CIBC 2019

Chicago International Breast Course
The Westin Chicago River North
November 1-3, 2019

2019 Chicago International Breast Course

CAD, Radiomics, and AI in Breast Imaging

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- 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, [now Qlarity Imaging] makers of QuantX – the first FDA-cleared machine learning system for aiding in cancer diagnosis.
- 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.

Recent & Current Graduate Students
Joel Wilkie, PhD
Martin King, PhD
Nick Gruszauskas, PhD
Yading Yuan, PhD
Robert Tomek, MS
Neha Bhooshan, PhD
Andrew Jamieson, PhD
Hsien-Chi Kuo, PhD
Martin Andrews, PhD
William Weiss, PhD
Chris Haddad, PhD
Natasha Antropova, PhD
Adam Sibley, PhD
Kayla Robinson, PhD
Jennie Crosby
Isabelle (Qiyuan) Hu
Jordan Fuhrman
Lindsay Douglas

Giger Lab

Research Lab
Karen Drukker, PhD
Hui Li, PhD
Heather Whitney, PhD
Yu Ji, MD
Chun Wai Chan, MS
Li Lan, MS
John Papaioannou, MS
Sasha (Alexandra) Edwards
Summer medical students, undergraduates, and high school students

Over the past 3 decades-- At the University of Chicago, we discover new ways to use computers (AI) to enrich the information extracted from medical images so that radiologists can better find, diagnose, and understand disease (such as cancer

CAD, Radiomics, and AI in Breast Imaging

- 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 **detect/diagnose disease early** and **give the right patient the right treatment at the right time.**

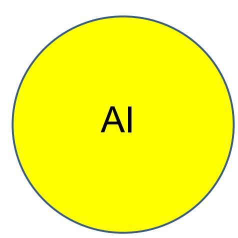
CAD, Radiomics, and AI in Breast Imaging

- What is CAD, Radiomics, & AI?
- Role in breast cancer detection
- Role in breast cancer diagnosis
- Role in breast cancer therapy
- Challenges
- Future

Artificial Intelligence (AI)

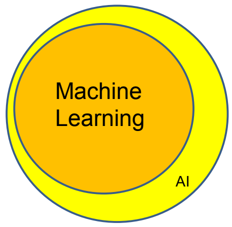
AI is the theory and development of computer systems able to perform tasks that usually require human intelligence, including:
- visual perception
- speech recognition
- decision-making

Examples: expert systems, machine learning, used in CAD



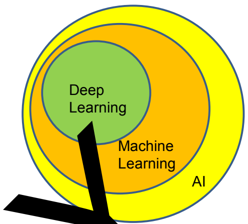
Machine Learning

Machine Learning is a type of artificial intelligence & includes systems that can
- learn from data
- identify patterns
- make decisions with minimal human intervention

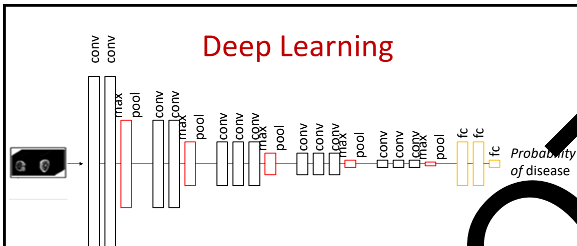


Deep Learning

Deep Learning is a type of machine learning methods based on learning data representations.

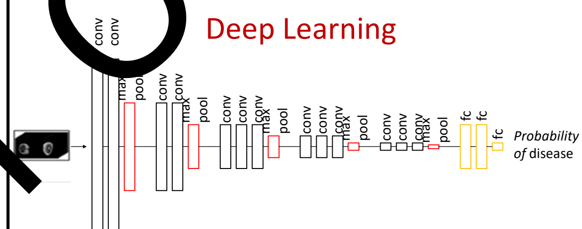


Deep Learning



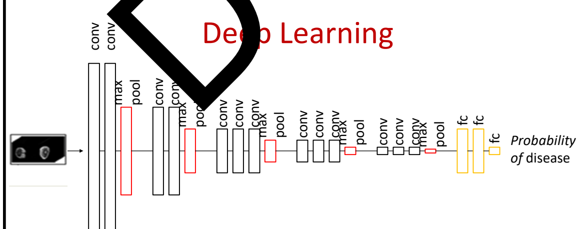
In deep learning, each level learns to transform its input data into a slightly more abstract and composite representation.

Deep Learning



Higher-level concepts are defined in terms of lower-level ones, the hierarchy of such features is called a deep architecture.

