ASSESSMENT OF THE INTEROBSERVER AND THE INTRAOBSERVER REPRODUCIBILITY FOR THE DETECTION OF RENAL CORTICAL DEFECTS IN ADULTS AND CHILDREN USING [^{99m}Tc]Tc-MAG3

First Author: Mohammed Hussain Hashlan

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Supervisor: Anita Brink

Division of Nuclear Medicine, Department of Radiation Medicine, University of Cape Town

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Declaration

I, Mohammed Hussain Hashlan, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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Abstract

Objectives:

One can assess cortical defects on the early images of [^{99m}Tc]Tc-MAG3 renography. We aim to assess interobserver and intraobserver reproducibility for detecting renal cortical defects using [^{99m}Tc]Tc-MAG3 for adults and children; identify causes for poor inter- and intraobserver reproducibility and to assess the effect of the kidney to background ratio (KTBR) on reproducibility.

Methods:

A 100 adult and 200 paediatric renograms were included. The observers reviewed the summed 1-min posterior images for the first four minutes to detect cortical defects. Interobserver reproducibility between three observers and intra-observer reproducibility for two observers were determined. Agreement was tested using percentage agreement, Krippendorff's reliability coefficient alpha and Cohen's kappa statistic. The association between KTBR and agreement was assessed.

Results:

Interobserver agreement on the 1-2 minute images was 78 (95% CI: 74.8 - 82.7%) and 79.7 (95% CI: 75.9 - 83.5%) for left and right kidneys respectively. Intraobserver percentage was 89.7% (95% CI: 86.2 - 93.1%) for the senior and 80.7% (95% CI: 76.2 - 85.2%) for the junior observer. In 13.5% (27) of the adult and 4.5% (19) of the paediatric kidneys the difference in image interpretation between the observers would have had a clinical impact. If the KTBR is ≤ 2, the percentage agreement was between 61.5% and 64.8%. In cases with a KTBR > 2, the percentage agreement was between 83.6% and 87.1%.

Conclusion:

The percentage interobserver agreement was moderate. Disagreement between normal and abnormal cases were infrequent. The interobserver reproducibility was decreased when the KTBR was ≤ 2.

Acknowledgments and contributions

There are no conflicts of interest.
This work is not funded nor going to be funded in future.

Dr Stuart More from Nuclear Medicine Department of Groote Schuur Hospital participated in evaluating the kidneys as per the data sheet which allowed us to have another observer to evaluate the interobserver reproducibility.

Elton Mukonda from the Department of Epidemiology of the University of Cape Town provided key statistical support in analysing the data and going to continue providing statistical consultations if needed in future.

I want to thank everyone who was involved in this work, and everyone assisted me or prayed for me to make this a reality including family members and friends.

To my parents and beautiful daughters ... Salwa, Fatima and Mariam.

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Abbreviations:

[^{99m}Tc]Tc-DMSA	Technetium-99m labelled Dimercaptosuccinic acid
[^{99m}Tc]Tc-MAG3	Technetium-99m labelled Mercaptoacetyltriglycine
KTBR	Kidney to background ratio
ROI	Region of interest
SPECT	Single photon emission computed tomography
GSH	Groote Schuur Hospital
RCWMCH	Red Cross War Memorial Children's Hospital
EANM	European Association of Nuclear Medicine
NMC	Nuclear Medicine Communications

Publication ready format

Chapter 1:

Introduction and literature review:

Renal imaging is a common procedure in nuclear medicine practice with several radiopharmaceuticals available to use for different indications. Technetium-99m labelled Mercaptoacetyltriglycine ([^{99m}Tc]Tc-MAG3) and Technetium-99m labelled Dimercaptosuccinic acid ([^{99m}Tc]Tc-DMSA) are widely used for renal scintigraphy. [^{99m}Tc]Tc-MAG3 is frequently used to assess the function and drainage of kidneys. It is known that one can assess cortical defects on the early images of [^{99m}Tc]Tc-MAG3 renography. The interobserver reproducibility to assess renal cortical defects by [^{99m}Tc]-DMSA was extensively investigated. As we frequently use [^{99m}Tc]Tc-MAG3 to assess for the presence of cortical defects, a need exists to establish the reproducibility for detecting cortical defects using [^{99m}Tc]Tc-MAG3.

[^{99m}Tc]Tc-DMSA scintigraphy is the gold standard for detecting renal cortical defects with 96% sensitivity and 96% specificity (1,2). [^{99m}Tc]Tc-DMSA binds irreversibly to the proximal tubular cellular proteins via disulphide bonds (3).

The interobserver and the intraobserver reproducibility for the detection of renal cortical defects using [^{99m}Tc]Tc-DMSA were evaluated by several studies with variable results. Patel et al. evaluated 57 paediatric [^{99m}Tc]Tc-DMSA scans which were reported by two nuclear medicine physicians using a standard set of criteria on two occasions to determine the interobserver and the intraobserver variability in the scan interpretation. They excluded six scans due to motion artefacts or poor-quality images. They reported high levels of interobserver (84.4%, $p<0.05$) and intraobserver percentage agreement (95.9% and 90.6% respectively, $p<0.05$). The weighted kappa values for intraobserver agreement were 0.8 - 0.9 for the first observer, 0.6 - 0.8 for the second observer and 0.4 - 0.7 for the interobserver agreement (4).

A multicentre trial to assess the interobserver reproducibility in reporting [^{99m}Tc]Tc-DMSA planar scintigraphy was conducted by De Sadeleer et al. in 2000. This study was conducted in Belgium by 42 nuclear medicine physicians who evaluated [^{99m}Tc]Tc-DMSA scans for 40 children and 10 adults. The median percentage of agreement for overall interobserver reproducibility was 92%. The found

good interobserver reproducibility in a large group of nuclear medicine physicians with differing levels of expertise (5).

