Evaluation of two diuresis renography decision support systems to determine the need for furosemide in patients with suspected obstruction

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ABSTRACT

Purpose: The purpose of this study was to compare the decisions regarding the need for furosemide made by two independent renal decision support systems, RENEX and CARTAN, with the need for furosemide determined in clinical practice and by expert readers using the baseline plus furosemide protocol.

Materials and Methods: RENEX and CARTAN are independent decision support systems that reach their conclusions without operator input. RENEX is a knowledge-based system and CARTAN is a statistical decision support system both trained using the same pilot group of 31 adult patients (61 kidneys) referred for suspected obstruction. Subsequently, both systems were prospectively applied to 102 patients (200 kidneys) of whom 70 received furosemide; decisions regarding the need for furosemide were compared to the clinical decisions and the decisions of three experts who independently scored each kidney on the need for furosemide and resolved differences by majority vote.

Results: RENEX agreed with the clinical and experts' decisions to give furosemide in 97% (68/70) and 98% (65/66) of patients, respectively, whereas CARTAN agreed in 90% (63/70) and 89% (59/66), respectively, p < 0.03. In contrast, CARTAN agreed with the experts' decision to withhold furosemide in 78% of kidneys (87/111) whereas RENEX agreed in only 69% of kidneys (77/111), p = 0.008.

Conclusions: Use of RENEX or CARTAN as decision support tools in the baseline plus furosemide protocol has the potential to help the radiologist avoid unnecessary imaging and reduce the technologist, computer, camera and physician time required to perform the procedure.
INTRODUCTION

In the evaluation of suspected ureteral obstruction, an international consensus panel recommended baseline imaging with Tc-99m mercaptoacetyltriglycine (MAG3) followed by furosemide administration and 15 minutes of additional imaging [1]. Some investigators have recommended strategies to eliminate the need for furosemide in selected patients [2]. The authors of the consensus report did note that baseline imaging might be sufficient to exclude obstruction in experienced hands but this option was not their general recommendation [1]. Nevertheless, if the baseline examination can exclude obstruction, the patient can be spared the administration of furosemide and additional imaging time and there will also be a cost savings due to the reduction of camera, computer and technologist time required to complete the furosemide component of the study and physician time required to interpret it.

In spite of these advantages, it may be challenging for a general radiologist to acquire the experience and expertise in diuresis renography to determine with confidence whether or not a kidney is obstructed or when furosemide is not required. Radiologists are required to master an ever-expanding knowledge base while the hours available to master this knowledge base and apply it to specific tasks are steadily shrinking due to the pressure to increase the number of studies each radiologist interprets. The convergence of an expanding knowledge base and escalating time constraints inevitably increases the risk of physician error. This is particularly true of low volume studies such as diuresis renography where radiologists may have had limited training and experience. In fact, a large percentage of the estimated 590,000 renal scans performed annually in the United States are interpreted at sites that perform less than three studies per week [3]. For these reasons, it is particularly important to develop and implement decision support tools to assist physicians in interpreting low volume studies so that they can be interpreted at a faster rate and at a higher level of expertise.

The digital and dynamic nature of Tc-99m MAG3 renal scan data has made it possible to quantify a variety of functional renal parameters to produce an expanded knowledge base. Two independent renal decision support systems (RENEX and CARTAN) are being developed to use this expanded knowledge base to determine the need for furosemide and to detect renal obstruction in patients referred for diuresis renography [4, 5]. RENEX (renal expert) uses a set of rules obtained from human experts to analyze the quantitative parameters obtained from MAG3 scintigraphy whereas CARTAN (classification and regression tree analysis) is a statistical method that grows and prunes a decision tree based on an analysis of these quantitative parameters in a training data set [6]. As an intermediate step to developing a decision support system to detect obstruction, this prospective study was performed to compare the decisions regarding the need for furosemide made by a heuristic approach (RENEX) and an analytic approach (CARTAN) with the need for furosemide determined in clinical practice and by expert readers.
SUBJECTS AND METHODS

This study was performed under the purview and with the approval of Emory's Internal Review Board. Data collection and database use were compliant with the terms of the Health Insurance Portability and Accountability Act.

