Title:

Will advances in functional renal MRI translate to the nephrology clinic?

Authors:

Alastair J. Rankin[1,2], Kaitlin Mayne[1,2], Sarah Allwood-Spiers[3], Pauline Hall Barrientos[3], Giles Roditi[1,4], Keith A. Gillis[1,2], Patrick B. Mark[1,2].

Affiliations:

1. Institute of Cardiovascular & Medical Sciences, University of Glasgow, Glasgow, UK
2. Glasgow Renal and Transplant unit, Queen Elizabeth University Hospital, Glasgow, UK
3. Department of Clinical Physics and Bioengineering, NHS Greater Glasgow & Clyde, Glasgow, UK
4. Department of Radiology, NHS Greater Glasgow & Clyde, Glasgow, UK

Corresponding author: Professor Patrick Mark
Office 234, Institute of Cardiovascular & Medical Sciences
BHF Glasgow Cardiovascular Research Centre
University of Glasgow
126 University Place
Glasgow, G12 8TA

E-mail: patrick.mark@glasgow.ac.uk
Twitter: @drpaddymark

Word count:	3347 words
References:	65

Tables:	1
Figures:	1
Supplementary material:	Yes

Abstract (217 words)

Characterizing structural and tissue abnormalities of the kidney is fundamental to understanding kidney disease. Functional multi-parametric renal magnetic resonance imaging (MRI) is a noninvasive imaging strategy whereby several sequences are employed within a single session to quantify renal perfusion, tissue oxygenation, fibrosis, inflammation, and oedema without using ionizing radiation. In this review, we discuss evidence surrounding its use in several clinical settings including acute kidney injury, chronic kidney disease, hypertension, polycystic kidney disease and around renal transplantation. Kidney size on MRI is already a validated measure for making therapeutic decisions in the setting of polycystic kidney disease. Functional MRI sequences, T1 mapping and apparent diffusion coefficient, can non-invasively quantify interstitial fibrosis and so may have a near-future role in the nephrology clinic to stratify the risk of progressive chronic kidney disease or transplant dysfunction. Beyond this, multi-parametric MRI may be utilised diagnostically, for example differentiating inflammatory versus ischaemic causes of renal dysfunction, but this remains to be proven. Changes in MRI properties of kidney parenchyma may be useful surrogate markers to use as end points in clinical trials to assess if drugs prevent renal fibrosis or alter kidney perfusion. Large, multi-centre studies of functional renal MRI are ongoing which aim to provide definitive answers as to its role in the management of patients with renal dysfunction.

Introduction

Over the past four decades the widespread application of diagnostic medical imaging has revolutionised the practice of modern medicine (1,2). However, the functional unit of the kidney, the nephron, is microscopic, and as such, the role of conventional imaging in the diagnosis of kidney disease is limited. Kidney imaging is still vital in the assessment of patients with kidney disease although its application is rudimentary and aims to answer very specific questions which differentiate only a minority of patients. Kidney size and shape, presence or absence of hydronephrosis and perfusion of the kidney are the key questions addressed, most of which can be reliably answered using simple imaging techniques (ultrasound, non-contrast computed tomography) and have not advanced despite major technological innovations over the past 20 years. While there have been advances in techniques to assess large vessel kidney perfusion, their application to the management of many aspects of chronic kidney disease remains uncertain (3). The dearth of imaging applications in nephrology may signal a missed opportunity to improve our diagnostic accuracy and to allow better risk stratification of patients. In Europe, between 10-30% of incident dialysis patients have kidney disease of uncertain aetiology(4). Given that incident dialysis patients represent the most severe ‘tip’ of the kidney disease ‘iceberg’ there are millions of people worldwide with life-limiting kidney disease who do not have an accurate diagnosis. Diagnostic tools in nephrology in routine clinical care are limited. Creatinine, glomerular filtration rate (estimated or measured), cystatin C and proteinuria are non-specific markers and poorly differentiate the aetiologies of kidney disease (5). Proportionately few kidney diseases have specific serological biomarkers (6), and although serological markers of renal disease are continuously expanding (7), most patients with positive serology still require confirmatory histology. As such, kidney biopsy remains the gold standard diagnostic tool (5). However, a kidney biopsy is an invasive procedure which risks life-threatening bleeding (8), has several relative complications and is vulnerable to

sampling error. Accordingly, there is a need for novel, non-invasive biomarkers of kidney disease to reduce risk exposure and increase diagnostic accuracy in kidney disease.(9) While advances in exome sequencing is likely to identify previously unknown actionable genetic diagnoses in just under 10% of the dialysis population(10), the nephology community should embrace as many state of the art advances in diagnostic technologies to advance application of precision medicine to patients with kidney disease.

Functional magnetic resonance imaging (MRI) of the kidney is a burgeoning area of interest where it is hoped that different MRI sequences can provide quantitative information regarding perfusion, tissue oxygenation, fibrosis, inflammation, and oedema, in addition to the standard anatomical and structural assessment that 3D imaging allows (11). Where these different sequences are acquired in a single sitting, typically lasting 30-60 minutes, it is referred to as ‘multi-parametric’ MRI.

MRI sequences of interest

Functional renal MRI can be performed on 1.5T or 3T MRI scanners, where T refers to tesla, the unit of magnetic field strength. Most clinical MRI scanners are 1.5T, and although, in theory, the stronger the magnet the greater the achievable image resolution, this is not always true in practice. Standard contraindications to MRI apply to renal MRI (12) and are becoming less restrictive with most implanted cardiac devices now deemed MRI conditional (13). Detailed description of each MRI sequence is beyond the scope of this review, but Table 1 summarises the most commonly acquired MRI sequences that are combined into a multiparametric protocol: diffusion-weighted imaging (DWI) using apparent diffusion coefficient (ADC) (14,15), T1 mapping (16,17), blood oxygen level dependent imaging (BOLD) (18,19) and arterial spin labelling (ASL) (20,21). These sequences do not require gadolinium based contrast, which is associated with a small risk of nephrogenic systemic fibrosis

following in patients with advanced kidney disease (22,23). Gadolinium based contrast agents are still critical for certain techniques such as contrast-enhanced magnetic resonance angiography (CE-MRA) and dynamic contrast enhanced (DCE) renal perfusion. Future renal MRI may adopt non-traditional MRI contrast agents including iron-based agents such as ferumoxytol (24,25). Supplementary material table S1 outlines a non-exhaustive list of additional sequences that may be included in imaging protocols relevant to functional renal MRI.

