

Towards the evaluation of 3D Tumour Volume for use in response assessment

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Marietta Scott

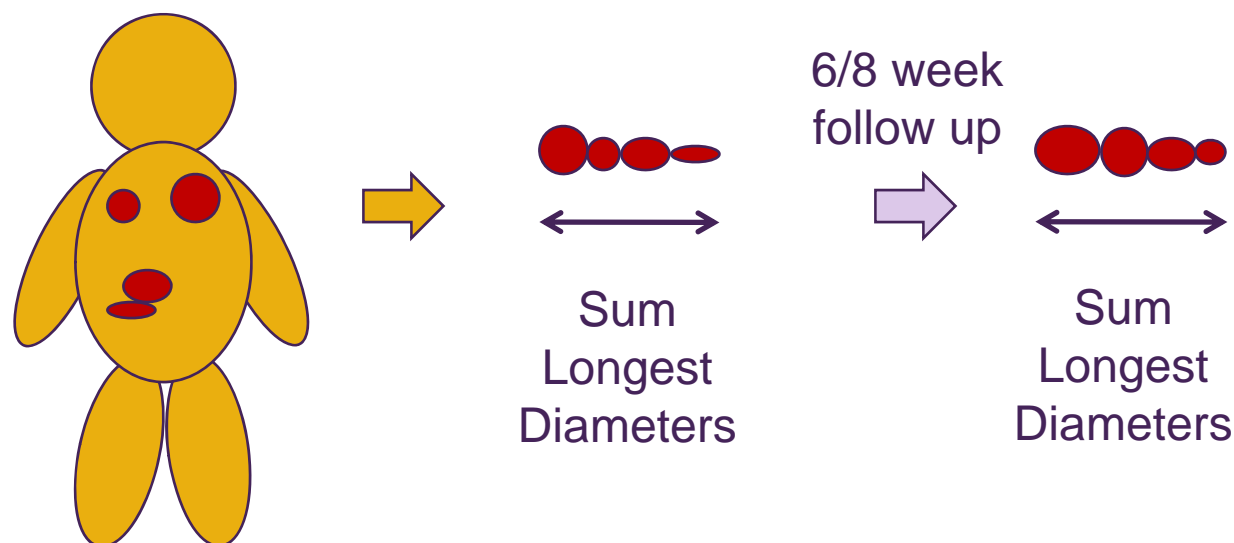


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Background - RECIST



Evaluation of target lesions:

- **Complete Response (CR):** Disappearance of all target lesions
- **Partial Response (PR):** At least 30% decrease in LD sum from baseline
- **Stable Disease (SD):** Neither PR nor PD
- **Progressive Disease (PD):** At least a 20% increase in LD sum from the smallest sum on study + min increase of 5mm.

Introduction

- RECIST provides a robust method for assessing tumour burden change, so...
- Why consider using Volume instead?
 - Potentially increased sensitivity to change over RECIST:
 - Whole tumour assessment (change may not be in-plane)
 - Increased dynamic range in volume data



