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Chapter

Imaging and Neuro-Oncology Clinical Trials of the National Clinical Trials Network (NCTN)

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Abstract

Imaging in neuro-oncology clinical trials can be used to validate patient eligibility, stage at presentation, response to therapy, and radiation therapy. A number of National Clinical Trials Network trials illustrating this are presented. Through the Imaging and Radiation Oncology Core's quality assurance processes for data acquisition and review, there are uniform data and imaging sets for review. Once the trial endpoints have been analyzed and published, the clinical trial information including pathology, imaging, and radiation therapy objects can be moved to a public archive for use by investigators interested in translational science and the application of new informatics tools for trial analysis.

Keywords: imaging, radiation therapy, clinical trials, targeted therapy, cancer treatment

1. Introduction

Over the past three decades, imaging has become an important component of successful execution and completion of clinical trials for the National Clinical Trials Network (NCTN) of the National Cancer Institute (NCI). Imaging used in clinical trials serves as a biomarker to validate patient eligibility, stage at presentation, and response to therapy. Once archived, imaging becomes an inexhaustible resource to compare response to historical standards and validate tools for analysis of trial outcome. The quality of the imaging archive is essential to the NCTN and clinical translational investigators. Data acquisition and management quality assurance processes are imbedded in trials to ensure that the required trial-specific imaging is collected and organized according to standards. Modern neuro-oncology clinical trials use anatomic and metabolic imaging with sequences and quality standards specific to each clinical trial charter. In this manuscript, we will review the history of imaging in clinical trials and the current status of neuro-oncology imaging in

the NCTN. Future initiatives and vision for image integration with subject-specific biomarkers in neuro-oncology trials will be presented.

2. History of imaging in the NCTN

There is a rich history of clinical trial development within the NCI's clinical trials network. In the early development of the cooperative group clinical trials program, emphasis was placed on clinical protocols with onsite physician assessment of response and site-associated application of radiation therapy treatment objects. Even in trials that required radiation therapy, little information was made available to the clinical trial investigators concerning the abnormality defined on imaging, choice of area treated with radiation therapy, and dose to target. Because computational algorithms for dose calculation were varied and driven in part by individual institutional structure and process, the initial quality assurance processes in radiation oncology placed emphasis on creating uniformity of these processes with less emphasis on imaging and the application of imaging to target. By 1972, committees in the cooperative groups identified mechanisms to acquire information about targets treated. This included review of radiation therapy kilovoltage (kV) simulation images and megavoltage (MV) therapy portal images to confirm that what was intended to be delivered was treated. The trial-required information had to be forwarded to quality assurance centers as hard copies, where it was reviewed for trial compliance. These quality assurance reviews were performed largely in retrospect, as trials reached closure, due to the cumbersome data submission process. As the data acquisition processes became more familiar to investigators, efforts were made to review hard copy objects early in the radiation treatment process to ensure that the treatment plan met study guidelines [1, 2].

By 1980, three-dimensional volumetric radiation therapy treatment planning was being introduced to clinical trials as well as using electronic media to transmit data. The initial effort in volumetric electronic data collected placed emphasis on prostate carcinoma; however, the importance of imaging in the quality review process for radiation oncology began to become more visible and prominent in multiple disease sites including lymphoma. In the Pediatric Oncology Group (POG) protocol 8725, the objectives of the study were to randomize the role of radiation therapy in what would be called intermediate to advanced stage subjects by modern standards. The subjects received eight cycles of hybrid chemotherapy and are then randomized to receive radiation therapy to all initial sites of disease or complete their care without radiation. In the initial publication of the trial, there was no added benefit to the addition of radiation therapy to this population of subjects. However, in a subset analysis, those subjects that were treated by study standards and had all sites of disease treated at presentation had a 10% statistically significant disease-free survival benefit [3]. In other words, excluding sites of original disease was detrimental to outcome. Imaging was essential to this interpretation as well as the application of diagnostic imaging to radiation therapy treatment execution. This was one of the first trials that acquired imaging both at baseline and at closure of chemotherapy as radiation therapy targets had to be designed to imaging parameters and sites of disease at presentation with response-adapted blocking applied to mediastinal disease. Without imaging submitted for trial review, this interpretation could not be made. Today the partnership between imaging and radiation therapy is synergistic, and radiation therapy is fully dependent on image-guided platforms for modern patient care [4, 5].