Clinical Applications of Renal MRI

Polycystic Kidney disease

Total kidney volume (TKV) measured on MRI is a validated prognostic marker in patients with polycystic kidney disease, such that the Food and Drug Administration and the European Medicines Agency have both approved height-adjusted TKV to guide treatment decisions in patients with polycystic kidney disease (26). This follows the seminal findings of the CRISP study, a longitudinal study of adult patients with polycystic kidneys which characterised the relationship between total kidney volume (TKV) and measured glomerular filtration rate and found that increasing TKV (resulting from gradual expansion of renal cysts) occurs prior to decline in eGFR and can predict future decline (27). These findings were confirmed by the PKD Outcomes Consortium (28), and featured in the inclusion criteria for the landmark trials showing that tolvaptan reduced the rate of eGFR decline in patients with PKD (TEMPO 3:4 (29) and REPRISE (30)). Height-adjusted TKV can also be combined with age to determine The Mayo Imaging Class, which has been shown to successfully distinguish patients at differing rates of progression (31). TKV is most accurately measured from cross-sectional images obtained by MRI or computed tomography using manual segmentation or stereology (where a square grid is super-imposed on each kidney slice before the number of grids containing kidney tissue are manually

counted). These processes are time-consuming but it is plausible that effortless TKV measurement will soon be possible using machine learning software (32). In the meantime, an alternative method using an ellipsoid equation, where coronal, sagittal and transverse diameters are used to estimate TKV have also been shown to be acceptable for majority of cases (31). Outside the setting of PKD, reducing kidney volume has been shown to correlate with reduced eGFR, including in the setting of living kidney donors (33,34).

Acute Kidney Injury

In a minority of patients with acute kidney injury (AKI), anatomical MRI sequences may support a specific diagnosis, for instance, there are well described appearances of renal cortical necrosis evident on T2-weighted images and contrast-enhanced T1 images (35,36). Similarly, specific patterns suggesting the sequelae of acute tubular necrosis or presence of pyelonephritis may be detected (37). Multi-parametric functional renal MRI has not been extensively studied in patients with non-transplant acute kidney injury (AKI). The only study of multi-parametric renal MRI in AKI included follow-up data for only seven participants (38). Nevertheless, this study identified significant increases in TKV, T1 relaxation time, and cortical perfusion that gradually improved during recovery from AKI. Interestingly, by three months serum creatinine returned to normal in all subjects, but the MRI parameters remained abnormal in some. Additional small studies focusing on single MRI sequences have also shown that perfusion measured by ASL and phase-contrast MRI was reduced in patients with AKI compared to healthy controls (39,40), while studies examining BOLD found no difference between AKI and healthy volunteers (although changes were evident in healthy volunteers after the administration of furosemide that did not occur in those with AKI) (41). Inoue *et al*. examined BOLD and ADC in a sub-group of 23 patients with AKI and found no correlation between either parameter and estimated glomerular filtration rate (eGFR) (42). This is not surprising given the

limited relevance of eGFR in AKI. Raman *et al*. found increased cortical T1 in 52 patients with COVID-19 (of whom 6 had AKI) compared to 28 controls (43).

MRI in AKI can be logistically challenging due to the need for participants with an acute illness to lie flat for up to one hour and co-ordinate multiple breath-holds (38). It is likely that technological advances in shortened acquisition times (through the use of methods such as compressed sensing) and free-breathing sequences will reduce this burden (44).

Clinical application of MRI in AKI:

- Unclear, potentially limited due to fluctuant clinical status and burden to patient.
- Future studies should address if functional MRI can distinguish AKI of haemodynamic versus inflammatory aetiology
- Serial scanning could guide prognostication of renal recovery in AKI, but this remains to be proven.

Chronic Kidney Disease

Reduction in kidney volume and loss of corticomedullary differentiation are established, non-specific markers of chronic kidney disease (CKD) that have been diagnosed using T1 weighted MRI images for over 30 years (45–47). Beyond anatomical assessment, there are numerous studies examining the role of functional MRI in patients with CKD. Inoue *et al*. examined BOLD and DWI in 119 patients with CKD and found ADC measured from the DWI sequence correlated with eGFR (r^2 = 0.56 in patients with diabetes, and 0.46 in non-diabetic CKD). In a subgroup of 37 patients without diabetes who underwent kidney biopsy, they found a significant correlation between the degree of fibrosis with ADC (r^2 = 0.48, $p<0.01$) and BOLD (r^2

= 0.23, p<0.01). Another prospective study, this time of 112 patients with CKD and 71 controls found that cortical oxygenation measured as R2* on BOLD, negatively correlated with eGFR, with those individuals with higher cortical values being three times more likely to develop a need for renal replacement therapy or a 30% increase in serum creatinine (48). Zhang *et al.* studied MR elastography and DWI in 97 adults with CKD to find the former negatively correlated with histological fibrosis (ρ = -0.397), while the latter positively correlated (ρ = 0.472) with the density of peritubular capillaries (a surrogate for fibrosis) (49). Two key studies adopted a multi-parametric approach. Buchanan *et al*. studied 44 patients without diabetes who had CKD (50). They found that multiparametric MRI was able to differentiate CKD from controls with normal kidney function (CKD values included higher T1, lower ADC, lower ASL), with correlation between MRI and clinical parameters (eGFR and urine protein:creatinine ratio). MRI parameters (T1 and ADC [both cortical values and cortico-medullary differentiation], as well as cortical perfusion on ASL), correlated with histology and were able to differentiate high versus low levels of fibrosis on histology with an optimal threshold of 40% fibrosis. Berchtold *et al.* used a multiparametric protocol in a study of 164 patients with CKD, although the majority of these were transplant recipients (51). In the 46 participants with native kidney CKD, the difference in cortex-to-medulla (Δ) ADC and ΔT1 values correlated with the % fibrosis r = 0.64, p < 0.001 and r = 0.71, p < 0.001 respectively. The association was still present, although weaker, when cortical values were used. Across the entire cohort (native and transplant kidneys), combining ΔADC, ΔT1 and eGFR into a multivariable model successfully distinguished patients with high and low levels of fibrosis. The model could identify patients with minimal fibrosis (<10%) with a positive predictive value (PPV) 95.5%, and those with high levels of fibrosis (>50%) with PPV = 88.8%. Perhaps most encouragingly there was no interaction between ΔADC, ΔT1 and eGFR, and model fit increased from r^2 = 0.30 for eGFR alone to 0.54 when the MRI

parameters were added. There are two ongoing, large scale multi-centre studies. The Prognostic Imaging Biomarkers for Diabetic Kidney Disease (iBEAt) study looks to recruit 500 participants with diabetic kidney disease and perform serial scanning over 3 years to identify prognostic MRI biomarkers (ClinicalTrials.gov Identifier: NCT03716401). The Application of Functional Renal MRI to Improve Assessment of Chronic Kidney Disease (AFiRM) study will recruit 450 participants to examine if multi-parametric renal MRI can characterise patients with and without CKD progression(ClinicalTrials.gov Identifier: NCT04238299). This study includes a mechanistic sub-study of 45 participants which aims to compare MRI findings with histology.

Clinical Application of MRI in CKD:

- The near-future clinical application of multi-parametric functional MRI in patients with CKD is the non-invasive quantification of fibrosis to inform prognostication and guide decisions regarding biopsy and management.
- MRI will also be able to inform if fibrosis on a kidney biopsy sample is representative of the organ as a whole
- Renal MRI may have a role as a surrogate outcome measure in future trials of clinical therapeutics
- It may be possible to use MRI to stratify which patients gain most benefit from future therapeutic strategies.
- A large multi-centre study is ongoing to assess if multiparametric MRI can distinguish patients with CKD who have progressive versus stable disease

Hypertension

Hypertension is the second leading cause of renal failure in the Western world (52) and MRI may disclose both causes of raised blood pressure and the effects of it (37). The commonest cause of secondary hypertension is renal parenchymal disease

(which may be multifactorial) while arteriosclerotic or fibromuscular renovascular disease and obstructive uropathy are also important causes. This especially so given that angioplasty for renal artery fibromuscular dysplasia or mechanical relief of hydronephrosis may effect a complete cure and be extremely cost-effective in the individual, negating the expense of many years of drug therapy, associated monitoring costs and potential drug side-effects.

