.4)	No pooled estimate due to heterogeneity in design and analysis and indirectness	⊕OOO VERY LOW
						Chiodini (prevalent fractures) Odds ratio (age adjusted) 5.8 (1.6 - 20.6)		
						Di Dalmazi (prevalent fractures) Odds ratio (adjusted) 1.1 (0.3 - 4.4) 6.5 (1.3 - 33)		
						Ellen-Vainchier (prevalent fractures) Relative risk (unadjusted) 1.81 (1.34 - 2.45)		
						Morelli		

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[3] Risk ratio is constrained

						(prevalent fractures) Odds ratio (adjusted) 12.3 (4.1 - 36.5)		
Cardiovascular events								
Di Dalmazi 2012 Morelli 2014	1 cross-sectional study, 1 cohort study	Potential (residual) confounding	No serious inconsistency	Serious indirectness (different definitions of exposure and outcome)	Serious (imprecise estimates)	Di Dalmazi (Prevalentt cardiovascular disease) Odds ratio (adjusted) 4.1 (1.5 - 11.4) 6.1 (1.4 - 26.5) Morelli (incident cardiovascular disease) Odds ratio (adjusted) 2.7 (1.0-7.1)	No pooled estimate due to heterogeneity in design and analysis and indirectness	⊕○○○ VERY LOW
Mortality								
Debono 2014	Cohort study	Potential (residual) confounding	Not applicable	Not applicable	Serious (imprecise estimates)	Hazard ratio (adjusted) 12.0 (1.6-92.6) 22.0 (2.6-188.3)		⊕○○○ VERY LOW

Appendix III

Question 2B: surgical (group I) versus conservative approach (group II) in autonomous cortisol secretion

Description of included studies

Reference [1], study design	Study population and study period	Follow-up	Outcomes	Number of event per subgroup (%)	Effect estimate (95%CI)	Remarks
Chiodini et al; Journal Clinical Endocrinology and Metabolism 2010 Cohort study	41 patients with adrenal incidentalomas and subclinical Cushing Subclinical Cushing defined as dexamethasone suppression test > 3 mcg/dl. Study period 2002-2007 Operated patients (group I) N=25 Non-operated patients (group II) N=16	Range 18-48 months	Improvement blood pressure	I: 14/25 (56%) II: 0/16 (0%)	Odds ratio (adjusted): 26 (2 to 300)	Residual confounding is potentially a bias, imprecise estimates, non-collapsibility of the odds ratio might play a role
			Improvement fasting glucose	I: 12/25 (48%) II: 0/16 (0%)	Odds ratio (adjusted): 26 (2 to [2])	
			Improvement LDL cholesterol	I: 9/25 (36%) II: 3/16 (19%)	Odds ratio (adjusted): 3 (0.2 to 40)	
Iacobone et al, Surgery 2012 Cohort study	35 patients with adrenal incidentalomas and subclinical Cushing Subclinical Cushing defined as dexamethasone suppression test > 5 mcg/dl. Study period 2000-2009 Operated patients (group I) N=20 Non-operated patients (group II) N=15	Mean follow-up 55 months	Normalization hypertension	I: 2/15 (13%) II: 0/12 (0%)	Risk difference 13% (-3 to 30%)	Confounding is potentially a bias, imprecise estimates
			Normalization diabetes mellitus	I: 1/10 (10%) II: 0/6 (0%)	Risk difference 10% (-9 to 29%)	
			Normalization hypercholesterolemia	I: 2/10 (20%) II: 0/7 (0%)	Risk difference 20% (-5 to 45%)	
Toniato et al, Annals of Surgery 2009 Randomized controlled trial	Patients with adrenal incidentalomas and subclinical Cushing. Subclinical Cushing defined as dexamethasone suppression test > 2.5 mcg/dl. Inclusion between 1991 and 2005. Patients randomized between laparoscopic surgery (group I, n=23) and a conservative approach (group II, n=22)	Mean 7.7 years	Normalization dexamethasone test	I: 23/23 (100%)[3] II: not reported		Study randomized, no blinded outcome assessment, imprecise estimates
			Normalization hypertension	I: 5/18 (28%) II: 0/15 (0%)	Risk difference 28% (7 to 48%)	
			Normalization diabetes mellitus	I: 2/8 (25%) II: 0/6 (0%)	Risk difference 25% (-5 to 55%)	
			Normalization hypercholesterolemia	I: 3/8 (38%) II: 0/7 (0%)	Risk difference 38% (4 to 71%)	

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[1] See for full bibliographical details main paper
[2] Confidence interval from table 5 conflicting with effect estimate
[3] Within 12 months

Reference [1], study design	Study population and study period	Follow-up	Outcomes	Number of event per subgroup (%)	Effect estimate (95%CI)	Remarks
Tsuiki et al, Endocrine Journal 2008 Cohort study	20 patients with adrenal incidentalomas and subclinical Cushing Subclinical Cushing defined as dexamethasone suppression test > 3 mcg/dl. Study period: 1995-2006. Operated patients (group I) N=10 Non-operated patients (group II) N=12	Range 7-69 months	Improvement hypertension	I: 5/6 (83%) II: 0/4 (0%)	Risk difference 83% (55 to 100%)	Confounding is potentially a bias, imprecise estimates
			Improvement glucose metabolism	I: 2/9 (22%) II: 0/6 (0%)	Risk difference 18% (-4 to 41%)	
			Improvement hypercholesterolemia	I: 6/9 (66%) II: 0/6 (0%)	Risk difference 66% (36 to 97%)	

Appendix IV

Question 2B: surgical (group I) versus conservative approach (group II) in autonomous cortisol secretion

GRADE tables

Studies[1]			Quality assessment			Study effects per study for surgical versus conservative approach	Pooled effect estimate (95% confidence interval)	Quality
	Design	Risk of bias	Inconsistency	Indirectness	Imprecision			
Improvement glucose regulation								
Chiodini 2010 Iacobone 2012 Toniato 2009 Tsuiki 2008	3 cohort studies, 1 randomized trial	Potential (residual) confounding by indication (cohort studies), no blinding (randomized trial)	No serious inconsistency	Serious indirectness (different definitions of exposure and outcome)	Serious (imprecise estimates)	Chiodini Odds ratio (adjusted): 26 (2 to [2])	No pooled estimate due to heterogeneity in design and analysis and indirectness	⊕○○○ VERY LOW
						Iacobone Risk difference 10% (-9 to 29%)		
						Toniato Risk difference 25% (-5 to 55%)		
						Tsuiki Risk difference 18% (-4 to 41%)		
Improvement hypertension								
Chiodini 2010 Iacobone 2012 Toniato 2009 Tsuiki 2008	3 cohort studies, 1 randomized trial	Potential (residual) confounding by indication (cohort studies), no blinding (randomized trial)	No serious inconsistency	Serious indirectness (different definitions of exposure and outcome)	Serious (imprecise estimates)	Chiodini Odds ratio (adjusted): 26 (2 to 300)	No pooled estimate due to heterogeneity in design and analysis and indirectness	⊕○○○ VERY LOW
						Iacobone Risk difference 13% (-3 to 30%)		
						Toniato Risk difference 28% (7 to 48%)		
						Tsuiki Risk difference 83% (55 to 100%)		

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[1]For full bibliographical details: see main paper
[2] See table description of included studies

Improvement hypercholesterolaemia								
Chiodini 2010 Iacobone 2012 Toniato 2009 Tsuiki 2008	3 cohort studies, 1 randomized trial	Potential (residual) confounding by indication (cohort studies), no blinding (randomized trial)	No serious inconsistency	Serious indirectness (different definitions of exposure and outcome)	Serious (imprecise estimates)	Chiodini Odds ratio (adjusted): 3 (0.2 to 40) Iacobone Risk difference 20% (-5 to 45%) Toniato Risk difference 38% (4 to 71%) Tsuiki Risk difference 66% (36 to 97%)	No pooled estimate due to heterogeneity in design and analysis and indirectness	⊕OOO VERY LOW

Appendix V

Question 3: open (OA) vs laparoscopic adrenalectomy (LA) for adrenal incidentaloma

Description of included studies

Reference [1], Study design	Study population	Study Period and follow-up	Interventions (OA = open adrenalectomy, LA = lapraoscopic adrenalectomy)	Outcome Measures	Results	Remarks
Brix et al; European Urology 2010 Cohort study	ACC stage I-III and Tumor size<10 cm;	1996-2009 FU 6-131 mo	LA (n=35) OA (n=117)	Survival	Hazard ratio mortality LA vs OA 0.98 (95% CI 0.5-1.92)	Analysis adjusted for baseline imbalances. Residual confounding potentially a bias
				Disease-free survival	Hazard ratio recurrence LA vs OA 0.91 (95% CI 0.56-1.47)	
				% R0 resection	LA 24/35=69%; OA 64/117=55%; p= 0.45	
Cooper et al; Surg Endosc 2013. Cohort study	ACC patients; metastatic disease excluded; T1-T4 stage; size 1-30 cm)	1993-2012 Median follow-up 34 months	LA (n=46) Two OA groups: OA other hospital (n=210) (OA1) OA from index hospital (n=46) (OA2)	% margin positive resection	LA 28.3%, OA1 17.6% and OA2 8.7%; p=0.01	Analysis local recurrence: R2 resections excluded; Analysis adjusted for baseline imbalances. Residual confounding potentially a bias
				Recurrence free survival (months)	LA 11, OA1 10, OA2 20 (p=0.005)	
				Overall survival (months)	LA 54 (95% CI 28-79), OA1 46 (95%CI 39-53), OA2 110 (95% CI 20-199); p=0.07 After adjusting for T stage survival was better for OA (P<0.001)	
Donatini et al; Annals of Surgical Oncology 2014, Cohort study	Stage I or II ACC, Tumor size<10 cm; no radiological sign of local invasion; R0 resection	1982-2011 Follow-up 0-132 months	LA (n=13) OA (n=21)	Overall and disease free survival	Overall survival: LA 11/13 (85%); OA 17/21 (81%); p=0.6 Disease free survival (months): LA 46, OA 47; p=0.9	Selected on complete resection in stage I/II tumor Residual confounding potentially a bias Low power to detect difference in effect due to small sample size
				Recurrence	Recurrence: LA 4/13 (31%); OA: 5/21 (24%); p=0.7	

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[1] See for full bibliographical details main paper

Reference [1], Study design	Study population	Study Period and follow-up	Interventions (OA = open adrenalectomy, LA = lapraoscopic adrenalectomy)	Outcome Measures	Results	Remarks
Fossa et al; Acta Oncologica 2013, Cohort study	Stage I-III ACC, tumor size 4-24 cm;	1998-2011 Follow-up range 0-227 months	MIA (n=17) OA (n=15)	Intraoperative complications (Grade III)	Intraoperative complications: MIA 3/17, OA 12/15	Residual confounding potentially a bias Low power to detect difference in effect due to small sample size
				Postoperative complications (Grade III-IV)	Postoperative complications: MIA 2/17, OA 3/15	
				% R0 resection	MIA 12/17; OA 12/15; p=1.0	
				Overall and progression-free survival, median	Progression-free survival (months): MIA 15.2; OA 8.1; p=0.06 Overall survival (median, months): MIA 104, OA 37; p=0.22	
Lombardi et al; Surgery 2012 Cohort study	ACC patients who underwent radical surgery (R0 resection) for stage I/II; tumor size 3-21cm	2003-2010 Follow-up: mean 42 months, range 1-192	LA (n=30) OA (n=126)	Overall survival (median/5yrs)	Median overall survival (months): LA 108; OA 60; p=0.2; p=0.12	Selected on R0 resection in stage I/II tumor Residual confounding potentially a bias
				Disease free survival (median/5yrs)	Median disease free survival (months): LA 72; OA 48, p=0.12	
				Postoperative complications	LA 1/30 (3%); OA 7/126 (6%), p=0.9	
Miller et all; Surgery 2012 Cohort study	ACC stage I-III; size 3-28 cm	2005-2011 Follow-up median (months) 26.5, range 1-188	LA (n=46) OA (n=110)	% positive margins	LA 30%, OA 16%; p=0.4	Stratified analyses performed for stage II and III and for patients with R0 resection Residual confounding potentially a bias
				Time to recurrence	Time to local recurrence, Stage II (months): LA 12 vs OA 31; (p=0.002) Time to local recurrence, Stage III (months): LA 6 vs OA 13 (p=0.19)	
				Survival	Survival Stage II (months): LA 51 vs OA 103 (p=0.002) Survival Stage III (months): LA 28 vs OA 44; (p=0.77)	

Miller et al; World Jou Surgery 2010; Cohort study	ACC, stage IV excluded, range tumor size 4-27 cm	2003-2008 FU median 36.5 months	MIA (n=17) OA (n=71)	% positive margins	MIA 50%, OA 18%	Residual confounding potentially a bias Low power to detect difference in effect due to small sample size Analysis according to tumor size included (small subgroups)
				Recurrence	% recurrence MIA 63%, OA 65% (p=0.22) Mean time to local recurrence (months): MIA 9.6; OA 19.2 (P<0.005)	
Mir et al; Annals of Surgical Oncology 2012 Cohort study	44 ACC patients, 13% with metastasis at baseline	1993-2011; Median follow-up 26 months	LA (n=18) OA (n=26)	Intraoperative complications	Intraoperative complications OA 1/26 LA 2/18, p=0.3	Cohort including metastasized patients Analysis adjusted for baseline imbalances. Residual confounding potentially a bias Low power to detect difference in effect due to small sample size
				% positive margin	% positive margin: LA 7/18 (39%), OA 10/26 (38%); p=0.5	
				Overall and recurrence free survival	2 yr overall survival: LA 39%, OA 60%; p=0.7 2 yr recurrence free survival: LA 58%, OA 54 %; p=0.6 Hazard ratio mortality OA vs LA =0.5 (95% CI 0.2-1.2) Hazard ratio recurrence OA vs LA=0.4 (95% CI 0.2-1.2)	
Porpiglia et al; European Journal Urology 2010 Cohort study	Stage I or II ACC, complete resection, size tumor 2-17 cm	2002-2008 FU median 35 mo, range 11-72	LA (n=18) OA (n=25) Surgical approach based on surgeon preference and expertise	Recurrence free survival	Median disease free survival (months): LA 23; OA 18 (p=0.8); Hazard ratio for recurrence OA vs LA= 0.57 (95% CI 0.2-1.8)	Selected on complete resection in stage I/II tumor Residual confounding potentially a bias
				Overall survival	3yrs survival LA 100%; OA 84% (p=0.3)	

