Radiomics and the Coming Pan-Omics Revolution

University of Michigan Medical School

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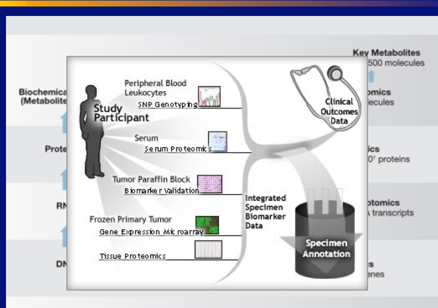
The "-Omics" World I

- **Definition:**
  - A field of study in biology ending in –omics (genomics, transcriptomics, proteomics or metabolomics)
- **Objective:**
  - Collective characterization and quantification of pools of biological molecules that translate into the structure, function, and dynamics of an organism(s)

Wikipedia.org

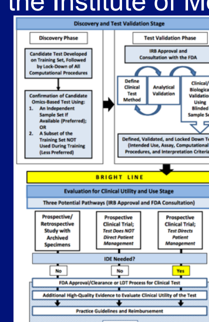
The "-Omics" World II

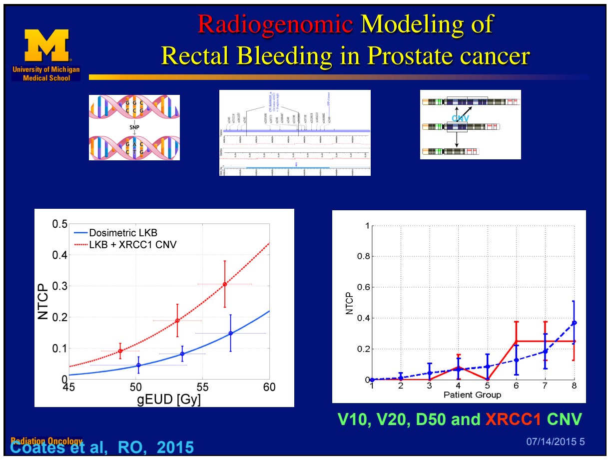


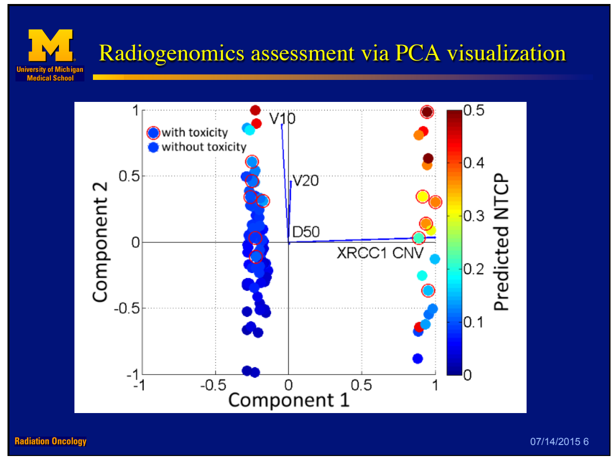
www.iupui.edu

Omics-Based Test Development Process

- According to the Institute of Medicine (IOM):







