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Incidental Adrenal Masses: Adherence to Guidelines and Methods to Improve Initial Follow-Up, A Systematic Review

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ABSTRACT

Objective: Incidental adrenal masses (IAMs) are detected in approximately 1%-2% of abdominal computed tomography (CT) scans. Recent estimates suggest that more than 70-million relevant CT scans are performed annually in the United States; thus, IAMs represent a significant clinical entity. Most clinical guidelines recommend an initial follow-up evaluation that includes imaging and biochemical testing after index IAM detection.

Methods: Systematic review of literature in the PubMed, EMBASE and Web of Science databases to determine whether guidelines regarding IAM evaluation are followed and to identify effective management strategies. Our initial search was in January 2018 and updated in November, 2019.

Results: 31 studies met inclusion criteria. In most institutions, only a minority of patients with IAMs undergo initial follow-up imaging (median 34%, IQR 20%-50%) or biochemical testing (median 18%, IQR 15%-28%). 2 interventions shown to improve IAM evaluation are IAM-specific recommendations in radiology reports and dedicated multi-disciplinary teams. Interventions focused solely on alerting the ordering clinician or primary care provider to the presence of an IAM have not demonstrated effectiveness. Patients who are referred to an endocrinologist are more likely to have a complete IAM evaluation, but few are referred. **Discussion:** Most patients with an IAM do not have an initial evaluation. The radiology report has been identified as a key component in determining whether IAMs are evaluated appropriately. Care teams dedicated to management of incidental radiographic findings also improve IAM follow-up. Although the evidence base is sparse, these interventions may be a starting point for further inquiry into optimizing care in this common clinical scenario.

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Introduction

In 2017, 74 million computed tomography (CT) scans were performed in the United States.¹ Detection of so-called “incidental” findings, including incidental adrenal masses (IAMs), is increasing.² Reported prevalence varies greatly, likely due to differences in study design, population studied, number of patients included, and inclusion/exclusion criteria, but is likely <1%-2% and increases with age; some studies suggest that as many as 10% of patients over 65 years who undergo abdominal imaging will have an IAM.³⁻⁶ Benign cortical adenomas are the most common (71%-87%), but even some of these are biochemically active and cause disease.^{7,8} Proportions of high-acuity lesions such as pheochromocytomas and adrenocortical carcinoma (ACC) are low but also vary widely depending on characteristics of the population under study, ranging from 4%-8%^{3,9} and 1.4%-10%,^{3,4,5,7} respectively. Thus, while non-functional adenomas are most common, the chance of discovering a clinically meaningful entity among IAMs evaluated in clinical practice appears to be approximately 25%.

Incidental imaging findings often present dilemmas for clinicians. It may be difficult to determine the nature or clinical relevance of an incidental finding, and initiating an evaluation may lead both clinician and patient down a confusing, anxiety-provoking, and ultimately clinically irrelevant pathway. Further, patients and the healthcare system may be exposed to unnecessary diagnostic investigations, treatments, and costs. On the other hand, failing to perform a recommended evaluation can lead to devastating consequences such as a missed opportunity for early detection of a malignancy.¹⁰

In 2002, the National Institutes of Health published the first consensus guidelines regarding evaluation of IAMs.¹¹ Since then, multiple professional groups have published management algorithms.^{2,11-14} Although IAM guidelines have evolved from 2002 until today, most IAMs are recommended to undergo an initial evaluation. Common objectives among guidelines are to determine [1] whether an IAM is malignant or benign, [2] whether it is hormonally active, and [3] whether specialized clinicians are needed. There is evidence that these established guidelines are effective at identifying patients with clinically meaningful lesions,¹⁵ that they are cost effective,¹⁶ and that adherence reduces missed opportunities for timely diagnosis.¹⁷ Because adherence to these guidelines and mechanisms that promote adherence are poorly understood, this systematic review was designed to accomplish the following two aims:

- review studies of adherence to guidelines for IAM evaluation;
- review mechanisms to promote evaluation and clinical management of IAMs.

