National Cancer Institute
Clinical Trials and Translational Research
Advisory Committee (CTAC)

Quantitative Imaging Network (QIN) Working Group

Working Group Report
March 12, 2020

The report was accepted at the March 12, 2020 CTAC Meeting

TABLE OF CONTENTS

CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE (CTAC)
QUANTITATIVE IMAGING NETWORK (QIN) WORKING GROUP REPORT

QIN WORKING GROUP REPORT, MARCH 2020

INTRODUCTION

Quantitative imaging is the extraction of quantifiable features from medical images to assess the status or change in a disease. It sits at the crossroads of imaging, analytics, and informatics to provide quantitative tools for clinical decision support. It can offer valuable anatomic, physiologic, metabolic, and molecular information, provide important insights into disease location and stage, and reduce the need for multiple biopsies.

The goal of National Cancer Institute's (NCI) Quantitative Imaging Network (QIN) is to improve the role of quantitative imaging for clinical decision making in oncology. The QIN does this by the development and validation of data acquisition, analysis methods, and tools to tailor treatment to individual patients and to predict or monitor the response to drug or radiation therapy.

To date, 67 QIN tools have been benchmarked to determine their readiness for clinical use. A link to a list of these tools can be found in Appendix 2. QIN roadmap benchmarks are listed below and in Appendix 4:

1. *Pre-Benchmark:* Evaluate imaging hardware performance
2. *Basic-Benchmark:* Create harmonization methods (software and protocol)
3. *Technical Test-Benchmark:* Create robust algorithms to extract quantitative information from images
4. *Clinical Trial-Benchmark:* Test and validate performance of algorithms
5. *Clinical Use-Benchmark:* Introduce candidate algorithms into clinical workflow

The recommendations outlined in this report focus on moving QIN tools towards clinical trial validation and clinical utility. Currently, of the 67 QIN tools, 13 have achieved QIN benchmarks for further clinical development with the ultimate goal of both clinical research and clinical implementation.

While the QIN has been remarkably productive in developing and benchmarking tools that should have clinical utility, it has experienced significant challenges in testing and validating tool performance due to the inability to introduce candidate tools into clinical workflow.

During the July 2018 Clinical Trials and Translational Research Advisory Committee (CTAC) meeting Dr. Robert Nordstrom (NCI Cancer Imaging Program, Director of QIN) presented on the QIN and the significant challenges it has encountered with testing and validating benchmarked QIN tools in clinical trials. The presentation was followed by a discussion on how to optimize the utilization of QIN tools in NCI's National Clinical Trials Network (NCTN). During the following CTAC meeting, CTAC members voted to form a Quantitative Imaging Network Working Group (QIN Working Group). The Working Group was charged with advising the NCI on strategies for enhancing the integration of quantitative imaging tools,

first into NCTN clinical trials, and ultimately into clinical practice. Specifically, the QIN Working Group was convened to assess the current status, identify barriers to QIN tool use, and recommend strategic approaches for enhancing integration of QIN tools into NCI-supported clinical trials.

The QIN Working Group was chaired by Dr. Janet Dancey (Queen's University, Kingston ON) and comprised of selected members from CTAC, as well as individuals from the scientific community with appropriate expertise (Appendix 1). The Group met via webinars between August and November 2019 to discuss challenges and solutions for the translation of QIN tools into clinical trial workflow. Discussions focused on methods to provide support to both the QIN investigators and the NCTN groups to realize the transition of QIN tools into the clinical environment. The Working Group also provided recommendations for developing QIN tools that fulfill identified needs of the NCTN groups. This document summarizes the Working Group's deliberations and recommendations for integration of QIN tools into NCTN clinical trials.

The Working Group concluded that three NCI programs (the NCTN, the Imaging and Radiation Oncology Core (IROC), and the QIN) need to work together to enhance the integration of quantitative imaging tools developed by QIN into the NCTN clinical trial workflow. Information on the three NCI programs is provided in the *Background* section of this report. In the *Recommendations* section, the Working Group provides six specific recommendations to facilitate these efforts.