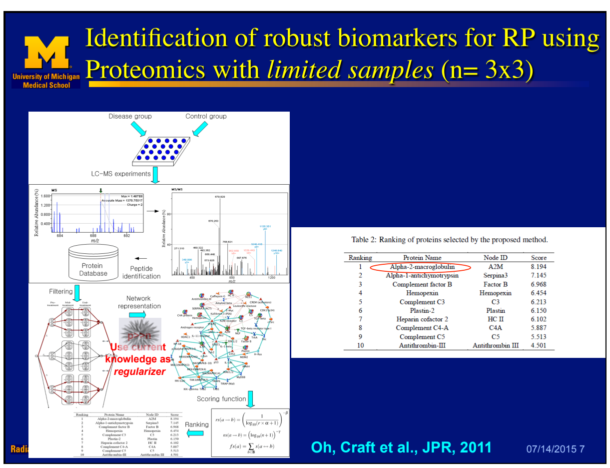
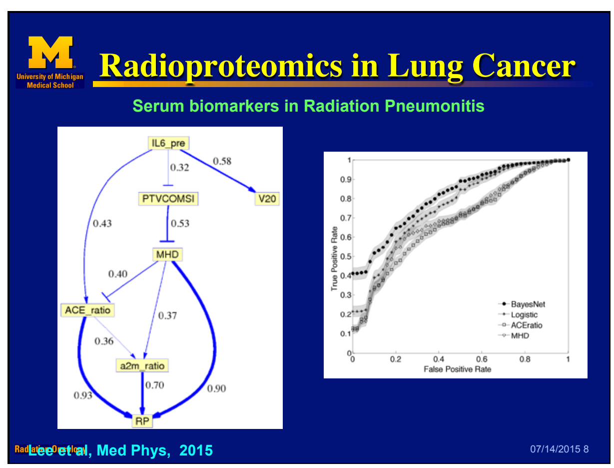
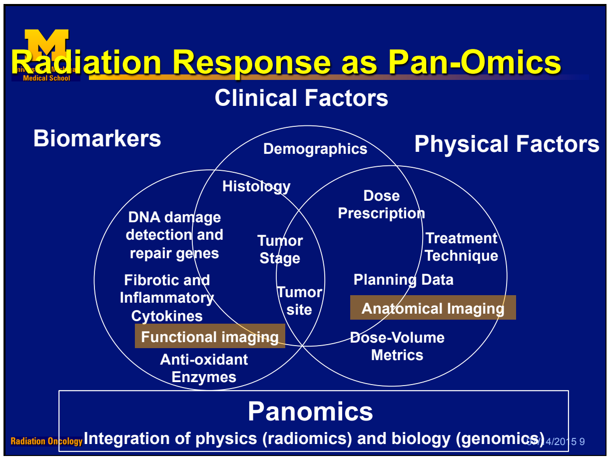
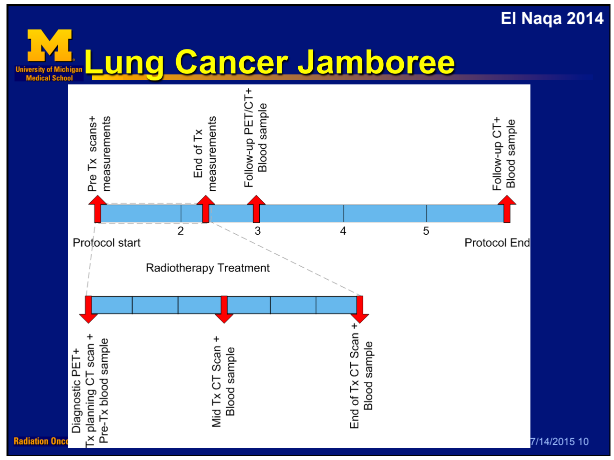


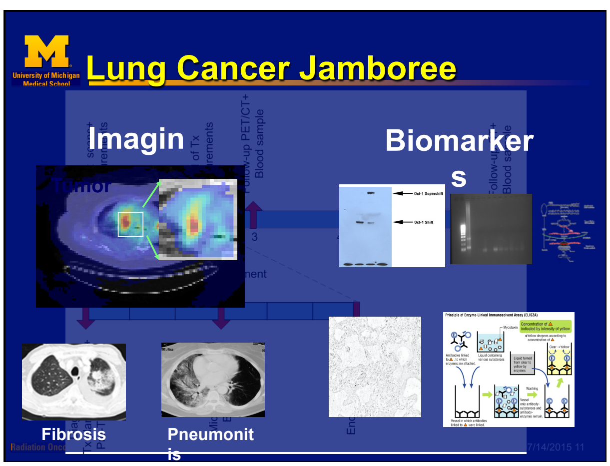
Table 2: Ranking of proteins selected by the proposed method.

Ranking	Protein Name	Node ID	Score
1	Alpha-2-macroglobulin	A2M	8.194
2	Alpha-1-antichymotrypsin	Serpina3	7.145
3	Complement factor B	Factor B	6.968
4	Hemopexin	Hemopexin	6.454
5	Complement C3	C3	6.213
6	Plastin-2	Plastin	6.150
7	Heparin cofactor 2	HC II	6.102
8	Complement C4-A	C4A	5.887
9	Complement C5	C5	5.513
10	Antithrombin-III	Antithrombin III	4.501



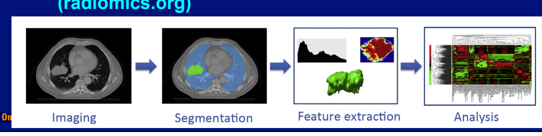






Radiomics

- A 'new' form of –omics
  - Quantitative information from multi-imaging modalities (PET, CT, MRI, etc) could be related to biological and clinical endpoints (Lambin et al, 2012)
  - In oncology, it is decoding the Tumor Phenotype with Non-Invasive Imaging (radiomics.org)



