

**National Cancer Institute, Clinical Imaging Steering Committee**  
***Improving Brain Tumor Characterization with Advanced Neuroimaging Methods***  
**NCI Shady Grove, Rockville MD, April 18-19, 2018**

*Committee Co-Chairs: Michael Knopp, M.D., Ph.D., Neil Rofsky, M.D.*  
*Leadership: Lalitha Shankar, M.D., Ph.D., Steven Reeves, Ph.D.*

**Introduction/Meeting Description:**

The Clinical Imaging Steering Committee (CISC) meeting was held April 18-19, 2018 at NCI-Shady Grove in Rockville, MD. Attendees included clinicians and researchers with expertise in neuro-oncology and clinical imaging. Subgroup focus areas were multiparametric and radiomic assessment, pediatric neuroimaging, and implementation of advanced imaging methods. Objectives were to discuss the development of brain tumor imaging techniques and how to integrate them into clinical trials, as well as to prepare recommendations for a subsequent white paper(s).

**Background:**

Recent NCI neuroimaging trials have focused on predictive and prognostic biomarker development and pharmacodynamic studies. Methods range from magnetic resonance imaging (MRI) based diffusion-weighted imaging (DWI) and magnetic resonance spectroscopy (MRS), to 3'-deoxy-3'-<sup>18</sup>F-fluorothymidine positron emission tomography ([<sup>18</sup>F]FLT-PET) imaging. There is a need to increase the impact of imaging in clinical trials for patient benefit. Integration of imaging markers as an inherent part of study design is a key step to reaching this goal.

**Challenges and Advances in Neuro-Oncology Subspecialties:**

Neuro-oncology relies on quality imaging methods. Progress in standardization, and international collaboration has resulted in guidelines to reduce variability and improve sensitivity and specificity. Neurosurgery's critical role is to remove a maximal amount of tumor while preserving function. Quantitative image guided methods are key to advance tailored therapy, localize deep lesions, and provide therapeutic delivery to the brain. Neurosurgery can provide validation of novel technologies and help distinguish tumor recurrence versus pseudoprogression. Similarly, intraoperative CT and MRI have shown benefit for real-time assessment of resection and reduction in brain shift, but need optimization to reduce cost and improve efficiency. The multi-modal nature of radiation oncology holds promise to selectively treat tumor. Goals are to reduce radiation risk to healthy tissue, improve methodology, and focus on patient well-being. Ultrasound, fluorescence, and photon imaging are viable, yet will require further study. The committee also discussed the need to collaborate with clinicians and researchers and to have CISC members advocate for committee interests.

**RANO/BTIP**

RANO (Response Assessment for Neuro-Oncology) expands on prior response criteria, with the inclusion of non-enhancing tumors, T2/FLAIR, pseudoprogression, and a requirement for response confirmation. FLAIR has been challenging to quantify and characterize, raising questions about its inclusion in future studies. Immunotherapy-RANO (iRANO) was developed in response to RANO's miscategorization of pseudoprogression in patients undergoing immunotherapy, which resulted in patients being prematurely removed from study. Consultation with the FDA highlighted standardization issues and led to the development of Brain Tumor Imaging Protocol (BTIP), now *required* by NCI CIP and CTEP for new studies.

Standardization is important for reducing variability caused by protocol differences and contrast timing. BTIP focuses on synergy and compatibility in clinical MRI protocols to maximize compliance and data quality and is now integrated in most new malignant glioma trials. Movement towards automatic volumetric segmentation and feature extraction will further improve data consistency and reliability.

Current literature supports use of 3D IR-GRE (inversion recovery fast gradient echo) imaging methods due to existing Alzheimers's Disease Neuroimaging Initiative (ADNI) standards, documented accuracy, and vascular enhancement that can verify tumor angiogenesis. Debate continues over the definition and occurrence rate of pseudoprogression, especially in immunotherapy, thus emphasizing the need for consensus. Future directions include developing 1) more effective ways to differentiate non-enhancing tumors, 2) measures of clinical deterioration, 3) instruments for measuring Quality of Life (QoL), 4) guidance for steroid requirements and 5) specific criteria for low- grade gliomas. Approaches combining imaging with neuro-cognitive function, growth trajectory and clinical outcomes will best enhance characterization. Furthermore, there is a focus on relating patient symptoms to diagnostic signs of progression and applying these findings to treatment decisions.

