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CDI Quality Institute PLE
Renal / Kidney Calculus AUC

Appropriateness of advanced imaging procedures* in patients with the following renal/kidney calculus clinical presentations or diagnoses:

*Including MRI, CT, renal scintigraphy, PET, and PET/CT

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Abbreviation list:

AAFP	American Academy of Family Physicians
ACR	American College of Radiology
AI	Adrenal incidentaloma
AMH	Asymptomatic microhematuria
APN	Acute pyelonephritis
AUA	American Urological Association
AUC	Appropriate Use Criteria
CT	Computed tomography
CT KUB	Computed tomography of the kidneys, ureters and bladder
CTU	Computed tomography urography
CUA	Canadian Urological Association
DTPA	Diethylene triamine pentaacetic acid
EAU	European Association of Urology
ENSAT	European Network for the Study of Adrenal Tumors
ESE	European Society of Endocrinology
IVU	Intravenous urogram
KUB	Kidneys, ureters, and bladder
MAG-3	Mercaptoacetyltriglycine
MDCT	Multidetector computed tomography
MET	Medical expulsive therapy
MH	Microhematuria
MRI	Magnetic resonance imaging
MRU	Magnetic resonance urography
NCCT	Non contrast computed tomography
PCN	Percutaneous nephrolithotomy
PET	Positron emission tomography
PLE	Provider Led Entity
RBCs	Red blood cells
RPG	Retrograde pyelogram
SWL	Shock wave lithotripsy
URS	Ureteroscopy
US	Ultrasound
UTI	Urinary tract infection

Atraumatic hematuria:

- **Green** – Multiphasic CT urography without and with IV contrast
- **Yellow** – MR urography without and with IV contrast in patients who are unable to receive CT contrast*
- **Yellow** – MRI abdomen and pelvis without IV contrast (with retrograde pyelogram) in patients who are unable to receive CT contrast**
- **Yellow** – CT abdomen and pelvis without IV contrast (with retrograde pyelography) in patients who are unable to receive CT contrast and who are unable to undergo MRI**
- **Yellow** – CT urography with IV contrast if the patient has had a CT KUB without contrast within 6 months
- **Red** – CT or MR for patients with a known, benign cause of hematuria (e.g., menstruation, renal infection or vigorous exercise); scintigraphy; PET/CT

*In patients with a low likelihood for renal calculus disease. If a patient undergoes MRU for the work-up of atraumatic hematuria, consideration should be given to cystoscopy with cytology for bladder evaluation.

**Premedication with steroid preparation may be appropriate in patients with a history of moderate or severe allergic reaction to IV contrast prior to undergoing retrograde pyelography.

Level of Evidence: CT with and without contrast: low; MRI with and without contrast: very low; CT with contrast: insufficient; CT without contrast: low; MRI without contrast: insufficient; scintigraphy and PET-CT: insufficient

Notes concerning applicability and/or patient preferences: none

Guideline and PLE expert panel consensus opinion summary:
The *American College of Radiology* [*ACR*] does not recommend imaging in hematuria patients with vigorous exercise, presence of infection or viral illness, or present or recent menstruation (Shen et al [*ACR*] 2014*). *A hematuria work-up may be indicated in these patients, however, if hematuria persists or if the patient has or develops significant risk factors* (PLE expert panel consensus opinion).

Multi-phasic CT urography without and with intravenous contrast… is the imaging procedure of choice [for asymptomatic hematuria (AMH)] because it has the highest sensitivity and specificity for imaging the upper tracts (Davis et al [*American Urological Association* (*AUA*)] 2012, Evidence Strength/Grade C; Sharp et al AAFP 2013).

For patients with relative or absolute contraindications that preclude use of multi-phase CT (such as renal insufficiency or contrast allergy) where collecting system detail is deemed imperative, combining MRI with retrograde pyelograms (RPGs) provides alternative evaluation of the entire upper tract (Davis et al [*AUA*] 2012, Expert Opinion).

For patients with relative or absolute contraindications that preclude use of multiphasic CT (such as renal insufficiency, contrast allergy) and MRI (presence of metal in the body) where collecting system detail is deemed imperative, combining non-contrast CT or renal ultrasound with RPGs provides alternative evaluation of the entire upper tracts (Davis et al [*AUA*] 2012, Expert Opinion).

For patients with relative or absolute contraindications that preclude use of multi-phasic CT (such as renal insufficiency or contrast allergy), MR urography (without/with IV contrast) is an acceptable alternative imaging approach (Davis et al [*AUA*] 2012, Evidence Strength: Grade C). However, MRU is poor at detecting stone disease, which is a common etiology of microhematuria (Sharp et al [*American Academy of Family Physicians* (*AAFP*)] 2013).

In patients with hematuria (except for those with vigorous exercise, presence of infection or viral illness, present or recent menstruation, or those with disease of renal parenchyma as the cause of hematuria) the *American College of Radiology* (Shen et al [*ACR*] 2014*) recommends CT abdomen and pelvis without and with IV contrast (9), CT abdomen and pelvis without IV contrast (6), x-ray retrograde pyelography (6), CT abdomen and pelvis with IV contrast (5), ultrasound kidneys and bladder retroperitoneal (5), and MRI abdomen and pelvis without and with IV contrast (5).

* The *American College of Radiology* guideline by Shen et al (2014) did not pass the AGREE II cutoff score of 90 (it scored a 75) or the rigor of development scaled domain score cutoff of 50% (it scored a 34%). It was included, however, because of its direct relevance to the hematuria clinical scenario.

<u>Clinical notes:</u>

- The origins of microhematuria (MH) are either urologic or nephrologic. Common urological etiologies are benign prostatic enlargement, infection, and urinary calculi (Davis et al [*AUA*] 2012).
- Assessment of AMH patients should include a careful history, physical examination, and laboratory examination to rule out benign causes of AMH such as infection, menstruation, vigorous exercise, medical renal disease, viral illness, trauma, or recent urological procedures (Davis et al [*AUA*] 2012, Clinical Principle).
- The presence of microscopic hematuria and dysmorphic red blood cells (RBCs), cellular casts, proteinuria, elevated creatinine level, or hypertension should raise suspicion for medical renal etiologies, such as immunoglobulin A nephropathy, Alport syndrome, benign familial hematuria, or other nephropathy (Sharp et al [*AAFP*] 2013).
- In many patients with MH, a specific cause or pathology is not found. However, formal evaluation is critical, as malignancies are detected in up to 5% of patients with AMH and up to 30-40% of patients with gross hematuria (Sharp et al [*AAFP*] 2013).
- The literature indicates that < 1% of AMH patients who had negative findings after a thorough work-up manifested a serious disease state during 14 years of follow-up (Davis et al [*AUA*] 2012).
- However, if asymptomatic microscopic hematuria persists on follow-up urinalysis, a full repeat evaluation should be considered within three to five years of the initial evaluation. Patients' risk factors for urologic malignancy should guide clinical decision making about reevaluation (Sharp et al [*AAFP*] 2013; Davis et al [*AUA*] 2012, Expert Opinion).
- Changes in the clinical scenario, such as a substantial increase in the degree of MH, detection of dysmorphic RBCs with concomitant hypertension and/or proteinuria, development of gross hematuria, pain, or other new symptoms, may warrant earlier re-evaluation and/or referral to other practitioners, such as nephrologists (Davis et al [*AUA*] 2012).
- CT urography is the imaging procedure of choice in the evaluation of microscopic hematuria because of its high sensitivity (91% to 100%) and specificity (94% to 97%), and its ability to provide excellent diagnostic information in a single imaging session (Sharp et al [*AAFP*] 2013).
- Reports of use of multi-detector-row computed tomography (CT) in detecting bladder cancers suggest a sensitivity and specificity of 95% and 92%, respectively (Shen et al [*ACR*] 2014).

- [For microhematuria] the use of ultrasound (US) and intravenous urography (IVU) does not exclude the need for additional imaging studies. In addition, the sensitivities and specificities of US and IVU are such that the possibility of missed diagnoses is significant. Both of these issues are avoided with the use of CT urography and MR urography (Davis et al [*AUA*] 2012).
- NCCT provides more information and creates greater diagnostic certainty than US. For certain patients [i.e. the pregnant patient], however, only US in combination with RPGs should be used (Davis et al [*AUA*] 2012).
- Although invasive, retrograde pyelography combined with renal ultrasonography has a sensitivity and specificity of 97% and 93%, respectively, for detecting urothelial filling defects (Sharp et al [*AAFP*] 2013).

<u>Technical notes:</u>

- Split bolus technique should be considered in patients at low risk for renal cancer (patients < 40 years of age) undergoing multiphasic CT or CT with IV contrast in order to limit radiation dose to the patient. The split bolus technique aims to combine the nephrographic and urographic phases of imaging into one acquisition. The patient receives 50 mL of contrast followed by an additional 50 mL eight minutes later, and the images are obtained 55 seconds after the second dose of contrast (PLE expert panel consensus opinion).
- Multiphasic CT urography should include a noncontrast CT KUB to evaluate for calculi, a contrast phase to evaluate for a renal mass, and an excretory phase to evaluate for urothelium of the upper and lower urinary tracts (Davis et al [*AUA*] 2012; PLE expert panel consensus opinion).
- Sagittal and coronal reconstructions should be utilized to increase the sensitivity and specificity of CT for ureteral calculi (PLE expert panel consensus opinion).

<u>Evidence update (2011-present):</u>

CTU versus unenhanced CT:

A 2012 retrospective study compared unenhanced vs. multiphase MDCT in 95 patients (mean age 35.9 years) with hematuria, flank pain, and negative ultrasound undergoing MDCT for urinary tract evaluation. All patients underwent MDCT within 12 hrs. Overall diagnosis of urinary stones revealed an accuracy of 97% for CT without contrast with 15 false positive observations, and 98.5% for multiphase MDCT with 3 false positive observations. In 7 of 18 cases (38.9%) the incidental pathology would have remained undetected by readers if unenhanced MDCT had been used as the only modality. The authors conclude contrast-enhanced multiphase MDCT is superior to unenhanced CT in the evaluation of patients with hematuria, flank pain and a negative ultrasound (Krauss et al 2012; low level of evidence).

A 2014 retrospective study compared CT urography (CTU) with unenhanced CT in evaluating upper urinary tracts (UUT) in adults < 50 years with asymptomatic microscopic hematuria. A total of 1516 CTU examinations were reviewed. A blinded radiologist reviewed the unenhanced images. Unenhanced CT interpretation had sensitivity of 100% (64/64) and specificity of 89.2% (337/378). CTU added no additional diagnostic benefit versus unenhanced CT in evaluating UUT. The authors conclude that using only unenhanced CT can reduce radiation and minimize contrast agent–associated risk, with < 1.0% risk of missing upper urinary tract hematuria-related malignancy (Lisanti et al 2014; low level of evidence). *This study may have limited applicability as the patient population (≤ 50 years) may have a lower incidence of malignancy than the Medicare population* (PLE expert panel consensus opinion).