The next iteration of Hodgkin lymphoma studies evaluated both early stage and intermediate stage subjects with response-adapted treatment. Because of the

non-compliant radiation therapy issues in POG 8725, the imaging and the radiation therapy treatment objects, as based on the disease at presentation, were reviewed by the Quality Assurance Review Center (QARC) before the start of radiation therapy. Pre- and post-chemotherapy imaging were reviewed to assess radiation therapy compliance. Compliance to radiation therapy was achieved; however, retrospective analysis of imaging response to chemotherapy demonstrated that central review disagreed with site assessment on 50% of cases [6]. Therefore, in the next iteration of trials evaluating intermediate risk subjects, imaging and radiation therapy objects were reviewed through a central mechanism in real-time pre-therapy, post two cycles of chemotherapy, post all chemotherapy, and pre-radiation therapy to ensure that response assessment was consistent with study objectives and radiation therapy was applied uniformly throughout the trial. Children's Oncology Group (COG) trial AHOD0331 accrued more than 1700 subjects and demonstrated that both anatomic and metabolic imaging and radiation therapy objects could be reviewed in an electronic format in real time at multiple study endpoints and permit adaptive therapy based on response to treatment. This infrastructure provided a platform to emphasize the importance of imaging in clinical trials as well as a mechanism to use imaging as a validation vehicle for successful execution of clinical trials. Because imaging can be simultaneously reviewed by multiple individuals including site and study investigators in real time, consensus between investigators could reach closure in a timely manner. Subject-specific issues and optimization of clinical trial management were addressed in a uniform manner and as early as the subject was enrolled on the trial [5, 7, 8].

The informatics platform quickly matured to support imaging in all pediatric and adult oncology radiology and radiation therapy disease service areas including neuro-oncology with real-time review of imaging objects to ensure study compliance. Protocols for standard risk medulloblastoma originating in the posterior fossa require no more than 1.5 cm^3 of residual disease and no evidence of disease on spine imaging at presentation. These objects are reviewed immediately in real time prior to subject entry onto study to ensure that the subject has entered onto the appropriate study and staged in a manner consistent with study objectives. Studies have confirmed that high-risk medulloblastoma patients unintentionally entered on low-risk studies have a significantly worse outcome, thus obfuscating interpretation of the study when evaluated on an intent to treat basis [9]. Completeness of resection is reviewed in real time for patients with ependymoma to ensure that the sequence of care including second surgical procedure as required by study is consistent with study guidelines. These changes in process serve to improve the quality of the study and are adjudicated by imaging. Imaging is identified as an essential component to successful clinical trial execution and by 1996 became well positioned to be recognized as a strong and independent discipline in the national clinical trials effort [3].

In 1997, Robert Wittes, MD, was the director of the Cancer Treatment Evaluation Program (CTEP) and recognized the need to develop an imaging program in clinical trials to function at an enterprise level. The NCI established a cancer imaging program under the direction of Daniel Sullivan, MD. In September of 1998, the American College of Radiology Imaging Network (ACRIN) was established under the direction of Bruce Hillman, MD, and Constantine Gatsonis, PhD. ACRIN had significant initial success managing important cancer screening trials including the digital mammography imaging screening trial (DMIST) and the National Lung Screening Trial (NLST). ACRIN has significant influence in credentialing institutions for imaging clinical trial participation and data management of clinical trials in all oncology disease areas including neuro-oncology imaging. ACRIN also participates in clinical trials including cardiology, interventional radiology, and

advanced technology neurological imaging in non-oncology-related areas serving to further expand their portfolio and scope of service. ACRIN has partnered with the Eastern Clinical Oncology Group (ECOG) to bring its robust imaging infrastructure to support activities in a strong cooperative group with multiple disease committees. As ECOG-ACRIN, a strong standard is established for clinical trial interactions between clinical scientists and imaging partners. The imaging information for ECOG-ACRIN is managed by the Imaging and Radiation Oncology Core office in Philadelphia (IROC Philadelphia).