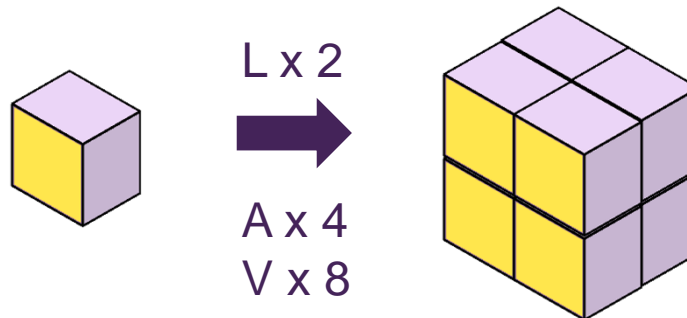
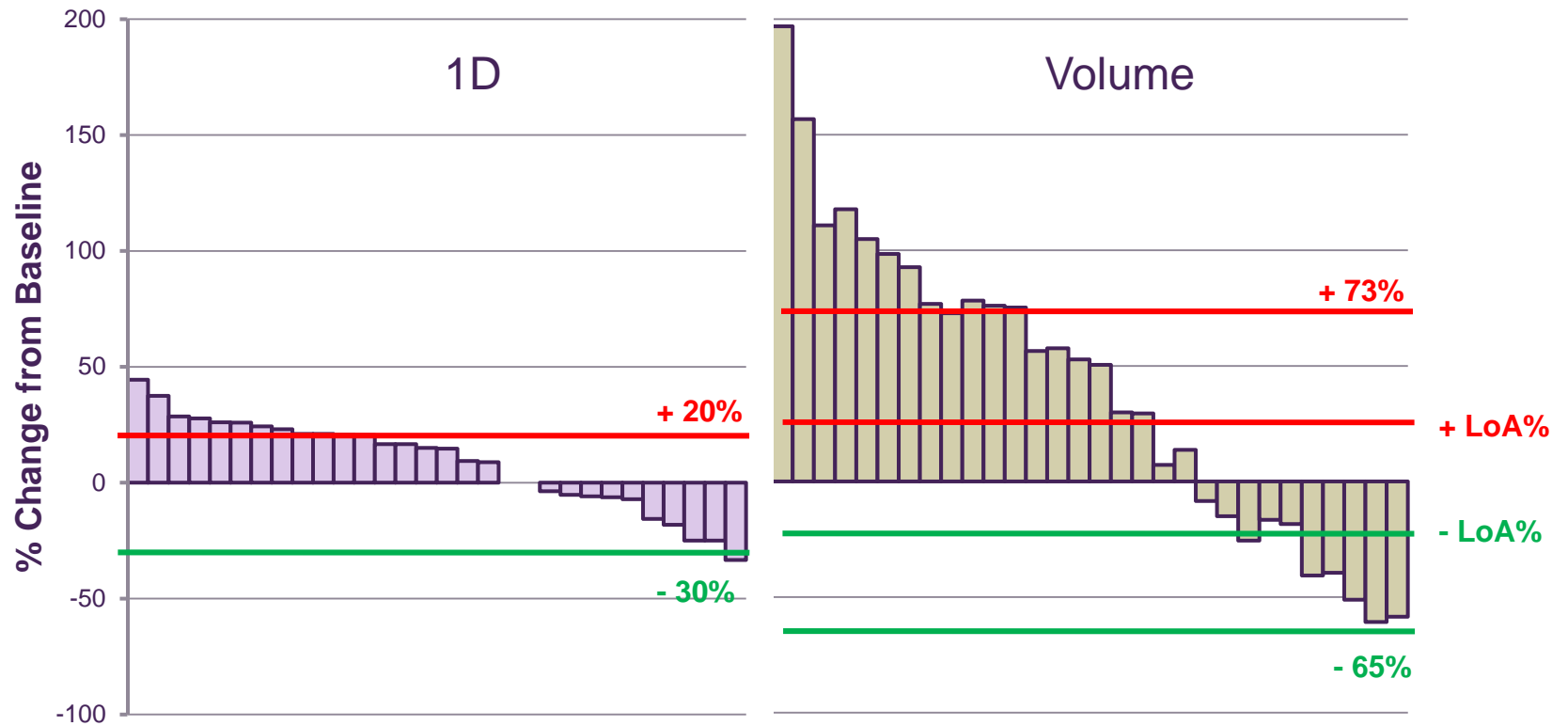
- Allow earlier detection of change
- Tease out slower responders/progressors in a Ph I trial
- Potential for use in patient segmentation strategies