Acquisition Protocol and Data Collection:

Patients were hydrated with approximately 10 ounces of water on arrival in the department. Imaging was performed with the patient supine and the scintillation camera detector placed under the table. A three-phase dynamic acquisition was begun at the time of injection of approximately 10 mCi of Tc-99m MAG3. Phase one consisted of twenty-four 2-second frames, phase two was sixteen 15-second frames, and phase three was forty 30-second frames. All patient studies were processed using the QuantEM™ 2.0 renal quantification program to generate the input parameters for RENEX and CART. The QuantEM™ software, developed specifically for Tc-99m MAG3 [7], has been validated in a multicenter trial [8], incorporates several quality control procedures to improve reproducibility and generates specific quantitative parameters recommended for scan interpretation.

To process the baseline renogram, a static image is summed from the 2-3 minute post-injection frames. Using a filtered version of this image, whole kidney, background and cortical regions of interest (ROIs) are automatically defined. The user can override any of these automatic ROIs and replace them with manual ROIs. Background-subtracted whole kidney and cortical curves are generated and 47 quantitative parameters are generated including patient demographics (height, weight, age, sex, body surface area), curve parameters (time to peak counts, and 20 min to count ratio for both whole kidney and cortical ROIs), voiding indices (post-void to pre-void and post-void to maximum count ratios), relative uptake and the MAG3 clearance. The MAG3 clearance is calculated from the 1-2.5 minute whole kidney uptake of MAG3 corrected for renal depth and attenuation and the pre-injection and post-injection images of the dose syringe [7-10].

Protocol Survey:

To estimate the frequency of use of the baseline plus furosemide protocol, one of the authors asked for a show of hands or keypad response from radiologists and nuclear medicine physicians attending renal lectures at the Educational Symposia Nuclear Medicine course in March, 2005, the Emory Course in Nuclear medicine in July 2005, the 2005 Northeast Regional Meeting of the Society of Nuclear Medicine and a 2005 educational course at the RSNA.

RENEX:

The architecture of RENEX was inspired by two previously developed expert systems, MYCIN [11] and PERFEX™ [12], and is the subject of a separate publication [5]. MYCIN is a pioneering rule-based expert system developed in the 1970s to help
physicians determine the appropriate antibiotic for patients with infections; the name
'MYCIN' was chosen because many of the available antibiotics included "mycin" in the
name of the antibiotic. PERFEX™ is a commercially available imaging expert system
developed to assist physicians in the interpretation of myocardial perfusion SPECT
studies [13].
Normal limits were established for 47 quantitative parameters extracted from the Tc -99m
MAG3 scans of 106 potential renal donors [14, 15]. These 47 parameters consisted of 7
demographic patient parameters, 20 left kidney parameters and 20 corresponding right
kidney parameters. From these data an expert in radionuclide scintigraphy (domain
expert) used his experience and published data [15] to estimate 5 boundary conditions for
each parameter: (1) definitely abnormal, (2) probably abnormal, (3) equivocal, (4)
probably normal and (5) definitely normal. A sigmoid-like fit constrained to these 5
boundary conditions was then generated to create a parameter knowledge library to be
used for converting the value of any individual quantitative parameter to a certainty
factor (alternative to conditional probability) regarding normality or abnormality. For example,
the certainty factor value of + 1 indicates that the parameter is "definitely abnormal" and
the value of - 1 indicates the parameter is "definitely normal"; the cut-off certainty factor
values between abnormal and equivocal and between normal and equivocal are + 0.2 and
–0.2, respectively (Figs 1A and 1B). Sixty heuristic rules (IF A THEN B) were extracted
from the domain expert to generate the knowledge base for detecting obstruction; twelve
of these 60 rules are specifically applied to the baseline study to determine the need for a
furosemide administration. Each rule uses the certainty factors describing the degree or
abnormality or normality for each parameter that the rule evaluates to generate a certainty
factor regarding the need for furosemide to exclude obstruction. These applied rules that
are chained together by a forward chaining inference engine. An inference engine is
software that selects and executes the rules; the design of the RENEX inference engine
follows the MYCIN inference engine by approximating Bayes theorem to combine the
certainty factors generated by the relevant rules to reach a conclusion (combined certainty factor) regarding the need for furosemide; the combined certainty factor can range from "definitely needs furosemide (+ 1.0)" to
"definitely does not need furosemide (-1.0)". A meta-rule states that patients whose study
has a combined certainty factor in the equivocal range (+ 0.2 to –0.2) should also receive
furosemide. A software component called a justification engine was implemented to
record the sequence of each rule that was fired and the certainty factor value of all input
and output parameters at the time of instantiation in order to track and justify the logic of
the conclusions [4, 5]. The justification engine allows a user to query RENEX to
determine the rules and parameter values that "justify" or explain the software's
conclusion regarding the need for furosemide.
To determine the need for furosemide, the entire system was trained using a pilot group of
31 patients (61 kidneys), 10 males and 21 females with a mean age of 58.8 ± 17.6 years.
Patients in the training set were obtained from our renal database of patients referred for
diuresis renography and they were specifically selected to include a wide range of
responses in order to develop a complete set of rules for determining the need for furosemide. Based on the decision of an expert panel (majority opinion of three of the authors, two institutions), 34 kidneys required furosemide and 27 kidneys did not require furosemide. The entire decision support system was fine tuned and optimized to agree with the expert decisions regarding each kidney in the training set. Processing time per patient is practically instantaneous using a 3.0 GHz PC programmed using IDL (Research Systems, Inc., Boulder, CO).

