AAPM Annual Meeting - 2014
Joint Imaging Education – Quantitative Imaging Symposium:

Genomics and Image-Omics for Medical Physicists

- Image-based Phenotyping and Genomics
  - Maryellen L. Giger, The University of Chicago
- Genetic Association Studies
  - Matthew Cowperthwaite, University of Texas - Austin
- Machine Learning in Image-omics
  - Mia Markey & Nishant Verma, University of Texas - Austin

AAPM Annual Meeting - 2014
Joint Imaging Education – Quantitative Imaging Symposium:

Genomics and Image-Omics for Medical Physicists

Learning Objectives

- Understand what are image-based phenotypes and their potential medical significance
- Learn about genetic studies
- Appreciate the complexity of Big Data

Q/A after completion of all three presentations

Image-based Phenotyping and Genomics

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Supported, in the past, in part by USPHS Grants R01-CA89452, R33-CA113800, P50-CA125183, DOD, and DOE

COI: M L Giger is a stockholder in R2/Hologic, a co-founder and equity holder in Quantitative Insights, and receives royalties from Hologic, GE Medical Systems, MEDIAN Technologies, Riverain Medical, Mitsubishi, and Toshiba

Image-based Phenotyping and Genomics

- What is image-based phenotyping?
- How can relating image-based phenotypes to genomics improve understanding of disease?
- How can Medical Physicists contribute? (a few examples)
  - Standardization (harmonization)
    - QI biomarkers
    - Big data (many data) from clinical practice vs. Limited cases from controlled QI clinical studies
    - QC/QA
  - Mathematical & computational expertise
    - CAD, QIA, modeling
  - System evaluation methods
- What resources are available?

Definition of a Phenotype

- The observable physical or biochemical characteristics of an organism, as determined by both genetic makeup and environmental influences.
- The expression of a specific trait, such as stature or blood type, based on genetic and environmental influences.

What is Genomics?

- Genomics is a discipline in "genetics that applies recombinant DNA, DNA sequiencing methods, and bioinformatics to sequence, assemble, and analyze the function and structure of genomes (the complete set of DNA within a single cell of an organism"
  - National Human Genome Research Institute (2010-11-08); A Brief Guide to Genomics

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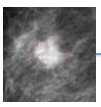
Decoding Disease with Image-based Phenotyping and Genomics

Involves *interdisciplinary* research:

- Development and/or customization of mathematical image analysis methods for extracting **information** from biomedical image data (computer vision) - *developed from CAD research*
- Investigations in the applications of these techniques to gain **knowledge** in (a) the ***management of the patient*** and in (b) the ***understanding of disease/normal***



Quantitatively Extract Lesion Characteristics (Computer Vision)

Patient-Specific Image-based Tumor Signature for Precision Medicine

Data-mining of Computer-Extracted Features on Large Datasets for **Population-based** Cancer Discovery

Imaging Genomics

Asks questions about the relationships between features "seen" in medical images and the biology of cancer

Data Sources

Medical Images

Histopathology, Molecular Classification

Genomics

Computer Segmentation of Lesions

Radiologist Descriptors

Computer-extracted Lesion Features (size, morphology, texture, kinetics)

Lead to Personalized Screening and Personalized Treatment

Which correlate and which are complementary?

Associations and/or Classification Relevant to Clinical or Biological Questions

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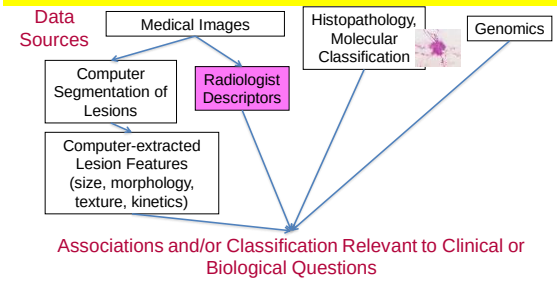
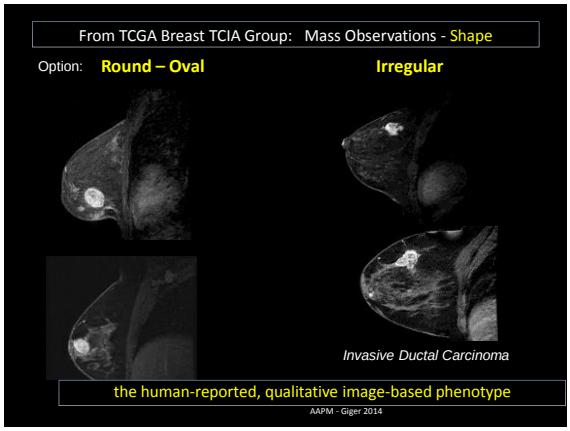
Asks questions about the relationships between features "seen" in medical images and the biology of cancer