Abbreviations: ACC = adrenocortical carcinoma; 95%CI = 95% confidence intervals;

Appendix VI

Question 3: Open (OA) vs laparoscopic adrenalectomy (LA) for adrenal incidentaloma

GRADE tables

Studies [1]	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Numbers and events per study	Pooled effect estimate (95% confidence interval)	Quality
			Quality assessment					
Perioperative mortality								
Brix 2010	Cohort studies	Potential (residual) confounding by indication	Not applicable	No serious indirectness	Serious (imprecise estimates)	OA 0/117 vs LA 0/35		⊕◯◯◯ VERY LOW
Intraoperative complications [2]								
Fossa 2013 Mir 2013	Cohort studies	Potential (residual) confounding by indication	Serious	No serious indirectness	Serious (imprecise estimates)	12/15 vs 3/17 (Fossa) 1/26 vs 2/18 (Mir)	Relative risk OA vs LA 2.6 (1.1-6.1)	⊕◯◯◯ VERY LOW
Major postoperative complications [3]								
Fossa 2013 Lombardi 2012	Cohort studies	Potential (residual) confounding by indication	No serious inconsistency	No serious indirectness	Serious	3/15 vs 2/17 (Fossa) 7/126 vs 1/30 (Lombardi)	Relative risk OA vs LA 1.7 (0.5-6.2)	⊕◯◯◯ VERY LOW
Completeness of resection (Absence of positive margins)								
Brix 2010 Cooper 2013 Fossa 2013 Miller 2012 Mir 2013	Cohort studies	Potential (residual) confounding by indication	Serious[f]	No serious indirectness	Serious	OA 64/117 LA 24/35 (Brix) OA1 37/210 and OA2 4/46 LA 13/46 (Cooper) OA 12/15 LA 12/17 (Fossa) OA 19/117 LA 14/46 (Miller) OA 10/26 LA 7/18 (Mir)	Complete resection OA vs LA 0.8 (0.6-1.1)[4]	⊕◯◯◯ VERY LOW

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[1] For full bibliographical details: see main paper
[2] Undefined in Mir et al, Grade III in Fossa et al
[3] Undefined in Lombardi et al, Grade III-IV in Fossa et al
[4] Random effects model, two control groups in Cooper merged

Median survival (months)[5]								
Cooper 2013 Fossa 2013	Cohort studies	Potential (residual) confounding by indication	Serious	No serious indirectness	Serious (imprecise estimates)	Time (in moths) LA 54 OA1 46 OA2 110 (Cooper)[6] LA 104 OA 37 (Fossa)	No pooled estimate due to inconsistency	⊕◯◯◯ VERY LOW
Mortality risk (time to event analysis)								
Brix 2010 Mir 2013	Cohort studies	Potential (residual) confounding by indication	Serious[f]	No serious indirectness	Serious (imprecise estimates)	Mortality risk OA vs LA 1.0 (0.5-2.0) (Brix) 0.5 (0.2-1.2) (Mir)	Pooled estimate mortality risk OA vs LA: 0.8 (0.5-1.4)	⊕◯◯◯ VERY LOW
Recurrence or progression-free survival (months)								
Cooper 2013 Fossa 2013	Cohort studies	Potential (residual) confounding by indication	Serious inconsistency	No serious indirectness	Serious (imprecise estimates)	Time (in months) LA 11, OA1 10, OA2 20 (Cooper) LA 15.2; OA 8.1 (Fossa)	No pooled estimate due to inconsistency	⊕◯◯◯ VERY LOW
Recurrence risk (time to event analysis)								
Brix 2010 Mir 2013	Cohort studies	Potential (residual) confounding by indication	Serious inconsistency	No serious indirectness	Serious (imprecise estimates)	Recurrence risk LA vs OA HR 0.91 (0.56-1.47) Brix HR 2.5 (0.83-5) Mir	No pooled estimate due to inconsistency	⊕◯◯◯ VERY LOW

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[5] Only studies reporting median survival in all operated patients
[6] Two OA control groups included with inconsistent results

Appendix VII

Question 4: Natural course of apparently benign AI (risk of malignancy or development of hormone excess)

Description of included studies

Reference [1], study design	Study population and study period	Follow up	Outcome measures	Results	Remarks
Anagnostis et al, Exp Clin Endocrin Diabetes (2009) Cohort study	Inclusion: adrenal incidentalomas without clinical and biochemical evidence of hormonal activity at baseline. 61 patients included. Mean maximum diameter 3 cm. Patients enrolled between 1989 and 2008	Mean 3.1 yrs (range 0-19)	Adrenal Malignancy	0/61 (0%)	Maximally 31 patients evaluated at year 1. High risk of bias due to attrition bias.
			Autonomous cortisol secretion (*cortisol >1.8µg/dl after DST*)	0/61 (0%)	
			Phaeochromocytoma	0/61 (0%)	
			Hyperaldosteronism	1/61 (2%)	
Cawood et al, European Journal Endocrinology (2009) Systematic review	Inclusion: studies on follow-up after a diagnosis of nonfunctioning adrenal incidentalomas. publication 1980-2008; 20 studies were included in the systematic review; n=1410 patients in total with benign, nonfunctioning adrenal incidentalomas	1.8 to 7.1 yrs No information on the use of protocols for follow up in original studies	Adrenal Malignancy	0.2% (95 CI 0.0 to 0.4)*	No information on methodological quality of included studies Individual studies included in the Cawood review not assessed *Pooled estimates
			Autonomous cortisol secretion	0.3% (0.0 to 0.7)*	
			Phaeochromocytoma	0.2% (0.0 to 0.4) *	
Cho et al, Korean Journal Internal Medicine (2013) Cohort study	Cohort of 282 adrenal incidentaloma patients. Follow-up data in 147 (imaging)/72 (biochemical analysis) Study period 2004 to 2011	Mean FU 23.1 months	Adrenal malignancy	0/72 (0%)	Selection of patients with follow-up data unclear
			Autonomous cortisol secretion (*post DST cortisol >2.0 µg/dL*)	2/47 (4%)	
			Pheochromocytoma	1/47 (2%)	
Comlekci et al, Endocrine (2010) Cohort study	Patients referred to institute with AI since 2002; malignancy excluded (CT) Study period 2002 to 2008	Median 24 months; range 6-132 months .	Autonomous cortisol secretion (*post DST cortisol > 1.8 µg/dl*)	3/162 (6.9%)	Selection of patients with follow-up data unclear

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[1] See for full bibliographical details main manuscript

Reference [1], study design	Study population and study period	Follow up	Outcome measures	Results	Remarks
			Phaeochromocytoma	0/162 (0%)	
			Hyperaldosteronism	0/162 (0%)	
Di Dalmazi et al, Lancet Diabetes and Endocrinonolgy 2014	Cohort study Nonfunctinong adrenal incidentaloma without malignant features N=129 Study period 1995-2010	Mean 7.5 yrs (26 months- 5 yrs)	Autonomous cortisol secretion (1.8 - 5 µg/dl after DST)	14/129 (11%)	
			Autonomous cortisol secretion (>5 µg/dl after DST)	1/129 (1%)	
Fagour et al, European Journal Endocrinology (2009) Cohort study	Consecutive nonfunctioning adrenal incidentalomas patients with benign appearance on CT; size ≤ 40 mm; <10UH); 27 patients with nonfunctioning adenomas included Study period 2001-2006	Mean 4.3 yrs ±1.6 yrs	Autonomous cortisol secretion (post DST cortisol > 1.8 µg/dl)	3/27 (11%) (non developed clinically overt Cushing)	Study aimed to assess the usefulness of adrenal scintigraphy
Giordano et al, European Journal of Endocrinology (2010) Cohort study	Nonfunctinong adrenal incidentaloma without malignant features (N=102)	1-10 years, median 3 years	Adrenal Malignancy	0/102 (0%)	No definitions of "clear overt endocrine disease"
			Autonomous cortisol secretion (*cortisol >1.8µg/dl after DST*)	0/102 (0%)	
			Phaeochromocytoma	0/102 (0%)	
			Hyperaldosteronism	0/102 (0%)	
Kim et al, Korean Journal of Internal Medicine (2005)	Patients with apparent benign nonfunctiong adrenal incidentalomas. N=24 Study period 1992 to 2003	Mean 20.8 months (range 5-72)	Adrenal Malignancy	0/24 (0%)	No information on biochemical analysis and cut-off values used
			Autonomous cortisol secretion	0/24 (0%)	
			Phaeochromocytoma	0/24 (0%)	
			Hyperaldosteronism	0/24 (0%)	

Reference [1], study design	Study population and study period	Follow up	Outcome measures	Results	Remarks
Morelli et al, Journal Clinical Endocrinology and Metabolism 2014 Cohort study	Patients with apparent benign nonfunctioning adrenal incidentalomas. N=167 Study period 1996-2012	Median 72.3 months; range, 60–186 months	Autonomous cortisol secretion (DST >3.0 mcg/dl)	15/167 (9%)	448 patients excluded due to criteria or < 5 years follow up No standardized protocol for follow up
Muth et al, British Journal of Surgery (2011) Cohort study	Patients with apparent benign nonfunctioning adrenal incidentalomas and without extra-adrenal malignancy. N=187 Study period 2002-2004	Mean 19 months Clinical and biochemical evaluation at inclusion and after 24 months	Adrenal Malignancy	0/187 (0%)	4 patients displaying biological abnormalities during FU but with no further investigation
			Endocrine active lesions	0/187 (0%)	
Vassilatou et al, Clinical Endocrinology (2009)	Patients with apparent benign nonfunctioning adrenal incidentalomas. N= 95 Study period 1993-2007	Median 60 months; range 12-154 months Clinical, biochemical and hormonal examination after 12 months and then every 12-24 months	Adrenal malignancy	Malignancy, N=0	39/95 lost to follow up/refused follow-up;
			Autonomous cortisol secretion (*cortisol >1.8µg/dl after DST*)	2/95 (2%)	
			Phaeochromocytoma	2/95 (2%)	
			Hyperaldosteronism	0/95 (0%)	

Appendix VIII

Question 4: Natural course of apparently benign AI (risk of malignancy or development of hormone excess)

GRADE table

Quality assessment						Range of estimates	Pooled effect estimate (95% confidence interval)	Quality
Studies[1]	Design	Risk of bias	Inconsistency	Indirectness	Imprecision			
Risk of adrenal maligancy								
Anagnostis 2009 Cawood 2009 Cho 2013 Giordano 2010 Kim 2005 Muth 2011 Vassilatou 2009	6 cohort studies 1 meta-analysis	Attrition bias	No serious inconsistency	Serious indirectness (different definitions of exposure, outcome)	Serious (imprecise estimates)	Risk of malignancy during follow-up 0-0.2%	No pooled estimate due to heterogeneity in design and analysis and indirectness	⊕OOO VERY LOW
Autonomous cortisol secretion								
Anagnostis 2009 Cawood 2009 Cho 2013 Comlecki 2010 Di Dalamzi 2014 Fagour 2009 Giordano 2010 Kim 2005 Morelli 2014 Muth 2011 Vassilatou 2009	10 cohort studies 1 meta-analysis	Attrition bias	No serious inconsistency	Serious indirectness (different definitions of exposure and outcome)	Serious (imprecise estimates)	Risk of autonomous cortisol secretion during follow-up 0-11%	No pooled estimate due to heterogeneity in design and analysis and indirectness	

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[1] For full bibliographical details: see main paper

	Quality assessment					Range of estimates	Pooled effect estimate (95% confidence interval)	Quality
Studies[1]	Design	Risk of bias	Inconsistency	Indirectness	Imprecision			
Hyperaldosteronism								
Anagnostis 2009 Comlecki 2010 Giordano 2010 Kim 2005 Muth 2011 Vassilatou 2009	6 cohort studies	Attrition bias	No serious inconsistency	Serious indirectness (different definitions of exposure and outcome)	Serious (imprecise estimates)	Risk of hyperaldosteronism during follow-up 0-2%	No pooled estimate due to heterogeneity in design and analysis and indirectness	⊕○○○ VERY LOW
Pheochromocytoma								
Anagnostis 2009 Cawood 2009 Cho 2013 Comlecki 2010 Giordano 2010 Kim 2005 Muth 2011 Vassilatou 2009	7 cohort studies 1 meta-analysis	Attrition bias	No serious inconsistency	Serious indirectness (different definitions of exposure and outcome)	Serious (imprecise estimates)	Risk of pheochromocytoma during follow-up 0-2%	No pooled estimate due to heterogeneity in design and analysis and indirectness	⊕○○○ VERY LOW

Appendix Table 9: Selected drugs that may interfere with results of the dexamethasone test* (adapted according (69))

Drugs that accelerate dexamethasone metabolism by induction of CYP 3A4

      Phenobarbital

      Phenytoin

      Carbamazepine

      Primidone

      Rifampin

      Mitotane

      Rifapentine

      Ethosuximide

      Pioglitazone

Drugs that impair dexamethasone metabolism by inhibition of CYP 3A4

      Aprepitant/fosaprepitant

      Itraconazole

      Ritonavir

      Fluoxetine

      Diltiazem

      Cimetidine

Drugs that increase CBG and may falsely elevate cortisol results

      Estrogens

      Mitotane

-   *This should not be considered a complete list of potential drug interactions.
-   Data regarding CYP3A4 obtained from http://medicine.iupui.edu/flockhart/table.htm.

