NCI Quantitative Imaging Network (QIN)

Opportunities for QI Tools in Breast Oncology

For QIN:
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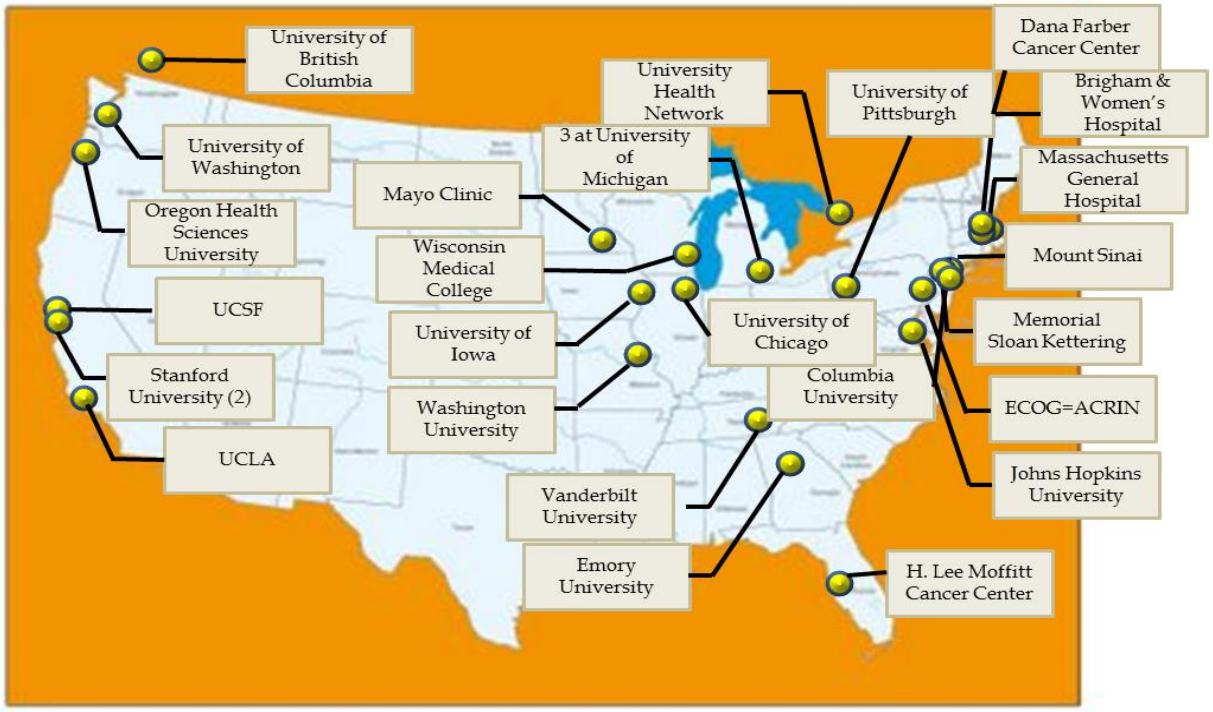
The Quantitative Imaging Network (QIN)

The QIN is an NCI Program joint initiative to bring quantitative imaging methods into clinical utility for measuring response to treatment and supporting clinical decision-making

25 teams in the QIN focus on improving quantitative results from clinical images for a specific cancer problem

Cross-Network Working Groups address: 1) Image Analysis and Performance Metrics (MRI and PET/CT Subgroups); 2) Bioinformatics/IT and Data-sharing; 3) Clinical Trials Design and Development

The Quantitative Imaging Network



Network intent: build consensus, share data and tools.

- 25 active teams (two funded through the Canadian Government)
- 12 associate members from US and 7 foreign countries
- Over 46 tools under development and validation

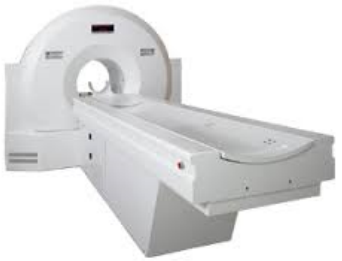
Quantitative Imaging

Quantitative imaging is the extraction of quantifiable (measurable) features from medical images for the assessment of normal or the severity, degree of change, or status of a disease, injury, or chronic condition relative to normal

It is the combination of imaging, analytical methods, and informatics

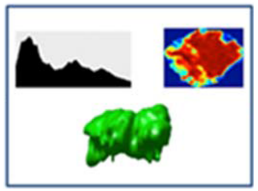
QIN: From Information to Knowledge

Patient Status



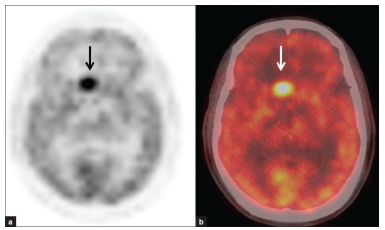
Clinical Decision

Image Acquisition

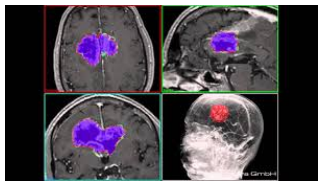


Quantitative Results

Patient Images



Algorithm Processing



The Complexities of Quantitative Tools in Clinical Trials

- Clinical challenge:
  - Identify the clinically most meaningful imaging marker for the study objective
- Technical challenges:
  - Image standardization
  - Image acquisition
  - Data transfer and/or analysis
  - Site versus central quantitative analysis
  - Image analysis tool distribution and validation

