About NBTS
National Brain Tumor Society (NBTS) is the largest nonprofit organization in the United States (U.S.) dedicated to the brain tumor community. Our mission is to find new treatments and ultimately a cure. We participate and partner broadly in the greater cancer and disease community and drive research forward through innovative grant-making and patient advocacy initiatives. Our funded research has helped discover many key biological underpinnings of brain cancer, as well as resistance mechanisms to treatments, and has led to the launch of several promising ongoing clinical trials.

National Brain Tumor Society believes that there is a critical need to support aggressive advancement of research in pediatric neuro-oncology. In the U.S., an estimated 4,630 individuals under the age of 19 will receive a brain tumor diagnosis this year, making them the most prevalent form of malignancy in the pediatric population. Furthermore, brain tumors are the leading cause of cancer-related deaths in infants and children up to 14 years of age. In this age group, tumors of the brainstem constitute approximately 10–15% of all central nervous system (CNS) tumors with the majority of these tumors being of glial origin (glioma). Diffuse intrinsic pontine glioma (DIPG) accounts for 80% of brainstem gliomas, and represents a heterogeneous group of pediatric glial tumors that are biologically distinct from other pediatric and adult high-grade gliomas (HGG). For DIPG, the mean age of diagnosis is 7-9 years old with a dismal prognosis and median survival of only 9 months. With no progress made over the past five decades for improving the outcome of this disease, DIPG represents a compelling therapeutic challenge for the field of pediatric neuro-oncology.

Diagnosis of DIPG is usually based on the association of a short history of less than 2 months, cranial nerve palsies, long tract signs, and ataxia with typical imaging findings. DIPG tumors are characterized by diffuse infiltration and swelling of the brainstem with an infiltrating tumor mass of at least 50% of the pons. These lesions appear hypointense on CT with non-delineated borders and are hypointense on T1 and hyperintense on T2 and FLAIR MRI sequences. Anatomic location makes gross total surgical resection impossible and use of biopsy for these tumors has been controversial and limited historically to unusual lesions on imaging. To date, radiation therapy (RT) is the only form of treatment that offers a transient benefit in DIPG. Chemotherapeutic strategies and the application of targeted therapies based on biological information from other types of pediatric and adult HGGs, have not provided any survival benefits. Such a stagnation of progress in advancing new treatments for DIPG has been due in large part to the unfounded assumption that DIPG is similar to other pediatric and adult gliomas; a myth enabled because of a lack of DIPG biopsy tissue at diagnosis to inform clinical care and development of targeted therapies.
State of the Field
As stated above, the decision to biopsy DIPGs in children remains controversial. In the past decade, however, advances in neuroimaging and stereotactic minimally-invasive surgical techniques have allowed some reconsideration of the use of biopsy of the pons of DIPG patients by experienced neurosurgeons.

Biopsy has been performed on classical DIPG lesions to exclude diseases other than DIPG (like PNET), or for atypical lesions that do not meet the clinical or radiographic criteria of DIPG. A number of studies on the use of stereotactic biopsies for DIPG have been published reporting high diagnostic yield (90-100%), morbidity rates ranging from 0 - 20% and a mortality rate of 0 - 3%. These results indicate that the procedure has an acceptable level of safety similar to that reported for other brain locations. Increased use and improvements in advanced imaging techniques for pre-operative planning like diffusion tensor imaging tractography to delineate the white matter (especially corticospinal tracts) and PET imaging to identify regions of interest, hold considerable promise for increasing safety and the diagnostic yield of the biopsy going forward.

Advances in biological sequencing techniques that allow whole genome, transcriptome and epigenetic profiling of tumors has brought about significant opportunities to characterize tumors at the molecular level to provide insight on underlying tumor biology. Recent data from DIPG patients suggest that there are distinct histologic subgroups of DIPG, with varying clinical and molecular features, involving somatic mutations that include histone H3 alterations, indicating that the tumor is, in fact, biologically distinct from other pediatric and adult HGGs. Studies have also discovered other alterations that could help to choose specific individualized targeted therapies and could be linked to prognosis for example: PDGFRA amplification and mutation, MET amplification and mutations, mTOR pathway alterations, and ACVR1 mutations. In this respect a recent update to the WHO classification of brain tumors incorporates the integration of molecular data into the diagnosis of several different types of brain tumors, including a newly defined entity termed diffuse midline glioma, H3 K27M–mutant and includes tumors previously referred to as DIPG. This change has been driven by recognition of the value of using genetic information for diagnosis and prognostication.

Precision medicine approaches, including drugs and devices, will be important to realize the potential of the recent discoveries in DIPG. Post-mortem autopsy material taken from DIPG patients has been useful for research purposes. However, autopsy tissue does not recapitulate the original tumor and its microenvironment because of tumor evolution and adaptation following radiation, and exposure to steroids and chemotherapeutic (if tried) treatments, among other challenges. In contrast, the ability to identify the whole mutational landscape of DIPG using tissue obtained by pretreatment biopsies provides compelling opportunities to improve diagnosis and prognosis as well as for the identification of potentially drugable targets and patient selection for clinical trials. Biopsy may also guide treatments at recurrence.

The increased availability of biopsy tissue samples and their genomic and epigenomic profiling has helped our understanding of DIPG disease mechanisms and has provided important insight into potential therapeutic targets. However, to continue to advance such research, histopathological
information and the identification of tumor biomarkers for assignment of patients to clinical trials of investigational, targeted therapies is required. Prospective national, multi-institutional clinical trials of up-front stereotactic biopsy of classic DIPG in newly diagnosed patients for target-based stratification are underway in several ongoing clinical trials (for example: NCT01182350 and NCT02233049). These trials require all neurosurgeons to undergo a training session on the biopsy of the pons in order to participate and involve significant regulatory oversight in order to maximize patient safety.

**NBTS Perspective**
National Brain Tumor Society believes that it is unethical to accept the current state of care for DIPG patient, as defined by an extremely poor prognosis that barely lasts the length of an average school year. National Brain Tumor Society supports all scientifically rational steps to improve outcomes for these patients, including the incorporation of pretreatment biopsy where possible. However, considerations for minimizing risk to the patient, and for maximizing the value and application of information obtained from biopsy, need to be guiding principles for clinical care and for advancing research to better treatments. NBTS holds this position based on a number of key reasons:

- The absence of including biopsy at diagnosis has limited the ability to develop novel and molecularly informed treatments for DIPG, and has resulted in children being exposed unnecessarily to ineffective, toxic and inappropriate treatments.
- A number of recent studies in DIPG patients that have incorporated intraoperative imaging and minimally-invasive neurosurgical techniques to obtain pretreatment biopsies, have provided a body of evidence supporting feasibility and acceptable relative safety for biopsy at diagnosis by experienced neurosurgeons at medical centers with the required resources.
- Application of state-of-art molecular biology techniques in oncology has highlighted the tremendous benefit that knowledge of tumor biology and genetics brings to informing the evaluation of investigational targeted agents in clinical trials and patient subpopulations, and has led to the development of clinically useful therapies.
- Biopsy is informative and confirms diagnosis, may identify actionable targets, and can stratify patients for both therapy (including potential clinical trials) and prognosis.
- The potential risks and benefits of pretreatment biopsy in DIPG patients need to be communicated clearly to the patients and parents by the physician.

However, NBTS believe that parents and patients should not be compelled or obligated to undergo biopsy.

Given the fatality of the disease and the dismal prognosis for DIPG patients, there is a clear need for incorporating biopsy of these lesions as part of standard practice – where possible and consented – to not only provide benefit for the patient from whom the biopsy was obtained but to also benefit all DIPG patients in the future.