Methods

This review was conducted in accordance with the PRISMA guidelines¹⁸ and was designed to [1] identify all studies of

guidelines-adherence in the management of IAMs and [2] to catalogue published interventions designed to improve the rate of appropriate IAM evaluation. Numerous guidelines have been published after the initial NIH guidelines in 2002, and there are differences among them; however, common to all, is recommendation for appropriate imaging follow-up (either interval or right away if the original study is indeterminate) and biochemical evaluation, depending to some degree on patient and lesion characteristics. Therefore, for the purposes of this study, we defined “adherence” as imaging follow-up and at least some biochemical testing. A literature search was developed with the assistance of a research librarian and was performed for all articles using the PubMed, EMBASE, and Web of Science databases in January 2018. Complete search terms are listed in Supplemental Appendix 1. All results were screened, using Covidence (Veritas Health Innovation Ltd., Melbourne, Australia) by TF and FTD. Disagreements were settled via primary reviewer consensus. Inclusion criteria included articles in English published from 2000 through 2019 that covered either adherence to contemporaneous IAM diagnostic guidelines or that specifically reported the tracking and accounting of IAMs. Conference abstracts without terminal publication were considered. Our search was updated on November 4, 2019 using the same terms and databases as in the initial search.

To assess for risk of bias, articles evaluating adherence to guidelines were evaluated using the JBI Methodologic guidance for observational epidemiology.¹⁹ Articles addressing management strategies with prediction models were evaluated using PROBAST.²⁰ All other IAM management studies were evaluated via the ROBINS-I scale²¹. Among IAM management studies, reported outcomes were too heterogeneous to combine results into a meta-analysis.

Consistent with our 2 objectives, the results are presented in 2 parts. Part I covers adherence to guidelines (defined above) and is divided into studies that report rates of dedicated adrenal imaging, studies that report biochemical testing, and factors detected in observational research that are associated with improved IAM evaluation. Part II covers management strategies for IAM evaluation, and is divided into four sections based on the broad categories of strategies revealed by our review.

Results

We screened 4,949 total studies. Nineteen studies pertaining to adherence and 14 studies pertaining to strategies for improvement met inclusion criteria. Two studies overlapped into both categories, which is noted in Supplemental Table 1. Ten studies are reported in abstract form only. [Figure 1](#) is the PRISMA diagram. Supplemental Table 1 summarizes all studies included in this review, including citation, year, setting, size, main findings, and for IAM management studies, the intervention under study. [Table 1](#) highlights seven studies cited based on the authors' assessment of high quality or relevance. Supplemental Table 2 reports the bias assessment. Most studies were judged to have a high risk of bias (17 of 31 studies).

Table 1 – A selection of seven papers the authors felt provided especially current, reliable, and useful information from our review of the literature.

Author	Design	N	Setting	Why included in Review?	What it showed	Why Selected?
Becker et al. (2018) ³⁴	Retrospective	209	Single center 2011-2014	Study of guidelines adherence and factors associated with adherence	18% had hormonal evaluation, 25% had imaging follow-up. Radiology report recommendations and specialist referral associated with increased biochemical follow-up	Data on both adherence and factors that impact follow up. Spans relatively long timeframe and includes moderate number of patients.
Maher et al. (2018) ⁴⁰	Retrospective	804	Single center study (5 years)	Study of guidelines adherence and factors associated with adherence	30% of patients received aggregate follow-up. Age, larger tumor size, management by the trauma team, and whether the reporting radiologist recommended imaging was associated with increased follow-up.	A recent analysis with a large patient sample and also a long timeframe. Reports data both on adherence to guidelines and factors that impact adherence.
Feeney et al. (2019) ³³	Retrospective	244	Single center study (1 yr)	Study of guidelines adherence and factors associated with adherence	14% had hormonal evaluation, 23% had imaging follow-up. Wording of radiology reports and location of index imaging (inpatient versus outpatient) associated with follow-up.	A recent analysis with both evaluation of adherence to guidelines as well as analysis of factors that impact adherence.
Eldeiry et al. (2018) ⁴³	Retrospective	1020	Single center 2013-2016	Standardized algorithm for IAM evaluation and link to algorithm in radiology report	No significant increase in proportion of follow-up imaging but significant increase in the proportion of patients undergoing appropriate hormonal testing.	This is a large and recent study that evaluates one potential intervention to increase follow up of IAMs.
De Haan et al. (2019) ³⁹	Retrospective	1112	Single center 2010-2012	Factors associated with adherence to guidelines	Using thorough descriptions of lesion is associated with higher proportion of imaging and biochemical testing.	This is a large recent study evaluating adherence and factors that impact adherence.
Goh et al. (2017) ⁴²	Prospective	228	Single Center 2010- 2016	Study of an MDT	Nursing led multi-disciplinary clinic could reliably identify functional or malignant lesions.	Recent data on the use of MDTs
Manikandan et al. (2013) ⁴⁵	Prospective	77	Single 1000 bed hospital in the UK	Study of an MDT	MDT identified 14% of IAM patients who had hormonal hypersecretion	Prospective study at large academic center that illustrates potential of MDTs as mechanism to increase guidelines-adherent evaluation of IAMs.

