A TRIBUTE TO LARRY CLARKE  
The Visionary and Innovator

Larry Clarke, the longtime NCI branch chief for imaging technology development, died on April 16, 2016. He was 72.

Clarke was a visionary in the field of medical imaging for cancer with a particular focus on quantitative imaging methods across a range of imaging modalities to support clinical decision-making and cancer research. He participated with others to establish several NCI programs and research networks for the development and validation of quantitative imaging methods for current and next-generation imaging platforms that support multi-center clinical trials and preclinical research, most notably the Quantitative Imaging Network (QIN).

His efforts as a co-chair of the Trans NCI-Center for Biomedical Informatics & Information Technology (CBIIT) imaging informatics working group stimulated the development of open-source informatics tools and imaging archives that permit the evaluation of clinical decision tools as applied to cancer and precision medicine.

Clarke was actively working with several international scientific societies, including SPIE, to support and adopt physical standards for imaging as a biomarker and to position imaging to play a significant role in NCI future precision medicine initiatives.

Larry was known as a driving force for cancer imaging innovation at the NCI and was instrumental to the development of academic-industrial partnerships to translate research and development of cancer imaging. Larry’s dedication to cancer research will always be remembered.

QIN BMRR Challenge

QIN recently started its Breast Metrics for Measuring Response
challenge. It is the first challenge that completed the QIN Executive Committee review.

The aims of the challenge are:

- To identify imaging metrics (predictors) derivable from contrast-enhanced breast MR images acquired in the ACRIN 6657 trial, that show statistically-significant association with RFS
- To demonstrate improvement in predictor performance over functional tumor volume (FTV), the primary imaging variable tested in ACRIN 6657.

Training data used will come from the TCIA and is comprised of 64 patients imaged at UCSF at multiple time points during neoadjuvant chemotherapy for invasive breast cancer. The test data, also provided by TCIA, will consist of 162 patients from the ACRIN 6657 trial, imaged at multiple institutions at multiple time points during neoadjuvant chemotherapy for invasive breast cancer.

**QIN Informatics**

The QIN BMMR Challenge will use [QIN SharePoint](http://qinlabs.cloudapp.net/competitions/9) to register the challenge. [QINLABS](http://qinlabs.cloudapp.net/competitions/9) has been developed to post detailed information about the challenge with evaluation criteria for the requirements and how the statistical evaluation will be performed at Brown University. [CodaLab](http://coda.cloudapp.net) is a cloud based environment, will be made available to assist participants on the management of the challenge. [NCIP-Hub](http://ncip.cloudapp.net) is gaining increasing usage as a collaborative tool offer by NCI to help participants communicate and discussed relevant issue regarding the challenge and deliberate on problem solving. Future plans are being developed to make the QIN SharePoint as the portal for access to dashboard information on the challenge that will connect participants to QINLABS, CodaLab, and NCIP-Hub.

**QIN Executive Committee**

In May, the 2016 QIN Executive Committee convened its first meeting after the April annual meeting. Larry Schwartz will serve as the EC chair for the coming year. The committee’s main focus will be to guide the QIN for clinical translation and will provide leadership on how to incorporate strategies within the QIN to ensure adequate progress is made to achieve this objective. One of the main drivers in this direction is creating and implementing a network framework to translate QIN tools and methods to clinical workflow. The Executive Committee will be considering methods to overcome obstacles in the path of translation into clinical utility for quantitative imaging tools. Schwartz is planning to present a number of guest lecturers at upcoming EC meetings to identify barriers and discuss strategies in the translation landscape.

**NCI-ITCR and the QIN**

The NCI established a funding mechanism titled Informatics Technology for Cancer Research (ITCR) to promote research-driven informatics technology across the development lifecycle to address priority needs in cancer research. Some QIN teams have secured support from ITCR to develop their informatics components to achieve the mission of the QIN. Since the start of the ITCR, a number of funded proposals not directly associated with a QIN team member support the goals and informatics aspirations of the QIN. These projects were recently demonstrated at the 2016 QIN Face-to-Face Meeting because of the amount of informatics related projects that support the networks efforts. Previous to the 2016 QIN Face-to-Face Meeting, the NCI –Center for Bioinformatics and Information Technology led a symposium in March for Cancer Informatics for Cancer Centers (Ci4CC) where QIN was well represented on panels and the lead program director for ITCR, Juli Klemm, expressed NCI firm support for the QIN in terms of NCI program support.

The ITCR has establish a Integration Working Group (IWG) to map out complimentary capabilities offered by ITCR U24 and U01 research groups where QIN has established good representation. The goal of the IWG will be to coordinate with ongoing ITCR working group efforts to develop prototypes demonstrating ability to integrate
ITCR tools from multiple ITCR research groups. The value of ITCR integration was emphasized at the Ci4CC Symposium to explore how to interface with industry to seek industry supported informatics tools for translational research.