Appendix Table 10

Comments to the Clinical Practice Guideline on the management of adrenal incidentalomas

by invited reviewers and members of the European Society of Endocrinology (ESE) and the European Network for the Study of Adrenal Tumors (ENSAT), representatives of associated societies of ESE and patient representatives

	Comments by reviewer	**Response to the reviewers by the authors**
Paul Stewart		
1.	Thank for you for asking me to take a look at this. What a tour de force - it is truly comprehensive and will undoubtedly be a great addition to the guidelines literature particularly in this space where the literature remains muddled. I offer these comments in constructive spirit - I know how hard it is to achieve any consensus in this area! 1. General style. I think at 85 pages it is too long and somewhat repetitive. It is at times too "chatty" - I am not sure the reader needs to know the level of debate or disagreement within your group on certain issues - what matters is that you have reached an internal compromise and all authors agree to its content.	We are grateful for the overall very positive feedback. We agree that the guidelines are rather long (and much longer than initially intended). We have now shortened some sections, especially the paragraphs with our "internal debates".
2.	2. At times I think you make it overly complicated. "Arterial hypertension" being a case in point in patients with possible cortisol excess. The important issue here is the flow of patients through a clinical pathway - I would hope that all patients would have had BP measured - without which you cannot proceed to a PRA/PRC ratio - so why wait until the result of the Dexa test before assessing this? Ditto other aspects of autonomous cortisol excess - I would have thought a more detailed screen for degrees of Cushing's severity in this group is indicated - to of course include glucose and bone mass, but also myopathy, skin, CVS risk over and above BP (thrombosis etc). I think stratifying additional tests based on the degree of cortisol excess is potentially incorrect - how many times have we been surprised by patients with florid phenotype yet relatively low levels of cortisol secretion.	We agree that the flow of the patients is very important. However, the first recommendation on assessment for hormone excess R.3.1 clearly states that EVERY patient with an adrenal incidentaloma should undergo careful clinical assessment (including BP measurement). However, in the spirit of your first comment we want to avoid lengthening the manuscript still further and would prefer just to refer to the "Cushing's guidelines" for assessment of phenotype. We agree that phenotype and lab values sometimes do not really correlate. However, as soon as the patient has clinical signs of overt Cushing's then the diagnostic procedure should follow the Cushing's guidelines. We have now clarified this in the Reasoning to R.3.1.
3.	3. In terms of the pathway I am now confused as to whether or not to measure DHAS/ DHEA (my routine practice) on screening presentation or to wait until a scan shows features suspicious of adrenal ca? Again I think you make this overly complicated.	After reviewing the literature, the panel felt that the value of measuring DHEAS in all patients with adrenal incidentaloma is too limited. Thus, we suggested in R.3.10 (now R.3.11) measurement of sex hormones and precursors only in patients imaging features suggesting of ACC. However, we now added in R.3.11. "clinical features of ACC".
4.	4. Size is important! Here the literature is confusing on defining a critical size for action or inactivity and I am afraid your guidelines muddy the water still further with <4 cm (R2.3) and <6cm (R4.3) being proposed as rate limiting indicators. What is the evidence here? With a 4cm mass can I really get away	We fully agree that size is an important factor. Within the guidelines we acknowledge that the evidence for a certain cutoff for size is limited. However, it seemed to us important to provide guidance on this important aspect.

1

	with no follow up imaging when earlier data suggested a 25% risk of future malignancy in a mass over 3cm? Figure 3 helps but I do think this section needs clarity. Personally I like the "arbitrary" analysis and the fact that between x and x (say 3-6cm) this becomes an individual decision based on risk from other tests.	However, at the time of "older data", imaging methods were less sophisticated and the panel is confident that a homogenous lesion < 4cm with "benign" radiological features is really benign. Thus, we prefer to stick with the arbitrary cutoff of 4cm for homogenous, lipid-rich lesions, because we believe that too much follow-up imaging does more harm (psychologically, financially and due to radiation exposure) than benefit.
5.	Nonetheless giving an indicator of size whereby ALL tumours should be removed would be useful. Presumably you are also saying that anything over 6cm should be an open procedure? Capsule rupture is referred to and because this is so critical in determining future prognosis (your own data!) I am personally nervous about any known ACC having a laparoscopic procedure. Again not clear.	The question, whether there is a size whereby all tumors should be removed, was intensively discussed. However, we opted against a fixed cutoff, because in many patients (not only in patients with comorbidities) it might be reasonable not to remove even an 8 cm obvious adenoma or myelolipoma. Nevertheless, to make this point clearer, we have altered the wording of the Reasoning in R.4.2.

We share your concern of capsule rupture, but we believe that the expertise of the surgeon is more important than the method of surgery. Thus, we have added in addition to R.1.1 a statement in the Reasoning of R.4.3 that an experienced surgeon is required for the best outcome. |
6.	5. Phaeo and primary aldo discussion is directly to other guidelines which is fine.	Thanks.
7.	6. The nice piece of work relates to "autonomous cortisol excess" and I see this as a real advance from the current unsatisfactory term subclinical Cushing's. I really like the move to defining autonomy (versus a physiological/ pathophysiological activation of an endogenous HPA axis through obesity, diabetes, stress - all of which of course are present ++ in this group of patients) and then a detailed screening for phenotypic features of any cortisol excess - in effect defining the degree of what is likely to be "mild" Cushings. I like Figure 2 as well - great job. The push back here which I seriously hope you take on board, is the definition of "autonomous". You are well aware of sensitivity and specificity values for the ON Dexa test - even with a cut off of 140nmol/L, 5-10% of the NORMAL population (higher in elderly, depressed, obese patients) will not suppress to such a value. These patients do not have autonomy but as above - physiological/pathophysiological activation of the HPA axis.	We are very grateful for this positive judgment of our efforts to replace the term 'subclinical Cushing's'. The terminology we have used was the subject of very lengthy debate and despite potential shortcomings, as you mention, we feel that it is as good or better, as any other. We agree that a single dex test is not always able to prove autonomy and that false positive results might be an issue. However, there are no convincing results that any other test can solve this issue convincingly. Furthermore, addition of several other tests result in the so called 'multiple testing' problem. In this respect it is crucial that our guidelines state that a single mildly elevated dex test is not a proof of autonomous cortisol secretion, which is an informal way of saying that specificity is not optimal. We now modified R3.3 and R3.4 and mention additional biochemical tests, and have emphasized the need to have more than just dex tests if surgical intervention is ever considered (see below).
8.	Here I do feel an ACTH measure is essential if you wish to define true autonomy. You also fail to mention the value (or not - but needs discussion) of a low DHEA/ DHAS in this context. Reading between the lines I suspect much debate amongst the group - but you can't really claim "autonomy" simply on the ON Dexa test alone.	Although measurement of ACTH has several limitations, we agree that ACTH is an important marker to define autonomy. However, in some patients cortisol is not only driven by ACTH. Nevertheless, it is (now) suggested in most patients with elevated cortisol post dex to measure plasma ACTH. However, the data on DHEA-S seemed to us too weak to recommend this test. See also comment #3.

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	Radu Mihai	
9.	Line 48 'established' is a very strong word. Most tests give you a probability of malignancy rather than firmly confirming B or M	We agree and have modified the wording.
10.	Line 59 "the degree of cortisol excess" suggests that there would be a threshold over which is more likely and such a threshold is not been defined	Later in the text we discuss this difficult issue in details, but space restrictions preclude it being done in the abstract.
11.	Line 120 Do we have evidence that imaging is so reliable that biochemical testing for phaeo is unnecessary in some patients?	Following comments by several reviewers we adapted this recommendation (see also our responses to comment #50)
12.	Line 150 if the second scan shows no change is patient discharged from further followup?	This is indeed an important point and we address this issue now in R.5.2.
13.	Line 339 would be good to have a comment about SUV threshold that raises concerns for malignancy or the benefits of adrenal/liver ration as a marker of malignancy	Unfortunately, current evidence for SUV threshold in incidentaloma is extremely poor. We now refer to imaging meta-analysis for more detailed analysis of the data.
14.	Line 546: of how many patients? And how long were the follow-up?	This information is now provided.
15.	Line 620 This section is rather abrupt. Until now the discussion was about incidentalomas and now we are dealing with confirmed ACC?	We agree and have added a short introductory sentence.
16.	Line 693 '.... when the initial assessment was normal'	Thanks, we have now clarified this.
17.	Line 884 do these ones need further testing with 2x2 mg DXM?	We have addressed this important issue of additional testing now in a separate recommendation R.3.4.
18.	Line 1228 Maybe a comment about the impact of surgical expertise on the decision of approach and the need for those suspected as ACCs to be operated in a referral centre (ideally)	In addition to the Reasoning to R.1.1, we are now referring also in the Reasoning to R.4.3 to this issue of "surgical volume".
19.	Line 1239 this leaves a gray area of having to assess worsening of osteoporosis (?repeat DEXA) or diabetes (?increased need for medication) or hypertension (increased dose/number of drugs)	Whilst we agree with you we believe that this is a judgment call for the local physician and that this has to be individualized.
20.	Line 1244 Should we have a comment that a RCT with sufficient power and long FU is highly desirable in this area?	We fully agree that an RCT would be desirable and we agree with the reviewer that follow-up is a clinically important question, and we address these issues in the section on future directions.
21.	Figure 4 : hormone excess: should NO/YES be swapped?	Thanks for bringing this mistake to our attention.
22.	Figure 4 adrenal biopsy: Here my suggestion would be to consider PET scan if suspicious of single adrenal metastasis - if PET excludes other metastatic deposits than adrenalectomy should be offered for oncological benefits.	Thank you, we now mention PET in the legend of Figure 4.
	Andre Lacroix	
23.	Dear Martin Thank you for giving me the opportunity to review these guidelines These guidelines will be well received and were carefully planned. As usual, reaching consensus is difficult given the current level of evidence and difficulties to compare outcomes when no one agreed on definitions in particular for the "subclinical issues". I suggest another terminology instead of "autonomous cortisol secretion", e.g.	Thank you for your positive overall judgment. We do agree that the proposed terminology has flaws (e.g. that autonomy is not easy to define, see also comments # 7, 8). However, as the concept of the dexamethasone test is to block pituitary ACTH secretion, we still believe that the term autonomous cortisol secretion is the most adequate, accepting that it is not ideal. After another round of intensive discussion, the panel voted against "modest or mild increase in cortisol secretion', because the dex test is not really intended

3

	"mild increase of cortisol".	to quantify "increase of cortisol secretion". As discussed in the guideline, we
	At least two reasons not to use the terminology autonomous 1. If it was fully "autonomous", there would not be any suppression with dexamethasone and in most cases of lesions secreting modest or mild amounts of cortisol, dex will partially suppress cortisol as low as 50 nmol/LO 2. The constitutive activation of cAMP production may be true in 50% of overt CS cases but aberrant regulation by factors other than ACTH can be present and thus cortisol secretion may not be "autonomous" from other factors although not being regulated by ACTH 3. Using the term modest or mild increase in cortisol production describes objectively the phenomenon.	hope that our definition will be replaced in the future - after properly performed prospective studies - by a more adequate definition.
24.	R.2.2 "We recommend that all adrenal incidentalomas undergo an imaging procedure to determine if the mass is homogeneous and lipid-rich and therefore benign (XOOO)." Replace 'therefore' by 'most probably'	We agree that 100% certainty is rarely achieved in medicine. However, we are convinced that the likelihood that a homogeneous and lipid-rich lesion is malignant is too low to modify the concept of this guideline, which aims, amongst other things, to reduce the number of patients subjected to imaging follow-up (and radiation exposure)
25.	R2.3. Add: Repeat imaging at least once at one year interval for lesions > 2 cm; for lesions closer to 4 cms would repeat yearly to r/o progression > 1 cm	This is a very important point and setting a cutoff in the lack of large prospective studies is difficult. However, we prefer to stick with the arbitrary cutoff of 4cm for homogenous, lipid-rich lesions, because we believe that too much follow-up imaging do more harm (psychologically, financially and due to radiation exposure) than benefit. See also comment #4
26.	R3.4 add: for mild increase of cortisol secretion, this remains to be determined	See our response to comment #23.
27.	Reasoning R 2.3: Line 784 If a lesion is stable at 4 cms, I agree. If a 3.9 cm benign appearing nodule is present for the first time, it is very bold to recommend not to very again at least 6-12 months. What should be the lowest size without any further imaging ? < 2cms ?? Prudent to verify at least once.	See our response to comment #25.
28.	Reasoning R. 3.3. Line 934 add 'and late night salivary cortisol'	Whilst the data on the value of late-night salivary cortisol in incidentaloma patients are conflicting, we have now added this.
29.	Legend Figure 2 add 'late night salivary cortisol'	Done.
30.	Reasoning R3.6 To limit to plain X ray and detection of vertebral fractures is minimalist; for me this is a clear indication to do bone mineral density and not to wait for reaching the stage of vertebral fractures.	This is a controversial issue and it is not obvious which method is the best to assess the risk for vertebral (micro-) factures in patients with cortisol excess. Therefore, we prefer to leave the decision on method to use up to the local physician.
31.	R.3.7 modify to: In all patients considered for surgery, suppression of ACTH by of level of cortisol excess should be confirmed in order to recommend coverage with glucocorticoid replacement until recovery of HPA axis.	As discussed above that ACTH is in theory the best marker, however, it has several flaws and there is evidence that even patients with normal plasma ACTH can experience postoperative adrenal insufficiency (Eller-Vainicher C Eur J Endocrinol. 2010 163(6):925-35). This has now been mentioned in the Reasoning of R.4.6.
32.	Reasoning R.3.7. line 1021. Instead of 'ACTH-independency' write	See above

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	'suppression of HPA axis'	
33.	R3.9 add 'or with hypokalemia'	We have now added hypokalemia.
34.	R.4.3. Impossible to reach consensus here I agree. In our center in suspicious lesions ie non homogeneous, 5 cms even without invasion we do PETCT before surgery; if very high SUV we do open oncologic adrenalectomy even without evidence of invasion even if we have very experienced minimally invasive surgeons.	We are certainly aware that this is a controversial issue. However, we discussed this in detail and decided to keep our recommendation, which is also in agreement with a guideline currently developed by the European Society of Endocrine Surgeons (manuscript just submitted).
35.	R.4.3. add 'If PET scan is highly suspicious of ACC, we perform open surgery'	See response to comment # 34.
36.	Reasoning R4.5., line 1139 I think this discussion should be part of ACC guideline and not adrenal incidentaloma	We agree that this statement fits more with an ACC guideline and have deleted it.
37.	Reasoning R.4.6., line 1150 Modify: ' evidence for '(possible) autonomous cortisol secretion' (post dexamethasone cortisol > 50 nmol/l (> 1.8 µg/dl)) even if there are no clinical sign of cortisol excess.' into 'evidence of suppression of ACTH below normal levels and mild increase of cortisol secretion even if there are no clinical sign of overt Cushing' syndrome.'	See response to comment #23.
38.	Figure 3: Would add high suspicion of malignancy to local invasion in right box	See comment # 34.
39.	R5.1. I would recommend at least one follow-up imaging at 6-12 months in any lesion > 2 cms even if HU < 10 at first examination. This is already much better than previous guidelines, but cutting to no imaging in a 3-3.9 cm initial image is very provocative. How many lesions > 3 cms have cortisol < 50 post 1 mg dex ? they need follow-up.	See responses to comments #4 and #25
40.	Reasoning R.5.3. add at the end '(ie cortisol < 50 nmol/L post overnight 1 mg dexamethasone test).'	We have added this as suggested.
41.	Reasoning R.5.4. Suppression of ACTH may occur without clinical signs; in such patients I do annual ACTH, late night salivary cortisol or repeat dex suppression.	After reviewing in detail the available literature and many discussions amongst the panel we conclude that the evidence showing such an approach is beneficial is too weak to recommend this for every patient. However, we have adapted the legend of Figure 2 to take account of "your direction".
42.	R6.1.3 In BMAH even if a lesion was 7 cm with indeterminate HU as often found, there is no surgical indication if there is no sufficient hormone excess	In general this is within the spirit of our guidelines. However, if the HU are clearly > 10 then an individualized approach seems to be appropriate.
43.	R.6.1.4 Many of those may be BMAH cases and once again for a differed reason the term ACTH-independent may be inappropriate here as local ACTH production may be involved	Thank you, we have deleted the term "ACTH-independent".
44.	Line 1306 add: ' unless urinary free cortisol is increased more than 3-4 fold.'	Acknowledging the limitations of measurement of urinary free cortisol, we would not rely on this single parameter as a decision point for surgery. However, we agree that most patients with urinary free cortisol > 3-4 fold above the upper reference value frequently have signs of overt Cushing's.
45.	Reasoning R6.1. line 1329 add 'family screening with 1 mg dexamethasone test and'	We have added this.