A 2012 retrospective study sought to determine the yield of CT urography in young adults with hematuria to see whether single phase unenhanced CT would have been sufficient. Of 5400 CT urograms performed, 375 (6.9%) in 359 patients aged ≤ 40 years with hematuria were included. A clinically significant source of hematuria was detected in 22.1% of CT urograms. Renal or ureteral calculi were found in 73 patients (75.3%) and malignancy in four. 94.8% of 97 clinically significant findings were evident on unenhanced images. All significant findings requiring contrast-enhanced images for diagnosis occurred in patients with predisposing medical conditions for urological disease. The authors conclude that single phase unenhanced CT may be sufficient for a majority of these patients without additional predisposing medical conditions (Lokken et al 2012; low level of evidence). *This study may have limited applicability as the patient population (≤ 40 years) may have a lower incidence of malignancy than the Medicare population* (PLE expert panel consensus opinion).

Repeat imaging:
A 2015 retrospective study evaluated the yield of repeat CT urography (CTU) in detecting urinary tract malignancies in 5,525 patients with hematuria. A total of 751 (13.6%) patients underwent repeat CTU at 1-3 years. Initial CTU showed no findings suspicious for malignancy in 103 (70%) of 148 patients. Of these, none had malignancy identified on repeat CTU. 45 patients (30%) had findings suspicious of malignancy on the initial CT. Malignancy was found in four patients (8.9%) on repeat CTU in this group. The authors conclude that in patients with hematuria, repeat CTU within 3 years is unlikely to show urinary tract malignancy (Mullen et al 2015; low level of evidence).

A 2013 retrospective study evaluated the role of repeated urological evaluation after negative initial diagnostic work-up of asymptomatic microhematuria (AMH) in 87 low-risk patients (56 women; mean age 52.4; range: 19-87). Patients had negative initial diagnostic assessment including ultrasound (US), cystoscopy, upper urinary tract (UUT) imaging using intravenous urography (IVU) or multiphasic computed tomography (CT), absence of risk factors and a follow-up period of ≥ 3 years. Three years after initial workup, cystoscopy confirmed no bladder carcinoma in any of the patients. Low-risk patients with persistent AMH after negative urological evaluation have a negligible risk of developing bladder cancer on follow-up (Pichler et al 2013; low level of evidence).

Ultrasound:
A 2014 retrospective diagnostic accuracy study was conducted on 95 patients with macroscopic hematuria who underwent ultrasound, CTU and cystoscopy within 12 months. Sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios of ultrasound for detecting urinary tract neoplasms were 35.3% (6/17), 89.9% (62/69), 46.2% (6/13), 84.9% (62/73), 3.48 (95% confidence interval, 1.34-9.02), and 0.72 (95% confidence interval, 0.5-1.3), respectively. The authors conclude that "sensitivity of ultrasound for evaluation of macroscopic hematuria in the era of MDCTU is lower than expected. Results of our study suggest that patients with macroscopic hematuria should undergo MDCTU as first-line imaging modality, with little added benefit from ultrasound". (Rheaume-Lanoie, 2014; low level of evidence).

A 2011 prospective study sought to define the indications for imaging the upper urinary tract (UUT) with CTU in 456 patients presenting with hematuria. All patients (mean age 56.7 +/- 16.6 years) underwent standard evaluation with history, physical exam, US of kidneys and bladder, cystoscopy, and cytology. CTU or MRU was performed in patients with abnormal findings on cystoscopy or US, and in high risk patients. KUB and US of the kidney/bladder in the radiology department were performed on the remaining patients. US findings (OR 7.7, 95% CI 4.0–14.9), P < 0.001) and type of hematuria (OR 2.6, 95% CI 1.3–5.1, P = 0.01) were significant predictors for abnormal cross-sectional urography result. 44/456 (9.6%) of patients with negative US results had positive findings on CTU/MRU, with most of these missed lesions being stones. The authors concluded that for patients who present with microscopic hematuria, US is sufficient to exclude significant UUT disease. For patients with macroscopic hematuria, the likelihood of finding UUT disease is higher, and a CTU as a first-line test seems justified (Cauberg et al 2011; low level of evidence).

A 2011 prospective study of 141 patients (average age 54.1, range 20-85) assessed efficiency of an imaging algorithm in the radiological management of hematuria. According to initial US findings, patients were divided into two groups: group 1 (n = 106) were those with normal US or minor abnormalities (non-obstructive renal or bladder stones, Bosniak class 1 simple renal cysts). These patients were further evaluated with IVU. The remaining 35 patients with important findings on US (Group 2) were scheduled for CTU. US and IVU results were congruent in 97 cases in group 1. Eight simple cysts were detected with US and 1 non-obstructing ureter stone was detected with IVU in remaining 9 patients. US and CTU results were congruent in 30 cases. Additional lesions were detected with CTU (3 ureter stones, 1 ureteral TCC, and 1 advanced RCC) in the remaining 5 patients. The authors conclude that imaging algorithms based on US selection can be effective in radiological investigation of patients with hematuria (Unsal et al 2011; moderate level of evidence).

MRI/MRU:

A retrospective study of 35 patients with hematuria, undergoing both CTU and MRU, compared diagnostic accuracy and diagnostic confidence of two radiologist readers. CTU provided better visibility of urothelial structures ($p < 0.01$) and allowed for greater diagnostic confidence (ROC area 0.994 vs. 0.938) than MRU, with a good inter-reader agreement (WK=0.62). The authors suggest that CTU has a higher detection rate for urothelial malignancy than MRU and should be preferred for patients with gross hematuria who are at high risk for malignancy (Martingano et al 2013; low level of evidence).

CT/CTU:

A 2016 prospective multicenter observational study identified outpatients referred by primary care providers for CT evaluation of abdominal pain, hematuria, or weight loss. In these three groups, leading diagnoses changed after CT in 53% (131 of 246), 49% (36 of 73), and 57% (27 of 47) of patients, respectively. Changes in provider's leading diagnoses and management after CT were common, and diagnostic confidence increased substantially (Pandharipande et al 2016; moderate level of evidence).

A 2015 prospective study compared split-bolus CTU, MRU, and flexible cystoscopy in 178 patients with macroscopic hematuria for the diagnosis of bladder tumor. Two uroradiologists individually reviewed the images without any clinical information. At flexible cystoscopy, MRU, and CTU, 32, 19, and 15 bladder lesions were identified, respectively. Histopathology showed that 13 of 29 biopsied lesions were transitional cell carcinomas. The authors conclude that patients with low risk of bladder cancer may forgo flexible cystoscopy if bladder tumor is identified by CTU or MRU, and proceed straight to transuretheral resection of the bladder (Gandrup et al 2015; low level of evidence).

A 2015 retrospective study included 771 patients in Denmark undergoing CT urography for either visible hematuria without symptoms, visible hematuria with symptoms, nonvisible hematuria without symptoms, or nonvisible hematuria with symptoms. In total, 18% of patients had a tumor or complex cyst found, 9% a calculi, and another disease (infection or anomaly) in 15%. 58% had no abnormality found. Lesions were found more frequently in patients with visible hematuria than in patients with non-visible hematuria (48% vs. 29%). Authors conclude that "CT urography with its low dose of contrast medium and radiation is a useful diagnostic imaging test for investigating patients with hematuria." (Bretlau et al 2015; low level of evidence).

A 2013 retrospective study reviewed the utility of CT urography for detection of bladder tumors in patients with microscopic hematuria. Sensitivity of CT urography was 29%, specificity 99%, PPV 67%, NPV 95%, and diagnostic accuracy 95%. Authors conclude that due to the low sensitivity of CT urography, “cystoscopy should be considered the standard for bladder evaluation of patients with microscopic hematuria” (Aguilar-Davidov et al 2013; low level of evidence).

A 2012 retrospective study of 1,209 patients (age range, 20–94) aimed to determine prevalence and characteristics of clinically important extraurinary findings on MDCT urography for hematuria evaluation. In 82 patients (6.8%), 85 clinically important incidental extraurinary findings were identified. Follow-up evaluation was available for 50.6% of findings by histologic diagnosis (n = 9), imaging evaluation (n = 31), or clinical information (n = 3). There were 11 (0.9%) examinations with acute findings, of which acute inflammation of the gastrointestinal tract and pancreaticobiliary system were most common. Seventy-two (5.9%) examinations revealed 74 nonacute but important findings. Lung nodules were most prevalent, followed by intraabdominal aneurysms and cystic ovarian masses. There were five (0.4%) histologically proven malignant neoplasms. The authors conclude prevalence of clinically important incidental extraurinary findings at MDCT urography performed for hematuria was 6.8%. (Song et al 2012; low level of evidence).

Flank pain with suspected renal or ureteral calculus:

- **Green** – CT abdomen and pelvis (KUB) without IV contrast
- **Yellow** – CT abdomen and pelvis with IV contrast to further assess unexplained pain or indeterminate findings on CT without IV contrast
- **Yellow** – MR abdomen and pelvis without IV contrast following a nondiagnostic or indeterminate US in patients who are unable to undergo CT (e.g. due to concerns such as radiation sensitivity)
- **Yellow** – MRI abdomen and pelvis with IV contrast to further assess unexplained pain or indeterminate findings on noncontrast MRI; MRI abdomen and pelvis with and without IV contrast to further assess unexplained pain or indeterminate findings on CT without IV contrast in patients in whom CT with contrast is contraindicated (e.g. moderate to severe allergy to CT contrast or renal insufficiency)
- **Orange** - Renal scintigraphy for assessing renal obstruction
- **Red** – PET; PET-CT

Level of Evidence: CT without contrast: high; CT with contrast: insufficient; CT with and without contrast: insufficient; MRI with contrast: insufficient; MRI without contrast: very low; renal scintigraphy: low; PET-CT: insufficient

Notes concerning applicability and/or patient preferences: none

Guideline and PLE expert panel consensus opinion summary:
Noncontrast CT (NCCT) is the preferred initial imaging study for the index patient suspected of having a ureteral stone (Fulgham et al [*AUA*] 2013; Level A Evidence).

Ultrasound should be used as the primary diagnostic imaging tool for suspected renal or ureteral stone. (Turk et al [*European Association of Urology* (*EAU*)] 2015). *The PLE expert panel thought that this had variable applicability because of limited ultrasound expertise and availability in some practice settings*.

In patients with a BMI >30, US may be less effective at identifying renal and ureteral calculi, and CT may therefore be more efficacious (PLE expert panel consensus opinion).

The combination of renal ultrasonography and KUB is a viable option for a known stone former who has previously had radiopaque stones. Sensitivities of 58%-100% and specificities of 37.2%-100% have been reported for this combination of modalities (Fulgham et al [*AUA*] 2013/Level C Evidence).

Renal ultrasonography is a viable option for a known stone former who has previously had radiolucent stones. If the patient has hydronephrosis on ultrasound or if the patient has persistent symptoms without hydronephrosis, CT can be obtained for further evaluation (PLE expert panel consensus opinion).

Following initial ultrasound assessment, NCCT should be used to confirm stone diagnosis in patients with acute flank pain, because it is superior to intravenous urography (Turk et al [*EAU*] 2015, Level 1a/Grade A Evidence).

If there is uncertainty about whether a calcific density represents a stone or a phlebolith at NCCT, intravenous contrast material can be administered and excretory phase images obtained for definitive diagnosis (Coursey et al [*ACR*] 2015*).

Ultrasound should be considered to evaluate for hydronephrosis in patients with renal insufficiency or a moderate to severe allergy to iodinated contrast (PLE expert panel consensus opinion).

