FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE PEDIATRIC SUBCOMMITTEE OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE (pedsODAC)

Afternoon Session

Wednesday, June 29, 2016

1:00 p.m. to 4:16 p.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31 Conference Center

The Great Room (Rm. 1503)

Silver Spring, Maryland

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(1:00 p.m.)

DR. PAPPO: Good afternoon. I think we are going to get started.

I would like to ask the FDA representatives that have just joined us this afternoon to please introduce yourselves, Drs. Nelson, Seidman, Sul, and Barone.

DR. NELSON: Skip Nelson, I am the deputy director and senior pediatric ethicist in the Office of Pediatric Therapeutics, FDA.

DR. SEIDMAN: Jeff Seidman, medical officer and pathologist in the Office of In Vitro Diagnostics and Radiologic Health in the CDRH.

DR. SUL: Joohee Sul, I am a medical officer in the Division of Oncology Products II in the Office of Hematology and Oncology Products.

DR. BARONE: Amy Barone, pediatric oncologist, also in the Division of Oncology Products II.

DR. PAPPO: Thank you very much.

We will now proceed with topic 3, diffuse

intrinsic pontine glioma. Dr. Lauren Tesh will read the conflict of interest statement for this session.

Conflict of Interest Statement

DR. TESH: The Food and Drug Administration is convening today's meeting of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 is being provided to participants in today's meeting and to the public.

FDA has determined that members and

temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws under 18 U.S.C. Section 208. Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

This session's agenda involves information to gauge on the current unmet need clinical need in

the nearly uniformly fatal brain tumor, diffuse intrinsic pontine glioma, which occurs predominantly in the pediatric group. The diagnosis of DIPG is typically based on characteristic radiographic and clinical features in lieu of brain biopsy and histological confirmation. Recent data has demonstrated that the biology and pathophysiology of these tumors differ.

There are no approved drugs for this disease. Clinical investigators seek to exploit precision medicine approaches to DIPG and use potentially predictive information from the genomic signature of tumors at either diagnosis or relapse.

This information can be used to select specific molecularly-targeted drugs based on the genetic aberrations of an individual patient's tumor.

The agency will seek the input of the subcommittee, including an assessment of benefit-risk, given the potential for an adverse event associated with a surgical intervention in

the brainstem.

This is a particular matters meeting during which general issues will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the topic at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. P.K. Morrow is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Morrow's role at this meeting is to represent industry in general and not any particular company. Dr. Morrow is employed by Amgen.

With regard to FDA's guest speakers, the agency has determined that the information to be

provided by these speakers is essential. The following interest is being made public to allow the audience to objectively evaluate any presentation and/or comments.

Dr. Nalin Gupta has acknowledged a research grant with Pfizer for the development of a pharmacologic inhibitor of histone demethylase.

We would like to remind members and temporary voting members that if the discussions involve any other topics not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the topic that could be affected by the committee's discussions.

Thank you.

DR. PAPPO: Thank you.

We will proceed with opening remarks from Dr. Sul.

FDA Introductory Remarks

DR. SUL: Good afternoon. First, we would like to thank the members of the committee, consultants, and guests for attending and participating in this discussion of the benefit-risk assessment of surgical biopsy for patients with diffuse intrinsic pontine glioma or DIPG, a disease with a significant unmet medical need.

DIPG is a brainstem tumor that occurs predominantly in children and has a dismal prognosis with a median survival of generally less than one year. There have been no significant meaningful advances made in improving outcomes for these patients, and this is likely, in part, due to the lack of understanding of the biology of these tumors.

Given the potential risk for morbidity and serious adverse events associated with biopsy of the brainstem, the diagnosis of DIPG has typically been made based on characteristic radiographic and clinical features in lieu of histopathology. As a

result, there has been limited tissue available to evaluate the molecular and cellular biology of this disease.

Treatment for children with DIPG is generally based on that for high-grade gliomas. However, data published over the past decade have demonstrated that the biology and pathophysiologies of these tumors are not the same.

Better understanding of the molecular biology and genomics that DIPG is clearly needed to identify specific strategies that may be effective in treating these tumors.

Over the past decade, biopsy of DIPG has become more frequently routine in some European countries, and similarly, endorsement of standard of care biopsy for patients with suspected DIPG in the U.S. has been on the rise.

The potential to identify druggable targets and to gain valuable data on the biology of these tumors are argued to outweigh the potential risks associated with surgical biopsy. We know that identification of molecular targets from tissue

biopsy to inform treatment assignment is common in adult oncology clinical trials and has allowed identification of specific populations most likely to benefit from the study drugs.

The centers at the FDA work closely together in assessing the potential risks and benefits patients face in clinical trials, and we look forward to a discussion from the participants today on assessing the benefit-risk of biopsy to obtain tissue in patients with DIPG.

Thank you.

DR. PAPPO: Thank you very much.

We will now continue with presentations from the FDA.

FDA Presentation - Robert Nelson

DR. NELSON: Good afternoon. With apologies to Shakespeare for my title.

(Laughter.)

DR. NELSON: Here is the inevitable disclaimer.

I am going to cover two topics in my presentation. The first is to give you a general

context, if you will, for the approach in the research setting of the ethical safeguards for children and then to talk specifically about the challenge of obtaining sufficient tissue-based information to justify biopsy during treatment protocols, comparing the clinical and the research paradigms and where those two paradigms may overlap.

As I have thought about the additional safeguards for children, I think it is often useful to go back and look at the National Commission's reasoning as they went through the development of these guidelines. They issued their report in 1978, and this ethical framework is often referred to as subpart D in the HHS regulations, which is 45 CFR 46, which was published in 1983.

The FDA adopted this in 2001. We won't have an explanation of the 17-year delay, but they adopted it in 2001. That's 21 CFR 50.

I think a review of their deliberation provides some important insights into understanding the ethical framework. There was very early

agreement about two categories of research. One is research not involving greater than minimal risk, and I am giving you the FDA citations, 50.51, or research where an intervention presents greater than minimal risk, but where the risk is justified by the anticipated direct benefit to the enrolled children and then the relationship of that benefit to risk is at least as favorable as the available alternative approaches. That's 50.52.

I have underlined "intervention" because what is important is the protocol may also have both beneficial and non-beneficial components, and you need to look at those separately. That is called component analysis.

Now, how they arrived at this and why they found these two categories fairly noncontroversial is they reasoned by analogy. They looked at the kinds of decisions that we generally allow parents to make in the course of life, and they said to the extent to which the research mimics these activities, they think it is appropriate for parents to be able to make the decision to enroll

their children in those kinds of activities.

In the first case, minimal risk, you get activities of daily life and routine childcare. I am not going to show you -- maybe later you will see the definition of minimal risk. That is how they came up with that definition.

In the second case, they talk about necessary clinical care, and so this category of prospective direct benefit was specifically designed to reflect that sort of clinical judgment about risk and benefit and whether it is worth taking place. So parents make those decisions every day, and to the extent that the research is similar to those kinds of decisions, the National Commission thought that was fine.

They then worried about the fact that -- they started talking about everything else having to go to a federal panel, and they had this image of a national advisory board, sort of a national IRB, if you will. They were concerned, though, that doing that would result in a lot of stuff that would be going to that committee,

because minimal risk was defined fairly narrowly.

They focused the discussion on trying to define criteria for what they called this "escape hatch," and that was their term, not mine. Some of those key components were public review and comment along oversight, sound ethical principles. So it wouldn't be unethical to do this, but it would be different than what could be applied by the other two categories.

It was looking at new and unanticipated state of affairs, because they recognized in 1976 that science will evolve. How could they possibly anticipate every situation that would arise? They thought this should be a serious health problem with major significance.

This is what resulted in our 50.54, which is that federal panel review, and although it took, again, 25 years to put such a panel in place, we actually have one.

This is the language. If the IRB refers this because they think it is a reasonable opportunity to understand, prevent, or alleviate a

serious problem, then the Secretary of HHS and/or the FDA Commissioner, depending on whose jurisdiction the protocol falls under, would hold a federal panel review, which happens to be the Ethics Subcommittee of the Pediatric Advisory Committee. Then if these criteria are met, reasonable opportunity, sound ethical principles, and then assent and permission as required, that that protocol could potentially go forward.

It turns out there was a protocol on DIPG which was submitted back in late 2008 for such a review by a local IRB. We held a meeting in April 2009 under this 50.54, but I will talk a little bit about a twist on that in a second.

We asked that group, which was a combination, I think, of the oncology drugs advisory committee and the pediatric -- I don't know if the Pediatric Subcommittee existed at that point. Yes, so the Pediatric Subcommittee. Greg's nodding. Then the Ethics Subcommittee.

We had a bunch of scientists and a bunch of ethicists sitting around the table, and here are

the questions they were asked: "Has the state of the science in drug targeting research progressed to where there is a reasonable expectation of success in identifying drug candidates to move into early phase clinical trials for DIPG?" 17 in favor, 6 opposed, 1 abstained.

The second vote: "Should children with DIPG undergo a nontherapeutic brain biopsy to advance the study of possible drug targets for research purposes only?"

The vote was closer, 14 in favor, 10 opposed.

Two comments, if I will, on this meeting. The first is that the decision was that this protocol at the end of the day was not actually FDA regulated. The lawyers told me that as I was well down the process, and we decided to hold the meeting anyway because we thought it was an important topic.

But it wasn't FDA regulated because it was an academic protocol. There was no tie to any particular drug administration, and there were no

plans for any particular development of an in vitro diagnostic device and so on and so forth. There was none of that on the table. It was simply get some tissue, go into the lab, and look for some targets in terms of the state of the science back in April 2009.

That partly explains the reason why FDA never had to go on record about a recommendation following this meeting, because there was no need to actually go on record. I will say, as the person who would have been responsible for drafting a letter that the Commissioner would have had to eventually have signed, I am not sure what I would have said, because what bothered me about this was that all of the ethicists except one voted against doing this.

Not all of the scientists voted in the favor. There were some that weren't that felt we should explore other options, but there was a clear difference of opinion, in my mind, about the science and the ethics at the time. Again, at the time, we are seven years later, and I think that is

important to keep in mind.

But then the National Commission was worried. If everything had to go to such a panel, it is either minimal risk or benefit and then everything else goes to a panel, they wanted to have another category. I will just mention this, which is this minor increase over minimal risk.

That category was and continues to be controversial. I suspect we are not going to be talking about brain biopsies as being only a minor increase over minimal risk. So this may not be as relevant to this discussion, but this is what resulted in 50.53 and what is eventually the structure of subpart D where you have got these two categories.

If there is no prospect of direct benefit, minimal risk, or a minor increase over minimal risk, this prospect of direct benefit, or this federal panel referral, and these are the four categories.

A local IRB is only allowed to approve things if it fits within these three categories.

Otherwise, they refer it and then, of course, parental permission and child assent. So that is currently our structure of subpart D, which is in place.

Let me talk a little bit about the challenge of obtaining sufficient tissue-based information to justify biopsy-driven treatment protocols and do it through comparing what I'm calling the clinical and research paradigms.

The clinical paradigm is what would you do with the information. When I go to my physician, they say, "Here is a test, you should go get that." I say, "Okay, that's fine." But what would you do with the information?

Are the risks, for example, of obtaining the biopsy worth the potential benefit to the patient of the information to be obtained or not? That is the clinical paradigm.

The potential benefit could be a number of different possibilities. One is that it is necessary to establish the diagnosis, meaning that noninvasive testing may not be sufficient to

adequately distinguish between diagnostic possibilities.

I will say that in preparation for this meeting, as well as a meeting a few months ago at NIDDK about kidney biopsies, I read through the literature over the last seven years to update myself. It looks like there is emerging data to suggest that this may be the case with DIPG, but that is why you are here, to talk about those data.

But in general, the benefit to a patient can be either therapeutic, allowing for a decision for a better treatment. It could also be prognostic. In fairness, you may do biopsies that simply provide prognostic data to a patient or family so that they can make better life decisions.

The assumption here is that there are at least two diagnostic possibilities absent the biopsy. As a clarification, I think as we get more into precision medicine, you can have what used to be the same phenotype really as two different drug targets, and legitimately, if we have two different drug targets, you could begin to think of that

being two different diagnoses as opposed to one. The phenotype targeting paradigm is important here.

The research paradigm, there are really two. One is the research only, and what I mean by that is there is absolutely no actionable intelligence from that biopsy. In that case, the family and the patient, if appropriate, would need to be told that the information would offer no benefit.

The question is, are the risks of obtaining the biopsy worth the potential benefit to future patients of the information to be obtained.

The alternative is that the biopsy information may serve as an important branch point in a clinical or treatment protocol. So that although there may be uncertainty about the relative merits of different treatment strategies -- it is not in the clinical setting that you are doing this. It is in the research setting -- there is sufficient information about diagnostic subtypes to allow for a biopsy-driven protocol decision.

In this case, the risks of the biopsy can be

balanced against the potential clinical benefit of the different treatment strategies. As opposed to the risk of the biopsy, if there is no benefit of having to fit within this minor increase over minimal risk, it would go to a federal panel.

If you can link that biopsy to a targeted therapy, the risks of the biopsy can then be balanced against the potential benefit from that targeted therapy.

That shifts the discussion out of the pure research paradigm into 50.52, which is much more similar to the clinical paradigm.

As I read the questions, I think that is what you are being asked to opine in is where at this point, now seven years later, do we see the state-of-the-art with respect to these types of protocols.

The challenge is how do we get from point A to point B. How do we obtain sufficient tissue-based information to justify biopsy-driven protocols, because you need some data to start with?

Some of the options, postmortem tissue specimens, this was one of the comments of the committee in 2009 was we need to utilize that as much as possible. But the difficulty is if this is postmortem, the biomarkers could have been altered by prior treatments.

It may only be useful for a limited set of biomarkers and drug targets, such as DNA. There are certain things that won't be available if you are not getting viable tissue or not getting tissue premortem. But on the other hand, postmortem tissue specimens could introduce sufficient diagnostic uncertainty.

In other words, if you began to see variability there, you might say, wait a second, maybe we need to look premortem and see if there is something we should be doing differently to guide clinical decision-making.

Animal models may be an option, but there you have to have some knowledge of the human tissue biology to make an assessment as to whether the animal model is or is not appropriate. It is not

my area of expertise.

Then the other is research-only biopsies, where you really have to ask patients and families to permit an invasive procedure that offers no clinical benefit. So that is the challenge. You need to get started somewhere. You don't go from nothing to suddenly having a biopsy-driven treatment protocol. That is the challenge.

Finally, some additional thoughts on obtaining a greater than minimal risk biopsy. Again, this is just my view. The science of drug targeting in a specific disease needs to have matured to where there is a, quote, "reasonable assurance" that a research-only biopsy may result in important knowledge. In some sense, there is a fishing expedition, but then there is fishing for salmon during the salmon run when you see a lot of them jumping in the river. It is how assured are you that you can do something with that biopsy.

Other sources of tissue ought to be fully explored before putting patients at risk for the benefit of scientific knowledge.

Approaching patients and families about obtaining a biopsy must be performed by someone who is not involved in the clinical care of the patient. If you are approaching them about a research biopsy, I think it can be somewhat confusing if the person approaching them is the person who is providing clinical care, and that could lead to some confusion.

Then clinical investigators who also care for these patients should also be transparent about their conflicting commitments when recommending a biopsy be performed for clinical reasons so that you are not in a setting where you really want to recommend a biopsy, because you want to do the research, and you give it sort of a clinical veneer to do it.

