Translation of Quantitative Imaging in Breast Cancer Image Analysis

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Grants and COIs

- Supported in parts by various NIH grants CA 195564 (Quantitative Imaging Network), CA 166945, and CA 189240; and The University of Chicago CTSA UL1 TR000430 pilot awards.
- MLG is a stockholder in R2/Hologic, shareholder in Qview, and receives royalties from Hologic, GE Medical Systems, MEDIAN Technologies, Riverain Medical, Mitsubishi, and Toshiba.
- MLG is scientific advisor, co-founder, and equity holder in Quantitative Insights, makers of QuantX -- the first FDA-cleared machine learning system for aiding in cancer diagnosis.
- MLG is President of SPIE – the international society of photonics and optics, and chair of the QIN executive committee
- It is the University of Chicago Conflict of Interest Policy that investigators disclose publicly actual or potential significant financial interest that would reasonably appear to be directly and significantly affected by the research activities.

Translation of quantitative imaging biomarker applications
from academic centers of excellence
to clinical research applications and, ultimately,
to the practice of precision medicine.

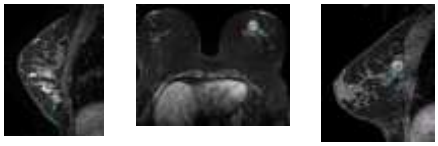
Example: Breast Cancer

What is a quantitative imaging biomarker?

A quantitative imaging biomarker (**QIB**) can be defined as an objectively measured characteristic derived from an in vivo image as an indicator of normal biological processes, pathogenic processes, or response to a therapeutic intervention.

QIBs & Radiomics

- The focus is the quantitative image analysis of images "**clinically & routinely**" obtained on the population.
- We want to ask questions about the relationships between features "seen" in medical images and the biology of cancer so that eventually we can **give the right patient the right treatment at the right time.**



Can we answer these questions by Harnessing Big Data and Quantitative Imaging?

- Tumors are different; can imaging capture the phenotypic differences and the heterogeneity within?
- Is it possible to decide targeted therapy based on imaging-genomics association results?
- Can imaging features inform important genomics features?
- Can integration of imaging and genomics features lead to higher power in prediction?
- Can imaging serve as a virtual digital biopsy?
  - non-invasive, covers complete tumor, & repeatable

How do we Harness Big Data of QIBs?

Two stage process:

- **Discovery stage** – finding **relationships** between imaging data and clinical data, molecular data, genomic data, and outcome data.
- **Application stage** – developing **predictive models** for use in risk assessment, screening, detection, diagnosis, prognosis, therapeutic response, risk of recurrence, etc.

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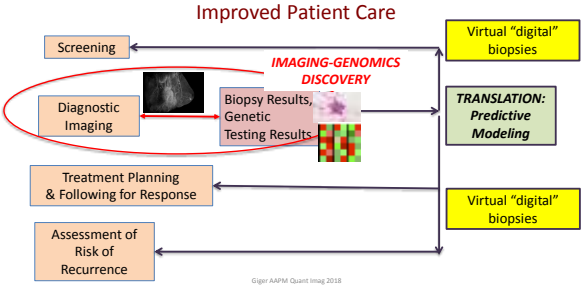
Two Stage Process: Discovery and Predictive Modeling for Improved Patient Care



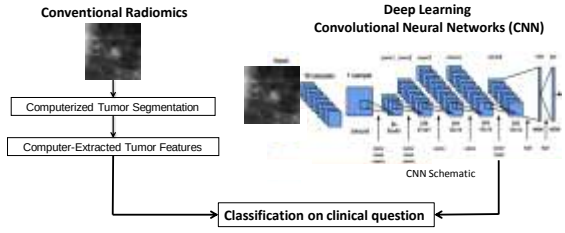
Learning from Actual Biopsies, leading to Virtual Digital Biopsies for Cancer Diagnosis (CADx)

Radiomics and Machine Learning in Breast Cancer Image Analysis

a. Hand-Crafted Radiomics CADx

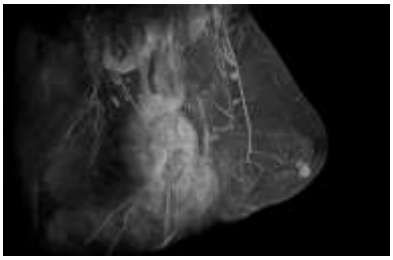
b. Deep Learning-based CADx

Quantitative radiomics in distinguishing between malignant and benign breast lesions -- CADx



Huynh B, Li H, Giger ML: Digital mammographic tumor classification using transfer learning from deep convolutional neural networks. J Medical Imaging 3(3), 034501 (2016).

