Quantitative Imaging in the Post-Genomic Era: Radiomics

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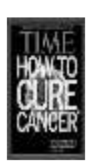
The good news

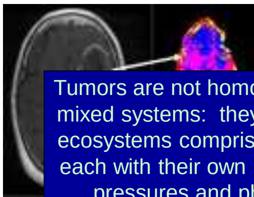
- Due to a tremendous effort, we have a profound understanding of cancer genetics, which can direct the precise use of targeted therapies.

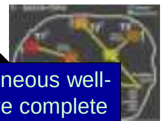
The bad news

- Despite a tsunami of cancer genetic data, Targeted Therapies are not "curing" cancer



Why targeted therapies fail: **Ecology**





Tumors are not homogeneous well-mixed systems: they are complete ecosystems comprised of habitats; each with their own local selection pressures and phenotypes.

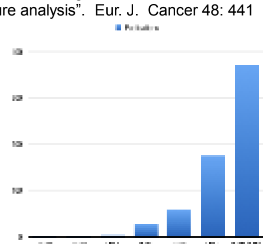
Bob Gatenby

How to Characterize this heterogeneity?

- Hypothesis: Deep analyses of radiographic images (“Radiomics”) can quantify tumor heterogeneity and longitudinally monitor evolutionary dynamical responses to therapy.

2012: First time “Radiomics” in Title:
Kumar et al. (2012) “Radiomics: The Process and the Challenges”. Magn. Reson. Imaging 30:1234
Lambin et al. (2012) “Radiomics: extracting more information from medical images using advanced feature analysis”. Eur. J. Cancer 48: 441

Number of papers with “Radiomics” in the title→



Radiomics: Images are data

Essentially Every Cancer Patient has multiple imaging sessions during the course of detection, diagnosis, therapy monitoring, and survivorship.

Gillies, Kinahan, Hrickah. Radiology 278(2), 563-77 , 2016

Radiomics: Images are data

nature COMMUNICATIONS

ARTICLE

Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach

Hugo J.W.L. Aerts, Emmanuel Rios Velazquez, Ralph T.H. Leijenaar, Chintan Parmar, Patrick Grossmann, Sara Cavalho, Johan Bussink, René Monshouwer, Benjamin Haibe-Kains, Derek Rietveld, Frank Hoebers, Michelle M. Rietbergen, C. René Leemans, Andre Dekker, John Quackenbush, Robert J. Gillies & Philippe Lambin

Artificial intelligence in radiology

Radiomics: Images are data

Cancer


Quantitative Imaging of Cancer in the Post-genomic Era: Radio(geno)mics, Deep Learning and Habitats

CANCER (invited review..192 refs)

Coming soon (H. Aerts corresponding): CA: A Cancer Journal for Clinicians (IF 187)

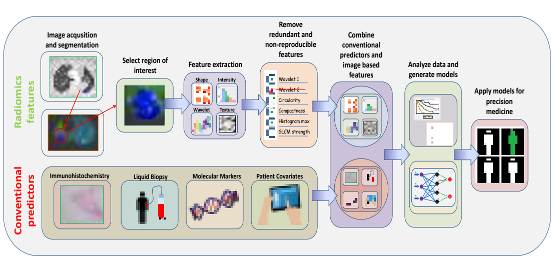
Three "Flavors" of Radiomics

U= user-defined
C= computer-defined

	Segmentation	Features
"Conventional"	U	U
"Habitats"	C	U
"Deep Learning"	C	C

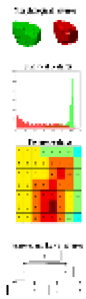
"Conventional" Radiomics

*N.B. Features can be **Agnostic** (Computed) or **Semantic** (Radiologist scored)*



User-Defined Radiomic Features

- Morphological
  - Volume, Surface area, Compactness, Sphericity, Location, Shape
  - Central Necrosis, Spiculation, lobulation, border contrast……
- Statistical Features
  - Mean, Variance, Skewness, Kurtosis, Median, Coefficient of variation, Energy, Root mean square…
- Textural Features
  - Gray level co-occurrence matrix, Grey level size zone matrix, Grey level run length matrix, neighborhood gray level difference matrix, texture spectrum…
- Wavelets and Laws features
- Radial Gradients
- Kullbeck-Leibler Divergence