Magnetic resonance imaging (MRI) can be used, as a second-line procedure, to define the level of urinary tract obstruction, and to visualize stones as a filling defect (Turk et al [*EAU*] 2015.

MR urography can be useful in the setting of IV contrast allergy, although stones are typically not well visualized directly with MR imaging (Assimos et al [*AUA*] 2016).

MRI is an excellent tool for the evaluation of hydronephrosis though is limited in its ability to detect small stones (Coursey et al [*ACR*] 2015*).

In patients with acute onset flank pain – suspicion of stone disease, the *American College of Radiology* (Coursey et al [*ACR*] 2015*) recommends CT abdomen and pelvis without IV contrast (8), CT abdomen and pelvis without and with IV contrast (if unexplained pain or abnormality revealed on CT without contrast that should be further assessed (6), and US color Doppler kidneys and bladder retroperitoneal (6).

* The *American College of Radiology* guideline by Coursey et al (2015) did not pass the AGREE II cutoff score of 90 (it scored a 64) or the rigor of development scaled domain score cutoff of 50% (it scored a 29%). It was included, however, because of its direct relevance to the suspected renal calculus clinical scenario.

<u>Clinical notes:</u>

- [For suspected ureteral/renal stone] with fever or solitary kidney, and when diagnosis is doubtful, immediate imaging is indicated (Turk et al [*EAU*] 2015, Level 4/Grade A Evidence).
- In patients with transplanted kidneys, unexplained fever, or unexplained failure to thrive, US or NCCT should be performed to rule out calculi (Turk et al [*EAU*] 2015, Level 4/Grade B Evidence). NCCT has a reported median sensitivity and specificity for the detection of ureteral calculi of 98% and 97%, respectively, far superior to other imaging modalities (Fulgham et al [*AUA*] 2013).
- Ultrasound can identify stones located in the calices, pelvis, and pyeloureteric and vesicoureteric junctions, [and can identify] patients with upper urinary tract dilatation. US has a sensitivity of 45% and specificity of 94% for ureteric stones and a sensitivity of 45% and specificity of 88% for renal stones (Turk et al [*EAU*] 2015).
- The sensitivity and specificity of KUB radiography is 44-77% and 80-87%, respectively. KUB radiography should not be performed if NCCT is considered, however, it is helpful in differentiating between radiolucent and radiopaque stones and for comparison during follow-up (Turk et al [*EAU*] 2015).

<u>Technical notes:</u>

- If NCCT is indicated in patients with BMI < 30, use a low-dose technique (Turk et al [*EAU*] 2015, Level 1b/Grade A Evidence; Fulgham et al [*AUA*] 2013).
- Radiation risk can be reduced by low-dose CT. In patients with body mass index (BMI) < 30, low-dose CT has been shown to have a sensitivity of 86% for detecting ureteric stones < 3 mm and 100% for calculi > 3 mm. A meta-analysis of prospective studies has shown that low-dose CT

diagnosed urolithiasis with a pooled sensitivity of 96.6% (95% CI: 95.0-97.8) and specificity of 94.9% (95% CI: 92.0-97.0) (Turk et al [*EAU*] 2015).

- Optimization of CT includes limited scanning protocols confined to an anatomical region of interest, adjustments of CT parameters for tissue thickness and body habitus, and limitation of phases (e.g., noncontrast only or combined injection and delayed phases) to reduce total radiation exposure (Fulgham et al [*AUA*] 2013).
- Sagittal and coronal reconstructions should be utilized to increase the sensitivity and specificity of CT for ureteral calculi (PLE expert panel consensus opinion).

Evidence update (2014-present):

Ultrasound:

A 2017 prospective study looked at 106 patients with ureterolithiasis undergoing both color Doppler US and CT. The study found that bigger and proximal ureteral stones tended to have more twinkling artifact (TA) on color Doppler US. The authors sought to evaluate the use of [color Doppler US] as an alternative imaging modality to CT, and concluded that [the color Doppler US with the findings of TA could be a safe alternative imaging modality compared with CT (Sen et al 2017; moderate level of evidence).

A prospective cohort study studied the negative predictive value of normal renal ultrasound (US) in 610 patients presenting to the ER with suspected renal colic. Of 341 patients receiving US as initial imaging modality, 30.8% were normal. At 90 day follow-up, 0 patients received urological intervention, and no significant abdominal pathology was identified in this cohort. The authors conclude "although US has less diagnostic accuracy compared to CT, patients with a clinical diagnosis of renal colic and a normal renal sonogram are unlikely to require urologic intervention within 90 days of initial ED visit and can confidently be managed conservatively with appropriate analgesia and clinical follow-up" (Yan et al 2015; moderate level of evidence).

A 2015 prospective study of 77 patients with symptoms of acute renal colic undergoing sonographic evaluation of the affected kidney sought to define variables on ultrasound (US) that significantly predicted need for hospitalization within 30 days. It found those patients with moderate hydronephrosis on US had higher admission rate (36%) than those with mild or no hydronephrosis ($p < 0.01$), and concluded that info from bedside US may help clinician determine which patients may benefit from hospital admission (Fields et al 2015; moderate level of evidence).

A 2016 retrospective analysis was conducted on 155 patients undergoing both US and NCCT within 1 day for evaluation of renal calculi. In 79 patients (51%), both US and NCCT identified a stone for size comparison. 58 patients (37.4%) had stone visualized on NCCT but not US, and 2 patients (1.3%) had stone documented on US but not on NCCT. US was found to overestimate stone size by 2.2 mm, and by 84.6% for stones < 5 mm, 27.1% for stones 5.1-10 mm, and 3.0% for stones > 10 mm. The authors conclude that US overestimated stone size, particularly for smaller renal calculi, with implications for downstream endourologic treatment options (Sternberg et al 2016; low level of evidence).

A 2014 retrospective study was conducted on 428 patients undergoing both NCCT and US imaging on the same day for symptoms of acute flank pain or hematuria. The study assessed efficacy of US for the detection of ureteral stone using NCCT as a standard reference. Of 856 ureters (428 patients), NCCT identified 171 stones in 169 patients. US detected 98 ureteral stones identified by NCCT, yielding a sensitivity and specificity of 57.3% and 97.5%, respectively. The detection sensitivity in the distal ureter was found to be lower than in other sites. The detection rate also varied with stone size. For stones > 5 mm, the sensitivity was high (69.8%; 81 of 116) compared with 30.9% for small stone < 5 mm. US detected 89 of 130 ureteral stones with hydronephrosis as opposed to 9 of 41 ureteral stones without hydronephrosis. Stone sizes measured by US strongly correlated with those by CT (Pearson correlation coefficient, 0.7733; P <.001). Authors concluded that US may be effective for the detection of ureteral stone and suggest that US should be considered for evaluation of both acute and follow-up of ureteral stone cases (Kanno, 2014; low level of evidence).

CT:

A 2016 prospective study of 835 ED patients with suspected nephrolithiasis examined rates of symptomatic stone disease or other acute diagnosis and rate of 90 day urological intervention after point of care limited ultrasound (PLUS) was added to results of STONE score. Presence of hydronephrosis increased sensitivity in low/moderate STONE score categories, from 3.2% to 64% and from 41% to 60%, respectively. The presence of moderate or greater hydronephrosis improved specificity from 67% to 98%, and from 42% to 92% in low- and moderate-risk patients, with likelihood ratios of 22 and 4.9, respectively. Of the 59 patients with high STONE score who received intervention within 90 days of ED visit, 48 (81%) had some degree of hydronephrosis, and hydronephrosis was overall 66% sensitive for predicting need for intervention in all groups. 54 acutely important alternate findings were identified on CT in 8.3%, 9.0%, and 1.8% of patients in low, moderate, and high risk STONE score groups, respectively. Presence of hydronephrosis further reduced risk of alternate diagnosis being identified (OR 0.31; 95% CI 0.16-0.60). The authors conclude hydronephrosis on renal PLUS modestly improved risk stratification in low- and moderate-risk STONE score patients. The presence or absence of hydronephrosis in high-risk patients did not significantly alter likelihood of symptomatic stone, but may aid in identifying patients more likely to require urologic intervention (Daniels et al 2016; high level of evidence). *The expert committee thought that the primary significance of this study was that patients with a low STONE score and no hydronephrosis on ultrasound had a low incidence of renal calculi on CT. The referring provider should consult the abdominal pain AUC recommendations when considering advanced imaging in these patients* (PLE expert panel consensus opinion*).*

A 2016 retrospective cohort study aimed to evaluate incidence of ureteral calculi on non-contrast CT (NCT) in patients with flank pain (FP) and determine if clinical variables are associated with higher detection rates. 613 patients underwent NCT; no stone disease was identified in 175 patients (28.5%). Analysis demonstrated a statistically significantly increased relative risk of stone formation given four clinical variables (hematuria, nausea/vomiting, and prior stone history) when compared with FP alone. Whereas isolated FP is associated with a lower rate of ureteral calculus detection, a significant increased relative risk of ureteral calculus is seen in patients with additional clinical variables associated with stone disease (Rapp et al 2016; moderate level of evidence).

A 2014 prospective cohort study was conducted to derive and validate a clinical prediction rule (STONE score) for the presence of uncomplicated ureteral stones in CT-eligible patients. Adult patients (mean age 44) with flank pain and suspected nephrolithiasis without history of trauma, evidence of infection, known active malignancy or renal disease, or previous urologic procedure were included. The derivation sample included 1,040 records, and found 5 factors to be most predictive of ureteral stone: male sex, short duration of pain, non-black race, presence of nausea/vomiting, and microscopic hematuria, yielding a (STONE) score 0-13. Prospective validation of 491 participants found that patients with low score (0-5) have < 10% probability of stones, moderate scores (6-9) have 50% probability, and high scores (10-13) have high (89%) probability. The authors conclude that “STONE score reliably predicts the presence of uncomplicated ureteral stone and lower likelihood of acutely important alternative findings” (Moore et al 2014; high level of evidence).

Technique:
A 2017 systematic review investigated whether reducing radiation dose of CT KUB impacts specificity, sensitivity, and detection of urolithiasis. Literature was reviewed for adult patients undergoing CT KUB or NCCT for renal colic or urolithiasis. 417 articles were identified, and after screening, seven articles (n = 1,104 patients) were included. Ultra-low dose CT and low-dose CT were found to be effective techniques, yielding high sensitivity and specificity. Although they yield comparable results against standard-dose CT KUB in detecting alternative diagnoses, they may not be as effective in detecting stones < 3 mm in size or in patients with body mass index of > 30. However, this should be first-line investigation for majority of renal colic patients (Rob et al 2017; moderate level of evidence).