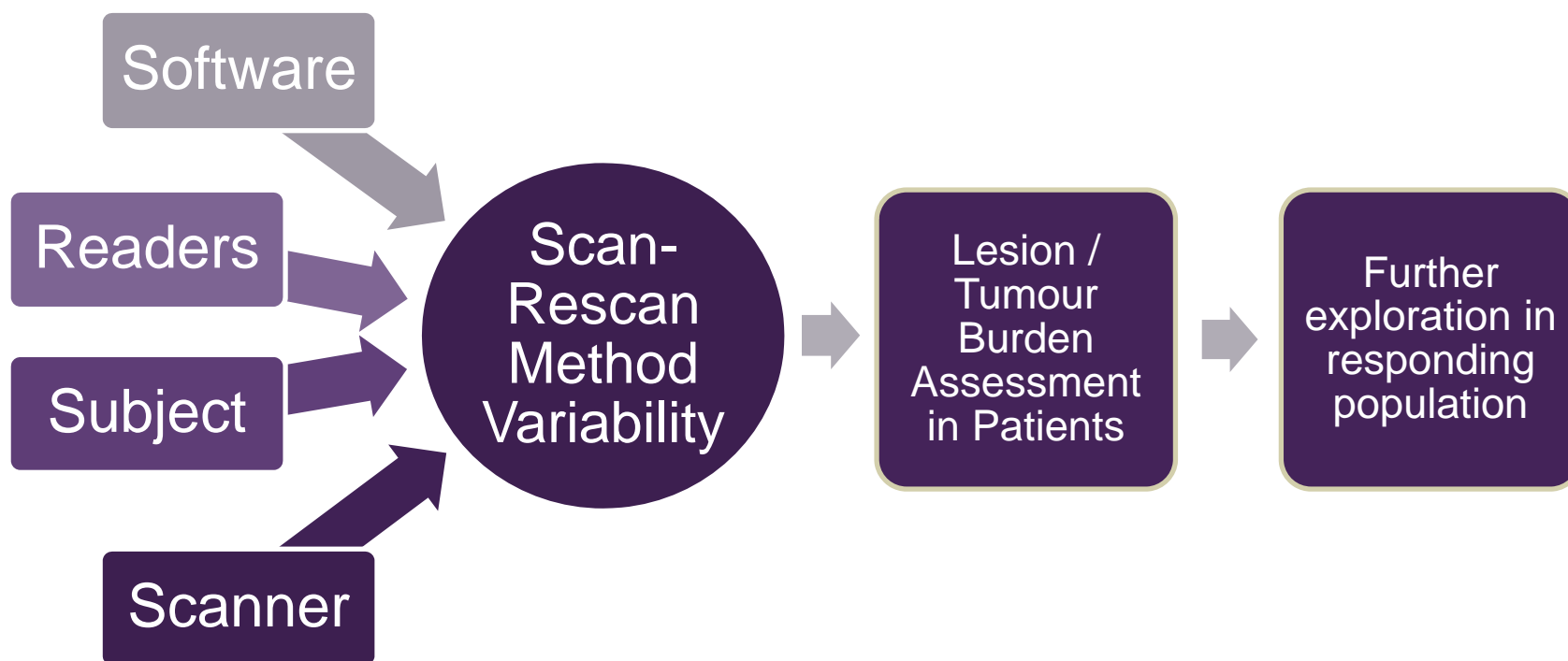
- Reduce cost, size and length of clinical trials



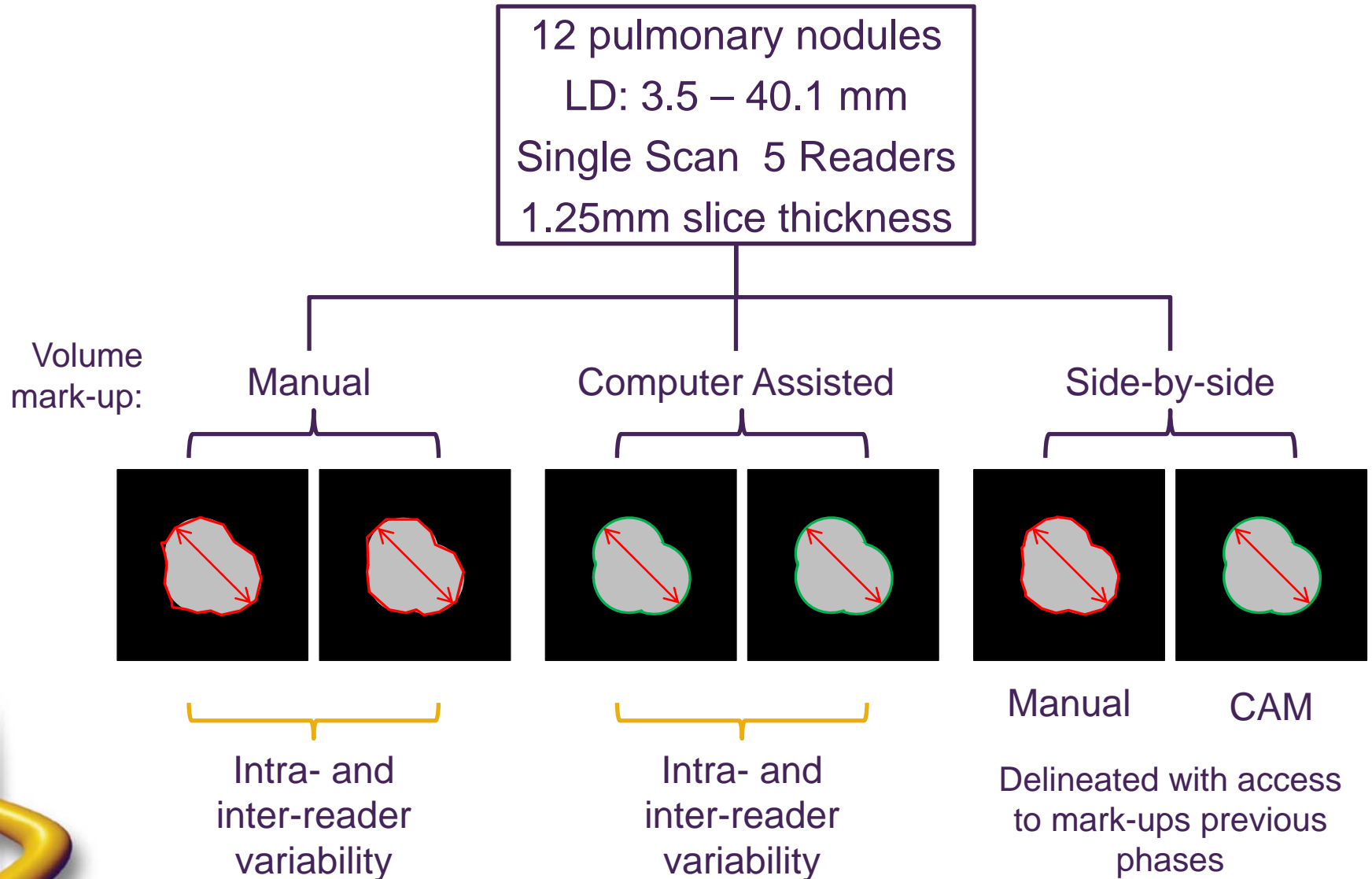
Increased sensitivity in assessment of tumour burden change



