Artificial Intelligence in Prostate Cancer Risk Stratification

Development, Validation, and Diagnostic Performance of a Radiomic Model for Prediction of Prostate Cancer Recurrence

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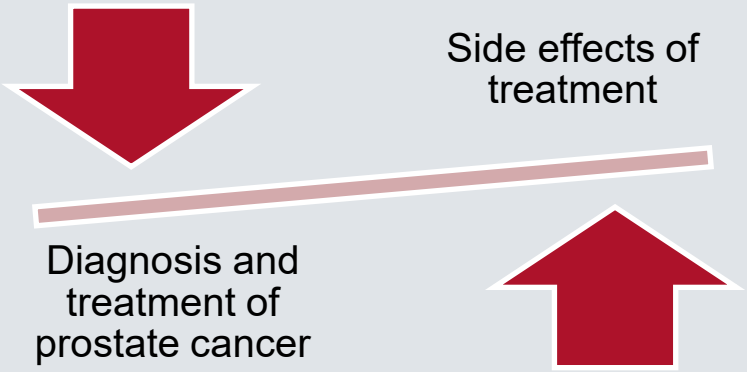
Disclosures

No conflicts of interest to disclose

Prostate cancer is characterized by indolence and long natural life history.

- Prostate cancer is the most common cancer among men
- Natural life history ranges between 10 – 15 years
- Treatment includes watchful waiting, surgery, and/or radiation
- Long-term sequelae from treatment is significant



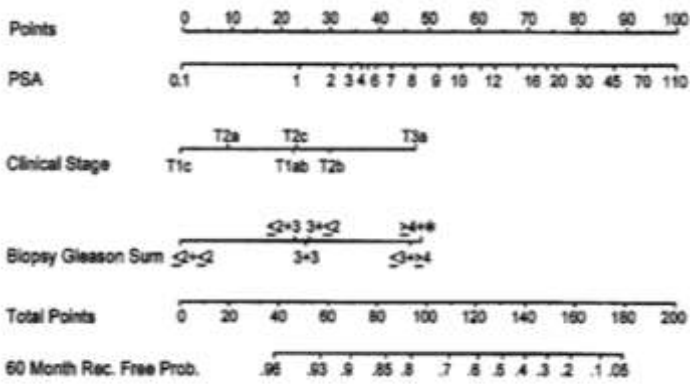
The clinical care pathway for offers several details for risk stratification.

PSA test	DRE	Biopsy	Imaging	Surgery/Radiation
<4 ng/ml 4-10 ng/ml >10 ng/ml	clinical stage	Gleason Grade Group	local regional distant	

Current risk stratification methods are based on “macro” clinicopathologic features

- Early prediction of recurrences may allow for proactive, disease-tailored treatment

Variable	Level	Points	Variable	Level	Points
PSA	2.0–6	0	T stage	T1/T2	0
	6.1–10	1		T3a	1
	10.1–20	2			
	20.1–30	3	% pos bx	<34%	0
	>30	4		≥34%	1
Gleason	1-3/1-3	0			
	1-3/4-5	1	Age	<50	0
	4-5/1-5	3		≥50	1