A 2016 retrospective study was conducted on 215 patients (age 17-101 years) who had CT of Kidneys, Ureter and Bladder (CT KUB) examinations ordered for evaluation of suspected ureteric colic. The purpose of this study was to identify the range of alternative diagnoses established by CT KUB in patients with suspected ureteric colic, and evaluate impact on patient management such as disposition, further imaging, and surgical intervention. The positive detection rate for ureteric calculi in males was 43.3% compared to 29.6% for females ($p < 0.05$). Almost two-thirds of patients were discharged following CT KUB imaging, and admission rates were significantly higher in those with alternative radiological findings ($p < 0.04$) Alternative radiological findings occurred in 72 patients (33.5%), including 15 (7.0%) who had clinically important alternative pathology. Surgical intervention was more common in patients with alternative radiological findings classified as gastrointestinal (18.2%) compared to non-gastrointestinal (3.6%), however this did not reach statistical significance ($p=0.07$). Authors concluded CT KUB imaging is the gold standard investigation in suspected ureteric colic and patients with alternative radiological findings were more likely to require admission. Non-urological surgical interventions were limited to laparotomy or laparoscopy (Sarofim et al 2016; low level of evidence).

A 2015 retrospective study reviewed findings of 322 non-consecutive patients presenting to ED with flank pain who underwent CT for diagnosis of nephroureterolithiasis. All patients had initial NECT, while 154 had additional CECT (contrast enhanced). CECT added information in 5.3% of cases but changed management in only 2%. Authors conclude that additional CECT in patients with a strong clinical suspicion of nephrouterterolithiasis may not be indicated (Agarwal et al 2015; low level of evidence).

A 2015 prospective, blinded observational study of 201 patients examined the sensitivity and specificity of a reduced-dose CT protocol for symptomatic ureteral stones, particularly those large enough to require intervention, using a protocol stratified by patient size. CT scans with both regular and reduced doses were conducted, with 63% of patients receiving the high BMI reduced-dose protocol. Ureteral stone was identified in 102 patients (50.7%) receiving regular-dose CT, with a ureteral stone > 5 mm identified in 26 (12.9%). CT with substantial dose reduction was 90.2% sensitive and 98.9% specific for ureteral stones in ED patients with a wide range of BMIs. Reduced-dose CT was 96.0% sensitive for ureteral stones requiring intervention within 90 days (Moore et al 2015; high level of evidence).

A 2014 single-center retrospective cohort study involved blind reviews of 1,000 routine abdominopelvic CTs performed with delayed excretory phase imaging to determine the added value of the latter phase in routine imaging, excluding patients with primary indication of lesion characterization. Two patients demonstrated a finding on delayed phase imaging that would have significantly affected management (a renal mass and unknown contrast-nephropathy) that would otherwise have been missed on portal-venous phase imaging. Additional incidental findings were characterized in 2-3% of patients. Relative to the approximately 60% increase in radiation dose, the authors conclude that routine delayed phase imaging is not of clinical benefit to patients. (Chan et al 2014; low level of evidence).

A 2014 cohort of 97 cases of non-contrast and contrast-enhanced CTs demonstrated that the detection of nephrolithiasis of $\geq$ 3mm is unhindered on routine portal-venous phase images, and that single-phase contrast-enhanced imaging may be utilized in evaluation of patients with suspected abdominal or flank pain secondary to renal stones without a decrement in the ability to detect such stones versus a non-contrast study. This reduces radiation dose and increases the sensitivity for the detection of non-stone-related causes for the patient's presenting symptoms (Dym et al 2014; moderate level of evidence).

Management:
A 2015 retrospective study evaluated prevalence, importance, and types of incidental findings (IF) in non-enhanced CT (NECT) scans performed for suspected renal colic, based on ACR white papers and other accepted radiographic recommendations. Review of 5,383 consecutive finalized reports of NECT using renal colic protocol was performed on adult ED patients over a 5.5-year period. Important IF were identified on 12.7% of scans. Prevalence of important IF increased with age: important IF in individuals age > 80 were 4 times more common than for those aged 18-30. Important IF occurred on 12.7% of NECT scans performed for suspected renal colic in the ED and are more common in older individuals (Samim et al 2015; moderate level of evidence).

A 2015 single-center retrospective study was conducted on 291 patients (age 18-50) presenting with "flank pain," excluding patients with end stage renal disease, UTI, pregnancy and trauma. The objective was to determine the proportion of patients with a dangerous alternative diagnosis in patients $\leq$ 50 presenting with uncomplicated (non-infected) suspected renal colic, and also to determine what proportion of these patients undergo emergent urologic intervention. Dangerous alternative diagnosis was determined by CT. One hundred and fifteen patients had renal protocol CTs, and zero alternative emergent or urgent diagnoses were identified (one-sided 95% CI [0-2.7%]). Of the 291 encounters, there were 7 urologic procedures performed upon first admission (2.4%, 95% CI [1.0-4.9%]). The prevalence of kidney stone by final diagnosis was 58.8%. The authors conclude that not all patients with suspected renal colic benefit from immediate CT, and provide some evidence that limiting or delaying scanning in non-infected patients under 50 may be safe (Schoenfeld et al 2015; low level of evidence).

Comparative Effectiveness:
A 2014 multicenter comparative effectiveness RCT randomly assigned 2,759 patients (age 18 -76 years) presenting to the emergency department (ED) with suspected nephrolithiasis to point-of-care ultrasonography (US) (n = 908), radiology US (n = 893), or CT (n = 958). Diagnostic accuracy for nephrolithiasis showed that US had lower sensitivity and higher specificity than CT. The sensitivity was 54% for point-of-care US, 57% for radiology US, and 88% for CT ($P < 0.001$), and specificity was 71%, 73%, and 58%, respectively ($P < 0.001$). Patients in US groups were less likely to undergo additional diagnostic testing with CT when they reported history of nephrolithiasis. Mean 6-month cumulative radiation exposure was significantly lower in US groups than CT group ($P < 0.001$). Serious adverse events occurred in 12.4% of patients assigned to point-of-care US, 10.8% to radiology US, and 11.2% to CT ($P = 0.50$). Related adverse events were infrequent (0.4%) and similar across groups. Return ED visits and hospitalizations did not differ significantly among groups. The authors concluded that although US was less sensitive than CT for diagnosis of nephrolithiasis, using US as initial test in patients with suspected nephrolithiasis (and using other imaging as needed) resulted in no need for CT in most patients, lower cumulative radiation exposure, and no significant differences in risk of subsequent serious adverse events, pain scores, return ED visits, or hospitalizations (Smith-Bindman et al 2014; high level of evidence).

Preoperative planning for known renal or ureteral calculus:

- **Green** – CT KUB without IV contrast before percutaneous nephrolithotomy, or to select best candidate for shock-wave lithotripsy vs. ureteroscopy
- **Green** – CT urography (CT abdomen and pelvis with and without IV contrast) in patients with complex stones prior to stone removal if the anatomy of the renal collecting system needs to be assessed
- **Yellow** – MR urography (MRI abdomen and pelvis with and without IV contrast) for complex stones or to assess renal collecting system anatomy in patients who are unable to receive CT IV contrast
- **Yellow** - MRI abdomen and pelvis without contrast for complex stones or to assess renal collecting system anatomy in patients unable to receive CT contrast and MRI contrast
- **Yellow** – Renal scintigraphy if loss of renal function is suspected
- **Red** – PET; PET-CT

Level of Evidence: CT without contrast: low; CT with contrast: low; CT with and without contrast: very low; MRI with contrast: insufficient; MRI without contrast: insufficient; MRI with and without contrast: insufficient; renal scintigraphy: low; PET-CT: insufficient

Notes concerning applicability and/or patient preferences: none

Guideline and PLE expert panel consensus opinion summary:
Non-contrast CT imaging is the most sensitive and specific imaging investigation in the diagnosis of upper urinary tract stone disease (Assimos et al [*AUA*] 2016).

Clinicians may obtain a non-contrast CT scan to help select the best candidate for shock-wave lithotripsy (SWL) vs. ureteroscopy (URS) (Assimos et al [*AUA*] 2016, Conditional Recommendation; Evidence Level Grade C).

Clinicians should obtain a non-contrast CT scan on patients prior to performing percutaneous nephrolithotomy (PCNL) (Assimos et al [*AUA*] 2016, Strong Recommendation; Evidence Level Grade C).

In patients with complex stones or anatomy, clinicians may obtain additional contrast imaging if further definition of the collecting system and the ureteral anatomy is needed (Assimos et al [*AUA*] 2016, Conditional Recommendation; Evidence Level Grade C). *The expert panel indicated that adding a contrast phase to the CT can be helpful in select patients with complex anatomy but is not required in all cases. Pyelography (either antegrade or retrograde) is routinely performed at the time of PCNL and this yields superior anatomical detail for the purposes of surgical decision-making*.

A contrast study is recommended if stone removal is planned and the anatomy of the renal collecting system needs to be assessed (Turk et al [*EAU*] 2015, Level 3/Grade A Evidence).

Enhanced CT is preferable in complex cases because it enables 3D reconstruction of the collecting system, as well as measurement of stone density and skin-to-stone distance. IVU may also be used (Turk et al [*EAU*] 2015, Level 4/Grade C Evidence).

For intracorporeal lithotripsy, preprocedural imaging, including contrast medium where possible or retrograde study when starting the procedure, is mandatory to assess stone comprehensiveness, view the anatomy of the collecting system, and ensure safe access to the renal stone (Turk et al [*EAU*] 2015, Grade A Evidence).

Clinicians should offer reimaging to patients prior to surgery if passage of stones is suspected or if stone movement will change management. Reimaging may include KUB x-ray, renal/bladder ultrasound or CT. Reimaging should focus on the region of interest and should limit radiation exposure to uninvolved regions (Assimos et al [*AUA*] 2016, Clinical Principle).

MR urography can be useful in defining anatomy …in patients with IV contrast allergy, although stones are typically not well visualized directly with MR imaging (Assimos et al [*AUA*] 2016).

Clinicians may obtain a functional imaging study (DTPA or MAG-3) if clinically significant loss of renal function in the involved kidney or kidneys is suspected (Assimos et al [*AUA*] 2016, Conditional Recommendation; Evidence Level Grade C).

<u>Clinical notes:</u>

- Use of CT for preoperative assessment in nephrolithiasis has gained widespread acceptance, as it defines stone burden and distribution, and provides information regarding collecting system anatomy, position or peri-renal structures, and relevant anatomic variants. It may also be used to predict operative outcomes and, in some instances, stone composition (Assimos et al [*AUA*] 2016).
- Consider the stone composition before deciding on the method of removal (based on patient history, former stone analysis of the patient, or HU in unenhanced CT. Stones with medium density > 1,000 HU on NCCT are less likely to be disintegrated by SWL) (Turk et al [*EAU*] 2015).
- Renal stone attenuation of < 900-1000 HU and a skin-to-stone distance of < 10cm can help predict success with SWL (Assimos et al [*AUA*] 2016)
- Contrast imaging studies can also include retrograde or antegrade pyelography, which can define the collecting system anatomy and help to determine the optimal treatment approach (Assimos et al [*AUA*] 2016).
- The use of ultrasonography alone to direct SWL or URS treatment planning should be discouraged as US is inherently inaccurate in determination of stone size, and provides no information on stone density (Assimos et al [*AUA*] 2016).
- The ability of nuclear renography to assess obstruction may be limited in cases of moderate to severe chronic kidney disease (Assimos et al [*AUA*] 2016).