AAPM - Giger 2014



Imaging Genomics

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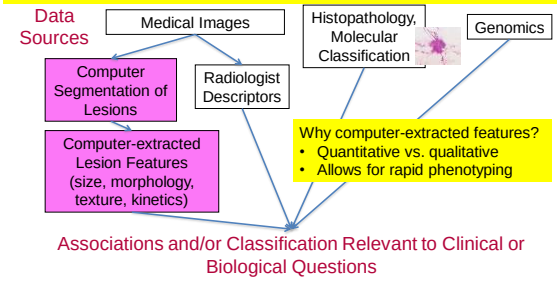

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Examples of Image-Based Phenotypes

- Lesion size (RECIST, volume) on CT
- Characterization of parenchyma texture
- Margin irregularity and sharpness
- Kinetic characterizaton (uptake, washout)
- SUV on nuclear medicine images

How to obtain computer-extracted quantitative descriptors?

- Draw from current fields using quantitative image analysis (QIA)
- CADe – computer-aided detection
- CADx – computer-aided diagnosis
- QIBs – quantitative imaging biomarkers - The measurements of anatomical, physiological, and biochemical states of the body through medical imaging (QIBA).

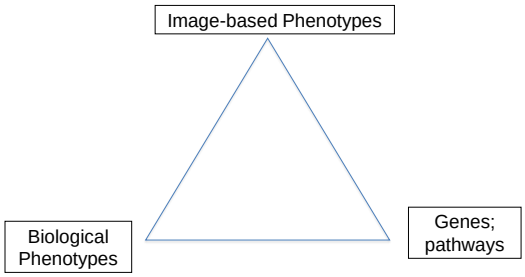
Example Studies Relating Image-based Phenotypes to Disease (e.g., breast, brain)

- Cancer subtypes
  - IDC vs. DCIS (vs. benign)
  - Supervised vs. unsupervised dataming
- Disease stage
  - Invasive vs. non-invasive
  - Metastatic (lymph node involvement)
- Molecular classification
  - ER- vs. ER+, triple negative
- Genetic classification
  - BRCA1/BRCA2 gene
  - UGT2B gene
- Genomics
  - Pathways

How do we relate image-based phenotypes to genes?

- Will learn how scientists related biological phenotypes (e.g., expressions) to genes from Dr. Cowperthwaite
- Need large datasets – big data
  - Problem: we don't have the images!
- How can we exploit existing phenotype-genotype knowledge?

Using Established Knowledge and Relationships



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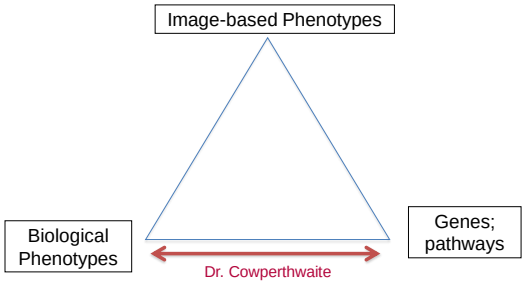

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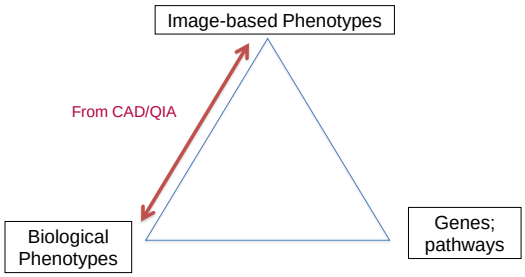

Examples: relating image-based phenotypes to biological phenotypes ("gene expression")

- Predicting breast cancer subtype and potential outcome
  - Relating image-based phenotypes to stage
  - Relating image-based phenotypes to molecular classification
  - Breast Cancer (TCGA/TCIA)
- Predicting response
  - Lung cancer
  - Brain disease– Mia Markey

