BOLD & Diffusion MRI for Evaluating Renal Oxygenation & Fibrosis in CKD

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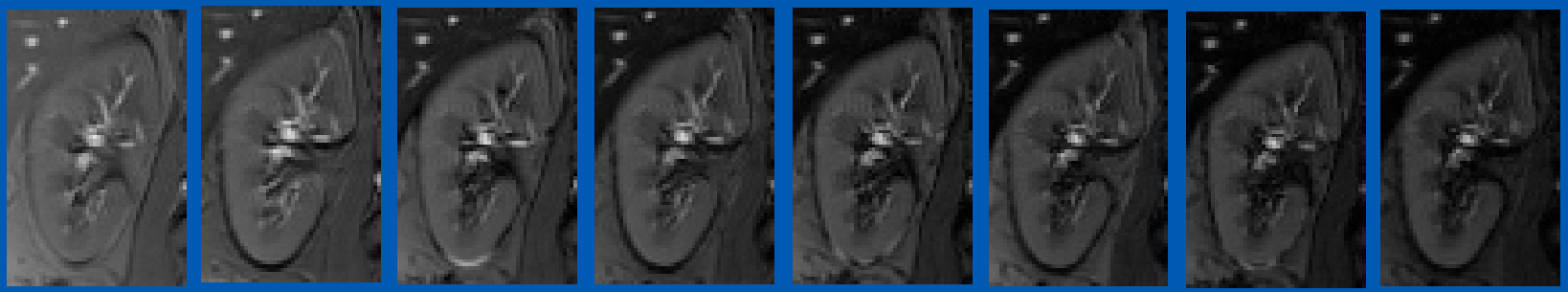
Motivation: Need for Novel Markers

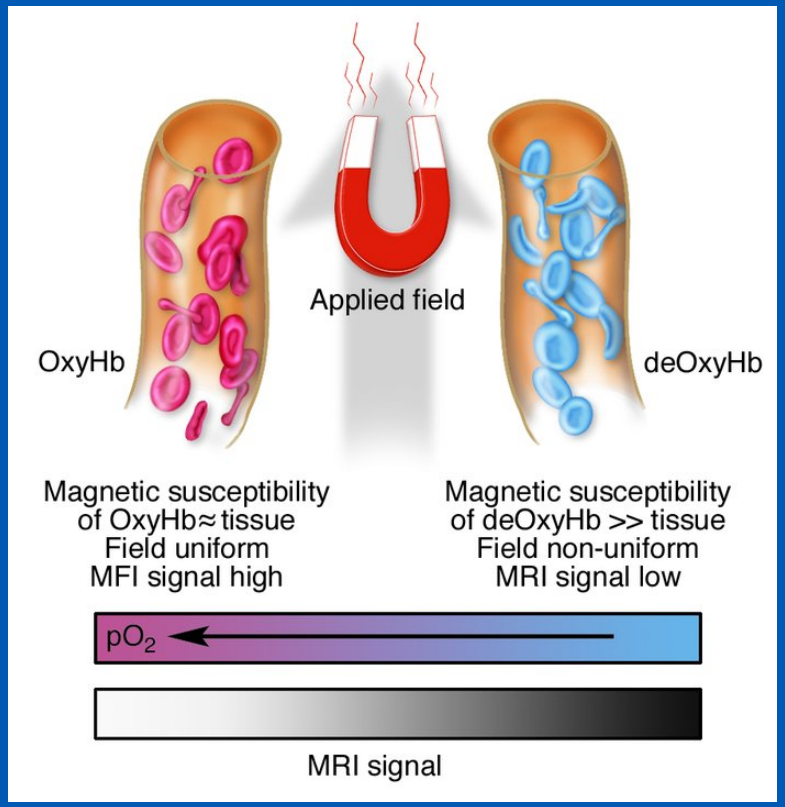
- Chronic Kidney Disease (CKD) is a slow and progressive loss of renal function
  - Based on current clinical marker (estimated GFR), 30 million people in US are classified to have CKD
  - About 120 K per year will progress to ESRD where the options will be limited to replacement
    - Need for markers for progressive CKD