CARTAN:

CARTAN used the same pilot group of 31 patients (61 kidneys), the same 47 parameters as used by RENEX and analyzed each kidney separately. Because there were a large number of parameters (47) relative to the number of kidneys (61), a statistical procedure known as CART (classification and regression trees) was implemented to classify kidneys and patients regarding the need for furosemide [6, 15, 16]. Computations were performed using the 'rpart' library in the R freeware statistical analysis package to grow and prune decision trees based on the pilot dataset [17]. A classification tree was constructed by first identifying a single parameter that determined the best separation between kidneys that required furosemide and kidneys that were not obstructed and did not require furosemide. Next, a second parameter was identified that determined the best separation between the two branches of the previous parameter. This process was continued and combined with cross-validation and pruning back of branches to limit the size of the decision tree and avoid over-fitting the data.

To reduce dependency on the training data and to stabilize the algorithm, 1001 classification trees were constructed by the common statistical technique of bootstrapping the training data [17, 19]. Bootstrap aggregation, or bagging, is a computationally intensive re-sampling technique that produces a different classification tree for each bootstrap often involving different dichotomized parameters.

Each of the 1001 classification trees was subsequently applied to the prospective set of 102 patients (200 kidneys) to predict the need for furosemide. The results of each prediction algorithm (furosemide needed or not needed) of each bootstrap sample were tallied and the conclusion was based on a simple majority vote regarding the need for furosemide for each of the kidneys in the prospective group.

Determination of the need for furosemide in clinical practice:

To determine the percentage of patients referred for suspected obstruction who required and who did not require furosemide, a retrospective review of renal scans was conducted from January, 1994 through August, 2002. A total of 711 MAG3 renal scans were performed for suspected obstruction between these dates; obstruction was excluded by the baseline scan alone in 221/711 studies (31%) and 490 patients (69%) received furosemide. These percentages were used to select patients in the furosemide and no furosemide categories for the prospective study so that the distribution of patients in the prospective study would match the distribution in clinical practice.
Prospective study population and expert panel review:
The prospective population consisted of 102 patients (200 kidneys), 56 males and 46 females with a mean age of 54.6±16.9 years. None of the 102 patients were included in the training set. To obtain a representative sample, 102 patients were randomly selected; 70 patients were randomly selected from a database of patients referred for suspected obstruction who were given furosemide and 32 additional patients were randomly selected from a database of patients for whom furosemide was considered unnecessary. The percentage of patients receiving furosemide (69%) was selected to match the need for furosemide observed in clinical practice (see above). Using only data provided on the scans, three experts (three of the authors) from 2 different institutions independently scored each kidney on the need for furosemide and resolved differences by majority vote. Results from RENEX and CARTAN were prospectively compared with the experts' decision and the actual clinical decision to give or withhold furosemide; results for the left kidney were compared to results for the right kidney. In addition, the experts' decision was compared with the clinical decision to give or withhold furosemide.