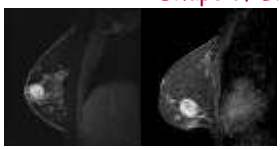
Clinical 3D Breast MRI image



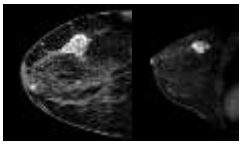
Examples of Quantitative image-based phenotypes

Computer-extracted objective phenotypes from breast MRIs

Shape of Breast Tumors



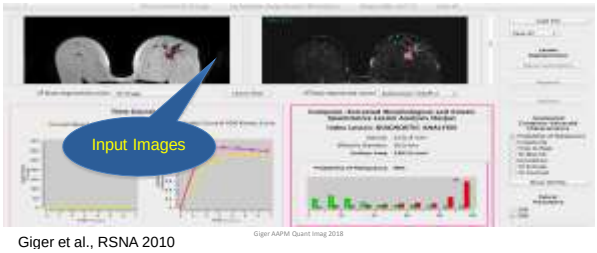
Sphericity: 0.80; 0.85



Irregularity: 0.65; 0.78

Converting Images to Numbers

What do we want from a Quantitative Radiomics Workstation?



Giger et al., RSNA 2010

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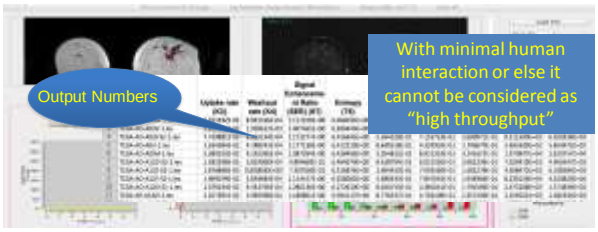
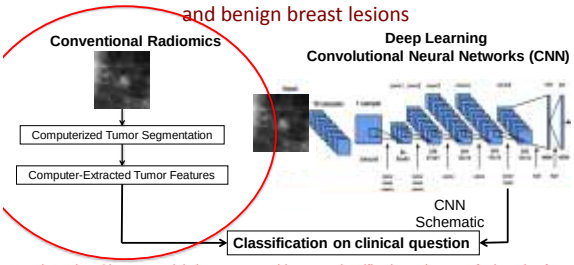


Giger et al., RSNA 2010

Quantitative radiomics in distinguishing between malignant and benign breast lesions



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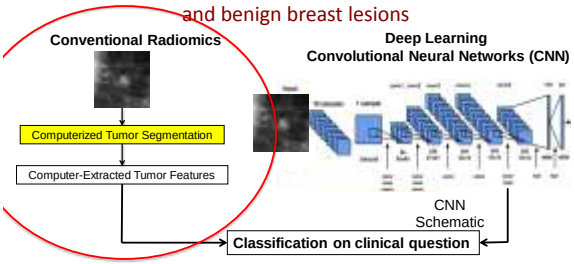
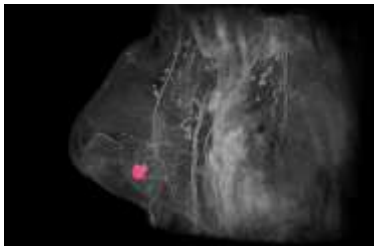


Huynh B, Li H, Giger ML: Digital mammographic tumor classification using transfer learning from deep convolutional neural networks. J Medical Imaging 3(3), 034501 (2016).