The interobserver agreement of [^{99m}Tc]Tc-DMSA for the detection of cortical defects in 46 children, with two scans each six months apart, was evaluated by De Guevara et al. Three observers independently evaluated the early scans alone, the late scans alone and both the early and late scans together. This resulted in a complete interobserver agreement in 75%, 78%, and 77% for the early scan, the late scan alone, and the late DMSA scan with the early scan for comparison, respectively. Complete agreement was considered when all three observers agreed on a normal, abnormal, or equivocal results. The total intraobserver agreement on the late scan alone and the late scan in the presence of the early scan was observed in 96%, 89%, and 86% for observers 1, 2, and 3, respectively (6).

Gacinovic et al. found poor interobserver agreement for the presence or absence of renal scars on [^{99m}Tc]Tc-DMSA scan. Seven experienced observers evaluated 32 kidneys on two separate occasions. The population included ten patients who were under the age of ten years. The interobserver agreement on the presence of scarring was poor; 51% on the first reading and 61% with the second reading (7).

Sixty paediatric [^{99m}Tc]Tc-DMSA scans were evaluated in 2009 by 61 observers to assess the interobserver reproducibility of each kidney as normal, abnormal, or equivocal/poor quality. They reported a median agreement of 93% and in 24% the agreement was less than 80%. In 13% (16 kidneys) there was a disagreement between normal and abnormal which could have had a clinical impact. The remaining differences were between normal and equivocal. Disagreement was mainly in cases with normal variants, congenital abnormalities, and small defects (8).

[^{99m}Tc]Tc-MAG3 is a tubular agent used to assess renal function and drainage of the kidneys. The extraction fraction of [^{99m}Tc]Tc-MAG3 is 40% to 50% (9). Most of the extracted [^{99m}Tc]Tc-MAG3 (96%) undergoes tubular secretion and 4% undergoes glomerular filtration (3). It is one of the recommended tracers for renography in children under two years (10). [^{99m}Tc]Tc-MAG3 is also preferred for renography in older patients with impaired renal function (11). The good cortical uptake of [^{99m}Tc]Tc-MAG3 has led to the proposal that cortical defects can be assessed on the summed parenchymal images.

In 1992, Gordon et al. studied 59 children, 110 kidneys, with previous urinary tract infections who underwent both [^{99m}Tc]Tc-DMSA and [^{99m}Tc]Tc-MAG3 within four weeks of each other. They found that [^{99m}Tc]Tc-MAG3 has a specificity of 88% and a sensitivity of 88% for the detection of a focal parenchymal defects when compared to [^{99m}Tc]Tc-DMSA (12).

The findings of [^{99m}Tc]Tc-DMSA and [^{99m}Tc]Tc-MAG3 images were compared in a group of 37 patients, 12 children and 25 adults. These patients had a [^{99m}Tc]Tc-DMSA and [^{99m}Tc]Tc-MAG3 scan within a 3 to 7 day interval. The scans were reviewed independently and 17 of the 19 cortical defects detected on the [^{99m}Tc]Tc-DMSA were identified on [^{99m}Tc]Tc-MAG3. The sensitivity and specificity of [^{99m}Tc]Tc-MAG3 for detecting cortical defects were 89% and 100% respectively (13).

The abnormal parenchymal findings on [^{99m}Tc]Tc-MAG3 renograms of 28 children who were strongly suspected to have acute pyelonephritis were compared to subsequent planar [^{99m}Tc]Tc-DMSA scans by two observers. The [^{99m}Tc]Tc-DMSA scans were performed within one week after the renograms. They did not only use the early images of the [^{99m}Tc]Tc-MAG3 they also included later clearance abnormalities as indicators of parenchymal dysfunction. Both scans showed focal parenchymal abnormalities for 24 patients. In four patients [^{99m}Tc]Tc-MAG3 was considered abnormal however, the corresponding DMSA scan was interpreted as normal. They also prospectively compared the scintigraphic findings of [^{99m}Tc]Tc-MAG3 renograms and [^{99m}Tc]Tc-DMSA SPECT (single photon emission computed tomography) scans for 57 children suspected to have acute pyelonephritis. The scans were interpreted by two groups of nuclear physicians. The first group interpreted the scans together, they agreed on the presence of cortical defects on [^{99m}Tc]Tc-MAG3 in 14 patients. In one patient they did not agree on the presence of cortical defects. Of the 14 patients with cortical defects on [^{99m}Tc]Tc-MAG3 five had normal [^{99m}Tc]Tc-DMSA studies. A second group of readers interpreted the scans independently. They agreed on the presence of cortical defects in ten and the absence of cortical defects in 32 patients. Disagreement between the readers in the independent interpretation group was seen in six patients. There were no patients with a positive [^{99m}Tc]Tc-DMSA scan and a negative [^{99m}Tc]Tc-MAG3 renogram. They concluded that [^{99m}Tc]Tc-MAG3 renogram was as sensitive as planar or SPECT [^{99m}Tc]Tc-DMSA scan in detecting regional parenchymal dysfunction or fixed focal defects (14).

The correspondence of visual assessment of cortical defects between [^{99m}Tc]Tc-MAG3 and [^{99m}Tc]Tc-DMSA was evaluated by four observers in a retrospective study conducted in 2005.

Eighty-three renograms, 49 adult and 34 paediatric patients were included. The two investigations were done within 3 months of each other. The correspondence for visual assessment of cortical defects ranged between 85 - 89% for the four observers. All four observers agreed on the presence of cortical defects in 18 [^{99m}Tc]Tc-DMSA studies. All those cortical defects were identified on the [^{99m}Tc]Tc-MAG3 studies. However, two observers reported more cortical defects on the corresponding [^{99m}Tc]Tc-MAG3 studies, 19 and 23 defects (15).

To determine if [^{99m}Tc]Tc-MAG3 can replace [^{99m}Tc]Tc-DMSA for the assessment of the renal cortex and split renal function a nuclear medicine consultant reviewed the scintigraphic results for 52 children (age ranged from 7 days to 10 years). Both studies were performed within 24 hours of each other, starting with [^{99m}Tc]Tc-MAG3. They performed [^{99m}Tc]Tc-DMSA scan on the same day if good clearance of [^{99m}Tc]Tc-MAG3 activity is seen. They performed [^{99m}Tc]Tc-DMSA scans on the following day if residual [^{99m}Tc]Tc-MAG3 activity was seen at the end of the 30 minute renogram. They found that [^{99m}Tc]Tc-MAG3 gave comparable findings to [^{99m}Tc]Tc-DMSA. They noted that [^{99m}Tc]Tc-MAG3 gave the added information on urodynamics, had a lower radiation dose to children and could lead to time saving (16). All the scars seen on [^{99m}Tc]Tc-DMSA were also detected by [^{99m}Tc]Tc-MAG3 however, the exact number of scars was not given in the paper.