BACKGROUND

Quantitative Imaging Network (QIN)

The QIN program was created in 2008 and currently consists of 20 research teams composed of US and international research investigators. The focus of QIN is facilitating clinical decision making through the development and clinical validation of quantitative imaging tools and developing methods for the measurement or prediction of tumor responses to therapies in clinical trials. QIN research projects focus on image-derived quantitative measurements of responses to therapy during clinical trials and standard clinical care. Projects include development and adoption/implementation of quantitative imaging methods, imaging protocols, and software solutions/tools (used with existing commercial imaging platforms and instrumentation), as well as application of these methods in current and planned therapeutic clinical trials (Appendix 2 and 3).

The QIN aims to carry out translation and validation of benchmarked tools into clinical trials, and ultimately into clinical practice. The NCTN provides an ideal venue for multi-site testing of QIN tools in the context of well-designed cancer clinical trials. Outreach efforts to NCTN clinical trialists have begun, with the goal of testing QIN tools in clinical trials as integrated markers and incorporating tools as integral markers in clinical trials once they are clinically validated.

QIN senior leadership has participated in NCTN group annual meetings (ECOG-ACRIN Cancer Research Group in 2016, Alliance for Clinical Trials in Oncology in 2017, and NRG Oncology in 2019) in order to introduce group disease committees to quantitative imaging tools. A visit to SWOG Cancer Research Network is on the QIN senior leadership schedule for April 2020. At each of these group meetings, tailored presentations on tool design and performance were made to the specific group disease committees where the tool would have relevance. Additionally, all the group imaging committees were

provided general presentations on the QIN tools. A number of NCTN clinical trials where QIN tools could be demonstrated were identified during these meetings.

Currently, 5 NCTN multi-site trials are using QIN tools (Appendix 5) and the QIN program aims to expand their interaction with the NCTN beyond these clinical trials. Suitable matches between QIN tools and NCTN clinical trials will allow tool translation, validation, and improvement in clinical trial endpoints, workflow, and clinical practice. The QIN Working Group provided recommendations to facilitate the clinical translation and validation of QIN tools within the NCTN, as well as the incorporation of QIN tools as integral and or integrated biomarkers into current and future clinical trials. A link to find additional information on this program is provided in Appendix 2.

NCI's National Clinical Trials Network (NCTN)

NCI's National Clinical Trials Network (NCTN) is a collection of organizations and clinicians that coordinates and supports cancer clinical trials at more than 2,200 sites across the United States, Canada, and internationally. The NCTN provides the infrastructure support for NCI-funded phase 2 and 3 therapeutic trials and primary advanced imaging trials. The NCTN consists of four adult network groups (Alliance for Clinical Trials in Oncology, Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN) Cancer Research Group, NRG Oncology, and SWOG Cancer Research Network) and one group focused solely on conducting clinical trials in childhood cancers (Children's Oncology Group (COG)). The Canadian Cancer Trials Group (CCTG) partners with the US Network Groups in the conduct of select late-phase multi-site therapeutic clinical trials. A link to find additional information on this program is provided in Appendix 2.

NCI's Imaging and Radiation Oncology Core (IROC)

To help monitor and ensure quality in NCTN trials utilizing radiation oncology and/or diagnostic imaging, NCI established IROC. IROC assists all the NCTN groups that use these modalities in their clinical trials. IROC offers integrated diagnostic imaging and radiation oncology quality assurance and control programs in support of the NCTN, ensuring that patients treated at different facilities receive the same doses, independent of operating machine, and assuring high quality data for NCTN clinical trials. IROC provides four main services to the NCTN groups: (1) establishment of appropriate quality assurance/quality control (QA/QC) procedures to support advanced medical imaging and radiotherapy; (2) consultation with the NCTN groups in the development of research protocols to assist with hypothesis generation and trial design that can be supported by effective QA/QC programs; (3) providing of resources for the collection, qualification, analysis, archive, and transfer of images, radiotherapy plans, and associated clinical data; and (4) development of qualification and credentialing policies to help ensure the delivery of appropriate protocol-specified radiotherapy and advanced imaging. A link to find additional information on this program is provided in Appendix 2.

RECOMMENDATIONS

Quantitative imaging tools have the potential to offer valuable anatomic, physiologic, metabolic, and molecular information to clinical trials, provide important insights into disease location and stage, and reduce the need for additional biopsies. These tools could be useful for identifying patients who are likely to do well with a specific intervention, providing valuable tools in the clinical armamentarium to

support clinical decisions. The QIN Working Group reviewed benchmarked QIN tools, along with their use in NCTN clinical trials to date, and provided the following high-level recommendations.