Improved baseline diagnostics, measures for T2/FLAIR, iRANO validation, and pathology based identification of residual disease are also in the pipeline.

#### **Utility of Advanced MR Techniques**

Dynamic contrast-enhanced (DSC) MRI of the brain has been available for decades, but rarely incorporated due to a lack of standardization. Difference in parameter selection have led to significant variability in reported outcomes. American Society of Functional Neuroradiology (ASFNR) recommendations have been used to guide standardization efforts and improve consistency in segmentation, lesion extraction, and post-processing. Single dose protocols with low flip angle are favorable due to low error rate and reduced need for contrast. Other key parameters are fractional tumor burden, which shows predictive value for OS, as well as repeatability, which is vital to determining statistical power/ trial size. Vessel size and architecture markers may aid future assessment of prognosis and response.

Permeability is another technique requiring standardization and updating since prior Quantitative Imaging Biomarker Alliance (QIBA) guidelines published in 2012. New methods such as compressed sensing and K-trans will help improve image frequency and coverage. Use cases include target engagement/early response, surgical resection guidance, and enhanced biopsy capabilities guided by K-trans. Automation, B1 correction and a balance between progress and standardization will be necessary moving forward. Arterial spin labeling (ASL) allows assessment of the complete vascular compartment. The technique is unaffected by the blood brain barrier (BBB) and provides a direct quantifiable measure of blood flow, best used in low grade tumors. Preliminary indications show ASL can be an effective quantitative imaging biomarker.

Diffusion is useful for clinical imaging due to its sensitivity to tissue properties like cell density. Approaches include isotropic DWI, apparent diffusion coefficient (ADC), diffusion tensor imaging (DTI), intravoxel incoherent motion (IVIM) and non-Gaussian techniques. ADC can provide whole

lesion metrics, voxel-based functional diffusion, and histogram tumor segmentation. Important considerations for standardization include centralization, mitigating system bias, and site certification for scanner performance. Isotropic techniques and high b-value microstructural tumor analysis are most promising for near-future studies. Another advanced technique, 2HG imaging, can easily be used to clinically monitor treatment due to a standard 97-ms detection time, high sensitivity and specificity. Currently, challenges exist with acquisition, voxel placement, shimming, data processing, and interpretation. New protocols are improving pre-processing, thus enhancing outcome data. International Society for Magnetic Resonance in Medicine (ISMRM) also recently published methodologies for application of these methods.

PET techniques continue to emerge and markers are being widely investigated. Applications for PET include distinguishing tumor growth from necrosis and monitoring response. FLT, FDG and FDOPA exhibit complementary strengths and enhanced background ratios. FDOPA has been used to detect prostate cancer and shows promise for an amino acid agent for metabolic tumor imaging. However, FLT methodology and clinical relevance remain to be established. PET/MR is also useful for response assessment to help address unexplained variability in patient outcome and provides functional and anatomical information about the brain. Information gained on differential tumor biology can facilitate personalized therapy. Current priorities are increasing patient accrual, shortening scan time, addressing multi-modality logistics, standardization, and availability of PET tracers. Finding methods to improve cost-effectiveness, and encourage patient participation, as well as obtaining site agreement on standard PET sequences will be beneficial.

### **Pediatric Neuroimaging**

Despite a sharp increase in knowledge of the genomics of pediatric brain tumors, the translation of this knowledge into clinical practice remains a challenge. Survival rates have been stagnant, prompting changes in treatment. Integrated genomics can aid in tumor classification as seen in medulloblastoma data showing poorer prognosis in WNT vs SHH tumors, and help guide treatment. Other efforts will focus on subgroup analysis of metastatic disease and the transition from morphological diagnosis to less invasive methods. Given the many heterogeneous tumor types requiring different imaging protocols, RAPNO (pediatric RANO) criteria needs to be expanded and should incorporate molecular subgroup analysis. Technical considerations include optimizing volume measurements, standardizing software, and incorporating advanced MR imaging metrics beyond T2 contrast.