A prospective study conducted in 2013 by Abdülrezzak et al. compared [^{99m}Tc]Tc-MAG3 and [^{99m}Tc]Tc-DMSA for the detection of renal scars. They included 135 kidneys from 68 patients (age 3 to 16 years) who were scanned using both radiopharmaceuticals within a two week time frame. There were concordant results in 38 kidneys with cortical defects and 91 kidneys with no cortical defects, kappa = 0.89. Discrepant results were found in six kidneys, with cortical defects called on three [^{99m}Tc]Tc-DMSA and [^{99m}Tc]Tc-MAG3 studies but not the corresponding [^{99m}Tc]Tc-DMSA and [^{99m}Tc]Tc-MAG3 studies. When considering [^{99m}Tc]Tc-DMSA as the reference scan, the sensitivity, specificity, and accuracy of [^{99m}Tc]Tc-MAG3 was 92.6%, 96.8% and 95.5%, respectively. The authors concluded that the performance of [^{99m}Tc]Tc-MAG3 was good despite its lower kidney to background ratio compared to [^{99m}Tc]Tc-DMSA (17).

To our knowledge there are no studies in the English literature which investigated the interobserver and the intraobserver reproducibility for detecting renal cortical defects when imaging with [^{99m}Tc]Tc-MAG3.

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Chapter 2:

Publication ready manuscript

ASSESSMENT OF THE INTEROBSERVER AND THE INTRAOBSERVER REPRODUCIBILITY FOR THE DETECTION OF RENAL CORTICAL DEFECTS IN ADULTS AND CHILDREN USING [^{99m}Tc]Tc-MAG3

Hashlan, Mohammed[a]; More, Stuart[a]; Mukonda, Elton[b]; Brink, Anita[c]

Authors and affiliations

[a] Division of Nuclear Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa.

[b] Division of Epidemiology and Biostatistics, University of Cape Town, Cape Town, South Africa.

[c] Division of Nuclear Medicine, Department of Radiation Medicine, Red Cross War Memorial Children's Hospital, University of Cape Town, Cape Town, South Africa.

Correspondence to Mohammed Hashlan, Division of Nuclear Medicine, Groote Schuur Hospital, Main Road, Observatory, Cape Town, postal code 7925. Tel. 0027-214044389;
Email: mhhashlan@moh.gov.sa

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Keywords:

Nuclear Medicine, renogram, reproducibility, renal cortical defects, renal scarring, [^{99m}Tc]Tc-DMSA, [^{99m}Tc]Tc-MAG3, kidney to background ratio, fast cortical clearance, Percentage agreement, Cohen’s Kappa and Krippendorff’s alpha.

Main manuscript

Introduction:

Renal imaging is a common procedure in nuclear medicine practice with several radiopharmaceuticals available to use for different indications. Technetium-99m labeled Mercaptoacetyltriglycine ([^{99m}Tc]Tc-MAG3) and Technetium-99m labeled Dimercaptosuccinic acid ([^{99m}Tc]Tc-DMSA) are widely used for renal scintigraphy. It is known that one can assess cortical defects on the early images of [99mTc]Tc-MAG3 renography. The interobserver reproducibility to assess renal cortical defects by [99mTc]-DMSA was extensively investigated. As we frequently use [99mTc]Tc-MAG3 to assess for the presence of cortical defects, a need exists to establish the reproducibility for detecting cortical defects using [99mTc]Tc-MAG3.

[^{99m}Tc]Tc-DMSA scintigraphy is the gold standard for detecting renal cortical defects with 96% sensitivity and 96% specificity (1,2). [^{99m}Tc]Tc-DMSA binds irreversibly to the proximal tubular cellular proteins via disulphide bonds (3).

The interobserver and the intraobserver reproducibility for the detection of renal cortical defects using [^{99m}Tc]Tc-DMSA were evaluated by several studies with variable results (4–8).

[^{99m}Tc]Tc-MAG3 is a tubular agent commonly used to assess renal function and drainage of the kidneys (3,9–11). The good cortical uptake of [^{99m}Tc]Tc-MAG3 has led to the proposal that cortical defects can be assessed on the summed parenchymal images. The sensitivity and specificity of [^{99m}Tc]Tc-MAG3 was reported to be high (88 - 93% and 88 to 100% respectively) when compared to [^{99m}Tc]Tc-DMSA (12–15). It was found that [^{99m}Tc]Tc-MAG3 provided added information on urodynamics, caused lower radiation dose to children and saved time (16).

To our knowledge there are no studies in the English literature which investigated the interobserver and the intraobserver reproducibility for detecting renal cortical defects when imaging with [^{99m}Tc]Tc-MAG3.

The aim of our study was to assess the interobserver and the intraobserver reproducibility for detecting renal cortical defects using [^{99m}Tc]Tc-MAG3 for adults and children. The causes for poor inter- and intraobserver reproducibility were investigated. The relationship between the kidney to background ratio and inter- and intraobserver reproducibility were assessed.

Patients and Methods:

The respective nuclear medicine databases were used to retrospectively identify 100 adult renograms performed in the Department of Nuclear Medicine at Groote Schuur Hospital (GSH) and 200 paediatric renograms performed in the Department of Nuclear Medicine at Red Cross War Memorial Children's Hospital (RCWMCH) from September 2015 to August 2019.

The first [^{99m}Tc]Tc-MAG3 renogram performed for each patient was included. Renograms of potential kidney donors and patients worked up for radiotherapy were excluded. The renograms of patients with solitary, transplant, auto-transplanted, ectopic, horseshoe, and fused kidneys were also excluded.