Representative tools developed by QIN teams

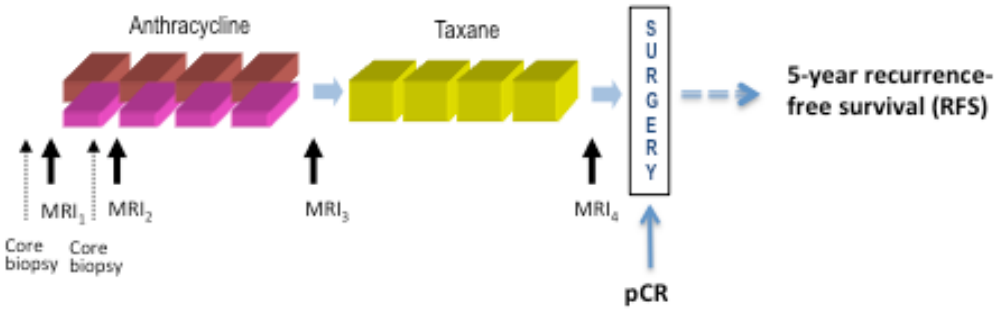
Tool	Modality	Purpose
Lymph node segmentation	MRI	Lymph node segmentation
Hologic Aegis SER	MRI	Volumetric breast tumor segmentation
Quantitative Insights QuantX	MRI	Volumetric tumor segmentation and machine learning diagnostics
Xcal	PET	Multicenter PET SUV cross-calibration
AutoPERCIST	PET	PERCIST response analysis for FDG-PET
Lung Segmentation	CT	Volumetric lung nodule segmentation
Radiomics analysis	CT	Lung, head and neck radiomics analysis
Mass estimation	CT	Muscle mass of cancer patients
ePAD	Image analysis	Image annotation and quantitative analysis
Slicer	Image analysis	Image analysis and surgical planning

Why we (the QIN) are here

- To identify oncology trials where quantitative imaging biomarkers and QIN tools can support outcomes by improving efficacy, efficiency, or study power
- QIN-NCTN Planning meeting recommendations (December 2016):
  - *QIN tool integration into clinical trials should start as early as possible in trial development*
  - *Increased dialogue needed between imagers and oncologists*
  - *Presentations by QIN members at (1) the Alliance Plenary session, (2) selected disease site committees, and (3) Imaging committee*

Breast Quantitative Imaging in Clinical Trials

I-SPY 1: ACRIN 6657 & CALGB 150007– Contrast-enhanced MRI for assessing breast cancer response to neoadjuvant chemotherapy



MRI at baseline, 1 cycle, between AC and T, and pre-surgery

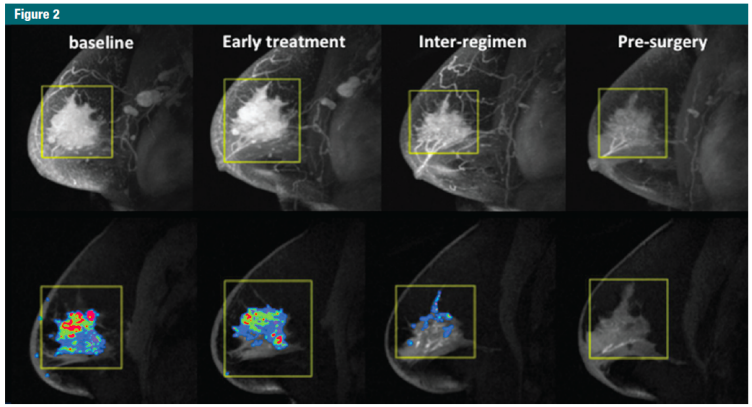
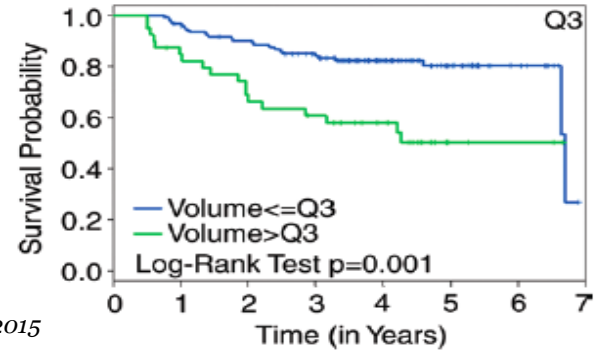


Figure 2: Longitudinal MR images and FTV maps. Maximum intensity projection images (top row) and corresponding FTV maps (bottom row) are shown for a patient with an excellent clinical response and disseminated residual disease. FTV measurements were 48.5 cm^3, 35.4 cm^3, 5.6 cm^3, and 0 cm^3, for the baseline, early treatment, inter-regimen, and presurgery time points, respectively (shown from left to right).