Statistical Analysis:
Statistical analysis was based on the exact form of McNemar's test for correlated proportions [19]. Due to some small sample sizes and generally good coverage, the Wilson score method was used for calculating confidence intervals for proportions [21, 22]. Significance was set at a p value < 0.05.

RESULTS
The baseline plus furosemide protocol recommended in the 1996 consensus report on diuresis renography appears to be in common use [1]. Based on a show of hands or key pad response, 50%, 90%, 85% and 80% of the participants attending the 2005 Educational Symposia nuclear medicine course, the 2005 Emory Course, the 2005 Northeast Regional SNM Meeting and a 2005 RSNA review course, respectively, used the standard protocol as either two separate acquisitions or a continuous acquisition with furosemide administered approximately after 20 minutes.

In regard to the need for furosemide, RENEX agreed with the clinical decision to give furosemide in 97% of patients (68/70) whereas CARTAN agreed in 90% of patients (63/70), p = 0.03 (Table 1). Similarly, RENEX agreed with the experts' decision to give furosemide in 98% of patients (65/66) whereas CARTAN agreed with 89% (59/66), p = 0.01 (Table 1). When the data were analyzed by kidney rather than by patient, RENEX agreed with the experts' decision to give furosemide in 94% of kidneys (84/89) compared to 82% (73/89) for CARTAN, p = 0.002. Sample studies are illustrated in Figs 2 and 3. The experts' decision agreed with the clinical decision to give furosemide in 94% of patients (66/70).

There was no difference between RENEX and CARTAN when the clinicians and experts deemed that furosemide was not necessary, p = 0.18 and 0.32, respectively (Table 2).
However, when the data were analyzed by individual kidneys (Table 2), CARTAN agreed with the experts' decision in 78% of kidneys (87/111) whereas RENEX agreed in 69% of kidneys (77/111), p = 0.008. The experts' decision agreed with the clinical decision to withhold furosemide in 100% (32/32) of patients.

Overall, RENEX agreed with the clinical decision in 89% (91/102) of patients, with the experts' decision in 87% (89/102) of patients and with the experts' decision in 81% (16/200) of kidneys. CARTAN agreed with the clinical decision in 87% (89/102) of patients, with the experts' decision in 83% (85/102) of patients and with the experts' decision in 80% (160/200) of kidneys. The experts' decision agreed with the clinical decision to give or withhold furosemide in 96% (98/102) of patients.

The performance of RENEX and CARTAN for the right kidney was compared to the performance in the left kidney. RENEX agreed with experts' decision to administer furosemide in 93% (40/43) of left kidneys and 96% (44/46) of right kidneys, p = NS (Table 3). Comparable results were obtained for CARTAN (Table 3). Similarly, there was no significant difference between the right and left kidney for RENEX and CARTAN when the results were analyzed based on the experts' decisions to withhold furosemide (Table 4).

DISCUSSION

Over the past several years, artificial intelligence methods have been investigated as a way to develop tools to improve diagnostic performance. Examples from nuclear medicine include neural networks [23-25] and case-based reasoning techniques [26] to provide computer-assisted diagnosis of planar and SPECT myocardial perfusion studies. In knowledge-based expert systems, a knowledge base of heuristic rules is obtained from human experts capturing how they make their interpretations. These rules are usually expressed in the form of IF A THEN B expressions. One major advantage of a knowledge-based expert system is that the system does not require the same large numbers of studies as are required to develop neural nets or case based reasoning approaches. A second advantage, especially from a learning perspective, is that it is possible to query a knowledge-based system to learn the rules that led to a specific conclusion. For example, RENEX disagreed with the experts in regard to the need for furosemide in the right kidney (Fig 3) but it is possible to query RENEX to determine the reasons for its decision. The primary reason that RENEX concluded furosemide was needed was the fact that the T½ was abnormal (20.8 minutes); RENEX recognized that there was moderate evidence that furosemide was not needed because the post-void to maximum ratio was 0.2 (upper limits of normal of 0.16, [15]) but RENEX gave greater weight to the abnormal T½. The experts were not queried but clearly gave greater weight to the images and the low post-void to max ratio. RENEX can be improved by comparing results and "reasoning" with expert decisions and adding new rules and/or adjusting the weighting factors. In this case, RENEX should be tested giving greater weight to the post-void to maximum count ratio than the T½.
The decision support approach is based on the combined approach of classification and regression tree (CART) analysis with bootstrapping. This approach can handle a relatively large number of variables and arrive at a prediction algorithm with a relatively small training set. CART analysis has been used to distinguish between healthy and diseased kidneys using magnetic resonance data that includes measurements of renal arterial blood flow and parenchymal perfusion [27]; to our knowledge, this is the first time CART analysis and bagging have been applied to a problem in nuclear medicine. CART agreed with the expert decisions illustrated in Fig 3 but CART cannot provide the rationale for these decisions; however, CART can use a large sample of test patients to determine which parameters and what parameter cut-off values provide the best separation in distinguishing when furosemide is needed or not needed or whether or not a kidney is obstructed. These parameters and cut-off values can be used to guide clinicians and RENEX in determining the need for furosemide and the presence or absence of obstruction.