The paediatric renograms used were acquired according to the relevant European Association of Nuclear Medicine (EANM) guidelines for standard and diuretic renography at the time of acquisition (17). The [^{99m}Tc]Tc-MAG3 dose was calculated using the applicable EANM dose card (18). The children were imaged on the same Philips Axis Dual Head camera (previously known as Picker and then Marconi) using a low energy high resolution collimator. Posterior images were recorded in a 128 x 128 matrix at one second per frame for the first two minutes. Thereafter the images were recorded at 15 seconds per frame for 40 minutes. The adult renograms were recorded on a dual head gamma camera (SIEMENS ECAM) using a low energy high resolution collimator. Posterior images were recorded using a 128 x 128 matrix size. The frame rate was 2 seconds per frame for the first minute, thereafter 10 seconds per frame for 40 minutes. When clinically indicated furosemide was administered 20 minutes after the injection of [^{99m}Tc]Tc-MAG3.

All raw data were retrieved from the archive and anonymized then reviewed by two senior observers and one junior observer to measure the interobserver reproducibility. Two observers (one senior and one junior) reviewed the same images again, the interval between the two reviews were at least one month.

The observers reviewed the summed 1-min posterior images for the second, third and fourth minutes of the renogram of each kidney for the presence of renal cortical defects. It was important to evaluate 1-2 min, 2-3 min and 3-4 min summed images separately to find potential reasons that reduce the reproducibility for detecting cortical defects.

Renal cortical defect was defined as an area of reduced or absent tracer localization and indistinct margins that did not deform the renal contour or defined as cortical thinning, flattening, or an ovoid or wedge-shaped defect (19,20).

The observers reported the number and location of the defects on a provided diagram (Figure 1). The certainty of detection of cortical defects was graded as follows:

- 1 where there was definitive certainty of a cortical defect,
- 2 where there was definitive certainty there was no cortical defect or
- 3 where was no clear certainty of detection of a cortical defect. If the reader was uncertain, the reason was reported for each kidney.

The principal investigator calculated the kidney to background ratio for each kidney as mean counts per pixel of the kidney region of interest (ROI) divided by the mean counts per pixel of the background ROI. The renal ROI was drawn around the whole kidney. The background ROI was C-shaped, two pixels wide and placed one pixel apart from the kidney (10).

The impact of kidney to background ratio on the interobserver agreement was also assessed by measuring the interobserver agreement when the kidney to background ratio was ≤2 and >2.

Statistical analysis:
The interobserver and intraobserver agreements were analyzed in Stata Version 14.0 (Statacorp, College Station TX). The inter-observer agreement was tested using percentage agreement and Cohen's kappa statistic for two observers and expressed as a proportion agreement with 95% confidence interval. The inter-observer agreement between all observers was tested using percentage agreement and Krippendorff's reliability coefficient alpha and expressed as a proportion agreement with 95% confidence intervals. The intraobserver agreement for each observer comparing the earlier and later readings was tested using percentage agreement and Krippendorff's reliability coefficient alpha and expressed as a proportion agreement with 95% confidence intervals. The levels of agreement were classified according to the classification defined by Landis and Koch (21).

The cases where there was a difference in agreement between the observers were analyzed to assess in what number of cases the difference in agreement would have a clinical impact, e.g. in

what number of cases were there a difference between the assessment of certain there was a cortical defect and certain there was no cortical defect.

The effect of kidney to background ratio on the interobserver agreement was analyzed by measuring the percentage agreement and the Krippendorff's alpha coefficient for each kidney when the kidney to background ratio was ≤ 2 or >2.

Results:

In total, 3000 observations were analyzed for 600 kidneys. The 1-2 minute images are routinely used to calculate the differential renal function(DRF) therefore, the results of the 1-2 minute images are presented in the text and the remaining results of all the analyzed images, 2-3 minute and 3-4 minute, are presented in Tables 1, 2 and 3.

The interobserver agreement for all patients between the three raters was measured by percentage agreement and Krippendorff's alpha coefficient. For the 1-2 minute images of the renogram, the percentage agreement for three raters for the left kidney was 78% (95% CI: 74.8 - 82.7%) for the right kidney it was 79.7% (95% CI: 75.9 - 83.5%). The corresponding Krippendorff's alpha was 0.51 (95% CI: 0.45 - 0.58) and 0.56 (95% CI: 0.49 - 0.62), Table 1. The percentage agreement between the three observers for the defect location was more than 90% for both kidneys.

The interobserver agreement for all patients between two senior observers was measured using percentage agreement and Cohen's Kappa. For 1-2 minute images, the percentage agreement between the two observers for the left kidney was 81% (95% CI: 76.5 - 85.5%) and for the right kidney it was 80% (95% CI: 75.5 - 84.6%). The corresponding Cohen's Kappa was 0.53 (95% CI: 0.45-0.62) and 0.54 (95% CI: 0.45-0.62), Table 2.

The intraobserver percentage agreement of the two observers for all patients on the 1-2 minute images of the left kidney were 89.7% (95% CI: 86.2 - 93.1%) for the senior observer and 80.7% (95% CI: 76.2 - 85.2%) for the junior observer. The corresponding Krippendorff's alpha was 0.75 (95% CI: 0.68 - 0.83) and 0.63 (95% CI: 0.55 - 0.70). For the right kidney, the intraobserver percentage agreement is 87.3% (95% CI: 83.6 - 91.1%) for the senior observer and 84% (95% CI: 79.8 - 88.2%) for the junior observer. The corresponding Krippendorff's alpha is 0.72 (95%

CI: 0.67 - 0.80) and 0.70 (95% CI: 0.63 - 0.77), Table 3. There was no significant difference in the intraobserver agreement results for adults and children.

All observers gave the same ratings for 215, 215 and 207 left kidneys on 1-2 min, 1-3 min and 1-4 min, respectively. For the right kidney, all observers gave the same rating in 215, 210 and 196 kidneys, respectively, Table 5.

All observers were not certain on 1-2, 2-3 and 3-4 minute summed images for ten left kidneys and 18 right kidneys. The median and range of kidney to background ratio for the 10 left kidneys was 2.85 and 2 - 8.1, respectively. The corresponding measures for the 18 right kidneys were 2.64 and 1.21 - 4.6.