Programme of Work



Reader Variability: Cornell



Slice Thickness: MSKCC

30 patients
118 lesions
Lung:Liver:Lymph
39:39:40
LD: 6.1 – 80.1mm



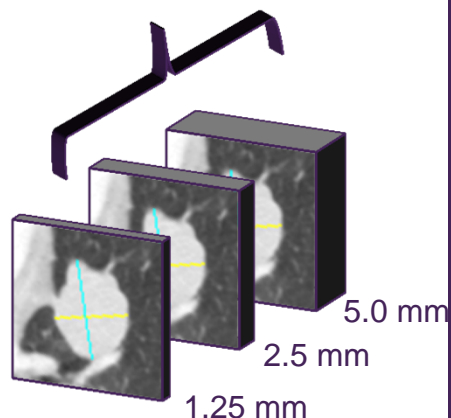
Reader 2

1st mark-up

Manual
Mark-up

1D

2D

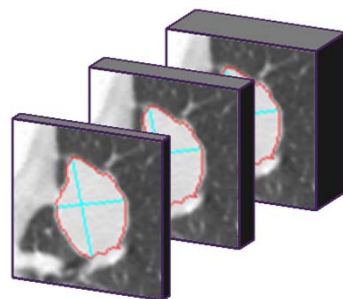


Computer
Assisted
Mark-up

1D

2D

Volume



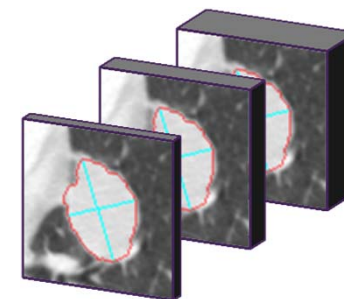
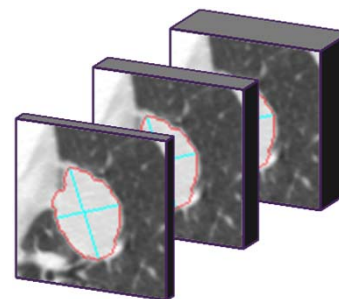
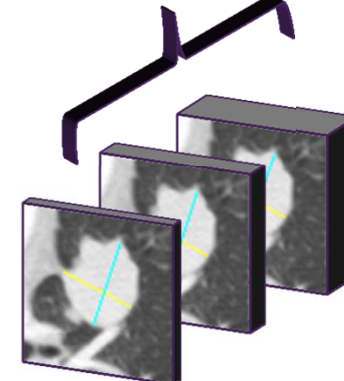
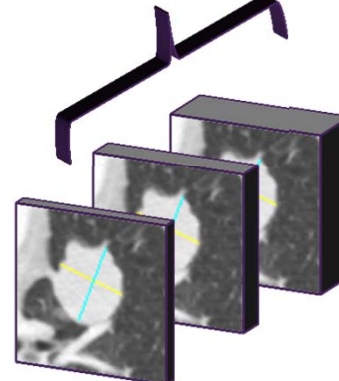
Inter-reader variability