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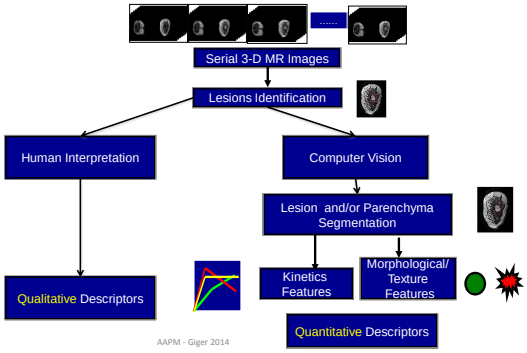
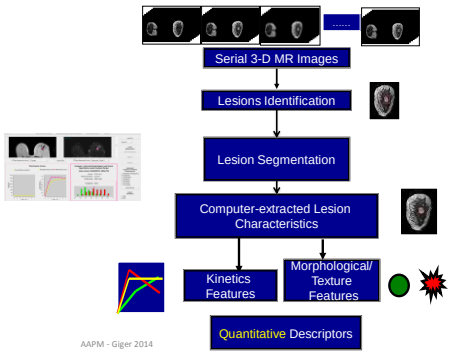
CADx/QIA in Image-based Phenotyping



CADx/QIA in MRI-based Phenotyping



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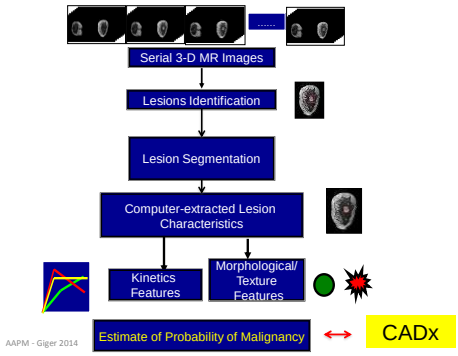

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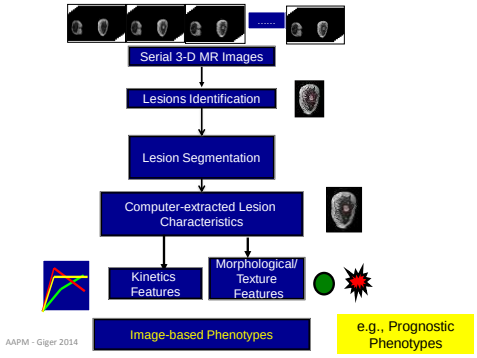


Data mining & Visual Representations of Breast Ultrasound Tumor Features in Cancer Discovery Research

Using Unsupervised t-SNE Dimension Reduction, the computer "learned" the relationships between the cases. (similar to data mining of genomics big data) to discover relationships and/or similar cases

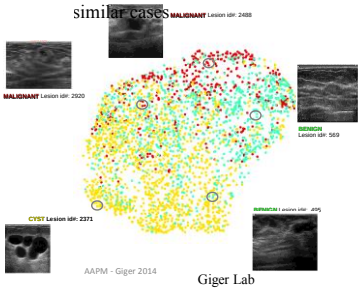
81D → 2D

1126 Cases (2956 Images)

- Benign Mass
- Benign Cystic
- Malignant

Cloud Computing on Beagle

Jamieson et. al Medical Physics (2010)



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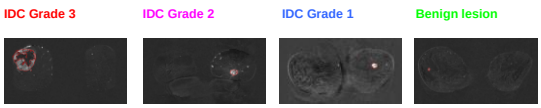
Characterization of Cancer Subtypes based on Tumor Grade

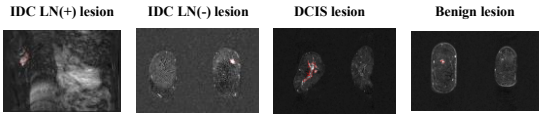


	IDC Grade 3	IDC Grade 2	IDC Grade 1	Benign
Irregularity	0.79	0.50	0.39	0.33
Circularity	0.65	0.81	0.89	0.93
RG	0.0094	0.014	0.020	0.023
Correlation	0.65	0.42	0.66	0.37
MaxCC	0.81	0.46	0.67	0.43
Variance	50.80	74.44	52.82	46.92
Sum Variance	169.84	221.62	197.15	159.98