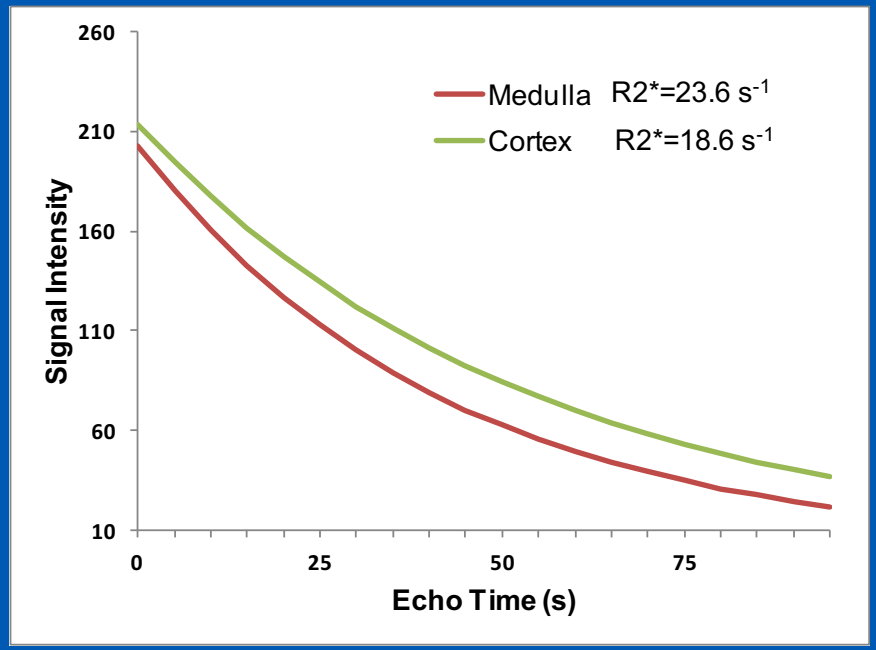
Motivation: Role for Oxygenation & Fibrosis in CKD

- Chronic Hypoxia Hypothesis
  - Fine LG et al., *Kidney Int Suppl* 1998; 65:S74-8
  - Initiating glomerular injury leads to loss of microvasculature, leading to development of hypoxia and fibrosis …
  - Translation to humans require non-invasive methods
    - » there are no non-invasive markers for renal oxygenation
    - » Histology remains the only accepted method to evaluate renal fibrosis

