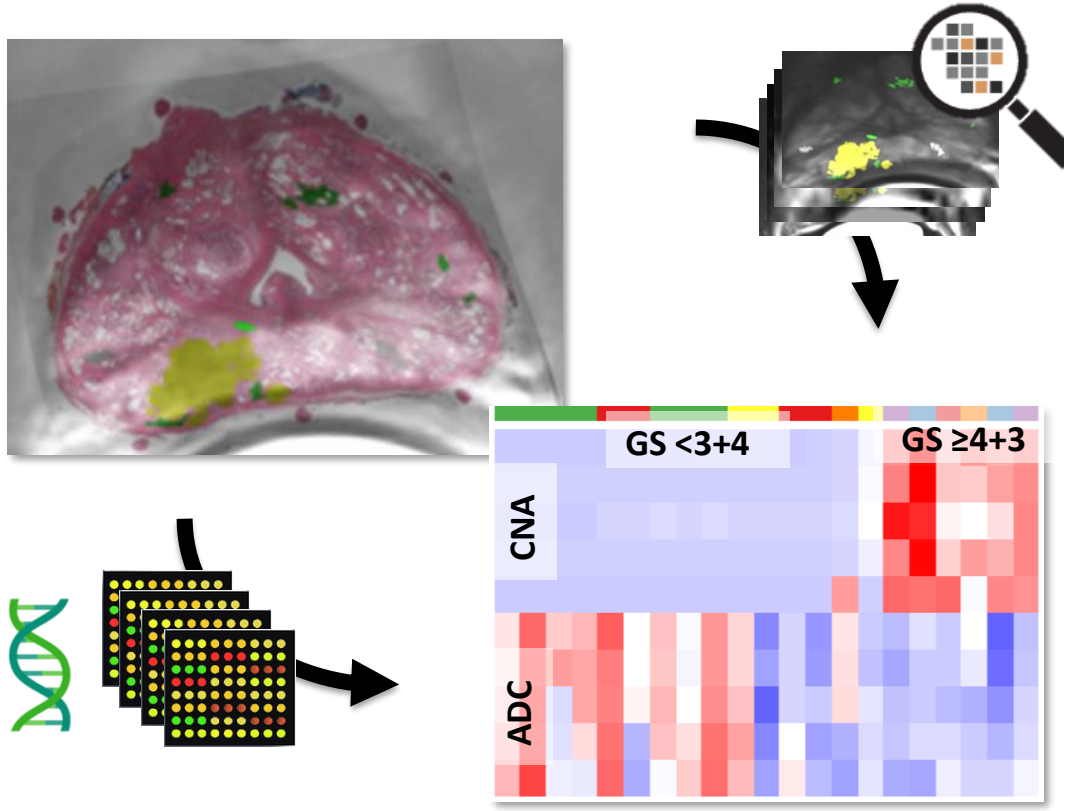
PD52-03: Multi-parametric magnetic resonance imaging (mpMRI) of multi-focal prostate cancer unmasks intra-prostatic genomic heterogeneity and novel radio-genomic correlates

Results of the Smarter Prostate Interventions and Therapeutics (SPIRIT) study



Presenter: Rohann J. M. Correa, MD, PhD
Radiation Oncology Resident, PGY-4
rohann.correa@lhsc.on.ca

Investigators: **Joseph L. Chin**, Erfan Aref-Eshghi, Ryan Alfano, Bekim Sadikovic, Aaron D. Ward, Paul C. Boutros, John M.S. Bartlett, Zahra Kassam, Stephen E. Pautler, Mena Gaed, José A. Gómez, Madeleine Moussa, **Glenn S. Bauman**

Disclosures

- No conflicts of interest

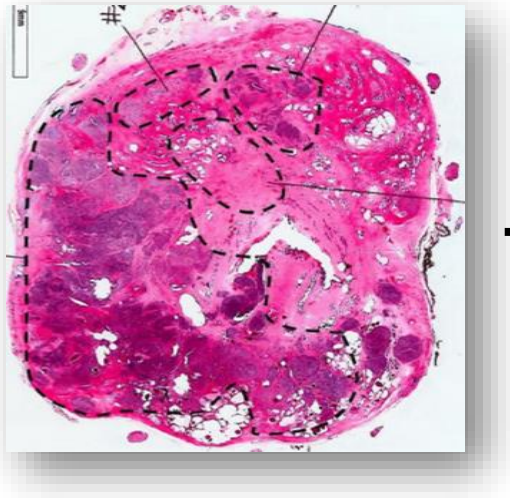
Introduction

- Multi-focal prostate cancer (PCa) exhibits genomic heterogeneity[1,2]
  - Can confound selection of most appropriate management
- mpMRI interrogates whole gland, can improve diagnostic yields[3]
- Radiomic features linked with specific genetic aberrations[4]