IAM = incidental adrenal mass. MDT = multi-disciplinary teams.

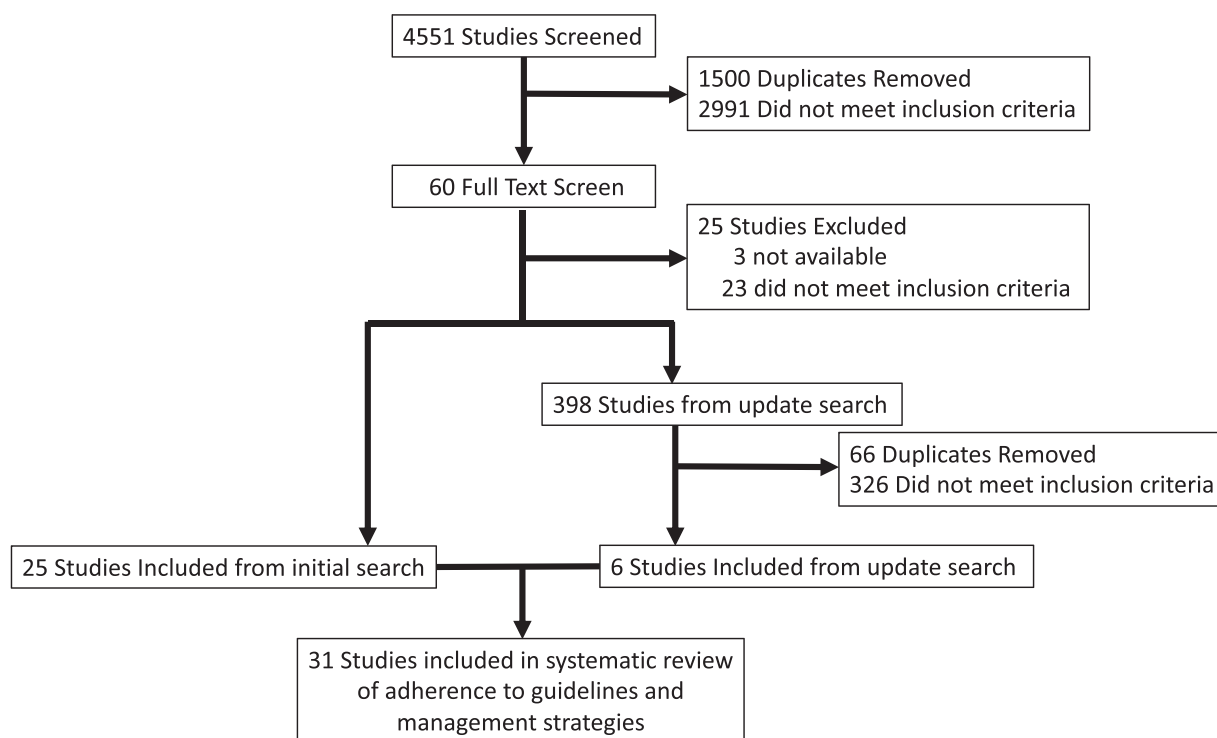


Fig. 1 – PRISMA Diagram.