I am not saying anybody is doing that, but I think you need to be careful that that clinical and research -- if you are wearing both hats at the same time, it needs to be clear to the patient how you are approaching them and in what role you are approaching them at the time.

I think that is the end of my remarks. Thank you for your attention.

DR. PAPPO: Thank you.

We will continue with presentations from the FDA.

FDA Presentation – Jeffrey Seidman

DR. SEIDMAN: I am from the Office of In Vitro Diagnostics and Radiologic Health, over at OIR from the Center for Devices and Radiologic Health. OIR gets involved in clinical trials when there is an investigational use of a medical device. If there is no device, we generally are not involved.

As a general overview of this talk on the regulation of investigational medical products, I am going to touch on tissue sampling for investigational use and for clinical care, on the variable risks for tissue sampling procedures, the importance of tissue sampling for development of precision medicine.

I note that opinion does vary as to the expectation and value of requiring an

investigational device exemption or IDE submission on the basis of risks arising from biopsy procedures.

In the regulation of investigational medical products, we have drugs and devices. We have INDs and IDEs. The main purpose of an IND is so that the product may be shipped lawfully for the purpose of conducting clinical investigations of that drug.

An IDE is also to permit lawful shipping of an investigational device, but in addition, the purpose of the IDE regulation is to encourage, to an extent consistent with the protection of public health and safety and with ethical standards, the discovery and development of useful devices intended for human use.

Our purview in CDRH includes the regulation of investigational in vitro diagnostic devices. In vitro diagnostic devices are generally laboratory tests performed on tissue after it has been removed from the human body. A risk determination from CDRH evaluates the level of risk of the use of the specific device in a specific trial.

In this determination, we do not consider potential benefit. We only look at risk, and if we determine that it is a significant risk use of an investigational device in a specific trial, then an investigational device exemption submission would be required.

An IDE application generally requires three things. First, the device must be clearly defined; second, the device must undergo a basic level of analytical validation; and, third, that there is informed consent and that this informed consent form includes certain information.

What is the purpose of an IDE review for a significant risk device? It is to determine that the risks to the subjects do not outweigh the anticipated benefits to the subjects and the importance of the knowledge to be gained.

Just to clarify here, once an IDE is required and submitted, then we do consider benefit, but to determine whether or not an IDE is needed, we only consider risk.

An IDE requires complete specification of

the device for the purpose of the investigation, and this may be essential for interpretation of results from a therapeutic product's biomarker-driven clinical trial. That is, if you don't have an analytically-validated device to measure the biomarker, it's going to be very difficult or impossible to interpret the trial results. In this way, the IDE provides some assurance that the device is going to do what it is supposed to do.

Finally, we also review the informed consent.

What are the risks with investigational use of in vitro diagnostic devices? Patients may forego known effective treatment. They may be exposed to excess adverse events with investigational treatment or additional diagnostic procedures.

There may be inaccurate detection or measurement of a biomarker that already has known importance, and there may be harms from procedures used to obtain specimens that are obtained for

investigational use.

What are the procedure-related harms in medical device investigations? There is a difference between therapeutic devices and in vitro diagnostic devices. Therapeutic devices, which are often implanted, for example, a prosthetic heart valve, for these types of investigations, the risk of the device is essentially the same as the risk of a trial.

In these types of trials, medical procedure risks are associated with the use of the device, and these procedures are often standardized as part of the investigational protocol. For in vitro diagnostic devices, medical procedure risks are associated with obtaining the specimens for testing, and it is important to note here that specimen acquisition and testing are separated by space and time. So the risk of specimen acquisition is a different question from the risk of the actual testing, and these could be two different risks.

What were some of the purposes of tissue

sampling in clinical trials? Real-time use for investigational purposes within the trial, for example, trial arm assignment. For example, a test may be used to determine if a biomarker is present, and that will determine which arm of the trial the patient will be assigned to.

Tissue sampling could be archived. Tissue could be archived for later use in the investigation of a specific diagnostic device. There may be tissue obtained for exploratory basic physiological research or correlative science that might drive the development of a treatment and/or a diagnostic device. Tissue may also be used in real-time for diagnostic and/or therapeutic purposes according to the standard of care.

We know that all patients are different, and procedures and sites widely vary in their risks. The risks with obtaining tissue depend on the sampling site, patient selection, and how the tissue is obtained. There are noninvasive or minimally invasive methods of obtaining tissue such as a blood draw or sputum.

There are biopsies at the lower risk end, such as skin biopsies and needle biopsy of a peripheral or a noncritical site, and then there are higher risk biopsies such as those of the mediastinum, pancreas, and the brain, for example.

The risk of a specific procedure depends on the site, the type of procedure, the patient's disease and underlying health. In addition, the institutional experience and support capabilities are important.

In the context of any trial, biopsy risk is assessed for each patient in real-time and may to an extent be controlled according to the clinical judgment of the healthcare providers.

In the context of therapeutic products and in vitro diagnostic devices for precision medicine, we recognize that there is recent and accelerating progress in oncology, that treatment is often targeted, and selection often relies on an in vitro diagnostic test result. There is an expectation that in vitro diagnostic devices will inform the best use of certain antitumor agents, and targeted

treatment often does involve tumors that are uncommon based on, for example, age, histology, or a particular biomarker.

We are here today, in part, because FDA seeks advice about how sponsors and how the agency can best evaluate and control tissue sampling associated risks in clinical investigations of in vitro diagnostic devices.

What's the bottom line? With respect to the performance of a biopsy in the context of a clinical trial, we recognize that biopsies are performed by purposes other than routine clinical care or for device development.

If the biopsy is being used to develop an investigational in vitro diagnostic device, an investigational device exemption for the device may be needed. It all depends on how the device is being used in the trial and the specifics of the trial.

Thank you.

DR. PAPPO: Thank you very much.

We will now proceed with presentation by

Drs. Kieran, Leonard and Gupta.

Speaker Presentation – Mark Kieran

DR. KIERAN: Thank you very much. My name is Mark Kieran. I am from the Dana Farber Cancer Institute in Boston Children's Hospital at Harvard Medical School.

What I was going to do was provide a little bit of a concept of actually the treatment options that have come out of the biopsy study that I have run, and then you are actually going to hear about that biopsy study and some of the issues related to DIPG from the subsequent two presenters.

As I said, I was the PI of the biopsy study that Dr. Nalin Gupta will present momentarily, and I am not going to go into a lot of detail about that, because he will do some of that. It is a clinical trial that has both an IDE and an IND, and, in fact, many of the people in the room were participants in that trial.

In addition, I have no stocks or patents or employment with any company, but I have a number of preclinical trial agreements and consulting roles

with many of the companies, including some for whom we are trying to develop new targeted therapies for these patients.

What I am going to do is just very briefly provide a little bit of the historical overview, not so much to redefine what DIPG is -- you are going to hear that from another one of the speakers -- but more to put into context the clinical trial that was run and the information that came out of it.

As you heard briefly at the beginning, DIPGs make up about 10 percent of all pediatric brain tumors. Those that are primarily of the pons are almost universally DIPG, although it turns out that there are a couple of other diagnoses that can mimic this. If it is a classic DIPG, it is 100 percent malignant even when the biopsy material comes out as low grade or benign in histology.

About 20 percent of the brainstem tumors are not primarily of the pons. They can often be of the pontomedullary or the ponto midbrain boundary, and there is often a lot of discussion with respect

to the specialists as to whether that patient has the disease or not, because as you can envision, the outcome for the patient populations with those different findings differ dramatically.

Median age of these children is typically 6 to 8. They come all the way down from less than 1. There are a few reported adult cases of DIPG, and, interestingly, the outcome for adult DIPG patients appears to be different when it is based solely on MRI and clinical characteristics.

The classic presenting symptoms of DIPG, the three classic symptoms of cranial nerve deficits, long-tract signs and ataxia, are present in many, if not virtually all children with the disease. Hydrocephalus is rare, and the duration of symptoms, depending on the study, is usually somewhere between less than 3 or less than 6 months. But the clinical people in the room know that most parents can tell you that the symptoms started last Tuesday night right after dinner kind of thing.

This is not the thing that goes on for a

long time and probably speaks very much to the rapidity with which the disease progresses. There are a large number of classic MRI findings that for the last 30 years have really been used in conjunction with the clinical findings, as the basis on which the diagnosis is based. Dark on T1, bright on T2 or FLAIR. It appears to have this pretend boundary between the pons and the medulla. It is certainly not present on autopsy, but it certainly will be seen on the MRI scans.

The tumor appears to envelope the basilar artery. The tumors are not diffusely enhancing. In fact, if they are, it suggests that they are a different tumor type. They typically involve somewhere between greater than 50 or 66 percent of the pons, depending on the individual study. Europeans sometime use slightly different criteria than we do, and they are typically present in the ventral pons more than the dorsal pons.

Based on those criteria, we have been pretty good, although not perfect, at preselecting the patients for whom DIPG is the most likely

diagnosis.

This is an example of an MRI scan. Again, the one on your left-hand side showing a patient with DIPG where again you can see, it looks like the basilar artery is within the tumor instead of sitting out on front of the pons compared to a normal appearing MRI scan on the right.

You are going to hear a little bit more detail about the specifics of DIPG and some of the other issues related to it. I wanted to lay that background because as we talk about how we have treated DIPG over the last number of years, I think some of that information becomes relevant.

The standard has really been the same for all tumors: surgery, radiation, and chemotherapy. I think it is well understood by everyone involved, complete surgical resection of the pons is not compatible with life and, therefore, never going to be a surgical modality for these patients. Obviously, surgical resection versus surgical biopsy is a different issue and the one that is the focus of today's discussion.

I am going to talk momentarily about the complete lack of success with multiple chemotherapy approaches and obviously, radiation, which I think today is considered the only standard approved but upfront palliative therapy for this patient population.

It is typically wide field photon therapy. We typically do doses of between 54 and 59 grey, but there are some variations on this, depending on the center. Proton therapy is not typically indicated.

In Boston, where we have had a proton machine for many years, this is really one of the only patient populations that excluded the goal by virtue of the fact that although they look very tight and well circumscribed on MRI scans, we know that these patients had very diffuse disease and radiation modalities that are too focal will actually miss some of that disease.

In spite of that, as I pointed out, however, radiation is still palliative for this patient population.

Since it is the only, quote, "temporarily effective therapy," there have been all kinds of approaches using very high doses, including up to twice the standard dose with enormous toxicity but no benefit. There are all kinds of hyper- and hypofractionated approaches that have been taken, none of which have improved the outcome of this patient population.

I could have showed you one of 250 different Kaplan-Meier curves for the outcome of this population. This is an example of two COG studies, ACNS0126, the radiation with temozolomide, the kind of standard adult high-grade glioma treatment, or CCG-9941.

Again, I think the obvious point of this graph is a couple of things. Event-free survival is typically about 6 months. The overall survival median is about 8 months, and pretty well by 2 years, virtually all kids are dead of their disease.

Not that we haven't been trying and this is something that I think really needs to be discussed

at exactly committees like this, over the last 20 or 30 years, as a pediatric neuro-oncologist and, again, with many of my colleagues in the room, we have now completed some 250 clinical trials for children with DIPG. Again, this was all based on the radiographic and the clinical picture. So this is pre-biopsy era.

This includes pre-radiation chemo, post-radiation chemo, pre- and post-radiation chemo, immunotherapy, biologic, radiation sensitizers, anti-angiogenic. We have really left no stone unturned, and I think it is fair to say that in spite of all of that trial, we really haven't succeeded in moving the bar forward at all.

We often summarize this by saying the patients died without benefit, but at least we tried. I think a critical component of what we have done over the last 30 years is to recognize these kids didn't just die of their disease. They died of all of the toxicity we gave them with no benefit whatsoever.

This idea that we can just blindly apply

drugs to this patient population and think we will hit the target clearly has not worked historically.

As we begin to move forward, the other thing that has really been paramount to those studies is when we run clinical trials on kids with DIPG, we usually combine it with kids that have supratentorial high-grade gliomas on the assumption that kids are just little adults and that the GBMs that we see in adults will, therefore, fit both for the brainstem and for the supratentorial compartment. We know that that conclusion is wrong.

Similarly, we know that many of the DIPG trials also include kids that have other brainstem lesions that are not DIPG, and as you will see momentarily, the biology is telling us that those are different tumors.

Obviously, one of the questions is -- and this was raised in some of the previous talks -- is this issue of there really are opportunities to learn. Unfortunately, I think one of the huge mistakes that pediatric neuro-oncology community

made in general was we used adult glioblastoma cell lines as the basis for virtually all of the studies that have been run over the last 30 years, in spite of mounting evidence that pediatric high-grade gliomas of the supratentorial compartment were different than adult tumors of the same location and the same histologic appearance.

Then when you add on top of that that now we are talking about the brainstem, the likelihood that they were different is even greater.

We have learned some things from autopsy cases. You have heard about those. The few patients that did get biopsy got biopsy because it wasn't clear what they really had, but obviously, whether those represent the true classic disease or not was in question. It is really now only in the context of having completed the upfront biopsies that there are now a number of true pediatric DIPG cell lines that are widely available to groups around the world.

This is just an example. This came from the Toronto group. This was predominantly an autopsy

study. As you heard, it obviously has the biases that all the tumors have already been irradiated and otherwise treated.

But it again shows that if you take pediatric DIPGs -- so these are the chromosomal analysis plots. The blues are deletions. The reds are gains. You can see, for example, on chromosome 14, almost all pediatric DIPGs have significant loss of the chromosome. If you compare that to pediatric malignant gliomas of the supratentorial compartment, you can see that the gene analysis plots are significantly different, again suggesting that the pathways and approaches to the tumors are themselves different.

The St. Jude group did a similar analysis. Instead of comparing the same tumor in the pons versus the supratentorial compartment, they compared them in the inferior, in the posterior fossa compartment, low grades versus DIPGs. Again, it is pretty obvious that the chromosomal abnormalities you see in DIPG are significantly different from those in pediatric low-grade

gliomas, perhaps not surprisingly.

Perhaps the biggest advance in the field came back in 2012 with the recognition that there was a specific and classic histone mutation, called the H3F3 and K27M mutation, in which there is a lysine at position 27 that is converted to a methylamine that is present in about 80 percent of kids with DIPG and suggested for the first time that there was a strong epigenetic component to this disease.

Based on that, all of the neuro-oncologists around the world really tripped over each other trying to get the first of what we would call histone modifiers into clinical trials on that kind of very simplistic approach, that if there was a histone abnormality, throw any histone-targeted drug at it, and you should cure these patients.

Obviously, the valproic acid and SAHA studies have already been completed and reported and are completely negative. The panobinostat is just starting and also unlikely to work, in part, because none of these three drugs even penetrate

the central nervous system to the point that they could likely be effective.

There are now a number of histone demethylases that are being developed, and again, we will wait for some of these to come along. There are certainly important opportunities for histone modulation, but we are going to need to find the right drug that penetrates in the right way.

You are going to see some of this later, but this is just an example of a child going for a biopsy of a diffuse pontine glioma. This is actually the co-registration. Again, this is a child that was part of the study that Dr. Gupta's going to present to you as the head of the neurosurgical component of the trial momentarily.