46.	R6.2.2 why MRI in adults 20-40 years of age? Cost vs justification in adults 20-40 yo old not clear particularly if not repeater frequently. OK for p53 mutation carrier but not all adults.	We added a statement to the Reasoning of R.6.2.2.
Quinton, Richard		
47.	*"To exclude cortisol excess, a 1-mg overnight dexamethasone suppression test should be performed (applying a cut-off value of serum cortisol ≤ 50 nmol/l."* Comment: • It is a cardinal error to extrapolate from Dexamethasone dose and Cortisol cut-off used for "Cushing's screen" in patients not known to have adrenocortical lesions. • If these proposals are adopted, it could result in lots of unnecessary referrals for adrenal surgery being made for alleged "adrenal Cushing's". • We should remember that the DST is actually an "ACTH suppression test" and that, where there is autonomous adrenocortical cortisol secretion, there is by definition no significant circulating ACTH. • Therefore, unlike the situation we face when we screen patients for Cushing's syndrome (all causes), there is no loss of sensitivity by using a higher dose of Dexamethasone in patients with adrenal incidentaloma, but there is a corresponding gain in diagnostic specificity. It's a very simple "mind experiment" that we can all perform.	As discussed above we agree that the dex test is not ideal. However, we are convinced that it is the best evaluated test for this situation. However, as elaborated in R.3.8 indication to surgery should never be based only on a single lab value or single test. Please see also the responses to comments #7, 8, 23.
48.	At the Mayo clinic, Bill Young routinely by-passes the overnight low-dose DST and goes straight for an 8mg DST.	We have added a short statement on the high dose dex test.
Tomasz Bednarczuk		
49.	We would like to congratulate the Authors for preparing the next ESE Clinical Practice Guidelines entitled Management of adrenal incidentalomas - a European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network of the Studies of Adrenal Tumors. The guidelines represent a novel point of view and I am certain that it will be very useful in daily practice. Enclosed please find our suggestions. At the same time, a Polish Society of Endocrinology expert working group prepared: "Adrenal incidentaloma in adults - management recommendations by the Polish Society of Endocrinology" which are now in press in Endocrinol Pol (enclosed please find the manuscript; the English version is now being corrected). In the majority of points, the recommendations are similar, supporting the notion of an individualized approach to patients with AI and possible referral to specialized multidisciplinary centers. Unfortunately the	Thank you for your kind words.

	quality of evidence concerning AI is usually low and the interpretation of the results may be different. In some points, especially follow-up, our recommendations are more "old-fashioned"; and we will attempt to change it in the next versions.	
N.N.		
50.	Dear Authors of the Guidelines, Thank you for these novel guidelines, and congratulations to your work. The guidelines are sound and well written. The initial imaging phenotype (your figure 4) could be divided into two, noncontrast or contrast CT. We have (reference 172, enclosed) previously demonstrated that you don't need to hormonally screen for pheo if HU of the adrenal mass is <10 on noncontrast CT. This really would save a lot of money and trouble. Pheos typically have an imaging phenotype on noncontrast CT that is above 20 HU You might wish to indicate in you figure 4, that hormonal screening for pheo is not needed if HU is < 10 (enclosed is a Figure on the suggested evaluation and follow-up that we have been using, you can pick something from it if you so wish).	As pointed out by several reviewers (see comments #11, 65, 91) the data that demonstrate that adrenal masses with HU<10 cannot be pheos are very limited. Thus, we believe it is too early to recommend waiving the pheo-specific biochemical work-up in all these patients, nevertheless, we have now modified R.3.9. However, we would hope that your data will be confirmed by other groups and that we can make a strong statement in the next version of this guideline.
51.	. I also enclose a follow-up study on adrenal incindentalomas published in Endocr Metabolism, indexed in PuBMed A 5-year Prospective Follow-up Study of Lipid-Rich Adrenal Incidentalomas: No Tumor Growth or Development of Hormonal Hypersecretion. Schalin-Jäntti C, Raade M, Hämäläinen E, Sane T.Endocrinol Metab (Seoul). 2015 Sep 10. [Epub ahead of print]. You might wish to include the findings – as there really are not prospective but rather retrospective series published on adrenal incidentalomas– that small lipid-rich adrenal incidentalomas (2 cm or less) do not grow during a follow-up of 5 years, neither do they turn into cortisol hypersecreting adenomas (not even subclinical). We also confirmed our finding that such incidentalomas with a noncontrast HU < 10 really do not secrete metanephtines/normetanephrines (as they typically are cortical adenomas and not adrenal medulla tumours).	We have added this reference.
Eystein Husebye, Ansgar Heck and Anders Jørgensen (on behalf of the Norwegian Endocrine Society)		
52.	General comment and summary on imaging In general, we agree to most of the recommendations regarding radiological examinations and follow-up. On the issue of second line imaging of lesions >10 HU we propose to present the different modalities (CT washout, MRI chemical shift and FDG-PET/CT) in a neutral way as reasonable alternatives.	We have now modified the section on "second line imaging".
53.	Specific comments and proposal for changes Page 17, line 464 – 479: Paragraph on Contrast-enhanced washout CT:	Thank you for this careful reading and bringing this typo to our attention.

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	Line 474 and 477: The ">" "greater-than sign" must be replaced by a "<" "less-than sign".	
54.	Washout CT is an accurate parameter for differential diagnosis between adenomas and non-adenomatous lesions and is an important tool in the characterization of lipid poor adrenal lesions as pointed out by the references 49, 83, 89, 90. Although they do not fulfil the criteria for literature selection, the evidence from these and multiple other studies should be taken into consideration in the paragraph "reasoning" from page 27.	It is also the clinical experience of several panel members that washout CT is of great value even though the literature search did not confirm this. However, as indicated above we have modified this section in the recommendations.
55.	Reasoning for R2.4, page 27, line 806-812; 834-836 1) It is stated that "Contrast washout CT has very limited and low quality evidence from studies", but the reference "(Bancos et al., under submission)" is not added to the reference list and to date (9.1.2016, pubmed search) not available on the internet. Reference to unavailable references makes it difficult to follow the reasoning.	We fully understand this concern and agreed now with the Editor in Chief of EJE that we will wait for the final print version of the manuscript until the meta-analysis is published and can be cited.
56.	2) In the reasoning section in its present form, there is a clear preference for FDG-PET/CT compared to CT washout (line 834-836). To our knowledge, there is no large study comparing the two methods in the setting of incidentalomas (line 826). The two methods both suffer from limitations in rare case of metastases from renal cell carcinomas and lymphomas (line: 814 and 815, ref. 161-163). In the present draft, the disadvantages of washout CT are pinpointed (line 806-810). Nevertheless, the combined results from the underlying studies (ref. 48, 89) can be interpreted differently, thus resulting in a lower proportion of malignant lesions falsely classified as benign. For further explanation, please see appendix. Further, FDG-PET/CT suffers from limitations in a similar disease spectrum as washout CT. In case of the most common cancers, washout CT performs with high accuracy (ref. 49, 83, 89). With the present evidence, no superiority of FDG-PET/CT can be claimed.	We have modified this section of the recommendations.
57.	3) Even if FDG-PET/CT may be demonstrated to perform better than washout CT in the future, the limited number of scanners, waiting time and the costs per scan have to be acknowledged. The present guideline draft may lead to a shift of valuable resources towards investigation of a what will mostly turn out to be lipid poor adenomas in a healthy population.	See above.
58.	Taken together we propose to include the wash out CT into the algorithm as a second line modality in lipid poor rich lesions in line with FDG-PET/CT. We propose therefore to specify R 2.4 as highlighted: R.2.4 If the adrenal mass is indeterminate on non-contrast CT and the results of the hormonal work-up do not indicate significant hormone excess, there are three options that should be considered by a multidisciplinary team considering the patient's clinical context: immediate additional imaging (washout CT, chemical shift MRI or FDG-	We agree with you and have modified this section.

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	PET/CT), interval imaging in 6 to 12 months (non-contrast CT (or MRI)), or surgery without further delay. Further, we propose to present the modalities without highlighting the panels preference (line 834 and 835), but rather as equal second line imaging methods as indicated in table 4.	
59.	We would like to comment on the accumulated numbers from reference 48 and 89 (line 806-810). It is stated "that approximately 5/63 malignant lesions (especially lymphoma and metastases), were falsely characterized as 'benign" on contrast washout CT (48, 89)". In reference 48 (Caoili et al., 2002), 3 of 36 lesions were classified as "benign" by washout criteria although they were non-benign lesions. These three lesions were: - one pheochromocytoma, - one adrenocortical carcinoma and - one renal cell carcinoma. Following good clinical endocrine routine practice and the present guideline draft, far more pheochmromocytomas would have been identified by screening with metanephrines (R3.8 and R6.3.1). More than half of adrenocortical carcinomas would be identified by measurement of sex hormones and steroid precursors (R.3.10; l.1048). In the setting of cancer follow up of known renal cell carcinomas, CT washout is not recommended (ref. 75) and in the setting of an incidentaloma, a renal or hepatic carcinoma most probably would have been discovered by the initial CT exam. Thus, only one non secreting adrenocortical carcinoma would not have been identified correctly in an incidentaloma setting, reducing the number of falsely identified benign lesions to 1/34 and not 3/36. In the other study (ref. 89) 2 of 24 non benign lesions were classified as benign, one patient with lymphoma and one with a metastasis of a colon cancer. Lymphomas usually have manifestations that would be identified by additional radiological features in the setting of incidentalomas. Thus following the present guidelines and not only isolated CT findings, the total combined number of lesions falsely classified as benign would not be 5/63, but 2 of 58 patients in these two publications taken together (ref. 48 and 89).	We have adapted now the Reasoning of R.2.4.
60.	General comment and summary on assessment for hormone excess We agree to most of the recommendations for assessing hormone excess and follow-up, and we also support the use of the term 'autonomous cortisol secretion'. However, we have some comments regarding taking 1-mg overnight dexamethasone suppression test in every patient.	We appreciate this positive judgment.

61.	Specific comments and proposal for changes *Page 3, line 96-97: Paragraph on Assessment for hormone excess* The current literature on the effect of adrenalectomy for patients with 'autonomous cortisol secretion' is of low quality and hard to interpret, as described in the draft. Randomized studies comprising hard endpoints are lacking. Results from several studies are expected during the coming two years. Generally endocrine testing is indicated when the patient has symptoms or findings which may indicate an endocrine disease for which there is documented therapy, and where the test result directly impacts the therapy, or further testing. 'Screening tests' in populations with low pretest probability of a disease should be avoided, considering that this leads to a high number of false positive test results. Figure 1 illustrates this principle exemplified with aldosteron/renin ratio, metanephrins and sex-hormones and steroid precursors. We suggest that the same principle should be applied to 'autonomous cortisol secretion'. If the patient has hypertension and/or diabetes mellitus, the physician finds no contraindication for adrenalectomy, and the patient is interested in such a therapy based on today's knowledge, ACTH should be measured. If ACTH is low, a 1-mg overnight dexamethasone suppression test should be performed and surveillance or operation discussed with the patient on an individual basis. Patients with symptoms of overt Cushing's syndrome should be assessed and treated according to established guidelines. We propose therefore to change R 3.2 as highlighted: We suggest that the following patients with adrenal incidentalomas undergo a 1-mg overnight dexamethasone suppression test; patients with hypertension and/or diabetes mellitus and low ACTH where the physician and the patient find that the advantages of adrenalectomy outweigh the disadvantages if '(possible) autonomous cortisol secretion' is documented (XXOO). If recommendation R.3.2 is changed as suggested other points and flowcharts leading up to the recommendation should be changed accordingly.	According to the literature search and our clinical experience the pre-test probability of 'autonomous cortisol secretion' in patients with adrenal incidentaloma is NOT low (approximately 10%), which is the reason behind the screening proposal. Furthermore, we do see major limitations of measuring ACTH (see also comments #8, 23) and decided after another intensive discussion to stick with the dex test as first step of the work-up.
	Regis Cohen	
62.	This work is original, clear, well-constructed and well referenced. Congratulations. If I can afford some suggestions: I was surprised that the work does not address the orientations depending on the size nor presents the interests of the adrenal catheterization in primary hyperaldosteronism Size Malignancy risk seems increased with size.	We thank you for this very positive feedback. The reason we did not discuss adrenal venous sampling is just the fact that this is covered by guidelines on primary hyperaldosteronism and therefore out of the scope of our guideline.