<u>Technical notes:</u>

- 3D reconstructive techniques are advocated by some for their perceived utility in improving preoperative PCNL planning (Assimos et al [*AUA*] 2016).
- Optimization of CT includes limiting scan protocols to an anatomical region of interest for evaluation of the distal ureter, adjusting CT parameters for tissue thickness and body habitus, and limiting contrast phases (e.g., noncontrast only or combined injection and delayed phases) to reduce total radiation exposure (Fulgham et al [*AUA*] 2013).
- CT urography should include a noncontrast CT KUB to evaluate for calculi, a contrast phase to evaluate the renal parenchyma, and an excretory phase to evaluate for urothelium of the upper and lower urinary tracts (Davis et al [*AUA*] 2012; PLE expert panel consensus opinion).

- Sagittal and coronal reconstructions should be utilized to increase the sensitivity and specificity of CT for ureteral calculi (PLE expert panel consensus opinion).

Evidence update (2015-present):
A retrospective study of 141 patients who underwent tubeless PCNL (TPCNL) for renal stones evaluated the accuracy of three stone scoring systems (Guy's, STONE, and CROES) in predicting outcomes. The initial stone-free and complication rates after TPCNL were 78.7% (111/141) and 17.0 % (24/141). While all 3 scoring systems were identified as significant factors of stone-free rate (SFR), logistical regression demonstrated that Guy's stone score and stone burden ≥ 385 mm^2 had significant correlations with stone-free status [OR = 3.220, p = 0.001 and OR = 6.451, p = 0.002, respectively]. Guy's score (OR = 1.879, p = 0.013) was also an independent risk factor for development of complications. The authors conclude that "of the three scoring systems, Guy's score was the only significant predictive factor for SFR and complication rates after TPCNL in the analysis. Stone burden was significantly associated with postoperative stone-free status (SFS)" (Choi et al 2017; low level of evidence).

A 2016 prospective cohort study was conducted on 220 patients presenting with renal or upper ureteric stones 5-20mm undergoing helical NCCT for measurement of stone attenuation value, skin-to-stone distance (SSD), and stone size, followed by shockwave lithotripsy (SWL) treatment. Higher attenuation and increased SSD were predictors of failure (P < 0.05). The authors concluded "for patients with stones having mean attenuation of > 1000 HU and/or large SSDs, alternatives to SWL should be considered" (Abdelhamid et al 2016; low level of evidence).

A 2016 retrospective cohort study was conducted on 736 patients with ureteral stones undergoing pre-operative imaging before ureteroscopy for stone removal. Patients were placed into 4 groups—(1) reference standard contrasted imaging study (IVU), (2) NCCT, (3) both, and (4) neither (ultrasound + abdominal XR). The stone-free rate after primary ureteroscopy was 87.1% in group 1, 88.2% in group 2, 96.7% in group 3, and 89.9% in group 4 (P=0.093). No significant differences were seen among the groups for complication rates. The authors concluded "ureteroscopic treatment of ureteral stones can be safely and effectively performed with no use of contrast study imaging, except in doubtful cases of anatomical abnormalities" (Bayrak et al 2016; low level of evidence).

A 2015 retrospective cohort study was conducted on 437 patients who underwent PCNL for renal stones at a tertiary referral center and subsequently had Guy's stone score (GSS) and CROES neprolithometry scores calculated. The overall stone-free rate was 75.1%, and there was significant correlation between the GSS and CROES score and stone-free status (P < 0.001, P < 0.001), operative time (P<0.001, P<0.001), and length of hospital stay (P=0.002, P=0.01). Authors conclude that "GSS and CROES nomograms had comparable accuracies in predicting post-PCNL stone-free status" and were both predictive of complications and operative time (Bozkurt et al 2015; low level of evidence).

A 2015 single-center retrospective cohort of 122 American patients with renal calculi receiving pre- and post-operative STONE scoring through CT imaging aimed to determine success of PCNL treatment. Nephrolithometry scores ranged from 5 to 13, and mean nephrolithometry scores for residual stone of 0-2, 3-4, and >4 mm were 8.87, 9.73, and 10.79 respectively (Akhavein et al 2015; low level of evidence).

Technique:
A 2017 systematic review investigated whether reducing radiation dose of CT KUB impacts specificity, sensitivity, and detection of urolithiasis. Literature was reviewed for adult patients undergoing CT KUB or NCCT for renal colic or urolithiasis. 417 articles were identified, and after screening, seven articles (n =

1,104 patients) were included. Ultra-low dose CT and low-dose CT were found to be effective techniques, yielding high sensitivity and specificity. Although they yield comparable results against standard-dose CT KUB in detecting alternative diagnoses, they may not be as effective in detecting stones < 3 mm in size or in patients with body mass index of > 30. However, this should be first-line investigation for majority of renal colic patients (Rob et al 2017; moderate level of evidence).

Follow-up of patients being treated for known renal or ureteral calculus:

- **Green** – *
- **Yellow** – CT with and/or without IV contrast in patients with ongoing symptoms
- **Yellow** – CT with and/or without IV contrast if hydronephrosis is present on ultrasound
- **Yellow** – CT without IV contrast for patients with radiolucent stones who have ongoing symptoms or who have not passed a stone
- **Orange** – CT in patients who have passed stones or who have undergone treatment (SWL or ureteroscopic extraction) without symptoms and without residual fragments/hydronephrosis on ultrasound/KUB
- **Red** – MRI, PET; PET/CT; renal scintigraphy

*Ultrasonography (US) with or without KUB radiography are often used for initial follow-up of patients being treated for renal or ureteral calculus (Fulgham et al [*AUA*] 2013).

Level of Evidence: CT without contrast: high; CT with contrast: insufficient; CT with and without contrast: insufficient; MRI with contrast: insufficient; MRI without contrast: very low; MRI with and without contrast: insufficient; renal scintigraphy: insufficient; PET-CT: insufficient

Notes concerning applicability and/or patient preferences: none

Guideline and PLE expert panel consensus opinion summary:
The quality of the body of evidence regarding the follow-up of a ureteral calculus is low (Fulgham et al [*AUA*] 2013).

Noncontrast computerized tomography has emerged as the most sensitive and specific modality for detecting ureteral calculi … [and is used] to a lesser extent in the follow-up of known ureteral calculi before and after treatment (Fulgham et al [*AUA*] 2013).

For patients undergoing medical expulsive therapy (MET) for a ureteral calculus in whom there is documented stone passage (stone in hand) and resolution of symptoms, no further imaging is necessary (Fulgham et al [*AUA*] 2013).

For patients undergoing MET for a ureteral calculus in whom there is documented stone passage and persistent symptoms, a renal sonogram can be obtained to demonstrate whether there is persistent obstruction. If hydronephrosis is present, CT of the abdomen and pelvis with and without IV contrast is indicated to identify an additional stone, residual edema or obstruction (Fulgham et al [*AUA*] 2013).

After a period of MET in a patient with a known radiopaque ureteral calculus < 10 mm in diameter with minimal to moderate associated hydronephrosis and no evidence of renal damage, assuming the symptoms are well controlled, ultrasonography combined with plain kidneys-ureters-bladder (KUB) radiograph offers the best combination of sensitivity/specificity with minimal radiation exposure compared to NCCT imaging (Fulgham et al [*AUA*] 2013).

For patients [undergoing MET] who have ongoing symptoms, the ultrasonography/KUB combination can assess stone progression as well as ongoing hydronephrosis. If ultrasonography and KUB radiograph fail to demonstrate hydronephrosis or persistent stone, further imaging with conventional radiographs or low dose NCCT limited to the area of interest may be warranted to definitively ascertain the continued presence of the stone (Fulgham et al [*AUA*] 2013).

For patients [undergoing MET] with radiolucent stones and ongoing symptoms, low dose NCCT can assess stone progression and the degree of hydronephrosis (Fulgham et al [*AUA*] 2013).

For patients undergoing shock wave lithotripsy (SWL), follow-up renal sonogram with KUB for radiopaque stones or without KUB for radiolucent stones will document stone clearance and demonstrate the presence or absence of hydronephrosis. If the patient is asymptomatic and KUB/sonogram shows no stones or hydronephrosis, no further imaging is required. If follow-up KUB/sonogram demonstrates hydronephrosis and/or residual fragments, further observation with repeat imaging or secondary treatment is indicated. Patients with radiolucent stones and no hydronephrosis who remain symptomatic and/or have not passed fragments should be further observed with repeat imaging (low dose NCCT) or intervention as indicated (Fulgham et al [*AUA*] 2013).

For patients who undergo intact stone removal and whose symptoms have resolved, a renal sonogram is sufficient to document resolution of hydronephrosis (Fulgham et al [*AUA*] 2013).

For patients who undergo intact stone removal and whose symptoms persist or asymptomatic patients with hydronephrosis on renal sonogram, CT of the abdomen and pelvis without and with contrast will determine the presence and/or site of obstruction, with further treatment dictated by the findings (Fulgham et al [*AUA*] 2013).

For patients who underwent ureteroscopy with stone fragmentation and who are asymptomatic, follow-up imaging with a sonogram/KUB (radiopaque stones) or a sonogram (radiolucent stones) will document the presence of residual fragments and/or hydronephrosis (Fulgham et al [*AUA*] 2013).

For patients who underwent ureteroscopy with stone fragmentation and who are symptomatic, follow-up imaging with a sonogram/KUB (radiopaque stones) or a NCCT (radiolucent stones) will document the presence of residual fragments and/or hydronephrosis (Fulgham et al [*AUA*] 2013).

If renal stones are not treated, periodic evaluation is recommended (after 6 months and yearly follow-up of symptoms and stone status [US, KUB, or CT]) (Turk et al [*EAU*] 2015, Grade A Evidence).

<u>Clinical notes:</u>

- After definitive surgical intervention for a ureteral calculus, follow-up imaging is obtained to assure complete stone removal and/or absence of obstruction. Ureteral instrumentation and particularly stone fragmentation warrant postoperative imaging to document 1) the clearance of the stone/ fragments, 2) the resolution of hydronephrosis and/or 3) the development of unanticipated obstruction such as that from ureteral stricture (Fulgham et al [*AUA*] 2013).
- The incidence of postoperative obstruction in asymptomatic patients is decidedly low (Fulgham et al [*AUA*] 2013, Level C Evidence).
- Obstruction with or without associated symptoms after ureteroscopy is generally due to obstructing stone fragments or ureteral stricture. With the low incidence of stricture (< 1% in most series), obstructing fragments are likely to comprise the more common etiology (Fulgham et al [*AUA*] 2013).

<u>Technical notes:</u>

- Optimization of CT includes limited scanning protocols confined to an anatomical region of interest for evaluation of the distal ureter, adjustments of CT parameters for tissue thickness and body habitus, and limitation of phases (e.g., noncontrast only or combined injection and delayed phases) to reduce total radiation exposure (Fulgham et al [*AUA*] 2013).
- Sagittal and coronal reconstructions should be utilized to increase the sensitivity and specificity of CT for ureteral calculi (PLE expert panel consensus opinion).

<u>Evidence update (2015-present)</u>:
A 2015 retrospective cohort evaluated 122 patients with renal calculi receiving pre- and post-operative STONE scoring through CT imaging to determine success of PCNL treatment. Nephrolithometry scores ranged from 5-13, and mean nephrolithometry scores for residual stone of 0-2, 3-4, and > 4 mm were 8.87, 9.73, and 10.79 respectively. The authors conclude that with use of strict CT imaging criteria for assessment of residual stone status, the STONE scoring system is reproducible and predictive of treatment success (Akhavein et al 2015; low level of evidence).