Deep Learning



The first representational layer may abstract the pixels and encode edges; the second layer may compose and encode arrangements of edges; the third layer may encode a anatomical patterns; and the fourth layer may recognize that the image contains a disease

Deep Learning and CNNs

- <u>**Learn from Scratch**</u> – requires millions of images
- <u>**Transfer Learning**</u>
  - 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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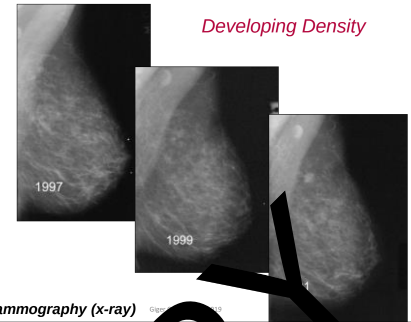
Developing Density



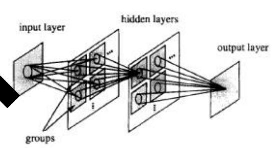
Mammography (x-ray)

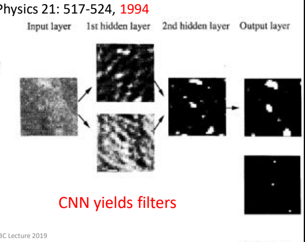
University of Chicago
1994 Prototype System for Computer-Aided Detection

Detection of Mass Lesions & Clustered Microcalcifications

AI/Deep learning example in 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





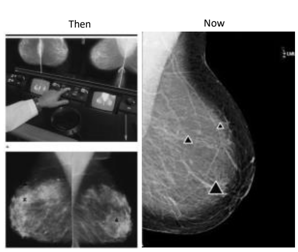
Zhang W et al. Proc. JSAP, 1988
Zhang W et al. Applied Optics, 29: 4790-4797, 1990
Zhang W et al. SPIE Proceeding 1709: 257-268, 1992
Zhang W et al. Medical Physics 21: 517-524 1994

CNN yields filters

CADe: Detection

2001 Prospective Study: increase the detection of early-stage malignancies

Status today: Mean proportion of digital facilities using CADe was 91.4% in 2008 and **92.3% in 2016** → stable usage



Freer et al. *Radiology* (2001)
Keen et al. *J Am Coll Radiol* (2018)

CADe in 3D Breast Cancer Screening

Change from Second Reader to Concurrent Reader

Role in improving efficiency over role in improving radiologists' performance

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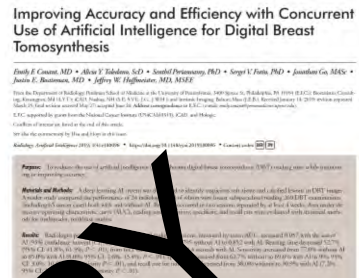
CADe in Automatic Whole Breast Ultrasound

- FDA-approved concurrent-read AI system (QView Medical) for 3D ultrasound
- Reduces ABUS exam interpretation time while maintaining diagnostic accuracy
- Uses deep learning


Interpretation Time Using a Concurrent-Read Computer-Aided Detection System for Automated Breast Ultrasound in Breast Cancer Screening of Women With Dense Breast Tissue

CADe in Breast Tomosynthesis

- FDA-cleared concurrent-read AI for breast tomosynthesis (iCAD PowerLook)
- Improves accuracy and efficiency
- Uses deep learning


Improving Accuracy and Efficiency with Concurrent Use of Artificial Intelligence for Digital Breast Tomosynthesis

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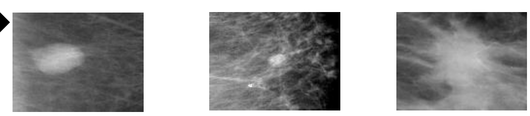
Computer-aided diagnosis in the work-up of suspect lesions: malignant vs. benign lesions

- Use computer output to help characterize (i.e., output descriptors of the lesion) and potentially indicate a computer-determined probability of malignancy of a found lesion
- The final decision on patient management is still made by the radiologist


Benign Malignant Malignant

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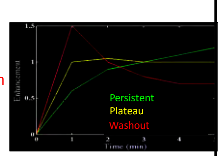
Dynamic Contrast-Enhanced Magnetic Resonance Imaging

- Tumors have increased blood vessels and differ in micro-vascular density and vessel permeability
- Dynamic-Contrast MRI [DCE-MRI]
  - Contrast agent (Gd-DTPA) shortens T1 relaxation time which leads to increase of signal in T1-weighted images
  - Pre-contrast and a series of post-contrast images are obtained to provide functional information regarding lesions



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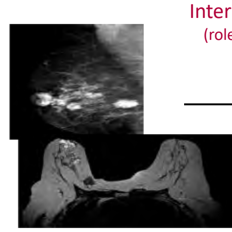
Interpretation of Breast Images
(role for Computer-Aided Diagnosis)



Multiple Digital Medical Images (arrays of numbers) → Both "original" digital images and processed images are displayed on monitors with CADe & some analysis overlays → Interpreted by a radiologist (subjective)

What is the likelihood of cancer and what should be the patient management?