Reproducibility of Features

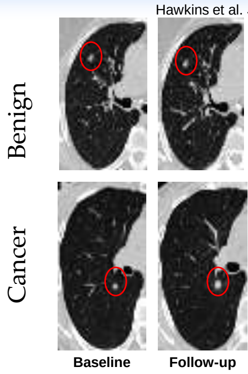
Ilke Tunali

Examples in Lung Cancer:

- Screening
  - (96% false positives currently)
- Prediction → Immune Therapy
  - (Cost/Toxicities)

Screening: Radiomics at Baseline

Hawkins et al. JTO 2016



Volume= 1.51cc
3D wavelet= 49.96
Entropy=4.89
Kurtosis=3.23
3D laws=0.02

Volume=0.2cc
3D wavelet= 0.02
Entropy=0.0001
Kurtosis=0.01
3D laws=0.0009

Radiomics report at initial screening

Radiomics Risk Score

Table 1: Risk Scores for 3 approaches from baseline NLST for predicting subsequent cancer

[illegible]

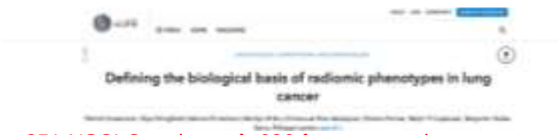
Model	Category	# Malignant	# Benign	Total	Accuracy
Overall	Total	[illegible]	127	185	
Lung-RADS ([illegible])	2	[illegible]	[illegible]	[illegible]	[illegible]
	3	[illegible]	[illegible]	[illegible]	[illegible]
	4A	[illegible]	[illegible]	[illegible]	[illegible]
	4B	[illegible]	[illegible]	4	[illegible]
	Total	[illegible]	127	[illegible]	[illegible]
McWilliams ([illegible])	Low	[illegible]	[illegible]	[illegible]	[illegible]
	Intermediate	[illegible]	[illegible]	[illegible]	[illegible]
	High	[illegible]	[illegible]	[illegible]	[illegible]
	Total	[illegible]	127	[illegible]	[illegible]
Radiomics ([illegible])	Low	[illegible]	[illegible]	[illegible]	[illegible]
	Intermediate-Low	[illegible]	[illegible]	[illegible]	[illegible]
	Intermediate-High	[illegible]	[illegible]	[illegible]	[illegible]
	High	[illegible]	[illegible]	[illegible]	[illegible]
	Total	[illegible]	127	[illegible]	[illegible]

[illegible]

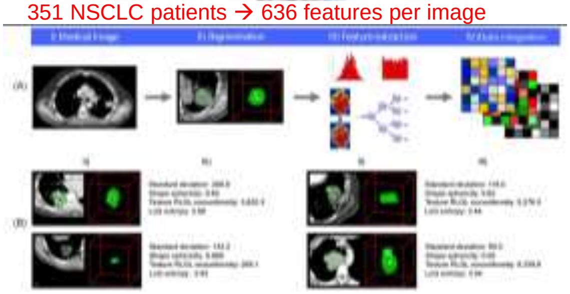
N.B. Radiomics is 93% accurate for 100/185 low and high risk pts.