Blood Oxygenation Level Dependent (BOLD) MRI

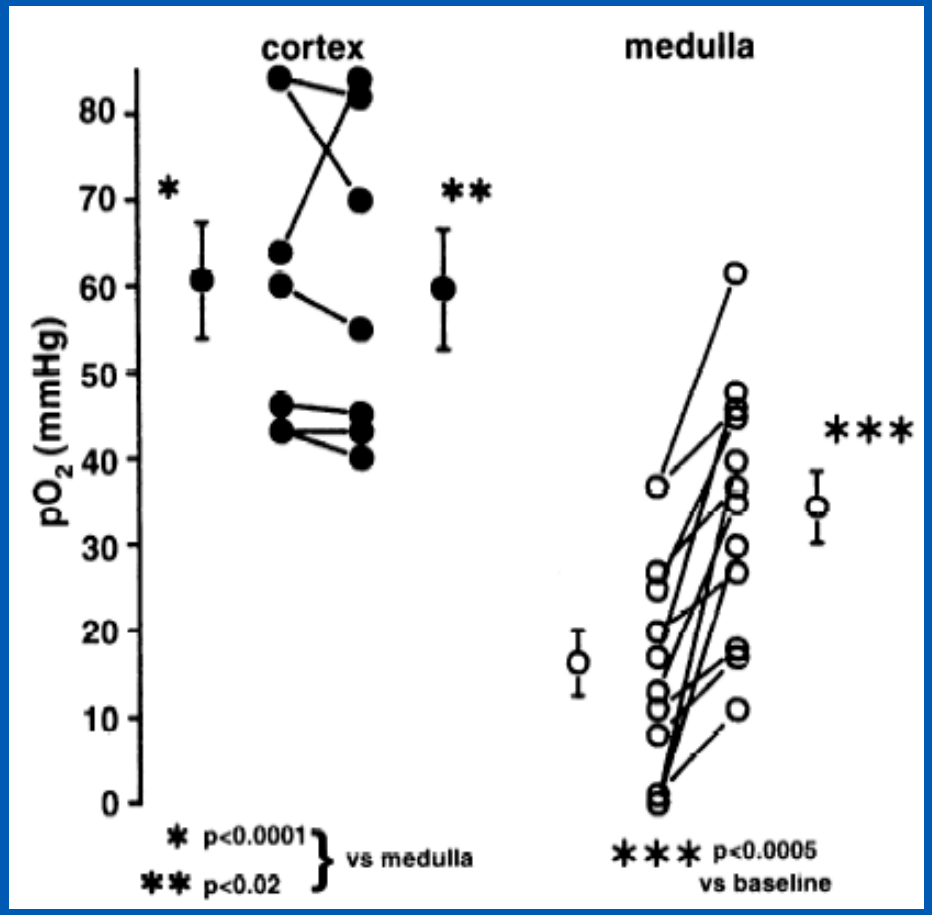






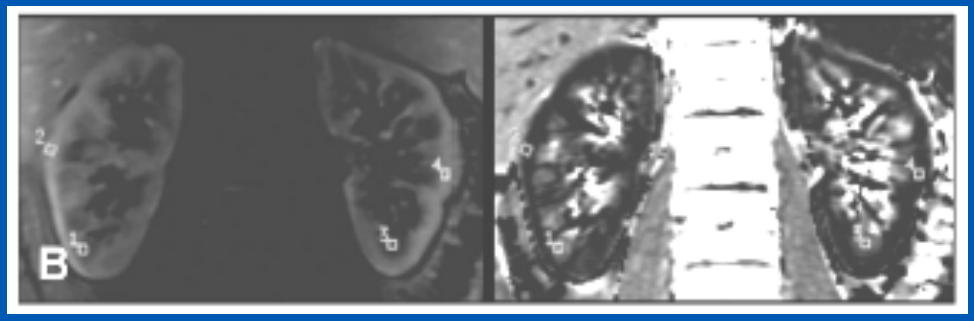
BOLD MRI: Replicates Invasive Measurements