Our long term goal is to develop decision support systems to determine if a kidney is obstructed. The dual statistical and knowledge based approaches have provided complementary information and helped target features that can be transferred or emphasized to improve the overall performance of both systems. At present, data are insufficient to determine if one approach is inherently superior to the other. Analysis of the baseline study to determine the need for furosemide may be useful for the 50-90% of institutions that use a baseline plus furosemide protocol; these decision support systems have the potential to serve as a second opinion to support a clinician's preliminary decision regarding the need for furosemide. Importantly, this study has also provided important data and direction for developing decision support systems to diagnose obstruction.

The focus of this research effort is to develop statistical and knowledge based decision support systems that will have a diagnostic performance in diuresis renography comparable to that of experts. This is not a trivial task; however, it could be argued that a better goal would be to develop decision support systems that use the clinical outcome as the gold standard rather than expert readers. This is an attractive goal but it is confounded by the fact that an obstructed or non-obstructed scan interpretation has a major impact on the clinical outcome and, consequently, this gold standard becomes biased. Additional problems of data analysis can be illustrated by a patient who had a pyeloplasty to relieve obstruction 6-24 months after a diuresis renography scan was interpreted as no obstruction. In this example, did the scan miss obstruction, was the study interpreted incorrectly or did the patient become obstructed 6-24 months following the scan? Using patient outcome as a gold standard can be an important goal but interpretation of the results is not straightforward. Moreover, regardless of the type of study, clinical practice should be improved if radiologists can provide an interpretation equivalent to that of expert readers.
probably more of a disadvantage for a statistical system such as CARTAN than for a knowledge based system but both of these systems could potentially be improved by increasing the size of the training set. This study addressed the diuresis renography protocol recommended by the international consensus report where baseline data are obtained followed by the administration of furosemide and an additional period of imaging [1]. There are other protocols in which furosemide is given 15 minutes before the radiopharmaceutical, at the same time as the radiopharmaceutical or 5 to 10 minutes later [1, 28, 29]. Obviously, the systems we describe do not apply to these protocols.

Finally, QuantEM 2.0 cannot detect and correct for patient motion and, at this time, the software cannot distinguish between diffuse retention with slow washout due to impaired function and focal pelvic retention with slow washout due to possible obstruction. Algorithms to detect and correct for motion and to distinguish between diffuse retention in a kidney and retention in a dilated renal collecting system need to be designed, implemented and tested.

CONCLUSIONS

RENEX performed better than CARTAN when clinicians and experts determined that furosemide was necessary to evaluate obstruction. When furosemide was not required, CARTAN performed better than RENEX when the results were analyzed by the individual kidneys; there was no difference when the results were analyzed by patients. Use of RENEX or CARTAN as decision support tools in the baseline plus furosemide protocol has the potential to help avoid unnecessary imaging, minimize patient inconvenience and reduce costs by saving technologist, camera, computer and physician time. Importantly, the results obtained from this study will assist in the more complex task of developing decision support systems for diuresis renography to evaluate obstruction.