Recommendation 1.   Form a pipeline oversight committee which includes NCTN, IROC and QIN leadership, as well as NCI program staff to assess advanced QIN tools for NCTN clinical trial validation.

Although the goal of QIN is to translate quantitative imaging methods and algorithms used as clinical decision support tools into clinical utility, QIN investigators are often not closely integrated with the clinic or clinical practice. This represents a significant barrier for communication between QIN investigators and the clinical trial community, and therefore translation of the developed tools into clinical workflow. This recommendation allows for active engagement and discussion between the QIN tool developers and NCTN clinical trialist to identify QIN tools that can be brought forward into clinical trials, and recommendations for the development and prioritization of QIN tools to fulfill identified needs within the NCTN.

Specific suggestions:

a. Formalize an NCTN-QIN Working Group that builds upon the current structure and includes QIN leaders, NCTN scientific committee members, and clinical trial leaders to guide QIN tool development and clinical assessment. This group would be tasked with identifying QIN tools for further development that will have the highest interest and greatest potential and impact within the NCTN. Members of this group would also be tasked with identifying—early on—NCTN trial concepts that would benefit from alternate endpoints using imaging quantification methodology.

b. Develop "Fit-for-Purpose assessment (FFP)" criteria for QIN tools to establish requirements for translating QIN tools into clinical workflow. FFP is defined as the process through which the operating characteristics and proposed deployment of specific tools are sufficiently designed to yield interpretable results that address the specific research question. Examples of FFP criteria include clinical site assessment, image data acquisition and analytics, standard operating procedure development, tool training, and quality assurance/quality control. An important component of FFP is the development of NCTN clinical trial adoption plans for QIN tool use in standard clinical practice to enable site and research involvement, education, and training, as well as promote the communication of materials. Additionally, FFP would ensure regulatory compliance with expertise available to plan and enable regulatory filing as needed.

Recommendation 2.   Provide opportunities for QIN and NCTN scientific leadership engagement and collaboration.

This recommendation encourages integration and communication between QIN and NCTN scientific leadership, with the goal of better representation of QIN investigators on disease and imaging committees across all NCTN groups. Ultimately, QIN investigators and clinical trialists need to work together at an early stage of trial development to better understand the needs of both groups and develop tools to meet those needs.

Specific suggestion:

Ensure interaction between QIN and NCTN scientific leadership so QIN investigators can assess, and be aware of, NCTN trial opportunities during the early stages of trial development. Additionally, NCTN scientific leadership can communicate their needs to the QIN leadership to

guide novel tool development and to prioritize existing QIN tools. To support these efforts, NCTN imaging committees with multi-disciplinary representation should be encouraged to include, or increase, quantitative imaging expertise in their membership. NCTN leadership should include or invite *ad hoc* QIN investigators to participate in NCTN group scientific committees, and QIN senior leadership should continue to present at annual NCTN group meetings.

Recommendation 3. Promote and incentivize QIN tool development and readiness for NCTN deployment.

This recommendation encourages the allocation of resources for the increased utilization of efforts already taking place at IROC and ECOG-ACRIN. Existing and ongoing efforts should be leveraged to ensure that QIN tools meet clinical needs and can be tested in the NCTN.

Specific suggestions:

a. Encourage the utilization of current imaging platforms, with a specific focus on IROC, to assess the clinical utility and validation of benchmarked QIN tools. In addition, IROC procedures should be utilized to capture image data from NCTN trials using QIN tools, focusing on biomarkers and trial endpoints. These activities may require additional datasets that are captured at the time of protocol development. Additional resources need to be made available to NCTN groups and IROC to support this goal.

b. Leverage current NCTN quantitative imaging expertise to increase quantitative imaging awareness within the NCTN. ECOG-ACRIN is charged with supporting imaging science, including quantitative imaging science, across all NCTN groups. Alliance, NRG, and SWOG also have well-developed and active imaging committees. NCI should incentivize NCTN groups to expand their clinical imaging committees and clinical trials portfolios to incorporate QIN tools.

c. Provide resources to NCTN group operations and statistical centers to include clinical translation and validation of QIN tools within their trials. Support should be provided for assistance with imaging devices, acquisition standardization, and collection.