Micro-electrodes

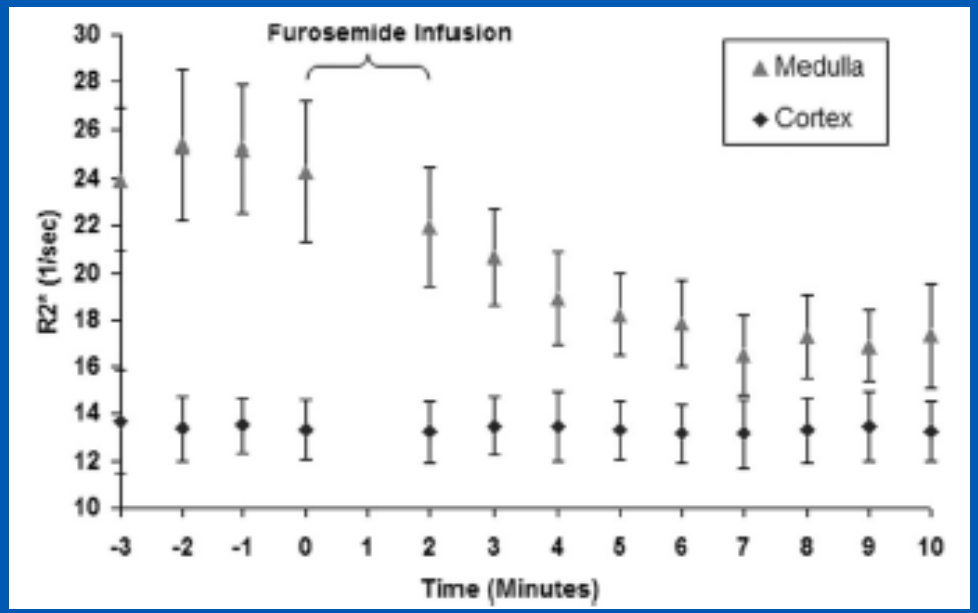


Effect of furosemide

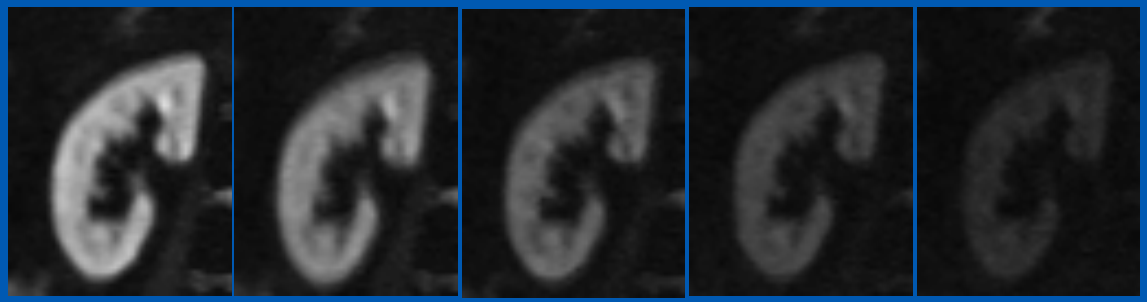
Am J Physiol. 1994;267:F1059



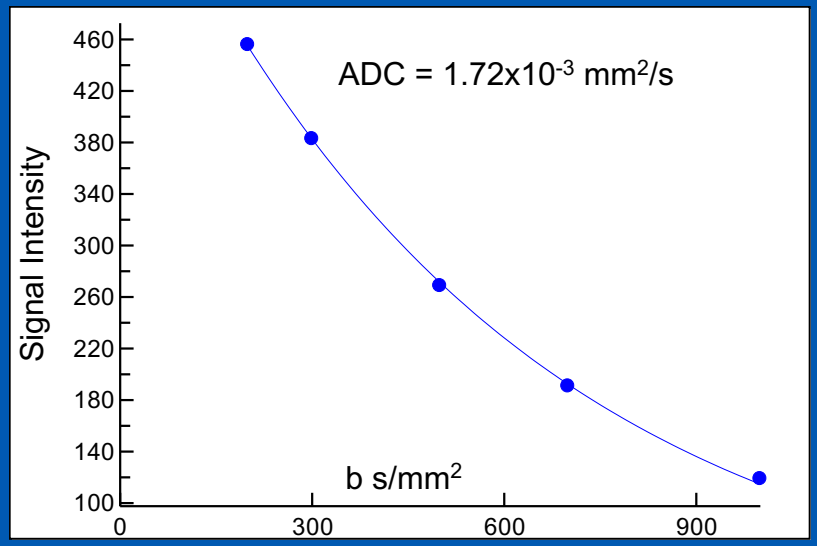
Invest Radiol. 2006 Feb;41(2):181



Diffusion MRI

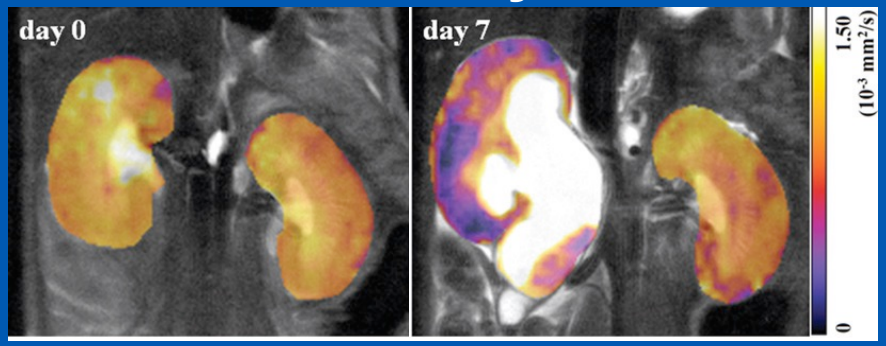


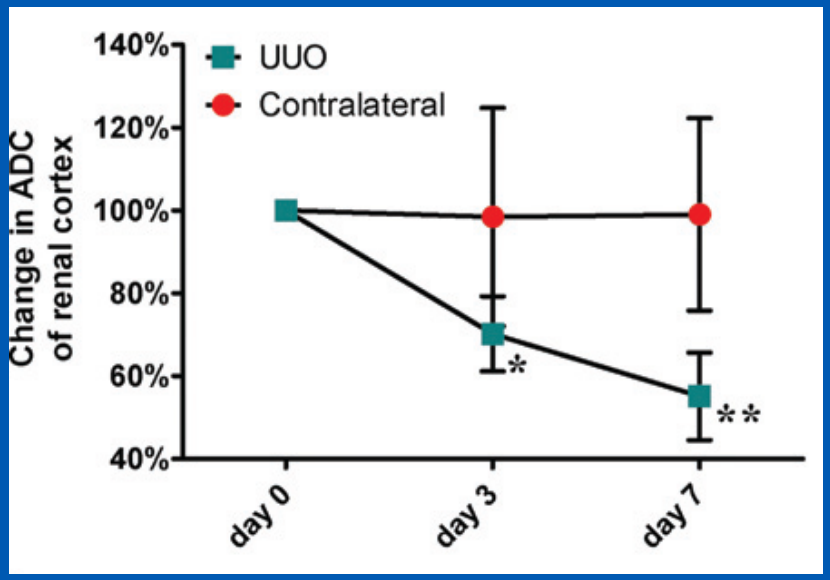