But the question was did we learn anything from that. Again, this was not a research biopsy trial. This was a trial that, as I said, had an IND and an IDE. It classified patients on EGFR, MGMT expression, and then treated accordingly. So this was a treatment-based protocol, but after

biopsying the first 13 kids, we asked the question, could you actually learn anything from those biopsies.

One thing that had happened in advance of that, when we originally proposed the biopsy in 2002, it was rejected seven years in a row and didn't open until 2009. The French, in 2007, started their biopsy study, and we began working with them.

Again, what they discovered that had been previously unknown at that time and had not come out of the autopsy studies was that newly diagnosed patients have specific mutations, about a third of them in PI3 kinase. A significant proportion, about 50 percent, have either activating mutations of PDGFR or amplification of PDGFR, and a significant number have abnormalities, loss of P10. Obviously, those are pathways for which there are already drugs available.

This is an example from the French group comparing DIPGs, demonstrated by the pink bar above, when compared to tumors that were

supratentorial, but otherwise the same grade. Again, you can see they have completely different patterns.

You will also notice that many of the tumors in the purple bars below, many of them are low-grade gliomas. They are not even considered malignant gliomas in spite of the fact that the median survival for patients with a low-grade DIPG is still eight months.

This is an example when you then sub-analyze those groups. We were now finding the DIPG probably isn't a single disease as represented by the histologic characteristics. It is more likely at least two diseases, and I think many of us think probably now at least three diseases.

The French break them up into the mesenchymal and the oligodendroglial-like tumors, but this is just to point out that there is enormous heterogeneity in this patient population.

These were some of the patients that came out of the original biopsy study. The ones in the third from the bottom row in dark green are the

DIPG samples that came out of the pons. Just as an example, here is a patient with a pontine glioma that has a P53 mutation.

This patient also has a PDGFR amplification and P10 loss with the classic H3.3 mutation. But here, for example, is another identical appearing tumor that also has the H3.3 mutation, but instead now has an ACVR1 mutation, has normal P10, but instead has an activating PI3 kinase mutation, suggesting that these, although they have some similarities, certainly are using different pathways in which to activate downstream signaling.

Then, obviously, if you look at other tumors, they are again different, and they are certainly different from their supratentorial counterparts.

When we did this first analysis originally on those first 13 cases, there are some things that come out of this. For example, you can see the ACVR1 group is rarely associated with the H3.3 mutation, whereas it is almost always associated with the H3.1 histone mutation, for reasons we

don't yet understand. It is almost never associated with P53, but it is strongly associated with PI3 kinase, suggesting that tumors are selecting the pathways that will be required to reach the eventual malignant state that causes death.

Understanding those both exclusive and strongly associated patterns is going to be important in terms of patient selection. So this is a map that I think is widely now by a variety of groups that shows that there are multiple diseases both within the pons, within the diencephalon, and within the cortex that have some overlap, but also significant differences.

We are beginning to understand that not just DIPG, but high-grade gliomas, in general, are a multitude of diseases with different pathways that seem to be responsible for their activation.

You had heard previously about this issue of what about the prognostic role of biopsy. One of the things that came out of these studies was the discovery that, for example, ACVR1 mutants are much

more frequent in girls. This was both from the French study and confirmed in the U.S. study, and that, interestingly, they have a much better prognosis, if one can really call it a good prognosis.

Their median time to death is 14 months instead of 8 months. It is almost double, but as you are developing clinical trials to look for things that bump the median survival, those are going to be important variables to keep in mind.

Then I just wanted to finish off. One of the things that came out of that first biopsy trial was our discovery of ACVR1. This is a mutation that had never been previously known to be involved in human cancer in adults and, therefore, wasn't on anybody's radar screen.

We and the French simultaneously discovered that the mutations that account for these tumors, present in about 30 percent of all of the kids, activate this well-known pathway. That is important because what we know about ACVR1 is its role in this unusual disease fibrodysplasia

ossificans progressiva, also called stone man's disease, as soft tissue starts to calcify and turn to stone.

What is interesting is these patients never get tumors and the patients with DIPG never have any calcification abnormalities, but when that mutation is in the context of the H3.1 and PI3 kinase mutation, it ends up leading to that malignant disease. That is important because there is now a drug being developed specifically for this disease, and the obvious question is could you use it for children with DIPG.

The one last thing that I wanted to remind ourselves is when we went back and looked at the 250 or so clinical trials that have been done in kids with DIPG, we noted that about 80 percent of them used drugs that already known not to penetrate the central nervous system. It wasn't appropriate to biopsy those kids, but it was okay to do a trial with a drug that doesn't penetrate. In many ways, didn't seem to make a lot of sense.

We started a program in conjunction through

the drug programs at the Dana Farber, Brigham and Women's, Boston Children's, and the Broad Institute with Nathalie Agar who has developed a technique for the assessment of brain penetration in which all drugs are now being screened.

I would argue that this is where we ought to put a lot more of our energy is making sure that if we are going to subject kids to a drug, that it is a drug that actually gets to the target.

In this case, you just take an animal. You can supply them with the drug. There is no brain tumor in this model. You simply remove the brain after the drug has been administered. You section the brain. You provide the matrix, and then you go basically cell-by-cell to look at the molecular signature of the drug that was provided.

This is just an example of AZ-628, but it could be any drug. You now know where the active drug and its metabolites fall on this spectral scale. You can now basically screen those brains -- this is an animal without a tumor -- and say each green dot represents where the drug has

penetrated the brain. The red is basically the hemoglobin signature so you know where the blood vessels are. You can obviously put the two together and come up to see whether or not a drug will actually penetrate into the areas that you are going to try and treat.

I show this because this is an ACVR1 inhibitor for which we are just about to apply to an IND in order to try and treat the first child with an ACRV1 progressive tumor.

In summary of this part of it, we definitely have the H3 targets, and we are incredibly excited about them. But again, simple thinking, I think, has taken over. We are largely using compounds that don't even penetrate the brain in order to treat those.

We now have a number of targets. We do have a PI3 kinase inhibitor that penetrates the brain. We do have a PDGFR inhibitor that penetrates the brain, and we do have an ACVR1 inhibitor that penetrates the brain, which means we do have some opportunity for these kids.

This is the new clinical trial that is just being developed now that follows up on the one that is just recently closed that Nalin Gupta is going to present.

These were the sites that took part in the upfront biopsy. The first North American study -- I wanted to give them credit. This is where the molecular analysis was done, so I wanted to give them recognition.

I should point out that this trial, every single grant application was rejected for this proposal over a seven-year period. One hundred percent of the funding of this trial came from the family of kids, all of whom had already passed away of DIPG. I'll stop there.

DR. PAPPO: Thank you.

We will move on to our next presenter, Dr. Leonard.

Guest Speaker Presentation - Jeffrey Leonard

DR. LEONARD: Thank you very much for having me today so we can talk about all the aspects of DIPG.

I am going to focus a lot about the anatomy, because in order to understand the risk when we do brainstem biopsies, we first have to understand what the tracts are, where the cranial nerves are running, and the fact that not all DIPGs are created equal.

First of all, I have no disclosures relevant to this talk.

Some fast facts, since Dr. Kieran had done a nice job of introducing DIPG. The bottom line is we are failing in the treatment of this disease. Survival is less than 10 percent at two years, with most patients being dead. I have been in practice now for almost 15 years, and this is the one disease where every single patient that I see has died. I have nothing to offer them.

Long-term survival is usually associated with atypical imaging features and clinical features that are not typical for DIPG or they have been misdiagnosed, leading to the understanding and realization that a better understanding of the biology that was just presented is important for

the treatment of this disease.

Multiple studies have been done, as he pointed out, investigating medical therapy in the absence of disease based on MRI evidence. They have all failed.

We have a disease here that has been around and been recognized for quite a while. The symptom duration is often very short. The symptoms are related to brainstem function because of the tracts that they end up affecting.

The pons is obviously affected, as he pointed out, greater than two-thirds. Bright signal on T2 and hyper-intense on T1. This is important, because when I recently moved to Nationwide, a few of the patients that I first showed up with the diagnosis of DIPG were actually exophytic brainstem tumors that end up undergoing complete resection.

The correction diagnosis of DIPG is important, and a lot of the studies that have not really been -- the early ones were not strict about this particular diagnosis.

This is important because not all DIPGs are created equal, and this will become more important as I present some of the cranial nerve tracts. The one in the center has a central cystic corridor to it with the one on the side showing a ring enhancing lesion, suggesting that this may be a higher grade tumor that would be important when you are determining whether this one needs to be biopsied.

DIPG, how are we doing, to reiterate what was going on, this is one of multiple studies, a recent one from Child's Nervous System in 2015 showing that the patients are dying. Within two years, they are all dead.

It is important, because it needs to be placed in the context of what we will talk about a little bit later in that when we talk about the risk of biopsies. This is the framework with which we are attempting to discuss this.

This is important, because in other areas of neuro-oncology, we are actually succeeding. In medulloblastomas, we have been able to diagnose and

categorize medulloblastomas with four separate categories, and this has been important in treatment and the construction of clinical trials because we are now able to try to reduce the amount of therapy we give to these patients, reduce the amount of surgical morbidity, because it is important in the treatment and long-term survival and quality of survival of these kids.

Current studies have not affected prognosis for the last 20 years. The biopsies, as has been shown, creates the opportunity to understand the biology, use the targeted therapy to create clinical trials, and potentially discuss new drug delivery systems, because if we understand the risk of biopsy, we can potentially also use it for conventional and enhanced delivery.

We can understand what is implied when we end up operating when we end up operating in this particular region of the brain.

This is one of the very recent patients that I saw when I came to Nationwide, and this is a 23-year-old male that came from a very

well-respected institution. He had presented with a left hemiparesis. This is another illustration that we don't understand the biology of this disease. This 23-year-old had been on multiple chemotherapeutic regimens, had a list of chemotherapeutic agents that was as long as two sheets. They had been treated with radiation.

The symptoms hadn't resolved, and they came to us discussing what are we going to do with this patient. Are we going to continue chemotherapy? How long is it going to be? What do we do in this particular situation?

I ended up biopsying him. After medicating our anesthesiologist while doing it, it also illustrated the effect of this biology. This did end up being a low-grade tumor or a grade 2 astrocytoma.

This was important, because it also illustrated the risk to this procedure, because every time I would do the biopsy, we had bradycardia associated with this particular disease process. The actual biopsy procedure did not take

very long, but waiting after each of the potential biopsies, we had to wait until he recovered and he woke up with no neurologic deficits.

It is also important, because one aspect of this that needs to be discussed is that we were pressured into obtaining enough tissue for cell cultures, because we wanted to understand the biology. And finally, in seeing how this patient behaved in the operating room, I said, "This is enough. We're not going to do anymore."

I actually adhered to, as Dr. Gupta will talk about, his particular structure that they created for the amount of tissue that is safe to obtain in this particular biopsy, in this particular region. We were able to obtain the diagnosis, obtain enough for genetics, and were able to move along in a semi-intelligent fashion in the treatment of this disease.

One of my things here is what have neurosurgeons said. Leland Albright was one of the lead author in one of the papers that talked about the role of certain neurosurgery in DIPG. We don't

have any.

Where has this gotten us? It has gotten us absolutely nowhere. I didn't go into this particular field, as did all the neuro-oncologists, to fail. So we have to evaluate new ways of doing things.

What we are saying here is that surgery is not the answer for gross total resection. Yes, we can't resect, and I will show you. This is important, but biopsy of this particular lesion can be done.

What I am going to show you is that it can be done with a reasonable degree of safety, not zero, but a reasonable degree of safety that outweighs when you put that within the context of the overall disease and what we know every single one of these patients will suffer is an important thing to consider.

There are two routes for biopsy of pontine lesions, transcortical and transcerebellar. The transcortical lesion comes from on top. It can sample lesions at all brainstem levels, and what I

will show you is it is, in my opinion, a biopsy that is of much higher risk, because a majority of the tracts within the brainstem are located -- you have to traverse these tracts in order to get to the areas of interest. Stereotactic navigation is necessary.

The transcerebellar route, which was used in this particular study, puts fewer eloquent structures at risk. It is preferred for upper medullary and pontine masses. It is a very simple procedure to do. If it is done by people that know the anatomy and are able to discuss with the patients in a reasonable fashion what the potential risk would be, it is something you can accomplish and provide tissue to direct therapy and tissue to direct prognosis in this particular disease process.

We can all talk about the studies, but I am going to show one from complications because I am going to talk a little bit about complications, what that means.

Overall morbidity in this particular study

of 130 was about 3 to 4 percent. They had worsening of preexisting ataxia. They had cranial nerve palsies, which I will show you why those occur. I will also show you they had an isolated VI nerve palsy. Four patients had small clinical insignificant hemorrhages. However, that is important when you talk about the brainstem region, because you will get that when you do biopsies. If you haven't gotten that in any of the biopsies, you haven't done enough.

Morbidity rates for all these studies varied between zero to 25 percent, indicating that there is a wide variation in the degree of morbidity that you associate with these biopsies.

Getting to my focus here, this is showing some of the anatomy within the region. The region of the brainstem is oriented in the same way we oriented biopsy for one of these pontine gliomas. As you can see, on the side of the lesion, you can get an ataxia of your limbs and gait, more prominent in bilateral involvement because you are involving the pontine nuclei. That is when you get

into the more lateral aspects of the lesion.

On the opposite side, opposite the lesion, you can get paralysis of the face, arm, and the leg when you start affecting the corticobulbar and corticospinal tract. This is important, because if you are seeking to biopsy something that is more medial within the brainstem because, say, it is ring-enhancing or you do your advanced imaging which shows that it is of higher diffusion restriction or you guide your biopsy in some way, you need to be able to counsel the family that you will put them at higher risk for developing a deficit afterwards.

You can also get proprioceptive deficits as you become more medial, because you will be affecting the medial lemniscus within the medial portion of the brainstem, and that we will talk about later.

I have a few slides on some of the eye findings, when we talk about some of the majority of the eye findings when you talk about pontine lesions.

This is why this becomes important. This is DTI imaging from one of our pontine gliomas showing what it does to the motor tract, and what it does is it envelopes the entire motor tract. So you can't differentiate where any of these lesions are, making it impossible to do surgical resections, but you have to -- again, to emphasize, the DTI is an approximation in this location, but what it does is it is running straight through where the tumor ends up being.

You have to know where that is in relationship to your biopsy, and it is important in discussing your risks and where you choose to target your biopsy and how much tissue you end up taking.

This is one of the biopsies that I ended up doing, and what it shows is that this is a very easy biopsy to do and technically fairly simple as long as you are making the correct choices. You journey through the cerebellar peduncle, and it leads to these cores, demonstrating gliomas in this situation.

But it also illustrates you need to find the amount that you end up taking from these locations, because the more you take, you increase your risk of incidental or symptomatic hemorrhages. You need to be able to find exactly what your objectives are, and you need to have a senior clinician that is able to say, because of what is happening in the operating room, when to say you have had enough tissue or the risks in proceeding forward are simply too great.

This is a more complicated drawing showing that the tracts that you do affect in the brainstem are quite important. This is one that shows the pons as it is oriented within a pontine glioma, and what you can see is the fourth ventricle and the more dorsal aspect showing the corticospinal tracts here. The cerebellar peduncles are here.

What this shows is that if you limit your biopsy to the very superficial aspect of a very homogenous tumor in the classic DIPGs, you can really minimize your chance of having an adverse outcome in this particular disease. But the deeper

you go, the more medial you go, you can begin affecting your sensory fibers. You can begin affecting your motor fibers if you end up having to biopsy something very low within the brainstem.