	Eventhougth there may be a bias that higher sizes are more often operated. Likewise some have mentioned a higher prevalence of silent (or not) pheochromocytoma and cortisolic adenoma in larger lesions (>3 cm). Conversely adenomas producing aldosterone are smaller.	
	Ambrosi, B., Peverelli, S., Passini, E., Re, T., Ferrario, R., Colombo, P., ... & Faglia, G. (1995). Abnormalities of endocrine function in patients with clinically" silent" adrenal masses. European Journal of Endocrinology, 132(4), 422-428.	
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Michiel Kerstens, Edward Buitenwerf, Peter Bisschop		
63.	The members of the guideline development group are to be commended for their extensive work in preparing an ESE guideline on the management of adrenal incidentalomas. A daunting task, for the quality of the currently available literature on this subject is rather poor. Nearly all studies are retrospective in design and are difficult to compare as a result of heterogeneity in size and composition of populations examined, methods applied and length of observation. Thus, it is often not possible to make firm recommendations. We would like to add the following comments:	Thanks for your positive judgment.
64.	R. 2.4 The recommended interval of 6-12 months for a repeat CT/MRI in case of an indeterminate adrenal mass is rather long. Purpose of this repeat imaging is to detect a malignant adrenal lesion such as an ACC. These are almost invariably characterized by a rapid growth within months, as the authors also have stated (line 1187-1189). Therefore, a shorter interval (e.g. 4-6 months) is likely to be more appropriate in this case.	We agree that a delayed imaging might lead to delayed diagnosis of an aggressive ACC. However, in our experience the likelihood of a very aggressive ACC that is small at the primary diagnosis and without clear radiological signs of malignancy is very low. We are more afraid of missing one of these slowly growing ACCs by imaging too early. However, we certainly would like to avoid a third or even fourth (unnecessary) imaging. Thus, we believe that the interval of 6-12 months is a good compromise, which allows the treating physician to choose the most suitable interval.
65.	R.3.8. It is recommended that measurement of metanephrines should not be performed in case of an adrenal lesion with imaging criteria of an adenoma. The authors refer to a single retrospective study by Sane et al. , containing only 9 patients with a pheochromocytoma. To our opinion, this is a quite a weak base for such a relatively strong recommendation. Moreover, intracellular fat-containing pheochromocytomas resulting in attenuation values of less than 10 HU similar to adenomas have been reported (Blake et al. AJR 2003; 181:1663–1668).	Following this and the comments of several reviewers (see also #11, 50 and 91), we discussed this issue once more and have now modified R.3.8. slightly.
66.	R.3.10 We agree that the analysis of a comprehensive urinary steroid profile	We added this reference.

	measured by GC-MS or LC-MS seems to be a promising new tool to discriminate benign form malignant adrenocortical tumors. We would appreciate if a recent paper on this subject from our group would be added as a reference (Kerkhofs et al. Horm Cancer. 2015 Aug;6(4):168-75). We found a sensitivity of 100% and a specificity of 99% for detecting ACC in a group of 152 patients evaluated for an adrenal mass.	
67.	Minor detail: line 763 - …(5%) were malignant (false positives),…. This should be false negatives.	Thank you for your comment. We had now fully modified the imaging section and refer to the imaging-meta-analysis on incidentalomas.
Anna Kasperlk-Zaluska		
68.	I studied carefully your Guidelines on Adrenal Incidentaloma I have in my material about 2700 such cases. My last international analysis was published in 2014 (ICE/ENDO 2014, June 21-24, Chicago) as poster Board Sat-0806, entitled Malignant Adrenal Incidentaloma - Is It a Tumor of Old Peopl? a Clinical Analysis of a Group of 2666 Patients Observed at aSingle Endocrinological Unit. My presentation on ENDO 2015 concerned treatment in a group of ACC patients. Your expertise is very useful, however I fear that it is a little too long. I accept a majority of your observations, well known from my practice. , However, I can't agree with tests Nr 133.. You suggest performing laparoscopic adrenalectomy in patients with unilateral adrenal masses with radiological findings suspicious of malignancy, but without evidence of local invasion. In my experience every adrenal tumor with density exceeding 25 j H (without any signs of invasion or hormonal hyperactivity) has to be removed by open adrenalectomy. In the nearest future a young woman (mother o 2 children), a patient of our Department (diagnosed less than 2 years ago as an "adenoma'", but with about 30 j H of density, without any sign of invasion) will be treated surgically for a disseminated adrenocortical carcinoma. It is a true tragedy. Only in patients with long-term congenital adrenal hyperplasia an adrenal tumor with high density could be considered as probably non malignant tumor. I know that I am a little in late with my letter, but I hope that you could hear my voice	We are certainly aware of your large series of patients with adrenal incidentaloma. However, as pointed out to comment #34, we are convinced that laparoscopic surgery by an expert surgeon in a small ACC without local invasion is oncologically as good as open surgery. Importantly, we believe that the expertise of the surgeon is more important than the method of surgery. See also comment #5.
Höfle Günter (on behalf of the Austrian Society of Endocrinology and Metabolism (ÖGES))		
69.	I appreciate the important work of this guideline publication. Optionally, the publication team considers to comment on the different definitions of subclinical Cushings syndrome, including the CRF test. Furthermore, as a cutoff for differentiating benign from malignant tumors by non-contrast CT some specialists simultaneously are aware of a more specific cutoff of 18 HU.	Thank you for your comments. The available evidence in the literature using the cutoff of 10 HU is much stronger than on 18 HU. We now refer to the imaging meta-analysis to illustrate this issue.

	I discussed the manuscript with an expert team in Austria (ÖGES board); and no further comments were made.	
Maria Candida		
70.	Abstract lines 42 -46 Other questions about adrenal incidentaloma 1) The lesion is in adrenal gland? 2) Hormone production is related to the metabolic syndrome, adrenergic syndrome? 3) Is there the possibility to analyze previous exams by any other indication (to evaluate the temporal evolution of the adrenal lesion).	We agree with you that these questions should be addressed during follow-up. However, due to space restriction we cannot address all possible issues in the Abstract.
71.	Line 49 - To exclude autonomy of cortisol production, a 1-mg overnight dexamethasone suppression test should be performed (applying a cutoff value of serum cortisol ≤ 50 nmol/l (1.8 µg/dl)). The analysis of dexa in serum should be indicate	The analysis of dexamethasone in serum is not widely available. Therefore, we could not recommend this.
72.	Line 51- For patients without clinical signs of overt Cushing's syndrome (add the more specific features of Cushing' syndrome on Table X): Proximal myopathy, Atrophic skin, Bruising due to minimal traumas, Facial plethora, fat cervical dorsal, Purplish striae> 1cm	Due to space restriction we just refer to the dedicated Cushing guidelines.
73.	Line 54 - 4) All patients with apparently benign disease and autonomous and possible cortisol' secretion should be screened for arterial hypertension, type 2 diabetes mellitus and dyslipidemia to ensure these are appropriately treated. The surgery should be indicated in cases of uncontrolled metabolic syndrome in this group of patients. = R3.5 line 108	The association with dyslipidemia is less proven, although biologically plausible. We discuss this in the Reasoning of the new recommendation R.3.6.
74.	Bone densitometrie should aldo be indicated	See response to comment #30.
75.	Line 82 R 2.3 We suggest that if the non-contrast CT is consistent with a benign adrenal (UH < 10 ??) mass < 4 cm no further imaging is required (XOOO).	Thanks, we added this clarification.
76.	Line 98 R 3.3 We suggest in selected cases measured the serum dexamethasone	See comment #71.
77.	Line 235 The frequency refers to US CT MRI exams??	Most of these imaging studies were CT studies, but some also MRI and other techniques.
78.	Line 239 In childhood, adrenal incidentalomas are extremely rare maybe bias because this group did not do frequently image exame?	We agree that there might be some bias, but as incidentalomas are defined by incidental findings by imaging and this is just less frequently done in children, we feel that the statement remains correct.
79.	Line 262 term "'autonomous cortisol secretion'" in the context of an adrenal incidentaloma throughout the guideline text (for the exact definition see chapter 5.3).	See also our responses to comments #8 and 23.

	I m a bit afraid with this term Autonomous cortisol secretion because this sounds ACTH-independent influence to produce cortisol but the majority of cases the ACTH is not suppressed in plasm so I suggest Partial Autonomous cortisol secretion.	
80.	Line 340 I suggest add the refe and comment that PETCT PMAH, a benign adrenal disease, may exhibit an intense 18F-FDG uptake on a PET/CT and should therefore be considered in the differential diagnosis of adrenal lesions with increased 18F-FDG activity, such as carcinomas and metastases. (18)F-FDG-PET/CT imaging of ACTH-independent macronodular adrenocortical hyperplasia (AIMAH) demonstrating increased (18)F-FDG uptake. Alencar GA, Fragoso MC, Yamaga LY, Lerario AM, Mendonca BB.J Clin Endocrinol Metab. 2011 Nov;96(11):3300-1. doi: 10.1210/jc.2011-1397. No abstract available.PMID: 22058378 High 18F-FDG uptake in PMAH correlated with normal expression of Glut1, HK1, HK2, and HK3.Cavalcante IP, Zerbini MC, Alencar GA, Mariani BP, Buchpiguel CA, Almeida MQ, Mendonca BB, Fragoso MC.Acta Radiol. 2015 Mar 11. pii: 0284185115575195. [Epub ahead of print]PMID: 25766729	Since the first publication is only case series of 3 patients and the second is published after our literature search, we cannot add it in the summary of the literature.
81.	Line 936 Figure 2: Assessment and management of 'autonomous cortisol secretion' in patients with adrenal incidentalomas I also suggest to consider the age of patients to indicate surgical proceeds such as: Young before 40 yrs (They will be submitted for long time to partial autonomous cortisol secretion and each case should be analyzed – for indication of surgery Middle age patients 40-65 yrs if the metabolic syndrome is in good control or not Old patients > 65 yrs of age Only observation – except surgical will be indicate only potential malignant nodule and severe metabolic syndrome.	We agree that age is an important variable and include it in the new recommendation R.3.4.
Jens Waldmann		
82.	General comment: Myelolipoma do not require surgery even if size is > 4 cm, because the diagnosis is radiologically 100% certain.	In general we agree. However, sometimes abdominal discomfort, risk of hemorrhage or anxiety of the patients may suggest surgery on an individualized basis. Thus, we are trying to avoid being too dogmatic.
83.	R4.1: what about asymptomatic pheos?? Do not operate on them ??	To avoid further lengthening of the guidelines, we refer to the new ENDO pheo guidelines (Lenders JCEM 2014).
84.	R5.1: Metanalysis in BrJ Surg 2015 Iacobone et al. report a clear benefit of surgical treatment of subclinical Cushing!!	Although this meta-analysis was published after our literature search, we reviewed this manuscript in detail. Careful examination of the data therein reveals large confidence intervals precluding reliance on the data to make

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		strong recommendations. The study from Iacobone 2012 was added to our evidence tables
85.	R6.2.1:why not adrenalectomy in the first place? No harm but potential benefit	Surgery as many other procedures comes always with some risk, although the risk might be very low as in laparascopic procedures.. Therefore, we do not want to suggest surgery for all young patients. Furthermore, we believe the first statements of the sections should give enough guidance.
86.	R6.3.5: Should adrenalectomy not be an option too? (as alternative to biopsy)	We added a statement in the Reasoning of R.6.3.5 and the Legends of Figure 4.
87.	Figure 2: Don't you think there are effects of the Cortisol secretion which cannot be monitored before it harms the patient. Is it not the first duty to prevent the disease rather than to treat it when already symptoms are present? Just a general comment.	Whilst this may be true, it is speculative, and without data to support a recommendation. It highlights the room to address important clinical questions in well-designed studies.
Anne-Paule Gimenez-Roqueplo		
88.	Just on the line ... Congratulations for your gorgeous work. I fully agree with R 3.8. Minor comments: I suggest that you use "hypertension" or "elevated blood pressure" rather than "arterial hypertension" within all the text. Several times, you talk about hypertension without definition. It would be worth adding the current definition of hypertension (blood pressure >= 140/90mmHg) in the text.	Thanks We have now used 'hypertension' throughout the text. However, since there are several slightly different definitions on hypertension are used in the different countries, we abstain from a definition, which would have to been explained.
Maurizio Iacobone		
89.	I would congratulate with you and all the panelists for the terrific effort in preparing these guidelines and for the result: I think that it'll be a cornerstone for clinical practice in the next years. However, I think that some points need to be clarified: 1) On a methodological point of view, literature search has been performed separately for each question (see line 424-426; for some question literature search stopped at July 2014, for other it included more recent papers (and even unpublished paper). Since these guidelines will be published in 2016, and since some relevant article, systematic review and metanalysis have been recently published, my suggestion is to use a more recent deadline in order to allow the inclusion of such papers. I'm sure that it'll not change the final recommendation of the panel, but might increase the evidence for some recommendations. For the same reason I would offer to the panel 2 of my references (a very recent systematic review - 2015 and a 2012 original paper) focusing on the role of adrenalectomy in "subclinical Hypercortisolism", that have not been included and may be of some interest: - Iacobone M, Citton M, Scarpa M, Viel G, Boscaro M, Nitti D. Systematic	Thanks a lot for this very positive feedback. This is an important point of discussion. For a stand-alone review it is a reasonable option to update the search and adapt the paper if necessary. Updating the search and review process for a guideline poses greater hurdles. For guideline panels to come to recommendations it needs a proper systematic review and the panel needs to discuss the results of such a review in a face-to-face meeting. Updating the search would in principle mean to re-open the whole process. We decided not to do this, also because guidelines will not be set in stone, as in a few years we hope to update the guidelines and thus the search. Thanks for pointing to the study form Iacobone 2012. The study was added to our evidence tables as this study was published before the search date.