- *Functional tumor volume (FTV) predicts recurrence-free survival (RFS)*
- *FTV is a stronger predictor of RFS than pathologic complete response (pCR)*
- *FTV predicts RFS as early as after 1 cycle of standard anthracycline-based chemotherapy*



Hylton et al., RADIOLOGY 2015

I-SPY 1: ACRIN 6657 & CALGB 150007– Contrast-enhanced MRI for assessing breast cancer response to neoadjuvant chemotherapy

- ***FTV predictive performance and optimal measurement time point differ by breast cancer subtype***

	HR+/HER2-	***HER2+***	***HR-/HER2- (TN)***
Early-treatment	HR+/HER2- Log-Rank Test p=0.636	HER2+ Log-Rank Test p=0.25	HR-/HER2-(TN) Log-Rank Test p=0.006
Pre-surgery	HR+/HER2- Log-Rank Test p=<0.001	HER2+ Log-Rank Test p=0.011	HR-/HER2-(TN) Log-Rank Test p=0.224

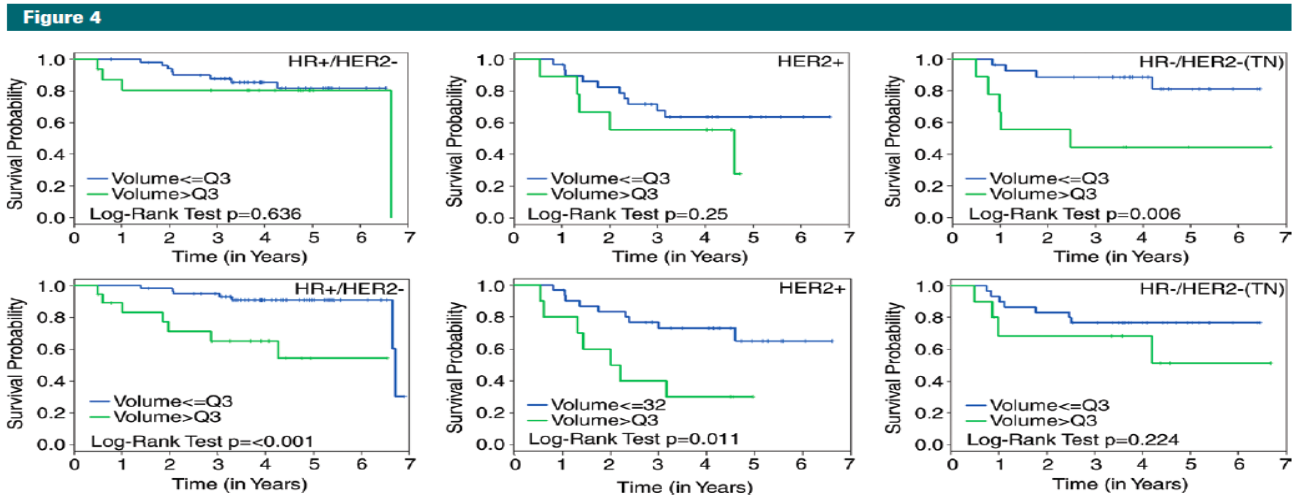
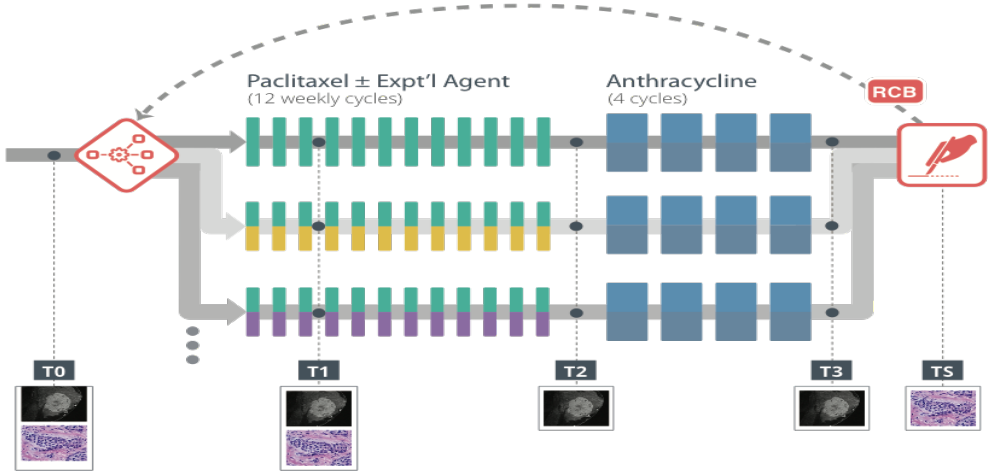


Figure 4: Graphs show Kaplan-Meier plots with RFS estimates by time point and HR and HER2 subtype. RFS stratified by FTV_2 (top row) is compared with FTV_4 (bottom row) by using the highest quartile *(Q3)* cut point for HR-positive *(HR+)* and HER2-negative *(HER2-)*, HER2-positive *(HER2+)*, and HR-negative/HER2-negative (*HR-/HER2-*; triple negative) subtypes, respectively, left to right. The log-rank test *P* value is shown for each plot.