Technique:
A 2017 systematic review investigated whether reducing radiation dose of CT KUB impacts specificity, sensitivity, and detection of urolithiasis. Literature was reviewed for adult patients undergoing CT KUB or NCCT for renal colic or urolithiasis. 417 articles were identified, and after screening, seven articles (n = 1,104 patients) were included. Ultra-low dose CT and low-dose CT were found to be effective techniques, yielding high sensitivity and specificity. Although they yield comparable results against standard-dose CT KUB in detecting alternative diagnoses, they may not be as effective in detecting stones < 3 mm in size or in patients with body mass index of > 30. However, this should be first-line investigation for majority of renal colic patients (Rob et al 2017; moderate level of evidence).

Flank pain with suspected infection:

- **Green** – CT without and/or with IV contrast after ≥ 48-72 hours of unsuccessful therapy, if symptoms resolve and recur within 2 weeks, if symptoms progress, or if symptoms are atypical
- **Green** – CT with and without IV contrast in diabetic patients or in immunocompromised patients if they do not respond promptly to treatment
- **Yellow** – CT without IV contrast after ≥ 48-72 hours of unsuccessful therapy, if symptoms resolve and recur within 2 weeks, if symptoms progress, or if symptoms are atypical and CT contrast is contraindicated
- **Yellow** – MRI with and without IV contrast after ≥ 48-72 hours of unsuccessful therapy, if symptoms resolve and recur within 2 weeks, if symptoms progress, or if symptoms are atypical and the patient is unable to receive CT contrast
- **Yellow** – MRI without IV contrast after ≥ 48-72 hours of unsuccessful therapy, if symptoms resolve and recur within 2 weeks, if symptoms progress, or if symptoms are atypical and the patient is unable or unwilling to be given CT and MRI contrast
- **Red** – PET; PET-CT; renal scintigraphy; MRI with IV contrast only

Level of Evidence: CT without contrast: insufficient; CT with contrast: low; CT with and without contrast: very low; MRI: insufficient; renal scintigraphy: low

Notes concerning applicability and/or patient preferences: none

Guideline and PLE expert panel consensus opinion summary:
[In patients with acute uncomplicated pyelonephritis], evaluation of the upper urinary tract with ultrasound should be performed to rule out urinary obstruction or renal stone disease (Grabe et al [*EAU*] 2015, Level 4/Grade C Evidence).

Otherwise healthy patients with uncomplicated pyelonephritis will typically need no radiologic workup if they respond to antibiotic therapy within 72 hours. If there is no response to therapy, CT of the abdomen and pelvis is the study of choice (Nikolaidis et al [*ACR*] 2012*).

In patients whose pyelonephritis symptoms do not improve within 3 days, or resolve and then recur within 2 weeks, repeated urine culture and antimicrobial susceptibility tests and an appropriate investigation, such as renal US, CT, or renal scintigraphy, should be performed (Grabe et al EAU 2015, Level 4/Grade B Evidence). *The PLE expert panel thought that 48-72 hours was a more appropriate interval and that patients with deterioration of their clinical condition should be imaged early* (PLE expert panel consensus opinion).

Diabetics or other immunocompromised patients should be evaluated with precontrast and post contrast CT within 24 hours of diagnosis, if response to therapy is not prompt (Nikolaidis et al [*ACR*] 2012*).

In patients with acute pyelonephritis – complicated patient (e.g., diabetes or immunocompromised or history of stones or prior renal surgery or not responding to therapy), the *American College of Radiology* (Nikolaidis et al [*ACR*] 2012*) recommends CT abdomen and pelvis without and with IV contrast (8), CT abdomen and pelvis with IV contrast (8), US kidneys and bladder retroperitoneal with KUB (6), CT abdomen and pelvis without IV contrast (6), and MRI abdomen and pelvis without and with IV contrast (6).

MRI and MRU are felt to be useful in patients in whom the use of iodinated contrast material must be avoided (particularly those with contrast sensitivity), but case-controlled studies fully documenting its efficacy have yet to be published (Nikolaidis et al [ACR] 2012*).

*The *American College of Radiology* guideline by Nikolaidis et al (2012) did not pass the AGREE II cutoff score of 90 (it scored a 62.5) or the rigor of development scaled domain score cutoff of 50% (it scored a 20%). It was included, however, because of its direct relevance to the acute pyelonephritis clinical scenario.

Clinical notes:

- Acute pyelonephritis is suggested by flank pain, nausea and vomiting, fever, or costovertebral angle tenderness, and can occur in the absence of symptoms of cystitis (Grabe et al [*EAU*] 2015).
- When the kidney itself is involved or when there is difficulty in differentiating lower UTI from renal parenchymal involvement, imaging studies are often requested, both for diagnosis and to plan management (Nikolaidis et al [*ACR*] 2012).
- Conditions thought to predispose a patient with lower UTI to renal involvement include vesicoureteral reflux, altered bladder function, congenital urinary tract anomalies, and the presence of renal calculi (Nikolaidis et al [*ACR*] 2012).
- Abdominal radiography (i.e., abdomen and pelvis [KUB]) is of very limited use in the setting of acute pyelonephritis, unless large coexisting staghorn or obstructing calculi are being followed (Nikolaidis et al [*ACR*] 2012).

Evidence update (2014-present):

A 2017 retrospective analysis was conducted on 100 patients undergoing triphasic abdominal CT scans for evaluation of suspected acute pyelonephritis and/or urolithiasis. The authors sought to evaluate the diagnostic accuracy of CT for these conditions in the nephographic phase only. The study concluded that CT assessment of acute pyelonephritis and urolithiasis can be accurately performed using only the nephrographic phase (Taniguchi et al 2017; low level of evidence).

A 2017 prospective study assessed the added-value of systematic unenhanced abdominal CT on emergency department (ED) diagnosis. The study included 401 consecutive patients 75 years of age or older, admitted to the ED with acute abdominal symptoms, and investigated by early systematic unenhanced abdominal CT scan. Systematic unenhanced CT significantly improved the accurate diagnosis (76.8% to 85%, p=1.1x10-6) and management (88.5% to 95.8%, p=2.6x10-6) rates compared to current practice. It allowed diagnosing 30.3% of acute unsuspected pathologies, 3.4% of which were unexpected surgical procedure requirement. Systematic unenhanced abdominal CT improves ED diagnosis accuracy and appropriate management in elderly patients presenting with acute abdominal symptoms compared to current practice (Millet et al 2017; moderate level of evidence).

Incidental/indeterminate renal mass or complex cyst:

- **Green** – CT with and without IV contrast
- **Green** – MRI with and without IV contrast
- **Yellow** – MRI without IV contrast in patients who are unable or unwilling to receive CT and MRI contrast
- **Yellow** – CT without IV contrast to detect fat in angiomyolipomas, or in patients who are unable to undergo MRI and unable or unwilling to be given CT IV contrast
- **Orange** – CT with IV contrast except in patients with prior noncontrast CT within 6 months
- **Red** – Renal scintigraphy; PET; PET-CT; MRI with IV contrast

Level of Evidence: CT without contrast: very low; CT with contrast: very low; CT with and without contrast: low; MRI with contrast: low; MRI without contrast: insufficient; MRI with and without contrast: low; renal scintigraphy: insufficient; PET-CT: insufficient

Notes concerning applicability and/or patient preferences: none

Guideline and PLE expert panel consensus opinion summary:
Ultrasound should be used for the initial evaluation of incidental renal lesions incompletely visualized or indeterminate on MRI or CT. If a simple cyst is noted on ultrasound, additional imaging is not indicated. Complex lesions not fulfilling the criteria of a simple cyst are considered indeterminate and require further evaluation (Heilbrun et al [*ACR*] 2014*).

Ultrasound may be useful to clarify a mass seen on CT that is probably a hyperdense cyst and is the modality of choice if IV contrast is contraindicated (Heilbrun et al [*ACR*] 2014*).

If a complex cyst is first identified on ultrasound, contrast-enhanced [CT or MRI] should be performed to better characterize the cyst (Richard et al [*Canadian Urological Association* (*CUA*)] 2017, Level of evidence: 4; Recommendation: D).

Multi-phasic CT urography with and without contrast had the most consistent and highest sensitivities and specificities for detecting lesions of the renal parenchyma and the upper tracts. The multi-detector CT scan appears to offer optimal imaging information (Davis et al [*AUA*] 2012).

CT is the modality of choice for evaluating indeterminate renal lesions that are suspicious for malignancy. For those patients who cannot tolerate iodinated IV contrast material due to allergy, MRI with gadolinium contrast is advised (Heilbrun et al [*ACR*] 2014*).

MRI appears to be more sensitive than CT and tends to upgrade cystic lesions. Thus, some caution is advised when using MRI findings to direct clinical management at this time (Heilbrun et al [*ACR*] 2014*).

In patients with indeterminate renal mass – patient with normal renal function, the *American College of Radiology* (Heilbrun et al [*ACR*] 2014*) recommends CT abdomen without and with IV contrast (9), MRI abdomen without and with IV contrast (8), and US kidney retroperitoneal with duplex Doppler (8).

In patients with indeterminate renal mass – patient with renal insufficiency (contraindication to intravenous contrast), the *American College of Radiology* (Heilbrun et al [*ACR*] 2014*) recommends US kidney retroperitoneal with duplex Doppler (8), MRI abdomen without IV contrast (7), biopsy renal mass (6), and CT abdomen without IV contrast (5).

* The *American College of Radiology* guideline by Heilbrun et al (2014) did not pass the AGREE II cutoff score of 90 (it scored a 64.5) or the rigor of development scaled domain score cutoff of 50% (it scored a 26%). It was included, however, because of its direct relevance to the indeterminate renal mass clinical scenario.

<u>Clinical notes:</u>

- MRI is more sensitive to contrast enhancement and is recommended for renal masses with inconclusive enhancement or for depicting enhancing nodules (Herts et al [*ACR*] 2018).
- MRI better detects and characterizes small renal cysts by their T2 hyperintensity and better detects enhancement in small renal lesions, and is not subject to pseudoenhancement as is CT (Herts et al [*ACR*] 2018).
- MRI depicts more septa or thickened walls in complex cystic masses, which may result in a higher Bosniak classification (Herts et al [*ACR*] 2018).
- Bosniak category I lesions are simple cysts that are considered benign. Transformation into a more complex cyst is rare and has been reported in only a handful of cases. As this is rare in occurrence, these cysts do not require follow-up (Richard et al [*CUA*] 2017, Level of evidence: 3; Recommendation: B).
- Bosniak category II lesions are minimally complex cysts also generally considered to be benign, but there are reports in the literature of them being malignant. Similar to category I cysts, a follow-up for properly classified Bosniak II cysts is not warranted (Level of evidence: 3; Recommendation: C). When there is doubt as to their categorization based on imaging characteristics, these lesions should be considered as being Bosniak category IIF lesions and followed accordingly (Richard et al [*CUA*] 2017).
- Bosniak category IIF lesions have a relatively high risk of malignancy and require follow-up (Level of evidence: 3; Recommendation: B). In view of the low metastatic potential of these lesions (if malignant), it seems reasonable to follow these lesions with a contrast-enhanced CT scan or MRI every six months for the first year (Level of evidence: 4; Recommendation: D). Ultrasound in combination with CT or MRI may be used if the lesion is stable on follow-up. Cases without progression should be followed annually for at least five years (Richard et al [*CUA*] 2017, Level of evidence: 4; Recommendation: D).
- Bosniak category III lesions have been found to be malignant approximately 54% of the time. Surgical excision is generally suggested (Level of evidence: 3; Recommendation: B). Active surveillance and thermal-ablation therapies may also be considered as appropriate treatment alternatives in select cases (Level of evidence: 4; Recommendation: D). There is currently no evidence to dictate any specific follow-up scheme. However, if active surveillance is considered, it seems reasonable to follow these lesions with abdominal imaging every six months for the first two years, followed by yearly imaging thereafter, if the lesion is stable (Richard et al [*CUA*] 2017, Level of evidence: 4; Recommendation: D).
- Bosniak category IV lesions have been found to be malignant approximately 80-90% of the time. Surgical excision is generally suggested (Level of evidence: 3; Recommendation: B). Nevertheless, most of these malignant cysts are thought to have low metastatic potential and thus, more conservative management may be safely considered in select cases (Richard et al [*CUA*] 2017, Level of evidence: 4; Recommendation: D).