For renovascular imaging magnetic resonance angiography (MRA) is key to providing an accurate depiction of the arteries and given the variability of anatomy and high spatial resolution required, contrast-enhanced (CE-MRA) techniques are preferred (figure 1) (53,54). The protocol can also integrate dynamic contrast evaluation to evaluate differential perfusion (55,56). Since the adjacent adrenal glands will also be imaged then adrenal secondary causes of hypertension in the form of primary aldosteronism (e.g. Conn's tumour) and phaeochromocytoma may be disclosed.

Kidney Transplant Recipient Imaging

Renal MRI has been studied actively in renal transplant recipients, largely driven by a very clear clinical question: can MRI distinguish rejection from other causes of transplant dysfunction? Most of these studies had small sample sizes and focused on a single MRI sequence with conflicting results (57). At present, it is not clear if any parameter, alone or in conjunction, can reliably distinguish causes of allograft dysfunction. Moreover, given the advances in urinary and serum biomarkers for acute rejection it is plausible that non-imaging techniques may fulfil this clinical need.(58,59) The ability of MRI to detect fibrosis in allografts has yielded more consistent and promising results. In addition to the study discussed above by Berchtold *et al.* (which included 118 participants with renal transplants) (51), there are 3 notable studies comparing multi-parametric renal MRI with renal histology.

Friedli *et al*. report MRI findings in 33 renal transplant recipients undergoing clinically indicated transplant kidney biopsy. They found that ADC and T1 were not sensitive for interstitial inflammation. However, ΔADC (defined as cortex minus medullary values) negatively correlated with histological fibrosis (r^2 = 0.64, p<0.001), such that a negative ΔADC yielded 100% sensitivity and 71% specificity to discriminate fibrosis of 40% or more. Wang *et al.* performed multi-parametric MRI in 103 renal transplant recipients who were undergoing clinically indicated biopsies (60). Again, ADC was found to negatively correlate with interstitial fibrosis (ρ = 0.77, p<0.001), with ASL and BOLD also significantly associated with fibrosis (r=0.77, p<0.001 and ρ = 0.61, p <0.001, respectively). Each variable was able to discriminate patients with and without 50% fibrosis with an area under the curve of ≥0.85. Bane *et al*. compared MRI findings in 27 renal transplant recipients in whom 15 had stable allograft function and 12 had chronic dysfunction (eGFR <30 ml/min/1.73 m^2). Once again, ADC and ΔT1 differentiated the functioning allografts from the fibrotic ones, with excellent cross-validated diagnostic performance when used in combination. They also found that cortical ADC and T1 had good performance at predicting an eGFR decline of ≥4 ml/min/1.73 m^2 per year at 18 months.

Magnetic resonance elastography, a technique that uses external mechanical vibration to quantify organ stiffness on MRI, is particularly suited to renal transplant recipients given allografts are placed much closer to the skin surface than native kidneys. However, there have been some divergent results in the studies so far (with one study(61) showing a positive correlation between elastography and fibrosis, while another found a negative correlation (62). The technique is also limited by the requirement for the vibration device which is not in routine clinical use.

The other indication for MRI in renal transplant recipients is where renal transplant artery stenosis is suspected, for example with the development of hypertension. CE-MRA allows imaging of a tortuous vascular anatomy to determine if a stenosis has developed and allowing a 3D road-map for any planned endovascular intervention.

Clinical application of MRI in renal transplant dysfunction:

- Functional MRI utilising T1 and ADC can reliably detect fibrosis in renal transplants. MRI may have a clinical role in discriminating transplant kidneys with extensive versus minimal fibrosis.
- The role of functional MRI in distinguishing causes of acute transplant dysfunction remains to be proven.

Potential Kidney Donor Imaging

Potential kidney donors require comprehensive imaging as part of their assessment to detect any incidental intrinsic renal disease or anatomical variants (particularly the vasculature) that would preclude donation. These altruistic donors are often young and merit a 'least harm' approach hence MRI, with its lack of ionising radiation, is preferred to multiphase CT. Given that the vasculature is the most fundamental part of this evaluation, CE-MRA is key to providing high spatial resolution depiction of the arteries and veins although a full imaging protocol can also include dynamic contrast evaluation to evaluate differential perfusion and an excretory urographic phase to image the pelvicalyceal systems and ureters (figure 1).

Barriers to the Clinical Application of Functional Renal MRI

MRI will always be limited by cost, availability, and contraindications in some patients (12,13). However, the clinical need for improved diagnostic tools and the burden of

existing techniques is sufficient to justify its inclusion into clinical practice if its utility is proven. As relatively new techniques, the functional MRI approaches also require standardisation of acquisition and validation of analysis methods, which must be widely-available and applicable across MRI vendors and clinical sites. This is being actively addressed by an international collaboration (63). Caution is needed when interpreting the results of studies comparing renal MRI findings to eGFR. For renal MRI to be useful in clinical practice it must offer information over and above that which can be more readily obtained from a routine blood test. Comparing MRI findings to histological fibrosis is more appealing and is both complimentary to renal biopsy and allows serial imaging. Interstitial fibrosis has been shown to be a key prognostic marker in CKD (64). Being able to confidently diagnose interstitial fibrosis without the need for invasive procedures could have major impact on the management and prognostication of a sub-group patients attending the renal clinic. Caution must also be applied when interpreting results that use corticomedullary differentiation (i.e. ΔT1, ΔADC). The reason for this is two-fold. Firstly, there is not a standardised method for comparing cortico-medullary differentiation, with some papers subtracting medullary values from cortical values, while others use a ratio (cortex divided by medulla) (65).The impact of this on results is likely to be small. Secondly, and more importantly, there is a risk of over interpreting the significance of cortico-medullary findings. Loss of cortico-medullary differentiation is an established, but non-specific, finding in CKD that is detectable on ultrasound, computed tomography and MRI (46). Any observed association between renal outcomes and ΔT1 or ΔADC may under-utilise MRI as a functional measurement and may instead detect a crude structural change that is prevalent in CKD, and which can be measured in simpler ways. Nevertheless, there is now sufficient data to suggest that ADC and T1 can be used to reliably detect renal fibrosis. Future studies (including

one that is already underway (ClinicalTrials.gov Identifier: NCT04238299)) should now look at the clinical utility of these parameters in addition to routine clinical care.

Conclusion

Multi-parametric functional MRI is an exciting area of research. In the near future it is expected that T1 and ADC measurements derived from MRI will be used to reliably and non-invasively quantify interstitial fibrosis in the renal clinic. While it is conceivable that the ultimate role of functional renal MRI will extend beyond this (for instance, differentiating inflammatory versus ischaemic causes of renal dysfunction) this is yet to be proven. Large, multi-centre studies of functional renal MRI techniques are ongoing which will hopefully provide definitive answers as to their role in the management of patients with renal dysfunction.