Of equal strength is the Wright Center of Innovation in Biomedical Imaging at the Ohio State University. Under the direction of Michael Knopp, MD, PhD, the Wright Center has obtained several major grant awards including a Frontier grant from the state of Ohio and a biomedical research and technology transfer award. The center houses expertise in microimaging, molecular imaging, animal imaging, as well as advanced technology imaging to support clinical trial processes. The Wright Center supports all the imaging needs including data management and real-time case review for the Alliance and SWOG clinical trial groups including significant expertise in neuroimaging and case evaluation. The Wright Center has developed processes to track compliance to anatomic and metabolic images acquired for clinical trials. The neuro-oncology committees are exceptionally strong, and neuro-oncology and neuroimaging are prominent disease-oriented committees in these important groups. Lawrence Schwartz, MD directs the imaging committees for Alliance and SWOG and works in close collaboration with the Wright Center for clinical trial execution. The office managing imaging information at the Wright Center for Alliance and SWOG is the Imaging and Radiation Oncology Core at Ohio (IROC Ohio).

Formerly known as Quality Assurance Review Center (QARC), the Imaging and Radiation Oncology Core center in Rhode Island (IROC RI) is responsible for imaging needs in COG. The imaging committee in COG became a formal discipline committee at the time of the merger between the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG). QARC worked with committee members to establish an informatics infrastructure required for digital image transfer. This was accomplished by Keith White, MD, in collaboration with the information technology group at QARC. Data acquisition tools were applied to the process that he used to acquire and display images for tumor board at his home institution. The acquisition process is now synergistic with the data acquisition for radiation therapy treatment objects, and these can now be displayed in the IROC RI database for remote review of objects in a side-by-side manner by site and study investigators. Clinical trial investigators in all clinical disciplines including imaging and radiation oncology can review study objects in a harmonized and single-session manner. Because clinical trials require real-time review of objects for response assessment-adaptive clinical trials and the subsequent application of radiation therapy, each month, there are hundreds of study investigator logins to assure adaptive trial design is met and response/disease progression is noted and assessed in a uniform manner (**Figure 1**). Neuro-oncology imaging is essential to mission for COG as brain tumors comprise 25% of pediatric oncology. It is important that all image datasets including pre-/post-surgery/therapy and outcome imaging be available for review on a real-time basis as needed. The image library housed at IROC RI is the largest collection of pediatric oncology imaging in the world on patients treated on clinical trials with a complete portfolio of images on neuro-oncology patients treated on clinical protocols. The IROC Houston office (formerly the Radiological Physics Center (RPC)) works with all radiation oncology discipline committees of the NCTN and is the central resource for credentialing institutions for participation in clinical trials managed through the NCTN.

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IROC is a single grant with overarching administrative structure to four grant offices in Houston TX, Columbus OH, Philadelphia PA, and Lincoln RI. Administrative support is provided by the American College of Radiology (ACR). IROC provides credentialing and data management for the NCTN in imaging and radiation oncology clinical trial participation (**Figure 2**). All offices that provide imaging data management services are involved in neuroimaging in NCTN clinical trials. The offices all collaborate with NCTN investigators to write uniform guidelines into all clinical trials involving the central nervous system (CNS) to ensure optimal clinical trial management and uniform response assessment. Modern guidelines include sequence acquisition requirements, slice thickness, and other acquisition parameters, which are written into every protocol by study investigators and IROC. The guidelines support both pediatric and adult clinical trials in neuro-oncology.