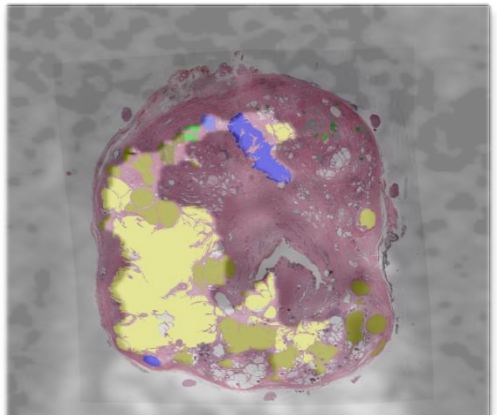
Objective: *To evaluate radio-genomic correlations between genome-wide copy-number aberration (CNA) and mpMRI in multi-focal PCa*

1. Lovf M. Eur Urol. 2019 Mar;75(3):498-505
2. Boutros P. Nat Genet. 2015 Jul;47(7):736-45.
3. Kasivisvanathan V. Eur Urol. 2019 Sep;76(3):284-303.
4. Kesch C. Sci Rep. 2018 Nov 12;8(1):16708.

Overview

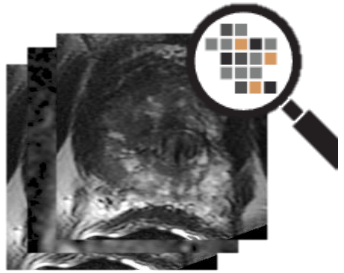


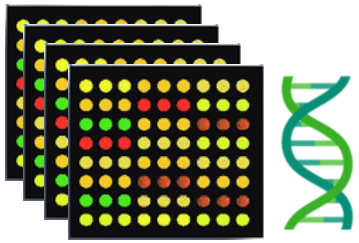
Multi-focal Prostate Ca



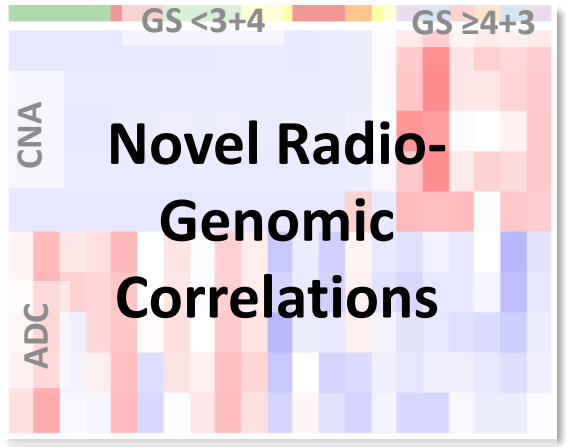
High-Fidelity Co-Registration

Radiomic Analysis



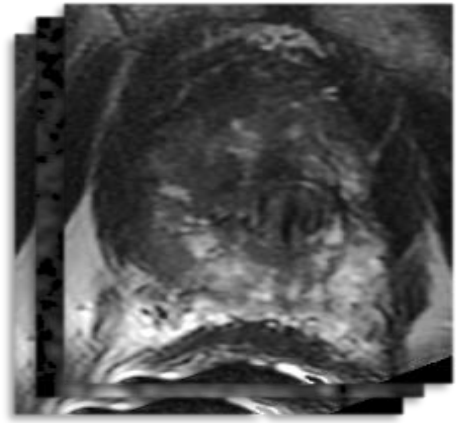


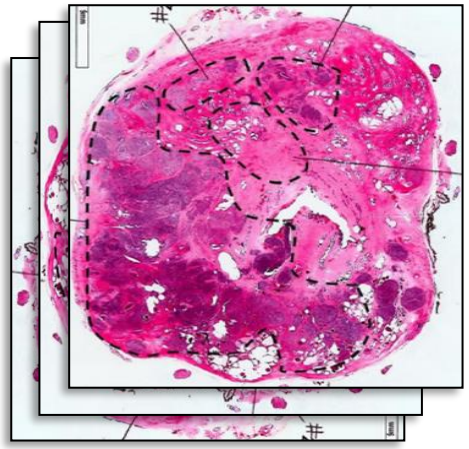
Genomic Analysis

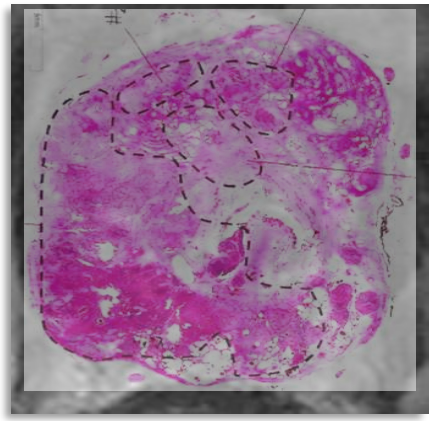


Methodology

1. Eligible men (n=35) underwent pre-operative mpMRI
2. Post-prostatectomy *ex vivo* mpMRI with fiducials
3. Axial, whole-mount tissue sections through whole gland
4. Fiducial-guided co-registration of mpMRI & histology