The possible clinical impact of intraobserver and interobserver discordant findings between those kidneys where there was certainty of no defect and certainty that there was a defect was assessed. In 13.5% (27) of the adult kidneys and 4.5% (19) of the paediatric kidneys the difference between image interpretation between the different observers would have had a clinical impact. The intraobserver discordant findings were higher for the junior observer 7.5% (45) than the senior observer 2.3% (14) of all the kidneys evaluated, Table 5.

Poor kidney to background ratio was reported as the reason for uncertainty in 72 out of 92 kidneys for the junior observer. For the more experiences observers this reason of uncertainty was cited in 32 of 74 kidneys and 34 of 51 kidneys. The second most common reason for uncertainty when reporting cortical defects was a small kidney. Other reported reasons were fast cortical clearance on the 3-4 minute images and hydronephrotic kidneys.

The mean kidney to background ratio for adults was 2.59 for left kidneys and 2.03 for the right kidneys while the mean kidney to background ratio for children was 3.36 for left and right kidneys.

The interobserver agreement based on kidney to background ratio is outlined in Table 6. When the kidney to background ratio is ≤ 2, the percentage agreement for the left kidney was 61.5% (95% CI: 51.7 - 71.4) and 64.8% (95% CI: 57.6 - 72) for the right kidney. The corresponding Krippendorff's alpha was 0.448 (95% CI: 0.324 - 0.572) and 0.478 (95% CI: 0.384 - 0.572). The kidney to background ratio was ≤ 2 in 66/300 (22%) left kidneys and 107/300 (35.6%) right kidneys. In contrast when the kidney to background ratio is more than 2, the percentage agreement for the left

kidney was 83.6% (95% CI: 79.5 - 87.6) and 87.1% (95% CI: 83.1 - 91) for the right kidney. The corresponding Krippendorff's alpha was 0.48 (95% CI: 0.40 - 0.56) and 0.54 (95% CI: 0.42 - 0.65).

Discussion:

The measured percentage interobserver agreement between all observers was classified as fair to moderate. We have comparable levels of percentage interobserver agreement with the previous studies that evaluated the reproducibility for [^{99m}Tc]Tc-DMSA (6). When compared to this study, slightly higher percentage agreement levels for [^{99m}Tc]Tc-DMSA were reported previously by Patel et al. while lower levels were reported by others (4,7,22). This shows how the published results for [^{99m}Tc]Tc-DMSA are variable and makes comparison with [^{99m}Tc]Tc-MAG3 results challenging. The interobserver level of agreement in our study of 78 – 79.7% this was lower than the median level of agreement of 92% to 93% recorded in large multicentre trials (5,8).

The interobserver agreement was higher for children than adults in our study. The average kidney to background ratio in the paediatric cohort was higher than that of the adult cohort. This means that on average the kidneys were better visualised for the paediatric population. In addition, the 70% of the paediatric cohort had no cortical defects compared to 51% of the adult cohort. The higher incidence of cortical defects in the adult cohort probably led to the lower average kidney to background ratio in this cohort. The hepatic background activity leads to a lower kidney to background ratio on the right compared to the left. It was postulated that the interobserver agreement would differ between the left and right kidneys. We found that the side of the kidney did not significantly impact on the overall interobserver agreement.

In this study we also used Cohen's Kappa and Krippendorff's alpha because percentage agreement does not account for random agreements. Unfortunately, the published levels of interobserver agreement for detecting cortical defects by [^{99m}Tc]Tc-DMSA were not analysed by Krippendorff's alpha coefficient.

The reader needs to be mindful for the possible presence of paradoxical results when using Kappa or Krippendorff's alpha. This paradox was reported by many researchers where they noted high percentage agreement value but low corresponding kappa value (21). This observation was believed to increase linearly as the distribution of a variable is less balanced. In such scenarios, the kappa values need to be reported but interpreted with caution. Since there were fewer kidneys with cortical defects (lower prevalence) in our study compared to kidneys with no defects, the

percentage agreement values are probably more representative than the Kappa or Krippendorff's agreement values when a paradox is demonstrated in the results.

We found high levels of intraobserver reproducibility with no significant change when measured for the combined populations or the separated populations. This was comparable to the published corresponding levels for [^{99m}Tc]Tc-DMSA which was 90.6% and 95.9% intraobserver percentage agreement while the range of weighted kappa was 0.8-0.9 and 0.6-0.8 (4). This was also comparable to the reported percentage intraobserver agreement reported by De Guevara et al. which was 96%, 89%, and 86% for observers 1, 2, and 3, respectively (6).

In the study protocol we evaluated 1-2, 2-3 and 3-4 min summed images. We established that on the 3-4 minute images of the paediatric renograms, the senior observer had a lower intraobserver agreement. This was accounted for the repeated observation of fast cortical clearance. This could be a potential pitfall when assessing cortical defects on [^{99m}Tc]Tc-MAG3 renography. On the other hand, Sfakianakis et al. used prolonged cortical retention on the later images as an indication of parenchymal dysfunction (14). One can argue that fast cortical clearance is in keeping with normal parenchymal function and makes the presence of cortical defects less likely. It is therefore probably not ideal to use the 3-4 min summed images to assess for cortical defects especially for the paediatric population.

The experience of the observers did not make a significant difference in the interobserver or the intraobserver reproducibility. This observation was also seen in previous work on [^{99m}Tc]Tc-DMSA were there was remarkable agreement between observers without high levels of expertise (5).

The effect of kidney to background ratio on the level of certainty to detect renal cortical defects and on the level of the reproducibility was prominent. Higher kidney to background ratio was associated with higher confidence and certainty as well as higher interobserver agreement. This is in line with a previous study that also highlighted the effect of kidney to background ratio on the reproducibility of (DRF) measurements using [^{99m}Tc]Tc-MAG3. The reproducibility of DRF measurement has been reported to be decreased when the kidney to background ratio is ≤2 (23). They found that 77% of the kidneys classified as right renal margins poorly visualised had a target to background ratio ≤ 2.

