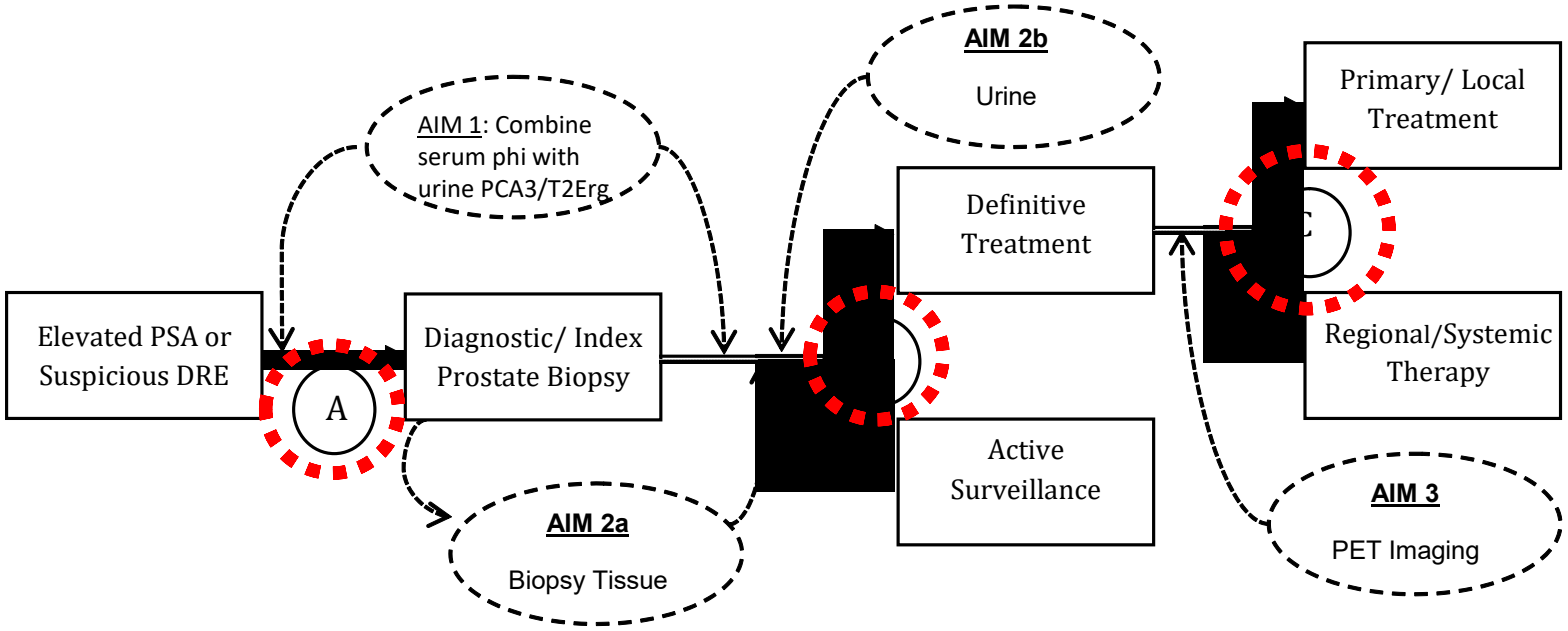
Clinical Decision Targets for Biomarkers in Prostate Cancer Early Detection



A) Who should undergo prostate biopsy?

B) Who should undergo treatment versus surveillance?

C) How extensive is the cancer (metastases) & impact on treatment extent?

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- Current state / clinical need
  - Existing biomarker (CT/bone scan): poor sensitivity, poor specificity
  - More accurate staging (appropriate treatment)
- Risk/benefit
  - False positive biomarker: unnecessary treatment (morbid)
  - False negative biomarker: status quo
- Analytic Translation
  - Reduce false negatives: Improve sensitivity *at high specificity*

EMORY

B) Who should undergo treatment versus surveillance?

- Current state / clinical need
  - Existing biomarker (PSA): poor sensitivity, ~specificity
  - Less invavise monitoring (avoid unnecessary re-biopsy)
- Risk/benefit
  - False positive biomarker: unnecessary treatment (morbid)
  - False negative biomarker: miss window for cure
- Analytic Translation
  - Improve specificity *OR* sensitivity (improve AUC of ROC)