I. Adherence to guidelines (19 studies systematically reviewed)

A. Dedicated adrenal imaging

Fifteen studies reported data on follow-up adrenal imaging and met our inclusion criteria^{22–36}. Imaging follow-up was performed more frequently than biochemical work-up. Appropriate imaging follow-up ranged from 6% to 55%,^{23–28} although there were also 2 outliers (comparatively weak study design) that reported 76%²⁹ and 100% follow-up adrenal imaging.³⁰ Among all 15 studies, the median proportion of imaging follow-up was 34% with an inter-quartile range (IQR) of 20%-50%. Not all of the studies included data as to whether follow-up imaging was done specifically to evaluate an IAM. 1 small case series found that 5 of 11 patients who underwent repeat imaging had the follow-up study specifically for an IAM evaluation,²⁴ but most other studies did not capture indications for repeat imaging, which would suggest that over-estimations are being reported. Moreover, some IAMs can be judged benign adenomas on the index scan (e.g., a non-contrast CT chest that detects an IAM with Hounsfield units [HU] <10). A 2012 study estimated that only 18% of IAMs were followed-up via formal adrenal protocol CT,³¹ but this study did not comment on whether the initial scan's protocol would preclude the need for additional imaging. Antonenko *et al.* did account for this issue in their analysis and found that 74% of patients who needed a follow-up CT based on initial HU values received one; however, only 41% of those with HU >10 had washout percentages calculated on the follow-up adrenal CT.³²

B. Dedicated biochemical testing

Fourteen studies reported data on biochemical work-up and met our inclusion criteria^{23–27,29,30,32–38}. Low rates of biochemical evaluation were reported, with a median of 18% and IQR of 15%-28%. Again, there were outliers. 1 study ($n=37$) found that approximately half of their patients had at least one follow-up biochemical test deemed appropriate by the authors,³⁵ and a 2018 study on the impact of an algorithm to improve follow-up, had baseline biochemical testing as high as 43% which increased to 69% after the algorithm was added to radiology reports.³⁶ 2 studies suggest that the most common biochemical evaluation is for pheochromocytoma.^{29,32} A retrospective review of IAMs at a large Veterans Affairs Medical Center found that evaluations for pheochromocytoma, autonomous cortisol production, and primary aldosteronism were rarely performed (8.4%, 2.4% and 5.3%, respectively), and no single patient received all indicated biochemical testing.²⁷

(Fig. 2) illustrates the distribution of follow-up percentages for both biochemical and radiologic follow-up for the studies included in this review. Of the 17 studies included, only 2 were based on a formal process for IAM management, and the others essentially represent a cross-section of “usual care.”

C. Factors associated with follow up of IAMs

The most consistent factor associated with improved follow-up is the radiologist's recommendation in the imaging report. Several studies have found that recommendations in the imaging report are associated with increased rates of IAM evaluation.^{25,33,34,36,39,40} In 1 study, this came in the form of a recommendation for an endocrinology referral, which was