Hawkins et al., JTO, 2016

Radiomics: Images are data

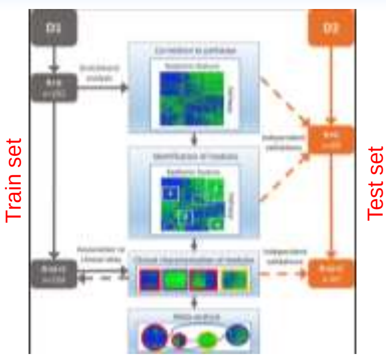


351 NSCLC patients → 636 features per image

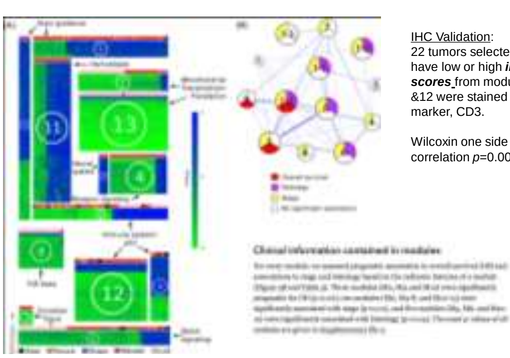


Data Analytics Workflow

R = radiomic
G = genomic
C = clinical



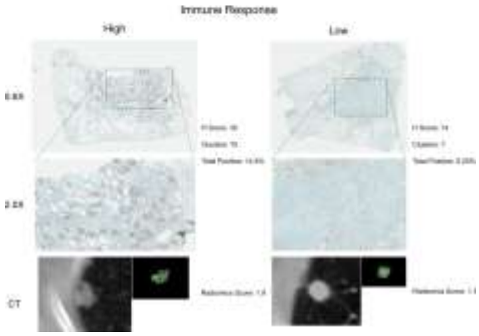
Bi-clustering → 14 "modules"



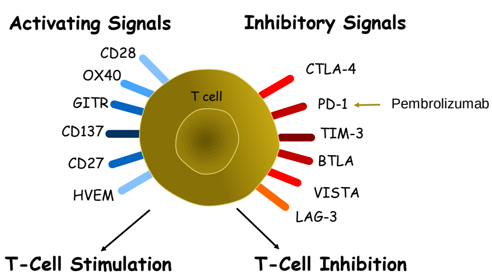
IHC Validation:
22 tumors selected to have low or high ***immune scores*** from modules 2, 9, &12 were stained for T-cell marker, CD3.

Wilcoxin one side correlation p=0.008

IHC Validation for immune infiltration



Immune Modulating Signals



Rizvi. *et al.* IASLC WCLC 2016

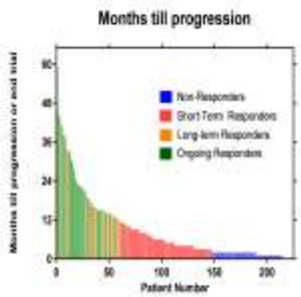
Immunotherapy in NSCLC

The NEW ENGLAND JOURNAL of MEDICINE

NOVEMBER 10, 2016

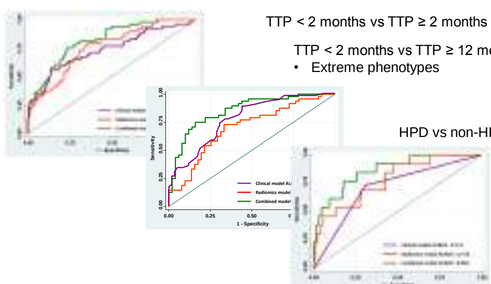
Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

Time to Progression in Moffitt cohort w/ anti-PD1 Ab



Response	# of patients
Non-responders (< 3 months)	74
Short-term responders (> 3 &< 12 months)	93
Long-term responders (> 12 months)	20
Ongoing responders (> 12 months)	41
TOTAL	228

Clinical-Radiomic Models to Predict Time to Progression



TTP < 2 months vs TTP ≥ 2 months

TTP < 2 months vs TTP ≥ 12 months
- Extreme phenotypes

HPD vs non-HPD

Tunali et al. (2018) JTO in review

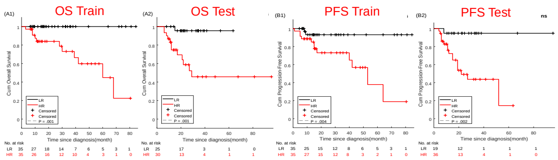
Habitat Imaging

- Distinct physiologies can be imaged in sub-regions of tumors by combining information from multiple imaging modalities.
- PET (metabolism) + CT (attenuation)
- With MR imaging, we typically use:
  - **Contrast enhancement → perfusion**
  - **Diffusion → cell density**
  - **Fluid attenuated → edema**
  - **T2w → anatomy**
- Hypothesis: Habitat imaging can inform tumor heterogeneity and be used for prognosis, prediction, and monitoring of therapy.