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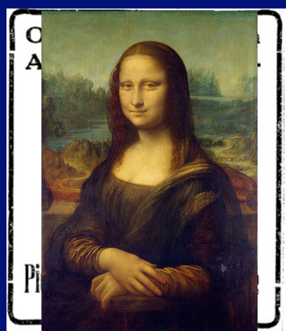
An image worth thousand(s) words



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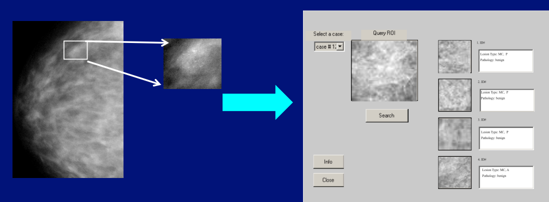
Our early radiomics work



El Naqa, Galatsanos, et al. IEEE TMI, 2002

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El Naqa, Galatsanos, et al. IEEE TMI, 2004

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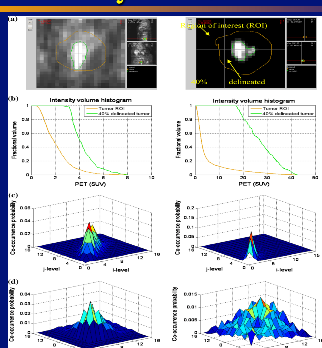
More recently: HNC PET



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El Naqa, Deasy, et al. PMB, 2009

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Common radiomics features

Category	Data	Comments
SUV descriptive measurements	Maximum	The highest single value within the region of interest (ROI)
	Peak	Derived from a circular ROI of 0.75–1.5 cm in diameter centered on the maximum-value pixel; the mean SUV within this ROI is evaluated
	Total lesion glycolysis	Mean SUV by tumor volume
	Other statistics	Mean, minimum, standard deviation, coefficient of variation
Intensity–volume metrics	V_x (5–100 in steps of 5 as percentage of the SUV uptake)	Percentage volume having x% intensity
	I_x (5–100 in steps of 5)	Minimum intensity to x% volume
	Heterogeneity metrics	Difference between I_x and V_x measures
Texture-based features	GLCM	2nd order histogram features (energy, entropy, contrast and homogeneity)
	NGTDM	Higher order histogram features (courseness, contrast, busyness, and complexity)
	RLM	Regional features
	GLSZM	Regional features
Shape-based features	Eccentricity	Geometric and topological characteristics
	Euler number	
	Solidity	
	Extent	
Kinetic parameters	K_1, k_2, k_3, and k_4	Compartment modeling parameters (cf. Fig. 2)
	Metabolic uptake rate (K-FDG)	FDG compartment analysis