Recommendation 4. Ensure imaging scientists, clinical radiologists, and clinical trial Investigators understand the utility of incorporating QIN tools and how to develop appropriate endpoints for those tools in their trials.

Recommendation 5. Ensure that NCTN sites are ready to open trials that include QIN tools.

This recommendation aims to ensure the clinical trial and the imaging protocol that is associated with it are ready for deployment (i.e., have the capacity to gather data and have quality assurance and control measures in place).

Specific suggestions:

a. Ensure that the quantitative imaging tools fit within the clinic workflow.

b. Provide support and resources to ensure the quality of image data acquisition, tool application, and data transfer for sites.

c. Define the plan for the analysis, interpretation, and reporting of data from QIN tools at the time of protocol development.

d. Have a quality control feedback mechanism in place; IROC and the QIN should provide feedback to the NCTN sites utilizing QIN tools.

Recommendation 6.   Support image data banking and sharing with accompanying metadata from NCTN trials in an archive such as The Cancer Imaging Archive (TCIA). The TCIA has the potential to be a valuable resource for future research.

Specific suggestions:

Potential data sources include images and results from:

a. NCTN trials (specifically, trials with imaging data); areas of particular interest include immunotherapy trials with image-based response endpoints and trials using emerging response measures for positron emission tomography (PET), e.g., PERCIST (PET response criteria in solid tumors) and magnetic resonance imaging (MRI).

b. Existing image repositories in IROC; these repositories should be catalogued for possible QIN tool testing.

CONCLUSION

It is critically important to distinguish patient characteristics sufficiently well enough in order to select patients who will benefit from an intervention. QIN tools can be key in this process, but only if the tools can be reliably utilized in the clinical workflow. For this to occur, the quantitative imaging tools must meet a clinical need, be validated and reliable, and be easy to use and interpret. To meet these demands, quantitative imaging tools developed by the QIN will need to be utilized in clinical trials to gain information on tool performance and for clinical validation. NCTN, IROC, and QIN (NCI programs) can work together toward integrating QIN tools into NCTN clinical trials but resources must be provided to do this.

This report outlines a series of recommendations that could be instrumental in addressing the most important challenges to enhance the integration of QIN tools into NCTN clinical trials. Although not exhaustive, this series of recommendations lays the groundwork for accelerating the translation and validation of benchmarked tools into clinical trials, and ultimately, to clinical practice.

APPENDICES

Appendix 1:   QIN Working Group Roster

Appendix 2:   Additional NCI Program Information

Appendix 3:   NCI QIN Principal Investigators

Appendix 4:   QIN Tool Benchmarking Progression Cycle & Benchmarked QIN Tools Ready for Clinical Validation Studies in NCTN Trials

Appendix 5:   NCTN Trials Using QIN Tools

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
Clinical Trials and Translational Research Advisory Committee

***Ad hoc* Quantitative Imaging Network Working Group**

CHAIR

Janet E. Dancey, M.D., F.R.C.P.C.
Professor
Department of Oncology
Queen's University
Director, Canadian Cancer Trials Group
Kingston, Ontario, Canada

MEMBERS

David F. Arons, J.D.
Chief Executive Officer
National Brain Tumor Society
Watertown, Massachusetts

John Buatti, M.D.
Professor and Chair
Department of Radiation Oncology
University of Iowa
Iowa City, Iowa

Susan Chang, M.D.
Director, Division of Neuro-Oncology
Director, UCSF Neuro-Oncology Gordon
Murray
  Caregiver Program
Co-Director, Sheri Sobrato Brisson Brain
Cancer
  Survivorship Program
University of California, San Francisco
San Francisco, California

Walter J. Curran, M.D.
Executive Director
Winship Cancer Institute of Emory University
Department of Radiation Oncology
Emory University School of Medicine
Atlanta, Georgia

Michael Knopp, M.D., Ph.D.
Professor of Radiology
Department of Radiology, Division of
  Imaging Science
Vice Chair of Research
Novartis Chair of Imaging Research
Director, Wright Center of Innovation in
  Biomedical Imaging
The Ohio State University
Columbus, Ohio