Having somebody senior like Dr. Gupta be the neurosurgery lead on the study is important, because he was available to talk about the indications for biopsy, what you would end up biopsying in this particular situation. It was very important in keeping the risk as low as you possibly can.

Again, to emphasize, the risk will never be zero, because you are dealing with the relay station for the entire central nervous system.

The other thing is you recognize when you talk about the biopsy trajectory, you have your facial colliculus, and you have your cranial nerve VII and VIII coming around to exit the cervical medullary junction right there, demonstrating the location.

If you do have swelling, if you end up biopsying something in the lower part of the

cerebellar peduncle, you will end up affecting those. The idea is to avoid them and choose your targets such that you know your anatomy, you know or can approximate where your tumor ends up, but again, what this illustrates is it is a high-priced piece of real estate.

What we end up doing a lot of times is trying to direct ourselves away from the critical structures, minimize our risk of biopsy, and hopefully not delay the chance of administration of the therapies that are standard in the treatment of this disease. So we may in the future be able to yield more diagnostic options for these patients that improves survival.

These are some of the eye findings. As you become more medial in the brainstem, you get the term "internuclear ophthalmoplegia," which you begin affecting the more medial structures of the brainstem, which is the communication between cranial nerves III and VI.

You can also affect the paramedian pontine reticular formation, and you can see here, this is

just a schematic showing the brainstem. You can get various lesions and eye findings depending on where your lesion ends up being within the brainstem.

It is important because these are all things to intelligently discuss with patients prior to counseling them on their risks of the biopsy, and it is important because the neurosurgeons, as they understand, it has to do with the role of neurosurgery, being able to discuss with them what are the potential implications when you do this biopsy.

In conclusion, for us, the transcerebellar biopsy is the preferred route, because it does minimize the risk. Most complications are temporary and do involve eye movement, because they are either VI or maybe VII nerve palsies. Deeper biopsies can be and are more risky.

These new approaches are needed, and these new ideas are needed, because we need to make progress in this particular disease. This is one of the only segments of pediatric neuro-oncology

where we are continuing to fail.

Some of the things that Dr. Kieran presented are very promising and deserve to move forward for treatment purposes because biopsy of this can be accomplished, and it is a necessary thing for the neurosurgeons to get behind.

Thank you very much for your time.

DR. PAPPO: Thank you. Last speaker.

Guest Speaker Presentation - Nalin Gupta

DR. GUPTA: Thanks for the opportunity to speak to the Pediatric Subcommittee of the ODAC.

Jeff, I think you said I was senior, right? I will take that as a compliment.

(Laughter.)

DR. GUPTA: I have obviously had the opportunity to interact with Jeff and Mark over the years, and I think I am not going to try to be too redundant in terms of my comments.

I would like to give you a little bit of background in terms of the philosophy that underwent some of the trials that have been referred to, both from a general perspective, and

also from a surgical perspective. I would like to close my comments really with looking at really a path forward in terms of how do we achieve success in this particular area.

I will say that all of us that really take care of these patients, I don't think there is anyone who isn't, in that group in this country, very highly motivated to try to achieve an answer. At the same time, we are both deeply frustrated because we have not accomplished even a glimmer of success in that, as Jeff and Mark have pointed out.

I think that motivation is what drives us to try to do this, and it is a tricky balance because at the same time, as I enjoyed listening to both Drs. Nelson and Seidman, there is a balance. There has to be an equipoise between the benefit to that individual patient and, of course, the information that these patients provide to us that allows us to take care of the next group of patients that we are going to be seeing in the years and months to follow.

As pointed out, I have a research grant for

which I received salary and research support from Pfizer. I usually forget all the acknowledgements, so I moved my acknowledgements slide to the beginning.

So these are the people that I work with and who are the talented members of our team. Nothing I am going to talk about today would be accomplished without that. And, of course, my fruitful collaborations with Mark and Jeff and the other neurosurgeons.

As Jeff alluded to, our nihilism about this disease is not ancient. It is relatively recent. MR technology became widely available in this country in the '80s and '90s, and there was an article. It is fruitful to go back and read it. Leland Albright, who is a wonderful man and an intelligent neurosurgeon, however, wrote this in his paper, which is that "MR scans should replace biopsies for the diagnosis of diffuse brainstem gliomas."

I think at the time that was appropriate. However, at the same time, I think that decision,

even though it was intellectually consistent and honest, has led to the place that we are with respect to the biological understanding of this disease.

As Mark said, the difficulty we had really designing the DIPG BATS study was very well illustrated I think by Dr. Nelson's comments, which was that we were faced with this issue of how do you do something where people really weren't that keen to do it surgically and there was really a risk, and yet, what was the benefit to the patient.

Obviously, the bar here is very different. We're not talking about acne. We're not talking about asthma. We're talking about a disease in which I have to go in along with the oncologist and tell the parent that their child is going to die, and that is a very different circumstance than nonlethal conditions.

We searched, and I will be the first one to confess that this was an imperfect study. It was imperfect because we were really on very, very limited data regarding these tumors. But I can

tell you exactly how we constructed it, which was based on really these papers and probably the misleading assumption that MGMT played a role in DIPG. We felt it must because of the nature of the pathology, and that's why MGMT expression was built into the study as a form of stratification.

EGFR, there was a little bit of data. There was a paper from Richard Gilbertson from '03. They had 7 specimens, and 4 of them demonstrated overexpression of EGFR. That was sufficient for us to at least say that there was some possibility that these tumors might respond to an EGFR-selective agent.

Then, of course, a priori, we didn't know. We didn't know what percentage of the patients would have MGMT overexpression and which patients would have EGFR expression. So we also had to have groups in the study that were those that had not expressed neither, expressed either, expressed both. That's really what constructed the entire study.

The hypothesis simply was that if we

stratified by these fairly simplistic markers that we would see some evidence of benefit. That was really the entryway into this study.

At that time, which is the late part of the aughts, there was also emerging data that the biopsy of these lesions was not what people thought it was. Jeff has gone over that. I won't repeat really any of that.

The two papers that came out, one was from the French group in '07 and actually from Dave Pincus in Florida. What they described at that time was really a very small number of patients, but that the percentage of deficits was relatively low and were mostly transient. In other words, they could be done, and certainly this is not definitive. But at that time, this was plausible, and at least we had some numbers with which to provide families.

This was how the study was constructed. It was upfront. It was not recurrent. I will give you my frank impressions of how I think studies in this disease should be constructed at the end. But

these are patients who were selected at diagnosis, and we selected patients that were classical.

In other words, patients who had atypical disease were really excluded or we didn't include them simply because we weren't interested in treating atypical tumors. We were interested in treating typical DIPG cases.

I spent a year at various meetings talking to the different surgeons and the different groups, having training sessions which really amounted to going over cases and talking about the best way to do this. We would have a training session on the phone as the study progressed for new sites that were enrolled, but the idea was to include patients that really, if you looked at the scan, you would be convinced that that was a DIPG.

Patients were biopsied, and the specimens were sent to a central laboratory at the Farber where they had MGMT methylation analysis, EGFR expression. The patients were stratified into the four groups.

The statistical analysis of the study, of

course, in classical studies, you base it on your dose escalation. You base it on expected anticipated results. In this case, we had no idea. Was there only going to be one cohort? Were there going to be four cohorts?

To Mark's credit, in the statistical design of the study, it was built out with the assumption that as we did the study, we would learn where these patients would fall, and that would ultimately determine it. As it turned out, most of the patients fell into two of these groups, not all, but most.

That was actually the very first thing that we learned from that study was that it's not homogenous at even an immunohistological level. There are differences in these tumors.

These were the objectives. It was essentially a phase 2 study, and I won't go through all of that.

The last part of it was important. We felt that this was important to say it explicitly. This was really a study that was going to be one of the

first prospective, if not really the first prospective study that was going to acquire upfront tissue for molecular analysis. In a sense, it was the building block toward the subsequent studies that will follow this.

At that time when we designed the study, which was probably 8, 10 years ago now, at the time, we had the sense that we would be doing sequencing and our sequencing abilities would be far better. This was a slide from that period of time, but I think what we are looking at is really a much more detailed level of sequencing than we could have conceived of back then.

We can talk about in terms of it is going to be all batch run at the study's close, and those analyses are actually going to be underway.

You have seen this slide. So these are the members that participated in the study. I will dwell on this just for a moment except to say we didn't know ahead of time how this was going to pan out at the IRB level. I just finished a five-year stint on our IRB. I obviously didn't review our

own study, but that was a very educational experience for me, because I realized what a difficult job that is.

These were the sites that participated in the study. Most of the sites did some biopsies. Some did more than others. Obviously, this study went through all of these IRBs. There was one center that originally started in the study where the study was not approved by the IRB.

I only say that because what that list represents is a review of this tissue-based upfront biopsy study by a great many institutional groups and oncologists and ethicists, et cetera. I give credit to the people at the individual institutions for reviewing it critically, but in all cases except for one, the study was approved, opened, and recruited patients successfully.

What did we set out initially? The goals of the surgical biopsy -- and again, we didn't know ahead of time exactly how this was going to pan out, but we decided to be fairly vague about how to specify what surgeons were going to do. The

surgeons were guided, and I told them their first goal was safety.

The structure of the study placed the decision-making as far as inclusion in equal terms for both the pediatric neuro-oncologists and the neurosurgeons. What I meant by that and we laid it out explicitly in that there was a medical and surgical co-PI at every site. The decision to do the biopsy had to be agreed to by both the neuro-oncologist and by the surgeon.

I told the surgeons explicitly that if there were features or factors about the patient on which you were concerned about safety or risk being greater than what you would expect as being minimal, then you should not include that patient in the study. There were definitely situations where that came up, and I made myself available in terms of not that I think I know any better, but sometimes it's helpful to talk about it.

We did circulate cases to the surgeons as a group on certain occasions asking whether this was something that the group would consider as a

consensus or would not. That was a very, very important exercise, because it brought together neurosurgeons from a variety of institutions, a variety of viewpoints. But I think in the end, we achieved -- this is not a substitute or to state it is a standard of care, but I think that we at least achieved a consensus amongst a great many major pediatric neuro-oncology sites.

The surgical biopsies were driven really by safety first and then these other target selection areas specified. The other things were not required, but could be done. We had no data to say whether high PET activity was specific for anything, but these were just simply recorded as aspects of the decision-making in terms of the procedure.

The ideal tumor features were those that we were looking for homogenous targets. We wanted to avoid necrotic or cystic areas. The tendency and the bias is to go after the enhancing area, but I think our experience with other tumor types is that if you target necrotic areas, you are just going to

get unanalyzable tissue.

Mark has shown you this picture. This is just from our teaching slide deck for the surgeons. The surgery is generally very well tolerated from what the patients go through. Our average length of stay is about a day or two. Our first night is usually in the ICU, and then typically either the patients go home within a day or two of the operation.

We use a navigation system which gets us down to an accuracy of about 1 to 2 millimeters, which is sufficient for this. There are more accurate systems, but I don't think they are required for this.

Jeff has shown you some pictures. I am not going to repeat those except to say that the majority of the biopsy is performed through the cerebellum and the cerebellar peduncle, and I think that really minimizes the degree of potential injury. We are really talking about a cerebellar path, and then I emphasized to the surgeons that if we focus on biopsying in the dorsal half of the

brainstem, I think that really also reduces dramatically the likelihood of causing some fairly significant complications.

These are just some examples of that. You can overlap some pathways. Those are the red and yellow outlines onto your plan. Again, I don't know if that's necessarily helpful or not, but there are definitely some things we can learn moving forward.

What we specified in terms of tissue handling was the following: The French groups were biopsying and obtaining up to 6 to 8 specimens. I felt uncomfortable with that.

The individual sizes of the tissue are small. They are probably in the range of about 0.5 to 0.8 millimeters in diameter and about 3 to 6 millimeters in length for each biopsy, and these are performed with a fairly standard side biting needle that is used for everything else we do in deep locations, thalamic, basal ganglia, et cetera. The tools and technology are entirely the same as what we do with every other tumor type in the

brain.

What we specified in terms of the specimens is that the initial specimen was selected for pathological confirmation. I can't remember in the study. We have had a couple of patients over the years who have ended up having diagnoses that weren't a glial tumor. So the first specimen was really for confirmation that this was a glial neoplasm.

We did not specify that the grade had to be specified or anything like that. That takes the permanent sections to do that. And then the subsequent specimens were shipped to Dana Farber flash frozen for both DNA and RNA analysis post hoc.

What are the adverse events related to the study from the surgical perspective? I do not have a complete table because the study recently closed, and I don't have the final data analysis, which is still underway. I didn't want to release numbers. That would be premature.

But basically, in terms of the actual

specifically that we thought were related to the biopsy, there were three patients: one patient who had somnolence possibly related to the biopsy; one patient who had a grade 1 intracerebral hemorrhage possibly related to the biopsy; and, then one patient with an epidural hematoma that was related to the biopsy. Again, this is not a comprehensive list of the adverse events, both serious or otherwise. That will follow shortly.

But I wanted to illustrate these as being of these patients in which there were greater than 50 patients enrolled prospectively. This is the risk profile in terms of serious adverse events.

The numbers I quote to the families in terms of risks are a 1 to 3 percent risk of high or serious morbidity leading to permanent neurologic dysfunction or death; a 10 to 15 percent risk of transient neurologic disability, which is usually, in my experience, a worsening of their cranial nerve deficits that they present with, whether it be eye movement abnormalities and/or swallowing difficulties. Typically, I think those are related

to the edema and a little bit of swelling, possibly some micro hemorrhages related to the biopsy, and they typically improve.

The second part of this is really a subsequent study that was done through a separate group that was called initially the Pediatric Neuro-Oncology Consortium, but now -- sorry. It's called the Pediatric Neuro-Oncology Consortium now. It started off as the Pacific Neuro-Oncology Consortium, but we have included other sites. Actually, this list is incomplete. There are a few others that have joined.

This group is a little bit smaller than Mark's collaborative group, and part of this was because we wanted to focus on just making sure the surgical procedure is really done consistently. This study has finished its first group of patients that were enrolled. That was about 16 patients, and there will be another 10 that are undergoing enrollment now.

This is directly related to some of the questions that Dr. Nelson raised. So this study,

the structure of it is that the patients are biopsied at presentation. The specimen is confirmed that there is an adequate amount of tumor present. The specimens are analyzed with whole exome sequencing and gene expression profiling by TGen, which is located in Arizona, and then that report is generated typically within about three weeks.

I will show you our success with that, and then there is a specialized tumor board that consists of several pediatric neuro-oncologists that issues treatment recommendation. The study also has a built-in option for repeat biopsy of the same patient and re-analysis to look at what happens over progression.

The feasibility was really the key thing. We wanted to know if we could do this. There were a bunch of secondary objectives.

In the first group, there were 17 patients enrolled, but two were ineligible. But 15 were available for analysis, and the bar graph right there basically shows you what happened in terms of

when did we get the data.

As you can see, for all the patients that were eligible for the study, that within 21 days we had a complete dataset in terms of whole exome sequencing, RNA-based expression analysis and a preliminary algorithm in terms of matching two potential targets.

This was obviously important in terms of timing, because patients usually started their radiation within about a week or so, week to two weeks of surgery, and then once their radiation is finished in six weeks, we had at least a treatment plan that we could recommend to the families.

