The Quantitative Imaging Network (QIN):

The Quest for Clinical Decision Tool Validation

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10 Years

July 11, 2018

NIH NATIONAL CANCER INSTITUTE

Imaging can offer useful information in clinical trials

Information can be gained over many different domains:

Anatomic to molecular

Can be combined with other biomarkers

Disease location & staging

Can reduce (or eliminate) biopsies

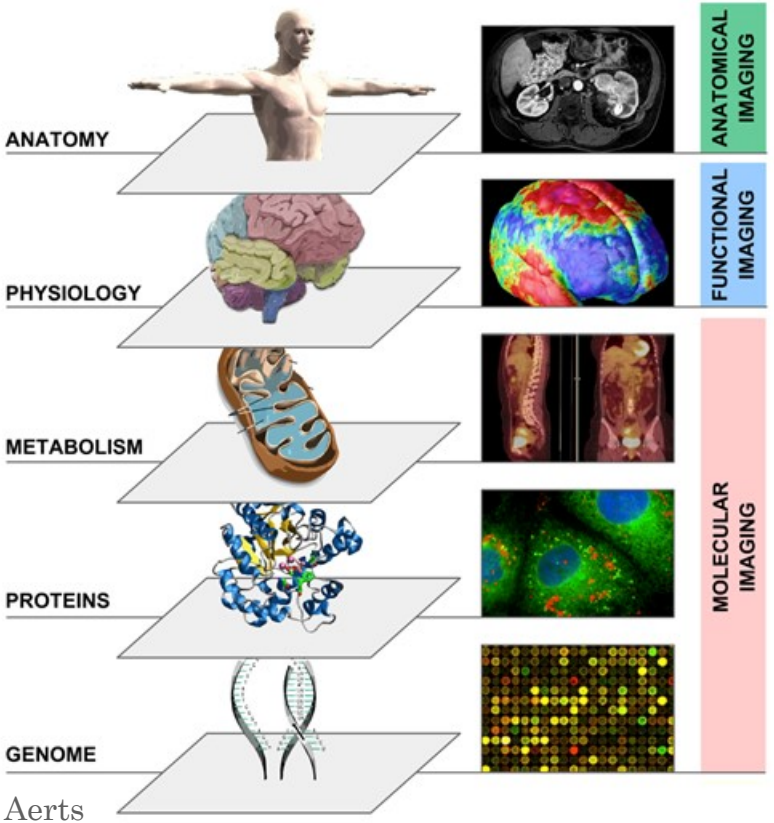


Image from Hugo Aerts

Imaging in the Age of Precision Medicine

- Provides more than just "pretty pictures"
  - Provides a phenotype of a disease process
  - Can evaluate the entire body
  - Can be used to determine multifactor characteristics of disease
  - Can be performed on current clinical technology

Clinical biomarker

- But, it does not come without effort
  - Needs a continuous process for technique and measurement validation
  - Needs a well trained workforce
  - Must be integrated with clinical workflows

Cautions

- Requires quantitation of image data along with image-based analyses

QIN

Hypothesis behind the program

- Hypothesis: The evolution of targeted drugs and radiation therapies in clinical trials can benefit from the integration of quantitative imaging with the treatment protocols.

  - These quantitative imaging methods must be developed on commercial platforms in order to have value in multi-center, multi-platform clinical trials.

- Goal: Create imaging tools and methods useful in clinical workflow that will measure response to cancer therapies or predict outcome.

Cancer Imaging Program Guidance

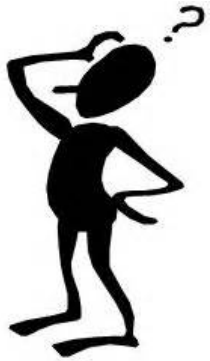
CIP Leadership

Paula Jacobs PhD

Janet Eary, MD

- From the Cancer Imaging Program vision & goals:
  - Create imaging methods to be validated as biomarkers
  - Implement an informatics infrastructures to optimize the value of cancer imaging data
  - Develop strategies of implementing science and methods to detect and treat cancers, and to monitor or predict response to therapy
  - Implement infrastructures based on standardized models for design and conduct of clinical trials using imaging or image-guided technologies.

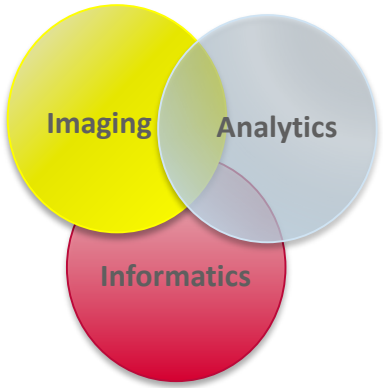
What is Quantitative Imaging?



- **Quantitative imaging:** extraction of quan[illegible]ble (measurable) data from med[illegible] for assessment of status or ch[illegible]

- Treatment planning
- Prediction of outcome
- Measurement of progression

- It sits at t[illegible]ging, analytics, and i[illegible]ovide quantitative tools for [illegible]decision support.



What is Quantitative Imaging?

- It seeks to reduce the noise and variability in clinical images to provide standardized and robust results useful across sites and time.
- It uses imaging protocol controls, informatics, and analytical methods to extract measurable data from medical images during clinical trials.
- It translates collected data into information useful for measuring response to therapy or predicting therapy outcome.

What is Quantitative Imaging?

- It is a part of translational research
  - Concerned with:
    - Standardization of methods
    - Harmonization across different imaging platforms and vendors
    - Reliable and repeatable results
    - User convenience and easily interpreted information
    - Seamless incorporation into clinical workflow

Translational research is not new….

The step from the laboratory to patient's bedside…is extraordinarily arduous and fraught with danger

Dr. Paul Ehrlich

Nobel Prize in Medicine 1908

It is the responsibility of those involved in today's biomedical research to translate the remarkable scientific innovations we are witnessing into health gains for the nation.

Dr. Elias Zerhouni:

NEJM, 2005


WARNING
CHALLENGES
AHEAD

The Quantitative Imaging Roadmap

1. Evaluation of imaging hardware performance
2. Creation of harmonization methods (software and protocol)
   - Reduce bias & variance during data collection
3. Creation of robust algorithms to extract quantitative information from images
4. Testing and validating performance of algorithms
5. Introducing candidate algorithms into clinical workflow
   - FDA and industrial interactions