Gillies, Grove and Gatenby; Radiology

PET-CT Habitats in Cervical Cancer

- **Patients** (stage IIB~IV)
- **Clinical significance**: Estimate the response of the standard chemo-rad therapy, and identify patients who need more aggressive treatment.
- Habitat imaging features (mutual features from low and high SUV)



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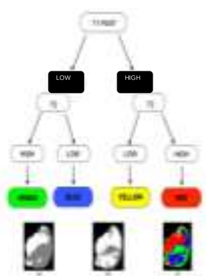
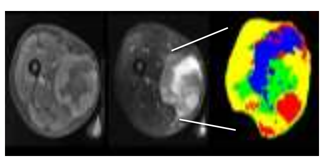
MRI Habitats in Sarcoma





CE T1 habitats

qT2

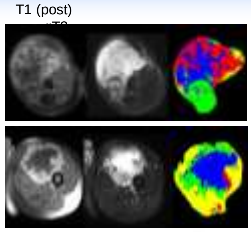
Rahridzadeh H et al. SPIE Medial Imaging. 2016.

Prognosis of Sarcoma

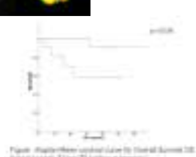
T1 (post)

Case 15. HG Liposarcoma. (alive)

Case 16. HG Rhabdomyosarcoma. (15 mo OS.)



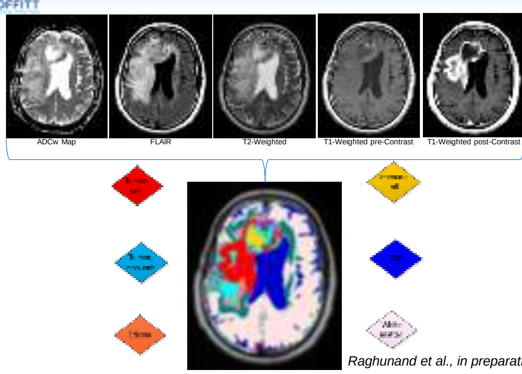
Covariates	OS(*p*)	PFS(*p*)
Age > Median vs Others	0.15	0.23
Grade: High vs Others	0.75	0.81
Longest Dia > 13.5cm (median)	0.15	0.23
Male vs Female	0.70	0.78
Margin: Free vs Positive	0.92	0.85
T1-high/T2 low (yellow) > 18%	0.036	0.05



Schema to define habitats (Otsu)

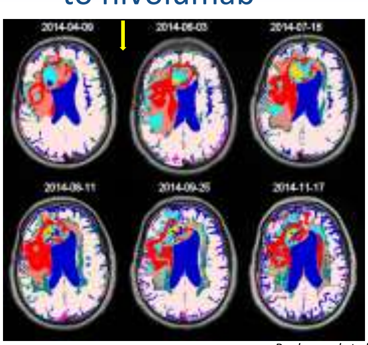
Natarajan Raghunand (Raghu)

Habitats in GBM



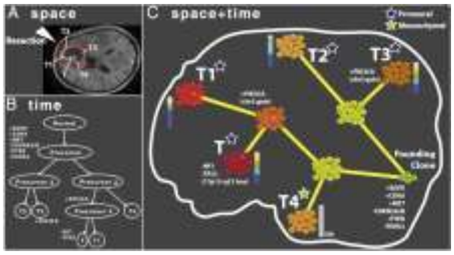
Raghunand et al., in preparation

GBM habitats in response to nivolumab



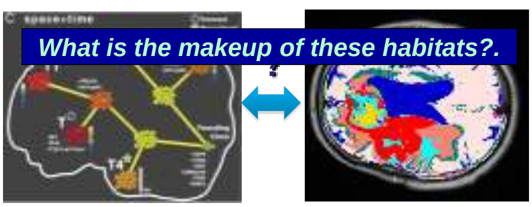
Raghunand et al., in preparation

Genomic heterogeneity in glioma

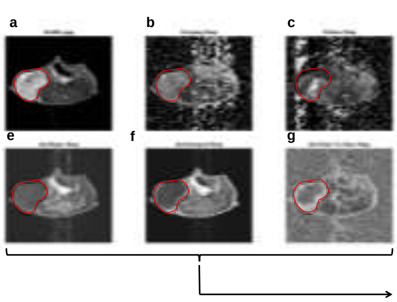


Sottoriva et al. PNAS, 2013

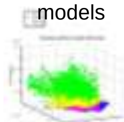
Radiogenomics Challenge:



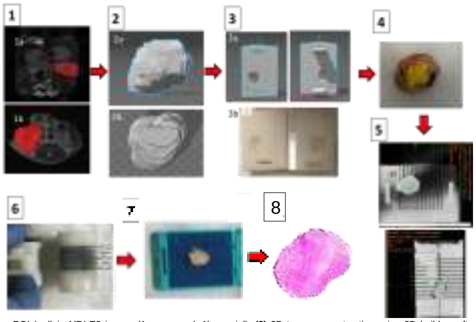
MRI habitats of pre-clinical b.c.