The interobserver disagreement between normal and abnormal which could have had a clinical impact was seen in 4.5% of the paediatric kidneys and 13.5% for the adult kidneys. This is similar to previous [^{99m}Tc]Tc-DMSA research. Tondeur et al. found that in 13% of paediatric [^{99m}Tc]Tc-DMSA scans there was an interobserver disagreement between normal and abnormal. One of the reasons why that value for the paediatric patients may be better is that in our study, the images were evaluated by three observers in comparison to the 61 observers included in the Tondeur study (8). Another reason could be that there were more normal scans in our paediatric population.

One of the strengths of this study was the number of the included renograms. A weakness of this study may have been the higher number of cases with no cortical defects included in the paediatric population as well as the small number. Therefore, future studies with more observers and fewer normal kidneys are still needed.

Conclusion:

This study demonstrated moderate interobserver reproducibility and substantial intraobserver reproducibility for the detection of renal cortical defects on the early 1-2 and 2-3 min images of [^{99m}Tc]Tc-MAG3 renography. The percentage interobserver agreement were comparable to the values reported in the literature for [^{99m}Tc]Tc-DMSA. Disagreement between normal and abnormal cases were infrequent and in keeping with levels reported for [^{99m}Tc]Tc-DMSA. The interobserver reproducibility was decreased when the kidney to background ratio was 2 or less.

Acknowledgements:

There are no conflicts of interest. This work is not funded.

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Figure 1. The diagram was used to report the number and location of the cortical defects.

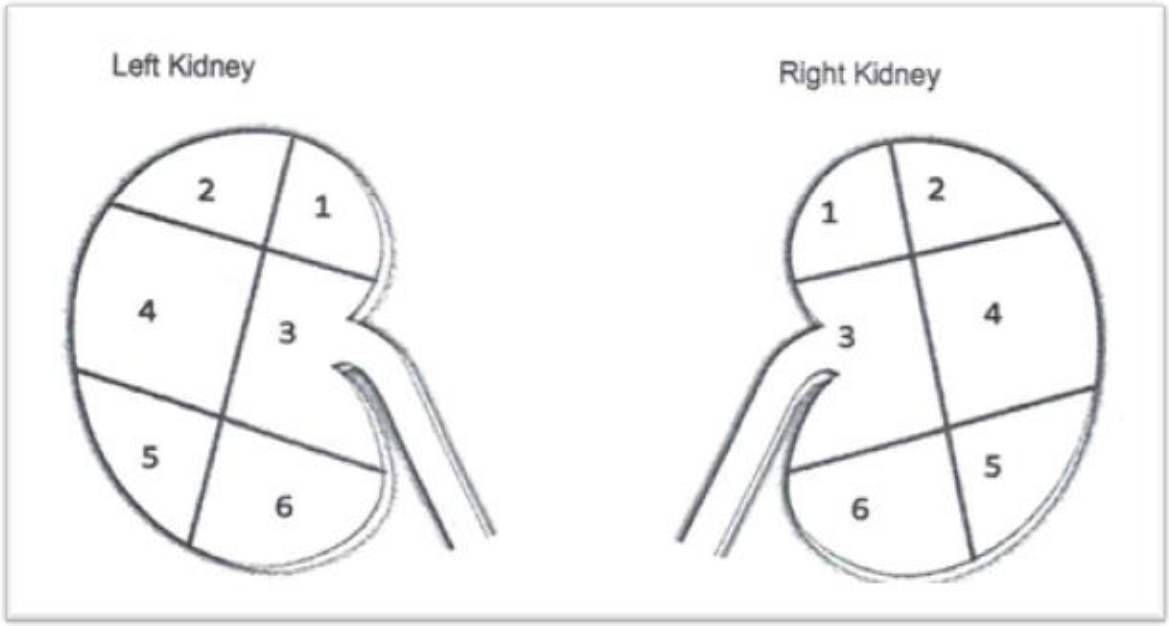


Table 1. The interobserver percentage agreement and Krippendorff's alpha results for three observers. The p-value is <0.001 for all the tabulated results.

	Percentage agreement			**Krippendorff's alpha**		
	Estimate	**95% Confidence Interval**		**Estimate**	**95% Confidence Interval**	
All patients (n 300)						
Left Kidney Defect (1-2 mins)	78.8	74.8	82.7	0.51	0.45	0.58
Left Kidney Defect (2-3 mins)	78.8	74.8	82.8	0.51	0.44	0.57
Left Kidney Defect (3-4 mins)	76.8	72.7	80.8	0.47	0.40	0.54
Right Kidney Defect (1-2 mins)	79.7	75.9	83.5	0.56	0.49	0.62
Right Kidney Defect (2-3 mins)	79.0	75.2	82.8	0.53	0.47	0.60
Right Kidney Defect (3-4 mins)	76.4	72.6	80.3	0.49	0.42	0.56
Adults (n 100)						
Left Kidney Defect (1-2 mins)	75.0	67.7	82.3	0.56	0.45	0.66
Left Kidney Defect (2-3 mins)	75.7	68.4	82.9	0.57	0.46	0.67
Left Kidney Defect (3-4 mins)	75.0	67.7	82.3	0.55	0.45	0.66
Right Kidney Defect (1-2 mins)	67.0	59.3	74.7	0.42	0.31	0.52
Right Kidney Defect (2-3 mins)	66.7	59.1	74.3	0.41	0.30	0.52
Right Kidney Defect (3-4 mins)	67.3	59.8	74.9	0.41	0.31	0.52
Children (n 200)						
Left Kidney Defect (1-2 mins)	80.7	76.0	85.3	0.46	0.38	0.54
Left Kidney Defect (2-3 mins)	80.3	75.6	85.1	0.44	0.35	0.53
Left Kidney Defect (3-4 mins)	77.7	72.8	82.6	0.40	0.31	0.48
Right Kidney Defect (1-2 mins)	86.0	82.0	90.0	0.64	0.56	0.73
Right Kidney Defect (2-3 mins)	85.2	81.2	89.2	0.62	0.53	0.71
Right Kidney Defect (3-4 mins)	81.0	76.6	85.4	0.53	0.44	0.63

Table 2. The results of interobserver agreement between two senior observers on the presence of renal cortical defect is analyzed by Percentage agreement and Cohen's kappa. The p-value is <0.001 for all the tabulated results.