b s/mm^2 = 200 300 500 700 1000



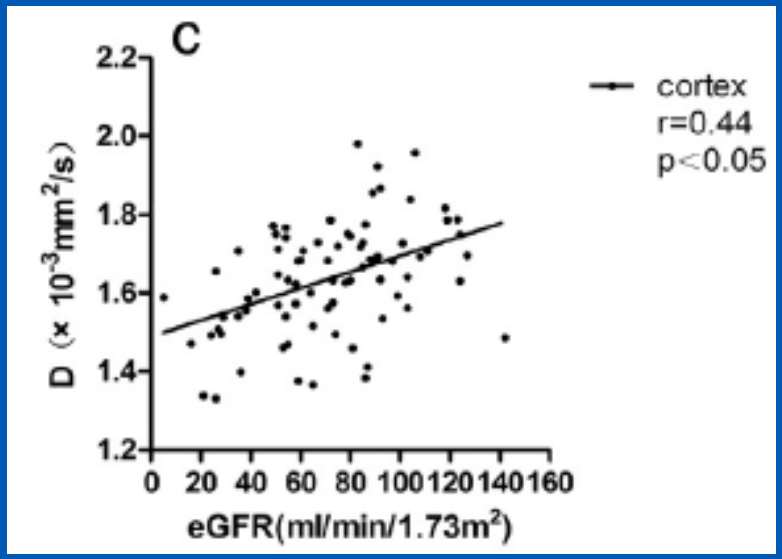
Diffusion: Dependence of fibrosis

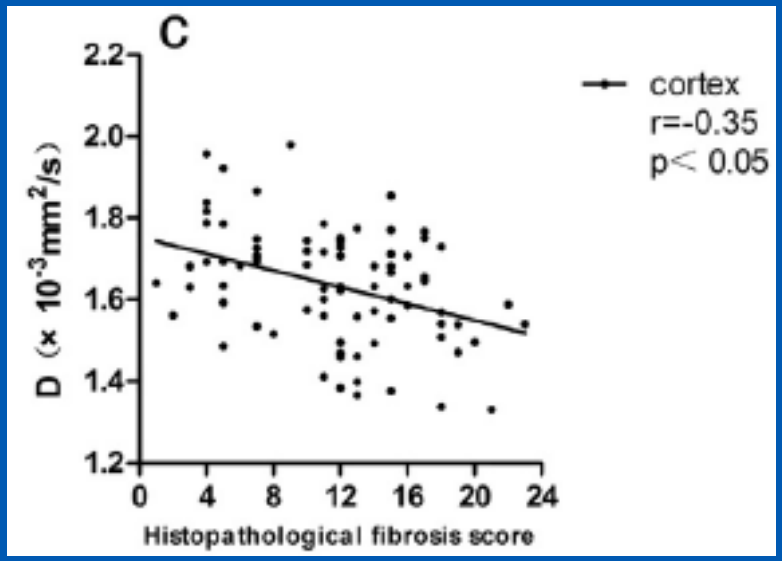
Kidney





Radiology (2010) 55: 3: 772-80



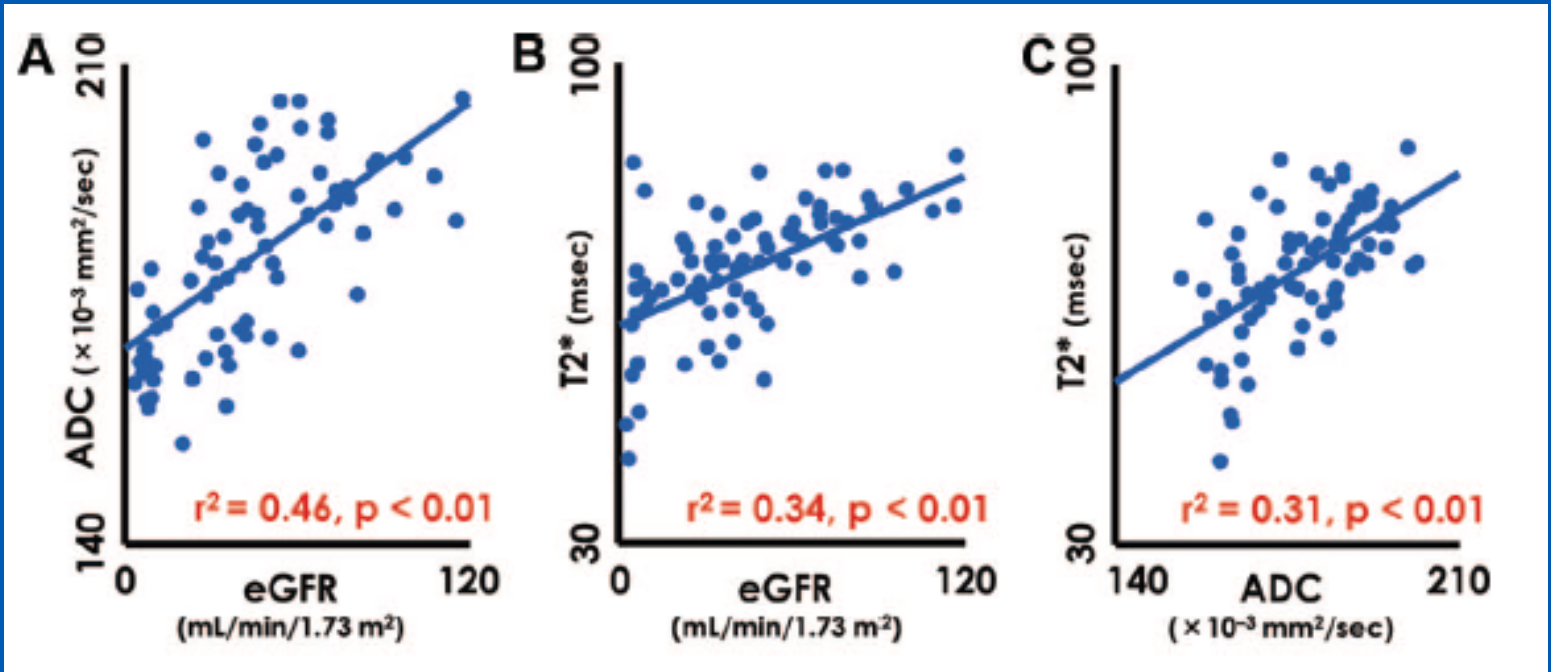


Magnetic Resonance Imaging 47 (2018) 118–124

Renal BOLD & Diffusion MRI: Current Status

- Both sequences readily available on major vendor platforms
  - Independent verification by investigators world-wide
- Both applied together in the context of CKD
  - Inoue T et al., *JASN*. 2011;**22**(8):1429-34
  - Prasad P et al., *PloS one*. 2015;**10**(10):e0139661