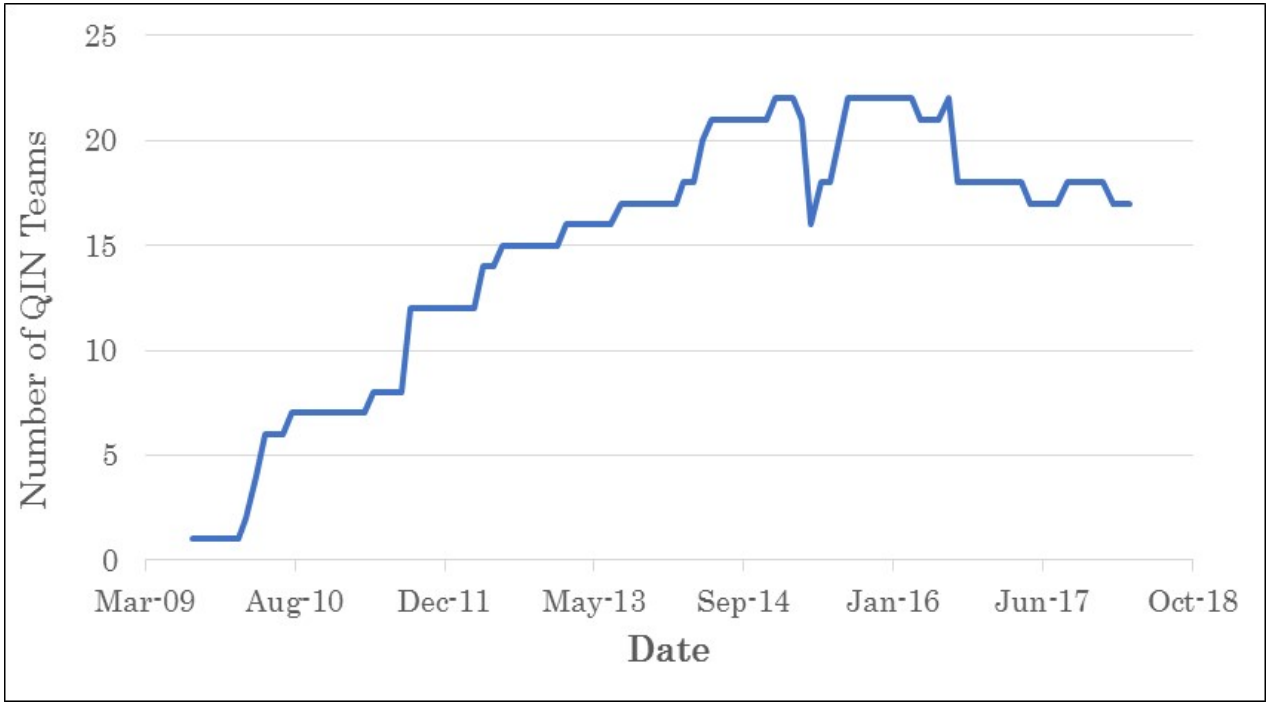
Challenge: Not all teams start at the same time

…so they aren't all at the same stage of development

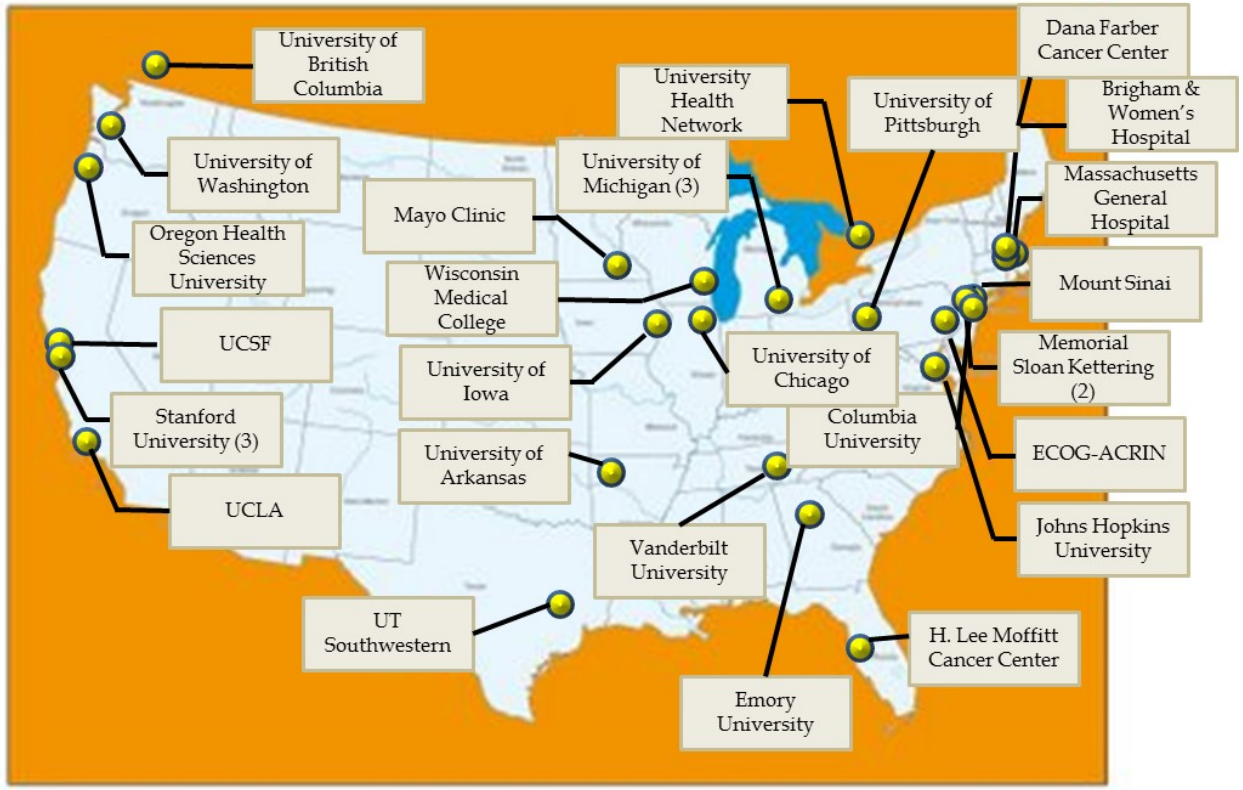
10 Years of Quantitative Imaging

276 received applications
35 awards made

U01 Cooperative Agreement used to create a network of research team.



Research Teams (Past and Present) in QIN



Associate Members in QIN

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(QIBA) https://www.rsna.org/QIBA/
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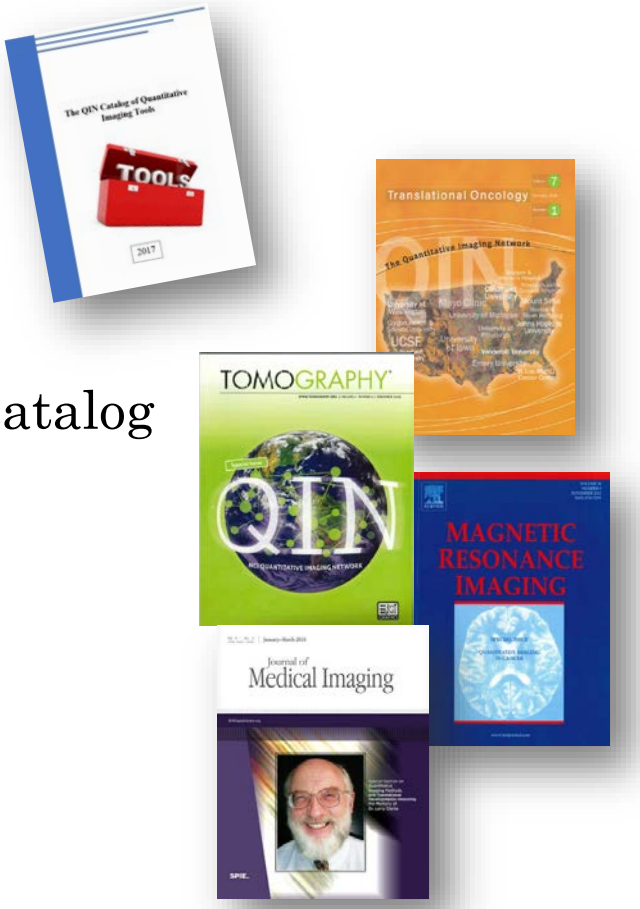
Accomplishments to Date