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90.	2)The Recommendation 3.8 recommend metanephrines measurement unless imaging clearly indicate a adenoma. In my personal opinion, this is based on a very low evidence. Small pheo may sometimes appear as adenoma at unenhanced CT ; in this condition, the lack of metanephrine measurements may lead to miss the diagnosis of pheo; in case of these patients will undergo surgery the consequences may be dangerous and life-treating. Thus, in my opinion Measurements should be systematically performed independently by radiological aspect (consider also that imaging may also be very subjective!)	We agree. Please see our response to comment #65.
91.	3)Finally, just a minor point concerning some typos: in references n° 38, 44, 132 the list of the authors is incorrect or redundant. Here you'll find the correct references 38 - Di Dalmazi G, Vicennati V, Rinaldi E, Morselli-Labate AM, Giampalma E, Mosconi C, Pagotto U, Pasquali R. Progressively increased patterns of subclinical cortisol hypersecretion in adrenal incidentalomas differently predict major metabolic and cardiovascular outcomes: a large crosssectional study. Eur J Endocrinol. 2012 Apr;166(4):669-77. doi: 10.1530/EJE-11-1039. Epub 2012 Jan 20. 44 -Chiodini I, Morelli V, Salcuni AS, Eller-Vainicher C, Torlontano M, Coletti F, Iorio L, Cuttitta A, Ambrosio A, Vicentini L, Pellegrini F, Copetti M, Beck-Peccoz P, Arosio M, Ambrosi B, Trischitta V, Scillitani A. Beneficial metabolic effects of prompt surgical treatment in patients with an adrenal incidentaloma causing biochemical hypercortisolism. Journal of Clinical Endocrinology & Metabolism 2010 95 2736-2745 132 - Di Dalmazi G, Vicennati V, Garelli S, Casadio E, Rinaldi E, Giampalma E, Mosconi C, Golfieri R, Paccapelo A, Pagotto U, Pasquali R. Cardiovascular events and mortality in patients with adrenal incidentalomas that are either non-secreting or associated with intermediate phenotype or subclinical Cushing's syndrome: a 15-year retrospective study. Lancet Diabetes Endocrinol. 2014 May;2(5):396-405. doi: 10.1016/S2213-8587(13)70211-0. Epub 2014 Jan 29.	Thank you for bringing these errors of the reference software to our attention.
Tomáš Zelinka		

92.	I have just only a very short comment to the Adrenal Incidentaloma Guidelines: - line 816-816 - pheochromocytoma is not always a benign tumor and so I would recommend to use for pheochromocytoma "apparently benign"	We agree and have added this.
G. P. Piaditis		
93.	1. Reading the text, the impression I obtained was that cortisol (F) is the important hormone secreted by the incidentalomas and it should be considered as the main hormone responsible for any harmful effect of incidentalomas peripheral tissues. Aldosterone (ALD) secretion has virtually ignored. This probably related to the fact that the autonomous ALD secretion (AAS) incidentalomas, compared to autonomous cortisol secretion (ACS), is considered a rare disorder. However, this is a long lasting misleading impression, which directly related to the inappropriate procedure followed so far for the diagnosis AAS. The LDDST is usually used for the diagnosis of ACS, which is a diagnostic test suppressive of CRH-ACTH-F axis. On the contrary the diagnosis of AAS based on the calculation initially of the basal ALD/RENIN ratio, which is a simple screening test, indicative, non-diagnostic of AAS, and if it is abnormal only the diagnostic of AAS saline loading test is performed, aiming to suppress the Renin Angiotensine-Aldosterone System (RAAS). This process is based on assumption that the basal ALD/RENIN ratio has 100% sensitivity. However, there are strong evidences that this is not true, as recent studies using a diagnostic AAS saline-loading test from the beginning of investigation, not after a screening test, in unselected hypertensive patients with an adrenal incidentaloma reveal that: a. The sensitivity of basal ALD/RENIN ratio is low and therefore AAS remains undiagnosed in a significant number of patients with incidentalomas. The prevalence of AAS in incidentalomas is similar (36%) to ACS, particularly patients with arterial hypertension, much higher than previously believed. 2. The observed AAS in hypertensive patients with an incidentaloma, contrast to cortisol, is positively correlated with systolic/diastolic blood pressure and 24h urinary K^+ concentrations, whereas is negatively correlated with serum K^+ levels. These data suggest that the AAS may be one of the main causes arterial hypertension in patients with incidentalomas. This is further supported the impressive blood pressure response to specific anti-hypertensive treatment with an ALD receptor blocker. These data suggest that ALD secretion incidentalomas is a major harmful factor which cannot be ignored by official guideline. 3. The official guideline recommends the calculation of basal ALD/RENIN ratio for the investigation of ALD secretion in incidentalomas, which however completely inadequate. I think that the use of a diagnostic saline loading test should be performed in those cases where incidentalomas and arterial	Thank you for your interesting comment. However, we suggest that these aspects be considered in the next version of the guidelines, when more groups have confirmed your results.

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hypertension co-exist.

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Gouli, Panagiotis Tsounas, Stelios Fountoulakis, Theodora Kounadi, Vas
Tsiama, Aikaterini Dasou, Alexandros Gryparis, Christianna Samara, Geo
Zografos, Gregory Kaltsas, George Chrousos and George Piaditis. Eur J C
Invest 2014; 44 (8): 697–706

Jeanette Wahlberg (Swedish Society of Endocrinology)	
94.	Two suggestions for consideration from The Swedish Society of Endocrinology 1) According to the suggested guidelines, AI with a diameter of less than 4 cm and HU>10 can be monitored in three ways. If you choose to perform a control based on size we suggest the follow up to be in 6 months and not in 6-12 months since there might be a small risk of malignancy and it is therefore better to find this within 6 rather than 12 months.	See response to comment #64.
95.	2) Regarding the suggested term "autonomous cortisol secretion" instead of the established term "subclinical hypercortisolism" there are in fact some studies suggesting that the cortisol secretion in "subclinical hypercortisolism in fact might be ACTH dependent (Olsen H et al). One might therefore reconsider the use of this term until it is established whether there is ACTH dependence or not.	We agree that there might be patients with 'autonomous cortisol secretion" that is not completely ACTH-independent. See also comment #8.

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	Comments by two reviewers of the American Endocrine Society Reviewer #1 (Tobias Else)	
96.	I truly appreciate the opportunity to review these outstanding guidelines. I particularly appreciate the authors' emphasis on initial work-up with only very selected minimal further follow-up. I also like the clarity in which these guidelines differentiate between hormone excess and malignancy as the major concerns. The authors do a very fine job in addressing the areas of uncertainty with regards to 'subclinical Cushing's '. I feel the differentiation of possible and autonomous cortisol secretion (although I would prefer the term production as there is no active secretion in the common sense involved). The authors make appropriate points about specific patient populations, the young and the elderly. I also feel that the panel did a remarkable job in integrating the little data of evidence and the obvious expert opinions that were present in their discussions. However, I do have some concerns, which are more in the category of opinion rather than evidence, but should be considered when making guidelines regarding a condition that affects a large proportion of the population.	We are very grateful for the very positive judgment and the thoughtful comments thereafter.
97.	A major concern is that after initial imaging (non-con CT) still 30% of lesions (or at least a significant proportion) are indeterminate. Are there any estimates after further work-up (MRI, wash-out) on how many lesions remain indeterminate. Clearly a number as high as 30% for potential surgery asks for more work up and surgery for all lesions would be likely overtreatment on a population basis. In addition the point of 10HU as a cut-off is discussed and described quite extensively.	We share this concern and would have loved to give clear recommendations about a second-line imaging method to determine these indeterminate masses. However, the evidence for washout CT, MRI, or FDG-PET is too weak to allow a strong recommendation. However, in the Reasoning of R.2.4 we clearly express that we are "in favor to fully characterize the adrenal mass on imaging".
98.	However, the second criterion 'homogeneity' needs some more attention. It should be made clear that only homogeneous – not heterogeneous - masses can be evaluated in initial non-con CT and further evaluation by MRI and wash-out. Perhaps an approach to the definition of homogeneous would be appropriate. It is a terribly neglected point even in the major studies. What area should there be measured in an inhomogeneous or heterogeneous lesion?	We completely agree that 'homogeneity' is of major importance. This aspect was or is now mentioned in R2.2., R.2.3, and Table 4. We added now a widely used definition of homogeneity in the legend of Table 4.
99.	I do think there needs to be some mentioning and balance with regards to potential radiation exposure of patients with an adrenal mass in initial, detailed and follow-up work-up (CT & PET). Although this area is a highly speculative issue, on the extreme end of the discussion one might find arguments to not work-up any adrenal masses as the procedures, associated risks and costs might cause more harm on a population basis than benefit by finding the small amount of prevalent cancers and pheochromocytomas. Of course this is an argument that may not be appropriate and certainly is difficult to sustain, when considering the single individual patient in clinic, where physician and patient usually want a definitive diagnosis. A short statement about, what the risks due	We agree that this is an important point, however, the topic of radiation safety seem to be beyond the scope of this guidelines. Nevertheless, we added a short sentence on the risk of radiation in the Reasoning of R.2.2/2.3.

	to radiation are would be great, possibly calling for some caution and greater value in utilizing non-radiation techniques, such as MRI. Even though most studies estimating the radiation risk are extrapolations of non-medical exposures, there is accumulating evidence that calls for caution or at least makes it necessary to mention these concerns.	
100.	A Cochrane analysis to be published by some members of the committee is mentioned several times. As this seems to be an integral part of decision making and a document available to the panel members, this data should be included in more detail – or the publication should be awaited before referring to it in the guideline. The simple mentioning of an unpublished manuscript makes a thorough review difficult for any referee.	See response to comment #55
101.	I would like to emphasize the contentious point regarding homogeneity vs. heterogeneity of lesions. There needs to be some more definition and discussion. For example, it is radiology standard that wash-out criteria cannot be used in cases of heterogeneous masses. This is not reflected in the guidelines. The authors should be clear that every heterogeneous mass (with the exception of probably myelolipoma and some other rare entities) is suspicious and further work-up with MRI or wash-out CT is not helpful. I feel there is a gap when discussing the further work-up of indeterminate masses. I am missing mentioning that further MRI or CT washout evaluation is not useful in inhomogeneous/heterogeneous masses, which automatically fall into the category of indeterminate nodules. It is also interesting that with regards to the differentiation of homogeneous vs. heterogeneous in times of all kinds of measurements conducted on cross-sectional imaging, we still seem to rely on the eye of the beholder (or experienced radiologist). Despite above criticism, I agree with the vast majority of recommendations, feel these are very well presented, thoughtful and practical guidelines. For the majority of points I comment on I would simply recommend a slightly more detailed discussion focusing on some of the concerns.	We agree and added such a statement in the Legends of Table 4.
102.	P2,45 – correct sentence D) – insert 'recommended'	Thanks, we added "indicated".
103.	P7, 228 & Table 1. – The authors must address the reoccurring discrepancy between the incidence of ACC (probably incidence ~ 1/mio & prevalence ~5/1mio) and the study numbers in Table 1. If one assumes even a prevalence of adrenal nodules of 1% and the cited 1-11% ACCs the epidemiological estimates for ACC and the estimates from the cited studies are at least by 10-100 fold different. I am well aware that this is a reoccurring problem in the available literature and seems to be used in whatever way is favorable for individual citations, but at least a mentioning of this discrepancy would be appropriate.	We address this issue now in the legend of Table 1 as indeed many studies do not reflect a random sample of patients with an adrenal incidentalomas.
104.	P7,232 – Even by stating 'the vast majority is benign', in terms of applying	As suggested we added the establishment of the true prevalence of ACC to

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	screening procedures, it is a huge difference, whether we aim to find the 1 in 10, the 1 in a hundred, or the needle in a haystick … . What matters more is the disease of concern (ACC, pheo, malignancy) – the disease to screen for! Therefore I think it would be appropriate to add as a research goal at the end of the guidelines: to establish the true prevalence of ACC amongst incidentalomas. Some less biased studies, such as Song et al. (153) do not find any ACCs in a large number of patients. However, I understand that their follow-up and work-up may not entirely suffice to clearly call a lesion benign or malignant.	the future research goal.
105.	P9,289 – This means that at least 30-40% of lesions will need an additional imaging work-up, which can pose significant procedure associated risk and costs. At least a short note regarding this issue would be helpful to provide a balanced perspective. In addition, it would be great to openly comment on the challenge of further work-up and resulting numbers of indeterminate lesion even when employing additional work-up.	We agree and discuss this problem e.g. in the Reasoning of R 2.4.
106.	P16,431 – I do think it is crucial that the Cochrane manuscript is not only under revision, but actually published. It is difficult to review guidelines that apply very stringent criteria to acceptable studies, but base their conclusions on several occasions on a study/meta-analysis that is not available for the reviewers. It also looks better in the final version, if the guidelines refer to a published and peer-reviewed study.	See comment #55
107.	P16,442-451 This is confusing. If malignant disease is 'disease positive' then true positive is all lesions >10HU, meaning sensitivity would mean all malignant lesions are truly malignant by imaging (and not the sensitivity to identify benign lesions as mentioned in the text). This would have nothing to do with the benign lesions as mentioned in this paragraph. Seems like specificity and sensitivity are interchanged here due to changes in perspectives of presentations – review this. I get the meaning, but it's confusing.	This paragraph has been modified.
108.	P16,453 It would be important to mention that any measurement of HU is truly only applicable to lesions with a certain degree of homogeneity and the panel should make a suggestion for heterogeneous lesions, in which further work-up by MRI or wash-out will not be helpful.	See responses to comments #99 and 102
109.	P16, 454 - 462 – please review if these studies truly used the cut-off of 10HU in truly homogeneous lesions. At least the study by Petersenn et al. analyzes ACCs, which all were inhomogeneous/ heterogeneous and therefore would not qualify for any HU analysis. In the study of Choi et al. only 68% of metastasis were homogeneous and would actually have qualified for further analysis. The Choi et al. study also is restricted to RCC and HCC metastasis, which is a fairly narrow spectrum and at least clear cell RCC is likely an exception as even native renal primary clear cell RCC can present with similar characteristics with	We agree that in an ideal world HU should be measured only in homogeneous lesions. However, if the reader is aware of this issue, even measurement of inhomogeneous lesions might be a value.