BOLD & Diffusion MRI in CKD



JASN. 2011;22(8):1429-34

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- Highly reproducible – comparable when repeated on the same day or up to 18 months apart
  - Li L et al., *JMRI* 2018 [in press]
- Preliminary data supporting use in multicenter trials
  - Prasad P et al., *Kidney Int. Reports* 2018 [in press]

Data from Multiple Sites in Advanced CKD

	Control/CKD	n	Mean±sd	*p*
Cortex R2* (s^{-1})	Control	13	18.8±2.4	**0.022**
	CKD	123	20.6±3.1	
Medulla R2* (s^{-1})	Control	13	29.0±3.9	**< 0.01**
	CKD	123	23.8±3.2	
Medulla ΔR2* (s^{-1})	Control	13	6.3±3.5	**0.002**
	CKD	54	2.5±2.5	
ADC $x10^{-3}$ mm^2/s	Control	13	1.67±0.08	**< 0.01**
	CKD	126	1.45±0.17	

***Kidney Int Rep.* 2018 (in press)**

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- Preliminary data supporting use in multicenter trials
  - Prasad P et al., *Kidney Int. Reports* 2018 [in press]
- Data supporting sensitivity to disease progression
  - Pruijm M et al., *Kidney Int*. 2018; 93(4):932-940
  - Li L et al., Poster #9
  - Srivastava et al., Poster #17

Progression in CKD: Cortical R2*, Δ(Med-Cor) R2*

Associations with yearly change in eGFR

	Fully adjusted* β	*p*
Cortex R2* (s^{-1})	-0.44(-0.76 to -0.11)	**0.009**
Δ(Med-Cor) R2*	0.45 (0.11 to 0.80)	**0.01**
Proteinuria (g/24 hr)	-1.49 (-2.65 to -0.33)	**0.012**

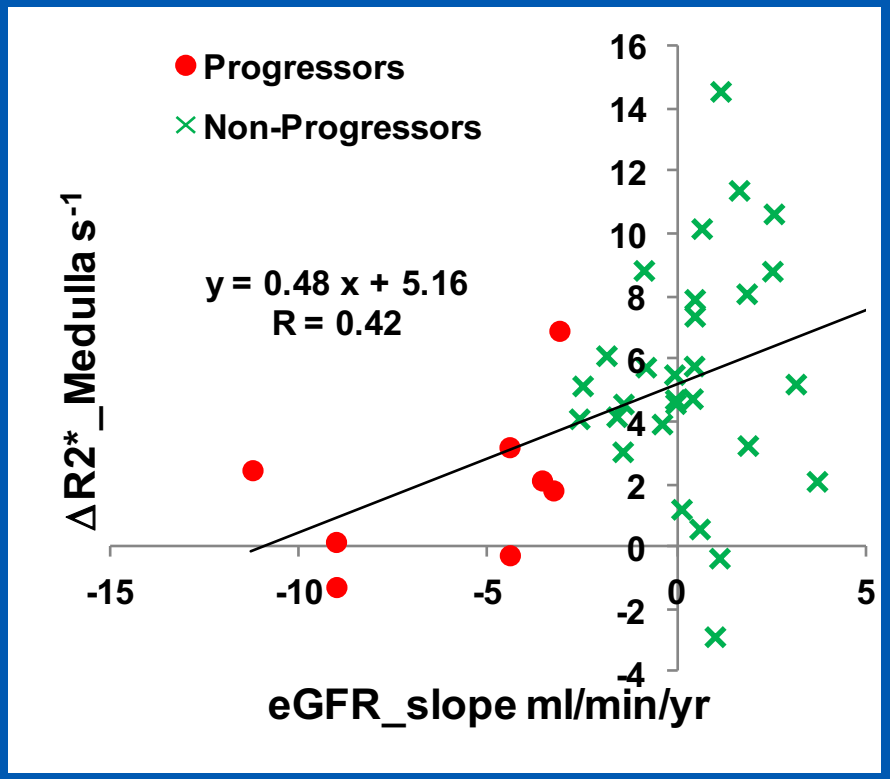
*Adjusted for age, sex, diabetes, eGFR, proteinuria, and use of RAS blockers