- Over 450 peer-reviewed publications
  - Many are collaborative across the network
  - Working groups are very productive
- 67 clinical decision tools in the current tool catalog
  - Working to prioritize and further validate
- Numerous challenges are ongoing
- 4 journal issues dedicated to QIN activities

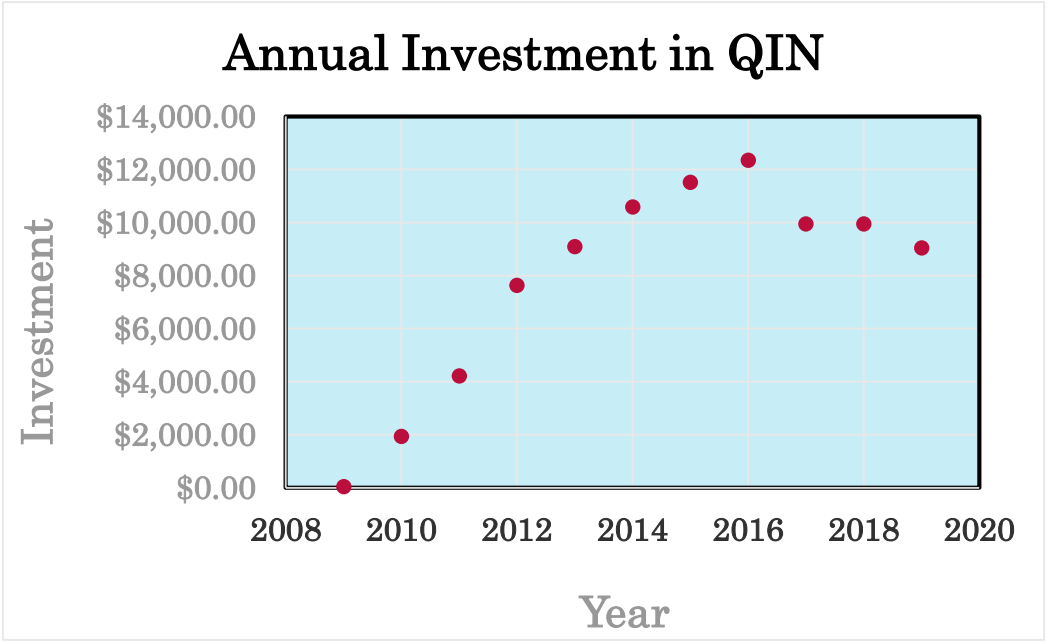


QIN network is efficiently organized

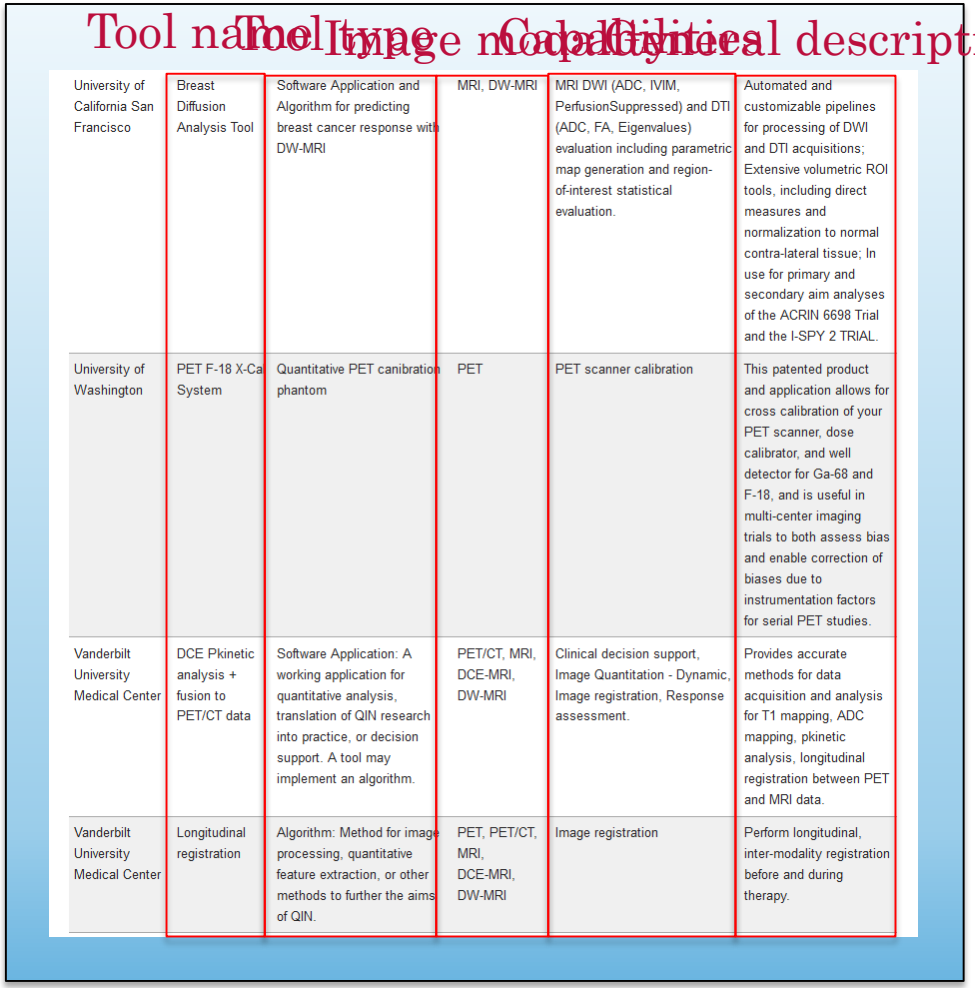
Average research team investment: $570,500 per year.

Same as a typical R01 investigator-initiated award.

QIN support amounts to 9% of the total Cancer Imaging Program R01 support over the same timeframe, and only 6% of the total CIP extramural support over that time.