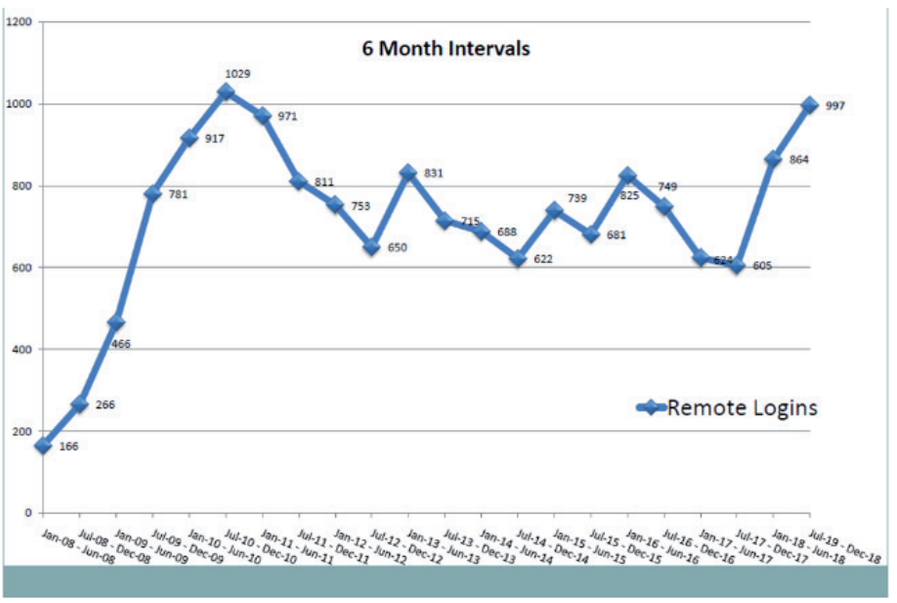

Figure 1.
Number of remote NCTN reviewer logins to terminal servers 2007–2019. Image courtesy of QARC.

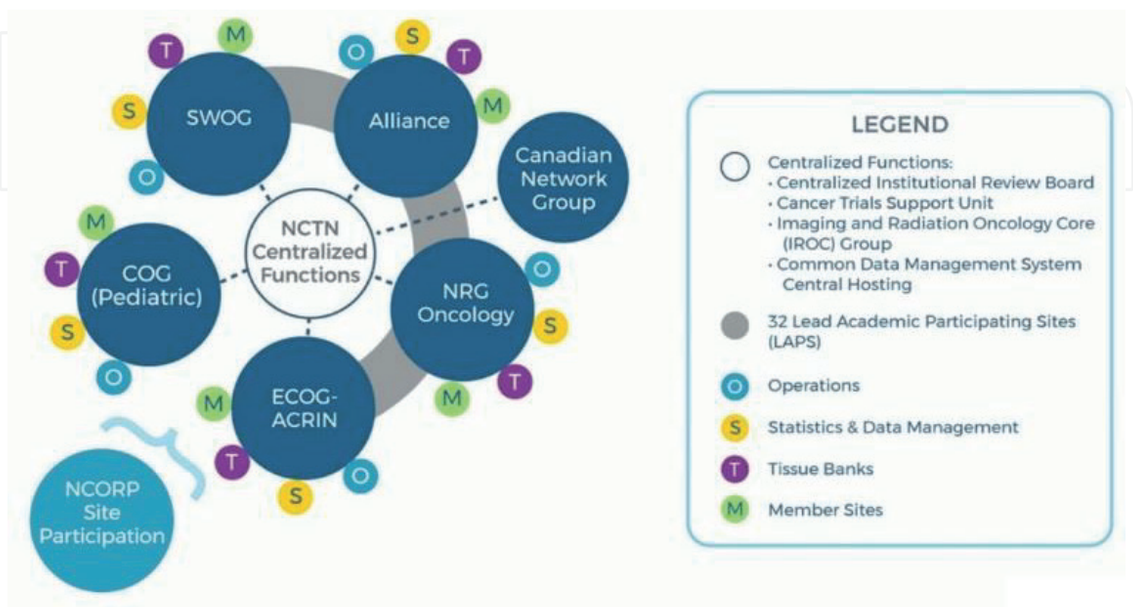

Figure 2.
NCI National Clinical Trials Network Structure. IROC is within the NCTN centralized functions. Image courtesy of the National Cancer Institute.

3. The importance of imaging applications in radiation therapy

Imaging platforms have become essential to daily operation in radiation oncology. From initial assessment of imaging for target definition to daily treatment alignment with cone beam computed tomography (CT), imaging has become an essential component of the infrastructure to successful delivery of daily radiation therapy. Imaging has likewise become essential for credentialing institutions to participate in clinical trials involving the CNS including the use of phantom technology for CNS magnetic resonance imaging (MRI) and application of radiation therapy. In an early iteration of the use of imaging as a credentialing vehicle, institutions received a planning image with a right temporal target and were asked to develop a therapy plan using a vertex field. This evaluated the ability of the institution to use three-dimensional modeling for therapy planning. Most radiation therapy planning systems are based on CT obtained in the therapy position with the appropriate immobilization device. CT, however, has significant limitations in defining targets for radiation therapy for lesions in the CNS. For clinical trials involving stereotactic radiosurgery (SRS), a credentialing vehicle was constructed where an institution would receive a planning CT with SRS coordinates. The target lesion was not visible on CT. An MR with a visible single lesion was provided, and the institution had to fuse the images into the site radiation planning system and provide x, y, and z coordinates for a stereotactic procedure [10]. The high-resolution and reality imaging registration processing evaluates both fusion tools and treatment planning capabilities. Anthropomorphic phantom tools have been developed by the IROC Houston office that require image validation for target definition as part of the credentialing process. This cross-validation has been essential for both documentation of image and assessment of the site computational planning algorithms (**Figure 3**).