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El Naqa, 2014

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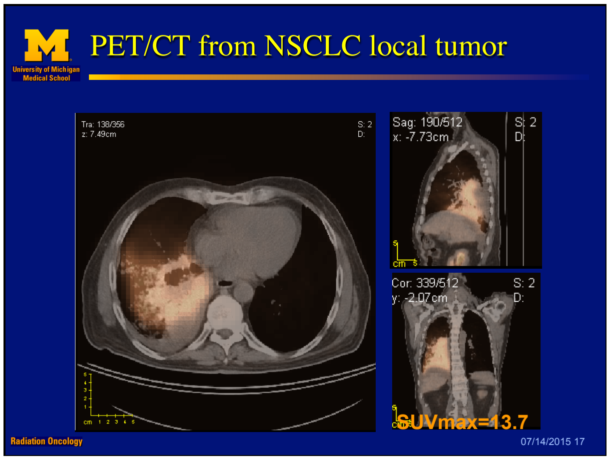
PET/CT from NSCLC local tumor
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Tra: 138/356
z: 7.49cm
Sag: 190/512
x: -7.73cm
Cor: 339/512
y: -2.07cm
SUVmax=13.7
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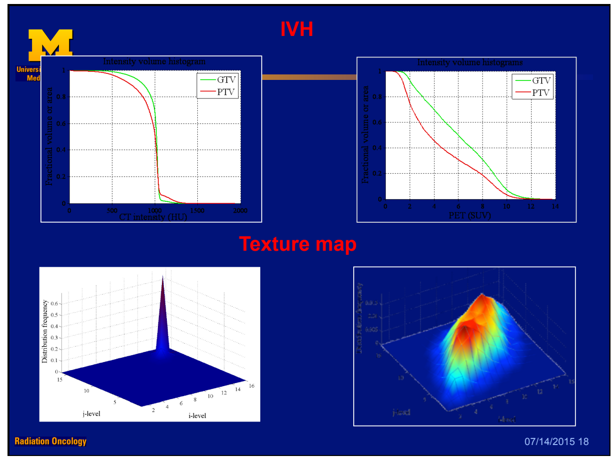
IVH
Texture map
GTV
PTV
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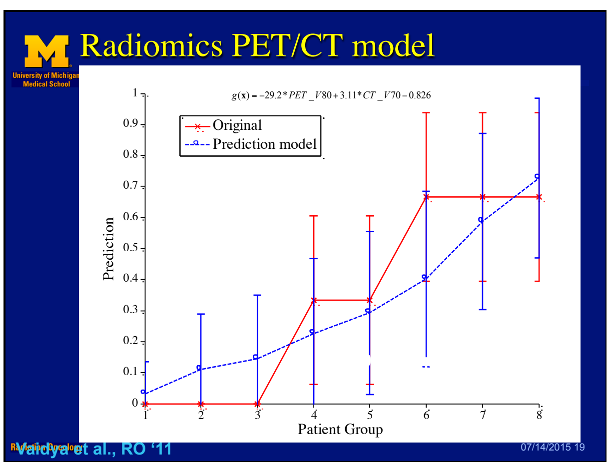
Radiomics PET/CT model
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g(x) = −29.2*PET_V80+3.11*CT_V70−0.826
Original
Prediction model
Prediction
Patient Group
Vaidya et al., RO '11
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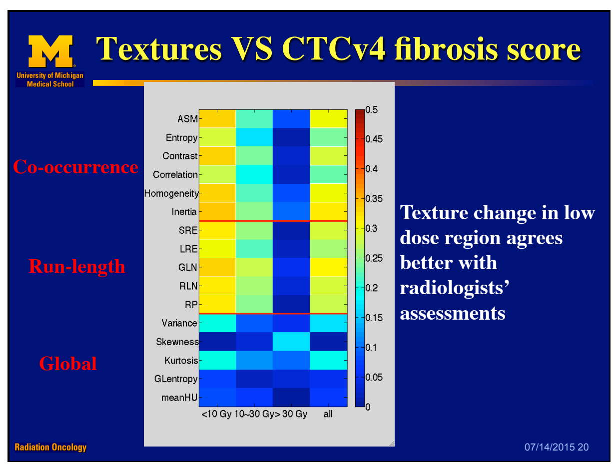
Textures VS CTCv4 fibrosis score
University of Michigan Medical School
Co-occurrence
Run-length
Global
ASM
Entropy
Contrast
Correlation
Homogeneity
Inertia
SRE
LRE
GLN
RLN
RP
Variance
Skewness
Kurtosis
GLentropy
meanHU
<10 Gy 10-30 Gy> 30 Gy all
Texture change in low dose region agrees better with radiologists' assessments
Radiation Oncology
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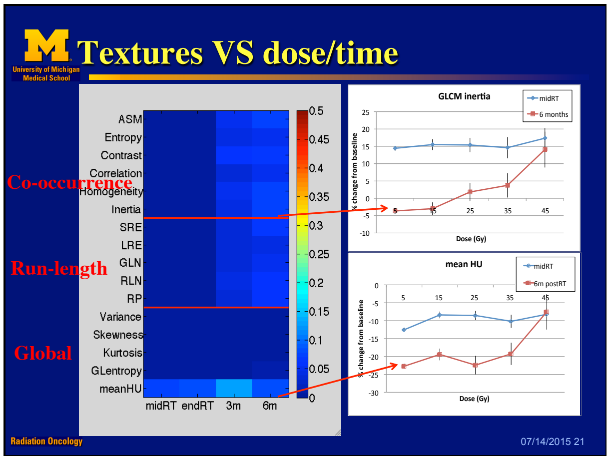
Textures VS dose/time
University of Michigan Medical School
Co-occurrence
Run-length
Global
ASM
Entropy
Contrast
Correlation
Homogeneity
Inertia
SRE
LRE
GLN
RLN
RP
Variance
Skewness
Kurtosis
GLentropy
meanHU
midRT endRT 3m 6m
GLCM inertia
midRT
6 months
% change from baseline
Dose (Gy)
mean HU
midRT
6m postRT
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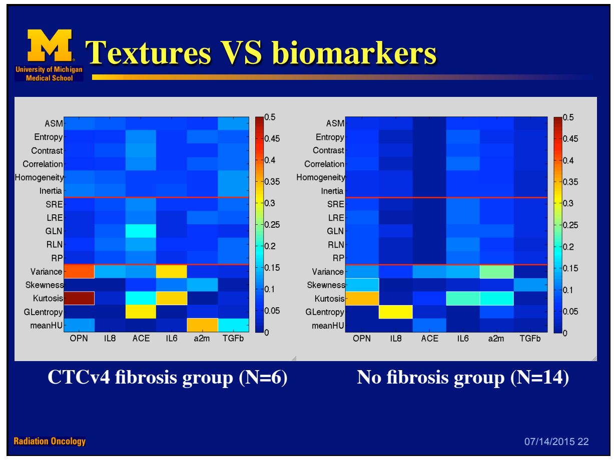
Textures VS biomarkers
University of Michigan Medical School
ASM
Entropy
Contrast
Correlation
Homogeneity
Inertia
SRE
LRE
GLN
RLN
RP
Variance
Skewness
Kurtosis
GLentropy
meanHU
OPN IL8 ACE IL6 a2m TGFb
CTCv4 fibrosis group (N=6)
No fibrosis group (N=14)