<u>Technical notes:</u>

- Any CT or MRI examination for renal lesion characterization should be performed with and without IV contrast using a dedicated renal mass protocol (Herts et al [*ACR*] 2018.

<u>Evidence update (2016-present):</u>
In a 2018 publication, the ACR Incidental Findings Committee (IFC) presented recommendations for renal masses that are incidentally detected on CT. These recommendations represent an update from the renal component of the JACR 2010 white paper on managing incidental findings in the adrenal glands, kidneys, liver, and pancreas. The Renal Subcommittee, consisting of six abdominal radiologists and one urologist, developed this algorithm. The recommendations draw from published evidence and expert opinion and were finalized by informal iterative consensus. Each flowchart within the algorithm describes imaging features that identify when there is a need for additional imaging, surveillance, or referral for management (Herts et al [*ACR*] 2018).

A 2017 retrospective study aimed to evaluate the ability of US to characterize hyperattenuating cysts detected as indeterminate hyperattenuating renal lesions on unenhanced and single phase enhanced CT. A total of 107 consecutive homogeneously hyperattenuating renal lesions underwent gray-scale and Doppler US. Mean lesion size ± SD was 20 ± 16 mm (range, 6–96 mm). 89.7% (96/107) of the lesions were visible on US, including all lesions that were ≥ 15 mm. US correctly classified 82% of lesions as simple cysts. Including the 11 (10%) nonvisible lesions reduced sensitivity and specificity for diagnosis of hyperattenuating cyst to 73.0% (95% CI, 66.9–75.9%) and 89.7% (95% CI, 74.2–97.2%), respectively. The authors concluded that US visualizes a substantial majority of hyperattenuating renal lesions including all lesions measuring ≥ 15 mm (Siddaiah et al 2017; low level of evidence).

A 2016 retrospective study reviewed 13,600 reports of abdominal sonographic examinations, and identified 120 small uncomplicated echogenic renal lesions in patients without known malignancy of any kind, tuberous sclerosis, or lesions > 1.0 cm. Advanced imaging (CT, MRI) and/or long term follow up was used as reference standard. None of the masses developed malignancy. The authors conclude that "small echogenic renal masses up to 1 cm in size that fulfill our study criteria are so likely to be benign that they can be safely ignored" (Itani et al 2016; low level of evidence).

A 2017 retrospective study sought to determine outcomes of hyperechoic renal lesions measuring < 1 cm on US. A total of 161 lesions were evaluated with follow-up US, CT, or MRI. At CT or MRI, 58.4% of lesions were confirmed to be angiomyolipomas. At CT or MRI, 11.8% of lesions had no correlate; 3.1% were not visualized at follow-up US. An additional 23.6% were stable at 2-year follow-up imaging or beyond. Overall, 1.9% of the lesions were either presumed malignant or indeterminate. The authors conclude that most hyperechoic renal lesions measuring ≤ 1 cm were clinically insignificant, suggesting that such lesions may not require additional imaging (Doshi et al 2017; low level of evidence).

A 2017 retrospective study evaluated what percentage of echogenic nonshadowing renal lesions > 4 mm found on US are angiomyolipomas (AMLs). Study data was obtained over 45 months, with follow-up data on 158 lesions (132 patients) available. A total of 98 (62%) lesions were AMLs, 8 (5.1%) were renal cell carcinomas, 3 (1.9%) were oncocytomas, 17 (10.8%) were artifacts, 7 (4.4%) were fat, 5 (3.2%) were calculi, 8 (5.1%) were scars, and 12 (7.6%) were complicated cysts. Mean age of patients with AML was significantly lower than those without (61.71 vs. 68.80 years; $p = 0.005$). There was also a female association with AMLs ($p < 0.001$). The authors conclude that echogenic nonshadowing renal lesions > 4 mm seen on US should not be assumed to represent an AML without follow-up because a percentage of renal cell carcinomas will be missed. Although certain US features can be useful in differentiating AML from renal cell carcinoma and CT is frequently diagnostic, an understanding of MRI is important for its potential to detect lipid-poor AMLs (de Silva et al 2017; low level of evidence).

Incidental/indeterminate adrenal mass or nodule – adrenal incidentaloma (AI):

- **Green** – CT without IV contrast*
- **Green** – CT with and without IV contrast
- **Green** – CT with IV contrast to further characterize an adrenal lesion identified with non-contrast CT of chest/abdomen in the last six months
- **Green** – MRI without IV contrast
- **Yellow** –MRI with and without IV contrast for preoperative staging
- **Yellow** – CT with IV contrast for preoperative staging
- **Yellow** – PET or PET-CT to further characterize an indeterminate lesion on CT or in a patient with a known primary neoplasm sensitive to PET
- **Red** – Renal scintigraphy; MRI with IV contrast

*If possible, the scan should be checked with the patient on the table and if the lesion measures > 10 HU, contrast should be administered in order to assess the washout.

Level of Evidence: CT without contrast: very low; CT with contrast: very low; CT with and without contrast: low; MRI: very low; renal scintigraphy: insufficient; PET-CT: low

Notes concerning applicability and/or patient preferences: none

Guideline and PLE expert panel consensus opinion summary:
All patients found to have an adrenal incidentaloma should undergo clinical, biochemical, and imaging examinations to determine the presence/absence of symptoms and signs caused by an excess of adrenal hormone and to determine whether the tumor is malignant (Lee et al [*Korean Endocrine Society*] 2017; C Level Recommendation).

We recommend that all adrenal incidentalomas undergo an imaging procedure to determine if the mass is homogenous and lipid-rich and therefore benign (Fassnacht et al [*European Society of Endocrinology* (*ESE*) & *European Network for the Study of Adrenal Tumors* (*ENSAT*) 2016; very low quality of evidence).

Non-contrast computed tomography (CT) is recommended as an initial imaging study to determine whether the adrenal tumor is benign (Lee et al [*Korean Endocrine Society*] 2017; C Level Recommendation; Fassnacht et al [*ESE & ENSAT*] 2016; very low quality of evidence).

We suggest that if the noncontrast CT is consistent with a benign adrenal mass (Hounsfield units $\leq$ 10) that is homogeneous and < 4 cm, no further imaging is required (Fassnacht et al [*ESE & ENSAT*] 2016; very low quality of evidence).

We suggest the use of MRI rather than CT in adults < 40 years of age if dedicated adrenal imaging is required (Fassnacht et al ESE & ENSAT 2016; Lee et al Korean Endocrine Society 2017; E Level Recommendation) …however, the adapted low-dose unenhanced CT protocols can limit radiation exposure and can be considered as an alternative (especially if the availability of MRI is limited) (Fassnacht et al [*ESE & ENSAT*] 2016).

In patients with an indeterminate adrenal mass (by imaging) opting not to undergo adrenalectomy following initial assessment, we suggest a repeat noncontrast CT or MRI after 6-12 months to exclude significant growth (Fassnacht et al [*ESE & ENSAT*] 2016; very low quality of evidence).

If a malignant adrenal tumor is suspected, but CT results are uncertain, positron emission tomography using F-FDG-PET or PET/CT can be performed selectively (Lee et al [*Korean Endocrine Society*] 2017; C Level Recommendation).

We recommend that in patients with a history of extra-adrenal malignancy, adrenal lesions, characterized as benign by noncontrast CT, require no further specific adrenal imaging follow-up (Fassnacht et al [*ESE & ENSAT*] 2016; Lee et al [*Korean Endocrine Society*] 2017; C Level Recommendation).

We suggest that in patients with a history of [a PET sensitive] extra-adrenal malignancy, FDG-PET/CT, performed as part of investigations for the underlying malignancy, can replace other adrenal imaging techniques (Fassnacht et al [*ESE & ENSAT*] 2016; Lee et al [*Korean Endocrine Society*] 2017; C Level Recommendation).

For indeterminate lesions in patients with a history of extra-adrenal malignancy, we recommend imaging follow-up assessing the potential growth of the lesion at the same interval as imaging for the primary malignancy. Alternatively, FDG-PET/CT, surgical resection, or a biopsy can be considered (Fassnacht et al [*ESE & ENSAT*] 2016).

In patients with incidentally discovered adrenal mass – no history of malignancy; mass 1-4 cm in diameter; initial evaluation, the *American College of Radiology* (Remer et al [*ACR*] 2012*) recommends CT abdomen without IV contrast (8), CT abdomen without and with IV contrast (8), and MRI abdomen without IV contrast (8).

In patients with incidentally discovered adrenal mass – no history of malignancy; mass 1-4 cm in diameter; follow-up evaluation for indeterminate lesion on initial evaluation, the *American College of Radiology* (Remer et al [*ACR*] 2012*) recommends CT abdomen without IV contrast (8) and MRI abdomen without IV contrast (8).

In patients with incidentally discovered adrenal mass – no history of malignancy; mass > 4 cm in diameter (if not typical for adenoma, myelolipoma, hemorrhage, or simple cyst, consider resection), the *American College of Radiology* (Remer et al [*ACR*] 2012*) recommends CT abdomen with IV contrast (8), MRI abdomen without and with IV contrast (8), and FDG-PET/CT skull base to mid-thigh (5).

* The *American College of Radiology* guideline by Remer et al (2012) did not pass the AGREE II cutoff score of 90 (it scored a 70.5) or the rigor of development scaled domain score cutoff of 50% (it scored a 31%). It was included, however, because of its direct relevance to the incidentally discovered adrenal mass clinical scenario.

<u>Clinical notes:</u>

- Previous recommendations and reviews have not considered adrenal incidentalomas < 1 cm…we agree with this approach and would perform additional diagnostic work-up only in lesions $\geq$ 1cm unless clinical signs and symptoms suggestive of adrenal hormone excess are present (Fassnacht et al [*ESE & ENSAT*] 2016).
- CT and MRI are techniques mainly aiming to identify benign lesions, therefore representing tools designed for the exclusion of adrenal malignancy. Conversely, FDG-PET/CT is mainly used for the detection of malignant disease (Fassnacht et al [*ESE & ENSAT*] 2016).