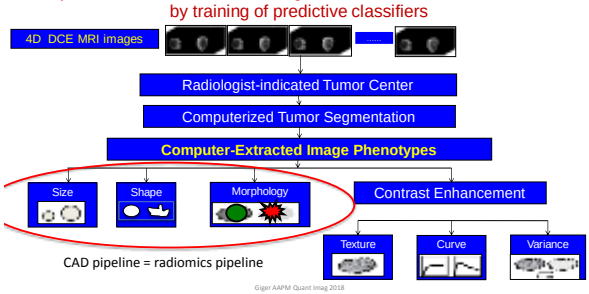
Computer-extracted Breast Cancer on MRI (can analyze as a **virtual digital biopsy** of the tumor)



- non-invasive
- covers complete tumor
- repeatable

Giger AAPM Quant Imag 2018

Computer-extraction of human-designed, lesion-based features followed by training of predictive classifiers



CAD pipeline = radiomics pipeline

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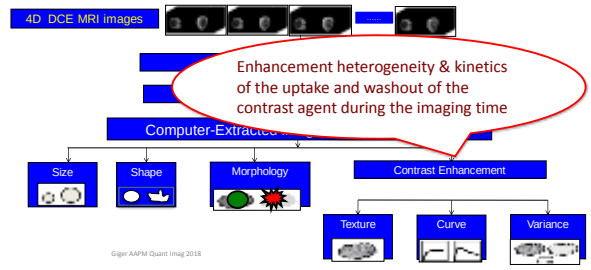

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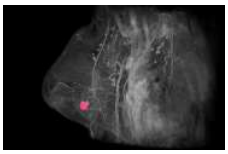
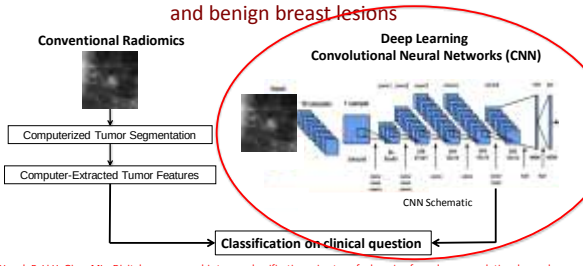
Conventional Mathematically-Engineered Radiomics CADx

- Center of the lesion is indicated
- Followed by automatic lesion segmentation
- After the lesion is segmented, image features (i.e., mathematical descriptors) areextracted from the lesion:
  - Lesion size
  - Lesion shape
  - Intensity features (e.g., average gray level, contrast)
  - Texture within the lesion
  - Margin morphology (e.g., spiculation and sharpness) of the mass
  - Kinetic enhancement features
- Features then **merged by a classifier** (e.g., LDA, SVM) to yield a **signature** indicating an estimate of the likelihood of malignancy



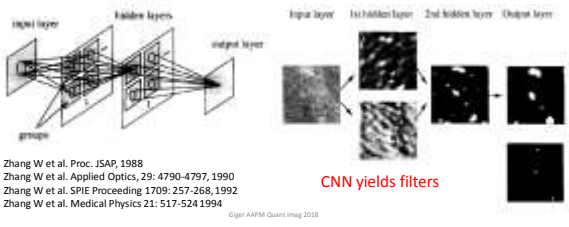
Quantitative radiomics in distinguishing between malignant and benign breast lesions



Huynh B, Li H, Giger ML: Digital mammographic tumor classification using transfer learning from deep convolutional neural networks. J Medical Imaging 3(3), 034501 (2016).

Deep learning example in Breast CADe

Shift-Invariant Artificial Neural Network (SIANN) for CADe in Mammography, Zhang W, Doi K, Giger ML, Wu Y, Nishikawa RM, Schmidt RA. Medical Physics 21: 517-524, 1994



Zhang W et al. Proc. JSAP, 1988
Zhang W et al. Applied Optics, 29: 4790-4797, 1990
Zhang W et al. SPIE Proceeding 1709: 257-268, 1992
Zhang W et al. Medical Physics 21: 517-524 1994

CNN yields filters

Deep Learning and CNNs

- **Learn from Scratch** – requires millions of images
- **Transfer Learning**
  - Apply CNN settings learned from one classification task to another classification task
    - Conduct **fine-tuning** by training only later layers of a pre-trained CNN to a new classification task

    OR
    - Use CNN as a **feature extractor** by extracting features from hidden layers and use a separate classifier (LDA, SVM…) for the classification task.