	Progressors	Non-progressors	*p*
Cortex R2*	21.3±2.6	20.2±1.9	**0.033**
Δ(Med-Cor) R2*	7.3±2.8	8.2±2.9	**0.038**

*Progressors: eGFR decline > 3 ml/min/yr

Kidney Int. 2018 Apr;93(4):932-940

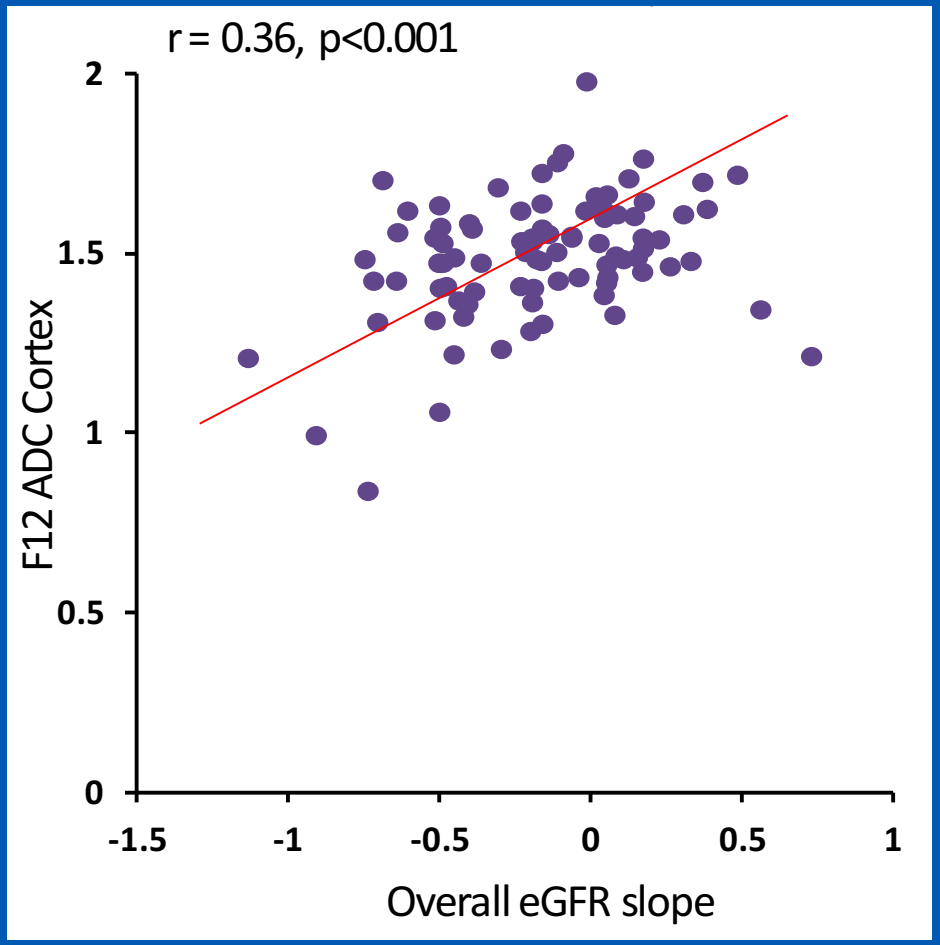
Progression in CKD: Medulla ΔR2*



	Progressors	Non-progressors	*p*
Medulla ΔR2* (s^{-1})	1.90±2.53	5.39±3.65	**0.007**

Li *et al*, Poster # 9

Progression in CKD: ADC



Srivastava *et al*, Poster # 17

What else do we need?

- Even though proof-of-concept evidence is available, further investigations necessary to
  - improve sensitivity and/or specificity
    - Important to translate to clinic where decisions need to be made on an individual basis
    - Reason to look at contrast agents for fibrosis
  - Demonstrate whether these markers can be used to monitor interventions
  - Include more non-invasive measures
    - PARENCHIMA includes ASL, T1, PC-BF
  - Develop objective analytical tools