Acknowledgements

PBM, GR and KAG hold a grant for studying clinical use of renal MRI imaging funded by Kidney Research UK (KS_IN_002_20180913)

Conflicts of interest

P.B.M. reports personal fees and/or non-financial support from Vifor, Napp, Pharmacosmos, Astra Zeneca, Astellas, Novartis and grants from Boehringer Ingelheim. K.A.G reports personal fees from Napp, Astrazeneca and Vifor.

References

1. Huang HK, Aberle DR, Lufkin R, Grant EG, Hanafee WN, Kangarloo H. Advances in medical imaging. In: Annals of Internal Medicine. 1990; 203–220
2. Howell JD. The CT Scan after 50 years — Continuity and Change. https://doi.org/10.1056/NEJMp2033374 *[Internet]* 2021; [cited 2021 Jul 11] 385: 104–105. Available from: https://www.nejm.org/doi/full/10.1056/NEJMp2033374
3. Plouin PF, Bax L. Diagnosis and treatment of renal artery stenosis [Internet]. *Nature Reviews Nephrology*2010; [cited 2021 Jun 4] 6: 151–159. Available from: https://www.nature.com/articles/nrneph.2009.230
4. Kramer A, Boenink R, Stel VS et al. The ERA-EDTA Registry Annual Report 2018: a summary. Clinical Kidney Journal *[Internet]* 2021; [cited 2021 Jul 13] 14: 107–123. Available from: https://academic.oup.com/ckj/article/14/1/107/6046935
5. Hebert LA, Parikh S, Prosek J, Nadasdy T, Rovin BH. Differential diagnosis of glomerular disease: A systematic and inclusive approach [Internet]. *American Journal of Nephrology*2013; [cited 2021 Jun 20] 38: 253–256. Available from: /pmc/articles/PMC3842189/
6. Mastroianni-Kirsztajn G, Hornig N, Schlumberger W. Autoantibodies in renal diseases - clinical significance and recent developments in serological detection. Frontiers in Immunology *[Internet]* 2015; [cited 2021 Jun 20] 6. Available from: /pmc/articles/PMC4426760/
7. Couser WG. Primary Membranous Nephropathy. Clinical Journal of the American Society of Nephrology *[Internet]* 2017; [cited 2021 Jul 13] 12: 983–997. Available from: https://cjasn.asnjournals.org/content/12/6/983
8. Lees JS, McQuarrie EP, Mordi N, Geddes CC, Fox JG, Mackinnon B. Risk factors for bleeding complications after nephrologist-performed native renal biopsy. Clinical Kidney Journal *[Internet]* 2017; [cited 2018 Jun 7] 10: 573–577. Available from: http://academic.oup.com/ckj/article/10/4/573/3072619/Risk-factors-for-bleeding-complications-after
9. Cooper JE, Wiseman AC. Acute kidney injury in kidney transplantation. Current Opinion in Nephrology and Hypertension *[Internet]* 2013; [cited 2018 Jun 6] 22: 698–703. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24076557
10. Groopman EE, Marasa M, Cameron-Christie S et al. Diagnostic Utility of Exome Sequencing for Kidney Disease. https://doi.org/10.1056/NEJMoa1806891 *[Internet]* 2018; [cited 2021 Jul 8] 380: 142–151. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa1806891
11. Caroli A, Pruijm M, Burnier M, Selby NM. Functional magnetic resonance imaging of the kidneys: where do we stand? The perspective of the European COST Action PARENCHIMA. Nephrology Dialysis Transplantation 2018; 33: ii1–ii3.
12. Dill T. Contraindications to magnetic resonance imaging [Internet]. *Heart*2008; [cited 2021 Jun 9] 94: 943–948. Available from: https://heart.bmj.com/content/94/7/943
13. Maralani PJ, Schieda N, Hecht EM et al. MRI safety and devices: An update and expert consensus. Journal of Magnetic Resonance Imaging *[Internet]* 2020; [cited 2021 Jul 20] 51: 657–674. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/jmri.26909
14. Caroli A, Schneider M, Friedli I et al. Diffusion-weighted magnetic resonance imaging to assess diffuse renal pathology: a systematic review and statement paper. Nephrology Dialysis Transplantation 2018; 33: ii29–ii40.

15. Ljimani A, Caroli A, Laustsen C et al. Consensus-based technical recommendations for clinical translation of renal diffusion-weighted MRI. Magnetic Resonance Materials in Physics, Biology and Medicine 2019 33:1 *[Internet]* 2019; [cited 2021 Sep 28] 33: 177–195. Available from: https://link.springer.com/article/10.1007/s10334-019-00790-y
16. Wolf M, de Boer A, Sharma K et al. Magnetic resonance imaging T1- and T2-mapping to assess renal structure and function: a systematic review and statement paper. Nephrology Dialysis Transplantation *[Internet]* 2018; 33: ii41–ii50. Available from: https://academic.oup.com/ndt/article/33/suppl_2/ii41/5078406
17. Dekkers IA, de Boer A, Sharma K et al. Consensus-based technical recommendations for clinical translation of renal T1 and T2 mapping MRI. Magnetic Resonance Materials in Physics, Biology and Medicine 2019 33:1 *[Internet]* 2019; [cited 2021 Sep 28] 33: 163–176. Available from: https://link.springer.com/article/10.1007/s10334-019-00797-5
18. Pruijm M, Mendichovszky IA, Liss P et al. Renal blood oxygenation level-dependent magnetic resonance imaging to measure renal tissue oxygenation: a statement paper and systematic review. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association *[Internet]* 2018; 33: ii22–ii28. Available from: https://academic.oup.com/ndt/article/33/suppl_2/ii41/5078406
19. Bane O, Mendichovszky IA, Milani B et al. Consensus-based technical recommendations for clinical translation of renal BOLD MRI. Magnetic Resonance Materials in Physics, Biology and Medicine 2019 33:1 *[Internet]* 2019; [cited 2021 Sep 28] 33: 199–215. Available from: https://link.springer.com/article/10.1007/s10334-019-00802-x
20. Odudu A, Nery F, Harteveld AA et al. Arterial spin labelling MRI to measure renal perfusion: a systematic review and statement paper. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association *[Internet]* 2018; [cited 2021 Jun 6] 33: ii15–ii21. Available from: https://pubmed.ncbi.nlm.nih.gov/30137581/
21. Nery F, Buchanan CE, Harteveld AA et al. Consensus-based technical recommendations for clinical translation of renal ASL MRI. Magnetic Resonance Materials in Physics, Biology and Medicine 2019 33:1 *[Internet]* 2019; [cited 2021 Sep 28] 33: 141–161. Available from: https://link.springer.com/article/10.1007/s10334-019-00800-z
22. H A, Y C, TR E, Y Z, MR P. A Systematic Review of 639 Patients with Biopsy-confirmed Nephrogenic Systemic Fibrosis. Radiology *[Internet]* 2019; [cited 2021 Jul 19] 292: 376–386. Available from: https://pubmed.ncbi.nlm.nih.gov/31264946/
23. JC W, RA R, J Y et al. Use of Intravenous Gadolinium-based Contrast Media in Patients with Kidney Disease: Consensus Statements from the American College of Radiology and the National Kidney Foundation. Radiology *[Internet]* 2021; [cited 2021 Jul 19] 298: 28–35. Available from: https://pubmed.ncbi.nlm.nih.gov/33170103/
24. Toth GB, Varallyay CG, Horvath A et al. Current and potential imaging applications of ferumoxytol for magnetic resonance imaging [Internet]. *Kidney International*2017; [cited 2021 Jun 4] 92: 47–66. Available from: /pmc/articles/PMC5505659/
25. Stoumpos S, Hennessy M, Vesey AT et al. Ferumoxytol-enhanced magnetic resonance angiography for the assessment of potential kidney transplant recipients. European Radiology *[Internet]* 2018; [cited 2021 Jun 4] 28: 115–123. Available from: https://pubmed.ncbi.nlm.nih.gov/28677065/
26. Chebib FT, Perrone RD, Chapman AB et al. A Practical Guide for Treatment