The ITCR productive grant mechanism and showing of support for the QIN has created an opportunity for the QIN to start ascertaining how to effectively engage its potential product output as a program asset. In the future, the Cancer Imaging Program will work with the Bioinformatics/IT & Data Sharing Working Group will explore how the QIN can leverage QIN associated ITCR activities.

QIN Publications

CTDD Working Group Making Progress on Manuscripts for Clinical Trials

An advantage of the QIN is that teleconferences and face-to-face meetings allow time for semi-structured conversations about challenges each team faces in development of quantitative imaging biomarkers. A common theme emerging from discussions in the Clinical Trials Design and Development working group was the difficulties faced by groups trying to open and accrue to prospective clinical trials. There is a literature addressing barriers and potential solutions for accrual to clinical trials for novel oncology therapies, but no study has addressed accrual to studies involving quantitative imaging. Led by working group co-chair Brenda Kurland (University of Pittsburgh, University of Washington) the group developed a survey collecting basic study information, imaging protocol (including the time requirement for participation), accrual goals, accrual challenges, and thoughts on addressing accrual challenges. The survey included both single-best answer questions and free text fields.

Responses for 25 prospective studies were received from 12 sites (10 QIN and 2 international affiliates). The median planned rate of accrual was 15 patients/year, ranging from 4 to 500. The median actual rate of accrual was 11 patients/year, ranging from 1 to 280, for a median actual/planned yearly accrual of 73.33%. Half of the studies reported meeting or exceeding their annual accrual goals. Only 3/22 (14%) were accruing at less than half the rate planned, the benchmark for triggering formal review of studies performed at comprehensive cancer centers. Selective reporting may play a large role in these results, but the respondents may achieve relative success by having an experienced and motivated group of investigators that are highly motivated to accrue patients for successful study completion.

Accrual success occurred in spite of ambitious accrual goals and did not appear to be related to the amount of time required for research imaging. However, the time burden of research participation was listed as a frequent reason researchers believe patients decline participation (16%). Another common reason was a lack of patients meeting trial eligibility. Together these results suggest that clinical trials to develop imaging biomarkers to improve cancer diagnosis and treatment can be improved by (1) simplifying imaging protocols and trial eligibility to make rapid progress feasible in high-impact areas, and (2) better engagement with study participants, including monetary compensation. A manuscript summarizing survey results is under preparation.

Funding Opportunities

- PAR-14-166 (R01): Early Phase Clinical Trial in Imaging and Imaging-Guided Intervention
- PAR-16-176 (R21): NCI Clinical and Translational Exploratory/Development Studies which allows for early phase correlative & intervention studies
The Informatics Technology for Cancer Research (ITCR) Program is a trans-NCI program to support investigator initiated informatics technology development driven by critical needs in cancer research. It has the following characteristics:

- Broad-based and investigator-initiated
- Cancer research-driven informatics development
- Funding mechanism that support the informatics development lifecycle
- A cancer informatics review panel focusing on potential impact and research needs.

It is comprised of the following mechanisms:

- **Algorithm Development**
  
- **Prototyping & Hardening**
  
- **Enhancement & Dissemination**
  
- **Sustain**

**From the QIN Director**

The Quantitative Imaging Network has become a recognized leader in the quest to lift quantitative methods in imaging to clinical recognition. The QIN is demonstrating methods for reducing bias and variance in image data collection and has developed a large array of software tools capable of extracting quantitative information from images in order to measure or predict response of patients to therapy. The nature and extent of the accomplishments from the QIN are remarkable, and they become even more so considering the relatively short period of time in which these accomplishments have been made.

Much of this success can be attributed to the foresight and direction provided by Larry Clarke while he was with us, but we cannot forget to give credit where credit is due. That goes to the dedication and commitment that the individual investigators have made to working in the network environment. Teleconferences notwithstanding, the environment of network research is very much different from the R01 *modus operandi*. The effort investigators are making to balancing the research proposed in their original application with activities thrust upon them by network ties has not gone unnoticed by the program staff. I cannot promise a reduction in this kind of pressure, however. In fact, the opposite will likely be true. Emphasis on translation into clinical workflow will usher in
additional activities and processes. Interactions with industry and FDA coupled with previously unforeseen activities such as challenges will grow as clinical endpoints become better defined.

In the midst of this increased activity, the Cancer Imaging Program was successful in renewing the QIN program announcement for yet another three years. The new PAR should be ready by the first of the calendar year. We anticipate that the February 2017 receipt date will probably not occur under the current announcement (PAR-14-116), and will instead be the first receipt date for the new announcement. We cannot say anything about the new announcement at this time, except that it will continue to emphasize the attributes of the previous announcements (development, optimization, and validation of quantitative imaging tools for prediction or measurement of response to therapy in cancer). There will also be some new features, which you will have to wait and see. In the meantime, the current program announcement is open for business and we will continue to accept applications for inclusion in the QIN.

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