Gaussian mixture models



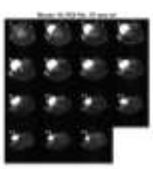
MR-guided Histology



(1) Tumor ROI (red) in MRI T2 image; (1a = coronal; 1b = axial); **(2)** 3D tumor reconstruction using 3D builder software (1a = coronal; 1b = axial) **(3a)** Mold designed in SOLIDWORKS; **(3b)** 3D printer mold **(4)** Tumor was painted to help the orientation; **(5)** CT image showing the tumor into the mold; **(6)** Tumor was cut in slices of 2 mm in thick; **(7)** Each slice was placed into individual

MR-Histology registration

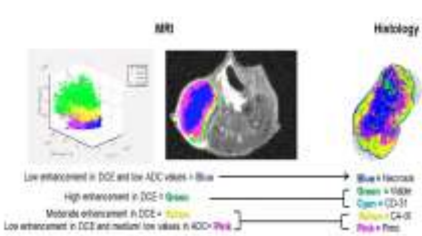
Cut orientations.
Grey is the tumor surface. Planes indicate estimated cutting planes. Black lines are contours from MRI slices.



Histology orientation.
Colors correspond to the contours on the surface presented on the left figure.

Jan Poleszczuk, Bruna J-Perassi

Distinct habitats were identified by MRI and are corroborated by histology



Deep Learning to predict malignant nodules in screening CT

Predicting Malignant Nodules by Fusing Deep Features with Classical Radiomics Features

R. Paul,[1] S.H. Hawkins,[1] M.B. Schabath,[2] R.J. Gillies,[3] L.O. Hall,[1] D.B. Goldgof[1]
[1]University of South Florida, Tampa, Florida, USA
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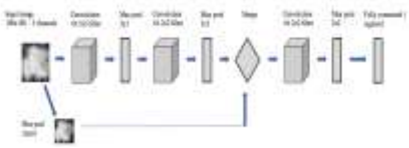


Best accuracy CNN = 76%,
cf. classic features = 80%

The Unreasonable Effectiveness of Data

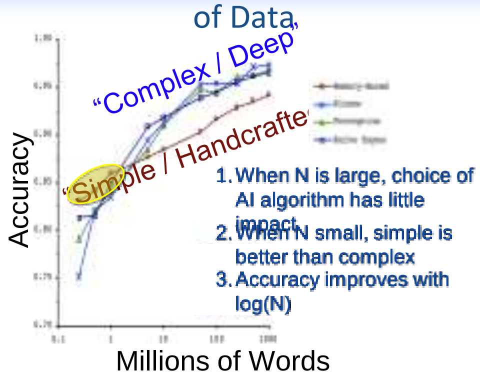
Scaling to Very Very Large Corpora for Natural Language Disambiguation

Michele Banko and Eric Brill
Microsoft Research
1 Microsoft Way
Redmond, WA 98052 USA
{mbanko,brill}@microsoft.com

Transactions of the Association for Computational Linguistics, 2001

Acknowledge Ross Mitchell

The Unreasonable Effectiveness of Data



Conclusions and Challenges

- Conclusion 1: Radiomics of standard of care images can greatly improve prognosis and prediction.
- Conclusion 2: Radiomics is very much a dynamic discipline, with extensions to habitats and deep learning

- Challenge 1: Image harmonization through post-processing.
- Challenge 2: Addition of serum biomarkers for power.
- Challenge 3: Parsimony.
- Challenge 4: Numbers are King, Quality is Queen. Great ***Need for large multi-institutional databases. (distributed learning)***

Clearwater Radiomics
Oct. 15-16, 201
Rachel.Snayd@Moffitt.org

Gillies lab (& friends)