Reader 1

1st mark-up

2nd mark-up

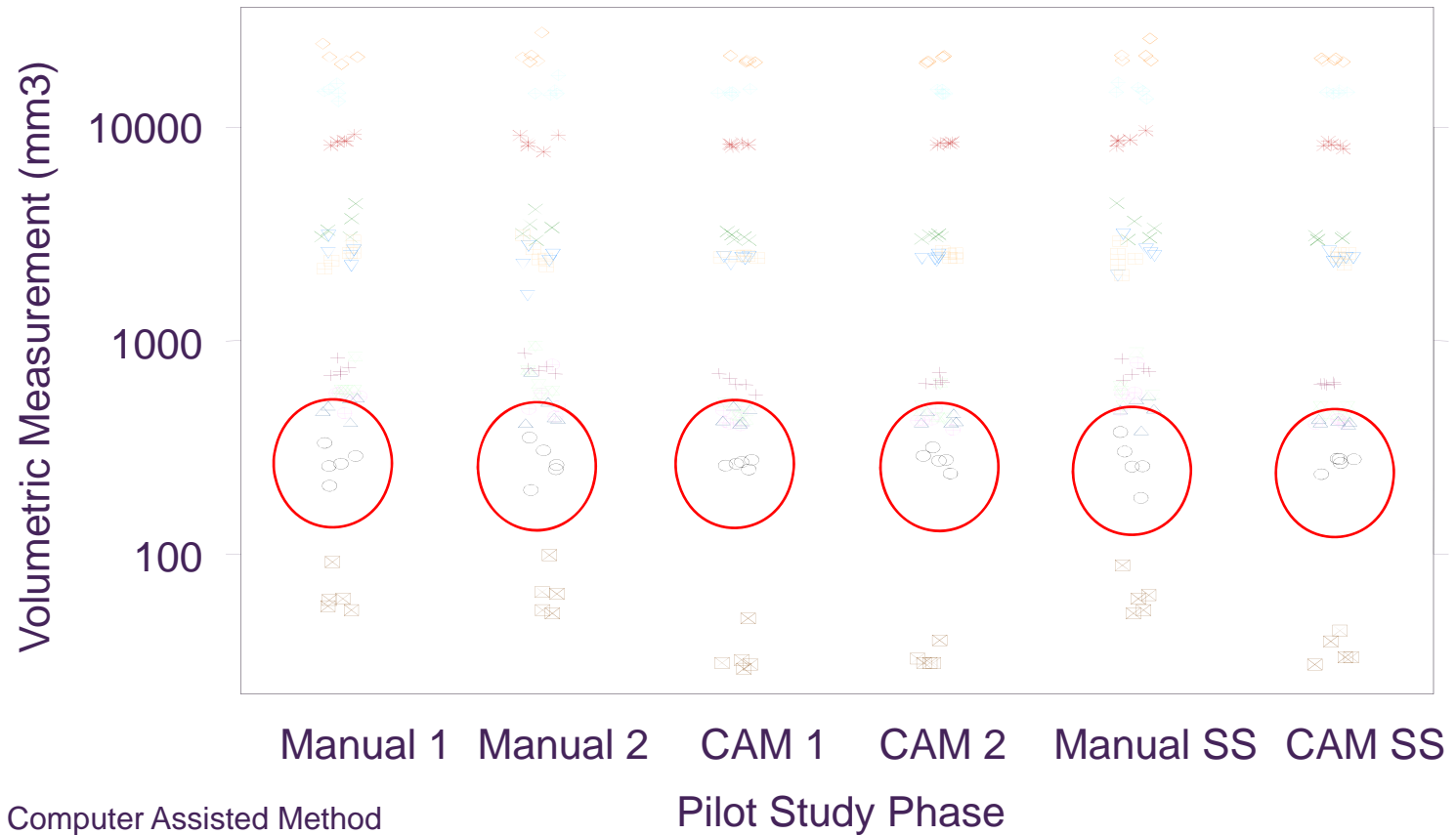


Intra-reader variability

AstraZeneca



Reader Variability: Volume by Phase



Reader Variability: Intra-Reader

- What is within-reader repeatability on same-scan mark-ups?
- What effect does 1D/volume or Manual/CAM have?