Because tumors of the central nervous system are better defined with advanced technology imaging including advanced MR sequences and spectroscopy, fusion of images in treatment planning CT is a great resource and significantly improves target definition and patient care. In current NCTN protocols, advanced MR sequences are integrated with new positron emission tomography tracers including amino acid imaging and spectroscopy to create multiple target volumes treated with dose painting to areas of sequence abnormality. This is of increasing importance. Historically, neurosurgeons would remove regions of contrast enhancement seen on

Figure 3.
Phantom tool developed by IROC Houston used in the RT site credentialing process. 1520 RT sites have passed at least one irradiation of this phantom. Image courtesy of IROC Houston.

CT and limited MR signal changes. Radiation oncologists, even on study, often treat the surgical resection site with a margin. With more primitive anatomical imaging, radiation oncologists performed poorly in defining the target volume of interest and may have not treated the entire tumor volume at risk on historical studies. New imaging models including amino acid imaging are demonstrating regions of tumor proliferation and tumor DNA synthesis which have been less visible and as a result, undertreated by radiation oncology. In primary brain patients, Investigators have confirmed that disease can reside in regions of FLAIR enhancement, thus influencing the choice of radiation therapy field placement. Spectroscopy may likewise be helpful moving forward in better defining targets at risk, and this is currently under evaluation with dose painting clinical trials in glioblastoma. Several papers have interesting reviews evaluating patterns of failure [11, 12]. In patients whose disease abutted central structures including the corpus callosum, failure patterns followed major nerve pathways into the contralateral hemisphere. If the anatomic and metabolic tumor target could be more optimally defined at presentation, we would potentially treat the patient more effectively with radiation therapy, hence possibly improving outcomes, as there is a high index of suspicion that simply targeting the region of contrast enhancement with margin may be insufficient for radiation therapy. Current protocols are using advanced imaging tools for target definition and dose painting. The volumes treated between T2 and FLAIR imaging were very different. Accordingly, the radiation fields are larger than targeting areas of contrast enhancement, and it will be important to monitor toxicity and pattern of failure with biomarker analysis [13].

Outcome imaging is important in clinical trials and often requires central review of imaging objects to provide consistent interpretation of treatment effect and disease progression. This is essential as often changes seen on MRI post-therapy can mimic disease progression. The NCTN pediatric and adult oncology databases include subjects with disease of the CNS including spine. These databases store imaging at presentation, pre- and post-surgery, radiation therapy treatment objects, and post-therapy. Because these images were obtained on study, the sequences and time points of data acquisition post-therapy are uniform in acquisition. These become optimal datasets for the development of machine learning and artificial intelligence tools to better evaluate this dilemma. The databases are linked to outcome through the statistical centers of each of the network groups and therefore are an invaluable resource to the field of neuro-oncology [9].

4. Current portfolio for neuro-oncology analysis in IROC

The Imaging and Radiation Oncology Core (IROC) houses all diagnostic imaging and radiation therapy treatment objects on subjects treated on clinical trials for the NCTN. The IROC office in RI works with the Children's Oncology Group (COG) and houses objects on subjects treated on clinical trials for more than 35 years. IROC RI also houses radiation therapy treatment objects for SWOG, Alliance, and ECOG-ACRIN. Trials include management of standard and high-risk medulloblastoma, ependymoma, primitive neuroendocrine tumors, germ cell tumors, and low-/high-grade glioma. Trials have studied the addition of chemotherapy to radiation therapy in multiple disease sites, sequence of management, and drug X-ray dose titration/augmentation. Modern protocols have applied adaptive strategies to titrate therapy to younger population, limit radiation boost dose to lesions that undergo gross tumor resection, and alter therapeutic application to medulloblastoma relative to tumor gene expression profiles. The IROC Ohio office manages neuro-oncology imaging for SWOG and Alliance. The Alliance group has an exceptionally