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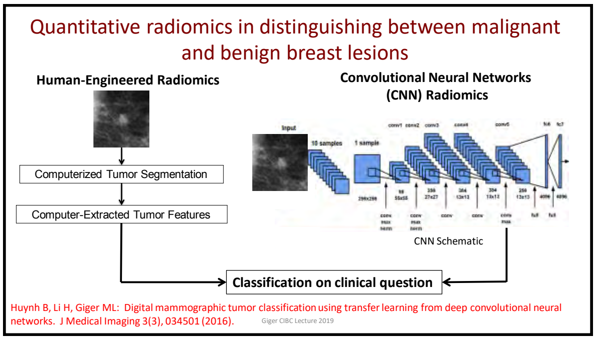
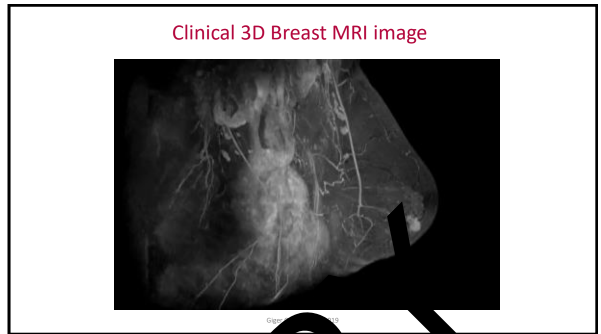
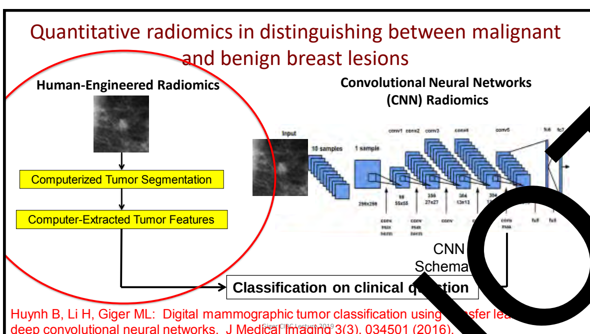
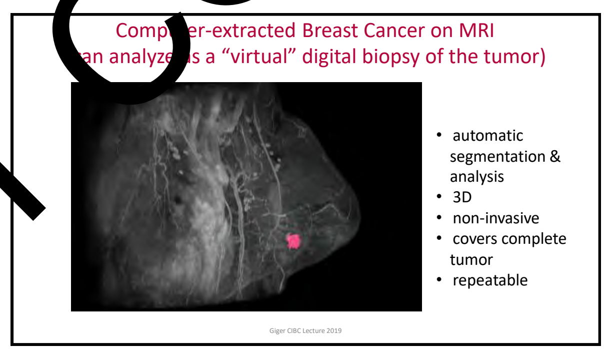
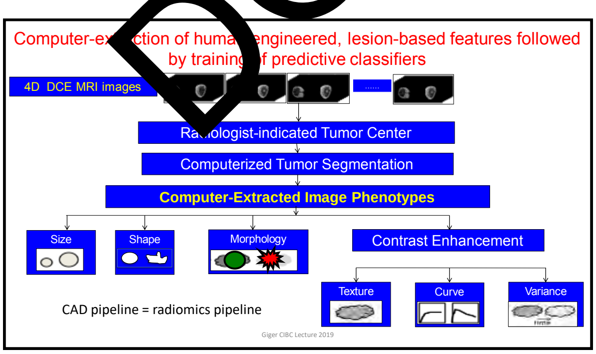
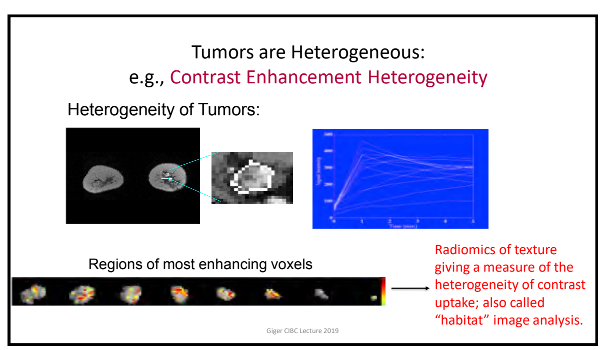






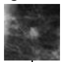






Quantitative radiomics in distinguishing between malignant and benign breast lesions

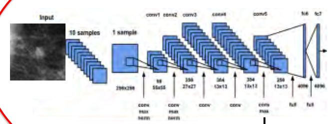
Human-Engineered Radiomics



Computerized Tumor Segmentation

Computer-Extracted Tumor Features

Convolutional Neural Networks (CNN) Radiomics



CNN Schematic

Classification or clinical question

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).