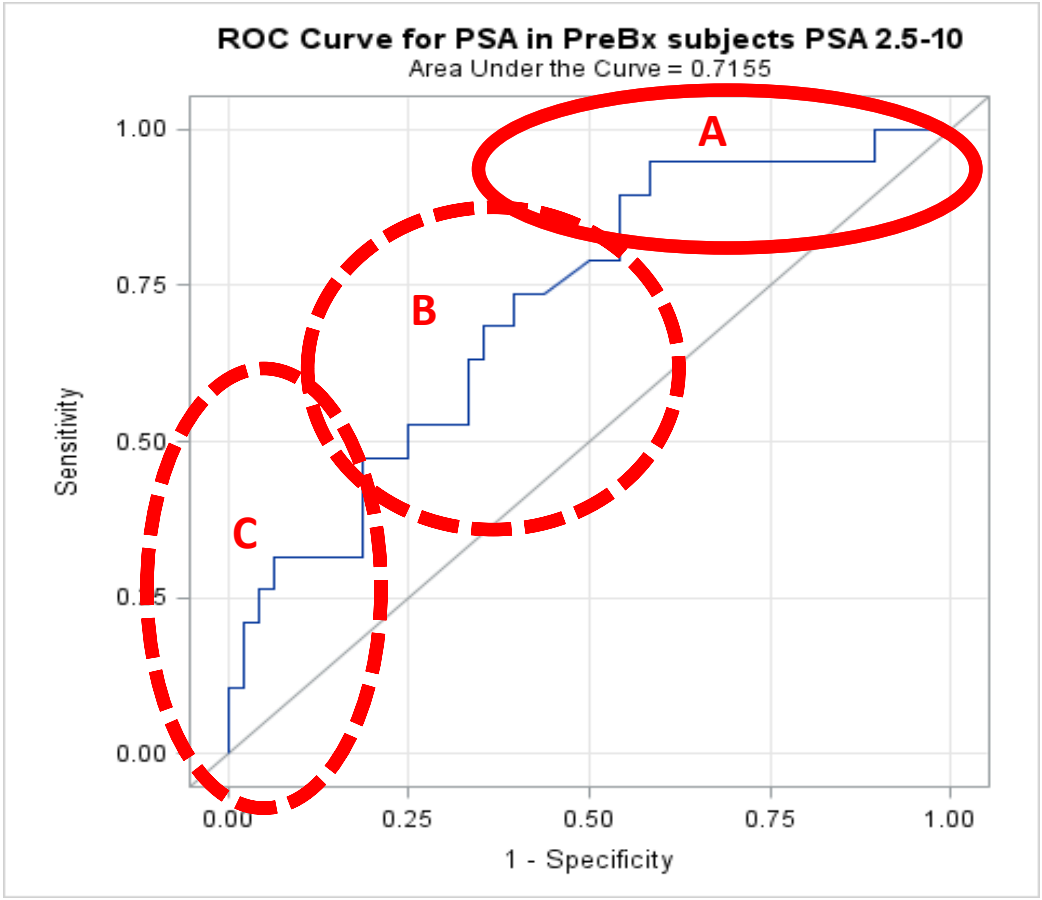
EMORY

A) Who should undergo prostate biopsy?

- Current state / clinical need
  - Existing biomarker (PSA): high sensitivity, poor specificity
  - Reduce unnecessary biopsy while preserving sensitivity
- Risk/benefit
  - False positive biomarker: unnecessary biopsy (accepted)
  - False negative biomarker: miss window for cure
- Analytic Translation
  - Reduce false positives: Improve specificity – while preserving sensitivity