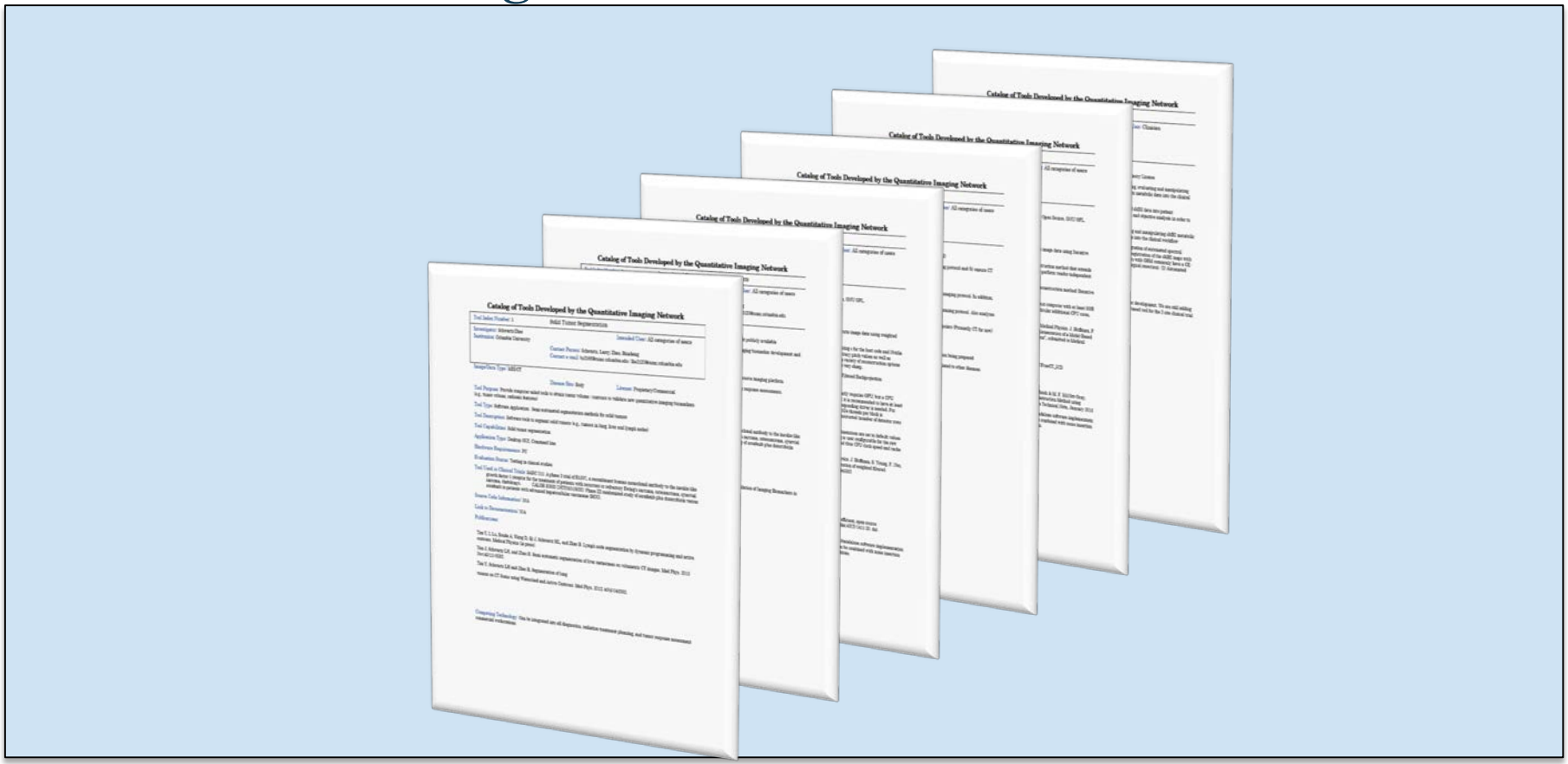


Tool View



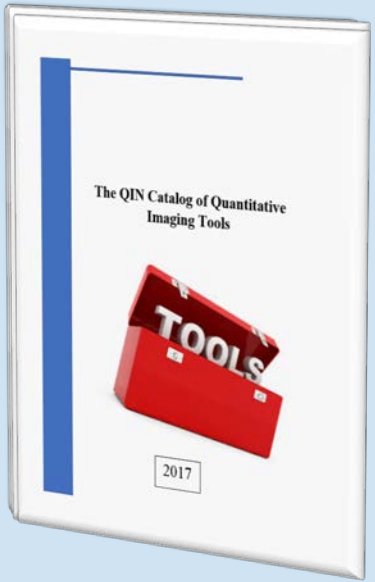
University of California San Francisco	Breast Diffusion Analysis Tool	Software Application and Algorithm for predicting breast cancer response with DW-MRI	MRI, DW-MRI	MRI DWI (ADC, IVIM, PerfusionSuppressed) and DTI (ADC, FA, Eigenvalues) evaluation including parametric map generation and region-of-interest statistical evaluation.	Automated and customizable pipelines for processing of DWI and DTI acquisitions; Extensive volumetric ROI tools, including direct measures and normalization to normal contra-lateral tissue; In use for primary and secondary aim analyses of the ACRIN 6698 Trial and the I-SPY 2 TRIAL.
University of Washington	PET F-18 X-Ca System	Quantitative PET canibration phantom	PET	PET scanner calibration	This patented product and application allows for cross calibration of your PET scanner, dose calibrator, and well detector for Ga-68 and F-18, and is useful in multi-center imaging trials to both assess bias and enable correction of biases due to instrumentation factors for serial PET studies.
Vanderbilt University Medical Center	DCE Pkinetic analysis + fusion to PET/CT data	Software Application: A working application for quantitative analysis, translation of QIN research into practice, or decision support. A tool may implement an algorithm.	PET/CT, MRI, DCE-MRI, DW-MRI	Clinical decision support, Image Quantitation - Dynamic, Image registration, Response assessment.	Provides accurate methods for data acquisition and analysis for T1 mapping, ADC mapping, pkinetic analysis, longitudinal registration between PET and MRI data.
Vanderbilt University Medical Center	Longitudinal registration	Algorithm: Method for image processing, quantitative feature extraction, or other methods to further the aims of QIN.	PET, PET/CT, MRI, DCE-MRI, DW-MRI	Image registration	Perform longitudinal, inter-modality registration before and during therapy.

The Tool Catalog



The Tool Catalog & Benchmarking

1. Pre-Benchmark
   ★
2. Basic Benchmark
   ★★
3. Technical Test Benchmark
   ★★★
4. Clinical Trial Benchmark
   ★★★★
5. Clinical Use Benchmark
   ★★★★★



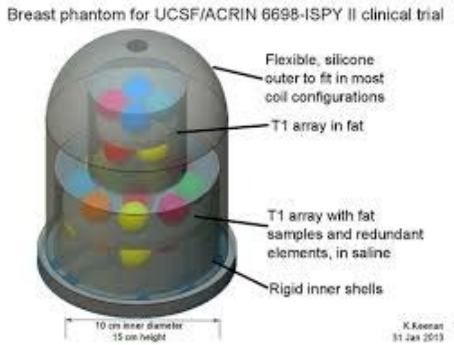
Representative tools developed by QIN teams

Tool	Modality	Purpose
Lymph node segmentation	MRI	Lymph node segmentation
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

An Assortment of Tools for Quantitative Imaging

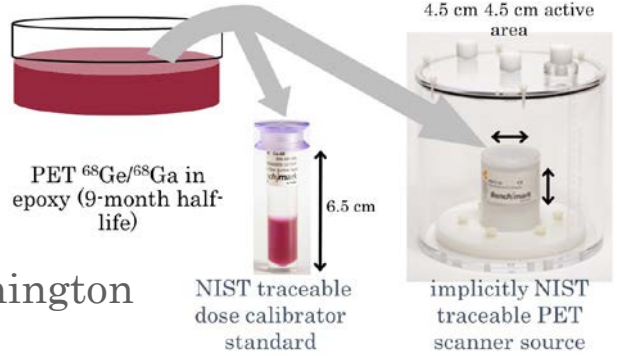
- Phantoms for quality control during data collection