strong neuro-oncology committee with primary emphasis in developing clinical trials for adult glioblastoma including studies directed to new modalities of care integrated with modern genomics and gene expression profiles. The IROC office in Philadelphia integrates the imaging strengths of imaging with ACRIN and the radiation oncology strengths of NRG (former NSABP, RTOG, and GOG). The emphasis of these groups is in the application of modern radiation oncology technology coupled with biomarker-driven applied chemo/targeted therapy for adult glioblastoma. Currently, IROC RI houses information on 24 protocols with datasets on over 3000 patients including imaging at presentation, post-therapy, relapse, and radiation therapy treatment objects for pattern of failure analysis. These include studies on primitive neuroectodermal disease, germ cell disease, high-/low-grade glioma, atypical rhabdoid lesion, medulloblastoma, and ependymoma. IROC Ohio houses images on more than 2000 patients treated for glioblastoma as well as images on protocols treating meningioma. The protocols include patients treated with vaccine therapy, antiangiogenetic therapy, and poly ADP ribose polymerase (PARP) inhibitors in patients with O[6]-methylguanine-DNA methyltransferase (MGMT) promotor hypermethylation as well as studies evaluating anaplastic and/or low-grade glioma treated with adjuvant PCV chemotherapy including those with 1p/19q co-deletions. IROC Philadelphia manages a similar volume of patients on study treated for glioblastoma with emphasis on radiation therapy target definition and technique. Each of the IROC centers manages advanced technology-driven imaging for radiosurgery for central nervous system metastatic disease. Neuro-oncology protocols managed by each of the IROC offices and available datasets are used for secondary clinical translational research objectives.

In the next generation of translational research for neuro-oncology, integration of biomarkers including genomics and applied gene expression profiles will need to be coupled with radiomics integrated with radiation therapy treatment plans. Ex vivo tissue unfortunately is an exhaustible resource and needs to be preserved for unanticipated biomarker evaluation in addition to current portfolios. Digital quantitative pathology will play an important role to integrate established and validated non-imaging biomarkers and biomarker processes with microscopy imaging signals to better predict outcome. Saltz and colleagues have integrated pathology biomarkers with imaging signals. Erickson and colleagues have identified radiomic signatures in glioblastoma patients that indicate and predict gene expression and methylation. Harmonization of this effort at an enterprise level will be the next step in developing improved tools for translational science [14–19].

5. The Cancer Imaging Archive (TCIA)

The Cancer Imaging Archive is a collaboration of many key investigators with Fred Prior, PhD (University of Arkansas), as the principal investigator. Processes within the NCTN clinical trial groups serve to protect all information of subjects participating on clinical trials including their tissue, imaging, and radiation therapy treatment objects. Once a trial has completed accrual and primary endpoints have been recognized and published, an important objective of the National Cancer Institute is to move study information to a public archive for use by all interested in translational science and application of new informatics tools for trial analysis. The objective is for all important material including tissue biomarkers and outcome information be available to investigators. TCIA has a strong infrastructure with expertise in informatics science, imaging, digital pathology, and clinical trial management. The archive currently houses a diverse portfolio of studies and is poised to function at an enterprise level to support translational science improvement. The

current portfolio of studies accessible through the TCIA includes studies involving low- and high-grade glioma with associated pathology. Over 1000 datasets are available on 11 studies. TCIA will be an invaluable resource for future translational science in neuro-oncology [20, 21]. Cancers of all disease types will be made available to investigators worldwide through this mechanism.

6. Conclusions

Neuro-oncology is an increasingly important component in the care of patients with cancer. Both primary lesions and metastatic disease affect a significant segment of the pediatric and adult populations. The care of these patients requires extended healthcare system resources for physician expertise and para health professionals for supportive and rehabilitative care. Progress will be made by optimizing uniform applications of imaging both at disease presentation and response to therapy. Informatics processes are established in the NCTN and the TCIA to help move this forward for patients afflicted with CNS disease. Information from trials will be available in a public TCIA archive to help investigators perform translational research through this mechanism and accelerate progress in this field.

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Conflict of interest

The authors declare no conflict of interest.

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