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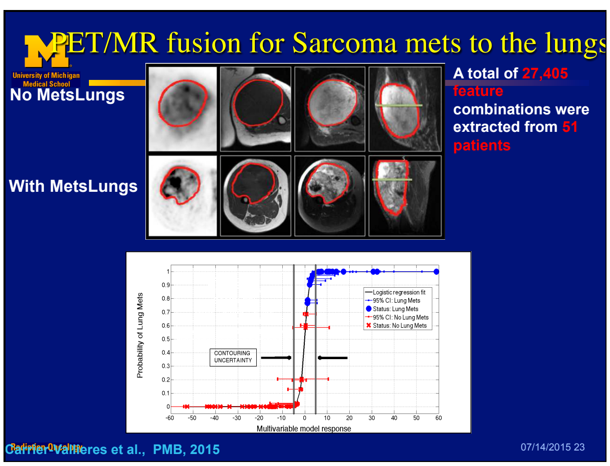
PET/MR fusion for Sarcoma mets to the lungs
University of Michigan Medical School
No MetsLungs
With MetsLungs
A total of 27,405 feature combinations were extracted from 51 patients
Probability of Lung Mets
CONTOURING UNCERTAINTY
Logistic regression fit
95% CI: Lung Mets
Status: Lung Mets
95% CI: No Lung Mets
Status: No Lung Mets
Multivariable model response
Vallières et al., PMB, 2015
Radiation Oncology
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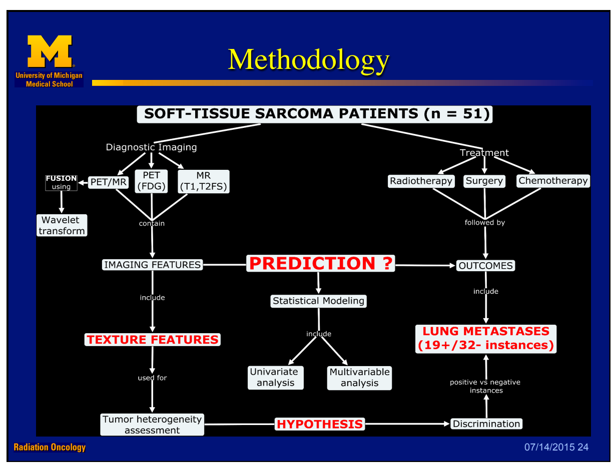
Methodology
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SOFT-TISSUE SARCOMA PATIENTS (n = 51)
Diagnostic Imaging
Treatment
FUSION using
PET/MR
PET (FDG)
MR (T1,T2FS)
Radiotherapy
Surgery
Chemotherapy
Wavelet transform
contain
followed by
IMAGING FEATURES
PREDICTION ?
OUTCOMES
include
Statistical Modeling
include
TEXTURE FEATURES
include
LUNG METASTASES (19+/32- instances)
Univariate analysis
Multivariable analysis
used for
positive vs negative instances
Tumor heterogeneity assessment
HYPOTHESIS
Discrimination
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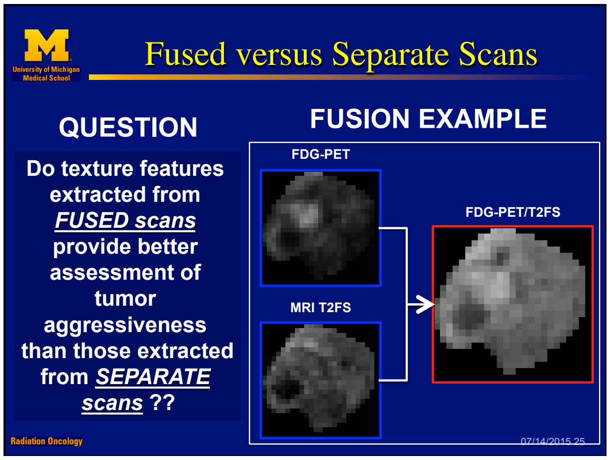
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Fused versus Separate Scans
QUESTION
Do texture features extracted from FUSED scans provide better assessment of tumor aggressiveness than those extracted from SEPARATE scans ??
FUSION EXAMPLE
FDG-PET
MRI T2FS
FDG-PET/T2FS
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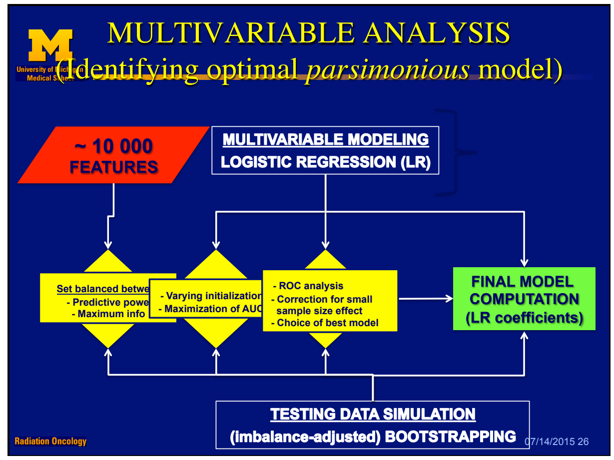
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MULTIVARIABLE ANALYSIS
(Identifying optimal parsimonious model)
~ 10 000 FEATURES
MULTIVARIABLE MODELING
LOGISTIC REGRESSION (LR)
Set balanced betwe
- Predictive powe
- Maximum info
- Varying initialization
- Maximization of AUC
- ROC analysis
- Correction for small sample size effect
- Choice of best model