Now, some of those families chose not to pursue that treatment plan, but most did. As I said, most of those patients are still undergoing analysis. I don't have the final results of that study, but this, at least to me, illustrated that, number one, the feasibility of doing fairly detailed genomic and genetic analysis of these tumors is possible.

These were all done in very small specimens.

The individual amounts of DNA and RNA required to do these now are very small. All of these analyses that you see were done on a single flash-frozen core measuring 0.5, 0.6 millimeters in diameter, 4 to 5 millimeters in length. So that is how much we need now.

The second part of this -- and I deliberately didn't show that slide because it is not final -- is that this goes along with the data that Mark showed from the post hoc analyses from other studies, that if you look at the genetic profile of these patients, there are some clusters, but these patients all have different profiles.

I think all of these patients have the K27M mutation, but then, in addition to that, they have other targets.

If you look at the individual treatment recommendations, there are certain drugs -- and I should say the study allowed up to four FDA-approved drugs to treat these patients. They all had different mixtures and combinations of drugs that they were treated with.

I think that is interesting, because it tells us that even if we are restricted to the universe of FDA-approved drugs, we can provide a customized solution or personalized solution to a lot of these patients.

Most of the patients so far in the study have had -- as expected, there have been just two or three with transient neurologic deficits. I want to show you one patient that just illustrates the danger of what happens to these patients. This is a somewhat unusual appearing patient, and this is his pre-op scan.

You can see this is a non-contrast T1, and there is some intrinsic T1 signal within the mass. The patient already had had an intratumoral hemorrhage. Biopsy was performed which confirmed that this was a DIPG, atypical, though, in appearance. I wouldn't have included this patient in Mark's study.

This patient is a week post-op, had a massive intra-pontine hemorrhage, and did not survive that event. It is not clear to me why the

hemorrhage occurred a week later, and the biopsy site was actually off to the side. We actually biopsied off to this corner, but the hemorrhage occurred ventral in that area.

I don't know if the biopsy for sure triggered the hemorrhage. I have to assume it did, even though the location that we did wasn't the same, but the presence of the initial intratumoral hemorrhage I think was a warning. Unfortunately, this patient did have a very bad outcome from this, and obviously, that is a very, very disappointing and humbling thing to go through.

Where are we moving forward with this? Obviously, obtaining biopsy alone is just the first step. This is a slide from Chris Bankiewicz, who is at UCSF, but started out his career at the NIH, and this is from one of his very, very early papers that showed when you can deliver drugs directly into the brain, you can achieve far greater and better distribution than we can ever achieve through intravenous or a systemic route.

I will show you a few slides that -- I think

that the treatment of these tumors has to be done upfront. I think treating these patients for recurrence is a fool's mission. These tumors are widely disseminated at recurrence. Our ability to achieve success in that setting I think is going to be almost zero. I think the chance of achieving success is going to be at presentation, and I think, obviously, it doesn't mean we don't treat patients at recurrence. But I think not to treat them at presentation is a mistake.

I think the treatment at presentation has to be both local in the brainstem and also systemic, and I think both have to be combined.

These are just some data from Chris showing that we can achieve excellent volumes of distribution with convection delivery. Mark Souweidane, one of our colleagues at Cornell, has really been the pioneer in this country with respect to this. He is finishing up his phase 1 study using a specific -- these are in just some earlier papers of his, but they are finishing up a 7-dose escalation study for direct

convection-enhanced delivery for patients with DIPG using CED. I think that is really going to be the future.

We have a study that is going to be opening soon, which is really a very non-precision-based study, but it is a CED, going to be, with using liposomal irinotecan for the brainstem. This will incorporate repeated infusion and with the goal of covering the entire visible tumor target.

Why do I say that I think the treatment has to be done upfront in terms of where we do this? This is a patient of mine that had an autopsy after recurrence. The H&E and the boxes are from where the sections were taken at biopsy. The H&E, you can't see this. It's too low power. But this is the K27M stain, which is a beautiful stain, actually. It really highlights in the area of the tumor.

There is really an unbelievable preponderance of K27M cells, positive cells. It is cerebellum, pons, and this is in the diencephalon and temporal lobe. If you do the frontal lobe

sections, you will see the same K27M positive cells.

This disease at recurrence, I believe, and for certain at death, certainly is a gliamatosis-type picture. The thing that I don't know is to what degree the dissemination has already occurred at presentation. That would be very discouraging if this degree of presentation is present at presentation. I hope it is not, because I think that the tools that we have to use this successfully will be a combination of selective targeting of molecular and genetic alterations delivered both at high concentrations locally and then, also, systemically to the central nervous system. I think that is the only path forward in terms of success with this disease.

That is really summarizing my last slide, and I will end with that. What can we do if we had unlimited resources and planning and all of that stuff?

I think we would treat these patients aggressively. We would characterize their genetic

and epigenetic changes in detail. The treatment would have to include both CED, and there are some new intra-arterial therapies that I think are also very promising.

There is a group in Britain that you are all aware of, Steven Gill's group at Bristol, which is using implantable systems for chronic delivery into these patients. That is a very frustrating study simply because they haven't circulated much data. They just presented it at the ISPNO last week, but we know very little about some of the technical issues related to that study.

I think multiple targets have to be treated simultaneously. I think there is not going to be a silver bullet for this disease. One drug is not going to work. I think multiple agents delivered over a wide geographic area at multiple time points is the path forward.

I will stop there. Thank you.

Clarifying Questions from Subcommittee

DR. PAPPO: Thank you very much.

We will now take clarifying questions for

Drs. Kieran, Leonard and Gupta. Please remember to state your name for the record before you speak, and, if you can, please direct your questions to a specific presenter.

We will start with Dr. Brown.

DR. BROWN: Question for Mark. The mutations that have been discovered in DIPG, what are the variant allele frequencies generally? Are they heterozygous? Are they very subclonal? Does it differ by mutation?

DR. KIERAN: In the upfront study, the molecular classification of the different tumors, about 50 percent of the tumors have the K27H3 mutation. When a tumor has that, 100 percent of the tumor cells have it.

About 30 percent have the H3.1 mutation. There is an enormous amount of biology because the H3.1 gene, histone gene, is exactly the same sequence as the H3.3. So they are the same exact thing, and, yet, the H3.3 is in 50 percent, 3.1 is in 30 percent, and 20 percent of patients do not have a histone mutation, which is why, again, many

people believe they are falling into the three different groups.

When you have the ACVR1 mutation, which is almost always associated with H3.1, it is always found in 100 percent of tumor cells, both at diagnosis and on autopsy at time of death, whereas, for example, the PI3 kinase mutations are always in subpopulations. Many patients will have multiple different co-expressed PI3 kinase mutations in a percentage of cells that themselves don't always even add up to 100. In that sense, there is variability.

There is more variability in the patients with the amplification of PDGFR with a mutation. There is also some heterogeneity, although less so, for PP1MD as well as ATRX, and so we are beginning to just understand that lay.

DR. BROWN: So is it fair to say then that the two histone mutations and the third mutation are really, you would think, the driver or the founder mutations, and then the others can occur in subclones that might be responsible for disease

progression or dissemination or higher proliferation rates?

DR. KIERAN: Yes, you would have wished that was it. Of course, the obvious experiment was we took animals and we mutated H3.3. None of them get a brain tumor. So we mutated ACVR1, and not a single one got a brain tumor. We mutated PDGFR, and all of the others. Then, of course, we combine -- and if you take a mouse where, for example, you combine the PI3 kinase ACVR1, H3.1 mutation, those mice don't develop tumors, which means it is still more complicated than we think.

The one issue is those experiments so far have all been done in mice after they are born, and some of the early data is suggesting that the original cellular mistake may happen in embryogenesis before the mouse is born. Obviously, those are tougher experiments to do.

The proof of principle experiment has so far not been successful, but it may be related to some of those developmental issues. It may be that if you put a H3.1 mutation and ACVR1 in at the right

time, that would be sufficient to cause the tumor.

The fact that at recurrence, 100 percent of the tumors 100 percent of those cells still have those mutations, makes us believe that they are being held on for a reason. We just don't quite understand why.

DR. BROWN: Then in terms of the targeted therapies, obviously, the kinase mutations, PI3 kinase, et cetera, the subclonal nature of those mutations in those tumors, there are obvious implications for the potential of that therapy to be effective, right?

DR. KIERAN: Yes. We have to be honest. I think we have an enormous ability as oncologists to underestimate tumors. We have been doing it for many, many years. The idea that a histone, an HDAC inhibitor was suddenly going to cure DIPG was excessively simplistic.

When we do something, these tumors are going to respond. So even when we get the right targets, those tumors have nothing to do all day but mutate and figure out a way around it. We have got to

assume that even with everything we know, there is going to be more to learn and do.

DR. PAPPO: Thank you.

Steve?

DR. DUBOIS: I will disclose I am at Dr. Kieran's institution and was formerly at Dr. Gupta's institution.

First, a question maybe for all of you. I am not sure who would be best to answer. But I presume that this information is not obtainable without biopsy, even in the setting of advances in circulating tumor DNA and MR spectroscopy and techniques such as that. I wonder what work is being done, particularly with the CT DNA, to try to obtain this information less invasively.

DR. GUPTA: Right. That's a very good question. We're collecting blood on the patients, obviously, in the PNOC 003 study, and there is some early data to suggest that there is sufficient tumor DNA or at least circulating cells with tumor DNA that you can do some analyses of this.

We are probably some years away from that

realistically, and, obviously, it doesn't get at the whole question, which I haven't talked about or any of us have talked about, is even though there is a subclonal, there is probably -- I think Mark's point about the tumors being embryogenic in origin, I think when you think about it, right, this tumor arises in one location at one time. There are 10. Yes, there is a bell curve, right? But in one location, in the ventral pons, at one time.

If we paid attention, for any embryology, that has got to be related to some kind of cooperating Hox gene expression in the early embryo.

The other thing you think about is the entire pons is involved, and these patients will have diplopia. If your entire pons is not working, you are not walking around worried about what are you going to do at home that evening, and that is what these kids are usually doing.

To me, there is no question, in my mind, that these tumors have been present in a low-grade infiltrating capacity for a long time, and

probably, probably the early cells were present before birth. Then there is no question in my mind they transform, because then those patients die. They die quickly.

I think the fundamental question, I think, biologically, with these tumors, is what are the cooperating mutations that lead to an infiltrative low-grade phenotype, and then what is the mutations that then lead to the transformed phenotype that leads to early precipitous death. I think that the treatment ergo has to focus will focus on both of those areas. I don't think we understand either of those as yet.

DR. DUBOIS: Then for Dr. Gupta, on the BATS trial and also on the PNOC 003, are you tracking or did you track the rates of refusals for parents to consent because of concern about biopsy and then tracking, as well patients who consented but the neurosurgeon declined to biopsy?

DR. GUPTA: I have to check with Mark if we looked at that for the -- the answer to the first question is that the -- and Mark can give you more

details. I think the simple answer to the question is more patients or most families usually consent.

We have had, obviously, refusals, but they tend to be in the minority. For 03 and for the other studies, we do track that.

The flipside of it really, though, pertains to I think what Dr. Nelson pointed out, that it is a combination of desperation. We have nothing else to offer these patients. We are not offering some cure here. We try to be circumspect and objective about it, but clearly, we are, also, us as clinicians and researchers, bringing a bias to the table.

That is a difficult one to walk, but I think the parents are looking at it and I would never -- I am a parent, and I wouldn't want to be in that position of the option is radiation and nothing or there is this narrow path forward.

I think from a parent, it is very difficult to say no to that situation, and I think we have to understand that, because it does sway people into -- I just can't believe that parents can be

objective in this circumstance. I don't see how you could be. There is no way.

You are going to be deeply emotionally subjective in your decision-making, and I think you have to build that into your counseling with families.

DR. KIERAN: I can answer some of the others. When we wrote the protocol, actually, there were a number of IRB issues with it. One of the issues was we didn't really think that Avastin, temozolomide, and erlotinib was suddenly going to cure the most incurable disease in all of pediatrics.

We actually wrote into the protocol that we would request autopsy tissue, as well, and there was enormous debate. Those are some of the issues that many of the IRBs had was requesting autopsy at an upfront study in which the patient hadn't even had a chance to start therapy yet.

The IRBs refused to allow us to collect patients at centers that refused to enroll in the protocol, because if they refused to enroll, you

couldn't know about them. They had decided not to. Unfortunately, although that dataset would have been enormously helpful, I think, it was forbidden to collect.

In terms of the patients that actually enrolled, three patients ended up not getting a biopsy, but none of them because the patient withdrew. One of them had a problem before they went to the OR, the kinds of things where all three of them had planned to go to the operation and then didn't. No patient pulled out once they consented, which is the only number we were actually able to track.

Based on the sense of how many patients called, I would say that on average, about 40 percent of families that asked about it ended up not enrolling, many of them because their kids were progressing rapidly, the docs wanted to do something else.

What was particularly interesting in the protocol was towards the end of the protocol, the FDA had mandated that we treat the first patient

and then wait six months and then treat the second patient and wait six months, and then after the fifth patient, wait another. So there were long delays.

By the end of the protocol, we were getting calls almost weekly, "My child has had a biopsy," or the surgeon would call up or the center would call, the neuro-oncologist would call up and say, "We did the biopsy. Now what?"

"Well, you weren't part of the protocol. You didn't prepare the material properly."

That word about biopsying had gotten out there, and now suddenly where people were biopsying and then finding out if there was a study which, of course, by definition, made them ineligible. We actually had some trouble finishing the accrual because of that.

DR. DUBOIS: Last question, promise. It is really just to satisfy my own curiosity. It is a little off topic, but what is known about germ line predisposition to these tumors and is anyone doing, for example, a GWA study and might that inform our

understanding of the biology of this disease?

DR. KIERAN: We have completed whole genome sequencing on now 45 of the 50 cases that have got usable biopsy material. So we're doing those.

There is no genetic predisposition that we are aware of to this disease, although we are finding multiple abnormalities in DAN repair genes, and one of the things we are now beginning to wonder is whether there could be a subtle predisposition. Obviously, none of these kids survive long enough to pass the gene on, and so that may be one of the issues.

The other thing we looked at very carefully is we reviewed the incidence of DIPG as reported, and, obviously, reporting bias here is a little bit of an issue. We looked specifically in Egypt, in South America, and in North America, and the incidences per population and age are the same, suggesting there are not large ethnic differences. Obviously, you could miss some important predisposition factors there, but given the breadth of the population we looked at, there was certainly

nothing major found.

DR. PAPPO: Thank you.

We have about three and a half minutes left, so I am going to do my very best to prioritize your questions.

Dr. Neville?

DR. NEVILLE: I think this is for all of you, and it is going to be quick. You may not have answers, but I am just wondering.

I know PNOC 003 was feasibility and safety. I am guessing you are collecting tertiary efficacy data, and I am wondering. Are you seeing targetable pathways, and are you seeing any drugs come up multiple times?

We are in a trial that is doing that with extracranial tumors, and we are starting to get to the secondary point where you start testing the same candidates that keep coming up over and over. I am just wondering, even though it is early, if you are seeing that.

DR. GUPTA: I actually have that slide. I didn't show it, because it is a public forum and

that data is not published yet. But in answer to your question, yes, there are certain drugs that are being used more frequently, and then there are others that only appear once.