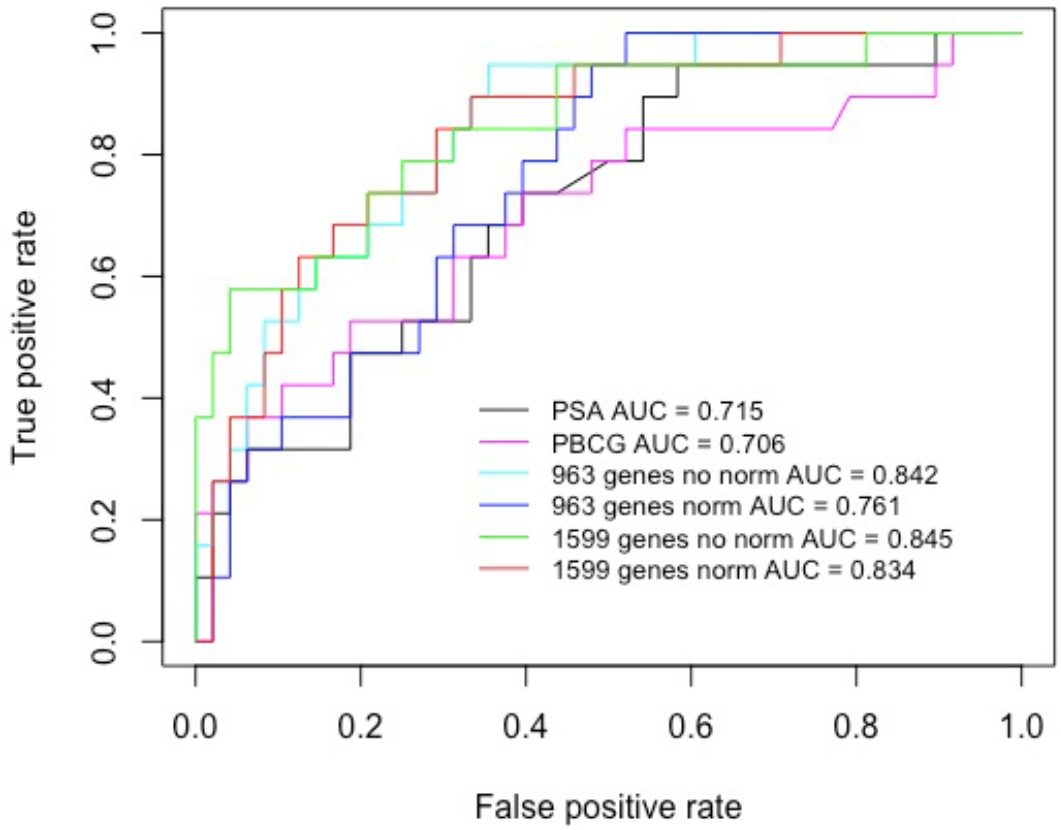
EMORY

A) Current State: PSA and Decision for Biopsy



A) Segment to enhance performance performance for selecting biopsy
B) Segment for enhancing performance to treat vs surveillance
C) Segment for enhancing performance in detecting metastases

Putative Biomarkers to Improve on PSA and Decision for Biopsy



Blue: modest AUC change but most impact on specificity at high sensitivity

Green: greatest AUC impact (better than blue) but not better in specificity at high sensitivity

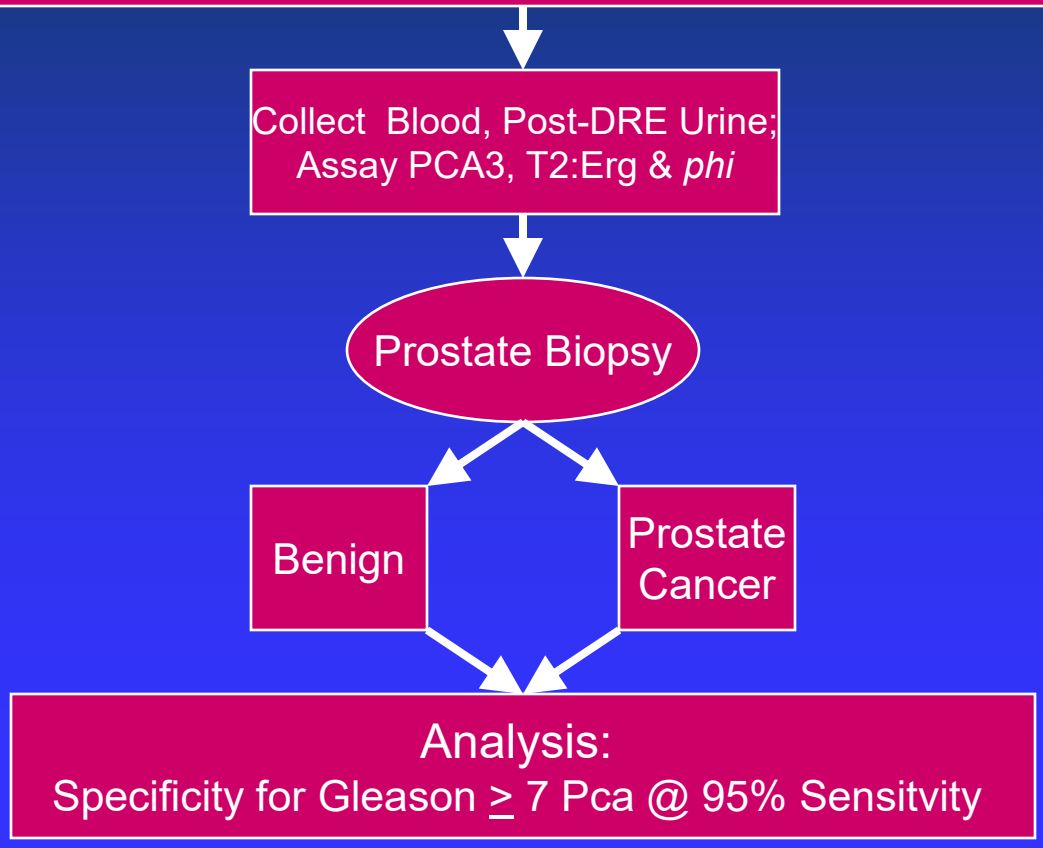
Sample Power Implications for Improving Clinical Decisions at Extreme Ends of ROC

