Introduction

* 1. ADNI purpose and motivation (lighter version of companion paper)
		1. Natural history study of AD
		2. Development test bed for clinical trials
			1. Site selection is driven by clinical recruitment not imaging acumen
			2. FDA cleared sequences only
			3. (minor mention) MR as partner for PET
	2. How are dx categories spread across scanners?
		1. By ADNI phase – ADNI-1 this was believed to a problem – early sites got the controls and recruitment wasn’t uniform.
	3. Neuro MR analysis changes 2004-present brief overview -- scanners change, scanner software and recon changes, many analysis methods have changed – some to improve outcome measures and others to maintain consistent output in the face of underlying changes (that may lead to impoved outcome measures as well. – might use Fox et al BSI evolution as a poster child for that. )

* 1. Importance of stable measures
		1. Cross sectional – combine across vendors/models
		2. Cross sectional – combine across major study revisions
		3. Cross sectional -- combine across studies
		4. Longitudinal – across vendor/model/software (MR doesn’t drive site selection)
		5. Longitudinal – across protocol changes
1. Materials and Methods
	1. Review of processing streams
		1. Volumetric/thickness Neuro anatomy is largely stable (structure still measuring focal, regional, global volume change). Choices about when to upgrade software may be harder than hardware and protocol – rework to back fill or not?
			1. Some methods have had minor upgrades (e.g. BSI -> Freeborough and Fox version up to current version)
			2. FreeSurfer has had updates to template etc from 4.x to 6.x. ADNI-2 for example does not have a FS 6 backfill.
			3. WMH (massive disconnect ADNI-1 to 2, empirically ADNI-2 to 3, but is that bridgeable?)
			4. HR Hippocampus (will lean on Sandy for help there)
		2. Diffusion
			1. Evolution in modelling, distortion correction
			2. Not a solved problem
		3. fMRI
			1. Methods have evolved – handling nuisance covariates is still an open problem – still impractical to get good physio measurements (belt, pleth)
			2. Graph metric analysis have come to light but generally fail to reach single subject significance
		4. ASL
			1. ASL is a messy sequence which may limit the evolution of analysis software
		5. T2\* weighted (single or multi-echo+SWI+QSM)
			1. Phase is almost always hard and highly vendor dependent. Makes crossover software difficult. Some scanners make it hard to save phase.
			2. Can’t compare ADNI-2 to ADNI-3 other than in T2\*-weighted magnitude images.
	2. Visual and Numeric QC
		1. This mirrors each of the sections under 2c
	3. Visual Grading
		1. CMBs
		2. Infarcts (UCD is doing that?)
			1. Phase is almost always hard and highly vendor dependent. Makes crossover software difficult. Some scanners make it hard to save phase.
			2. Can’t compare ADNI-2 to ADNI-3 other than in T2\*-weighted magnitude images.

* 1. Approaches to do quant comparisons
	2. Approaches for homogenization across changes
		1. Image level
		2. Summary stat / model level
1. Results
	1. Overall numbers of enrollees and scans by site (ADNI-1 had site bias with early approval sites getting relatively more controls – that can make your scanner mix correlate with dx)
	2. QC break down
	3. Visual Grading results
	4. Quant comparisons /homogenization
2. Discussion
	1. Change is inevitable (tending toward improvements)
	2. Figure(s) of merit for reproducibility
	3. Cross-over in longitudinal studies w/o direct overlaps limits what you can measure
	4. TBD depending on results