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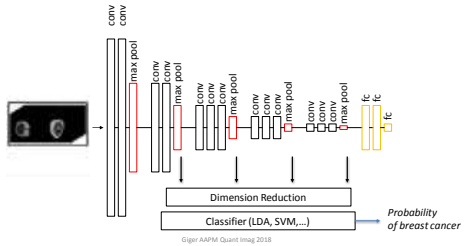
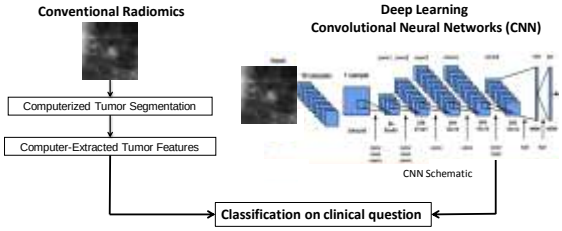
Transfer Learning: **Feature Extractor**

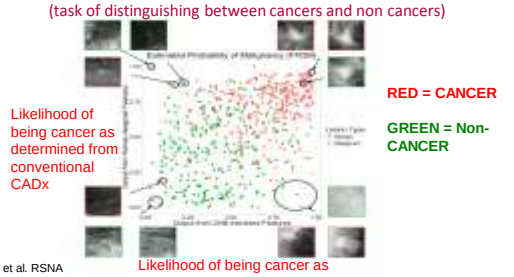


Quantitative radiomics in distinguishing between malignant and benign breast lesions



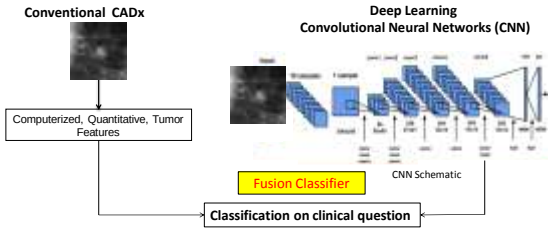
Huynh B, Li H, Giger ML: Digital mammographic tumor classification using transfer learning from deep convolutional neural networks. J Medical Imaging 3(3), 034501 (2016).

Conventional CAD/Radiomics & Deep Learning CAD/Radiomics (task of distinguishing between cancers and non cancers)



Huynh et al. RSNA annual meeting 2016

Conventional CADx vs. CNN CADx in distinguishing between malignant and benign breast lesions



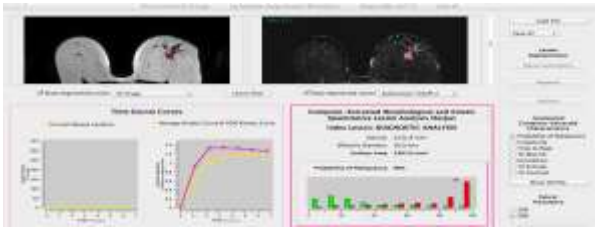
Conventional CADx & Deep Learning CADx
(**diagnostic** task of distinguishing between cancers and non cancers across breast imaging modalities; ROC analysis)

Breast Imaging Modality	Number of Cases	Conventional CADx (AUC)	Deep Learning CNN (AUC)	Combination Conventional CADx & CNN (AUC)
Digital Mammography	245	0.79	0.81	0.86
Ultrasound	1125	0.84	0.87	0.90
DCE-MRI	690	0.86	0.87	0.89

Antropova N, Huynh BQ, Giger ML: A deep fusion methodology for breast cancer diagnosis demonstrated on three imaging modality datasets. Medical Physics online doi.org/10.1002/mp.12453, 2017.