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	regards to wash-out (and sometimes even non-contrast) characteristics. The inclusion of this study might lead to an underestimation of the overall value of wash-out studies. Does wash-out perform better for lung cancer, melanoma and breast cancer than for RCC? A short comment on the short-coming of the evidence of all imaging analysis with respect to ACCs is also necessary. Hardly any of the studies included ACCs in large numbers.	
110.	P17,465 – What about the studies Caoili et al Radiology 2002 and Caoili et AJR 2000, which both should qualify for this analysis as well (or at least the follow-up study, which includes the initial 112 pts) – according to the eligibility criteria. Why was Szolar et al Radiology 1998 excluded? I can only imagine that the initial scan modality was not mentioned. However, that should be a secondary criteria as both studies evaluate washout criteria in adrenal incidentalomas.	We have had to exclude a lot of studies mainly due to failure to clearly define their population and due to unacceptable reference standard (histology in malignant tumors, appropriate imaging follow up or histology in benign adrenal tumors). For more information, please refer to the meta-analysis.
111.	P18, 501-516 – It's of course always fairly contentious to suggest one's own publications (which I will do twice in this review and I apologize for that), but I would like to mention the study by Williams et al EJE 2014 as this study reports the diagnostic performance of sensitivity separately (other than mentioned in the paragraph 'None of the studies reported diagnostic performance of adrenal biopsy in adrenocortical carcinoma separately from other malignancies'. Of course this study only looks at ACCs that had a biopsy and that is of course a shortfall.). The main message of this study is that adrenal biopsy specimen most often can be classified as adrenal cell specimen, but are often difficult to be classified as benign or malignant (which is also the main reasoning on P48,1434) as even adenomas show a significant degree of pleomorphism and other features that might predict malignancies in other tissues, but not the adrenal gland.	We now refer to this study.
112.	P18, 519-530 It is certainly a challenge to identify studies based on the same criteria, which ideally should be the same ones as later used in the recommendations (profile 3). However, the identification of studies using very different criteria (all of which are somewhat suggestive of hypercortisolism), is concerning, particularly when later defining cut-offs and making recommendations based on these different studies. As I actually think the panel does the right thing, it would be helpful to add some criticism and concerns to this.	Thanks for this positive judgment.
113.	P21,620-633. This is the second incidence of mentioning one of our own studies: In Else et al. JCEM 2014 we report a difference in overall survival (but not recurrence free survival) with a significant increased HR for death in the laparoscopic group of 1.6 in ~230 evaluable patients in multivariable analysis. This study might not have qualified for other reasons, just felt it is worthwhile mentioning. I think a simple practical mentioning of the greater the lesion, the	Your study was not included, because the patient characteristics of this particular subgroup were not clearly available and many patients were most likely reported in the two studies by Miller et al..

	more likely an ACC and the safer an open approach might be helpful. Of course the true challenge is not the decision for surgical approach for a known ACC, but the vast amount of overtreatment, when approaching all larger masses (which clearly are not all ACC) with open surgery.	
114.	P23,688 correct to 'follow up for cancer'	Thanks.
115.	P26, 748 Homogeneous is a contentious term. If there is a definition, please provide. If homogeneity is what homogeneity is in the eye of a trained radiologist this should be mentioned and defined as such.	See comments #99 and 101.
116.	P26, 766 correct 'as malignant'	Thanks you.
117.	P27, 793 This is another place where I wonder what the committee suggests with inhomogeneous/ heterogeneous masses, which per definition are indeterminate. This is an important point to address. I do think this is also the place, where some concern with regards to radiation exposure might be warranted, which would be another argument for MRI. I do think it would be concerning to consider wash-out or FDG-PET for up to the 30% of all incidentalomas that are indeterminate when considering estimates of 1 in 1000 CT scans causing a fatal cancer. I am not trying to argue against any of the recommendations, I simply think this concern has to be mentioned. A practical example – in application of the guidelines, what would be the next step for a heterogeneous lesion of 3cm (with HU majority of 9HU, but areas of 2HU and areas of 40HU)? I doubt the right answer would be MRI or washout CT, which are only helpful in homogeneous lesions. I guess follow-up, surgery or PET would be viable options – although none is perfect.	And to your example: The decision on such a lesion can only be made in the context of this patient (age, co-morbidity, patients preference etc.), and repeat follow up imaging if appropriate.
118.	P29, 857 … risk of tumor dissemination … I agree that this is a risk, but really only a theoretical one. It truly has to my knowledge only been described in 1 case of ACC, which was a patient with a transhepatic approach, which likely has a much higher seeding potential – this patient was actually cured after surgery for the track metastasis. All other reports are about metastatic lesions, where even tumor spread does not alter stage and in which the adrenal gland might not have been the best place for biopsy to begin with	We agree and add now your reference Williams et al.
119.	P30,870 correct … rapidly developing …	Modified as suggested.
120.	P31,912 correct – delete was	Thank you - changed.
121.	P34,999-1022. I think it would be worthwhile to mention 'patient preference' in this paragraph as an influencing factor. I don't see patient preference mentioned anywhere, but taken that all evidence is x0000 or xx000 a patient opinion is a considerable factor.	We fully agree and we refer to 'patient preference' as important factor several times (e.g. Abstract, R.3.8, R.6.1.4)
122.	P34,1028-1034. The cited study (170) only holds ~2/21 pts with completely normal metanephrines/ catecholamines – that would make 10% rather than 25%. Normotensive pheochromocytomas may be clinically silent, but not biochemically silent – most tumors in (170,171) had biochemical metanephrine	We have shortened this section, but we still mention that normotensive pheo might lead to trouble during surgery.

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	or normetanephrine production, simply no hypertension. I think it is important to point out that for patients with incidentalomas that have imaging characteristics of a pheochromocytoma any elevation of metanephrines is concerning (no usual rule of 2 or 4 fold – too high of a pretest probability). However, it is probably ok to not assume a pheochromocytoma in patients with completely normal metanephrines – otherwise we would have to block everybody with anything that could be a pheochromocytoma that does not produce metanephrines. But probably a;; patients with any metanephrine elevation should be considered for further presurgical work-up or blockade.	
123.	P34,1037-1041 – What about hypokalemia? I would suggest to consider aldo/renin also in patients with hypokalemia.	We agree, and have added hypokalemia.
124.	P35,1058 I would consider adding the citation of Kerkhofs et al Hormones & Cancer 2015	Done.
125.	P37, 1107-1138 Is there value in suggesting a resection of large adrenal masses by an experienced endocrine/adrenal surgeon?	We agree and add such a statement now to the Reasoning to R.4.3-5.
126.	P41, 1203-1206. In both studies (179,180) probably less than 50% of tumors would have shown growth over the course of 6-12 months. These studies are the only studies evaluating the growth of lesions prior to the diagnosis of ACC. It would be great if there was evidence suggesting that ACCs 'usually grow very fast', however I do not think there is any published evidence, particularly for the early stages. Both studies included all patients identifiable with a prior adrenal lesion in two large cohorts. I think the panel's argument is very acceptable, when talking about large lesions, but both studies included fairly small lesion preceding the diagnosis of ACC, most of them with indeterminate characteristics. I do think a recommendation for repeat imaging and follow-up should be more detailed. My take would be the following: We decided on the recommendation of 6-12 months despite published evidence that this will likely miss a considerable amount of ACCs weighing overall benefit (diagnosis of ACC) against risks (XRT induced cancers) and costs. Otherwise – what would is the support for the panel's recommendation of the 6-12 month recommendation?	We are pleased with your assessment which is completely in line with our own. We have clarified further the procedure during follow-up in Reasoning to R.5.2.
127.	P43,1274-1289. It might be worthwhile to suggest measuring 17OHP in the morning.	We agree that this would be ideal. However, in CAH or ACC, 17OH progesterone is usually highly elevated (beyond any diurnal rhythm).
128.	P45,1328. The panel states to consider ARMC5 testing – what does that provide for further clinical care? As there is currently no consensus or benefit for a patient that is ARMC5 positive vs. negative nor is there a real established advantage for prospective surveillance of ARMC5 mutation carriers, I would abstain from suggesting any genetic testing. If kept, I would recommend adding a sentence, that genetic testing should only be conducted after careful genetic counseling. However, the panel never mentions that genetic testing for	Thanks for these kind words. We agree with you and have deleted the genetic testing comment in this context.

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	patients with pheochromocytoma should be recommended, where it is much more important. I would suggest staying away from any genetic recommendation. The guidelines are great in keeping their topic focused (not like a lot of other guidelines that overstep their territory). Therefore I would keep the guidelines as beautiful as they are and keep the genetics aspect out of it.	
Comments by two reviewers of the American Endocrine Society Reviewer #2		
129.	Overall, it looks well done with very good table and figure illustrations that are important for readers and clinicians. Well, in general, I think the Adrenal Incidentaloma guideline is well written. There are a few typographical errors I will not comment on. Comment 1: page 34: in addition to reference 170 and 171 regarding "normotensive" pheochromocytoma, I suggest to also consider these references, acknowledging that "small" (< 1 cm size) pheochromoctyomas and those in hereditary syndromes such as von Hippel Lindau syndrome, may not "oversecrete" (cutoff threshold for plasma free metanephrines) 1. Walther, M.M., R. Reiter, H.R. Keiser, P.L. Choyke, D. Venzon, K. Hurley, J.R. Gnarra, J.C. Reynolds, G.M. Glenn, B. Zbar, and W.M. Linehan, *Clinical and genetic characterization of pheochromocytoma in von Hippel-Lindau families: comparison with sporadic pheochromocytoma gives insight into natural history of pheochromocytoma.* J Urol, 1999. 162(3 Pt 1): p. 659-64. [PubMed: 10458336] 2. Weisbrod, A.B., M. Kitano, K. Gesuwan, C. Millo, P. Herscovitch, N. Nilubol, W.M. Linehan, and E. Kebebew, *Clinical utility of functional imaging with 18F-FDOPA in Von Hippel-Lindau syndrome.* J Clin Endocrinol Metab, 2012. 97(4): p. E613-7. [PMC free article: PMC3319180] [PubMed: 22259055] 3. Kudva, Y.C., W.F. Young, G.B. Thompson, and e. al., *Adrenal incidentaloma: an important component of the clinical presentation spectrum of benign sporadic adrenal pheochromocytoma.* Endocrinologist, 1999. 9: p. 77-81. 4. Motta-Ramirez, G.A., E.M. Remer, B.R. Herts, I.S. Gill, and A.H. Hamrahian, *Comparison of CT findings in symptomatic and incidentally discovered pheochromocytomas.* AJR Am J Roentgenol, 2005. 185(3): p. 684-8	We are thankful for this very positive statement. However, we believe that the scenario in patients with known genetically driven disease is quite different from adrenal incidentaloma.

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130.	Comment 2: Page 28/29: "…..There are no published size or volume cutoffs commonly agreed or with evidence base to support that they indicate growth suggestive of malignancy; the expert panel agreed that an increase in > 20% of the largest tumor diameter together with an at least 5 mm increase in this diameter should be considered as suspicious." I suggest to include this interesting recent study, although it is done by a very skilled ultrasonographer (and not imaging by CT or MRI): Ultraschall Med. 2015 Nov 3. [Epub ahead of print] Adrenal Incidentaloma and Subclinical Cushing's Syndrome: A Longitudinal Follow-Up Study by Endoscopic Ultrasound. Collienne M[1], Timmesfeld N[2], Bergmann SR[1], Goebel J[1], Kann PH[1]. Abstract Purpose: Adrenal incidentaloma (AI) and adrenal masses in cases of subclinical Cushing's syndrome (SCS) initially require follow-up imaging. In this study we used endoscopic ultrasound (EUS) as a method for high-resolution imaging. The aim was to evaluate the growth rate of AI and SCS by EUS. Materials and Methods: This retrospective analysis included 93 out of 229 patients with AI or SCS who were investigated longitudinally by EUS in our university hospital between 1997 and 2013. The longitudinal follow-up required at least two investigations by EUS and evaluation of endocrine function. Plasma renin, serum aldosterone, 24 h urinary catecholamines and 2 mg dexamethasone suppression test were performed. EUS was performed at baseline and during follow-up. Each time, the maximum diameter was measured. Three groups were defined: non-functioning adenomas (NFA), non-functioning nodular hyperplasias (NFH) and SCS. Results: 86 patients had non-functioning masses [NFM] (59 NFA, 48 NFH) and 7 patients had SCS (10 masses). At baseline the mean diameter was 19.4 (±9.3) mm (NFM) and 19.6 (±9.2) mm (SCS). The mean follow-up period was 31.6±28.7 months. The estimated mean growth rates per year were low: They were 0.35 mm/yr [NFA], 0.02 mm/yr [NFH] and 0.53 mm/yr [SCS]. Furthermore, there was no malignant progression of any mass. Conclusion: The growth rate as determined by EUS was low for all tumor entities observed in this study. There was no difference in tumor growth between the groups.	Thanks for bringing this interesting and very recent study to our attention. However, since endoscopic ultrasound is not widely available and the number of patients is limited, we decided not to cite this paper.
Hadas Globerman (on behalf of the Israel Endocrine Society)		
131.	My comments are based on the panel's analysis. I didn't read the references. As the authors themselves state, the quality of the evidence is very low/low grade. In addition, some of the evidence is unpublished, i.e., "under submission". Thus, the recommendations and suggestions are not well-based.	Thank you for these comments. We do not agree, however, that our guideline is in contrast to the Endocrine Society guidelines on the diagnosis of Cushing's syndrome, because those guidelines explicitly mention that the recommended cutoff of the overnight