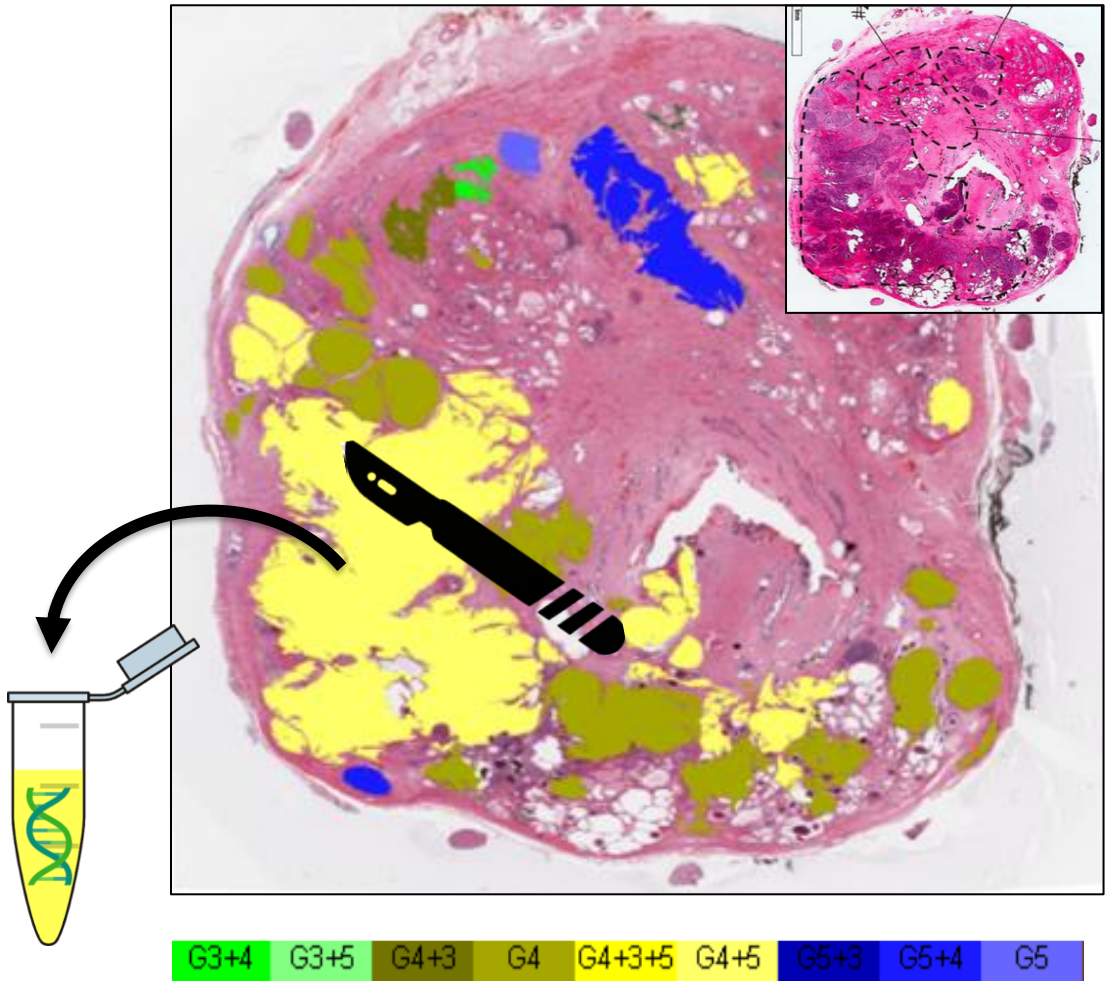






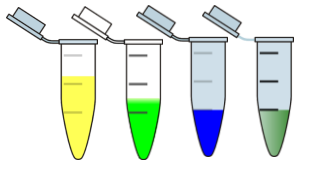
Methodology

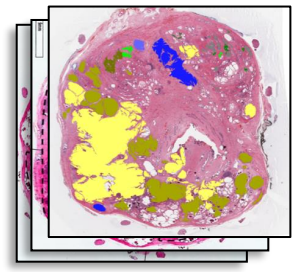
5. Subset (n=8) with multi-focal PCa for genomic analysis
6. High-resolution segmentation of disease foci (pathologist)
7. Macro-dissection of foci for DNA extraction

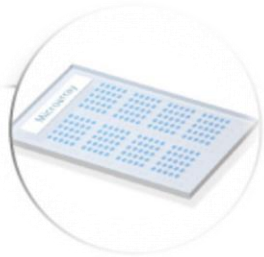


Methodology

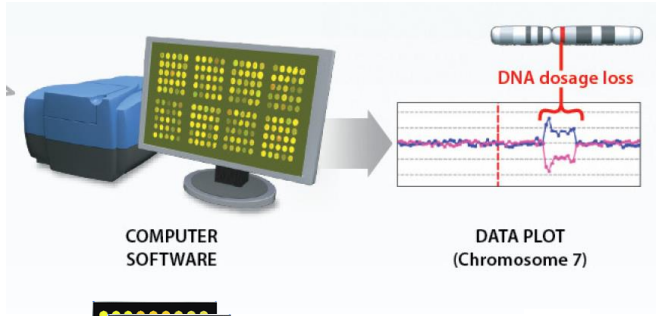
8. Multi-region genomic copy-number profiling
9. Bioinformatic and radiomic analysis
10. Radio-genomic correlative studies