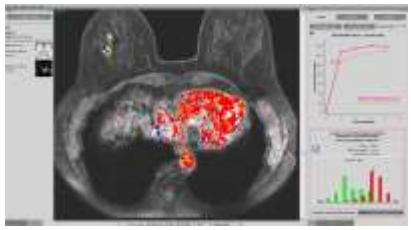
Quantitative Image Analysis Workstation for the High Throughput MRI Phenotyping of Breast Lesions – **DIAGNOSTIC TASKS**

Automated Lesion Segmentation, Feature Extraction [volumetrics, morphological, texture, kinetics] and Estimation of the Probability of Malignancy



Giger et al., RSNA 2010

Example of Translation of Breast CADx from NCI-funded Academic Research to Commercialization & FDA-Clearance for Clinical Use



University → QuantX

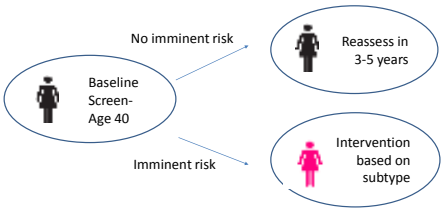
Virtual Digital Biopsies for Cancer Risk Assessment for Personalized Screening Protocols

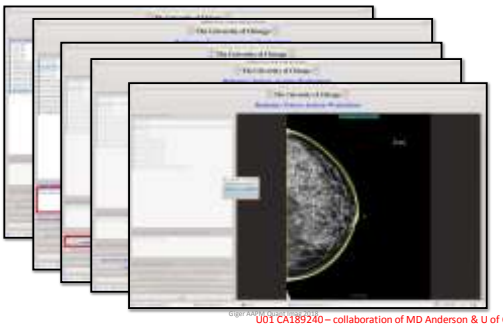
U01 CA189240 – collaboration of MD Anderson & U of Chicago

Current state of breast cancer screening

- One size fits all screening strategy
  - Over screening of many to benefit a few

Ideal future state using Virtual Digital Biopsies

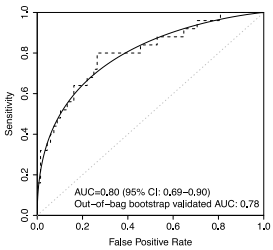




U01 CA189240 – collaboration of MD Anderson & U of Chicago

Evaluate subtype specific discriminatory performance of features: Model Predicting HER2+ Breast Cancer

- Mammographic parenchymal features appear to discriminate between cancers and controls in subtype specific fashion.
- These data suggest opportunity to develop mammographic signatures of risk to guide screening.
- Refine model by integrating blood biomarkers with the QIA signature
  - Prospective validation



Giger AAPM Quant Imag 2018

Virtual Digital Biopsies for Predicting Prognosis

QIN CA 195564: Giger Lab UChicago

Giger AAPM Quant Imag 2018

Extension of CADx: Radiomics in Prognosis: Characterization of Cancer Subtypes (tumor grades)

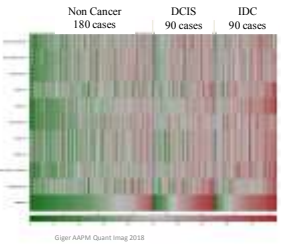
	IDC Grade 3	IDC Grade 2	IDC Grade 1	Benign
Irregularity	0.79	0.50	0.39	0.33
Circularity	0.65	0.81	0.89	0.93
RG	0.0094	0.014	0.020	0.023
Correlation	0.65	0.42	0.66	0.37
MaxCC	0.81	0.46	0.67	0.43
Variance	50.80	74.44	52.82	46.92
Sum Variance	169.84	221.62	197.15	159.98

Bhooshan N, Giger ML, et al: Computerized three-class classification of MRI-based prognostic markers for breast cancer. PMB 45: 5995-6008, 2011

Rapid high-throughput image-based phenotyping yielding a MRI prognostic array

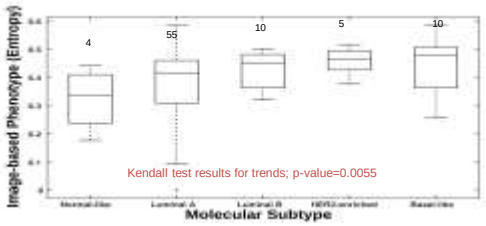
Computer-extracted MRI lesion characteristics —>

Research on correlation between automatically-determined, image-based tumor signatures (phenotypes) and histopathologic data



Giger Lab

From the TCIA Radiomics -- Enhancement Texture of Tumor Heterogeneity appears Predictive of Molecular Subtype – **Clinical Prognostic Value**



Li H, Zhu Y, Burnside ES, ... Perou CM, Ji Y, Giger ML: Quantitative MRI radiomics in the prediction of molecular classifications of breast cancer subtypes in the TCGA/TCIA Dataset. npj Breast Cancer (2016) 2, 16012; doi:10.1038/npjbcancer.2016.12; published online 11 May 2016.