Hylton et al., RADIOLOGY 2015

I-SPY 2 breast cancer trial



- *I-SPY 2 is an adaptively-randomized phase II trial testing novel agents for breast cancer*
- *Incorporates MRI tumor volume in the patient randomization algorithm*

- Drugs "graduate" from I-SPY 2 when they reach a Bayesian predictive probability of achieving 80% success in a subsequent phase III study
- Drugs graduate within subtypes defined by hormone receptor (HR) status, HER2 status and Mammaprint score
- Drugs can be dropped for futility

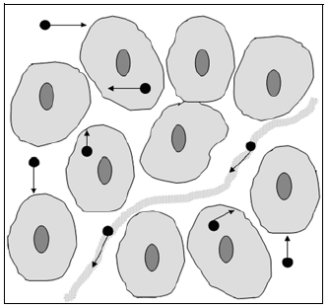
>2150 patients registered; >1220 randomized; >1070 with surgery as of Oct 2017
6 drug graduates to date

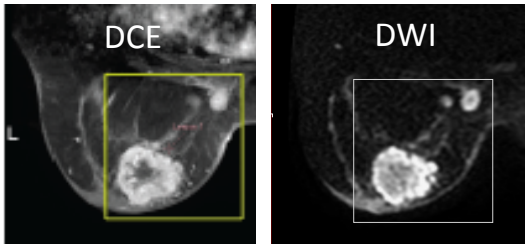
ACRIN 6698 - Breast diffusion-weighted MRI (DWI) to predict response to neoadjuvant chemotherapy

- ACRIN 6698: sub-study of I-SPY2 testing diffusion-weighted MRI (10 sites)
- 406 I-SPY 2 patients enrolled; 272 on treatment combined for analysis
- DWI added to standard DCE-MRI
- Apparent diffusion coefficient (ADC) measured using DWI
- Preliminary results *(presented at ASCO 2017)*:
  - ***ADC and change in ADC at mid-therapy and pre-surgery predict pCR***
  - ***Variable prediction by subtype, highest in HR+/HER2-***

DWI measures the random motion of water in tissue

Provides information about cell density and microstructure





Multi-focal invasive ductal carcinoma. Pre-treatment DCE MRI_1 (left) and DWI b800 (right)

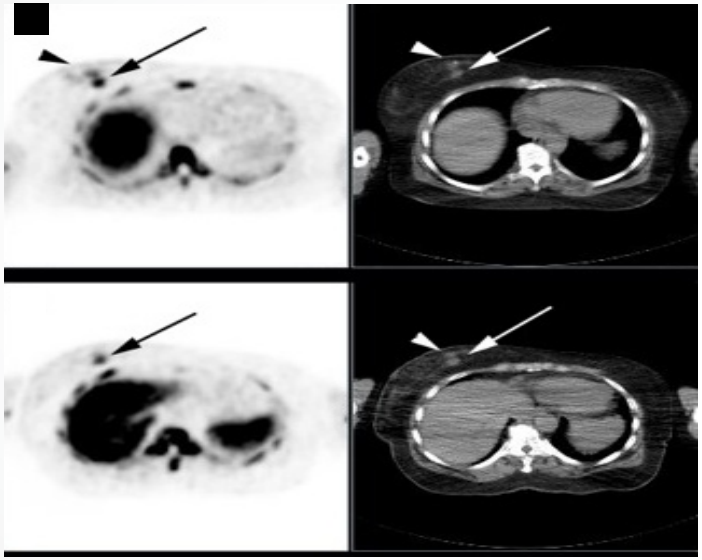
CALGB 40903: Phase II Single-Arm Study of Neoadjuvant letrozole for ER(+) postmenopausal DCIS (PI: Shelley Hwang)

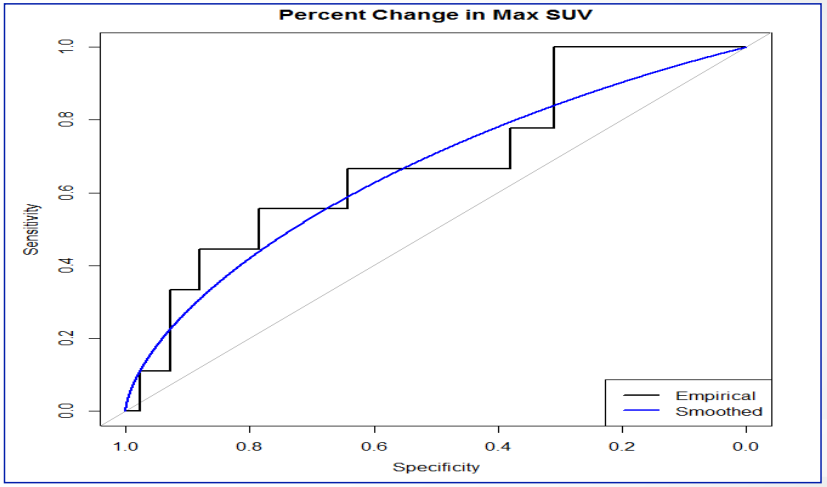
- **Endpoints:**
  - Primary: radiographic response letrozole on MRI
    - Change in MRI tumor volume
  - Secondary:
    - Mammographic extent of disease
    - Candidacy for breast conservation
    - Frequency of re-excisions
    - Path CR
    - Invasive cancer at excision

ACRIN 6688: FLT PET to Measure Early Breast Cancer Response
(PI: Lale Kostakoglu)

Pre-Therapy

7 d Post-





Best ΔSUV_{max} cut-off for predicting pCR = -51% (sensitivity 56%;specificity 79%).