External testing yields AUC 0.6 – 0.8

Falagario 2023

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PSA test	DRE	Biopsy	Imaging	Surgery/Radiation
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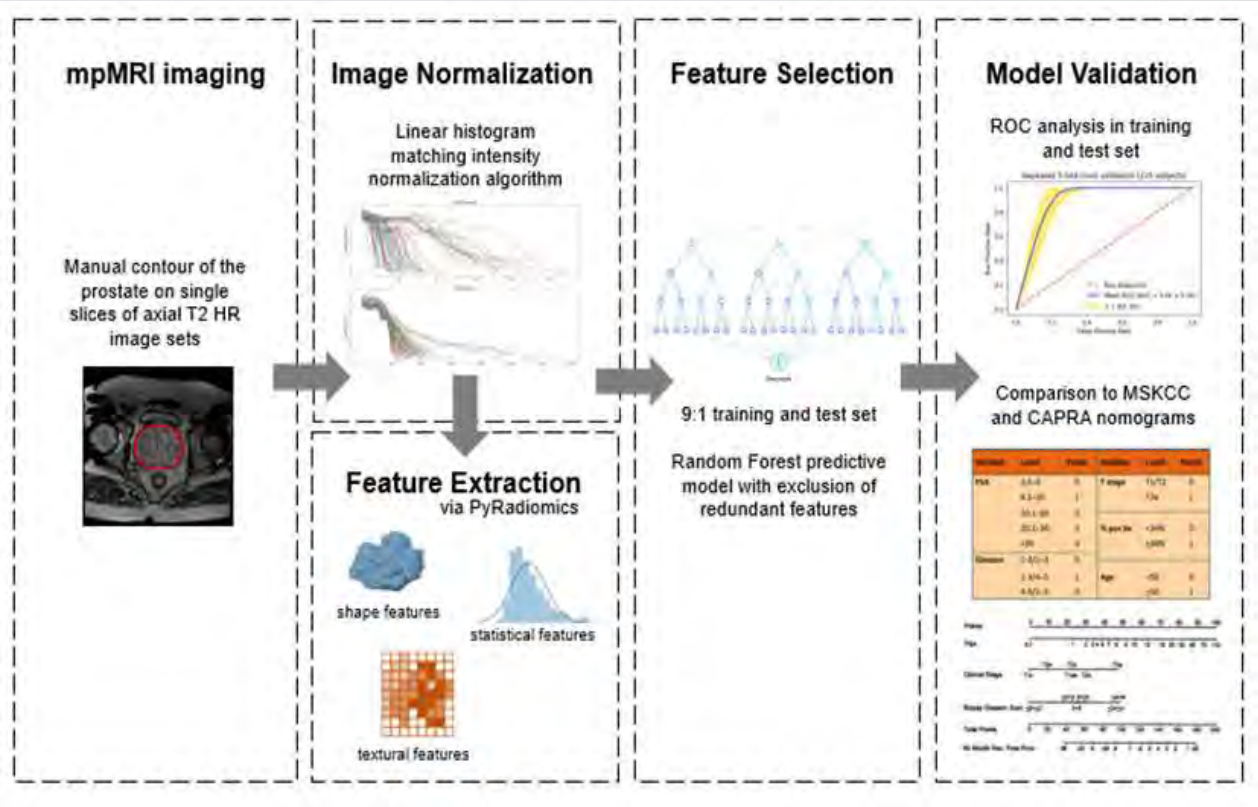
Macro

Micro

Radiomics can extract sub-visual, “micro” features from medical imaging.



MRI-derived radiomics were often used to predict grade and stage, but seldom applied to treatment response.

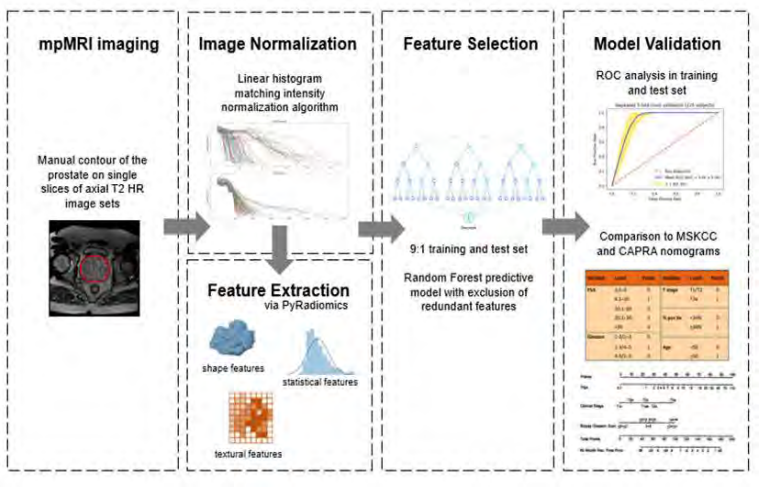
Huynh 2022

Methodology in currently available studies were highly heterogenous.

Author	n=	Images Used	Feature Selection	Region of Interest	Feature Number	Model Validation	Results
Bourbonne (2020)	195	T2WI ADC	Multilayer Perceptron Network, SPSS v24.0	Lesion	NR	107 training 88 external testing	Clinical AUC=0.68 Radiomic AUC=0.82 Clinical and radiomic AUC=0.86
Li (2021)	198	T2WI DWI ADC	Minimum redundancy maximum relevance (mRMR)	Prostate	5	5-fold, 10-run cross-validation 71 training 127 testing	Training model HR=7.01, 95%CI: 1.21-40.68, p<0.05, independent of preoperative and clinicopathologic parameters in multivariable analysis Testing model HR=1.9, 95%CI: 1.4-2.7, p<0.05
Yan (2021)	485	T2WI	Deep survival radiomic neural network	Lesions	155/702	368 training 34 external testing 83 external validation	3-year BCR training AUC=0.84 3-year BCR external testing AUC=0.85 3-year BCR external validation AUC=0.84 5-year BCR training AUC=0.83 5-year BCR external testing AUC=0.88 5-year BCR external validation AUC=0.88 Significantly improved accuracy compared to GG-RP, CAPRA-S, NCCN, and CAPRA
Shiradkar (2022)	133	T2WI ADC	Random forest (RF) & Cox proportional hazards regression model	Prostate Lesions	10	Cross-validation 2:1 training: testing	3-year BCR HR: 2.91, 95%CI: 1.45-11.51, p=0.02 Significantly improved accuracy compared to clinical characteristics, CAPRA, CAPRA-S, and Decipher scores