Virtual Digital Biopsies for Predicting Therapeutic Response & Recurrence-free Survival

QIN CA 195564: Giger Lab UChicago

Predicting Risk of Recurrence

Multi-gene assays of risk of recurrence

Radiomics for "virtual" biopsy

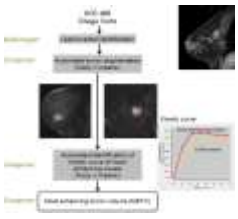
	Good Prognosis Case (left)	Poor Prognosis Case (right)
Cancer Subtype	Luminal A	Basal-like
OncotypeDX Range [0, 100]	14.4 (low risk of breast cancer recurrence)	100 (high risk of breast cancer recurrence)
MammaPrint Range [0.848, -0.748]	0.67 (good prognosis)	-0.54 (poor prognosis)
PAM50 ROR-S (Subtype) Range [-7.42, 71.76]	-2.2 (low risk of breast cancer recurrence)	56.3 (high risk of breast cancer recurrence)
PAM50 ROR-P (Subtype+Proliferation) Range [-13.21, 72.38]	0.96 (low risk of breast cancer recurrence)	53.2 (high risk of breast cancer recurrence)
MRI Tumor Size (Effective Diameter) Range [7.8 54.0]	16.8 mm	21.7 mm
MRI Tumor Irregularity Range [0.40 0.84]	0.438	0.592
MRI Tumor Heterogeneity (Entropy) Range [6.00 6.59]	6.27	6.51

Li H, Zhu Y, Burnside ES, ... Perou CM, Ji Y*, Giger ML*: MRI radiomics signatures for predicting the risk of breast cancer recurrence as given by research versions of gene assays of MammaPrint, Oncotype DX, and PAM50. Radiology DOI: http://dx.doi.org/10.1148/radiol.2016152110, 2016.

Most-enhancing tumor volume by MRI radiomics predicts recurrence-free survival "early on" in neoadjuvant treatment of breast cancer

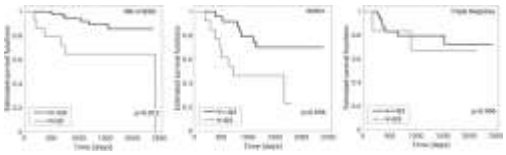
A subset, based on availability, of the ACRIN 6657 dynamic contrast-enhanced MR images was used in which we analyzed images of all women imaged at

- pre-treatment baseline (141 women: 40 with a recurrence, 101 without) and
- all those imaged after completion of the first cycle of chemotherapy, i.e., at early treatment (143 women: 37 with a recurrence vs. 105 without).



Drukker K, Li H, Antropova N, Edwards A, Papaioannou J, Giger ML: Most-enhancing tumor volume by MRI radiomics predicts recurrence-free survival "early on" in neoadjuvant treatment of breast cancer. Cancer Imaging 18:12, 2018

Most-enhancing tumor volume by MRI radiomics predicts recurrence-free survival "early on" in neoadjuvant treatment of breast cancer



Kaplan-Meier recurrence-free survival estimates for METV at the early treatment time point using the highest quartile cut-point (Q3) with corresponding p-values by hormone-receptor status subgroup: hormone-receptor positive and HER2 negative (N=66, left), HER2 positive (N=38, middle), and triple negative (N=36, right) with corresponding p-values (for 2 cases the hormone receptor status was unknown)

Drukker K, Li H, Antropova N, Edwards A, Papaioannou J, Giger ML: Most-enhancing tumor volume by MRI radiomics predicts recurrence-free survival "early on" in neoadjuvant treatment of breast cancer. Cancer Imaging 18:12, 2018

Virtual Digital Biopsies in Breast Cancer Discovery

NCI TCGA/TCIA Breast Phenotype Research Group

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Mapping of Breast MRI Phenotypes to Histopathology and Genomics