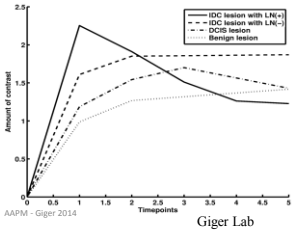
AAPM - Giger 2014

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

Characterization of Cancer Subtypes based on Lymph Node Status



Characteristic Kinetic Curves:

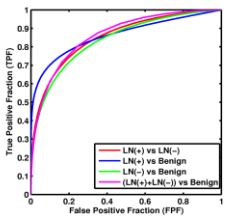


Bhooshan, Giger et al: Image-based Prognostic Markers from Computerized Characterization of a Clinical Breast MRI Database. Radiology 254: 680-690, 2010

Giger Lab

Performance of Computer-extracted MRI Phenotypes in Distinguishing Subcategories

Subcategories	AUC ± SE
IDC lesions with LN(+) vs. IDC lesions with LN(-)	0.85 ± 0.04
IDC lesions with LN(+) vs. Benign	0.86 ± 0.03
IDC lesions with LN(-) vs. Benign	0.83 ± 0.03
Cancer [IDC lesions with LN(+) and LN(-)] vs. Benign	0.84 ± 0.06



Number of lesions: 54 LN(+), 64 LN(-), and 132 Benign

Bhooshan N, Giger ML, Jansen SA, Li H, Lan L, Newstead GM. 'Cancerous Breast Lesions on Dynamic Contrast-enhanced MR Images: Computerized Characterization for Image-based Prognostic Markers" Radiology. 2010 Mar;254(3):680-90.

Database: Molecular Classifications of 168 cases

	Molecular Classification & Cases	
HER2	**HER2-**	**HER2+**
	142	26
ER	**ER-**	**ER+**
	50	118
PR	**PR-**	**PR+**
	75	93
Triple Negative	**Triple Negative**	**All Others**
	40	128

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HER2+ breast cancers tend to be more aggressive and have a poorer prognosis than HER2/neu-negative cancers. However, it is not clear whether HER2/neu status is an independent risk factor.

Database: Molecular Classifications of 168 cases

	Molecular Classification & Cases	
HER2		
ER	**ER-**	**ER+**
	50	118
PR	**PR-**	**PR+**
	75	93
Triple Negative	**Triple Negative**	**All Others**
	40	128

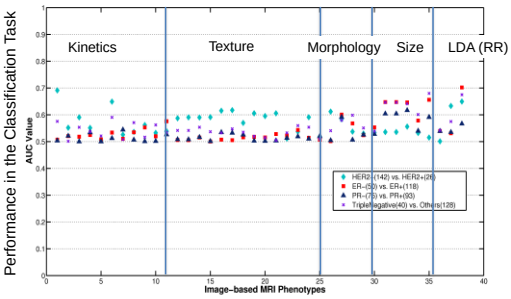
ER+ and PR+ cases have lower risks of mortality compared to women with ER- and/or PR- disease.

Database: Molecular Classifications of 168 cases

	Molecular Classification & Cases	
HER2	**HER2-**	**HER2+**
	142	26
ER		
PR		
	75	93
Triple Negative	**Triple Negative**	**All Others**
	40	128

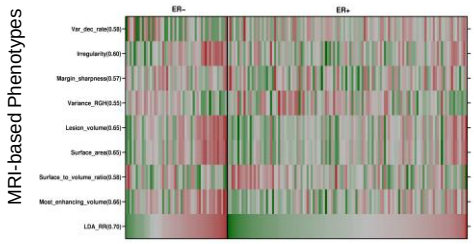
Triple negative cases (HER2-, ER-, PR-) overall do not respond well to treatment, and thus account for a large portion of breast cancer deaths.