But if you look at the treatment recommendations for each individual patient, it is remarkable how different they are from patient to patient based on the predictive algorithm that is used to generate the alteration drug analysis. That is also a separate unknown is how accurate is that. That part is also a little unclear in terms of its validity, but I think we are learning a lot about that in terms of how to do that.

DR. NEVILLE: Are you seeing or have you seen any with no targetable? Maybe you can't answer that.

DR. GUPTA: No, but we have had a couple of patients where they have been really quite bland, really the genetic -- but that is a rarity. There are much less genetically abnormal than adult GBMs, and that is true in general for pediatric tumors. But in general, and there are a couple that were

really super kind of quiet on the genomic level.

Now, we haven't done epigenetic analysis on those tumors, and that is probably the next step.

DR. PAPPO: Dr. Armstrong?

DR. ARMSTRONG: Just a quick question. It is kind of the alternative to the biopsy question. Has anybody looked in -- your pattern of spread suggests that there is maybe CSF spread, and I didn't know if anybody has actually looked to see if you can isolate cells from the CSF, which would certainly be an alternative.

My second question is I am just interested in that typical age of onset, and is there a gender predominance of the disease?

DR. KIERAN: Vis-a-vis the gender predominance, no, there is not major gender predominance. There is a little bit in pediatric brain tumors just in general, but again, this is where the ACVR1 much more common in girls, with a longer survival. The non-H3 mutated and the H3.3, by definition, slightly more common in boys, just to make up the rest.

One of the issues is that although the protocol wrote to allow to collect CSF at diagnosis and at the time of diagnosis, extensive imaging studies do not identify metastatic disease, the issue is that the way the biopsy tracts are done out of that study, I think out of the 50 patients, I believe we got -- don't quote me on the number -- I think 6 CSFs, and I think 5 of those were at progression, not at upfront.

It is not an easy question to answer, but actually, what we are doing is from the plasma and serum, we are looking at the cell free markers. Can you pick up the ACVR1 mutation in CSF or blood? We have had some success on that, but as you heard, the amount of validation that will be required to do that, those are still some time off before one would actually use it as a diagnostic structure.

DR. GUPTA: In terms of the pattern of spread, I actually think that even though on the histopath you see these tumors extending out into the PL surface, their predominant spread, unlike medullo. So medullo preferentially has a spread

through CSF pathways, and you will see that sugar coating -- these don't spread like that.

These spread through the brain parenchyma, and they spread through the white matter. So when you look at serial sections at autopsy, if you actually look at serial sections all the way through the brain, you will see these infiltrating K27M positive cells drifting through the parenchyma at great distance from the original site.

DR. ARMSTRONG: Can I ask if you looked at ECAT here in these tumor cells? Just because that is a pattern we see.

DR. GUPTA: Protein or gene?

DR. ARMSTRONG: Protein, but just because that is a pattern we see with loss of ECAT adherence in other tumors.

DR. GUPTA: That has not been done. I can probably determine the -- we can track that because we have the whole exome sequencing on the N expression. We can track that on genetic and expression data, but no.

We have all the specimens banked, and if

there is a legitimate target, we can go back and look at that.

DR. ARMSTRONG: It is really more of a pattern of spread. I don't know if there are really any targets for it.

DR. KIERAN: It has not been protein based. It has been RNA based, and what we have been doing is looking at single cell RNA expression on multiple samples to try and begin to understand some of that heterogeneity so you could go backwards. It would be a select sample.

Remember that although we are getting a couple of cores, they are all the same core from basically the same burr hole so it is not a complete distribution of the tumor itself. Because it is in the pons where we think the tumor started, it may have less to do with some of the highly invasive stuff that you might pick up better if you were actually biopsying the frontal lobe where the real invasive stuff is happening.

DR. PAPPO: We will have to stop here with questions. We are going to take a quick 6-minute

break.

Panel members, please do remember that there should be no discussion of the meeting topic during the break, and we will resume at 3:05.

(Whereupon, at 3:00 p.m., a recess was taken.)

Open Public Hearing

DR. PAPPO: We are going to get moving.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written and oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors.

For example, this financial information may

include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance to the meeting.

Likewise, the FDA encourages you, at the beginning of your statement, to advise the committee if you do not any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for the open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when

recognized by the chairperson.

Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. SCHLOBOHM: Good afternoon. On behalf of the National Brain Tumor Society, my name is Cord Schlobohm, and I serve as a volunteer board member and chair of the society's program committee; in addition to my daughter, Sydney, died of a DIPG. So I have a personal knowledge of the topic of this afternoon's session.

We thank the FDA for the opportunity to address the FDA's Pediatric Oncology Subcommittee.

The National Brain Tumor Society is the largest nonprofit organization in the United States 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 and resistance to treatments and has led to the launch of several promising ongoing clinical trials.

The National Brain Tumor Society believes that there is a critical need to support aggressive advancement of research to pediatric neuro-oncology. In the U.S., brain tumors are the leading cause of cancer-related deaths in children and infants up to 14 years of age.

Diffuse intrinsic pontine glioma accounts for 80 percent of brainstem gliomas and represents a heterogeneous group of pediatric glial tumors that are biologically distinct from other pediatric and adult high-grade gliomas. For DIPG, the mean age of diagnosis is 7 to 9 years old, with a dismal prognosis and a 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. We want the FDA to know that we believe precision medicine approaches, including drugs, devices, and surgical interventions will be important to realize the potential of the recent discoveries in DIPG.

Today, we will focus our remarks on the importance of biopsy in DIPG. The National Brain Tumor Society believes that it is unethical to accept the current state of the field defined by the extremely poor prognosis of DIPG patients. Our position is that all the rational steps to improve outcomes of these patients should be taken, including the incorporation of pretreatment biopsy, where possible.

However, consideration for minimizing risk for the patient and maximizing the value application of information obtained from biopsy need to be guiding principles for clinical care and advancing research for 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 molecular informed treatments for DIPG and children being exposed unnecessarily to toxic and inappropriate treatments. A number of recent studies in DIPG that have incorporated intraoperative imaging and minimally invasive neurosurgical techniques to obtain pretreatment biopsies -- since I am almost over, I am going to speak to you also as a parent.

I strongly believe that biopsy is an important part of establishing treatment, because unlike other types of pediatric brain tumors, surgical resection, brainstem tumors like DIPG has not been an option. But given the advances in precision medicine, including understanding of tumors and the development of new surgical technologies, it is important that the biopsy is considered as an available and a useful procedure.

If a biopsy can lead to a greater understanding of the tumor and enable precision medicine and target a child's tumor with the right drugs and the devices and the right dose at the right time, then it is inherently a valuable

surgical intervention.

I urge the FDA to please advance research and treatment for these deadly DIPG tumors with such a poor prognosis of 9 months' life expectancy. I want to thank the FDA for their time in looking into this today. Thank you.

DR. PAPPO: Thank you.

Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. MOSIER: Good afternoon. My name is Jenny Mosier, and I am here as a volunteer for the National Brain Tumor Society, as the executive director of the Michael Mosier Defeat DIPG Foundation, and as the parent of my son, Michael, who died of a DIPG tumor.

I appreciate the opportunity to share our family's story with the Pediatric Subcommittee today.

As a parent and a DIPG advocate, I respectfully urge the FDA to adopt the view that

pretreatment biopsy is an ethical and potentially essentially surgical intervention that could benefit children facing this disease that is presently considered terminal in diagnosis.

On September 4, 2014, one week after my son Michael's 6th birthday and his first week of kindergarten, we learned that he had a tumor in his brainstem. In shock, we were told that surgery to resect the tumor was not an option and that he likely would not make it to his 7th birthday. The doctors explained that Michael's MRI scans revealed he likely had DIPG, but the scan did have some atypical characteristics.

This gave us some hope that Michael had a different type of brainstem tumor, which would have had an increased chance of survival and a different treatment regimen. The doctors explained that we could have a biopsy of the tumor to definitively determine the tumor type, though as with any surgery, biopsy had risks.

Members of the treatment team had different view on how significant the departures were from

the textbook presentation of DIPG. This was not the only time that we heard different opinions about what MRI images showed about the tumor as later there was also some uncertainty as to how the tumor was responding to treatment and whether the tumor had progressed.

We opted for a biopsy. The results were not what we hoped, but it was valuable to have a definitive DIPG diagnosis to focus our next steps.

Although this occurred just under 2 years ago, at the time, more advanced molecular biology sequencing techniques were not commonly applied. While Michael did have a biopsy, we were not able to take advantage of any genetic information that could have been gleaned from the tissue samples in order to help us choose individualized therapy for our son.

This left us in the agonizing situation of grappling with which clinical trials to choose without a real basis for ranking the options. Our doctors could not advise us that one experimental therapy would be more likely to work than another

for Michael, and we were choosing a treatment that would be our 6-year-old son's only chance of surviving.

We would have wanted any additional information we could gather to guide us toward the most promising therapy. Beyond his survival, the information may have also informed our decision to fill his body with toxic treatments that he hated taking and that had their own side effects in the event that there was no expected benefit.

Michael fought for 8 and a half months, and he suffered tremendously from this disease. As expected, he did not make it to his 7th birthday.

Every family must make their own decision about what treatment, if any, is the best fit for their child. But the existing options are simply insufficient and unacceptable. DIPG is biologically distinct from other adult and pediatric tumors, and within DIPG, there are different subtypes.

Parents need the option of better evaluating tumors through biopsy to help them choose

individualized targeted therapies. We also need the chance of improving the delivery of treatment through surgical interventions that are safe and effective.

Parents with children who have a disease with a median survival of only 9 months and overall survival near 0 percent need incorporation of pretreatment biopsy to allow for more informed decision-making.

Thank you to the FDA and specifically to this subcommittee for allowing me and other fellow parents to speak today.

DR. PAPPO: Thank you very much.

Will speaker number 3 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. PEABODY: Hi. My name is Lisa Peabody. I am here with the National Brain Tumor Society. I have no financial relationships with any vendors.

My 9-month-old daughter, Caroline, did not reach her crawling milestone. At 11 months, we

started physical therapy. She celebrated her 1st birthday in the usual Peabody way with her first taste of cake and the exploration of life and learning to love her other three brothers and sisters.

At 13 months, we were referred to a neurologist, because Caroline had muscular asymmetry. That led us to an MRI and to a diagnosis of pilocytic astrocytoma in her brainstem. We were seen by Dr. Packer and Dr. Root at Children's, and they made this decision based on her clinical evaluation and her images. We also were recommended for a biopsy to confirm this diagnosis, but we moved forward with a chemo regimen of 18 months.

We had the biopsy. It was awesome and fast, and she was home. A few days after, she seemed to weaken. Her shoulder was drooping, and by the end of the day, she seemed to be getting worse. I took her back to Children's, and she was admitted.

As the days passed, three or four, she lost more and more of her body functions. She couldn't

move. She couldn't wiggle her toes. She couldn't bend her knees. She couldn't nod her head. She couldn't smile. She couldn't frown. Her vocal cords were frozen, and when she cried, it just leaked. There was no sound. Then she lost her swallow and was intubated.

At the 10th day, she was in the ICU anesthetized and dying from pilocytic astrocytoma, and Dr. Packer and Dr. Root were so surprised. It was a really unexpected outcome, and even though the biopsy confirmed it -- it was 2004, and these gentlemen are talking about these expansive types of biopsy.

Caroline could have benefitted greatly had we been able to see different parts of her tumor and not just that localized part that they got, which was a grade 1. They think she had a mixed tumor, a hybrid, that parts of it were grade 3 and grade 4.

I understand in 2004 there wouldn't have been a drug, but now with this new targeted therapy, there could have been a chance for her.

There wasn't, because the biopsy was so limited.

I urge you to approve this type of device that gives a more comprehensive biopsy so that doctors are getting all of the best information they could.

Also, one of the doctors mentioned how patients are not biopsied to protect them, but then they are treated with a medication that is unproven to be effective. That is the position we were in.

After she was in this dying mode and we were in salvage, she did a direct radiation trial at NIH that was for adults. It had never been tried on pilocytic astrocytoma, never on a 13-month-old, and never in the brainstem. It was the direct radiation that took her life. The tumor became necrotic.

They learned great information from her participation, but it is that same idea that if we had more information, they wouldn't have had to even just crapshoot a radial therapy.

Again, I urge you to include biopsy as part of diagnosis and evaluation of brainstem tumors.

Thank you.

DR. PAPPO: Thank you very much.

Will speaker number 4 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. AGIN: Good afternoon. My name is Jonathan Agin, and I am the general counsel, institutional official, and development liaison of the Children's Cancer Therapy Development Institute, the executive director of Max Cure Foundation. I am also the child cancer advocacy and awareness co-editor of the Cancer Knowledge Network and founding member and on the steering council of the DIPG Collaborative.

My story has a personal connection. My daughter, Alexis, was diagnosed at 27 months old in January of 2006. She survived for 33 months. She is considered by many a long-term survivor.

Our personal experience began on April 10, 2006, where she was diagnosed at INOVA Fairfax and later transferred to Children's National Medical

Center for confirmation of diagnosis. She was diagnosed following episodes of vomiting at night and her right eye began to invert.

Upon diagnosis, we were immediately advised that her life expectancy was 9 to 12 months with current treatment options. There wasn't any hope provided to us, and I'll put in parentheses "real hope" versus false hope, because I don't think that any clinician treating a family with DIPG would give them false hope through the course of a biopsy.

Treatment options that we were provided with were standard radiation, and at that time, there were phase 2 radiosensitizer trials or a metronomic chemotherapy regimen. We chose radiation for Alexis.

In terms of our discussion with our clinical team on the issue of biopsy, we were told that there was no option to perform a biopsy at that time, and specifically, the neurosurgery team at Children's National said that they would not do biopsies.

Alexis presented with an exophytic component. She was neurologically intact, and there was no option for anything but two therapies that we were choosing from that we knew she wasn't going to survive, even though we had hope based upon a number of other things upon her presentation. There was no option to learn anything greater about her tumor on the genetic level, molecular level.

She came through radiation, finished in June 2006. As her parents, we continued to drive the discussion with respect to various treatment options along with our treatment team. We constantly searched the website clinicaltrials.gov, communicated with other parents, researchers, raised money for research funding. We did everything in our power possible to try and give her every chance.

The treatment team that we worked with provided what options they had at the time. They were limited, and there wasn't any hope. Most of them were phase 1s, and it was essentially a dart

against the wall.

Each treatment option we weighed, as her parents capable of making that decision. Parents are absolutely capable of making decisions with respect to their child and with respect to what treatment to be put on if they are properly counseled as well.

Parents are constantly pushing caregivers and the treatment teams for options that would work. We considered nonstandard treatment options, the quote/unquote, "controversial clinics." We would have done anything and everything at that time to save her life.

Changing perspectives in the DIPG community have been driven by parents and frustrated clinicians. We have had to drive the discussion to shift the paradigms of DIPG and stop the continued cycle. The DIPG community is demanding change in survival outcomes, demanding more aggressive options, and demanding biopsy.

The first time I heard the discussion of biopsy was in 2011 DIPG symposium where Zaghloul

presented his paper and talked about the 82 biopsies he performed with two transitory morbidities, if I'm remembering that correctly.

There is increased information from tissue analysis, both at diagnosis and postmortem. This should be driving more aggressive treatment options and drive greater scientific understanding of targeted therapies, drug development, and drug availability. They are all part and parcel, and we need to be aggressive on all of those fronts.