### **Clinical Trial Issues/Logistics/Patient Perspective**

Patients are becoming more informed on their diagnosis and treatment, requiring equal dedication and innovation from the clinical team. Standards must be developed to reduce scanner variability and establish early detection strategies. The patients are the core of the clinical trial and their perspectives and experience should be considered to minimize patient burden, improve imaging protocols, and provide necessary incentives and outcome information. Additional communication with the clinician, dedicated imaging manuals, and more timely reporting were suggested to increase site compliance, and reduce ambiguity and inconsistency in protocol language.

### **Emerging Metric and Radiomics**

Clinically relevant metrics require robust methods, widely available software, intuitive processes that

can be readily interpreted, and timely image generation and visualization. Emerging ideas are metrics tailored to the analysis needed, down to the lesion level. Multi-site studies analyzed with statistical rigor are key to understanding the full potential of quantitative imaging. Radiomics fits into the context of big data and machine learning. Efforts to move away from qualitative image interpretation and traditional radiology reports have led to new software such as VASARI, which allows quantitative standardization at the time of feature capture. Regional tumor texture, intensity, morphology and prognosis, can also be determined. Similarly, a defined path of progression is desired for future quantitative imaging biomarkers. Discussion covered the goal of increasing data availability and the timing and methods to do so. Suggested approaches to advance methodology into clinical trials were NCTN/NCORP supported analytics with large clinical data sets and capitalizing on deep learning and automated techniques.

**Consensus & Recommendations:** (Immediate/3-5 years)

There are promising technologies that could profoundly impact diagnosis, monitoring and treatment, but need standardization, method development and well-controlled clinical trials.

Subgroup Reports:

**Implementation of Advanced Imaging Methods in Clinical Trials**

- Adopt BTIP methodology in clinical trials
  - QC efforts headed by Michael Knopp
  - BTIP-centric trials to study tumor size, growth rate, and morphology as risk factors
- Obtain FDA approval of standard analysis for segmentation to encourage consistency
- Develop new PET agents, address availability and potential to identify microglial activation
- Improve standardization across all methods; apply to multi-center setting
- Reassess the validity of validation process for trial sample selection
- Find new ways to incentivize trial participation
- *Implement trial designs focused on a specific diagnostic problem*

**Multi-Parametric and Radiomic Assessments**

- Identify computational methods to extract quantitative features from radiographic images informative of patient/disease status, and feasible for incorporation in clinical trials
- Anticipate and address the needs of the oncologist and clinical trialists
- Balance innovation with necessity of standardization
- *Refine definition of pseudoprogression within the context of iRANO criteria*

**Pediatric Neuroimaging**

- Shorten trial completion and reporting time
- Standardize and differentiate image protocol design in clinical trials
- Create superuser group to facilitate uniform imaging practice and dissemination across clinical imaging sites
- Incorporate latest WHO classification schemes (e.g. molecular subgroups) in protocols
- Integrate functional data and quantify long-term sequela of treatment effects
- Include artificial intelligence and machine learning for big data analyses (short/long term)
- Develop imaging data processing pipelines for centralized processing
- Test novel molecular probes and theranostic agents

*(This Executive Summary presents the consensus arising from the CISC Workshop. These recommendations are not meant to address all clinical contexts, but rather represent priorities for publicly funded clinical research.)*

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**NATIONAL CANCER INSTITUTE  
CLINICAL IMAGING STEERING COMMITTEE (CISC)  
Improving Brain Tumor Characterization with Advanced Neuroimaging Methods  
April 18<sup>th</sup>-19<sup>th</sup>, 2018**

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**AGENDA**

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**DAY 1 – WEDNESDAY, APRIL 18, 2018**

8:00 AM – 8:30 AM	Registration	
8:30 AM – 8:40 AM	Welcome and Overview	Lalitha Shankar, MD, PhD