Preliminary Results: Performance in terms of AUC for the MRI-based Phenotypes & Tumor Signatures



Giger et al. IWDM 2014

MRI-based Prognostic Array (heat map) - Patients: ER- and ER+



Examples: relating image-based phenotypes to biological phenotypes ("gene expression")

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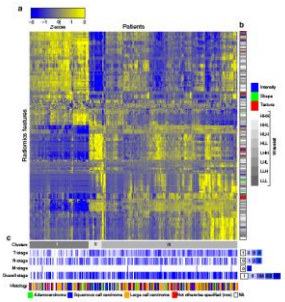
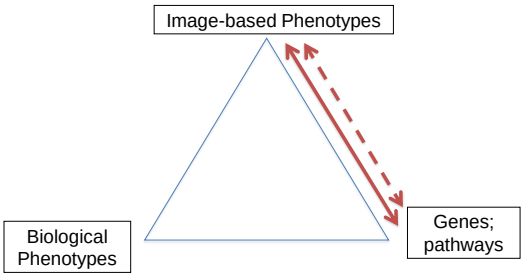
Radiomics heat map (lung cancer)

Radiomics heat map. (a) Unsupervised clustering of lung cancer patients (Lung1 set, n=422) c the y axis and radiomic feature expression (n=440) on the x axis, revealed clusters of patients with similar radiomic expression patterns (b) Clinicall patient parameters for showing significant association of th radiomic expression patterns with primary tumor stage, overall stage a histology. (c) Correspondence of radiomic feature groups with the clustered expression patterns.

Aerts H. et al. Nature Communications 2014



Using Established Knowledge and Relationships

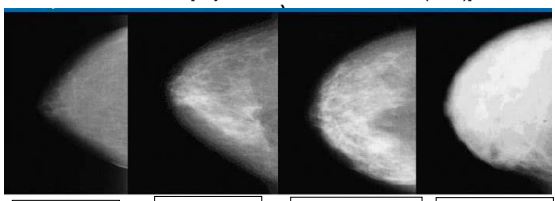


Examples: relating image-based phenotypes to biological phenotypes ("gene expression") AND genomics

- Cancer Risk Assessment
  - UGT2B genes
- Predicting tumor response
  - Lung cancer
- Predicting breast cancer subtype and potential outcome
  - Breast Cancer (TCGA/TCIA) and pathways

Mammographic Breast Density and Breast Cancer Risk

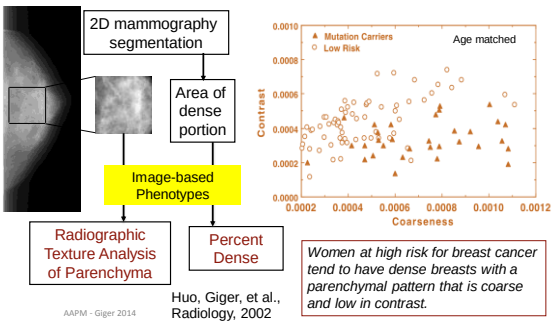
Women with dense tissue in 75% or more of the breast have a risk of breast cancer four to six times as great as the risk among women with little or no dense tissue. [Boyd NF, et al. JNCI 87:670-675 (1995)]



BI-RADS 1	BI-RADS 2	BI-RADS 3	BI-RADS 4
fatty breast < 25% dense	scattered densities 25%-50% dense	heterogeneously dense 51%-75% dense	extremely dense > 75% dense

From Cummings et al, Journal of the National Cancer Institute. 2009;101(6):384-398

Computerized Image-based Cancer Risk Assessment on Mammography (age matched) to guide personalized screening



Huo, Giger, et al., Radiology, 2002

Women at high risk for breast cancer tend to have dense breasts with a parenchymal pattern that is coarse and low in contrast.

Role of Image-based Phenotypes in Cancer Discovery – Relating Image-based Phenotypes to Genotypes

Pilot association study to examine the genetic contribution of UGT2B genes to inter-individual variation in breast density and mammographic parenchymal patterns

Li H, Giger ML, et al.: Association study of image-based phenotypes and genomic biomarkers: potential in breast cancer risk assessment. Medical Physics 41, 2014

- Candidate-gene-based studies (not GWAS)
  - fewer SNPs, smaller dataset needed
  - UGT2B gene family for this study
- 179 subjects -full-field digital mammograms (FFDM); blood DNA samples
- 123 SNPs with minor allele frequency above 5% were genotyped for the UGT2B gene clusters
- UGT2B enzymes play an important role in the metabolism of steroid hormones, thus, it has been proposed that variations in the UGT2B enzymes are involved in the development of breast cancer.
- Steroid hormone levels are correlated with mammographic density, thus, genetic variation in UGT2B family may influence mammographic density by altering enzyme activity or gene expression and, as a consequence, steroid hormone levels.

