NCI Quantitative Imaging Network (QIN)

Opportunities for QI Tools in Breast Oncology

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

- 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

Network intent: build consensus, share data and tools.
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
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

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

- 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

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

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**

*Figure 4*

<table>
<thead>
<tr>
<th>HR+/HER2-</th>
<th>HER2+</th>
<th>HR-/HER2- (TN)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="HR+/HER2-" /></td>
<td><img src="image2" alt="HER2+" /></td>
<td><img src="image3" alt="HR-/HER2- (TN)" /></td>
</tr>
</tbody>
</table>

*Figure 4:* Graphs show Kaplan-Meier plots with RFS estimates by time point and HR and HER2 subtype. RFS stratified by FTV (top row) is compared with FTV (bottom row) by using the highest quartile (Q3) cut point for HR-positive (HR+) and HR-negative (HR-); 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

- 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

- 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

>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 (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)

Best $\Delta$SUV$_\text{max}$ cut-off for predicting pCR = -51% (sensitivity 56%; specificity 79%).

(Kostakoglu, J Nucl Med, 2015)
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

4D DCE MRI images

Radiologist-indicated Tumor Center

Computerized Tumor Segmentation

Computer-Extracted Image Phenotypes

Size

Shape

Morphology

Contrast Enhancement

Texture

Curve

Variance

CAD pipeline = radiomics pipeline
Input to Classifier (LDA, SVM)
NIH QIN Grant U01CA195564
Multi-institutional, Multi-disciplinary Collaboration

The Cancer Genome Atlas
[cancergenome.nih.gov]

Breast Cancer cases

Clinical /Histopathology / Genomic data downloaded by TCGA Assembler & Molecular subtyping / risk of recurrence values by Perou Lab

MRIs of 91 cases (GE 1.5T) collected by TCIA

Tumor location on MRI determined by consensus of three of the TCIA radiologists

MRIs of 91 cases downloaded to UChicago for computational MRI tumor phenotyping (radiomics)
From the TCIA Radiomics -- Enhancement Texture of Tumor Heterogeneity appears Predictive of Molecular Subtype – **Clinical Prognostic Value**

![Box plot showing Kendall test results for trends; p-value=0.0055](image)

Kendall test results for trends; p-value=0.0055

Clinical Therapeutic Response Assessment Value

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

Multi-gene assays of risk of recurrence

Radiomics for “virtual” biopsy

IMAGING GENOMICS – USING VIRTUAL BIOPSIES
PATHWAY TRANSCRIPTIONAL ACTIVITIES ASSOCIATED WITH MRI QUANTITATIVE FEATURES

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

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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

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<td>Experimental Therapeutics</td>
<td>Paul Kinahan and Amita Dave</td>
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<tr>
<td>GI</td>
<td>Larry Schwartz and Hugo Aerts</td>
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<td>GU</td>
<td>Michael Jacobs and Andry Fedorov</td>
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<td>Lymphoma</td>
<td>Rich Wahl and Dave Mankoff</td>
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<td>Neuro-Oncology</td>
<td>Michael Knopp and Jaysharee Kalpathy</td>
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<td>Radiation-Oncology</td>
<td>Hui-Kuo Shu and Yue Cao</td>
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<td>Respiratory</td>
<td>John Buatti and Michael McNitt-Gray</td>
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<tr>
<td>IROC</td>
<td>Xiao, Rosen, Knopp, and Fitzgerald</td>
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