	Percentage agreement			Cohen's kappa		
	Estimate	95% Confidence Interval		Estimate	95% Confidence Interval	
All patients (n 300)						
Left Kidney Defect (1-2 mins)	81.0	76.5	85.5	0.53	0.45	0.62
Left Kidney Defect (2-3 mins)	81.3	76.9	85.8	0.53	0.45	0.62
Left Kidney Defect (3-4 mins)	78.3	73.6	83.0	0.48	0.39	0.57
Right Kidney Defect (1-2 mins)	80.0	75.5	84.6	0.54	0.45	0.62
Right Kidney Defect (2-3 mins)	80.3	75.8	84.9	0.53	0.45	0.62
Right Kidney Defect (3-4 mins)	76.3	71.5	81.2	0.46	0.38	0.55
Adults (n 100)						
Left Kidney Defect (1-2 mins)	72.0	63.1	81.0	0.49	0.37	0.62
Left Kidney Defect (2-3 mins)	73.0	64.2	81.9	0.51	0.38	0.64
Left Kidney Defect (3-4 mins)	72.0	63.1	81.0	0.49	0.36	0.62
Right Kidney Defect (1-2 mins)	65.0	55.5	74.5	0.37	0.24	0.50
Right Kidney Defect (2-3 mins)	65.0	55.5	74.5	0.37	0.24	0.50
Right Kidney Defect (3-4 mins)	65.0	55.5	74.5	0.36	0.23	0.49
Children (n 200)						
Left Kidney Defect (1-2 mins)	85.5	80.6	90.4	0.55	0.43	0.66
Left Kidney Defect (2-3 mins)	85.5	80.6	90.4	0.53	0.41	0.65
Left Kidney Defect (3-4 mins)	81.5	76.1	86.9	0.45	0.33	0.58
Right Kidney Defect (1-2 mins)	87.5	82.9	92.1	0.65	0.54	0.76
Right Kidney Defect (2-3 mins)	88.0	83.5	92.5	0.65	0.54	0.77
Right Kidney Defect (3-4 mins)	82.0	76.6	87.4	0.53	0.41	0.65

Table 3. The intraobserver agreement measured by Percentage agreement and the Krippendorff's alpha for all patients. The p-value is <0.001 for all the tabulated results.

	Percentage agreement			**Krippendorf's alpha**		
	Estimate	**95% Confidence Interval**		**Estimate**	**95% Confidence Interval**	
Senior observer						
Left Kidney Defect (1-2 mins)	89.7	86.2	93.1	0.75	0.68	0.83
Left Kidney Defect (2-3 mins)	90.3	87.0	93.7	0.77	0.69	0.84
Left Kidney Defect (3-4 mins)	82.7	78.4	87.0	0.64	0.56	0.72
Right Kidney Defect (1-2 mins)	87.3	83.6	91.1	0.72	0.67	0.80
Right Kidney Defect (2-3 mins)	86.7	82.8	90.5	0.71	0.63	0.78
Right Kidney Defect (3-4 mins)	77.7	72.9	82.4	0.57	0.48	0.65
Junior observer						
Left Kidney Defect (1-2 mins)	80.7	76.2	85.2	0.63	0.55	0.70
Left Kidney Defect (2-3 mins)	80.3	75.8	84.9	0.62	0.54	0.70
Left Kidney Defect (3-4 mins)	80.3	75.8	84.9	0.62	0.54	0.70
Right Kidney Defect (1-2 mins)	84.0	79.8	88.2	0.70	0.63	0.77
Right Kidney Defect (2-3 mins)	83.7	79.5	87.9	0.70	0.62	0.77
Right Kidney Defect (3-4 mins)	84.0	79.8	88.2	0.70	0.63	0.77

Table 4. The number of kidneys where all three observers completely agreed to rate as certain for the presence of a defect, certainly no defect or not certain. The number of kidneys where there is no complete agreement is also included. The table also shows how the agreement differs when using 1-2 min image alone, when using 1-3 min images and when using all 1-4 min images to assess for renal cortical defects.

	Left kidneys on 1-2 min		**Left kidneys on 1-3 min**		**Left kidneys on 1-4 min**		**Right kidneys on 1-2 min**		**Right kidneys on 1-3 min**		**Right kidneys on 1-4 min**	
Group	Adult	Paediatric	Adult	Paediatric	Adult	Paediatric	Adult	Paediatric	Adult	Paediatric	Adult	Paediatric
No defect	53	141	53	141	53	134	48	139	46	137	46	124
There is defect	9	2	9	2	8	2	2	6	2	6	2	6
Not certain	5	5	5	5	5	5	6	14	6	13	6	12
Complete agreement	67	148	67	148	66	141	56	159	54	156	54	142
No complete agreement	33	52	33	52	34	59	44	41	46	44	46	58

Table 5. The number of instances where difference between certain there is no defect and certain there is a defect occurred.

	Right kidney (n 300)	Left kidney (n 300)	Total / percentage
Interobserver differences			
Adult	18	9	27 (13.5%)
Children	7	12	19 (4.5%)
Total	25 (8.3%)	21 (7%)	46 (7.6%)
Intraobserver differences for the junior observer			
Adult	9	8	17 (8.5%)
Children	11	17	28 (7%)
Total	20 (6.6%)	25 (8.3%)	45 (7.5%)
Intraobserver differences for the senior observer			
Adult	7	2	9 (4.5%)
Children	3	2	5 (1.2%)
Total	10 (3.3%)	4 (1.3%)	14 (2.3%)

Table 6**.** The interobserver agreement for three observers is given based on kidney to background ratio (KBR) for all patients on 1-2 minute of the renogram. The interobserver agreement is given for each kidney when the target to background ratio is ≤ 2 or >2. The p-value is <0.001 for all the tabulated results.