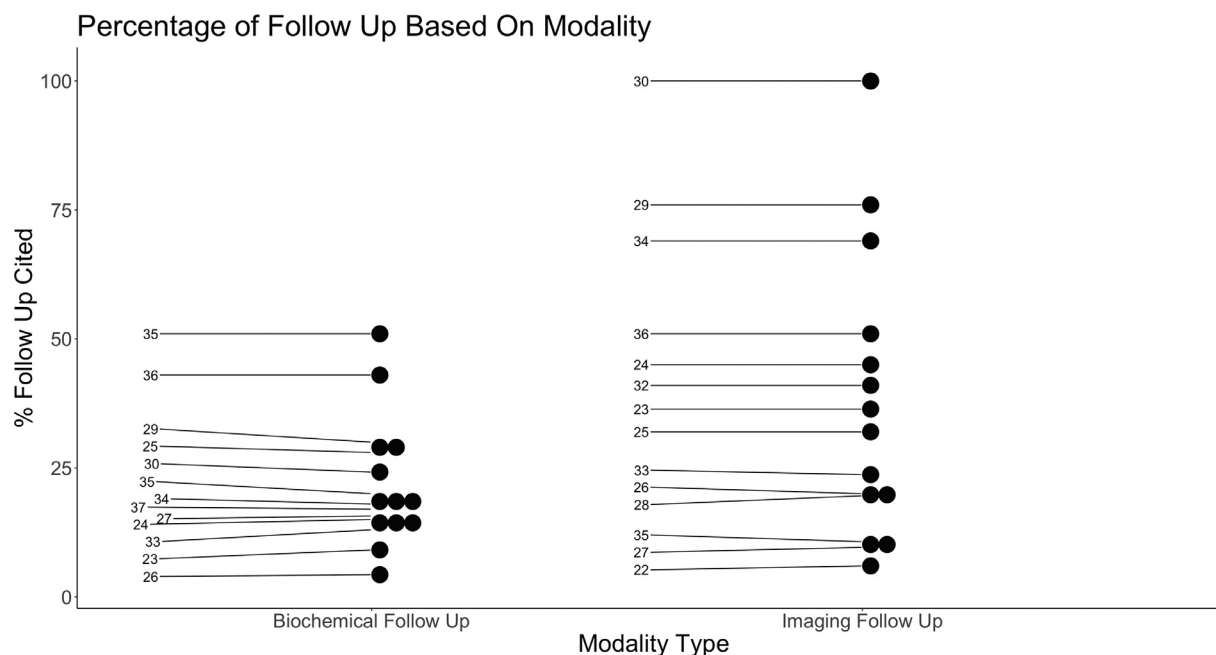


Fig. 2 – The distribution of guideline-based follow up percentages reported in the literature and stratified by type: Biochemical or Imaging Follow-up. Numbers in the figures correspond to reference numbers for the studies reviewed.

followed 100% of the time.²⁵ Referral to an endocrinologist also has a positive association with rates of follow-up. In 1 study ($n = 209$), 75% of those referred to an endocrinologist had complete biochemical workup compared to 9.3% among those not referred.³⁴ de Haan et al. showed that more specific wording in the radiology report lead to increased follow-up imaging (25% versus 3%) and follow-up biochemical testing (17% versus 2%).³⁹ They considered language such as ‘nodule’, ‘lesion’, ‘mass’, and ‘adenoma’ to be specific compared to reports in which, for example, the report noted an ‘adrenal incidentaloma.’ In probably the most rigorous study of this topic ($n = 805$), Maher et al. showed that specific IAM recommendations in the radiology report was associated with increased overall IAM evaluation, including in a multivariable model adjusted for other characteristics such as mass size, patient age and sex.⁴⁰ A similar increase was also seen in a study by Eldeiry et al.³⁶ Further, Feeney et al. showed that terms such as “indeterminate” versus the phrase “likely benign” or other benign-sounding terminology increased the rate of indicated, adrenal-dedicated imaging from 5% to 37%, but there was no significant association with biochemical testing (10% versus 17%).³³

A final characteristic observed to have an association with follow-up is the clinical context of the index study. Studies ordered as an inpatient (including the ED) are less likely to be followed-up compared to those ordered as an outpatient (11% versus 27%, respectively).³³ (Fig. 3) highlights factors associated with IAM follow-up.

II. Management strategies for initial evaluation and follow-up of IAMs: (14 studies systematically reviewed)

The ideal system of managing adrenal incidentalomas should incorporate seamless communication of incidental findings

to a responsible clinician who then performs a guidelines-adherent evaluation or refers to an appropriate subspecialist.⁴¹ Following systematic review of articles on IAM management, we identified mechanisms previously studied and grouped them into 4 categories: multi-disciplinary teams, automated notification and risk stratification systems, non-automated “manual” communication, and dedicated reporting mechanisms within the final radiology report.

A. Multi-disciplinary teams (MDTs)^{42–45}

MDTs may include nurses, advanced practitioners, radiologists, surgeons, and endocrinologists. There is no standardized model for this approach. In 1 case, a nursing-led adrenal incidentaloma clinic was established where nurses evaluated patients and recorded information using a standardized form. All of the patients were clinically evaluated by nurses for signs and symptoms of active hormonal disease, and 11.4% of those referred to the IAM clinic were diagnosed with functional disease.⁴² At least 3 additional studies describe the establishment of MDTs.^{43–45} Hanna et al. found that average time between IAM detection and diagnostic decision by the MDT was 6 months. The pattern of follow-up testing they describe was not standardized, and 50% of patients still had an unclear diagnosis after 6 months, although the authors posit that this might be worse without an MDT.⁴³

Lambert et al. discuss the performance of an MDT in the evaluation of adrenal lesions, but this paper did not compare MDT performance to “usual care” at their institution.⁴⁴ Despite that limitation, their results demonstrated that 29 of 38 patients referred to the MDT (76%) had follow-up with biochemical testing, which is quite high compared to the descriptive literature. The remaining 9 were excluded from testing due to small lesion size (<1cm) and absence of clinical comorbid conditions; thus, this study demonstrated 100% adher-