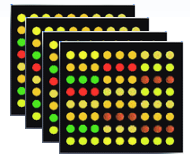






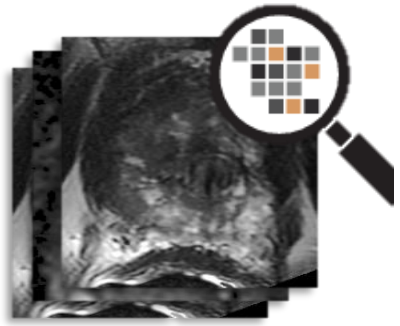
Bioinformatic Analysis

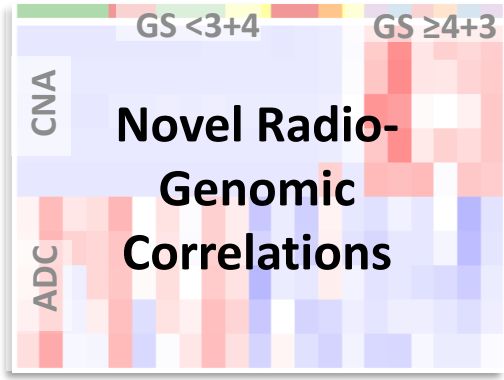




Genomic CNA Data

Radiomic Analysis





1. Theisen, A. (2008) *Nature Education* 1(1):45

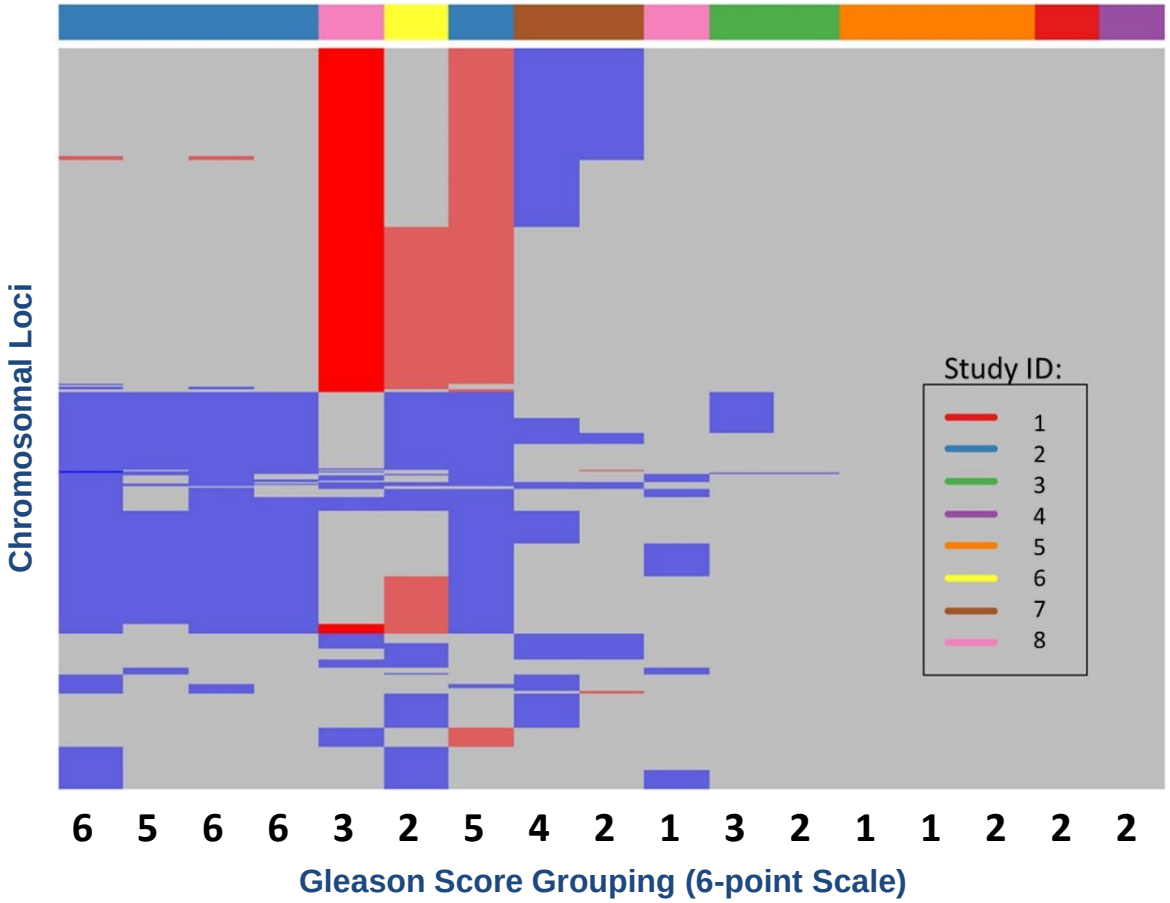
Results: Patient Characteristics

Study ID	TNM Pathologic Stage	Gleason Grade	Margin Status	BCR	Additional Treatment	Follow-Up Duration (months)	Status at Last Follow-Up
1	pT2cN0	3+4	-	-	None	62	NED: PSA undetectable
2	pT3bN1	5+4+3	+	-	Adj. RT + ADT	29	Lost to FLUP: PSA undetectable on ADT
3	pT3bN0	3+4+5	-	+	Salvage RT	66	Well: BCR @ 29 months, rising PSA (0.55)
4	pT3aN0	3+4	-	-	None	66	NED: PSA undetectable
5	pT2cN0	3+4	-	-	None	62	NED: PSA undetectable
6	pT3bN0	3+4+5	+	-	Adj. RT	58	NED: PSA undetectable
7	pT3aN0	4+3	-	+	ADT → Apalutamide	48	Alive with disease, PSA rise immediately post-op → ADT, CRPC @ 38 mo.
8	pT3bN0	4+3+5	-	-	None	46	Well, slowly-rising PSA since 18 mo. (0.12)