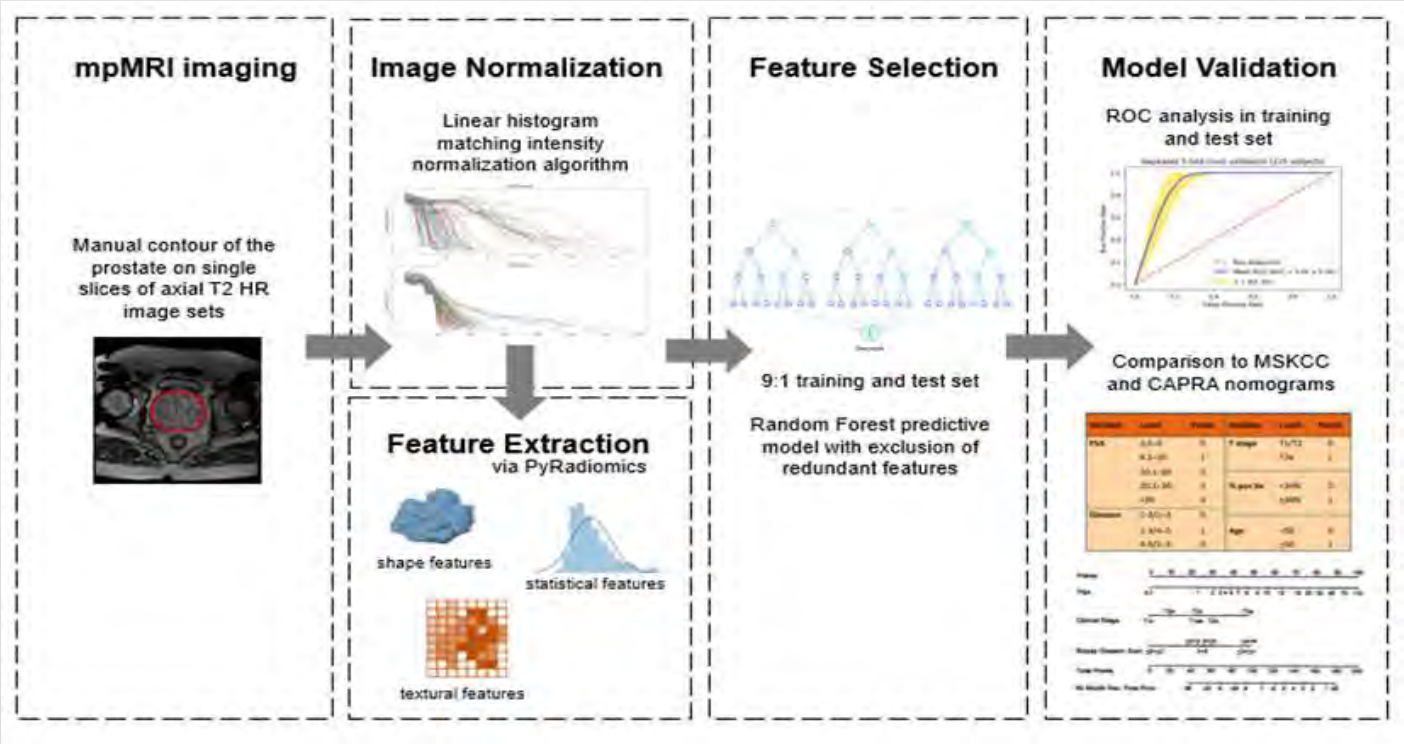
Huynh 2022

The radiomics pipeline is highly variable and unstandardized.



- Image acquisition: MRI, CT, PET, U/S
- Image pre-processing: regions of interest, manual/automatic segmentation, histogram matching
- Feature extraction: density, texture, contrast, brightness, # of features
- Data integration and analysis: feature reduction, cross-validation, clinical features
- Model validation: multi-institutional recruitment, external validation, n:n ratios..

Intentional modifications to the radiomic pipeline increased clinical utility and reproducibility.