University of California
San Francisco

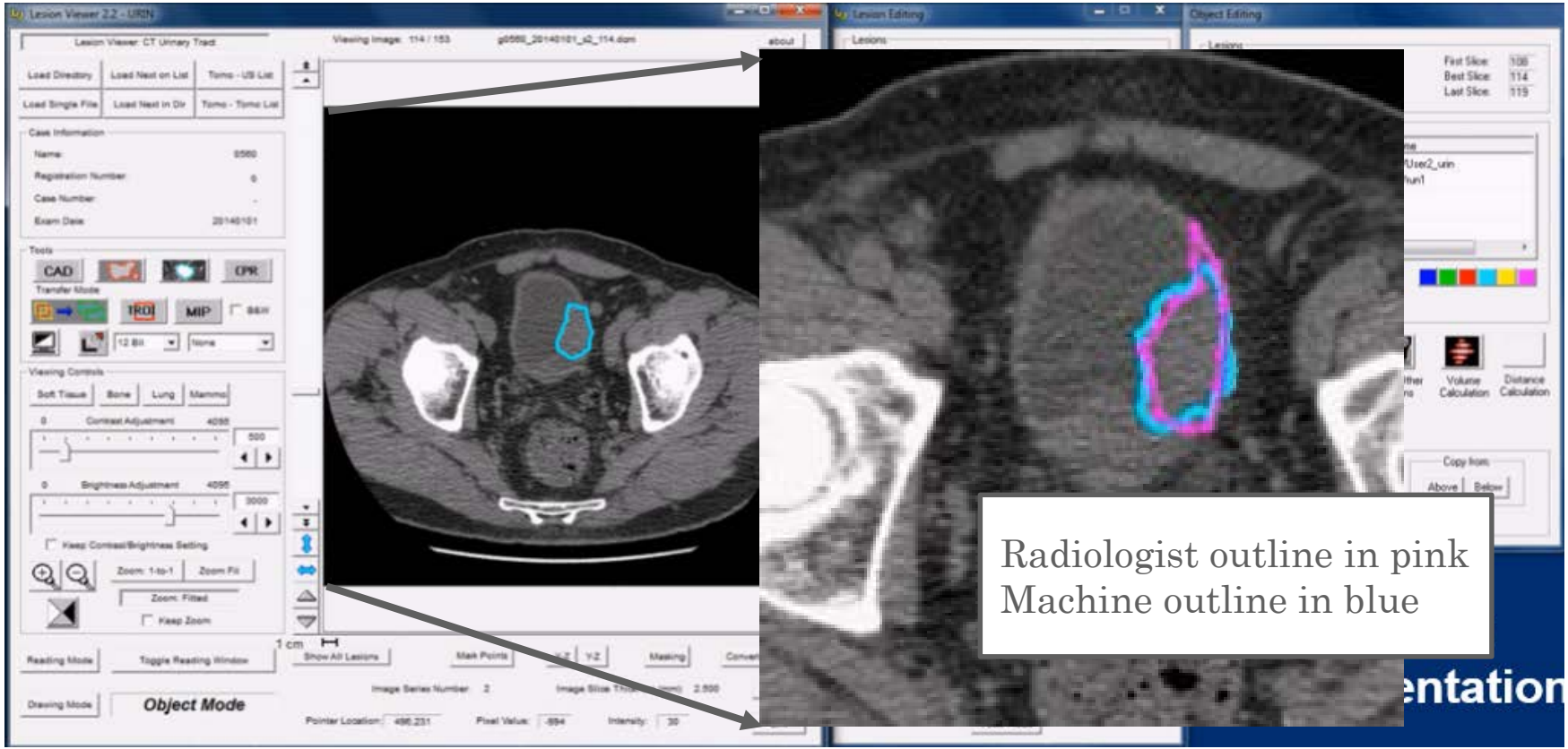


- Calibration kits for PET cross-calibration

University of Washington



Interactive Stations for Optimization & Training

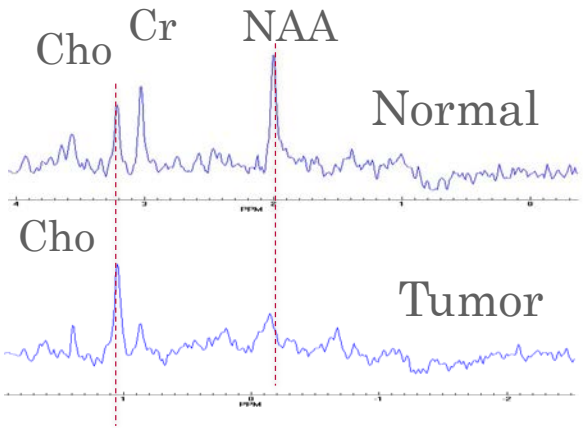


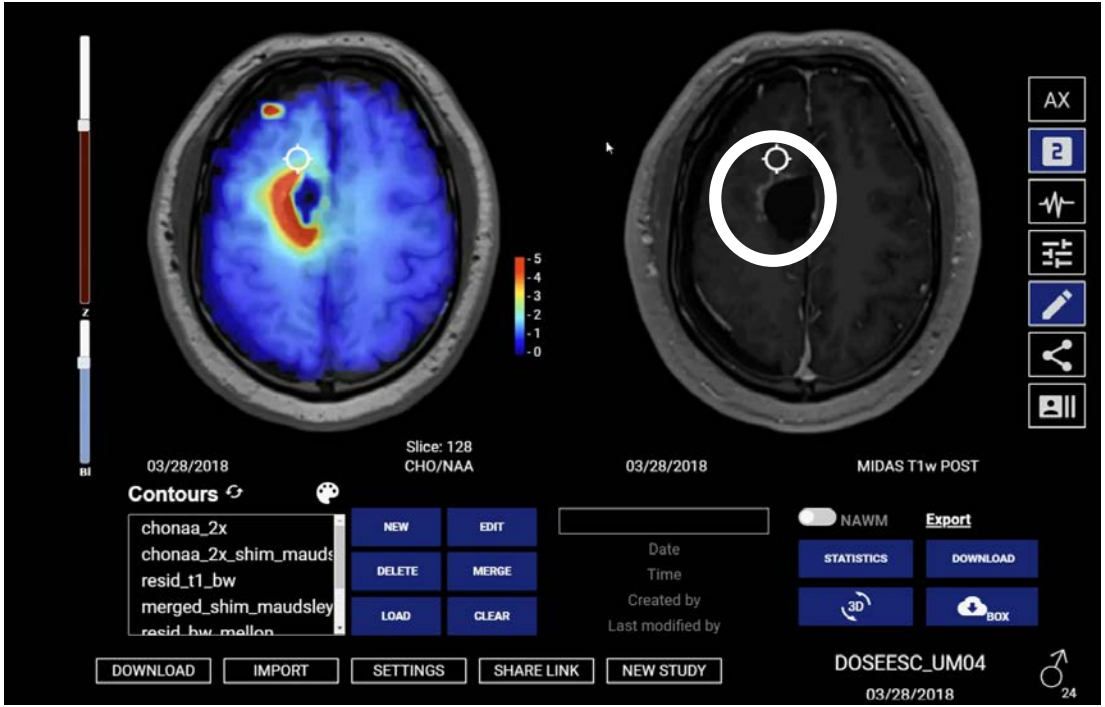
University of Michigan

Enhancement of Infiltrating Tumors

Tumor only weakly visible on T1 weighted image.

Choline/NAA ratio in tumor delineates tumor and shows infiltration.