TNM – Tumour, node, metastasis staging system; **PSA**, prostate-specific antigen; **NED**, no evidence of disease; **FLUP**, follow-up; **BCR**, biochemical recurrence; **CRPC**, castrate-resistant prostate cancer

Results: Recurrent (>1 patient) CNAs

- Broad range of loci affected
- Most common AMP/DEL on chr. 1p, 6q, 7p, 7q, 8p, and 18q
  - *EGFR, BRAF, CHD1*, and *STC1*
- Highly-recurrent (≥4 patients): DEL of cytobands 8p21 and 18q21
  - *NKX3-1* and *PPP2R2A*
- Findings consistent with prior multi-region genomic studies[1,2]

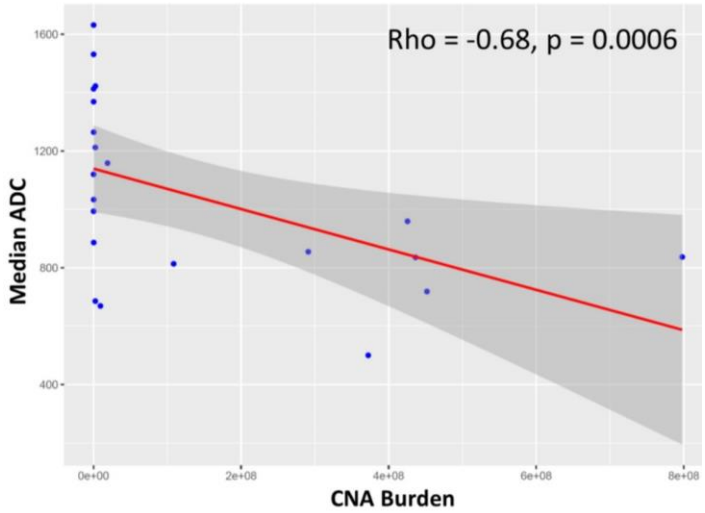


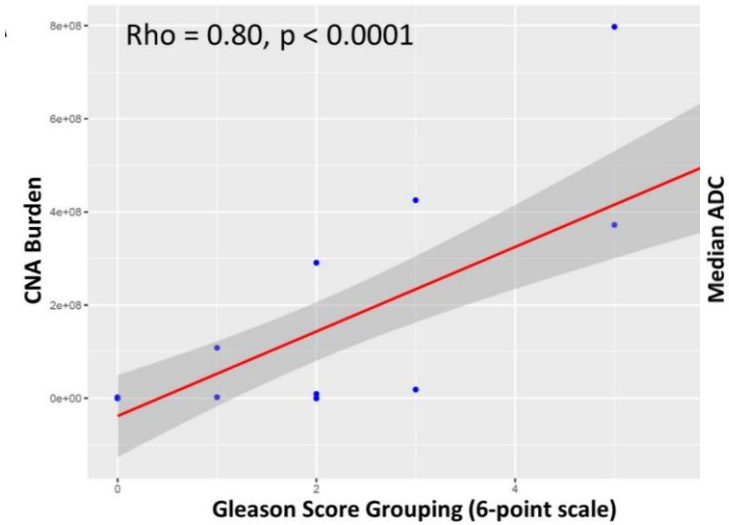
6-point scale: 0=benign, 1=3+3, 2=3+4, 3=4+3, 4=4+4, 5=4+5, 6=5+4

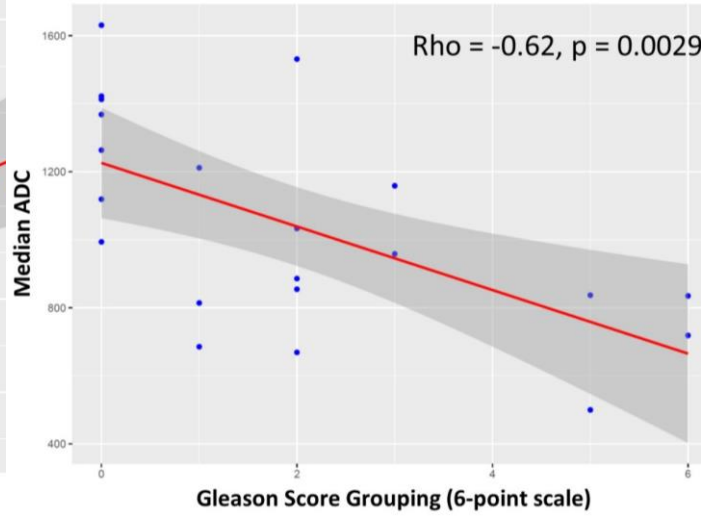
(1) Lovf M. Eur Urol. 2019 Mar;75(3):498-505 (2) Boutros P. Nat Genet. 2015 Jul;47(7):736-45.