(Kostakoglu, J Nucl Med, 2015)

ACRIIN and U Wash QIN U01

Next Steps:

Benefit of using existing and future Clinical Trial data

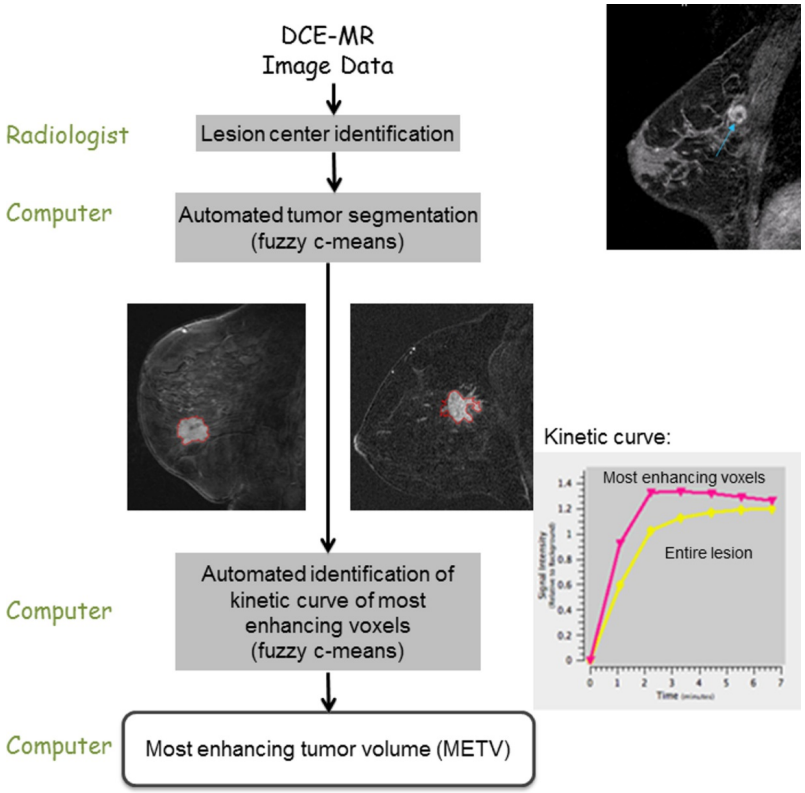
Increase effectiveness & efficiency

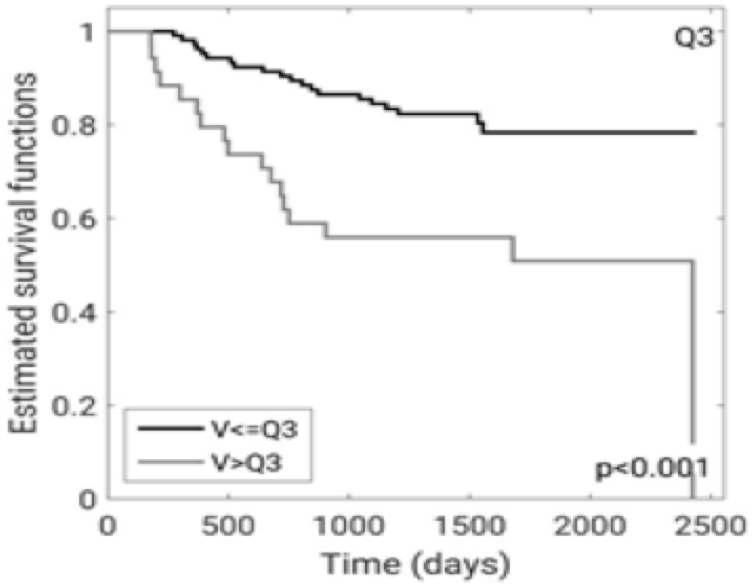
Incorporate automated, objective computer-extracted biomarkers (radiomics) & develop decision tools using machine learning.

Enable efforts to standardize, verify quality, and validate with existing and future Clinical Trial data.

Incorporating automated computer-extracted characteristics (radiomics) into response assessment

(METV on ACRIN 6657 data: only pre-treatment & early treatment imaging exams)