Measurement (Cornell)		Intra-reader (+ residual) Coefficient of Variability at 1.25mm	
1D	Manual		7.1%
Volume	Manual		10.1%
	CAM		6.7%
Volume-derived 1D	Manual		3.4%
	CAM		2.2%

- Intra-reader reproducibility is good
- CAM improves CoV compared to Manual
- Volume improves CoV compared to 1D

Reader Variability: Inter-Reader

- What is the between-reader reproducibility on a given lesion?
- What effect does 1D/volume or Manual/CAM have?

Measurement (Cornell)		Inter-reader Coefficient of Variability at 1.25mm	
1D	Manual		2.7%
Volume	Manual		11.2%
	CAM		3.5%
Volume-derived 1D	Manual		3.7%
	CAM		1.2%

- Inter-reader reproducibility is good
- CAM improves between-reader CoV compared to Manual
- Between-reader CoV for Volume is comparable to 1D

Reader Variability: Limits of Agreement

- Is there any evidence of bias between the repeat mark-ups?

Measurement (Cornell)		Mean % Diff	95% Limits
1D	Manual	1.2%	-16.9 to 23.4%
Volume	Manual	0.5%	-23.9 to 32.8%
	CAM	1.0%	-16.0 to 21.6%
Volume-derived 1D	Manual	0.2%	-8.7 to 9.9%
	CAM	0.3%	-5.6% to 6.7%

- No evidence of bias between repeat mark-ups
- Suggests a change in measured volume by more than ~33% for an **individual nodule** has a 95% likelihood of being real change or change due to different scans rather than measurement error
- For 1D, change ~25%

CT Slice Thickness

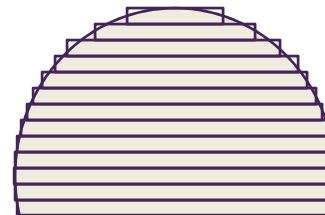
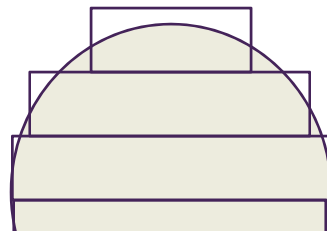
- What effect does CT slice thickness have on bias and reproducibility of mark-up methods?

Measurement (MSKCC)		Section Thickness (mm)		Mean % Diff	95% Limits
1D	CAM	1.25	5.0	7.6%	-6.7 to 24.1%
		2.5	5.0	5.4%	-7.7 to 20.2%
		1.25	2.5	2.2%	-10.3 to 16.3%
Volume	CAM	1.25	5.0	-5.7%	-35.5 to 37.9%
		2.5	5.0	-2.5%	-27.1 to 30.5%
		1.25	2.5	-3.3%	-26.3 to 26.8%
Volume-derived 1D	CAM	1.25	5.0	-1.9%	-13.6 to 11.3%
		2.5	5.0	-0.8%	-10.0 to 9.3%
		1.25	2.5	-1.1%	-9.7 to 8.2%

Agreement best between 1.25 and 2.5 mm, then 2.5 and 5.0mm, then 1.25 and 5.0mm

CT Slice Thickness

- What effect does CT slice thickness have on bias and reproducibility of mark-up methods?
- 1D:
 - Bias towards larger measurements with thinner slices
 - Thinner slices = more slices for mark-up, better defined edges
- Volumetric:
 - Bias towards smaller measurements with thinner slices
 - As $\text{Volume} = \text{Surface Area} \times \text{Slice thickness}$
 - Larger average difference in measures between different slice thicknesses for smaller nodules, due to slice availability



Summary

- Volumetric measures reduce within-reader CoV when compared like-for-like with 1D measures
- CAM reduces both within- and between-reader CoV of Volumetric measures
- No evidence of bias in repeated mark-ups
- CT slice thickness does introduce bias, direction dependent on measurement method