of Rapidly Progressive ADPKD with Tolvaptan. Journal of the American Society of Nephrology *[Internet]* 2018; [cited 2021 Jul 8] 29: 2458–2470. Available from: https://jasn.asnjournals.org/content/29/10/2458
27. JJ G, VE T, AB C et al. Volume progression in polycystic kidney disease. The New England journal of medicine *[Internet]* 2006; [cited 2021 Jul 11] 354: 2122–2130. Available from: https://pubmed.ncbi.nlm.nih.gov/16707749/
28. RD P, J N, AB C et al. Therapeutic Area Data Standards for Autosomal Dominant Polycystic Kidney Disease: A Report From the Polycystic Kidney Disease Outcomes Consortium (PKDOC). American journal of kidney diseases : the official journal of the National Kidney Foundation *[Internet]* 2015; [cited 2021 Jul 11] 66: 583–590. Available from: https://pubmed.ncbi.nlm.nih.gov/26088508/
29. VE T, AB C, O D et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. The New England journal of medicine *[Internet]* 2012; [cited 2021 Jul 11] 367: 2407–2418. Available from: https://pubmed.ncbi.nlm.nih.gov/23121377/
30. VE T, AB C, O D et al. Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease. The New England journal of medicine *[Internet]* 2017; [cited 2021 Jul 11] 377: 1930–1942. Available from: https://pubmed.ncbi.nlm.nih.gov/29105594/
31. Irazabal M V., Rangel LJ, Bergstralh EJ et al. Imaging Classification of Autosomal Dominant Polycystic Kidney Disease: A Simple Model for Selecting Patients for Clinical Trials. Journal of the American Society of Nephrology *[Internet]* 2015; [cited 2021 Jul 11] 26: 160–172. Available from: https://jasn.asnjournals.org/content/26/1/160
32. Sharma K, Rupprecht C, Caroli A et al. Automatic Segmentation of Kidneys using Deep Learning for Total Kidney Volume Quantification in Autosomal Dominant Polycystic Kidney Disease. Scientific Reports 2017 7:1 *[Internet]* 2017; [cited 2021 Sep 27] 7: 1–10. Available from: https://www.nature.com/articles/s41598-017-01779-0
33. Saxena AB, Busque S, Arjane P, Myers BD, Tan JC. Preoperative renal volumes as a predictor of graft function in living donor transplantation. American Journal of Kidney Diseases *[Internet]* 2004; [cited 2021 Jul 11] 44: 877–885. Available from: http://www.ajkd.org/article/S027263860401087X/fulltext
34. D L, A H, A R et al. Renal volume assessed by magnetic resonance imaging volumetry correlates with renal function in living kidney donors pre- and postdonation: a retrospective cohort study. Transplant international : official journal of the European Society for Organ Transplantation *[Internet]* 2018; [cited 2021 Jul 11] 31: 773–780. Available from: https://pubmed.ncbi.nlm.nih.gov/29575113/
35. JY J, SH K, JS S et al. MR findings of renal cortical necrosis. Journal of computer assisted tomography *[Internet]* 2002; [cited 2021 Jul 19] 26: 232–236. Available from: https://pubmed.ncbi.nlm.nih.gov/11884779/
36. AV A, JG F, CW I, G R, B Y. Acute renal cortical necrosis in a series of young men with severe acute pancreatitis. Clinical nephrology *[Internet]* 2006; [cited 2021 Jul 19] 66: 223–231. Available from: https://pubmed.ncbi.nlm.nih.gov/17063988/
37. Roditi G. MR in hypertension. Journal of Magnetic Resonance Imaging *[Internet]* 2011; [cited 2021 Jul 19] 34: 989–1006. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/jmri.22675
38. Buchanan C, Mahmoud H, Cox E et al. Multiparametric MRI assessment of renal structure and function in acute kidney injury and renal recovery. Clinical Kidney Journal *[Internet]* 2020; [cited 2021 Jun 6] Available from: https://academic.oup.com/ckj/advance-