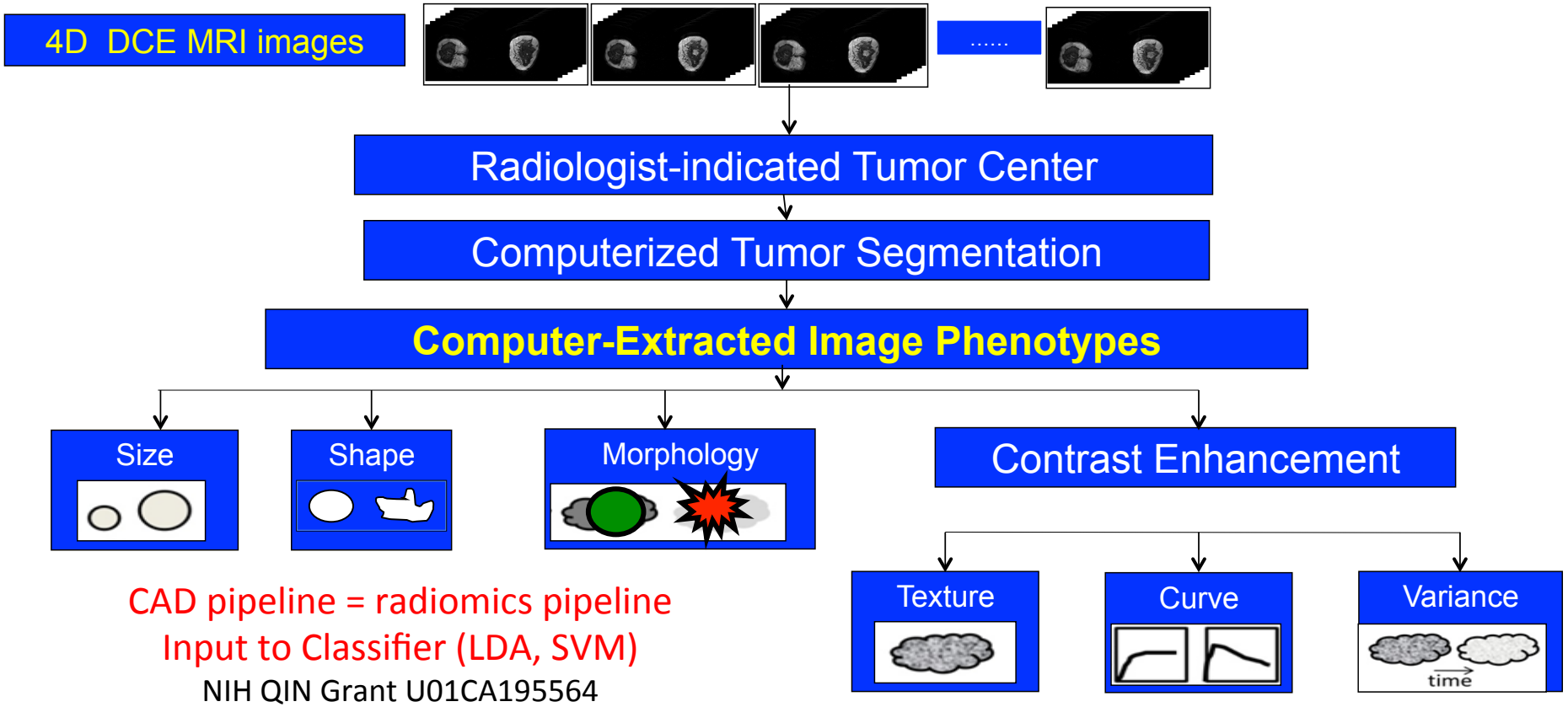


Estimated Kaplan-Meier recurrence-free survival estimates for METV

NIH QIN Grant U01CA195564

Incorporating machine learning into assessing diagnosis, molecular classification, & response assessment

Computer-extraction of biomarkers (features) followed by training of predictive classifiers