Results: Burden of CNAs

- CNA burden = loci length x copy number Δ
- CNA burden correlates with median ADC
- CNA burden & ADC also correlate with Gleason Score

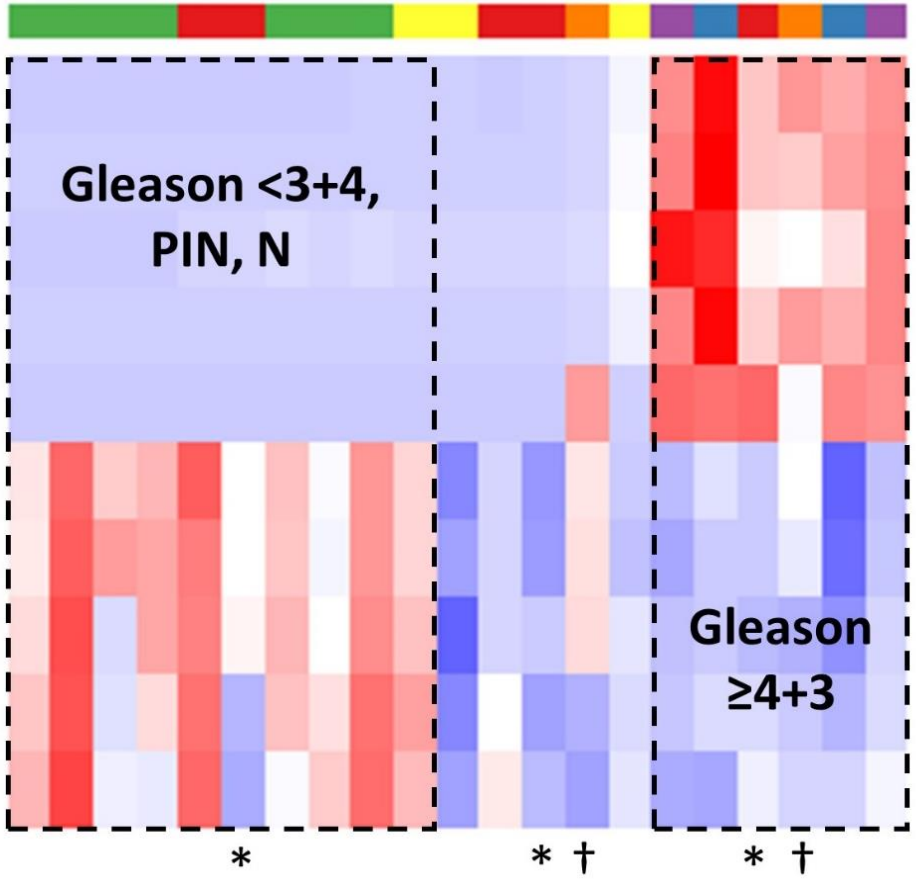






Results: Clustering Analysis

- Foci cluster by ADC & CNA:
  - Low-grade/Benign: CNA low, ADC high
  - Higher-grade: CNA high, ADC low
- Gleason 3+4 & 4+3:
  - Some intermediate
  - Some cluster with low- or higher-grade



CNA Burden
CNA Length
CNA Number
CNA Gene Rate
High-Frequency CNA Count
Mean ADC
Median ADC
10th Percentile ADC
1st Percentile ADC
Minimum ADC

Gleason:
3+3
3+4
4+3
4+5
5+4
Benign

Discussion

Limitations:

- Small sample size, exploratory study
- Potential of overfitting with multiple comparisons

Strengths:

- Whole-mount with high-fidelity, fiducial-guided co-registration
- Both central/transition & peripheral zone lesions sampled