New mechanisms for delivery, CED, we need to continue to drive new treatments and new ways to deliver these treatments. Then new private ventures aimed at out-of-the-box treatment and therapeutic drug selection, including the one I am involved in with at the Children's Cancer Therapy Development Institute as well as then finally legislation to change the way drugs are provided to parents.

Breaking the endless cycle, Einstein's quotation of insanity is very apt for the way DIPG has been handled. We're continuing to do the same

thing and expecting a different outcome.

We need more aggressive options, and I've got two questions there that I'm not going to repeat.

This is the price of inaction. Do we provide parents that are demanding it more aggressive options, or do we continue to repeat the cycle?

Thank you. I appreciate it, and I appreciate this discussion.

DR. PAPPO: Thank you very much.

Will speaker number 5 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. SHUMAKER: My name is Jesse Shumaker. I am the director of the Nebraska chapter of the Cure Starts Now, which is one of the foundations that make up the DIPG collaborative which funds the registries and some of the research that has been talked about today.

I am here because of our daughter, Madelyn.

She was our only child. Just lost her in December. Some photos of her.

She was diagnosed in January of 2015 in Omaha. We immediately went to St. Jude, where she participated in a PBTC trial. We were fortunate that she had an excellent initial response. Her pons went back to almost normal size. We had seven symptom-free months that we made the most out of it and made back-up plans during that time because we knew the prognosis.

At the first sign of an inconclusive scan, we went to Sloan Kettering where Dr. Mark Souweidane performed a biopsy, which went smoothly. I will talk more about that in a minute. Then she was enrolled in a molecular-guided therapy trial out of Helen Devos Children's Hospital in Grand Rapids, Michigan at that time.

As part of that translational genomics did whole exome and RNA sequencing. The research team looked at drug-gene interactions.

It was an inconclusive scan which led us to take this step, but a week after the biopsy, we

were at St. Jude for a checkup. That was when progression was confirmed.

Just a week later, so just over two weeks after the biopsy, she began treatment on that trial.

A little bit more about that, it is similar in nature to some of the trials that have been discussed here, but it wasn't specific to DIPG. They are on the third iteration of this trial and analysis pipeline. They look for genetic variants, particularly looking for driver pathways, checking against cross-indicated drugs.

There were basically about 140 drugs that were eligible under this trial, and they were looking for drugs that don't show resistance, look at things like efflux pumps and so on, and take all that into account.

The tumor panel had people from various backgrounds, so pediatric neuro-oncology, cancer biologists, DIPG genetic experts, pharmacists, bioinformaticians. They developed a 4-agent treatment plan customized similar in nature to what

was talked about earlier.

This just goes to show how the variants. They take a huge amount of information and vary it down. This actually came from some postclinical analysis, but it mirrors some of the main pipeline that was done in the treatment process to get to really several variants that they focused on in the tumor board.

To give some context to that, my daughter actually had the ACVR mutation that was talked about. That was inactionable because there weren't any agents to address that. She did have the PIC3CA, and that was targeted. Then additional analysis identified some other candidates later.

Our personal experience with this, the biopsy itself went very smoothly. As progression was confirmed and we were getting close to get to Michigan, she lost almost all her strength on the right-hand side in the couple days before treatment.

Once we started that 4-agent chemo and we added the main gradually to verify safety, she

actually started to improve, gaining strength back on her right-hand side. This is at the time when we were decreasing steroids, and that is just not expected to see improvement from the chemotherapy approach at progression. Really, radiation is the only thing that has shown a chance there.

After several weeks, that proved to be ineffective, as well, and she did pass within a couple of days.

I want to echo the sentiments earlier that if we take this approach at diagnosis, I think this has a lot more possibilities.

You guys want to know about biopsy. So these photos are from the day after biopsy. The morning after, Maddie insisted on resuming work on her report and typing up her report on the state of Tennessee. She was a very ambitious 8-year-old girl, and then we were celebrating Halloween that night.

The DIPG Registry is an area where we are collecting information about patients. It is funded by the DIPG Collaborative, and we have over

1,000 patients enrolled in this. I am bringing this up because we are talking about tissue right here, and that comes up in biopsy and autopsy.

Tissue is harder to get, and so right now, the international registry has about close to 50 biopsies and 50 autopsies. The majority of those biopsies are coming from the European registry, where they do biopsy as a matter of course, particularly in France.

We need more information to more effectively do precision medicine. If you think about one patient, we need to be able to compare that to a cohort of patients suffering from the same issue, the same phenotype, and then compare that to other cohorts which may be brain tumors with a better prognosis. There is a lot more you can do with that sort of data to know what is the noise and what are the variations that are really making a difference in the analysis.

I am trying to go to the next slide, but it looks like that may not play. There we go.

Researchers are trying to get to

classification groups based on the genetics and identify therapeutic agents for those. I think it is important that families do know that biopsy is an option even at diagnosis.

The delivery mechanisms are critical here for convection-enhanced delivery to get the agent there in a sufficient quantity to make a difference. The therapy also has promise.

We know these tumors are different from kid to kid. Right now, a lot of the trials are just kind of going blindly, and we know biopsy can be done. But it has to be done by someone with the right experience, as doctors here have been talking about all of that.

We have seen that precision medicine can make a difference. One other thing I want to point out here is that as more precision medicine comes into use here, you are going to see more applications for compassionate use because some of the analysis, those types of analyses, can pull up potential agents that you might not have approved for pediatric use, things like that.

Just like all the other parents and doctors here, the status quo is not acceptable, and our kids deserve a chance.

Thanks so much for letting us speak here. These are some of the researchers involved, and the foundation is involved to fund some of this. Thanks.

Questions to the Subcommittee and Discussion

DR. PAPPO: Thank you very much.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

I would like to make a statement that Dr. Kathleen Neville has left because she had to catch a plane.

We will now proceed with questions to the committee and panel discussions. I would like to remind public observers that while this meeting is

open for public observation, public attendees may not participate except at the specific request of the panel.

We will start with question number 1.

DR. BARONE: Consider changes over time in the adverse event rate associated with surgical biopsy of the brainstem to obtain DIPG tissue for biology studies and more recently, to select molecularly-targeted drugs for therapy.

DR. PAPPO: If there are no questions or comments concerning the wording of the question, we will now open the question to discussion.

DR. WARREN: I think there is no question at this point in time that it has been proven to be safe or at least as safe as other brain biopsies and that we should move forward.

The question in my mind is when should we be doing these biopsies. If it is for precision medicine purposes, should it be done prior to receiving the precision medicine and not at diagnosis?

DR. PAPPO: Thank you.

Dr. Weigel?

DR. WEIGEL: This actually dovetails into the question that I was going to raise. And a comment is that I think there is no question that the pendulum has changed to have a skilled neurosurgical team at sites.

It seems that what we need to do is work towards having that be more disseminated across more sites. There are very selected sites right now with the experience to do multiple biopsies, and I think that one of the real goals would be to have this available more broadly with real clear guidelines of how and when to do the biopsies, so that there is more availability and not just at very selected sites where the neurosurgical team may or may not agree to do the biopsy.

How to get there and what those guidances are, I leave open. But I think we need to work to have it more generally accepted.

DR. PAPPO: Dr. Glade Bender?

DR. GLADE BENDER: With regard to your comment, Kathy, at an institution where we are

doing sequencing of every new diagnosis, what we have found is that if you delay it to the time of relapse, particularly in a tumor that is expected to progress in a very short period of time, if you wait, you often don't have time to act; because between the time of the biopsy and the processing and the analytic pathway and then getting your hands on the drug, should it be difficult to get your hands on the drug, you end up losing a lot of time.

In some ways, although I have argued even the opposite even in the context of this meeting, perfect can be the enemy of good. I think for this particular disease, I would probably advocate upfront, because I think that once this disease progresses, that is the point at which they are going to want a new option. Until our timelines get much tighter in terms of turnaround, I am not sure waiting till the progression works.

DR. PAPPO: Dr. Warren?

DR. WARREN: I get a rebuttal. I guess I should have clarified. Not necessarily at

diagnosis. I think the bigger question here is should we be routinely approving biopsy of DIPGs or brainstem tumors at diagnosis so that anybody at any site can do them at any time, or should they continue to be part of a research protocol?

I would favor that they continue to be part of a research protocol where we are trying to answer a specific objective. Again, we know that some of these targets that we are looking for can change over time. They can change with radiation. You are exposing the patient to a biopsy with all the risks that may be involved and give them a drug that may be toxic later on and that target may not be there when you need it.

DR. PAPPO: You took the words right out of my mouth.

I think that it still needs to be done within the context of a research protocol. Whether you want to expand this to other institutions to increase the availability and applicability of this approach, but I am just afraid that if this starts being done in a variety of centers, especially

without the expertise that you need to have to do this, we may run into a lot of trouble.

DR. WARREN: I am going to give another rebuttal. So one of the biggest issues that has been going on over the past couple of years is sites are getting more comfortable performing biopsies, and they send the tissue to FoundationOne or some equivalent. Parents are given this list of drugs that they can potentially give for their child.

We end up learning nothing about the drugs, the drug safety, or whether or not it worked for their child. And if it did work, why; if it didn't work, why.

They need to be done in a context of a research trial so we learn something applicable to the entire DIPG population.

DR. PAPPO: Dr. Weigel?

DR. WEIGEL: Adding to that, my comment was very much in support of within the context of a clinical trial, but making it more broadly available at institutions that can perform it and

to build the skill set. But absolutely, it has got to be a part of a generalized trial to learn.

DR. PAPPO: Does anybody have any other comments or suggestions, or am I allowed to summarize our comments?

Summarize the comments. The panel feels that at this stage, there has definitely been a change over time on how applicable and how safe this procedure is. The panel fully supports moving forward with this procedure within the context of a clinical trial not only to expand the availability of this approach to other institutions, but also to gain additional knowledge as to what the findings of this approach will be in the applicability of precision medicine.

Is that fair?

(No response.)

DR. PAPPO: Okay. We will move to question number 2

DR. BARONE: Consider the benefit-risk assessment of surgical biopsy of DIPG for molecular analysis of both newly diagnosed and progressive on

current therapy on tumors for the purpose of selecting an appropriate molecular phenotype directed, targeted therapeutic agent for patients with this disease.

DR. PAPPO: If there are no questions or comments concerning the wording of the question, we will now open the question for discussion.

We sort of answered that question on the previous question, but Dr. Brown has a comment.

DR. BROWN: I was just going to say that the previous comment, the previous answer speaks to the fact that I don't think the benefit is clear at all yet, which is why the clinical trial aspect of this, doing this as a research endeavor is so important so that this ratio can be better defined over time.

I think the risk is low enough and the potential benefit high enough that it is favorable, but how favorable will remain to be seen and requires a concerted research effort.

DR. PAPPO: Dr. Seibel?

DR. SEIBEL: I agree, but I think it has to

be in the context of a clinical trial with an honest discussion and full visibility to the family, particularly if it is a basket trial and there is therapy associated with it, the chances that they match and if they do match, the chances that they may have a drug in a formulation that the child will be able to take. The family has to have full knowledge to make an informed decision in that setting.

Also, it is important to do the biopsies within a trial so we can have a better idea of the actual complications and the percentages and the incidence of the complications and the types.

DR. PAPPO: Thank you.

Dr. Weigel and then Dr. Reaman.

DR. WEIGEL: I would echo that I think it is important to consider biopsy at both diagnosis and at progression because we may get different information,. and, actually, the risks may be different. I think we don't know that unless we actually do that within the context of a trial.

I agree. I think it has to be an open,

honest discussion with the family that targets may change, risks may change. I think unless we ask the question, we are not going to gain that information in a systematized way. I think we actually have to look at both to really understand what is happening with the disease.

DR. PAPPO: Dr. Reaman?

DR. REAMAN: I just wanted maybe a little bit more clarification about the context of a clinical trial and what the objectives of that clinical trial might be because I think to some individuals, doing the biopsy and getting the list of potential aberrations for which there might be approved targeted drugs available and then having some tumor board describe a mixture of drugs for an individual patient, I have difficulty seeing how that fits into the context of a clinical trial.

But I think if we are looking for druggable targets and we have agents or products that are appropriate for that target, then an objective to evaluate efficacy of a particular drug in that situation, I think would be reasonable. I think,

also, to get more and more information about the complications, short-term, long-term, pre-therapy, post-radio therapy biopsies is important.

But I just want to make sure we are all on the same page as far as clinical trial here.

DR. PAPPO: Steve?

DR. DUBOIS: I think perhaps a better term might be "systematic investigation" rather than one-off experiences to try to move the field forward. I concur with my colleagues that this is obviously something that is critical to do collaboratively and systematically.

I think as part of that by doing this as a systematic research endeavor, it allows for the banking of leftover material that I think should be made available to the wider research community, and then as well, development of less invasive techniques like we discussed with CT CNA.

DR. PAPPO: Thank you.

Dr. Armstrong?

DR. ARMSTRONG: Given the rarity of this disorder and the fact that at least within

pediatric oncology, you guys are fortunate enough to have precedent for some of your diseases which are essentially only treated at academic institutions where you have the surgical skills, the potential for doing the right kind of biopsy, processing it in the right way, getting it to the right place, and I would think this disorder should be treated that same way.

Community pediatric oncologists don't treat acute leukemias, and they shouldn't. They shouldn't be treating these patients, either. So I don't think it is without precedent.

You guys have done a very good job with a series of studies. It may be baby steps, but those baby steps have improved the outcome over the years. That's really what this needs.

Calling it a clinical trial or whether you call it centralized treatment with potential molecular-guided options, I don't know what you would call it, but there is no question in my mind that none of these children should be treated except at some place where there is experience

treating these disorders.

DR. PAPPO: Dr. Warren?

DR. WARREN: I think we have to be much more creative in our study design and specify the exact objectives that we want to learn from our studies. I think we are beyond safety and toxicity and giving the same agent over and over again. But if we specify the primary objective is to see if the tumor board can come up with something that is safe or the primary objective is to see if this target actually is hit in this patient's tumor and does the patient benefit, that would be a much better clinical trial.

I also think we have to be adaptive. I think Mark Kieran's trial -- Mark, was it nine years it took for you to get that up and running?

It was essentially outdated by the time it started. Again, we have to build into our trial designs some kind of room for newer technologies and newer agents.

DR. PAPPO: Thank you.

Ms. Haylock?

MS. HAYLOCK: I think that this is a fabulous place, as Dr. Armstrong stated, about treating these kids in an academic setting. But I think the advocacy groups can be immensely helpful in helping patients find these places. For example, where I come from in Texas, there are not a lot of these places in local areas. So if I were a parent looking for a place, I am not sure where I would find one other than the big one in Houston.

I think that we need to work together and be partners in getting that information out to the community of people who are affected.

DR. PAPPO: Dr. Warren?

DR. WARREN: I am just going reply to the comment. So the DIPG Registry that one of the parents spoke about does actually list the sites across the country and around the world that deal with DIPG.

DR. PAPPO: Julie?

DR. GLADE BENDER: I was just advocating, again, with this disease, which is a disease for which families will likely have less than a year

together, I also think that it is very important to make sure that there are adequate numbers of sites included in order to keep families together during what may be a limited time that they have together.

I think to assume that neurosurgeons don't have the expertise is probably not the right way to go. I think that there is training and mentoring and doing one together, even traveling to make sure that your technique is adequate. But I think neurosurgeons need to learn to do this, particularly at any academic medical center. They should be able to do it.