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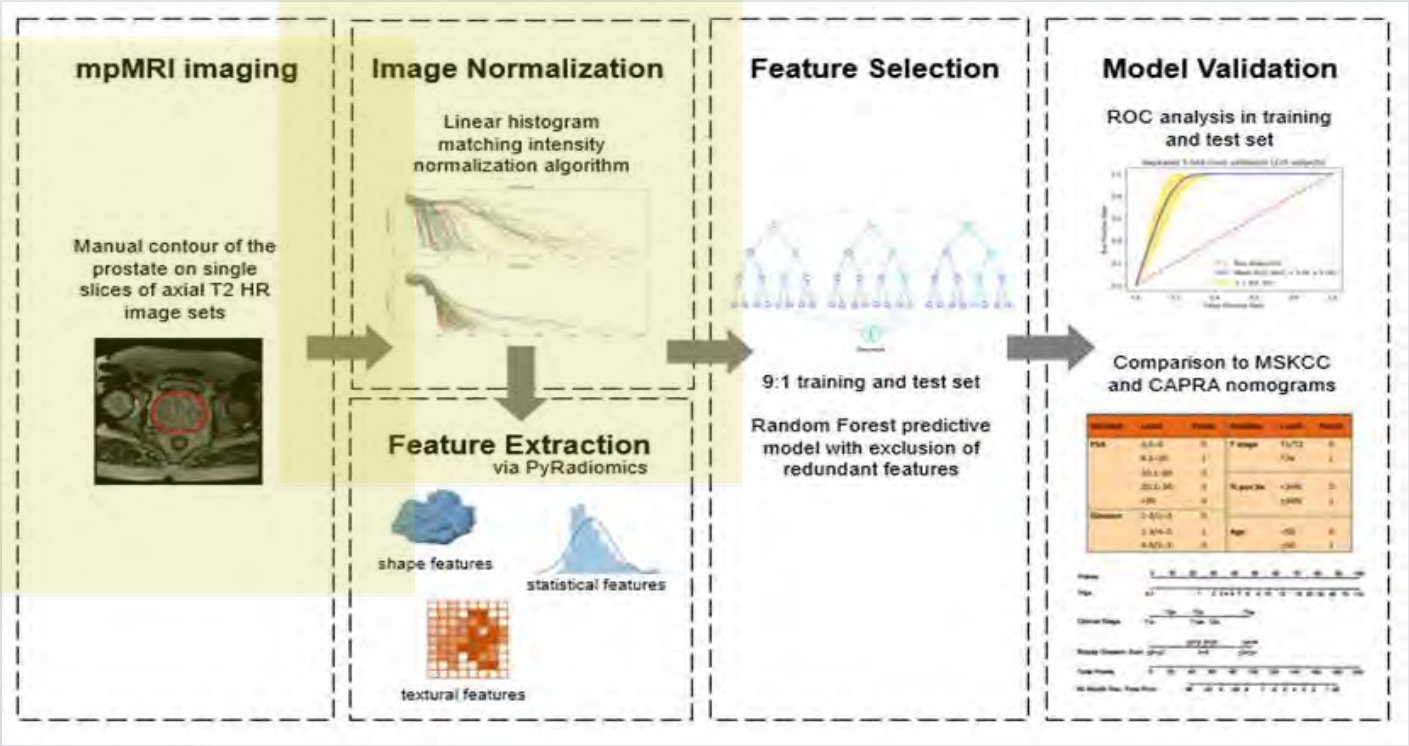
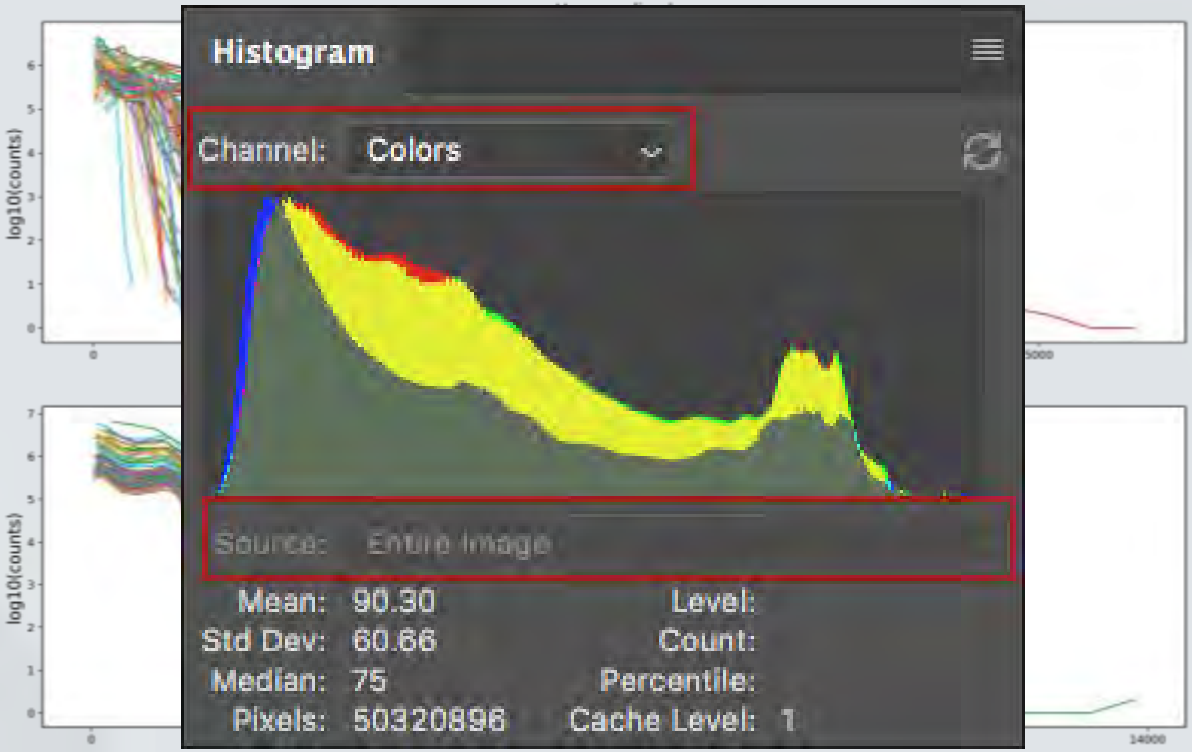


Histogram matching improves feature stability for model development.