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	However, analysis of the literature is of value, especially if it will be used to set up prospective multicenter studies. Specific comments: Some recommendations may contradict the Endocrine Society Guideline on the diagnosis of Cushing's syndrome. According to the ESE Guideline, after an overnight 1 mg dexamethasone suppression test, a cortisol level of 50-141 nmol/L, for example, should be followed only, whereas, according to The Endocrine Society Guideline, the result would count as 1 of 2 abnormal tests diagnostic of Cushing's syndrome, a condition which requires treatment. The problem with the ESE recommendation is that in certain circumstances, one may miss a diagnosis of Cushing's syndrome including from etiologies other than a secreting adrenal incidentaloma, e.g., the patient may have Cushing's disease which may be missed and a non-secreting adrenal incidentaloma . The ESE guideline recommends ruling out ACTH- dependency only before adrenal surgery. I think this needs to be ruled out in all cases of abnormal dexamethasone suppression.	1mg dex test might be not applicable to patients with adrenal incidentaloma. Moreover, the pre-test likelihood when testing for Cushing (you only do so in patients with clinical suspicion) is different from the pre-test likelihood in the context of an adrenal incidentaloma.
132.	"Subclinical" Cushing's is sometimes due to cyclical cortisol secretion, and this may be missed with a one-time dexamethasone suppression test. It may be diagnosed on a repeat dexamethasone suppression test or a 24-hour urinary free cortisol.	The prevalence of cyclic "subclinical Cushing" is not really investigated and, therefore, we would like to abstain from recommendation to screen for it in an incidentaloma population.
133.	In several cases, important points mentioned in the "reasoning" paragraph are not reflected in the recommendation itself. For example, the recommendation mentions "benign" imaging, whereas I think it would be better to specify that the term "benign" is used to mean that on adrenal CT the attenuation of all the lesion is ≤10 HU.	We agree and have modified this suggestion (e.g. R.2.3.)
134.	Where the evidence is very low/low grade (e.g., establishing "benign" based on an adrenal CT), I think it would be better to err on the side of over-testing rather than under-testing, e.g., repeat imaging at least once after the initial "benign" CT. Also, if the lesion is ≥4 cm, additional follow-up imaging may be appropriate. Other examples are: for "indeterminate" incidentaloma, (6-) 12 months until repeat imaging, seems too long an interval, and additional imaging may be appropriate.	Thank you for this comment, but we do not completely agree. As discussed in our response to the comments # 4 and 25 we are confident that a homogenous lesion < 4cm with "benign" radiological features is really benign. Thus, we prefer to stick with the arbitrary cutoff of 4cm for homogenous, lipid-rich lesions, because we believe that too much follow-up imaging does more harm (psychologically, financially and due to radiation exposure) than benefit. In line with your view, for the lesions > 4cm we recommend additional follow-up, but we conclude that the interval of 6 to 12 months is most adequate. See also response to comment #64 and #126.
135.	I think the panel should reconsider recommendations that are not evidence-based, e.g., discuss in a multidisciplinary team, or where evidence is very low/low grade, e.g., recommendation against resection of "benign" non-functioning adrenal mass (of unspecified size).	We are convinced that such a guideline has to provide guidance especially in situations in which no results from good studies are available. In this context, an expert opinion is not "not-evidence-based".
136.	When stating "biopsy", I think the type of biopsy should be specified – e.g.,	Techniques, and routes of adrenal biopsy vary (percutaneous, ultrasound

	needle aspiration for cytology.	guided, core, FNA). We have tried to communicate this issue in the sentence: "Studies had variable population inclusion criteria, reference standards and biopsy techniques." Data are quite poor overall and it is difficult to discern outcomes based on technique. Given a huge variability in above, we have decided not to go in much more detail than already described in the text.
137.	"Overt" Cushing's should be defined.	Due to space restrictions we prefer to refer to the 'Cushing guidelines".
138.	If, as the authors state, there is no evidence that a growth velocity of 5 mm in 6-12 months distinguishes benign from malignant, I think the panel should reconsider if these numbers should be included in a recommendation (or only mentioned in the "reasoning").	We did not state that there is no evidence. There is indeed no published evidence, however, our clinical experience says that a tumor with no growth in 6-12 months is extremely unlikely a malignant tumor.
139.	In page 26 line 763, I think it should state False Negative and not False Positive.	With the systematic review in press, we refer to the manuscript. This allowed us to significantly shorten the text.
140.	Regarding indications for surgery, the authors might consider addressing the question of incidentaloma size and risk of bleed.	We agree that tumor size might correlate with the risk of intraoperative bleeding. Thus, we strongly suggest that larger tumors should be removed in expert centers.
141.	Some of the recommendations are vague, e.g., "sex hormones and steroid precursors" (figure 1, page 25).	We agree that a figure is only a short summary. However, in the Reasoning of R.3.11 we clearly specify which sex hormones and precursors we recommend to measure.
142.	I think editing and proof-reading the manuscript would be of benefit.	Thank you.
Alicja Hubalewska-Dydejczyk		
143.	The guideline is perfectly prepared. Congratulation for this great work! Small remarks: The exact place of Contrast-enhanced washout CT in diagnostic pathway is not clearly explained	Thanks a lot for this positive appraisal. We have now modified the section on 'second-line imaging'.
144.	In section describing the PET/CT it could be added: "18F-2-deoxy-D-glucose (FDG-PET/CT or FDG-PET/MR" and "mostly combined with CT" could be removed ; - line 279	We have added this.
145.	In case of non-functioning begin lesion < 4 cm (adenoma, lipoma etc…) ultrasound examination 1 year and/or 5 years after the first evaluation could be considered.	As pointed out to comment #64, we do not want to recommend regular imaging follow-up for obviously benign lesions. Ultrasound has the advantage of lack of radiation and is relative cheap, however, it is quite dependent on the operator's experience and patient's body composition.
Marcus Quinkler (on behalf of the German Society of Endocrinology)		
146.	- R4.1 and R4.2: Due to the fact that an increasing number of surgeons is performing adrenal sparing surgery, the expert group should comment on this procedure for these specific points	We agree that this is an increasingly debated topic. However, it is almost exclusively a topic for pheos and maybe aldosterone producing adenoma. Thus, this is clearly beyond the focus of our guidelines.
147.	- R5.2: The sentence "We suggest surgical resection…. (in addition to at	We have now clarified this section and provide clear suggestions what to do

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	least a 5mm increase in maximum diameter)…" is not clear enough. Does it mean increase by at least 5mm or 20% ? Please clarify. The whole subject is unclear: In the case that after 6 months an adrenal lesions shows a growth of 18% (eg 40mm to 47mm) – the expert panel would recommend that this is enough and the lesion should not be investigated again. This is a recommendation without any evidence and might oversee slow growing malignant tumours. A further suggestion might be: if growth is 10% or lower in 6-12 months, then no follow-up investigation; if growth is 10-20% in 6-12 months - an additional CT or MRI should be done after another 6-12 months.	with lesions that grow slightly.
148.	- The experience of diverging qualities of pathological reports on adrenal tumour specimen raises the question if it would be helpful that the expert panel gives a recommendation which aspects/parameters should be mentioned *at least* in a pathological report regarding an adrenal tumour. This could be done as table format.	We see your point. However, detailed recommendations on pathology are beyond the scope of these guidelines. However, we have now included a short statement in the Reasoning to R.1.1.
Krystallenia Alexandraki		
149.	Dear panel, thank you for this great job please find below some comments lines 152-154; since we do not offer any follow-up in patients with an adrenal incidentaloma (AI) less than 4cm, how can we know whether new clinical signs of endocrine activity appear or a worsening of comorbidities?	Thanks for your positive feedback. The available literature (although limited) suggests that the likelihood that new clinical symptoms appear is very low and does not justify annual follow-up.
150.	line 451; please add a dot at the end of the sentence.	Thanks.
151.	lines 1087-1088; since we admit that the cutoff of 4cm is arbitrary, how can we ask from the patients not to follow-up an adrenal lesion of 3,5cm and to follow-up one of 4,5cm?	Guidelines are not law and every physician can decide with the patient an individualized approach. However, we would like to give guidance and feel that we have provided reasonable recommendations. In line, the terminology is in line with the weak evidence as we mostly use 'suggest' and not 'recommend'.
152.	1203-1205; may be it would be safer to accept this risk only after the large population multicenter study that the panel suggested at the end of the guidelines.	We see your point, however, as pointed out in our response to comment #4 follow-up imaging comes also with a downside.
Pia Burman		
153.	This will be very useful guideline, congratulations! Some quick questions; - In many hospitals a new CT scan is performed also in clearly "lipid-rich"	Thanks you for your comments. Obvious adenomas require probably no follow-up imaging. However, many

	adenomas if the size is above 4 cm, but this is something that you do not support? If so, maybe this could be mentioned??	patients with adrenal incidentalomas > 4 cm have undergone adrenalectomy in the past and the literature on follow-up of non-operated large adrenal incidentalomas is scarce. Thus, one follow-up imaging after 6-12 months might be reasonable (see also Reasoning to R.5.1).
154.	- In my hospital some colleagues do a 2-day dexamethasone test if the overnight test is not normal, is this really helpful from a clinical point of view?	We have addressed this important issue of additional testing now in a separate recommendation R.3.4.
155.	- In lipid-rich rich adenomas, do metanephrines have to be checked at all?	See response to comment #50.
156.	- Recently Roche modified their serum cortisol assay that measures now 20% less than it used to be. How does this affect your proposed cutoffs?	This is indeed a very important point. However, we believe that this is beyond the scope of these guidelines and we prefer just to keep our general word of caution (see section 2.4).
Felix Beuschlein		
157.	Big opus Page 34 post-dex cutoff is given in µg/dl (<5) and once in nmol/l (<140). This should be standardized	Thanks you for your comments. We have now standardized and provide both units.
158.	Autonomous cortisol secretion is always in quotation marks. I would suggest to introduce the term once and then use without quotation mark. It looks a little bit you do not believe in your own terminology. Believe in yourselves :)	We discussed this issue internally and believe that by using quotations marks this term is easier to recognize and, therefore, kept these.
159.		
Rossella Libe		
160.	Thank you very much for this interesting document. Please see below my comment. Could you cited the following paper on CT density? Chambre C1, McMurray E1, Baudry C1, Lataud M1, Guignat L2, Gaujoux S1, Lahlou N1, Guibourdenche J1, Tissier F1, Sibony M1, Dousset B1, Bertagna X1, Bertherat J1, Legmann P1, Groussin L1"The 10 Hounsfield units unenhanced computed tomography attenuation threshold does not apply to cortisol secreting adrenocortical adenomas." Eur J Endocrinol. 2015 Sep;173(3):325-32. doi: 10.1530/EJE-15-0036.	Unfortunately, this paper was published after the time we stopped our analysis. As it did not change the recommendations nor the reasoning we decided not to included it, because then we would have to fulfill all requests for citations.
Peter Guest		
161.	A labour of love! Very good. 2 comments – 1. shame the panel can't decide whether to recommend 6 or 12 month follow-up – obviously depends on the level of concern but this is not defined – size? Heterogeneity age? Actual HU? Obviously no evidence but expert guidance would have been good	Thanks for your positive judgement. We agree that this would be desirable. We believe that we cannot recommend a definitive time, because the scenarios might be too heterogeneously. Thus, we favor an individualized approach, but we agree that we should provide some more guidance in the Rational; e.g. "…The exact timing of this imaging should be individualized. However, especially in cases with a low likelihood of a malignant tumor the panel favors a time interval of 12 months."
162.	2.Section 2.3 – make in clear in para 2 sentence 3 that the density suggesting malignancy is <10HU not just 10. Sentence 4 is clear.	Thanks, we have adapted this.

N.N. Patient representative from the German ACC patient group		
163.	R*ecommend and suggest are only 2 categories of the «advice» whereas th quality of evidence has 4 categories*	We decided right from the beginning that we follow the GRADE system (as most other clinical guidelines do) and GRADE uses these categories. The reason behind the apparent discrepancy between the number of quality categories and the two categories of advice is that there is no direct translation from evidence to advice. For advice many additional considerations come into play (costs, side-effects, value of the endpoints studied, preferences), not only evidence.
164.	R.2.3 Any follow up? Hardly recommended	Yes, you are right, in the group of benign tumors <4cm we recommend against follow-up imaging. See also our responses to comments #4 and 25.
165.	R.2.4 I 'm missing a step by step solution. What about: 1st clarify malignancy by additional imaging. Depending on the results interval imaging or surgery	We discussed this issue a lot, but the evidence for one of these approaches (including additional imaging) is just too weak to allow a clear step by step solution.
166.	1mg overnight dexamethasone test or overnight 1mg dexamethasone test - Be consistent.	We now use '1-mg ON dexamethasone test' throughout the text.
167.	R.3.11 replace 'suggest' with 'recommend' Due to the high levels of sex hormones (testosterone) ACC was finally discovered in several patients (not statistical evidence, only personal experience from patients' fori). This is a very helpfully tool specially by/for women for the diagnosis «adrenocortical carcinoma» See recommendation in page 31. there you recommend, what is of common sense . «R.3.1 We recommend that every patient with an adrenal incidentaloma should undergo careful assessment including clinical examination for symptoms and signs of adrenal hormone excess.»	As pointed out in R.3.1 in every patient careful clinical assessment for hormone excess (including androgen excess) is required. However, we decided against the measurement of sex hormones in all patients with incidentaloma.
168.	R.5.3. instead of annual follow-up, use 6-12 months	We discussed this again, but believe that 'annual' is for the majority of patients the most suitable time interval. Of course, every physician can decide to do this re-assessment for cortisol excess earlier.
169.	R.6.2.3: What is "poor general health" or "high degree of frailty"?	We agree that this terminology is vague. However, it is beyond the aim of this guideline to provide an exact definition.
170.	R.6.3.2 Don't agree. How unspecific is a PET/CT? even when combining the two techniques - you only know that something is there, but not what that really is!	A negative FDG-PET has a high predictive value that the lesion is benign. Thus, we feel comfortable to skip additional imaging in this particular case.
171.	Section 2.3. I would like to add something like: Other imaging techniques under investigation/ development have been not considered.	We added now a sentence at the end of section 2.3.
172.	Section 4.1. "102 lesions" or "102 patients"	We clarified this now.
173.	Section 4.1. outcome - change in biochemical profile - what is the median duration of the follow-up of these three studies?	This information is now provided
174.	Section 4.3. " Only three studies reported on the subgroups of patients in	We have clarified this sentence.

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	whom complete resection of the tumor was achieved (138, 140, 144)" - of how many subgroups?	
175.	Section 4.3 - recurrence-free and overall survival- what was the range of survival time?	PFS and OS varied between the different studies. More details will be given in the Appendix.
176.	R.1.1 Reasoning - "standardized pathology report is VERY highly recommended".	We agree that this is important. However, "highly recommended" is already a very strong statement.
177.	Reasoning R.2.3. replace "recommend that additional imaging is not necessary..." by suggest. What about the possibility of a false negative? Is the financial burden for the health system more important than a human? The text is very subtle, in that way that the freedom of a physician to CAN DECIDE is going los/killed, with a hidden strong recommendation.!	As discussed above it is not only the costs for the health system, but also the psychological burden of the patient and the risk of secondary malignancies by additional radiation by additional imaging procedures. See for instance the concern of one reviewer (see comment #100).
178.	R.2.4 - Why imaging interval not already at 3 months?	See our response to comment #64
179.	R.4.3 Reasoning add "high" before expertise.	Done.
180.	R.4.3 Reasoning: Skip " Although we cannot provide a specific number of required operations per year, we have no doubts that surgical volume correlates with better outcome", because numbers make never sense.	We do not agree, because expertise is a matter of experience and therefore "numbers" (although this is certainly not everything.)
181.	R.4.6 Reasoning: Please EMPHASIZE the need of OH-Cortison after removal of the tumor mass.	We are convinced that the recommendation R.4.6. is by itself already quite strong.
182.	Reasoning R.5.2. "..by an increase of 20% of the largest diameter" In which frame of time?	We suggest using the recommended 6-12 months interval.
183.	R.6.2.1 "adults < 40 years" Was not 45 yr the average? And especially female	We discussed this cutoff a lot and agree that 40 years is completely arbitrary - as 45 years would be.
N.N. Patient representative from the German patient group for pituitary and adrenal disease		
184.	From a patient perspective there are no comments and I do completely agree with the guidelines. We hope that from now patients will be treated according these recommendations.	Thanks a lot for your positive feedback.

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