Conclusions

- Novel correlation of low ADC with high genome-wide CNA burden
  - Assoc. with genomic instability & worse prognosis[1,2]
- Proof-of-principle of our radio-genomic analysis platform

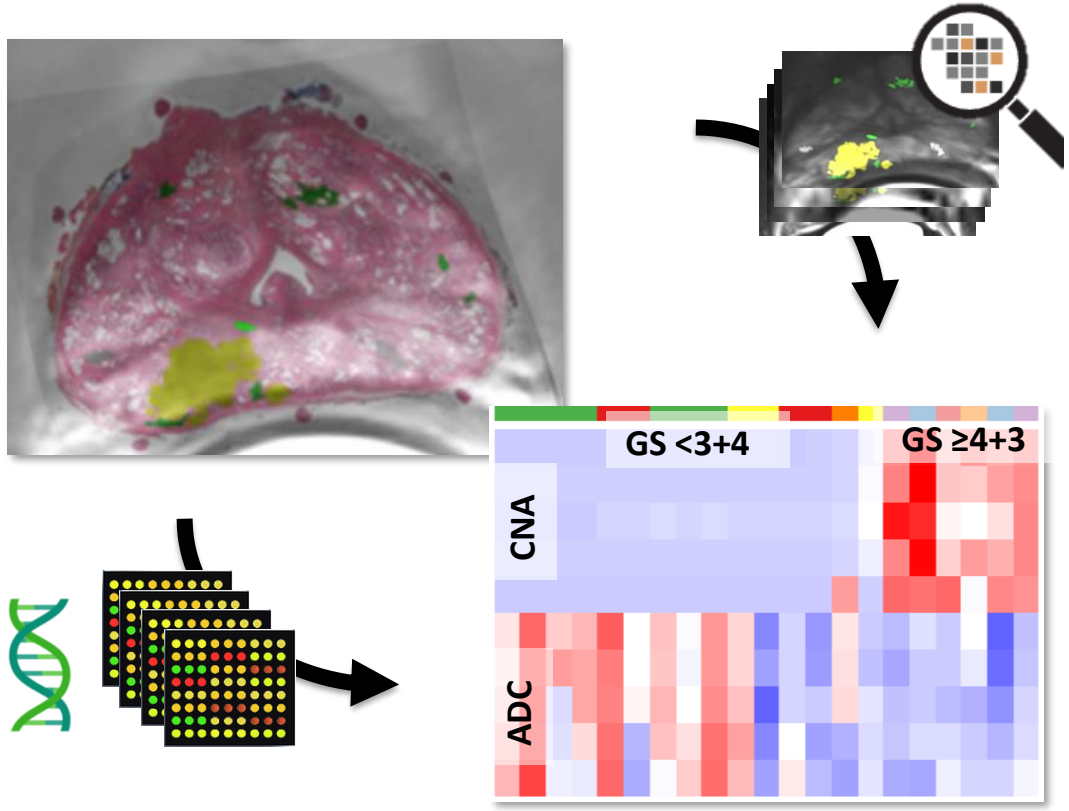
Future Work

- Expansion cohort to increase sample size
  - Additional radio-genomic correlations: PSMA-PET & whole-genome DNA methylation
- ADC radiomics to supplement mpMRI interpretation criteria

1. Hieronymus H. Proc Natl Acad Sci U S A. 2014;111(30):11139-44
2. Chua M. Eur Urol. 2017 Nov;72(5):665-674.

PD52-03: Multi-parametric magnetic resonance imaging (mpMRI) of multi-focal prostate cancer unmasks intra-prostatic genomic heterogeneity and novel radio-genomic correlates

Results of the Smarter Prostate Interventions and Therapeutics (SPIRIT) study



Presenter: Rohann J. M. Correa, MD, PhD
Radiation Oncology Resident, PGY-4
rohann.correa@lhsc.on.ca

Investigators: **Joseph L. Chin**, Erfan Aref-Eshghi, Ryan Alfano, Bekim Sadikovic, Aaron D. Ward, Paul C. Boutros, John M.S. Bartlett, Zahra Kassam, Stephen E. Pautler, Mena Gaed, José A. Gómez, Madeleine Moussa, **Glenn S. Bauman**