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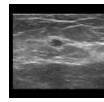
Deep learning example: Transfer Learning for *Feature Extraction*



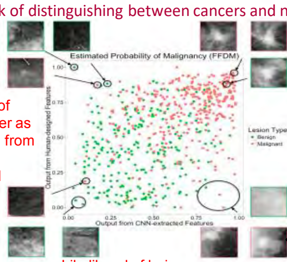
Deep Learning Feature Extraction → Classification (LDA, SVM) → Answer to Clinical Question

- CNNs extract features from entire ROIs without localization or segmentation of lesions.
- Advantage: No lesion segmentation is required
- Advantage: No extraction of segmentation-based features, such as size, shape, margin sharpness, texture, and kinetics

Conventional CAD/Radiomics & Deep Learning CAD/Radiomics

(task of distinguishing between cancers and non cancers)

Likelihood of being cancer as determined from human-engineered CADx



RED = CANCER

GREEN = Non-CANCER

Likelihood of being cancer as determined from deep learning

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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	Human-Engineered CADx (AUC)	Deep Learning CNN (AUC)	Combination Human-Engineered & 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.

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Effect of Three MRI Input Protocols on CNN Performance (Malignant Lesion)

Central slice of the 2nd post-contrast MRI
2-D information

Central slice of the 2nd post-contrast subtraction MRI
2-D information
Temporal information

Maximum intensity projection (MIP)
2-D information
Temporal information
Volume information

Antropova N, Abe H, Giger ML: Use of clinical MRI maximum intensity projections for improved breast lesion classification with deep CNNs J Med Imaging 2018 Jan;5(1):014503.

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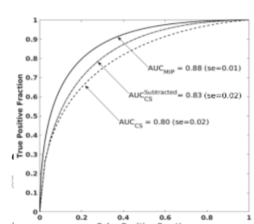
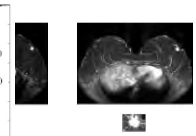
Effect of Three MRI Input Protocols on CNN CADx





2nd post-
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Maximum intensity projection (MIP)
2-D information
Temporal information
Volume information

improved breast lesion classification with deep CNNs J Med Imaging 2018 Jan;5(1):014503.

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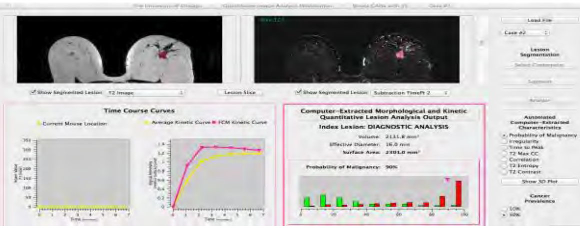
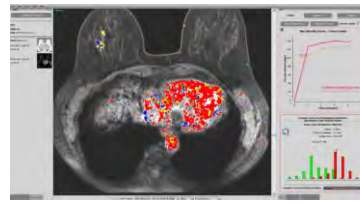
Radiomics/Machine Learning Workstation for the High Throughput MRI Phenotyping of Breast Lesions – DIAGNOSTIC TASKS

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



Giger et al., RSNA 2010

CADx for Breast MRI



QuantX™ Machine Learning for Cancer Diagnosis

Quantitative Insights is now QLARITY IMAGING

First FDA-cleared, machine-learning driven system to aid in cancer diagnosis (de novo clearance)

CADx for Breast Ultrasound

- Koios DS (Decision Support) Breast 2.0 is intended for use to assist physicians analyzing breast ultrasound images.
- Aligns a machine learning-generated probability of malignancy with the appropriate BI-RADS category.
- 510(k) clearance

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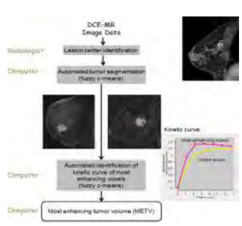
Predicting recurrence-free survival "early on" in neoadjuvant treatment of breast cancer (most-enhancing tumor volume by MRI radiomics)

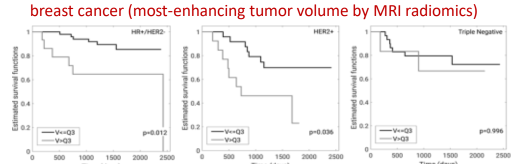
A subset, based on availability, of the ACRIN 6657 dynamic contrast-enhanced MR images was used in which we analyzed images of all women imaged at

- 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

Predicting recurrence-free survival "early on" in neoadjuvant treatment of breast cancer (most-enhancing tumor volume by MRI radiomics)



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

Predicting Risk of Cancer 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.