Nyul 2018

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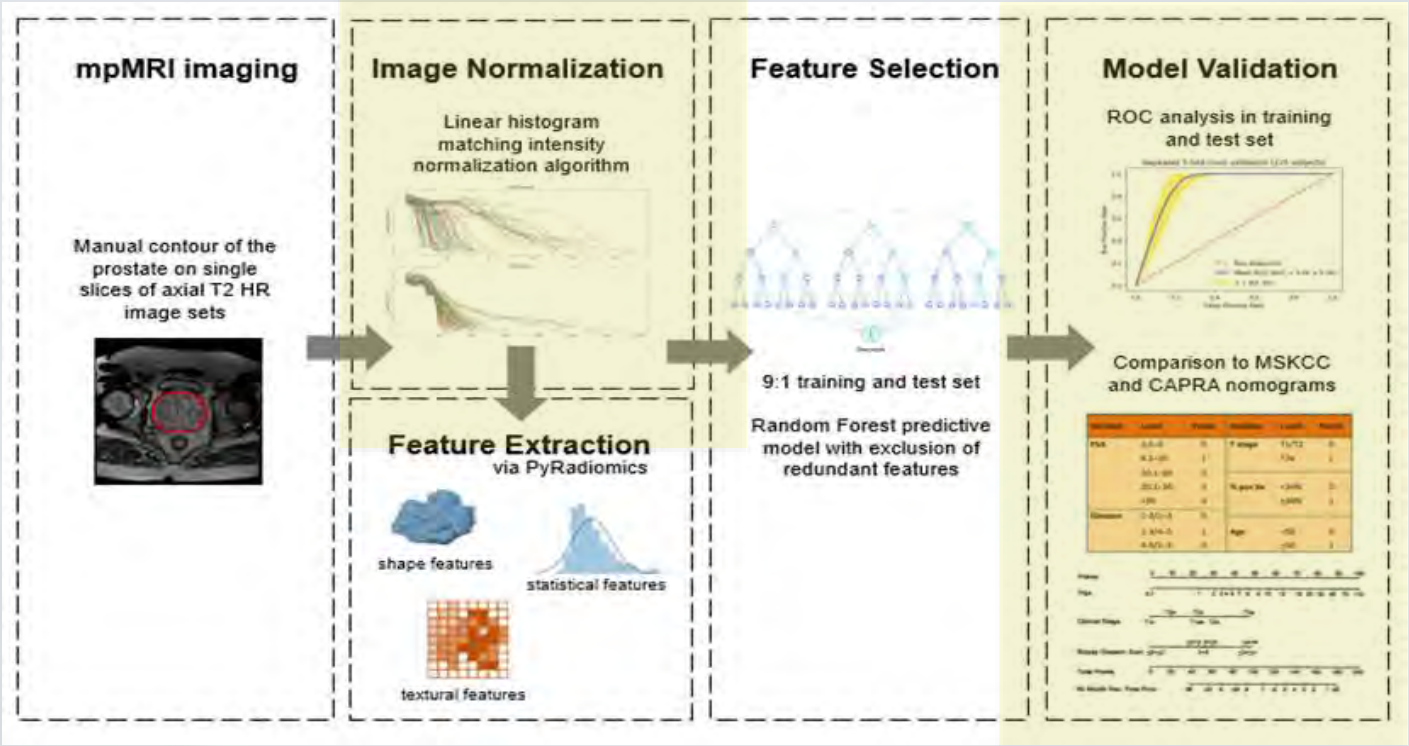


Stepwise analysis facilitated robust model development and testing.