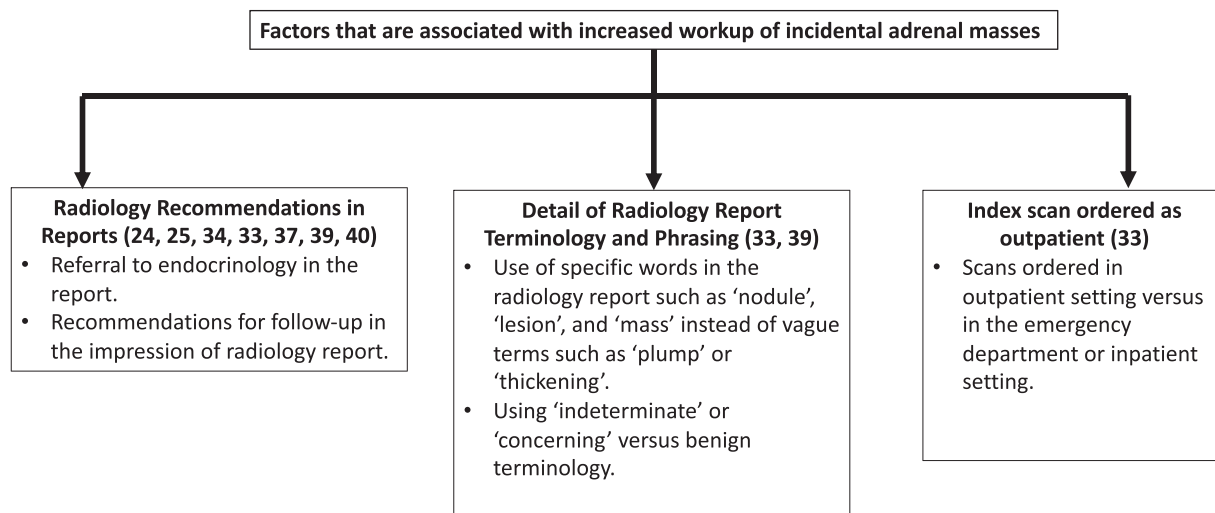


Fig. 3 – Summary of factors that have been shown to improve follow-up of incidental adrenal masses. Numbers in the figures correspond to reference numbers for the studies reviewed.

ence to guidelines in evaluating IAMs.⁴⁴ Manikandan et al. describe a similar experience.⁴⁵ They established an MDT in 2008 that received referrals through an ‘Adrenal Incidentaloma Referral Pathway’. Referrals were discussed monthly by multi-specialty clinicians to formulate workup plans. Performance of this MDT was retrospectively evaluated, and the authors found that 14% of referred IAMs were hormonally active (4 pheochromocytomas, 2 primary aldosteronism, 3 hypercortisolism). They concluded that the system worked well to identify masses that might previously have been missed.⁴⁵

B. Automated notification and risk stratification systems^{28,46–48}
These are computerized methods to facilitate communication regarding IAMs. Some automated modalities are used simply to designate “ownership” of the IAM to a responsible clinician such as PCP or the ordering provider. More complex examples include prediction models that can alert providers about patients who are more likely to have a pathologic diagnosis. The simpler methods utilize keyword search terms to identify language in radiology reports suggestive of an incidental lesion and then generate a notification to a relevant clinical provider. Spearman et al. evaluated performance of an automated notification system at their institution.²⁸ Certain radiologic findings generated an automated email message to notify the ordering provider; in some cases, additional imaging studies were recommended. These recommendations were followed only 19.6% of the time.

Alternative approaches involve predictive modeling to identify at-risk patients. 1 example is a prediction score based on hormonal testing and imaging characteristics that could identify patients who are unlikely to need an operation—importantly, however, this required pertinent data points to be collected by the clinical teams.⁴⁶ Another group utilized natural language processing to identify patients at high risk of malignancy or excess hormonal secretion based on existing data in the medical record.⁴⁷ Foo et al. tested an algorithm to predict malignancy among a retrospective cohort of patients with an IAM.⁴⁸ None of these three risk-prediction studies has

been evaluated as a component of an overall system for IAM management.