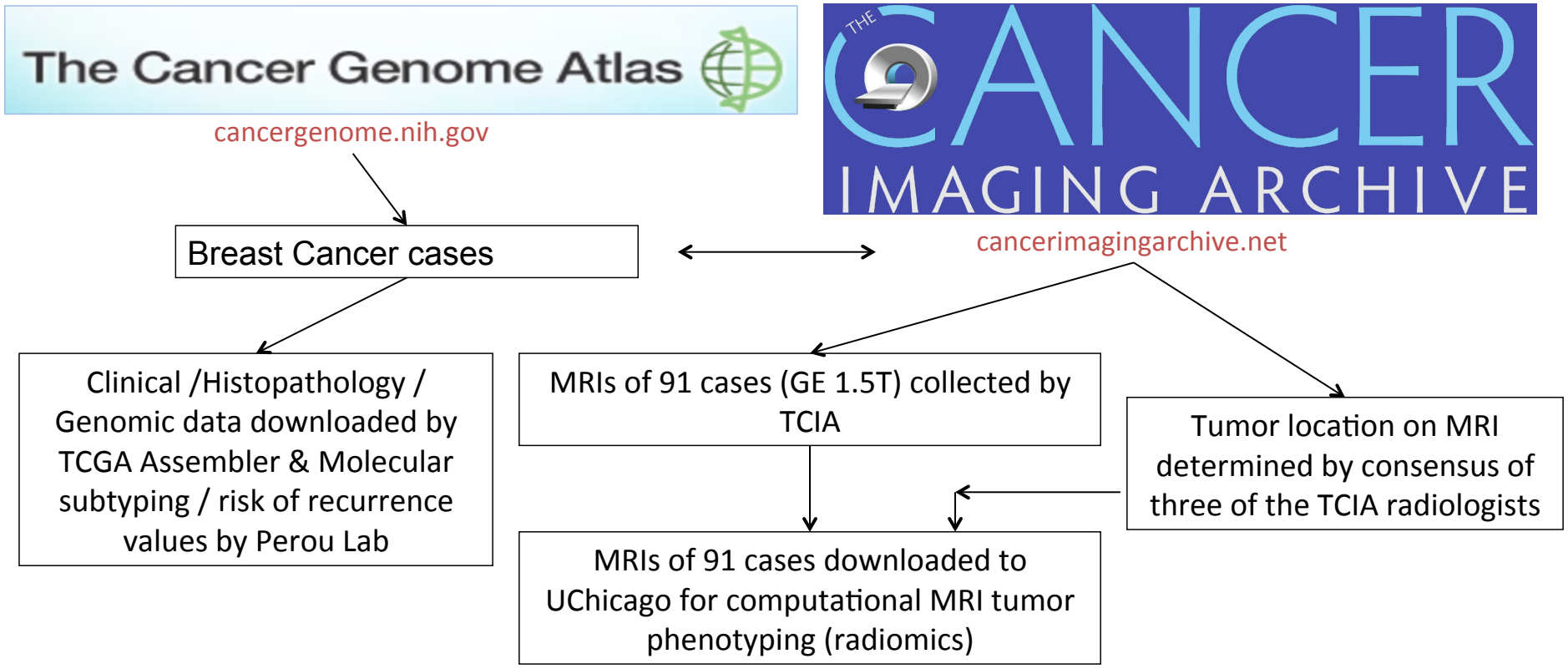


CAD pipeline = radiomics pipeline

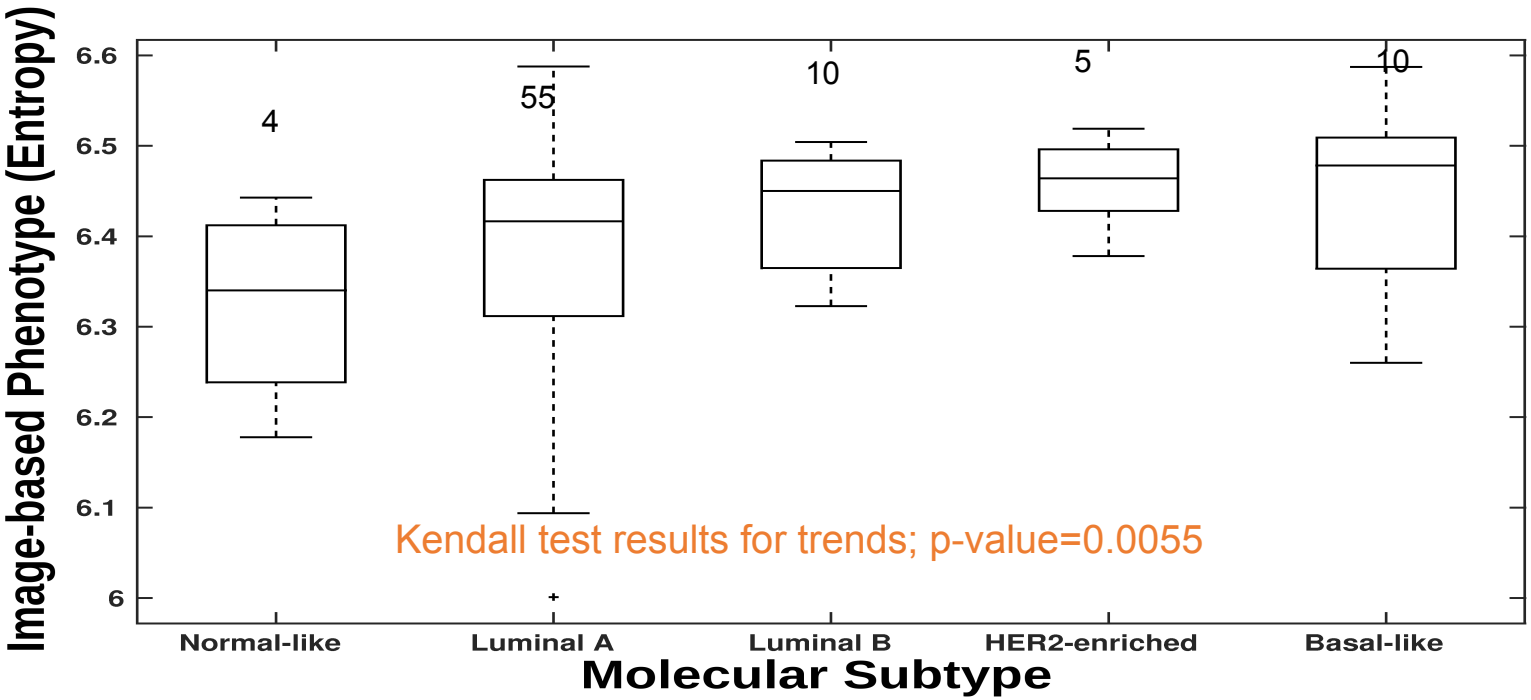
Input to Classifier (LDA, SVM)

NIH QIN Grant U01CA195564

Multi-institutional, Multi-disciplinary Collaboration

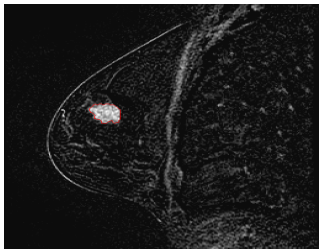


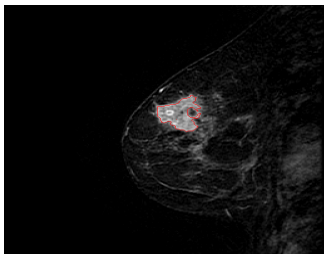
From the TCIA Radiomics -- Enhancement Texture of Tumor Heterogeneity appears Predictive of Molecular Subtype – **Clinical Prognostic Value**



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.