Aug 2022

- Preliminary analysis with 76 patients from UNMC

N=76 patients (2, 1, 1)

Training AUC = 0.95
Testing AUC = 0.67
100% specificity
33% sensitivity

Lacked external validation

June 2023

- Final(?) analysis with 251 patients from UCI & UNMC

+65 patients (1, 2, 4)
+110 patients (1, 50+, 50+)

Training AUC = 0.89
Testing AUC = 0.78
86% specificity
60% sensitivity

Lacked clinical comparison

Sept 2023

- Actual final analysis with 339 patients from UCI & UNMC

+88 patients (1, 50+, 50+)

Cross-Validation AUC=0.82
Testing AUC = 0.72
56% specificity
88% sensitivity

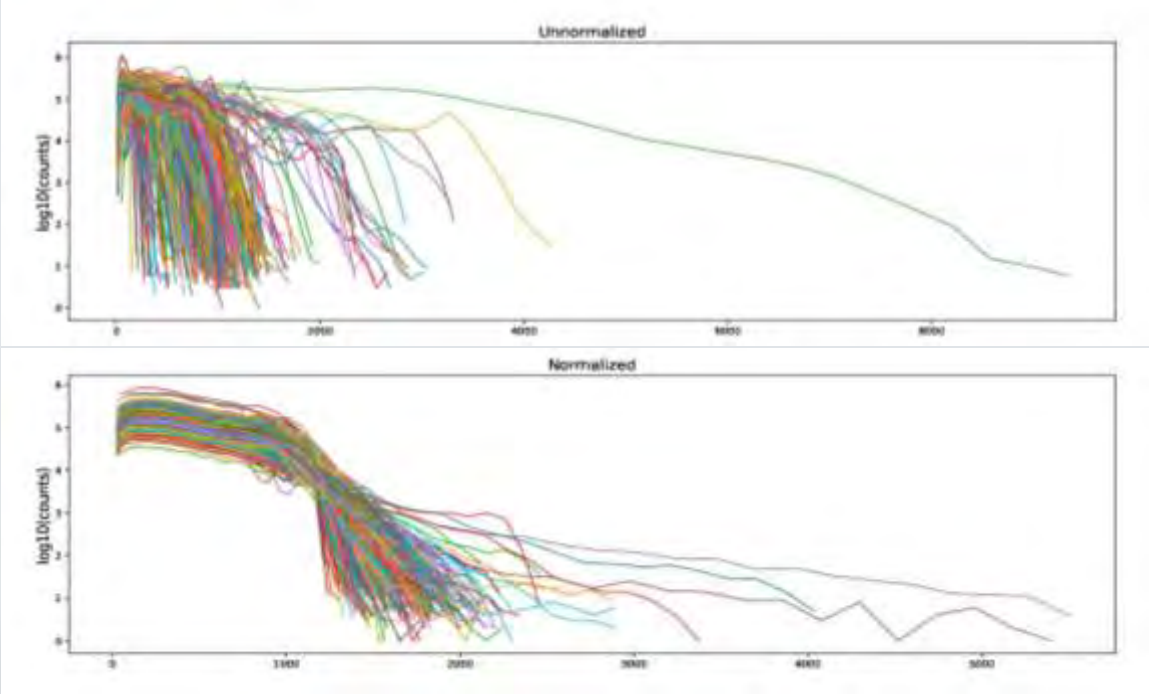
Significantly improved against CAPRA & MSKCC

The final cohort was representative of prostate cancer patients.

Age: 64.4 ± 7.4 years
Preoperative PSA: 9.4 ± 9.3 ng/mL
Follow-up Time: 3.4 ± 1.9 years

	Training		Testing		
	n	%	n	%	p
Pathologic Tumor Stage					0.739
2a	93	32.1	17	34.7	
2b	61	21.0	8	16.3	
2c	22	7.6	6	12.2	
3a	91	31.4	15	30.6	
3b	21	7.2	3	6.1	
4	2	0.7	0	0	
Pathologic GGG					0.137
1	28	9.9	7	14.6	
2	148	52.1	20	41.7	
3	63	22.2	7	14.6	
4	13	4.6	4	8.3	
5	32	11.3	10	20.8	
Seminal Vesicle Invasion	26	9.0	4	8.2	0.241
Extraprostatic Extension	91	31.4	15	30.6	0.911
Lymph Node Invasion	6	2.1	1	2.0	0.771
Positive Surgical Margins	88	31.1	14	28.6	0.867
Biochemical Recurrence	52	17.9	8	16.3	0.785

Image normalization allowed for comparability across all four surgeons (and >100 different imaging protocols).