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A knowledge library was generated for each parameter to convert any given parameter value into a certainty factor. Fig 1A illustrates the parameter knowledge library to convert any time to half maximum count value for the left kidney (whole kidney region of interest) to a certainty factor value. The boundary values (see Methods for more detail) were 8, 11, 13, 15, and 20 minutes respectively.

Fig 1B: The figure shows the parameter knowledge library to convert any 20 minute/maximum count ratio for the left kidney (cortical region of interest) to a certainty factor value. The boundary values were 0.17, 0.27, 0.32, 0.43, and 0.92 respectively.
A 50 year old female was referred for a MAG3 scan because of suspected obstruction. The baseline scan showed no infiltration; the MAG3 clearance was reduced. The right kidney showed prompt uptake and excretion and was not obstructed. The left kidney showed a reduction in relative function (18%). There was uniform uptake in the left kidney with slow washout but, importantly, there was no retention of the tracer in the collecting system. Clinically, the study was interpreted as not obstructed and furosemide was not administered. RENEX, CARTAN and the experts agreed with this decision.
Fig. 2B: An expanded review display shows the patient values for the MAG3 clearance, void/max ratio for whole kidney and cortical ROIs as well as the normal ranges for each of these values. The expanded review page also shows an enlarged parenchymal image obtained at 2-3 min, an enlarged display of the 19-20 min image and quality control images showing the pre and post-injection syringe counts and time of the bolus arrival in the kidneys. The post-void/maximum count ratio of the left kidney is slightly elevated at 23% but this ratio tells the clinician that almost 80% of the maximal activity has washed out of the left kidney by the conclusion of the study and such a high washout percentage is strong evidence against obstruction.
A 40 year old male was referred for a MAG3 scan because of suspected obstruction. The baseline scan showed no infiltration; the camera-based MAG3 clearance was normal. The left kidney showed rapid uptake and washout of the tracer in the sequential 2-minute images (center); the relative uptake of the left kidney was 56%, the whole kidney T½ was 10.8 minutes and post-void to maximum ratio was normal (Fig 1B) excluding obstruction. The relative function of the right kidney was 46% and the right kidney showed dilatation of the renal pelvis which can be appreciated on the 2-min image as well as on the enlarged 2-3 min image (Fig 3B). The T½ for the whole kidney ROI was prolonged at 20.3 minutes and the 20 min to maximum ratio was elevated at 0.58. On the other hand, visually the pelvis empties after voiding and the post-void to maximum ratio was 0.20 (Fig 3B). Although a post-void to maximum ratio is slightly elevated (0.16 is the upper limit of normal[15]), the experts and the clinical decision was that furosemide was not indicated. CARTAN agreed with the experts but RENEX concluded that furosemide was needed to exclude obstruction of the right kidney (see Discussion).
Fig 3B: An expanded review display shows the patient values for the MAG3 clearance, residual urine volume, percent relative uptake and the Tmax, 20 min/max, T ½ and post-void/max ratio for whole kidney and cortical ROIs as well as the normal ranges for each of these values. The expanded review page also shows an enlarged parenchymal image obtained at 2-3 min, an enlarged display of the 19-20 min image and quality control images showing the pre and post-injection syringe counts and time of the bolus arrival in the kidneys. In particular, the enlarged 2-3 minute image shows the dilated renal pelvis and the post-void to maximum ratio for the right kidney is slightly elevated.
Table 1: Performance of RENEX and CARTAN compared with expert consensus and clinical decisions to administer furosemide

<table>
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<th></th>
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*P = 0.03 ~ P = 0.01 *P = 0.002

Table 2: Performance of RENEX and CARTAN compared with expert consensus and clinical decision that furosemide was not necessary

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*P = 0.18 ~ P = 0.32 *P = 0.008

Table 3: Performance of RENEX and CARTAN compared with expert consensus and clinical decision to administer furosemide
Table 3: Performance of RENEX and CARTAN compared with expert consensus to administer furosemide for the right and left kidneys

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<tr>
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<td>Right</td>
<td>46</td>
<td>0.96 (0.85-0.99)</td>
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Table 4: Performance of RENEX and CARTAN compared with expert consensus that furosemide was not necessary for the right and left kidneys

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<td>56</td>
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