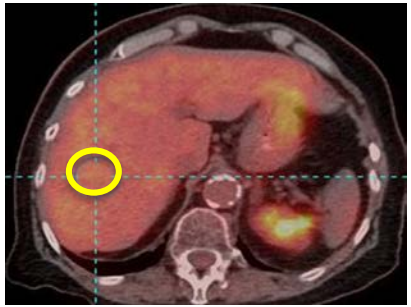




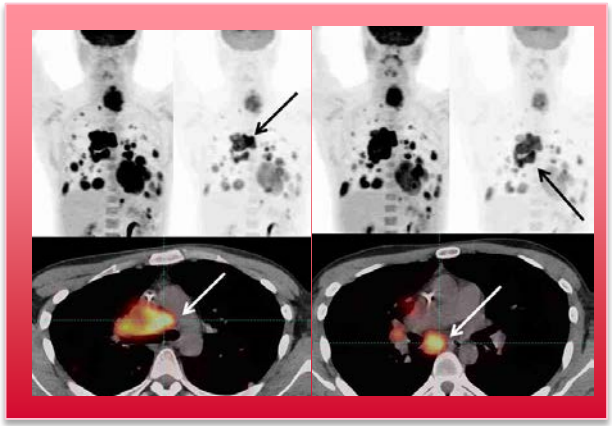
Photos from Emory University

PET Imaging Response Criteria

Johns Hopkins University
and Washington University



Liver region for background reading.



Hottest lesion, baseline and follow-up.

PERCIST

Complete metabolic response:

Complete resolution of FDG uptake, with uptake less than the mean SUL of the liver and indistinguishable from the surrounding background.

Partial metabolic response:

A decrease of greater than or equal to 30% and of at least 0.8 SUL units between the most intense evaluable lesion at bae-line and the most intense lesion at follow-up.

Stable metabolic disease:

An increase or decrease of less than 30% in a target lesion, nad no SUL_{peak} of less than 30% is required.

Progressive disease:

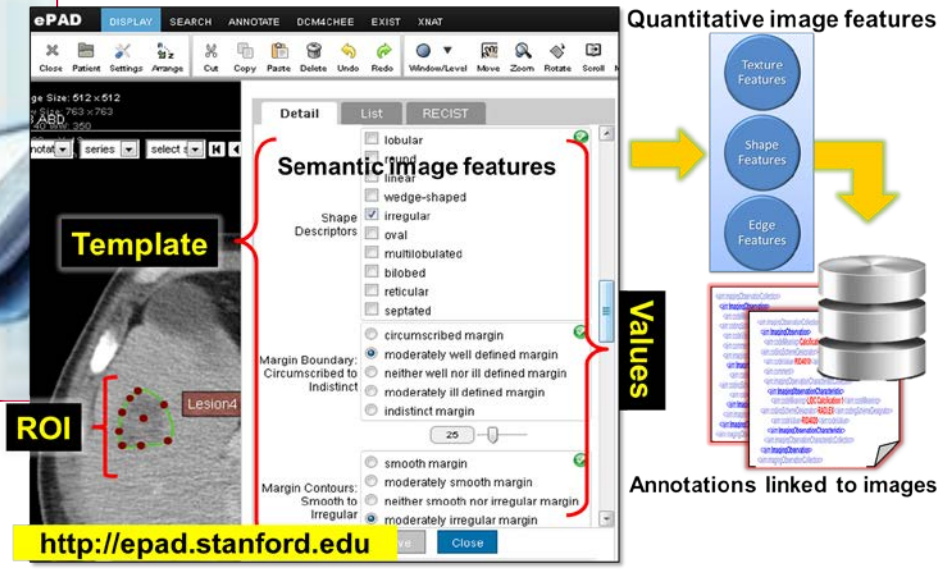
Greater than 30% and an increase of at least 0.8 SUL units in a target lesion.

Informatics and Clinical Data Display

ePAD

Image annotations
Semantic features
Segmentation
Analysis

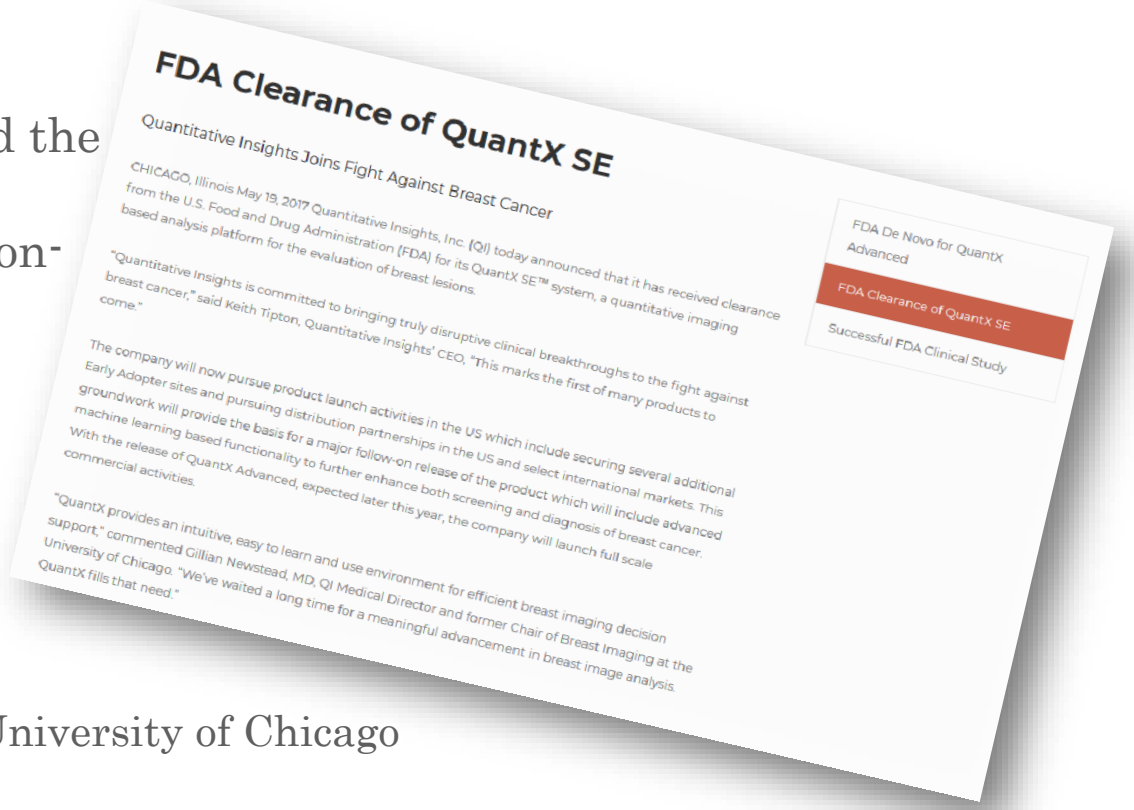
Tool pipelines



Stanford University

Pathway to FDA Clearance

A QIN team has completed the path to FDA clearance on software for clinical decision-making prior to beginning work on the QIN project. This will streamline the process for clearance for many QIN teams.



FDA Clearance of QuantX SE

Quantitative Insights Joins Fight Against Breast Cancer

CHICAGO, Illinois May 19, 2017 Quantitative Insights, Inc. (QI) today announced that it has received clearance from the U.S. Food and Drug Administration (FDA) for its QuantX SE™ system, a quantitative imaging based analysis platform for the evaluation of breast lesions.