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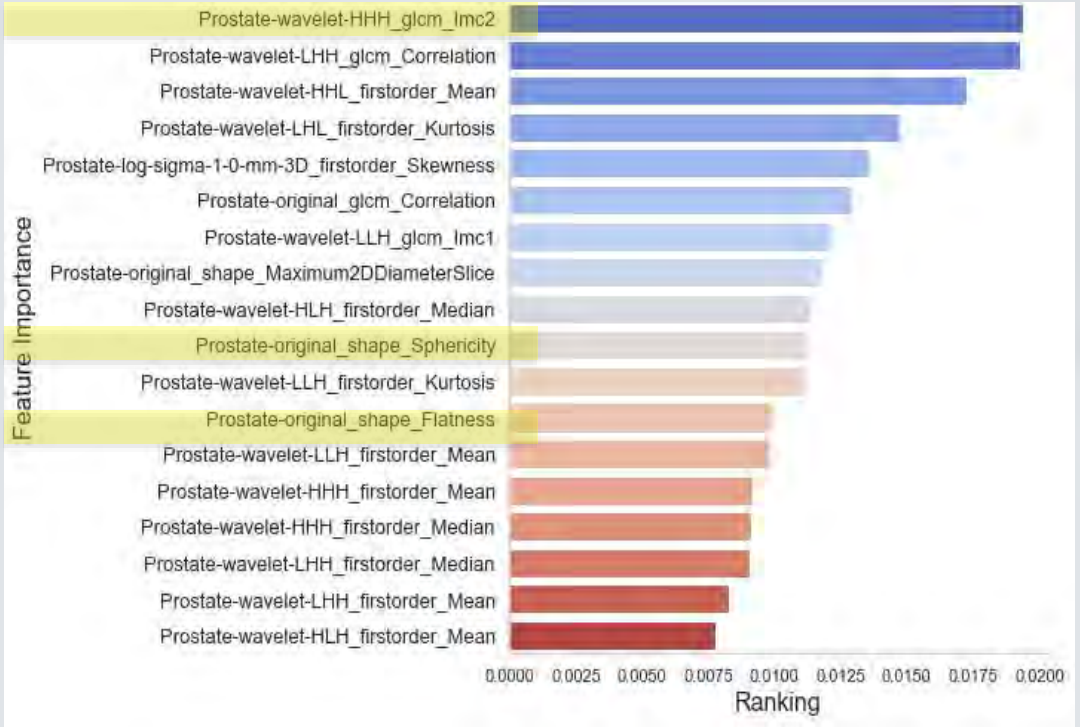
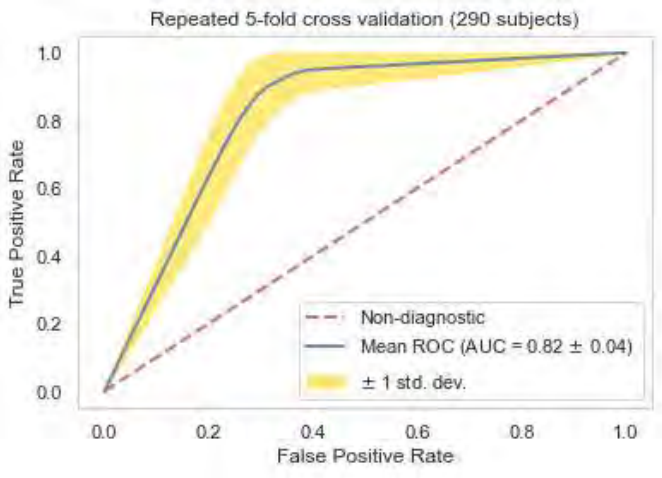
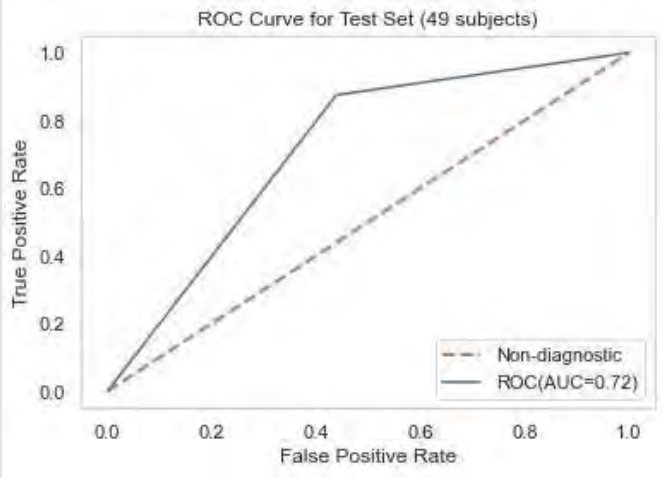
Eighteen radiomic features were non-redundant and highly correlated with recurrence.



Cross-validation yielded AUC=0.82, compared to 0.66 and 0.64 for the UCSF nomogram and CAPRA score.





UCSF-CAPRA score

AUC=0.66±0.05

MSKCC Nomogram

AUC=0.64±0.04

UCSF-CAPRA score

AUC=0.61

MSKCC Nomogram

AUC=0.73

Radiomic features also correlate well with clinicopathologic features.