FINAL MODEL COMPUTATION (LR coefficients)
TESTING DATA SIMULATION
(Imbalance-adjusted) BOOTSTRAPPING
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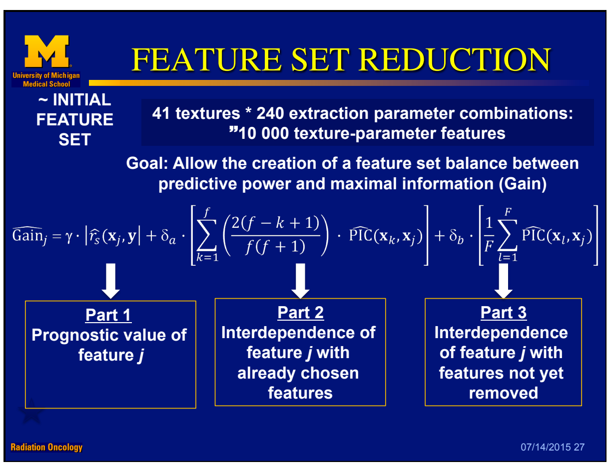
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FEATURE SET REDUCTION
~ INITIAL FEATURE SET
41 textures * 240 extraction parameter combinations: ≈10 000 texture-parameter features
Goal: Allow the creation of a feature set balance between predictive power and maximal information (Gain)
$\widehat{\mathrm{Gain}}_j = \gamma \cdot |\hat{r}_S(\mathbf{x}_j, \mathbf{y})| + \delta_a \cdot \left[\sum_{k=1}^{f} \left(\frac{2(f-k+1)}{f(f+1)}\right) \cdot \widehat{\mathrm{PIC}}(\mathbf{x}_k, \mathbf{x}_j)\right] + \delta_b \cdot \left[\frac{1}{F}\sum_{l=1}^{F} \widehat{\mathrm{PIC}}(\mathbf{x}_l, \mathbf{x}_j)\right]$
Part 1
Prognostic value of feature j
Part 2
Interdependence of feature j with already chosen features
Part 3
Interdependence of feature j with features not yet removed
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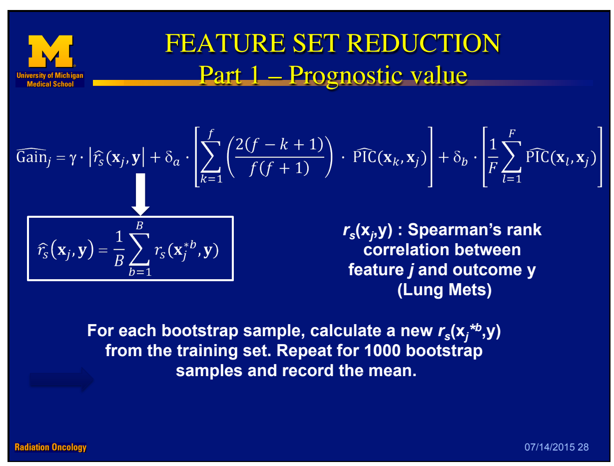
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FEATURE SET REDUCTION
Part 1 – Prognostic value
$\widehat{\mathrm{Gain}}_j = \gamma \cdot |\hat{r}_S(\mathbf{x}_j, \mathbf{y})| + \delta_a \cdot \left[\sum_{k=1}^{f} \left(\frac{2(f-k+1)}{f(f+1)}\right) \cdot \widehat{\mathrm{PIC}}(\mathbf{x}_k, \mathbf{x}_j)\right] + \delta_b \cdot \left[\frac{1}{F}\sum_{l=1}^{F} \widehat{\mathrm{PIC}}(\mathbf{x}_l, \mathbf{x}_j)\right]$
$\hat{r}_S(\mathbf{x}_j, \mathbf{y}) = \frac{1}{B}\sum_{b=1}^{B} r_S(\mathbf{x}_j^{*b}, \mathbf{y})$
$r_s(x_j,y)$: Spearman's rank correlation between feature j and outcome y (Lung Mets)
For each bootstrap sample, calculate a new $r_s(x_j^{*b},y)$ from the training set. Repeat for 1000 bootstrap samples and record the mean.
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FEATURE SET REDUCTION
Part 2 – Interdependence with selected features