- A size greater than 4-6 cm on a CT scan, a tumor with an irregular margin or heterogeneity, an attenuation coefficient of $\geq$ 10 HU in a non-contrast CT, washout of the contrast agent after 10-15 minutes of < 40%, calcification, and invasion into surrounding tissue all suggest malignancy (Lee et al [*Korean Endocrine Society*] 2017).
- The most useful tool to determine whether an adrenal tumor is malignant is a CT scan. When the tumor is < 4 cm, the risk of adrenal cancer is less than 2%, but when the size is $\geq$ 6 cm, the risk increases to 25% (Lee et al [*Korean Endocrine Society*] 2017).
- Ultrasonography (US) does not detect adrenal masses with the same sensitivity as CT or MRI (Terzolo et al [*Italian Association of Clinical Endocrinologists* (*AME*)] 2011).

Technical notes:

- In many adenomas, more than 50% of the contrast agent disappears 10 to 15 minutes after the administration of contrast agent. Adrenal cancer, pheochromocytoma, and metastatic cancer all show less than a 50% loss. This finding has very high sensitivity and specificity (Lee et al [*Korean Endocrine Society*] 2017).
- The adrenal washout determination is based on the principle that adrenal adenomas rapidly wash out contrast material. Adrenal washout is calculated using CT scans through the adrenal gland and measuring Hounsfield Unit (HU) regions of interest (ROIs), ideally pre-IV contrast (A), post-IV contrast in the portal venous phase (B), and after a 15 minute delay post IV-contrast (C). When feasible, the ROI circle should cover at least half of the representative area of the adrenal lesion where it is best seen. Images may be obtained through the adrenal glands only to reduce radiation dose (Dunnick & Korobkin 2002).
- The Percentage of Relative Washout is calculated by taking the HU measurement post-contrast in the portal venous phase (B), subtracting measurement post-delay (C), and then dividing by the measurement from the portal venous phase: (B-C)/B. If this number is > 0.40 (40%), the lesion has high likelihood of being an adenoma (benign) (Dunnick & Korobkin 2002).
- The Percentage of Enhancement Washout is calculated by taking the HU measurement from the portal venous phase (B) and subtracting the measurement in the delayed phase (C) and dividing this number by the subtraction of the non-contract HU measurement (A) from portal venous phase measurement (B): (B-C)/(B-A). If this number is greater than 0.6 (60%), the lesion has a high likelihood of being an adenoma (benign) (Dunnick & Korobkin 2002).

Evidence update (2011-present):

A 2017 retrospective observational study was conducted among 216 patients who underwent unilateral adrenalectomy for adrenal mass to characterize the predictive utility of CT findings on final surgical pathology. Malignant tumors were significantly larger in diameter (9.5 cm vs 2.7 cm) and all tumors that were identified as benign on CT imaging were also found to be benign on final surgical pathology. The authors conclude "regardless of size, when interpreted as benign on CT scan, laparoscopic adrenalectomy, if technically feasible, should be the technique used when surgery is offered, or close surveillance may be a safe alternative" (Azoury et al 2017; low level evidence).

A 2016 retrospective study of adrenal carcinoma incidence within incidentally discovered adrenal nodules was conducted on 653 patients (mean age 66 years) undergoing CT scans for other indications. After 3 years of follow-up in 392 patients, no nodules < 4 cm were malignant. The authors conclude that "in patients without pre-existing cancer, additional imaging for small incidental adrenal nodules is unnecessary" (Young et al 2016; low-level of evidence).

A 2016 single center prospective study was conducted on 38 patients (age range 27-76 years) with adrenal masses that were incidentally detected on abdominal ultrasound examination (14 patients) or CT examination of the abdomen that was performed for various clinical conditions (24 patients). The study aimed to compare the accuracy of CT and MRI in characterizing adrenal masses. Every lipid-rich adenoma (15 masses) was accurately diagnosed on both CT and MRI. Two masses of six lipid-poor adenomas were correctly diagnosed on both CT and MRI, and three masses were correctly diagnosed by CT alone and MRI failed in diagnosis. These adenomas had CT attenuation values ranging from 28-37 HU. Both CT and MRI failed in diagnosis of one mass. This resulted in a statistically significant McNemar test (P=0.083). Overall, washout CT had superior sensitivity to chemical-shift MRI. All nonadenomas (24 masses) were correctly diagnosed on both CT and MRI. The sensitivity for diagnosis of adenoma by MRI versus CT was 81% (17/21) versus 95% (20/21), respectively, and specificity was 100% (24/24) for both CT and MRI. In adenomas measuring > 20 HU, the sensitivity was 0% (0/4) and 75% (3/4) for MRI and CT, respectively. There was significant difference between CT and MRI in terms of accuracy for lipid-poor adenoma characterization, but there was no significant difference between CT and MRI in terms of diagnosing lipid-rich adenoma and nonadenomas (P=1.00). Authors concluded that the washout CT study is more sensitive and accurate than the chemical-shift MRI in characterizing lipid-poor adenomas. Overall, washout CT had a superior sensitivity compared to chemical shift MRI in characterizing the adrenal masses (Warda et al 2016; very low level of evidence).

A 2015 retrospective study of 647 patients (mean age 62.7) investigated outcomes of adrenal incidentaloma (AI). Patients had radiologic (CT or MRI) and hormonal evaluation performed at baseline; mean AI size was 25.3 ± 17.0 mm. 91.4% of adrenal lesions were hormonally normal. Hormonally active tumors were larger than nonfunctional ones (39.3 ± 24.3 mm vs. 23.9 ± 15.6 mm; P < .001). Bilateral adrenal tumors were discovered in 11% of patients. Four cases of adrenal cortical carcinoma (ACC) were detected, with mean tumor size 91 ± 34 mm; in 2 cases, tumors were hormonally active. Fourteen patients (2.2%) were diagnosed with adrenal gland metastasis, with mean tumor size 39.1 ± 23.0 mm. A total of 593 patients (93%) were followed ≥ 24 mo. In 86.3%, the size of tumor was unchanged by time of last follow-up. Almost all (99.6%) nonfunctioning AIs remained hormonally inactive during follow-up period. The authors conclude most AIs were benign, but a small number were functional and malignant. The prognosis of patients with adrenal metastasis was extremely poor, but otherwise, mortality rate was similar to that of general population. Follow-up of AIs < 4 cm with initial nonfunctional profile and benign radiologic appearance appears unwarranted (Patrova et al 2015; low level of evidence).

A 2015 retrospective study examined imaging characteristics of adrenal tumors preceding the diagnosis of adrenocortical cancer (ACC). 20 patients with a diagnosis of ACC and a prior adrenal tumor were identified among 422 patients. Chart and image review for patient characteristics and initial, interval, and diagnostic imaging characteristics (size, homogeneity, borders, density, growth rate) were conducted. Of the initial tumors, 25% were < 2cm in size. Surveillance led to diagnosis of ACC within 24 months in 50% of patients. The growth pattern was variable, with some lesions showing long-term stability (up to 8 years) in size. Antecedent lesions in patients with a diagnosis of ACC are often indeterminate by imaging criteria and can be small. The authors conclude that, given the rarity of ACC, the increased risk of additional evaluation may not be warranted (Nogueira et al 2015; low level of evidence).

A 2014 retrospective chart review aimed to determine the incidence of a secondary imaging modality (SIM) in the workup of adrenal masses and the usefulness of this additional imaging in changing surgical management among adult patients who underwent at least one imaging study prior to surgery. A multivariate logistic regression model was constructed to identify patient factors that predisposed SIM. A total of 264 cases met inclusion criteria, of which 98 (37%) were identified to have SIM. Patients with cancer, incidentaloma, and pheochromocytoma were more likely to undergo additional imaging. MRI was the most commonly obtained SIM. The authors conclude that the high incidence of unnecessary additional imaging performed in patients undergoing adrenalectomy is counter-productive to efforts towards high quality healthcare (Lou et al 2015; low level of evidence).

A 2014 retrospective study analyzed 29 lipid-rich adrenal adenomas in 28 adult patients to determine the diagnostic accuracy of FDG PET-CT in predicting the hormone-secretion status of lipid-rich adenomas. Based on a modest sensitivity (0.69), specificity (0.81), and PPV (0.76) of the SUV ratio on FDG PET-CT for detecting hormone-secreting adenomas, the authors concluded that additional endocrinologic investigations are strongly recommended when an FDG-avid lipid-rich incidentaloma is detected on FDG PET-CT (Takanami et al 2014; low level of evidence).

A retrospective cohort study of 282 adrenal incidentalomas on routine abdominal CT found that a majority of tumors are nonfunctional and benign, with a small number of tumors (13.8%; more common in women and among those with HU > 10) being functional adrenal tumors, with even fewer representing malignancy. Few changes were observed over a mean 23 month follow-up period, and the authors conclude that initial imaging characteristics and biochemical workup are of significantly greater diagnostic value than follow-up examinations. No discussion was made of initial diagnostic accuracy at first imaging (Cho et al 2013; low level of evidence).

A 2013 retrospective study was conducted on 188 patients (age range 23- 95 years) with adrenal masses 1-4 cm to determine whether morphologic features of adrenal masses detected at initial contrast-enhanced MDCT differentiate benign from malignant disease. There were 171 (81%) benign and 40 (19%) malignant adrenal masses (all metastases diagnosed in patients with known extraadrenal malignancy). For individual morphologic features in diagnosing malignancy, irregular margins had 30–33% sensitivity and 95–96% specificity and an enhancing rim had 5–13% sensitivity and 98–99% specificity. No imaging features were reliable in predicting benignity. When an adrenal mass was deemed suspicious, sensitivities for malignancy ranged from 54%-74% and specificities from 96%-97%. No malignant lesions occurred in patients without a known history of cancer. Authors concluded that when an adrenal mass has malignant morphologic features it likely represents a malignant lesion. The remaining morphologic features, (e.g., smooth margin and homogeneous density) can be seen in both benign and malignant disease, and are not sufficient for characterization of adrenal masses, particularly in patients with a known history of malignancy (Song et al 2013; low level of evidence).

A 2011 prospective cohort study investigated the incidence, clinical features, and natural history of incidentally discovered adrenal mass lesions (adrenal incidentaloma [AI]) in patients undergoing radiological exam over an 18-month period. Inclusion criteria was incidentally discovered adrenal enlargement or mass lesion in patients without extra-adrenal malignancy on detection. Of 534 patients assessed for eligibility, 226 (mean age 67 years, 62.4% women; mean lesion diameter 23.9 mm, 22.6% bilateral) were included. Mean follow-up was 19.0 months. No primary adrenal malignancy was found. A total of 6.6% of patients with an AI had surgery, and benign hormone-producing tumors were verified in 3.1%. Repeat CT and hormone evaluation after 2 years did not increase the sensitivity for diagnosis of malignant or hormone-producing tumors (Muth et al 2011; moderate level of evidence).

Guideline exclusions:

- Renal trauma,
- Renal transplant evaluation,
- Renal or bladder cancer staging or follow-up,
- Prostate cancer detection, staging or follow-up,
- Lower urinary tract symptoms,
- Renal failure,
- Renovascular hypertension,
- Pregnant patients,
- Pediatric patients, and
- Dual energy CT