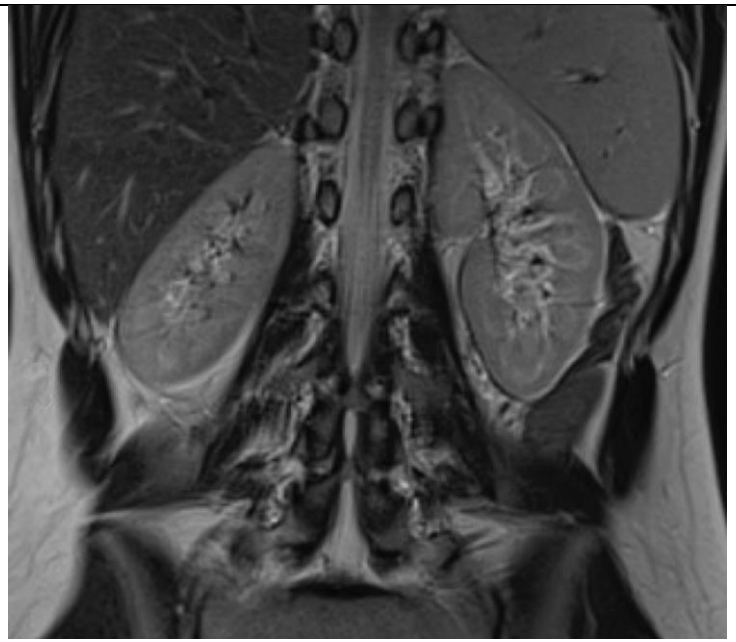
article/doi/10.1093/ckj/sfaa221/6132064
39. Jian D, Li Y, Tao S et al. SCIENCE CHINA Quantitative assessment of acute kidney injury by noninvasive arterial spin labeling perfusion MRI: a pilot study. Springer *[Internet]* 2013; [cited 2021 Jun 6] 56: 745–750. Available from: www.springer.com/scp
40. Prowle J, Molan M, … EH-C care, 2012 undefined. Measurement of renal blood flow by phase-contrast magnetic resonance imaging during septic acute kidney injury: a pilot investigation. journals.lww.com *[Internet]* [cited 2021 Jun 6] Available from: https://journals.lww.com/ccmjournal/fulltext/2012/06000/Measurement_of_renal_blood_flow_by_phase_contrast.11.aspx?casa_token=J4pv_fYtJfwAAAAA:-4-q0xcSV1OA3tzapKG9sWN1flKkTCX4_IAjcoMXCYV5AibLWbm-MDrIrajxPcCOt_zB5f2lqSF9fgR9GUh0vQsbWC0
41. Bauer F, Wald J, Bauer FJ et al. Detection of acute tubular necrosis using blood oxygenation level-dependent (BOLD) MRI. Kidney and Blood Pressure Research *[Internet]* 2017; [cited 2021 Jun 6] 42: 1078–1089. Available from: https://pubmed.ncbi.nlm.nih.gov/29197870/
42. Inoue T, Kozawa E, Okada H et al. Noninvasive evaluation of kidney hypoxia and fibrosis using magnetic resonance imaging. Journal of the American Society of Nephrology *[Internet]* 2011; [cited 2021 Jun 6] 22: 1429–1434. Available from: https://jasn.asnjournals.org/content/22/8/1429
43. Raman B, Cassar MP, Tunnicliffe EM et al. Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. EClinicalMedicine *[Internet]* 2021; [cited 2021 Jun 19] 31. Available from: http://creativecommons.org/licenses/by-nc-nd/4.0/
44. Feng L, Benkert T, Block KT, Sodickson DK, Otazo R, Chandarana H. Compressed sensing for body MRI [Internet]. *Journal of Magnetic Resonance Imaging*2017; [cited 2021 Jun 6] 45: 966–987. Available from: /pmc/articles/PMC5352490/
45. Baumgartner BR, Nelson RC, Torres WE, Malko JA, Peterson JE, Bernardino ME. Renal corticomedullary junction: Performance of t1-weighted mr pulse sequences. Investigative Radiology *[Internet]* 1989; [cited 2021 Jul 20] 24: 884–887. Available from: https://pubmed.ncbi.nlm.nih.gov/2807803/
46. Semelka RC, Corrigan K, Ascher SM, Brown JJ, Colindres RE. Renal corticomedullary differentiation: observation in patients with differing serum creatinine levels. Radiology *[Internet]* 1994; [cited 2019 Jul 4] 190: 149–152. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8259395
47. VS L, M K, L B et al. What causes diminished corticomedullary differentiation in renal insufficiency? Journal of magnetic resonance imaging : JMRI *[Internet]* 2007; [cited 2021 Jul 20] 25: 790–795. Available from: https://pubmed.ncbi.nlm.nih.gov/17335025/
48. M P, B M, E P et al. Reduced cortical oxygenation predicts a progressive decline of renal function in patients with chronic kidney disease. Kidney international *[Internet]* 2018; [cited 2021 Jul 9] 93: 932–940. Available from: https://pubmed.ncbi.nlm.nih.gov/29325997/
49. Zhang J, Yu Y, Liu X et al. Evaluation of Renal Fibrosis by Mapping Histology and Magnetic Resonance Imaging. Kidney Diseases *[Internet]* 2021; [cited 2021 Jun 10] 7: 1–12. Available from: www.karger.com/kdd
50. Buchanan CE, Mahmoud H, Cox EF et al. Quantitative assessment of renal structural and functional changes in chronic kidney disease using multi-parametric magnetic resonance imaging. Nephrology Dialysis Transplantation *[Internet]* 2019; : 1–10. Available from: https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfz129/5525254
51. Berchtold L, Friedli I, Crowe LA et al. Validation of the corticomedullary

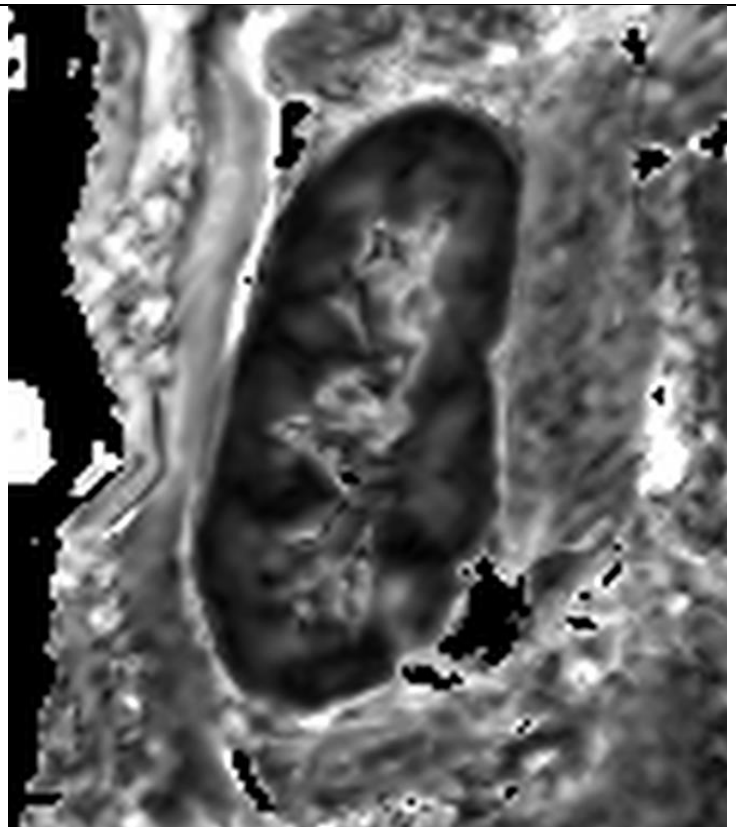
difference in magnetic resonance imaging-derived apparent diffusion coefficient for kidney fibrosis detection: A cross-sectional study. Nephrology Dialysis Transplantation *[Internet]* 2020; [cited 2021 Jun 21] 35: 937–945. Available from: https://academic.oup.com/ndt/article/35/6/937/5273480
52. Johansen KL, Chertow GM, Foley RN et al. US Renal Data System 2020 Annual Data Report: Epidemiology of Kidney Disease in the United States. American Journal of Kidney Diseases *[Internet]* 2021; [cited 2021 Jul 20] 77: A7–A8. Available from: http://www.ajkd.org/article/S027263862100024X/fulltext
53. SO S, J R, CH W et al. High-spatial-resolution MR angiography of renal arteries with integrated parallel acquisitions: comparison with digital subtraction angiography and US. Radiology *[Internet]* 2005; [cited 2021 Jul 19] 235: 687–698. Available from: https://pubmed.ncbi.nlm.nih.gov/15770035/
54. M S, J Z, L K, M L. Contrast-enhanced MR angiography utilizing parallel acquisition techniques in renal artery stenosis detection. European journal of radiology *[Internet]* 2010; [cited 2021 Jul 19] 75. Available from: https://pubmed.ncbi.nlm.nih.gov/19671492/
55. UI A, SP S, SO S et al. Comprehensive MR evaluation of renal disease: added clinical value of quantified renal perfusion values over single MR angiography. Journal of magnetic resonance imaging : JMRI *[Internet]* 2010; [cited 2021 Jul 19] 31: 125–133. Available from: https://pubmed.ncbi.nlm.nih.gov/20027580/
56. SW L, C C, DL B, PA K, SP S. Prediction and assessment of responses to renal artery revascularization with dynamic contrast-enhanced magnetic resonance imaging: a pilot study. American journal of physiology. Renal physiology *[Internet]* 2013; [cited 2021 Jul 19] 305. Available from: https://pubmed.ncbi.nlm.nih.gov/23804449/
57. Yu YM, Ni QQ, Wang ZJ, Chen ML, Zhang LJ. Multiparametric functional magnetic resonance imaging for evaluating renal allograft injury [Internet]. *Korean Journal of Radiology*2019; [cited 2021 Jun 8] 20: 894–908. Available from: /pmc/articles/PMC6536799/
58. Eikmans M, Gielis EM, Ledeganck KJ, Yang J, Abramowicz D, Claas FFJ. Non-invasive biomarkers of acute rejection in kidney transplantation: Novel targets and strategies [Internet]. *Frontiers in Medicine*2019; [cited 2021 Jun 8] 6: 358. Available from: www.frontiersin.org
59. JYC Y, RD S, TK S et al. A urine score for noninvasive accurate diagnosis and prediction of kidney transplant rejection. Science translational medicine *[Internet]* 2020; [cited 2021 Jul 8] 12. Available from: https://pubmed.ncbi.nlm.nih.gov/32188722/
60. Wang W, Yu Y, Wen J et al. Combination of functional magnetic resonance imaging and histopathologic analysis to evaluate interstitial fibrosis in kidney allografts. Clinical Journal of the American Society of Nephrology *[Internet]* 2019; [cited 2021 Jun 10] 14: 1372–1380. Available from: https://doi.org/10.2215/CJN.00020119
61. Kirpalani A, Hashim E, Leung G et al. Magnetic resonance elastography to assess fibrosis in kidney allografts. Clinical Journal of the American Society of Nephrology 2017; 12: 1671–1679.
62. Garcia SRM, Fischer T, Dürr M et al. Multifrequency magnetic resonance elastography for the assessment of renal allograft function. Investigative Radiology *[Internet]* 2016; [cited 2021 Jun 10] 51: 591–595. Available from: https://pubmed.ncbi.nlm.nih.gov/27504796/
63. Selby NM, Blankestijn PJ, Boor P et al. Magnetic resonance imaging biomarkers for chronic kidney disease: a position paper from the European Cooperation in Science and Technology Action PARENCHIMA. Nephrology Dialysis Transplantation 2018; 33: ii4–ii14.
64. Srivastava A, Palsson R, Kaze AD et al. The Prognostic Value of