DR. PAPPO: Any additional comments or questions?

(No response.)

DR. PAPPO: I want to try to summarize. The committee again is very supportive of continuing to explore the surgical biopsy for patients for DIPG. We believe that the benefit-risk assessment needs to be further defined, and this would be best done within the context either of a clinical trial or, as Steve put it, a systematic study with a specific

research endeavor.

This would allow us to better define the complications of this therapy, the complications of biopsy either at diagnosis or at the time of relapse, and to elaborate specific questions that could be easily measured. For example, tumor boards to better identify therapies, the feasibility of obtaining tissue, or other similar endpoints.

Is that reasonable?

(No response.)

DR. PAPPO: Also, I believe that it will be important also to either identify or guide parents as to which are the academic centers or the big centers, at least initially, that are able to perform this and eventually expand this to other centers.

Did I misquote anybody or did I - Katherine, was that okay?

DR. WARREN: It was okay.

DR. PAPPO: Okay. Good. Not great? You're supposed to say it was great. Okay. Good.

Now question number 3.

DR. BARONE: Please discuss whether the benefit-risk assessment is favorable.

DR. PAPPO: If there are no questions or comments concerning the wording of the question, we will now open the question to discussion.

DR. ARMSTRONG: I have a question with the wording. Is this the benefit-risk assessment of biopsy? Is that what this question is about, treatment, radiation, what?

DR. REAMAN: Biopsy and then defining a targeted drug for treatment.

DR. PAPPO: Ms. McMillan?

MS. MCMILLAN: Gigi McMillan, patient representative. I want to reiterate, as was so eloquently put by our public speakers, that the parents are demanding and want and are fully capable of making these difficult decisions. You have to give them the right information.

There is a difference between giving and offering an opportunity to understand it. So you can imagine your child has been diagnosed and you

have all these things going on in your head and you are upset and you are desperate. There is a lot of white noise going on in your head, and there are a lot of people giving you a lot of important information.

You want to bring your very best self to make this decision on behalf of your child. Sometimes there is a delay in the time that information is given to you and the absorption rate and your ability to come up with an intelligent decision.

I would say that the timing of the request of the information delivery is sensitive and important and that there is a time when a parent is fighting for the life of their child, and then there is a time where there is a gradual realization that there has to be an acceptance that the life of their child will end soon. There are two different energies in those periods.

Sometimes this idea of a biopsy, it might need to be presented more than once because there is a journey going in on the mind of a parent.

I want to encourage the researchers and physicians not to be too hesitant or squeamish or almost over-sensitive to bringing up these kinds of topics with the parents because many of them, we want our children to live. We also want to honor the life that our child has here, and if we can contribute to generalizable knowledge, that is part of honoring our child.

But I thank the public speakers. Your message was well taken.

DR. PAPPO: Thank you.

Dr. Dunkel?

DR. DUNKEL: The question disappeared from the screen, but I think there are two answers to the question. I think if the question is, is the risk-benefit ratio favorable to an individual child today, I agree completely with Pat that I think it is very uncertain.

I think if the question is, is the risk-benefit ratio for society and for future children with DIPG, I think this is an extremely promising strategy and definitely, I see it as

being favorable.

DR. PAPPO: Thank you.

Any other additional comments?

Yes, Dr. Nelson?

DR. NELSON: Skip Nelson, FDA. Just three comments and they are not really on the question, but I was thinking of labeling my talk instead of the Shakespearian reference was "which came first, the arrow or the target?"

I am just curious. It is not a question for today, but to the extent to which you have an arrow, which is a drug, and so if you find something, you think it is a target, but whether it has any impact on the disease is an open question. I think that is a bit of a struggle.

I heard two things, the biopsy route, the plan was a very disturbing observation. For parents to go through a biopsy and then for someone to call up and say "I've got a biopsy, but I don't know what do," that says why it has to be in a research setting.

That comment that you made was to me very

disturbing that there is people out there doing that and then calling up and saying, "I don't know what to do with it. Can you tell me what to do with it?"

Biopsies outside of non-targeted protocols, I think in my mind would also be problematic because then there is no link between the biopsy and what you are actually doing.

Just a couple of comments, as I sit here listening to it, having been listening to this conversation since just prior to 2009.

DR. PAPPO: Thank you very much.

Any additional comments or questions?

(No response.)

DR. PAPPO: The panel believes that the benefit-risk ratio is favorable. The applicability of targeted drug therapy currently is uncertain, but there is certainly a promise for future applicability of this way of targeting tumors with specific drugs for the future.

That is pretty much all I have to say.

Anybody else want to say anything else?

Julia?

DR. GLADE BENDER: I just want to respond to what the families so eloquently put. We are about to embark on a nationwide Pediatric MATCH, and I guess this question is very important. But we are going to have drugs available through a generalized mechanism, and I just wonder why DIPG wouldn't be part of some kind of national effort like that.

DR. SEIBEL: They are.

DR. GLADE BENDER: They are?

DR. SEIBEL: They are. They will accept a biopsy from diagnosis.

DR. PAPPO: Any additional comments or questions?

Yes, Ms. Haylock?

MS. HAYLOCK: I just want to say that the purpose of the biopsy at this point isn't for the individual child, but the purpose is really information-seeking and adding to -- as people said, we have to learn more about this disease, and we won't unless we have that information. So again, this systematic approach to finding

information and using what we have available is important.

DR. PAPPO: Thank you.

Dr. Reaman?

DR. REAMAN: Actually, I think the discussion or at least what we had hoped would be a discussion was not the biopsy for generalized information, but we were talking about a biopsy specifically within a research setting to guide the choice of a specific therapy for that patient. That hopefully would contribute ultimately to generalizable knowledge, which I think is what we clearly need to do here.

But when we are talking about benefit-risk assessment, we are not talking about the benefit for the entire population and populations to come with DIPG, but individual patients with that disorder and what the risk is with respect to the biopsy and selection of a particular therapy. So that was the question.

DR. PAPPO: Dr. Warren and then Dr. Armstrong.

DR. WARREN: I think to address your point, we don't yet know the benefit. However, right now, we are selecting clinical trials empirically. We are shooting from the hip, and I think that having a target and having a drug that potentially hits that target should be more beneficial hopefully than just selecting something empirically.

But I think we also have the opportunity at biopsy to maybe incorporate maybe a phase zero portion of it where you see if the drug is actually getting there, as well. It would be difficult to guess which target and select, but we have to again be creative with our study design.

DR. PAPPO: Dr. Armstrong?

DR. ARMSTRONG: Based on the data presented, 30 percent of these kids have a biopsy. Then another 10 percent have tissue at autopsy. So whoever is seeing these people are voting with their feet that not only -- they are not even willing to do it to establish the diagnosis. So then you talk about doing it for research purposes.

To me, there has to be a paradigm shift,

too. You need to start saying -- is there any other disease where we start treatment without having a diagnosis? There isn't.

I think that needs to be the first paradigm shift which is that anybody who thinks -- if there is a thought that this is the disorder, there should be a diagnostic biopsy done in the safest way possible, but that should also be information gathering for therapeutics. Today, that includes genomics, whether it is on a trial or in any way, shape, or form.

We were talking about research biopsies, but there is not even a standard of care at least in the database. The standard of care is that the majority of these kids never even get a diagnostic biopsy. I think that is wrong.

DR. REAMAN: But do you think we heard sufficient data to support that there is information that would be provided by a biopsy that would actually guide treatment? I think that is the sort of missing part of the benefit equation.

These patients are treated without a biopsy

because there is no effective standard therapy. They respond initially to radiation, and that has been the treatment of choice.

But I think it is not that people have not wanted to biopsy. I think I was around when Leland Albright made the statement that these patients should never be biopsied.

But I think we have come a long way, and now I think we have an opportunity to learn something. I think it is that learning that has to be structured within the context of a trial or some systematic investigation. But I think that is the paradigm shift that I think is actually already occurring to some extent.

DR. WARREN: Can we say today that that biopsy is going to change the therapy? No, we can't say that for sure, but it gives you the potential to identify something that is therapeutic.

To me, that's the first step. I don't think we can tell anybody that doing that biopsy is definitely change things for your child, but it

will give you the potential to identify something that might ultimately have an impact. I think that is all you can say.

When I have a patient with recurrent breast cancer, I don't necessarily have to biopsy, but if their HER2 status has changed, it is going to change their therapy. They are willing to go through the risk for that.

I think with proper information of the decision-makers, the parents, I suspect most of them would want to do a biopsy if there was some possibility that this might change the natural history of this disorder.

DR. REAMAN: But the example you just gave, if their HER2 status has changed and you have a drug available, we don't know whether there is a drug available for any of the targets that might be identified at this point. So that's an issue that I think --

DR. WARREN: It is cyclical now. You don't do the biopsy so you don't have the information so you don't have data on the majority of these

patients.

DR. PAPPO: Steve?

DR. DUBOIS: I think for me the balance is relatively straightforward. We have heard from our neurosurgical colleagues that the risks with newer techniques appear to be acceptable. We know the outcome with our current best therapy in this disease is terrible, and we have heard as well that a subset of these patients will have P10 loss or PIC3CA mutations. Another subset with PDGFR mutations. We heard this morning about the very remarkable activity of TRK inhibitors in TRK fusion tumors. A very subset of these tumors will also have TRK fusions.

I think there is the potential, and I think weighing all of those things, I think the ratio is favorable.

DR. PAPPO: Dr. Nelson?

DR. NELSON: I was just going to maybe give a context. When I'm asked not to answer this question, but I'm often asked within the FDA as the pediatric ethicist to comment on the risk-benefit

of any particular protocol, the way I frame the question, I say, first of all, is there a prospect of direct benefit. Now, the language is prospect, not is there a direct benefit. Is there a prospect?

Proof of concept, is there any evidence that if you hit that target in any tumor that something happens good to that tumor and, therefore, good to that patient? Is there an animal model? Is there anything? Where is that? Is it in vitro, in vivo, whatever? Can you give me some data that says that that's a target as opposed to it just happens to be an innocent bystander that gets hit, but has no relationship?

Then the question is, is that prospect sufficient to justify the risk. Obviously, the less risk you need, the less evidence you need on the prospect of direct benefit because there is a balancing. In other words, if it was a really risky thing to do, you want a lot of evidence about benefit. If it's not that risky, you don't need as much evidence.

Then that whole balance is set in the context of the alternative. So if you look at 50.52, it says the risk prospect must be sufficient to justify each other and then comparable to the available alternatives. The available alternatives here are death.

That basically takes the evidence that you need, and it changes it relative to say it might be a disease where, let's say, you already at this point have a 20-year survival where you would expect a much more robust risk-benefit profile.

That is how at least I think about trying to get to the answer to this question. Is there some evidence that if you hit this target anywhere in an animal, in any animal, that something good happens? Then relative to the risks that you are proposing, is that sufficient to justify it? Then what are the alternatives, and work through those three questions.

DR. PAPPO: Dr. Raetz?

DR. RAETZ: I just wanted to say I agree with what Steve said and echo that. I think in my

mind, the benefit-risk ratio is favorable for all of those reasons.

I think another thing that sways me in thinking that the benefit-risk ratio is favorable is now there are mechanisms to get drugs. I used to struggle a lot with if you had the information and you had something, would there even be a mechanism to provide that agent.

I think through the MATCH trial and through other processes now, it seems like it is much more feasible and realistic to be able to offer drugs and to be able to do it in a way that you study it and that information is learned.

DR. PAPPO: I personally think that now you are at a crossroads where you have a lot of information that would tell you that it is worthwhile pursuing this option of biopsy and, quote/unquote, "targeted therapy." Whether it is really going to provide a true benefit or not, I do not know, but it does offer the prospect for benefit to the patient.

You have the genomic landscape of these

tumors, which was virtually unknown four or five years ago. You have drugs that are currently being developed or have been developed that could potentially target these genomic aberrations.

I think that you need to move forward and you need to try this, and it doesn't mean that it is going to be a homerun, right? We don't know if the drug is going to get 100 percent on the CNS, and we do not know if that is going to be the driver of the mutation or other concomitant mutations will prevent this drug from working. But I think that you have enough information that you have to test this hypothesis.

The perfect example is crizotinib in neuroblastoma, right? It really wasn't the homerun that we thought. Yet, it is a homerun for ALK rearranged tumors, so they might be. But we learned something from that.

I think that is the same thing here. In my opinion, it definitely offers the prospect for benefit to the patient, and given the relatively low morbidity that has been presented to us, I

think it is worthwhile pursuing.

Dr. Sul?

DR. SUL: I just have a comment about the concept of risk. I think that for neurosurgery in particular, there is almost like a historical and maybe even emotional kneejerk reaction to think that anything related to brain biopsy or any kind of brain surgery is not warranted or too dangerous.

But I think it is important also to think about where we are now in terms of the science and technology and make sure that we are making decisions about risk based on the experiences that we have now rather than what we think of as neurosurgery being inherently dangerous.

I am not trying to make light of the fact that these biopsies are not serious and that they shouldn't be thought of as procedures that really need to be thought of and discussed with patients and their families. But I just want to make sure that this sense of the neurosurgical procedure as being too risky is not just based on older data.

I think for neurosurgeons and for

neuro-oncologists, there is less squeamishness with moving forward with these procedures. Sometimes I think for neuro-oncology, we have lost some ground because there has been some reluctance to move forward with getting tissue for these patients.

DR. PAPPO: Thank you very much.

Any additional comments?

(No response.)

DR. PAPPO: Dr. Reaman will now provide closing remarks.

Closing Remarks

DR. REAMAN: Thanks for that opportunity.

I again want to thank the panel, thank our guest speakers, and especially thank the speakers for the open public forum because everything you said made a difference and makes a difference so thank you. I know it is not easy. It is not easy to hear. It certainly can't be easy to tell those stories over and over again.

I think we have come a long way. I think what was very encouraging was the relatively low adverse event rate. I would agree with Dr. Sul

that we have been very squeamish about biopsying things that aren't immediately accessible.

I think that is the nature of pediatric oncology. If it wasn't a bone marrow biopsy or a skin biopsy, it was unheard of to do a biopsy. Now, thinking about brain and brainstem, but I think it is the beginning of a new cycle and hopefully a new cycle in the understanding the biology of DIPG and hopefully identifying new therapeutic options.

I would definitely encourage a broader training program and making the process and procedure more accessible. I think you have done a great job of starting with making sure that quality assessments are well documented and being able to assure that those kind of quality metrics are going to be obtainable at multiple sites is very important.

I think we have to start because I think we have done the same thing for 40 years, 50 years or longer, and it doesn't work. The opportunity is now to explore whether new information is going to

provide new strategies for therapy.

I would strongly encourage that it really be done in a structured systematic fashion. I get very nervous about individual families who go and through their own personal resources have sequencing studies done and then expect practitioners to come up with a cocktail of targeted drugs.

But I think there is a real opportunity here to not only systematically obtain and analyze tissue, but to systematically analyze that tissue in such a way that we systematically put it to good use for scientific inquiry and for clinical benefit of individual patients. Thank you all very much

Adjournment

DR. PAPPO: Thank you very much, Dr. Reaman.

We will now adjourn the meeting. Panel members, please leave your little name tags by the placard over here, and thank you very much.

(Whereupon, at 4:16 p.m., the afternoon session was adjourned.)