Feature	Correlation Coefficient	p- value	95% CI Lower	Upper
Prostate-log-sigma-1-0-mm-3D_firstorder_Skewness Pathology GGG	0.150	**0.012***	0.034	0.262
Prostate-original_glcm_Correlation – Pre-Treatment PSA	-0.111	0.064	-0.225	0.006
Prostate-original_shape_Flatness - Pre-Treatment PSA	0.127	**0.034***	0.010	0.241
Prostate-original_shape_Maximum2DDiameterSlice - Age	0.153	**0.009***	0.038	0.264
Prostate-original_shape_Sphericity – Biopsy GGG	-0.101	0.090	-0.215	0.016
Prostate-wavelet-HHL_firstorder_Mean – Positive Surgical Margin	0.126	**0.034***	0.010	0.239
Prostate-wavelet-HLH_firstorder_Median – Pathology GGG	0.113	0.057	-0.003	0.227
Prostate-wavelet-LHH_firstorder_Median – Positive Surgical Margin	0.099	0.096	-0.018	0.213
Prostate-wavelet-LHH_glcm_Correlation – Biopsy GGG	-0.133	**0.026***	-0.245	-0.016
Prostate-wavelet-LHH_glcm_Correlation – Pathology GGG	-0.150	**0.011***	-0.262	-0.034
Prostate-wavelet-LLH_firstorder_Mean - Age	-0.122	**0.039***	-0.234	-0.006
Prostate-wavelet-LLH_glcm_Imc1 - Age	0.113	0.056	-0.003	0.226

Increased sample size introduced significant heterogeneity but improved generalizability.

- Increased sample size
  - Higher power
  - Higher number of patients with recurrence
  - Higher number of features included in the final model
- Introduction of heterogeneity (in the right places)
  - Higher likelihood of generalizability to external centers
- Improved methodology
  - Improved image normalization
  - Improved feature stability testing

On the horizon...

- Combined clinicopathologic and radiomic nomograms for prostate cancer risk stratification
- Intersection between pathomic, radiomic, and histiomic models to identify tumor heterogeneity and microenvironment
- Development of cross-disciplinary tissue-level targets to enhance treatment response

The fact that progress has actually been made,
in the most part,
by ordinarily clever people,
building step by step
from the work of their predecessors
makes the story more remarkable.

John Gribbin
"Science: A History"

University of Nebraska Medical Center

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Logistical nightmare.

Four surgeons provided a representative population of prostate cancer patients undergoing surgery.

Inclusion Criteria:
- Diagnostic 3Tesla prostate mpMRI prior to radical prostatectomy
- No history of neoadjuvant or adjuvant therapy
- At least two years of follow-up following surgery, via postoperative serum PSA

Exclusion Criteria:
- Received radiation therapy or additional therapies after radical prostatectomy
Had PSA persistence following radical prostatectomy

Internal Dataset (2 surgeons at UNMC) n= 87	External Dataset 1 (1 surgeon from a referral-based practice) n= 187	External Dataset 2 (1 surgeon from UC Irvine) n= 65

The intersection between prostate cancer and radiomics was in its infancy.

The Use of Magnetic Resonance Imaging-derived Radiomic Models in Prostate Cancer Risk Stratification

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In recent years, the advancement of precise medical imaging has facilitated the establishment of radiomics, a computer-based method of extracting and quantifying subvisual imaging characteristics.[1] These features (ie, qualities of intensity, texture, shape, or wavelet) can be extracted from a variety of medical images (CT, MRI, or positron emission tomography) using advanced mathematical algorithms, aggregated into predictive models via machine learning, and applied to enhance personalized therapies. In the last decade, several studies have highlighted the enormous potential of radiomics in enhancing care for a variety of diseases. These include, but are not limited to, cancers of the gastrointestinal tract

diction beyond initial diagnosis and toward risk stratification, prognostication, and prediction of therapy response.

Of the 218 articles published on MRI-derived prostate radiomics in the last 5 years, 42 (19.3%) have utilized MRI-derived radiomics specifically for prostate cancer risk stratification and prognostication. Prediction of Gleason grade group and adverse pathologies, including seminal vesicle invasion, extraprostatic extension, and lymph node involvement, were primary endpoints in 21 (50%) and 11 (26.2%) published articles from 2017 to 2022. In studies predicting Gleason score, radiomic models differentiated well between Gleason score risk groups and in predicting Gleason grade group upgrading (ROC AUC 0.63-0.89).[2,3] Studies predicting adverse pathology also yielded

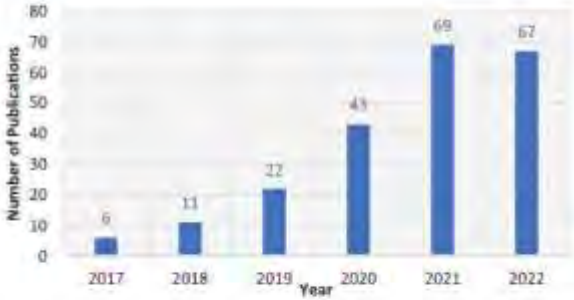

Figure. Number of prostate cancer radiomics publications from 2017 to 2022.

have included external validation of their radiomic models, and it is clear that further exploration is required before clinical integration can be considered.

As an MD/PhD scholar at the University of Nebraska Medical

sponse. Given the high heterogeneity of prostate cancer, the quantitative characterization of tumor heterogeneity and identification of imaging-based biomarkers may enable disease-tailored treatment planning. Direct application


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