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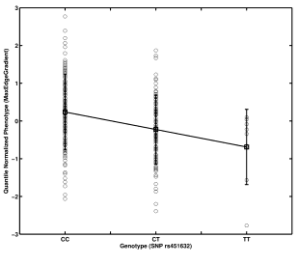

Linear regression of the image-based phenotype MaxEdgeGradient on a genotype SNP position at 69630002 (rs451632) in chromosome 4 resulting in an adjusted p-value of 0.022.

Results indicate that UGT2B gene variation may contribute to inter-individual variation in mammographic parenchymal patterns and breast density.

Understanding the relationship between image-based and genomic biomarkers may help understand the biologic mechanism for image-based biomarkers and yield a future role in personalized medicine.

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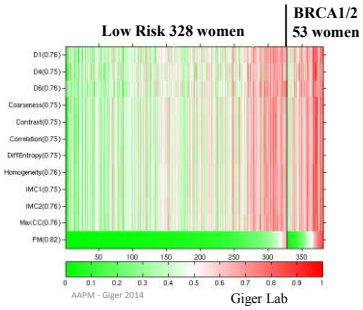
Rapid high-throughput image-based phenotyping yielding a Mammographic Breast Cancer Risk Array

(next is to include clinical information, histopathology, and genomics into association studies and incorporation into the " **risk signature**")

Computer-extracted mammographic characteristics —>



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

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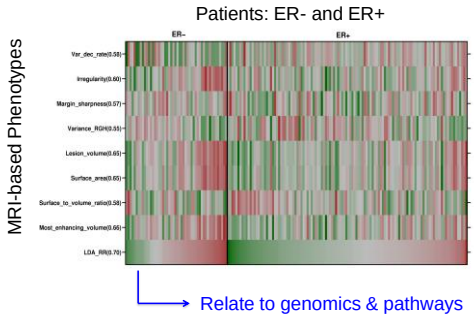
What is a Pathway?

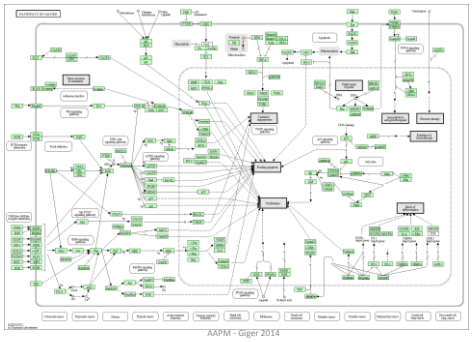
- "A biological pathway is a series of actions among molecules in a cell that leads to a certain product or a change in a cell.
- Such a pathway can trigger the assembly of new molecules, such as a fat or protein.
- Pathways can also turn genes on and off, or spur a cell to move."

www.genome.gov

Future: MRI-based Prognostic Array



Future: Collaboration with Colleagues in Genomics to relate image-based phenotypes to pathways



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Definition of a Biomarker

A characteristic that is objectively measured and evaluated as an indicator of normal biologic or pathogenic processes or pharmacological response to a therapeutic intervention.

Goal to have

- Right treatment for right patient at right time
- Avoid trial and error treatment
- Reduce variability of interpretation

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QIBA & AAPM

- AAPM members in QIBA
- AAPM members in NCI QIN
- Recent AAPM-QIBA grant application
- What does it mean to have a qualified biomarker?
- How is related to image-based phenotypes

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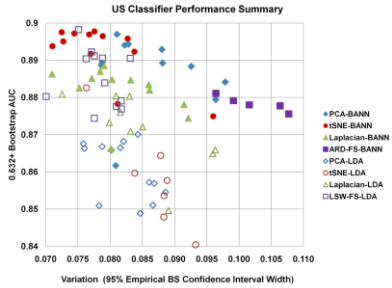
Ultrasound Classifier Performance: Summary in Task of Distinguishing between Cancer and NonCancer

A.R. Jamieson et. al Medical Physics (2010)