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$$\widehat{\mathrm{Gain}}_j = \gamma \cdot \left|\widehat{r_S}(\mathbf{x}_j, \mathbf{y})\right| + \delta_a \cdot \left[\sum_{k=1}^{f}\left(\frac{2(f-k+1)}{f(f+1)}\right) \cdot \widehat{\mathrm{PIC}}(\mathbf{x}_k, \mathbf{x}_j)\right] + \delta_b \cdot \left[\frac{1}{F}\sum_{l=1}^{F}\widehat{\mathrm{PIC}}(\mathbf{x}_l, \mathbf{x}_j)\right]$$

PIC = 1-MIC
Potential information coefficient

$$\boxed{\widehat{\mathrm{PIC}}(\mathbf{x}_k, \mathbf{x}_j) = \frac{1}{B}\sum_{b=1}^{B}\mathrm{PIC}(\mathbf{x}_k^{*b}, \mathbf{x}_j^{*b})}$$

MIC : Maximal Information coefficient (Reshef et al., Science 334, 2011). **Has the ability to capture any simple of complex relationship types of association between two variables (independent to the modeled outcome)**

FEATURE SET REDUCTION
Part 3 – Interdependence with unselected features

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$$\widehat{\mathrm{Gain}}_j = \gamma \cdot \left|\widehat{r_S}(\mathbf{x}_j, \mathbf{y})\right| + \delta_a \cdot \left[\sum_{k=1}^{f}\left(\frac{2(f-k+1)}{f(f+1)}\right) \cdot \widehat{\mathrm{PIC}}(\mathbf{x}_k, \mathbf{x}_j)\right] + \delta_b \cdot \left[\frac{1}{F}\sum_{l=1}^{F}\widehat{\mathrm{PIC}}(\mathbf{x}_l, \mathbf{x}_j)\right]$$

PIC = 1-MIC
Potential information coefficient

$$\boxed{\widehat{\mathrm{PIC}}(\mathbf{x}_l, \mathbf{x}_j) = \frac{1}{B}\sum_{b=1}^{B}\mathrm{PIC}(\mathbf{x}_l^{*b}, \mathbf{x}_j^{*b})}$$