Computer-Extracted Phenotypes & Data analysis/associations

University of Chicago
- Maryellen Giger
- Hui Li
- Karen Drukker
- Li Lan

Imaging, Computer Vision, Machine Learning

NorthShore University
- Yuan Ji
- Yitan Zhu
- Wentian Guo

Computational Genetics

NCI:
- Carl Jaffe
- John Freymann
- Erich Huang
- Justin Kirby
- Brenda Fevrier-Sullivan

NCI

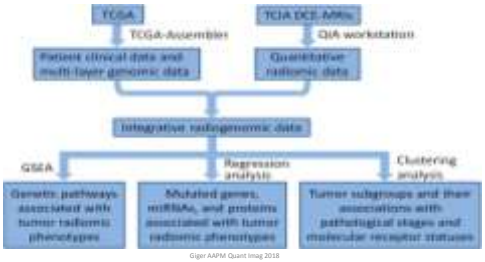
Radiologists:
- Elizabeth Morris – MSKCC
- Ermelinda Bonaccio – Roswell
- Kathleen Brandt – Mayo
- Elizabeth Burnside – U Wisconsin Madison
- Basak Dogan – MD Anderson
- Marie Ganott – Magee
- Jose Net – U Miami
- Elizabeth Sutton – MSKCC
- Gary Whitman – MD Anderson
- Margarita Zuley – U Pittsburgh
- H. Carisa Le-Petross – MD Anderson

Radiologists

Molecular Subtyping & Risk of Recurrence Scores – Univ. North Carolina
- Charles M. Perou
- Katherine A. Hoadley
- Cheng Fan

Cancer Biology

Imaging Genomics Flowchart



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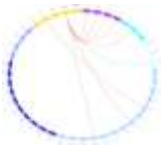
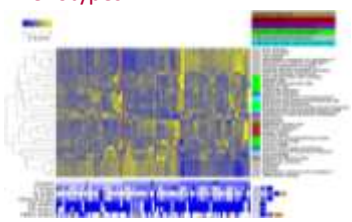
Exploratory Cluster Analysis of the MRI Tumor Phenotypes



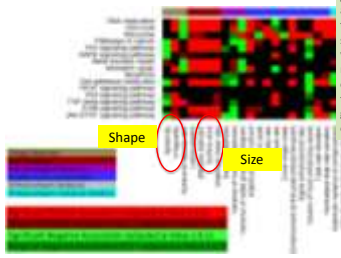


Significant associations between radiomic features and clinical outcomes evaluated by *t*-tests.

- Guo W, Li H, Zhu Y, ..., Giger ML*, Ji Y*: Prediction of clinical phenotypes in invasive breast carcinomas from the integration of radiomics and genomics data. J Medical Imaging 2(4), 041007 (Oct-Dec 2015).
- Zhu Y, Li H, ... Giger ML*, Ji Y*: Deciphering genomic underpinnings of quantitative MRI-based radiomic phenotypes of invasive breast carcinoma. Nature – Scientific Reports 5:17787 (2015)[18]

IMAGING GENOMICS – USING VIRTUAL BIOPSIES

PATHWAY TRANSCRIPTIONAL ACTIVITIES ASSOCIATED WITH MRI QUANTITATIVE F



Transcriptional activities of various genetic pathways were positively associated with tumor size, blurred tumor margin, and irregular tumor shape and that miRNA expressions were associated with the tumor radiomics phenotypes of size and enhancement texture -- suggesting that miRNAs may mediate the growth of tumor and the heterogeneity of angiogenesis in tumor.

Zhu Y, Li H, .. Giger ML*, Ji Y*: Deciphering genomic underpinnings of quantitative MRI-based radiomic phenotypes of invasive breast carcinoma. Nature – Scientific Reports 5:17787 (2015)

Can we answer these questions by Harnessing Big Data and Quantitative Imaging?

- Tumors are different; can imaging capture the phenotypic differences and the heterogeneity within?
- Is it possible to decide targeted therapy based on imaging-genomics association results?
- Can imaging features inform important genomics features?
- Can integration of imaging and genomics featur in prediction?
- Can imaging serve as a virtual digital biopsy?
  - non-invasive, covers complete tumor, & repeatable

Need to include assessment of databases, annotations, testing, standardization, & robustness.

Thank you & Acknowledgements

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