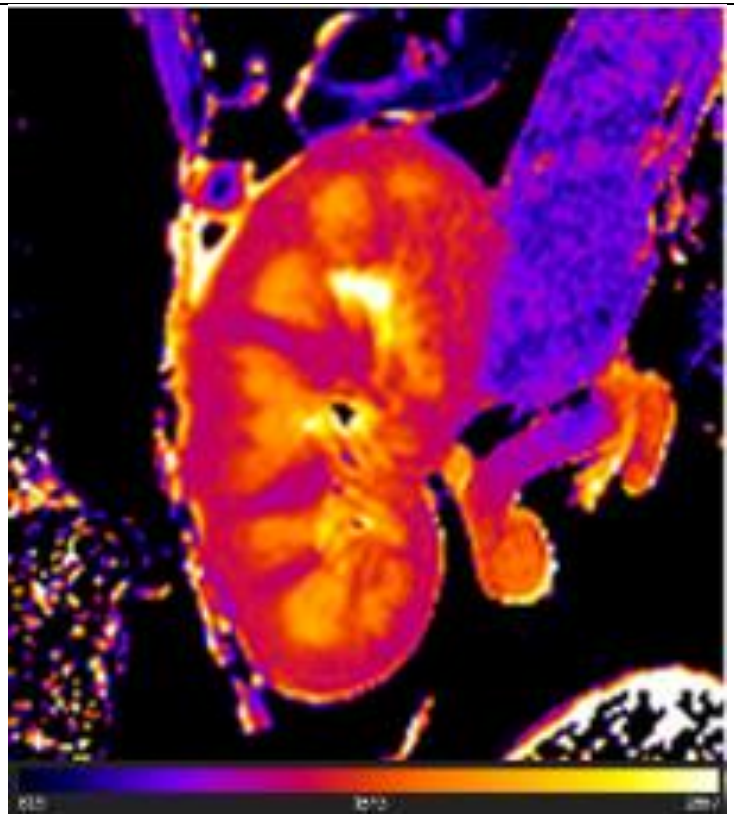
Histopathologic Lesions in Native Kidney Biopsy Specimens: Results from the Boston Kidney Biopsy Cohort Study. Journal of the American Society of Nephrology *[Internet]* 2018; : ASN.2017121260. Available from: http://www.jasn.org/lookup/doi/10.1681/ASN.2017121260

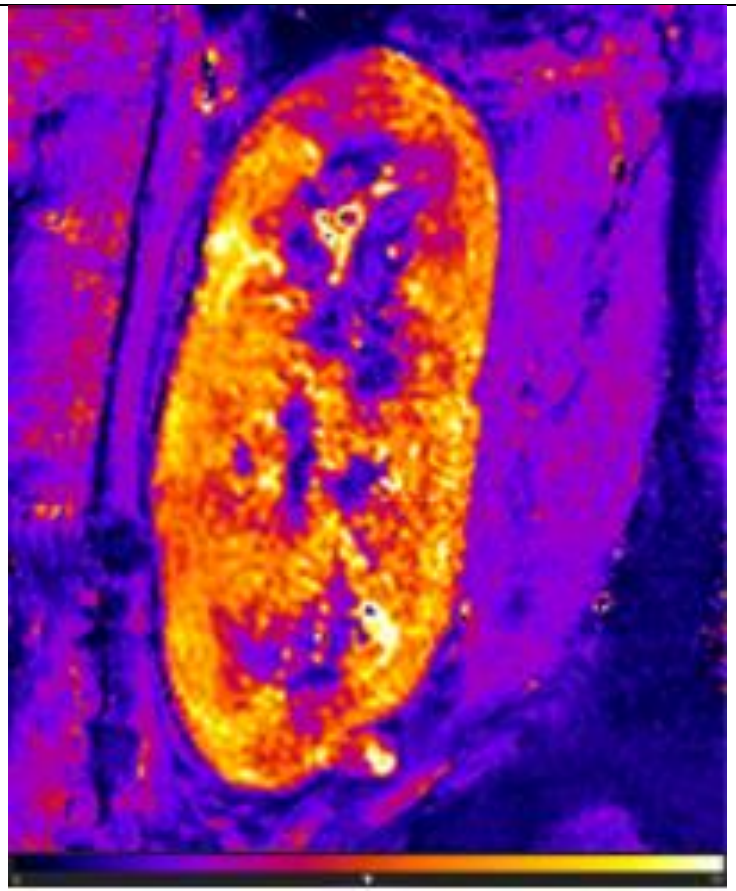
65. Dekkers IA, de Boer A, Sharma K et al. Consensus-based technical recommendations for clinical translation of renal T1 and T2 mapping MRI. Magnetic Resonance Materials in Physics, Biology and Medicine *[Internet]* 2020; [cited 2021 Jun 23] 33: 163–176. Available from: http://link.springer.com/10.1007/s10334-019-00797-5

Table 1: The main MRI sequences included in a multiparametric renal MRI protocol. Representative images acquired using 3T MRI.