**Perspectives with a focus on areas that need help from clinical neuroimaging**

8:40 AM – 8:50 AM	Brief overview of neuroimaging in NCI Trials	Brian Rodgers, MD
8:50 AM – 9:00 AM	Biomarker Study Designs	Erich Huang, PhD
9:00 AM – 9:20 AM	Current Issues in neuro-surgery	Mike Vogelbaum, MD
9:20 AM – 9:40 AM	Current Issues in neuro-oncology	Mark Gilbert, MD
9:40 AM – 10:00 AM	Current issues in Radiation Oncology	Kevin Camphausen, MD
10:00 AM – 10:20 AM	Patient perspective	David Arons, JD
10:20 AM – 10:40 AM	Panel Discussion	Neil Rofsky, MD

10:40 AM – 11:00 AM Break

**Neuroimaging Techniques**

11:00 AM – 11:20 AM	RANO Updates	Patrick Wen, MD
11:20 AM – 11:40 AM	The development of BTIP for morphological imaging and update on RANO	Benjamin Ellingson, PhD, MS

11:40 AM – 12:30 PM Lunch (*on your own*)

**Utility of advanced MR techniques in Multi-Center Phase II and III Trials**

12:30 PM – 12:45 PM	Current Clinical Trial Issues	Daniel Barboriak, MD
12:45 PM – 1:00 PM	DSC	Jerrold Boxerman, MD, PhD
1:00 PM – 1:15 PM	Permeability	Daniel Barboriak, MD

**DAY 1 – WEDNESDAY, APRIL 18, 2018 (CONTINUED)**

1:15 PM – 1:30 PM	ASL	Xavier Golay, PhD
1:30 PM – 1:45 PM	Diffusion	Thomas Chenevert, PhD
1:45 PM - 2:00 PM	2HG Spectroscopy	Alexander Lin, PhD
2:00 PM – 2:30 PM	Panel Discussion	Daniel Barboriak, MD
2:30 PM – 2:50 PM      Break		
<b>PET</b>		
2:50 PM – 3:10 PM	Clinical PET (and Potential/promising PET agents)	Dan Silverman, MD
3:10 PM – 3:30 PM	PET/MR	Elizabeth Gerstner, MD
3:30 PM – 4:00 PM	Panel Discussion	Steven Larson, MD
<b>Pediatric Neuroimaging</b>		
4:00 PM – 4:20 PM	Biological considerations	Vijay Ramaswamy, MD, PhD
4:20 PM – 4:40 PM	Radiological considerations	Tina Young Poussaint, MD, FACR
4:40 PM – 4:50 PM	Discussion	

**DAY 2 – THURSDAY, APRIL 19, 2018**

8:30 AM – 8:45 AM	Welcome and summary of Day 1	Michael Knopp, MD, PhD
<b>Trial Logistics and Considerations from the core lab</b>		
8:45 AM – 9:00 AM	Current State of Neuroimaging in NCTN	Michael Knopp, MD, PhD
9:00 AM – 9:15 AM	Quantitative tools for clinical trials and clinical care	Tim Kaufmann, MD, MS
9:15 AM – 9:30 AM	Emerging MR Metrics	Sarah Nelson, PhD
9:30 AM – 9:45 AM	Radiomics	Jayashree Kalapathy-Cramer PhD
9:45 AM – 10:10 AM	Panel Discussion	Michael Knopp, MD, PhD
10:10 AM-10:20 AM	Break	
<b>Reports back from subgroups</b>		
10:20 AM -10:50 AM	Implementation of advanced imaging methods in trials	Daniel Barboriak, MD Michael Knopp, MD, PhD
10:50 AM -11:20 AM	Multiparametric and Radiomic Assessments	Jayashree Kalapathy-Cramer PhD, Thomas Chenevert, PhD
11:20 AM -11:50 AM	Pediatric Neuro-oncologic imaging	Tina Young Poussaint, MD, FACR Zoltán Patay, MD, PhD
11:50 AM -12:20 PM	Next steps, action items	Lalitha Shankar, MD, PhD Daniel Barboriak, MD Michael Knopp, MD, PhD
12:20 PM	Meeting Adjourns	

**References/Literature** (To be completed by committee leadership)

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