Sample Power for Different Clinical Design	**N=140**	**N=500**
Improve AUC	0.84	1.00
Improve Spec @ 95% Sens	0.39	0.73

Clinical Question A) Decision for Biopsy: Example

Combining Urinary PCA3, T2:Erg to Refine PCa Detection

Development Cohort: 3 Sites, N = 516
Validation Cohort: 10 Sites (EDRN PCA3 Trial Group) N = 561



Combining Urinary T2:Erg and PCA3 RNA

EDRN Team Participants: BDL, CVC, BRL,DMCC

Biomarker	Assay Threshold for > 95% Sensitivity To Predict Gleason ≥ 7	Specificity
PSA	3.0	**18%**
PCA3	6.3	17%
T2-erg*	---	0%
PCA3-T2erg	19.1, 7.6	**39%**

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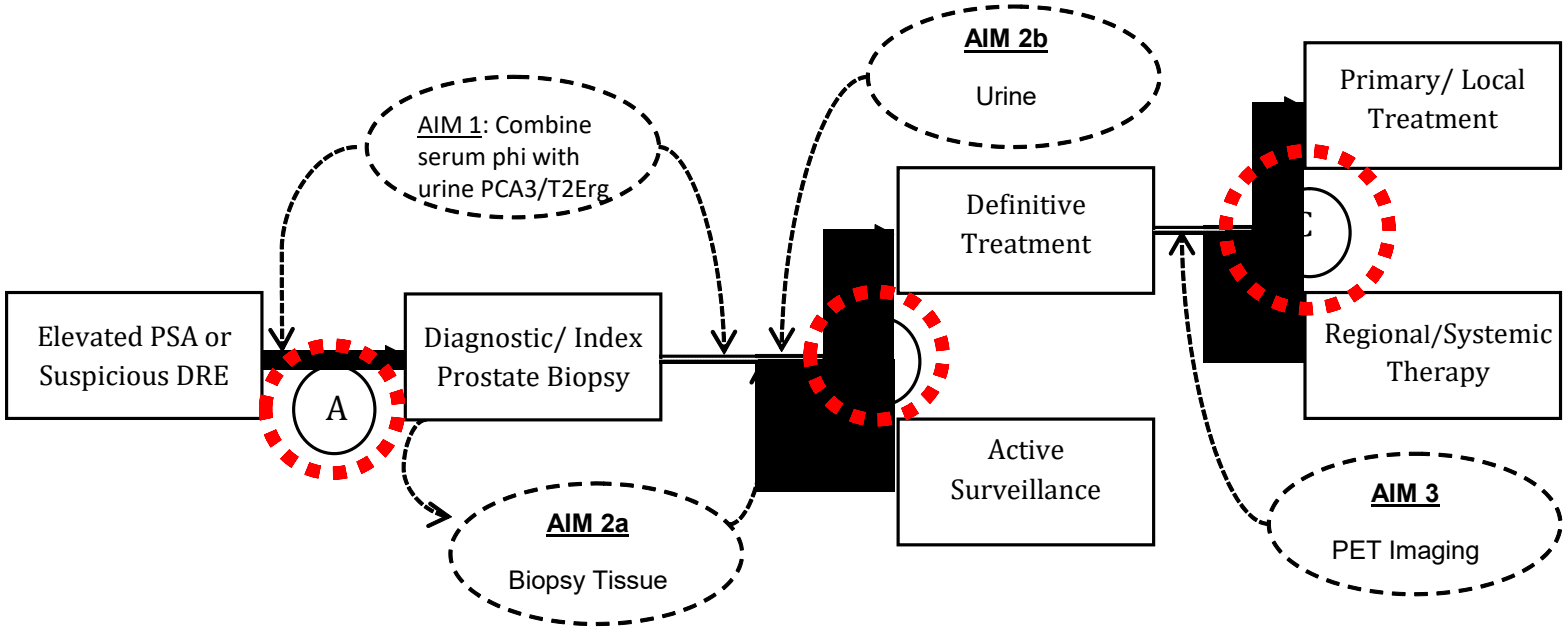

A) Who should undergo prostate biopsy?

- *Design: Improve specificity @ high sensitivity*

B) Who should undergo treatment versus surveillance?

- *Design: Improve AUC*

C) How extensive is the cancer (metastases) & impact on treatment extent?

- *Design: Improve sensitivity @ high specificity*

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