C. Non-automated “manual” communication^{51,52}

Manual communication is the most basic IAM management strategy beyond simply recommending “clinical correlation” in the radiology report. This strategy involves specific communication to highlight the IAM such that a responsible clinician will “take ownership” of the finding and coordinate the appropriate next steps. Such interventions are frequently highlighted in the “grey literature.”^{49,50} Only 2 peer-reviewed studies have specifically evaluated a dedicated notification system for incidentalomas that includes IAMs. Ekeh et al. described a mechanism in which an incidental lesion information sheet was given to trauma patients.⁵¹ The forms included data on what was found, what the patients should do next, and recommended timeframe for follow-up. The study did not assess whether the information sheet impacted rates of follow-up. A study by Sierink et al. described implementation of more stringent documentation requirements.⁵² Prior to intervention, accurate documentation among patients with moderately or severely concerning findings was only 20%. Documentation of incidental radiographic findings within the trauma report was subsequently mandated, but no patient-level outcomes were reported.

D. Standardized recommendations in the radiology report^{36,53–55}

Several studies included in this review have specifically investigated how the radiology report itself can be utilized to improve follow-up. 1 described approach is a system called ‘Code Abdomen,’⁵³ which simplified and standardized reporting of incidental lesions. Radiologist utilization was 94% after implementation, although there was no data on whether rates of incidentaloma follow-up improved. Paterson et al. developed a decision pathway based on size and HU to assist radiologists in determining appropriate recommendations for next steps.⁵⁴ These recommendations for referrals or additional testing were included in the report. Clinical outcomes

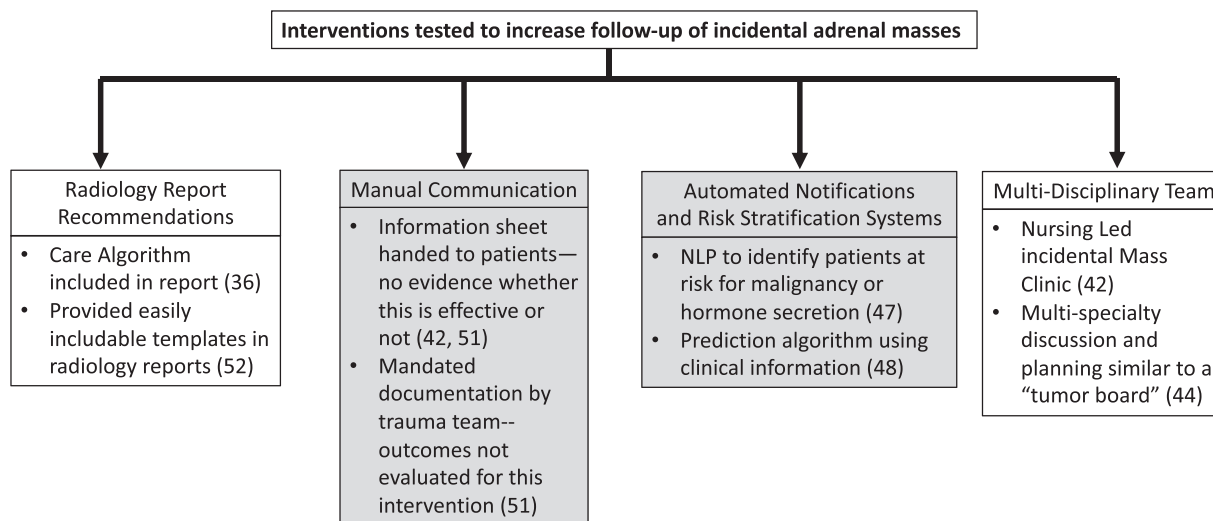


Fig. 4 – Interventions that have been studied to further improve follow up. Gray boxes indicate interventions that have not been shown to increase follow-up. White boxes highlight interventions that have been associated with increased follow-up. Numbers in the figures correspond to reference numbers for the studies reviewed.

have not yet been evaluated. Eldeiry et al. also implemented a structured radiology recommendation for IAMs and found improvements in the rate of follow-up in a study of 1020 patients.³⁶ Patients whose imaging reports included the structured algorithm were compared to those whose imaging reports were dictated in the standard fashion without structured recommendations. Reports that contained the algorithm were associated with a 30% increase in biochemical evaluation.