Clinical Therapeutic Response Assessment Value





Multi-gene assays of risk of recurrence

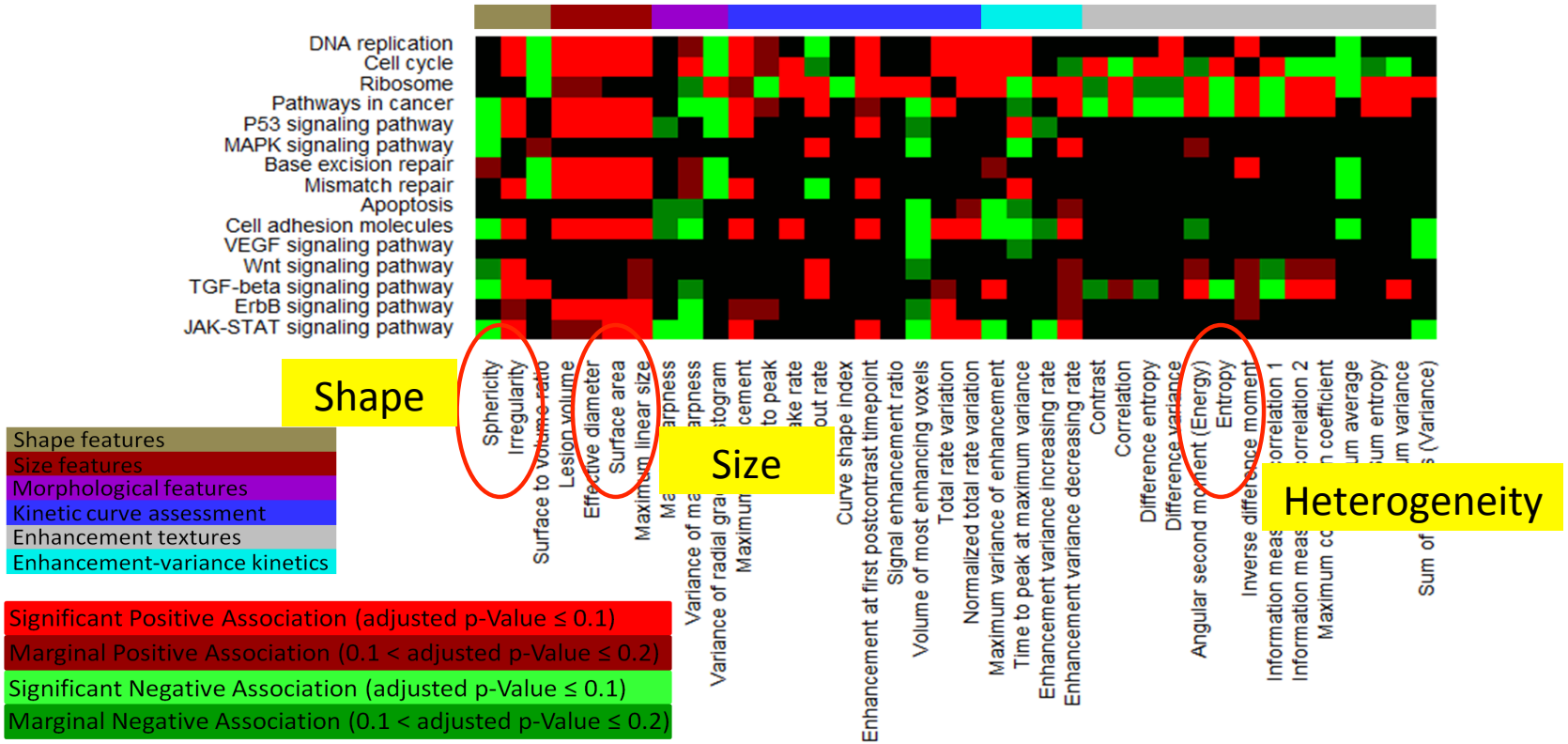
Radiomics for "virtual" biopsy

	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.

IMAGING GENOMICS – USING VIRTUAL BIOPSIES

PATHWAY TRANSCRIPTIONAL ACTIVITIES ASSOCIATED WITH MRI QUANTITATIVE FEATURES



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)

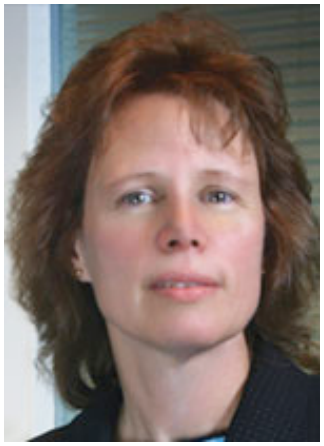
Opportunities for NCTN-QIN Collaborations

1. QIN can provide expertise to guide imaging needs for NCTN trials
   - QIN investigators are eager to participate in NCTN trials
2. QIN investigators seek opportunities to add exploratory biomarkers to NCTN trials, often without added cost
   - QIN team are funded to develop QI tools, and relish the chance to test tools prospectively in trials
   - Add imaging translational science to NCTN trials
3. Enhanced partnership for oncology and imaging investigators in NCTN trials
   - Common goals of improved the quality and efficiency of cancer clinical trials

QIN Contact Information

QIN program office

Robert Nordstrom nordstrr@mail.nih.gov
Image-Guided Interventions Chief, Cancer Imaging Program



Lori Henderson hendersonlori@mail.nih.gov
Program Director, Clinical Trials Branch, Cancer Imaging Program

QIN Presentations at Alliance Annual Meeting

Committee	QIN Representative
Breast	Nola Hylton and Maryellen Giger
Experimental Therapeutics	Paul Kinahan and Amita Dave
GI	Larry Schwartz and Hugo Aerts
GU	Michael Jacobs and Andry Fedorov
Lymphoma	Rich Wahl and Dave Mankoff
Neuro-Oncology	Michael Knopp and Jaysharee Kalpathy
Radiation-Oncology	Hui-Kuo Shu and Yue Cao
Respiratory	John Buatti and Michael McNitt-Gray
IROC	Xiao, Rosen, Knopp, and Fitzgerald