Patrick, J. Loehrer, Sr., M.D.
Director
Indiana University Melvin and
  Bren Simon Cancer Center
Associate Dean for Cancer Research
Indiana University School of Medicine
Indianapolis, Indiana

David A. Mankoff, M.D., Ph.D.
Gerd Muehllehner Professor of Radiology
Vice-Chair for Research
Department of Radiology
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Lawrence H. Schwartz, MD
James Picker Professor and Chair
Department of Radiology
Columbia University Medical Center
Service Chief and Attending Physician
New York-Presbyterian Hospital
New York, New York

Executive Secretary

Steven A. Reeves, Ph.D.
Program Director
Coordinating Center for Clinical Trials
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

Additional information about NCI's IROC, NCTN, and QIN programs can be found at the following links:

IROC: https://www.irocqa.org/

NCTN: https://www.cancer.gov/research/areas/clinical-trials/nctn

QIN: https://imaging.cancer.gov/programs_resources/specialized_initiatives/qin/about/default.htm

The QIN currently has two grant support announcements. The first calls for a two-phase research project to develop and then validate quantitative imaging tools designed to provide clinical decision support to measure or predict therapy response during clinical trials. In the first phase (a UG3 mechanism), investigators develop software tools and methods to measure or predict therapy response from medical images recorded during clinical trials or standard of care. The development phase includes the construction and testing of imaging phantoms or calibration kits for image device evaluation, use of retrospective image data to test and train algorithms, or any other activity that will prepare the research for eventual validation in clinical trials. The second phase of this support mechanism (a UH3 mechanism) is dedicated to validation of the tools in one or more clinical trials.

The second grant support mechanism is the standard NIH R01 application. Originally, the mechanism for QIN support was the cooperative agreement U01. This was used to include NCI program involvement with network organization at the start of the program and was eventually converted to the R01 mechanism after network organization and details were established. Listed in the table below are the names of QIN Principal Investigators along with their affiliated institution:

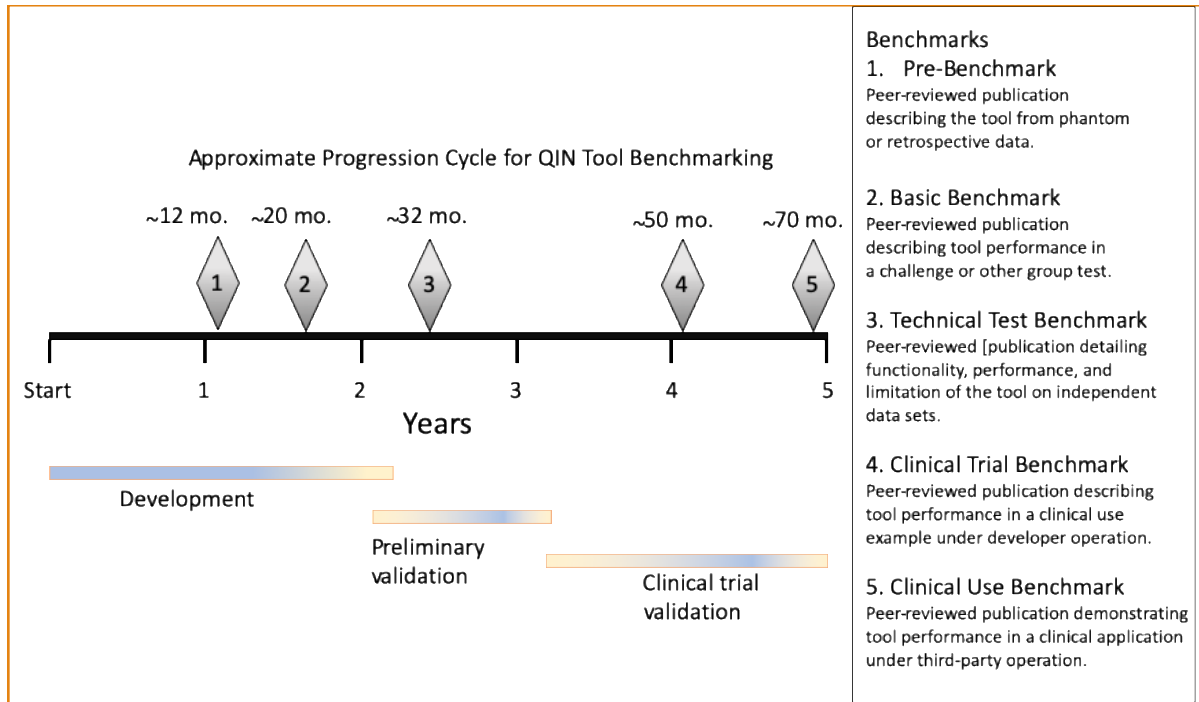| Investigator	Institution
Hugo Aertz	Dana Farber Cancer Center
Robert Avedry	Children's Hospital of Philadelphia
John Buatti	University of Iowa
Yue Cao	University of Michigan
Amita Dave	Memorial Sloan Kettering
Brad Erickson	Mayo Clinic
Fiona Fennessey	Brigham & Women's Hospital
Eric Frey	Johns Hopkins University
Maryellen Giger	University of Chicago
Robert Gillies	Moffitt Cancer Center
Lubomir Hadjiyski	University of Michigan
Wei Huang	Oregon Health & Science University
Nola Hylton	University of California, San Francisco
Gne Kim	New York University
Harrison Kim	University Alabama at Birmingham
Paul Kinahan	University of Washington
Anant Madhuranthakam	University of Texas, Southwestern Medical Center