"Quantitative Insights is committed to bringing truly disruptive clinical breakthroughs to the fight against breast cancer," said Keith Tipton, Quantitative Insights' CEO, "This marks the first of many products to come."

The company will now pursue product launch activities in the US which include securing several additional Early Adopter sites and pursuing distribution partnerships in the US and select international markets. This groundwork will provide the basis for a major follow-on release of the product which will include advanced machine learning based functionality to further enhance both screening and diagnosis of breast cancer. With the release of QuantX Advanced, expected later this year, the company will launch full scale commercial activities.

"QuantX provides an intuitive, easy to learn and use environment for efficient breast imaging decision support," commented Gillian Newstead, MD, QI Medical Director and former Chair of Breast Imaging at the University of Chicago. "We've waited a long time for a meaningful advancement in breast image analysis. QuantX fills that need."

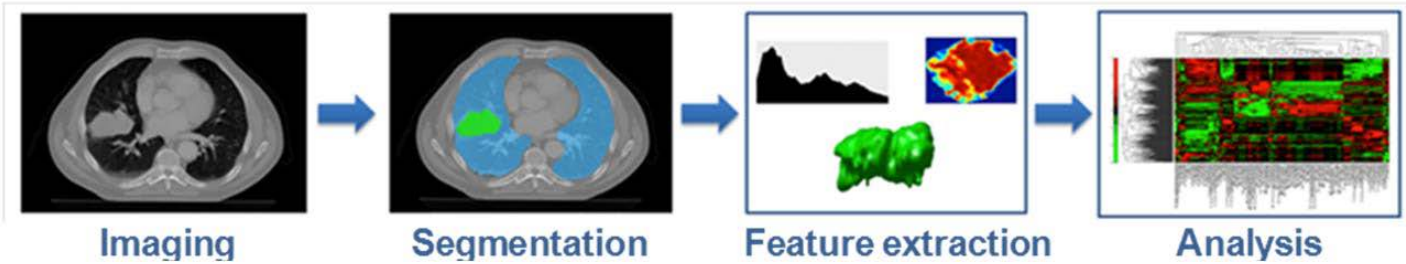
FDA De Novo for QuantX Advanced

FDA Clearance of QuantX SE

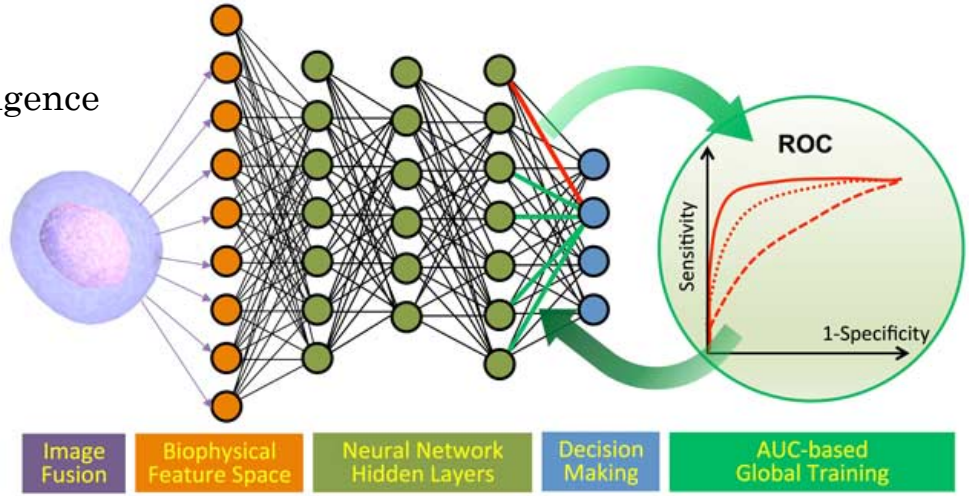
Successful FDA Clinical Study

University of Chicago

QIN embracing the use of Radiomics



Deep learning
Artificial intelligence



Big Issues in Big Data Facing NCI

From Dr. Sharpless

Workforce and career development

EHR Mining

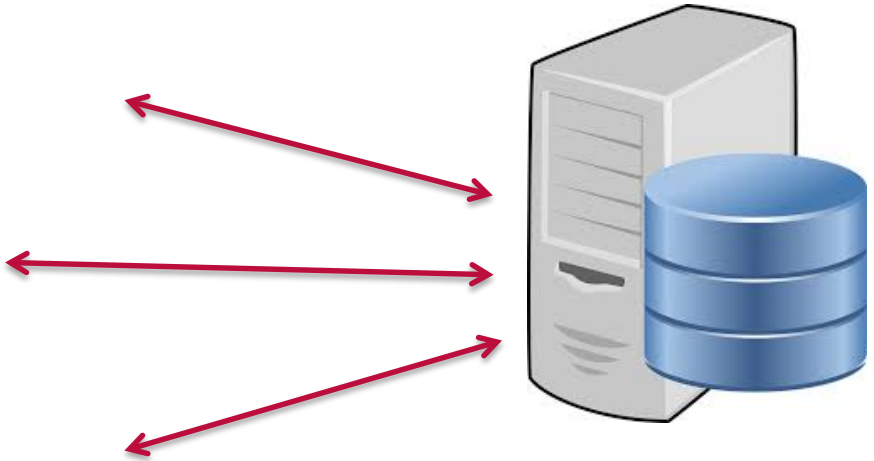
Storage – What? How Long? Cloud?

Security, privacy and de-identification

Use of challenges / prizes

CBIIT leadership

Challenges help to qualify tool performance



Common data set with training and testing imaging data outcome data

Current list of QIN challenges

	Title	Challenge or Collaborative project
1	PET Segmentation	Challenge- PET-CT WG
2	Dynamic PET/MISO	Collaborative Project- PET-CT WG
3	Interval Change using NLST Chest CT Scans	Challenge- PET-CT WG
4	CT Image Feature	Collaborative Project- PET-CT WG
5	Breast DCE-MRI	Collaborative Project- MRI WG
6	DCE-MRI Arterial Input Function	Collaborative Project- MRI WG
7	QIN ADC	Collaborative Project- MRI WG
8	DICOM Storage - Parameter Map Storage	Collaborative Project- MRI WG
9	DSC MRI	Challenge- MRI WG
10	Validation of Gradient non_Linearity Bias Correction	Collaborative Project -MRI WG
11	Breast MRI Metrics of Response (BMMR)	Challenge - MRI WG
12	Cerebral Blood Volume DSC MRI	Collaborative Project MRI WG
13	Differentiation of high-grade prostate cancer with DWMRI	Collaborative Project MRI WG
14	PET Hypoxia Measurement	Collaborative project PET-CT WG
15	Informatics Pipeline	Collaborative Project BIDS WG

Vision provided by Dr. Sharpless

- Clearly there are three bins of activity
  - Things we have to do
  - Things we want to do
  - Things we are already doing (but need ongoing attention)

- For the QIN, the things we have to do are the things we want to do.
- So let's look at the things we are doing vs. the things we still have to do.