MIC : Maximal Information coefficient (Reshef et al., Science 334, 2011). **Has the ability to capture any simple of complex relationship types of association between two variables (independent to the modeled outcome)**

Model Order Selection

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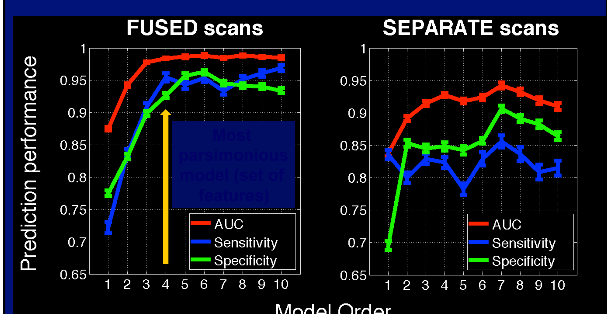

COMPLETE PREDICTION MODEL

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IDENTIFIED SET OF FEATURES

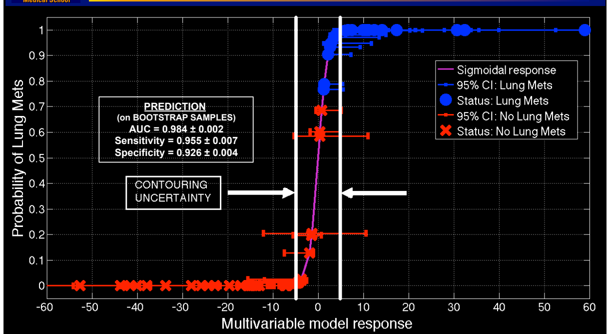
1. **PET/T2FS -- *SZE* : *Small Zone Emphasis* texture extracted on fused PET/T2FS scans**
2. **PET/T1 -- *ZSV*: *Zone Size Variance* texture extracted on fused PET/T1 scans**
3. **PET/T1 -- *HGZE*: *High Gray-Level Zone Emphasis* extracted on fused PET/T1 scans**
4. **PET/T2FS -- *HGRE*: High Gray-Level Run Emphasis extracted on PET/T2FS scans**

FINAL MULTIVARIABLE MODEL RESPONSE

g*(x$_i$) = -256 × PET/T2FS -- *SZE
+ 5360 × PET/T1 -- *ZSV*
+ 1.75 × PET/T1 -- *HGZE*
+ 3.16 × PET/T2FS -- *HGRE*
+ 26.7

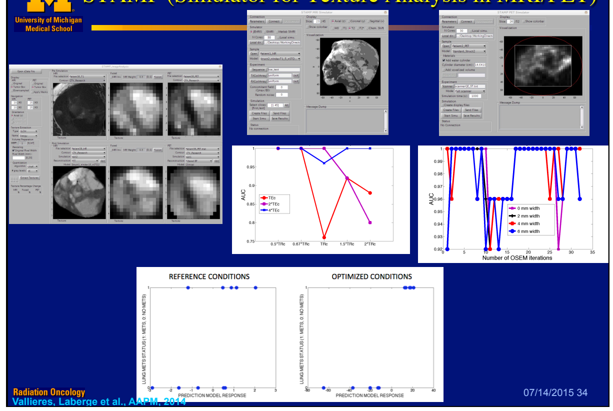
$$\pi(\mathbf{x}_i) = P(y_i = 1 \mid \mathbf{x}_i) = \frac{e^{g(\mathbf{x}_i)}}{1 + e^{g(\mathbf{x}_i)}}$$

PREDICTION MODEL RESPONSE



Carrier-Vallieres et al., PMB, 2015 https://github.com/mvallieres/radiomics

STAMP (Simulator for Texture Analysis in MRI/PET)



Vallieres, Laberge et al., AAPM, 2014

Conclusions

- **Treatment outcomes are multifactorial (Pan-Omics)**
  - **Combination of physical (radiomics) and biological (radiogenomics) factors**
- **Radiomics is an essential element of the Pan-Omics world and constitute a powerful tool to interrogate wealthy imaging imaging information**
  - **Single and multiple modalities**
    - Separate and fused
- **Radiomics involves two main steps**
  - **Robust feature extraction**
  - **Robust modeling**

ACKNOWLEDGMENTS

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- **Jan Seuntjens, PhD**
- **Sonia R. Skamene, MD**
- **Sangkyu Lee, PhD candidate**
- **Martin Carrier-Vallieres, PhD Candidate**