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How do we Harness this Imaging Big Data?

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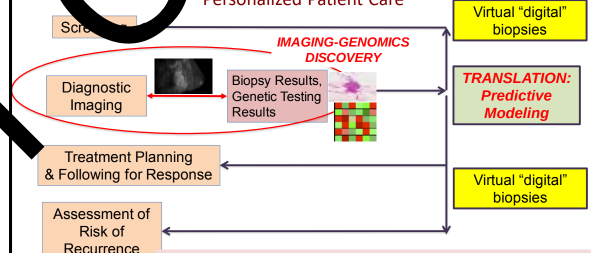
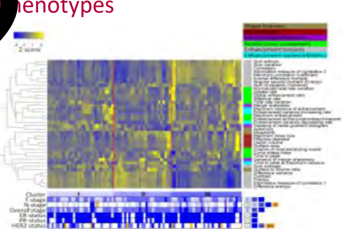
Two Stage Process: Discovery and Predictive Modeling for Personalized Patient Care



Use virtual biopsy for when an actual biopsy is not practical

Giger Lab; U Chicago

Exploratory Cluster Analysis of the MRI Tumor Phenotypes

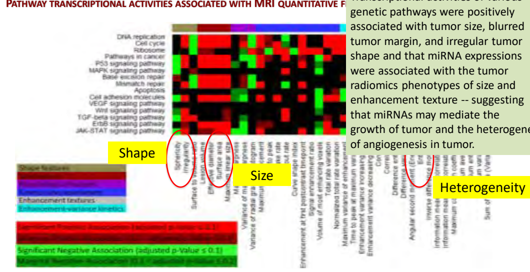


Significant associations between radiomic features and clinical outcomes evaluated by *t*-tests.

- 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)

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)

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Robustness: Concerns

Differences in image acquisition or the population may affect computer-extracted image-based phenotypes

- Manufacturer
- Imaging protocol
- Geographic location
  - Racial differences in disease prevalence and characteristics
- Actual outcome data such as survival may not be available and intermediate alternatives may need to be used

Big data (Standard of care) ↔ Medium data (Clinical trials) ↔ Small data (Pilot studies)

If the sample does not accurately represent the population of interest, statistics are not meaningful.

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Robustness: Radiomics

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- Spatial resolution
- Noise
- System gain

Big data (Standard of care) ↔ Medium data (Clinical trials) ↔ Small data (Pilot studies)

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- Manufacturer
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- Disease prevalence
- Geographical
- Single vs. multiple institutions
- Lack of harmonization

Big data (Standard of care) ↔ Medium data (Clinical trials) ↔ Small data (Pilot studies)

If the sample does not accurately represent the population of interest, statistics are not meaningful.

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Robustness: Radiomics

Differences in image acquisition or the population may affect computer-extracted image-based phenotypes

- Manufacturer
- Imaging protocol
- Geographic location
  - Racial differences in disease prevalence and characteristics
- Actual outcome data such as survival may not be available and intermediate alternatives may need to be used

- Size and distribution of dataset will depend on task
- Quality of annotations; truth

Big data (Standard of care) ↔ Medium data (Clinical trials) ↔ Small data (Pilot studies)

If the sample does not accurately represent the population of interest, statistics are not meaningful.

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Communicating AI to the end user

- Human/Computer Interface
- If radiologists do not find the interface user-friendly, the AI will not be used!
- Explanatory AI

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Chicago International Breast Course
The Westin Chicago River North
November 1-3, 2019

CIBC 2019

Integration into workflow

- Seamless integration of AI into the clinical workflow
- FDA clearance so that the system will be actually used in clinical arena
- "Radiologist has to do a day's work in a day, and not more"

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Future potentials and plans for AI In radiology

AI → Answer to some Biomedical Question → Use as an aid by radiologist (secondary or concurrent reader) / Use as a primary reader / Use in cancer discovery

- Specific Task
  - Clinical question
  - Image formation/reconstruction
  - Workflow enhancement
- Data: Images and truth
- Cautious of "Garbage in, Garbage out"
  - Issue of Robustness

Thank you to Giger Lab

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