Another look at the QIN roadmap…

✓ Things we are doing

- ✓ Evaluation of imaging hardware performance
- ✓ Creation of harmonization methods (software and protocol)
  - ✓ Reduce bias & variance during data collection
- ✓ Creation of robust algorithms to extract quantitative information from images

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- ✓ Testing and validating performance of algorithms
- ✓ Introducing candidate algorithms into clinical workflow
  - FDA and industrial interactions

To Participate in Precision Medicine

- It is important to distinguish patient characteristics sufficiently well to be able to select patients who will benefit from an intervention, sparing the expense and side effects from those who will not.
  - Quantitative Imaging can be a key player in this process.
  - But, quantitative imaging can only have value in this area if it can take a place as a reliable tool in clinical workflow.

The Great Divide

J Eary 2018


WARNING
Even more
CHALLENGES
AHEAD

Two Aspects to Clinical Utility

- Does the tool offer results that are useful to the oncologist?
  - It serves a clinical need
  - It is reliable and repeatable
- Does the tool fit into clinical workflow without disruption?
  - The tool is easy to use
  - The results are compatible with other clinical data

Engineering

Clinical

Bridging the Gap: Validating Tools

- Engaging in challenges to compete tools against one another on fixed data sets to determine superior performing tools
- Teams are using archived imaging data retrospectively to confirm tool performance characteristics
- Inserting tools into single-site clinical trials to gain information on tools performance in a clinical environment

Teams are reluctant to cross from development to validation.

Bridging the Gap: A Proposed New Mechanism

For new research team without experience in quantitative tool development and validation:

- Use the UG3/UH3 mechanism to create different network incentives.
  - Focus on algorithm software creation and verification in UG3.
  - Must focus on clinical validation & translation in UH3.
- UG3 no more than 2 years, UH3 not more than 4 years.
  - Total program: 5 years.
  - Transition from UG3 to UH3 is reviewed by program.

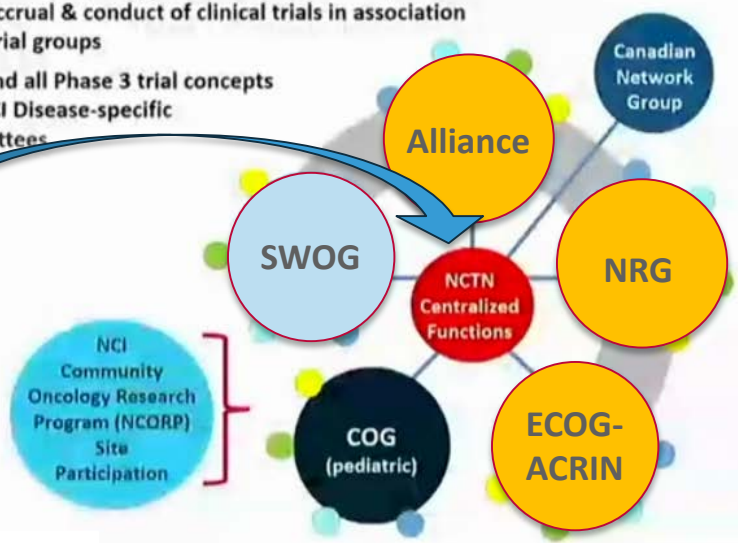
Bridging the Gap: A Proposed New Mechanism

For research teams experienced in quantitative tools development:

- Conversion of U01 cooperative agreement to R01 research grant
  - Transfer control of the network to the research teams, not NCI
  - Investigator-initiated research in the standard RPG pool
  - Center for Scientific Review panel will include clinical emphasis
  - Transition teams into other grant possibilities such as Academic Industrial partnership (PAR-18-009), and parent grant opportunities
    - Bring more industry perspective into the network

NCI National Clinical Trials Network (NCTN) Structure

- 5 US groups (4 adult & 1 pediatric) and 1 Canadian group
- Centralized functions for operational efficiencies & integrated with NCORP
- 30 Lead Academic Participating Sites provide leadership in development, accrual & conduct of clinical trials in association with the adult trial groups
- Large Phase 2 and all Phase 3 trial concepts evaluated by NCI Disease-specific Steering Committees



LEGEND:

- Centralized Functions:
  - Centralized Institutional Review Board
  - Cancer Trials Support Unit
  - Radiotherapy/Imaging Cores
  - Common Data Management System with Central Hosting
- 30 Lead Academic Participating Sites (LAPS)
- Operations Centers
- Statistics & Data Mgt Centers
- Tumor Banks
- Member Sites

IROC™
IMAGING AND RADIATION ONCOLOGY CORE
Global Leaders in Clinical Trial Quality Assurance

http://www.cancer.gov/clinicaltrials/nctn

QIN "SWAT" team to carry message to cooperative groups

- Robert Nordstrom, PhD: NCI
- Janet Eary, MD: NCI
- David Mankoff, MD: University of Pennsylvania and ECOG-ACRIN
- Paul Kinahan, PhD: University of Washington and ECOG-ACRIN
- Larry Schwartz, MD: Columbia University and Alliance
- Michael Knopp, MD, PhD: The Ohio State University and IROC
- Hui-Kuo Shu, MD, PhD: Emory University and NRG
- John Buatti, MD University of Iowa and NRG
- Maryellen Giger, PhD: University of Chicago

ECOG-ACRIN as a Member of QIN

- Aim 2: Develop the ECOG-ACRIN QIN Resource to support retrospective testing for single- or multi-site QIN projects that seek to develop effective and efficient metrics and analysis methods for trials using advanced imaging.
  - Use ECOG-ACRIN imaging and outcome data from completed ACRIN clinical trials as testbeds for QIN tool validation.
- Aim 3: Develop the ECOG-ACRIN resource to support prospective testing of novel imaging methods developed in the QIN.
  - Coordinate access to ACRIN clinical trials where prospective studies of QIN tool performance can be evaluated.

QIN tools are working in clinical trials

- **NCT02154490 Lung-MAP: Biomarker-Targeted Second-Line Therapy in Treating Patients With Recurrent Stage IV Squamous Cell Lung Cancer**

  Radiomics tools to assess response to therapy

- **A031704 PD-inhibitor (Nivolumab) and Ipilimumab followed by nivolumab vs. VEGF TKI cabozantinib with nivolumab in metastatic untreated REnal Cell CancEr [PDIGREE]**

  Volumetric / Necrosis / Radiomics tools to assess predictive and prognostic imaging biomarkers of response and progression

- **ALLIANCE A021602 - Randomized, Double Blinded Phase III Study of Cabozantinib versus Placebo in Patients with Advanced Neuroendocrine Tumors after Progression on Everolimus (CABINET)**

  Volumetric / Necrosis / Radiomics tools to assess predictive and prognostic imaging biomarkers of response and progression

- **A Randomized Phase 2 Study of Peptide Receptor Radio-Immune Therapy (PRRIT) in Gastro-Entero-Pancreatic Tumors, with Somatostatin Receptor Expression, and have progressed on Somatostatin Analog Therapy**

  Auto PERCIST tool

What more can QIN do to distribute tools?

- We are publishing and promoting tools at all possible opportunities.
- We are motivating teams to move to validation as quickly as possible.
- We are increasing industry and FDA participation in the network.
- We look to CTAC for additional ideas.
  - Are there ways to reduce the hurdles into clinical trials?
  - What would CTAC like us to do?


I'M LOOKING FOR THE ANSWER TO LIFE, SCHROEDER.. WHAT DO YOU THINK IS THE ANSWER?


Quantitative Imaging
!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!

www.cancer.gov

www.cancer.gov/espanol