	Percentage agreement			**Krippendorff's alpha**		
	Estimate	**95% Confidence Interval**		**Estimate**	**95% Confidence Interval**	
Left Kidney Defect (1-2 min) when KBR is ≤ 2	61.5	51.7	71.4	0.44	0.32	0.57
Left Kidney Defect (1-2 min) when KBR is > 2	83.6	79.5	87.6	0.48	0.40	0.56
Right Kidney Defect (1-2 min) when KBR is ≤ 2	64.8	57.6	72.0	0.47	0.38	0.57
Right Kidney Defect (1-2 min) when KBR is > 2	87.1	83.1	91.0	0.54	0.42	0.65

Data Sheet

Study Number: Date of birth:

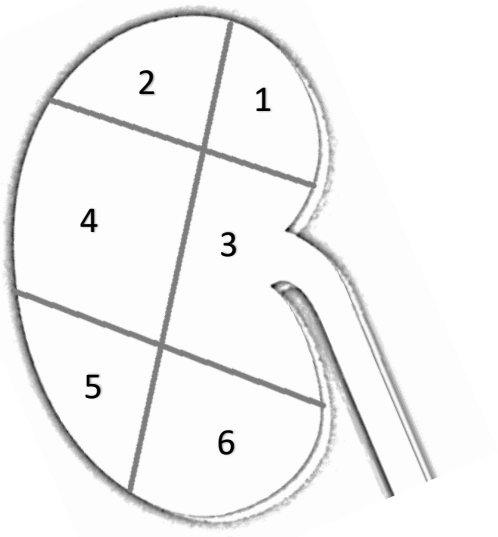
Study Date: Observer:

Please fill the table with 1 if you see defect, 0 if not seen or 2 if you are not sure

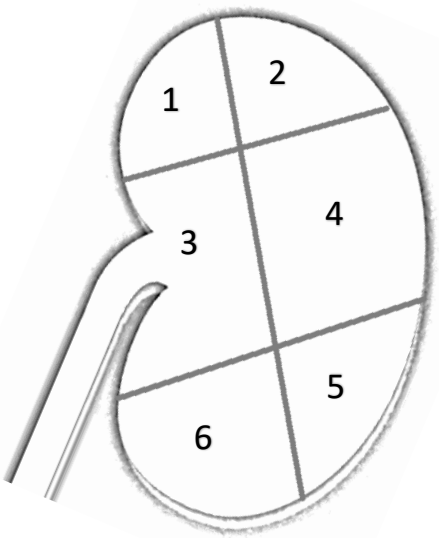
Left Kidney			**Right Kidney**		
Summed 1-2 min image	**Summed 2-3 min image**	**Summed 3-4 min image**	**Summed 1-2 min image**	**Summed 2-3 min image**	**Summed 3-4 min image**

If you see a cortical defect, please mark the location of the defect using **X**

Left Kidney



Right Kidney



Observer A:

Left Kidney	Right kidney
mean counts/pixel	mean counts/pixel
background mean counts/pixel	background mean counts/pixel
Calculated target to background ratio	Calculated target to background ratio

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

07 January 2020

HREC REF: 870/2019

Dr Anita Brink
Room A3.62 Division of Digital Imaging
Department of Nuclear Medicine
Red Cross War Memorial Children's Hospital

Dear Dr Brink

PROJECT TITLE: ASSESMENT OF THE INTEROBSERVER AND INTRAOBSERVER REPRODUCIBILITY FOR THE DETECTION OF RENAL CORTICAL DEFECTS IN ADULTS AND CHILDREN USING 99mTc MAG3. (MASTER DEGREE - DR MOHAMMED HASLAN)

Thank you for submitting your new study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 January 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period. (Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledges that the student: Dr Mohammed Hasian will also be involved in this study.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence

Yours sincerely

PROFESSOR MARC BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

HREC/ref: 870/2019
OL

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.01.2022
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	11/1/21

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol Information

Date (when submitting this form)	08 January 2021		
HREC REF Number	870/2019	Current Ethics Approval was granted until	30 Jan 2021
Protocol title	Assessment of The Interobserver and Intraobserver Reproducibility for The Detection of Renal Cortical Defects in Adults and Children Using ^{99m}Tc MAG3		
Protocol number (If applicable)			
Are there any sub-studies linked to this study?	☐ Yes ☑ No		
If yes, could you please provide the HREC Ref's for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study			
Principal Investigator	Anita Brink		
Department / Office Internal Mail Address	Room A3.62, Nuclear Medicine Department, Medical Imaging, Red Cross Children Hospital.		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

UNIVERSITY OF CAPE TOWN
FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.01.23
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	27/1/22

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol Information

Date (when submitting this form)	25 January 2022		
HREC REF Number	870/2019	Current Ethics Approval was granted until	30 Jan 2022
Protocol title	Assessment of The Interobserver and Intraobserver Reproducibility for The Detection of Renal Cortical Defects in Adults and Children Using ^{99m}Tc MAG3		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes ☑ No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Anita Brink		
Department / Office Internal Mail Address	Room A3.62, Nuclear Medicine Department, Medical Imaging, Red Cross Children Hospital.		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Nuclear Medicine Communications

Online Submission and Review System.

Guidance for Authors (this page)

Guidance for Authors on the Preparation and Submission of Manuscripts to Nuclear Medicine Communications

Note: These instructions comply with those formulated by the International Committee of Medical Journal Editors. For further details, authors should consult the following article: International Committee of Medical Journal Editors. "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" *N Engl J Med* 1997; **336**: 309–315. The complete document appears at www.icmje.org.

Scope

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Acknowledgements

Acknowledgements should be made only to those who have made a substantial contribution to the study. Authors are responsible for obtaining written permission from people acknowledged by name in case readers infer their endorsement of data and conclusions.

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Articles in journals

Standard journal article:
Jager, PL, Gietema, JA, van der Graaf, WTA. Imatinib mesylate for the treatment of gastrointestinal stromal tumours: best monitored with FDG PET. *Nucl Med Commun* 2004; **25**:433-438

Books

Book:
Maisey MN, Britton KE, Gilday DL. *Clinical nuclear medicine*. London: Chapman and Hall, 1991

Chapter in a book:
Lazarus C. Radiopharmaceuticals. In: Maisey MN, Britton KE, Gilday DL, eds. *Clinical nuclear medicine*. London: Chapman and Hall, 1991: 515–541.

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