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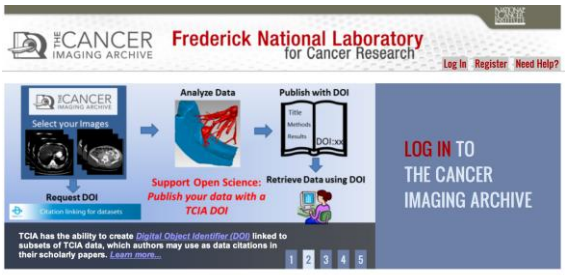
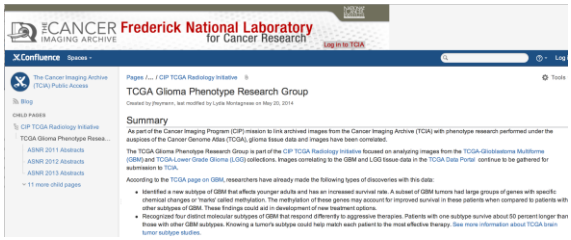
Imaging Genomics: Resources

- NCI TCGA/TCIA
- NCI QIN
- RSNA/AAPM QIBA
- NCI TCIA white paper – Larry Clarke
- Available software
- AAPM FOREM on Imaging Genomics
  - Future white paper

TCIA



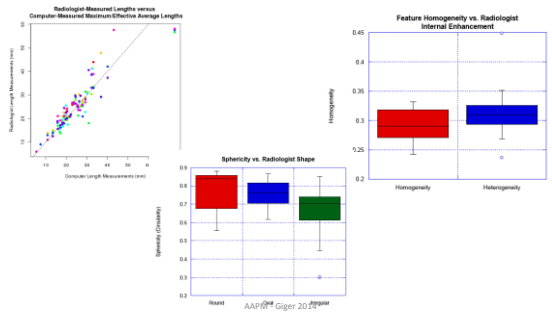
TCGA Glioma Phenotype Research Group



TCGA Breast Phenotype Research Group

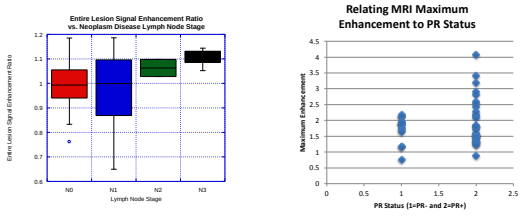
Preliminary Results

Comparison: Radiologist vs. Computer Vision



NCI Cancer Imaging Archive (TCIA)

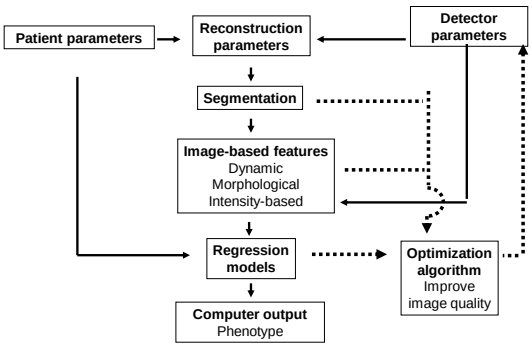
TCGA Breast Phenotype Research Group – Preliminary Results



Future

- Task-based improvement of the image-based phenotypes by integrating **optimization** of the **multi-modality** acquisition systems with quantitative image analysis
- Further **understanding** of the relationship between imaging, histopathology, and genomics by imaging across scales (anatomical to cellular) and data mining large datasets
- Conduct routine rapid high-throughput image-based **phenotyping** along with clinical and genomic tests for an integrated signature enabling personalized precision medicine (CAD) -- Pre-clinical and clinical
- Images not just for qualitative viewing but for **quantitative measurement**

Unified Framework for optimizing Image-based Phenotypes



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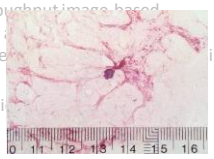

Can we integrate the "silos" to further advance cancer understanding and personalized medicine?

In vivo Image-based biomarkers

Histopathology & gene expression biomarkers

Genomic biomarkers

Future

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Thank you & Acknowledgements

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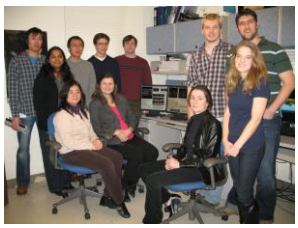
Karen Drukker, PhD
Karla Horsch, PhD
Hui Li, PhD
Mike Chinander, PhD
Li Lan, MS
Chun Wai Chan, MS
Jeremy Bancroft- Brown, BA
Stephanie Burda
Summer medical students, undergraduates, and high school students



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