A slightly more intensive intervention was also shown to increase utilization among radiologists.⁵⁵ A searchable reference document summarizing guidelines for multiple types of incidental lesions was created. Automated macros, which enable insertion of standardized text into radiology reports, were developed. Finally, radiologists were instructed in use of the reference document and macros, and periodic reminders were generated. This intervention did improve reporting, and radiology recommendations were in agreement with accepted guidelines 80% of the time after the intervention, compared to 67.5% of the time prior to the intervention.⁵⁵

(Fig. 4) summarizes methods used to facilitate effective management of IAMs. The 4 categories of IAM management are listed in increasing order of resources, labor, and personnel commitments. High investment strategies such as MDTs and lower investment strategies such as radiology reporting templates have both shown an association with improved IAM follow-up. Automated notification and risk stratification methods may hold promise but have yet to be properly evaluated in a pragmatic setting. Manual communication appears to have little impact, though prospective data are lacking.

Discussion

This systematic review has illuminated several aspects of contemporary IAM management. Rates of initial evaluation are consistently low, both for imaging and biochemical testing.

Hormonal workup tends to occur less frequently than imaging. Descriptive studies have consistently shown that concrete recommendations in the radiology report are associated with higher rates of IAM follow-up.

In terms of IAM management strategies, while several methods to improve IAM management are described in this review, for many studies, the primary endpoint – how many IAMs receive adequate evaluation – is not actually measured. We identified four categories of interventions and 23 studies that specifically evaluated some aspect of a dedicated follow-up process for IAMs. From these studies, we can report that 2 evidence-supported processes have been shown to improve the evaluation of IAMs: a process to embed guidelines in the radiology report and the establishment of MDTs. Much still needs to be done to understand why most IAMs do not receive necessary follow-up and what implementation methods would improve the status quo. Larger studies conducted over longer time periods and that measure rates of IAM evaluation may allow us to better compare mechanisms to improve initial IAM care.

The findings reported in this systematic review indicate that guidelines are not, in and of themselves, adequate to improve appropriate evaluation of IAMs. Strategies to promote adherence are necessary, and understanding the barriers faced by healthcare systems and individual clinicians is part of meeting the challenge. The field of implementation science, in which effective strategies are studied as interventions in a “real world” context, may offer many advantages for future work in this space.⁵⁶ For instance, basic implementation metrics, such as adoption and uptake measurements, costs and cost-effectiveness, feasibility, and sustainability need to be considered alongside metrics such as rates of biochemical and radiographic evaluation.

This study was limited by the low number of studies available and the heterogenous approaches taken to studying our outcomes of interest. Few analyses used similar methods and the outcomes evaluated often did not align in a way that al-

lowed for direct comparison or for cumulative methodologies such as meta-analysis. Additionally, because so few studies exist, we included those in abstract form that were not taken to full publication. We utilized the same search terms for Objective 1 and Objective 2, which may be considered a limitation, but we do not feel this hindered our ability to find all relevant studies.

In conclusion, the majority of patients with an IAM are not managed appropriately. Under “usual care,” approximately 1-third of patients (median 34%, IQR 20%-50%) can be expected to undergo necessary radiographic follow-up and only 1-fifth of patients (median 18%, IQR 15%-28%) will undergo any component of a biochemical evaluation. The radiology report has been identified as a key factor in determining whether IAMs are evaluated. When patients are referred to an endocrinologist, they nearly always have an appropriate evaluation, but few are referred. MDTs and guidelines embedded within the “impression” section of the radiology report are two interventions supported by the literature that lead to improved rates of IAM evaluation. Other interventions may also be effective, but studies with relevant endpoints are rare. Millions of CT scans are performed annually, and research dedicated to optimizing management of IAMs is necessary; indeed, we found only 14 studies in our systematic review of the last 20 years. This is an area rich in opportunities for further research and quality improvement.

Author contributions

Feeney: concept/design, acquisition of data, analysis, drafting the work, final approval, accountability. **Madiedo:** concept/design, acquisition of data, critical revision, final approval, accountability. **Knapp:** concept/design, critical revision, final approval, accountability. **Gupta:** concept/design, critical revision, final approval, accountability. **McAneny:** concept/design, critical revision, final approval, accountability. **Drake:** concept/design, analysis, drafting the work, critical revision, final approval, accountability

Conflict of interest

The authors declare that there are no conflicts of interest.

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Disclosure

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Supplementary materials

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