Investigator	Institution
Michael McNitt-Gray	University of California, Los Angeles
James Mountz	University of Pittsburg
Sandy Napel	Stanford University
Sadek Nehmeh	Memorial Sloan Kettering
Fred Prior	Washington University
Chad Quarles	St. Joseph's Hospital
Bruce Rosen	Massachusetts General Hospital
Brian Ross	University of Michigan
Daniel Rubin	Stanford University
Mitch Schnall	ECOG-ACRIN
Hyunsuk Shim	Emory University
Kathleen Schmainda	Medical College of Wisconsin
Larry Schwartz	Columbia University
Bachir Taouli	Mount Sinai
Richard Wahl	Johns Hopkins University
Thomas Yankeelov	Vanderbilt University

QIN Tool Benchmarking Progression Cycle

Approximate Progression Cycle for QIN Tool Benchmarking

Benchmarks

1. **Pre-Benchmark**
Peer-reviewed publication describing the tool from phantom or retrospective data.

2. **Basic Benchmark**
Peer-reviewed publication describing tool performance in a challenge or other group test.

3. **Technical Test Benchmark**
Peer-reviewed [publication detailing functionality, performance, and limitation of the tool on independent data sets.

4. **Clinical Trial Benchmark**
Peer-reviewed publication describing tool performance in a clinical use example under developer operation.

5. **Clinical Use Benchmark**
Peer-reviewed publication demonstrating tool performance in a clinical application under third-party operation.

Benchmarked QIN Tools for Clinical Validation in NCTN Trials

Information on the benchmarked tools can be found at the following link:

https://imaging.cancer.gov/programs_resources/specialized_initiatives/qin/tools/default.htm

NCTN trials using benchmarked QIN Tools:

- SWOG Lung-MAP (NCT03851445): A Master Screening Protocol for Previously-Treated Non-Small Cell Lung Cancer
    - Solid Segmentation tool
- Alliance CALGB-80802 (NCT01015833): Sorafenib Tosylate With or Without Doxorubicin Hydrochloride in Treating Patients With Locally Advanced or Metastatic Liver Cancer
    - Solid Segmentation tool
- Alliance A021602 (NCT03375320): Cabozantinib S-malate in Treating Patients With Neuroendocrine Tumors Previously Treated With Everolimus That Are Locally Advanced, Metastatic, or Cannot Be Removed by Surgery
    - PET Tumor Segmentation tool
- Alliance A021202 (NCT01841736): Prospective randomized phase II trial of pazopanib versus placebo in patients with progressive carcinoid tumors (CARC)
    - PET Tumor Segmentation tool
- Alliance CALGB-50604 (NCT01132807): Chemotherapy Based on Positron Emission Tomography Scan in Treating Patients With Stage I or Stage II Hodgkin Lymphoma
    - PERCIST tool
- ECOG-ACRIN 1183: FDG PET to Assess Therapeutic Response in Patients with Bone-Dominant Metastatic Breast Cancer, FEATURE
    - AutoPERCIST Tool