MRI Parameter	**Example image**	**Explanation**
Anatomical images (e.g. Half-Fourier acquired single turbo spin-echo (HASTE))		Standard anatomical images. These are rapidly acquired in coronal, sagittal and transverse planes over a series of breath-holds. They allow standard clinical structural assessment (e.g. excluding hydronephrosis), measure renal volume (if sufficient slices are taken) and can be used to plan subsequent functional sequences.

Diffusion weighted imaging (DWI) (14,15)		ADC map. The diffusibility of water within an individual voxel is quantified by the apparent diffusion coefficient (ADC) (mm^2/s). This is therefore reduced by fibrosis and inflammation, as well as the presence of microstructures such as glomeruli and capillaries.

T1 mapping (16,17)		T1 map. T1 (ms) represents the time constant for the recovery of longitudinal re-magnetisation of protons following a pulsed MRI signal. T1 is longer for increased water content. T1 time increases in the presence of fibrosis, inflammation and oedema.

Blood oxygen level dependent imaging (BOLD) (18,19)		T2* map. T2* refers to the observed (rather than natural (T2)) transverse relaxation time constant on MRI (ms) which is affected by magnetic inhomogeneities in the tissue. Deoxyhaemoglobin shortens T2*, and so T2* (or R2*, which is 1/T2*) mapping produced by BOLD imaging reflects local tissue oxygen bioavailability.

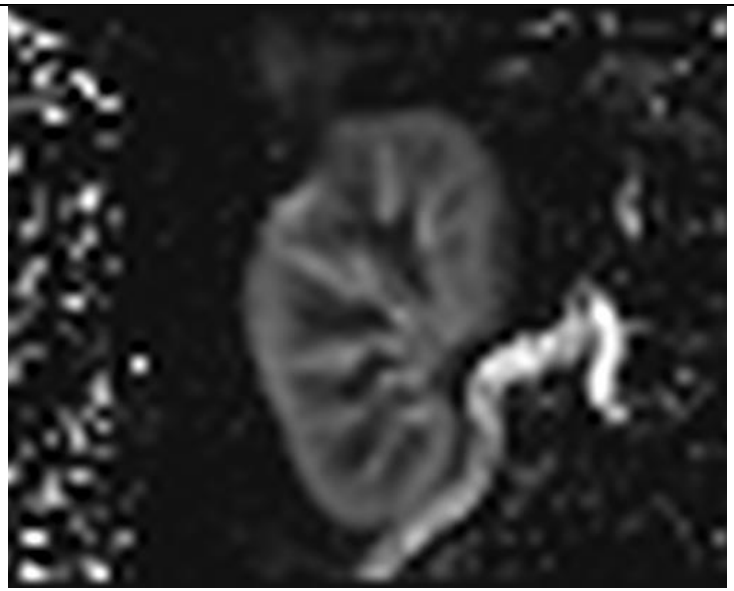
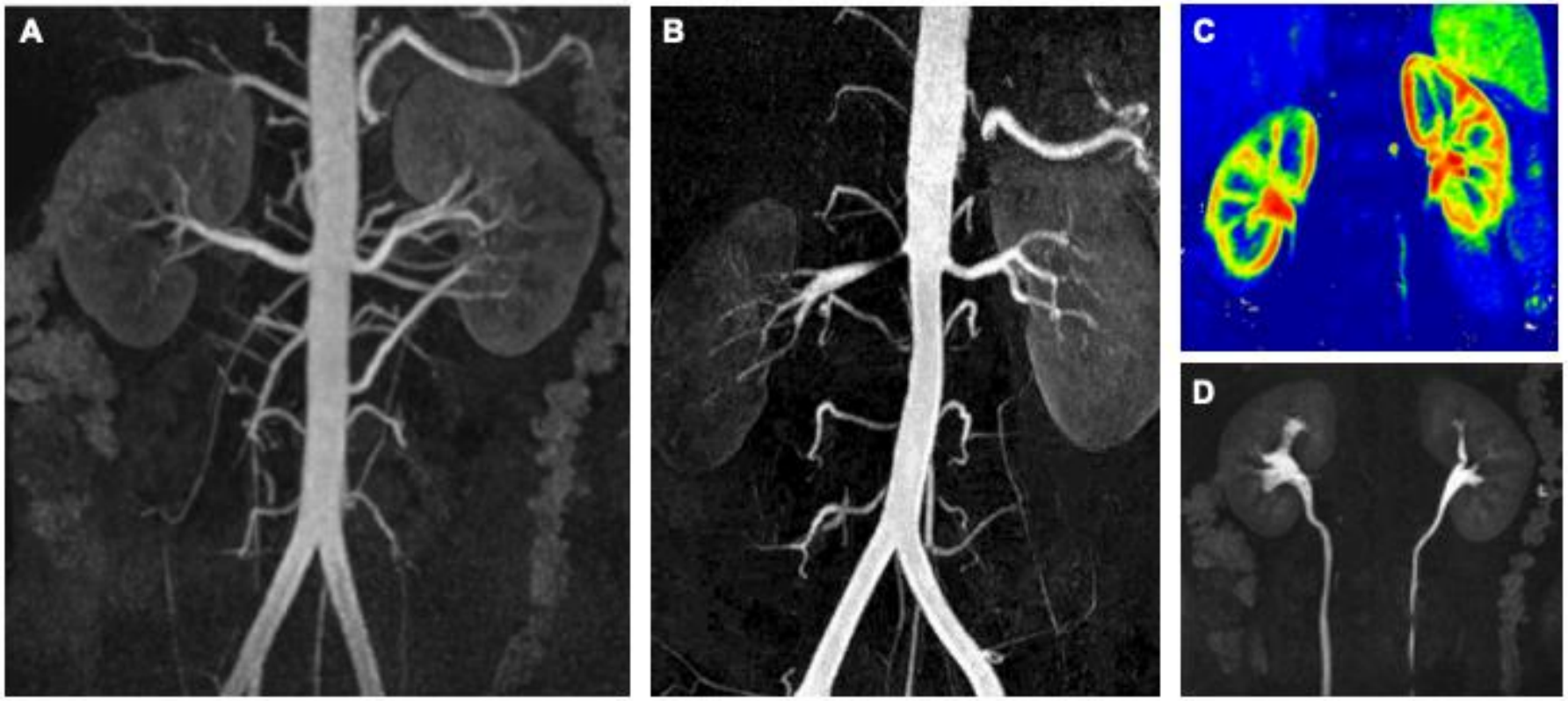
Arterial spin labelling (ASL) (20,21)		Measures renal perfusion (ml/100g/min) without exogenous tracer using magnetically labelled protons in blood.

Figure 1. Representative images of contrast-enhanced magnetic resonance angiography showing normal renal vasculature including accessory left renal artery (A) and an example right renal artery stenosis due to fibromuscular dysplasia - fibrointimal variant (B). With appropriate modification of the MRI protocol, it is also possible to evaluate regional renal perfusion using dynamic contrast enhanced (DCE) (C) and excretory phase urography (D).



Supplementary Material table S1. Non-exhaustive list of additional MRI sequences that are relevant to renal MRI