

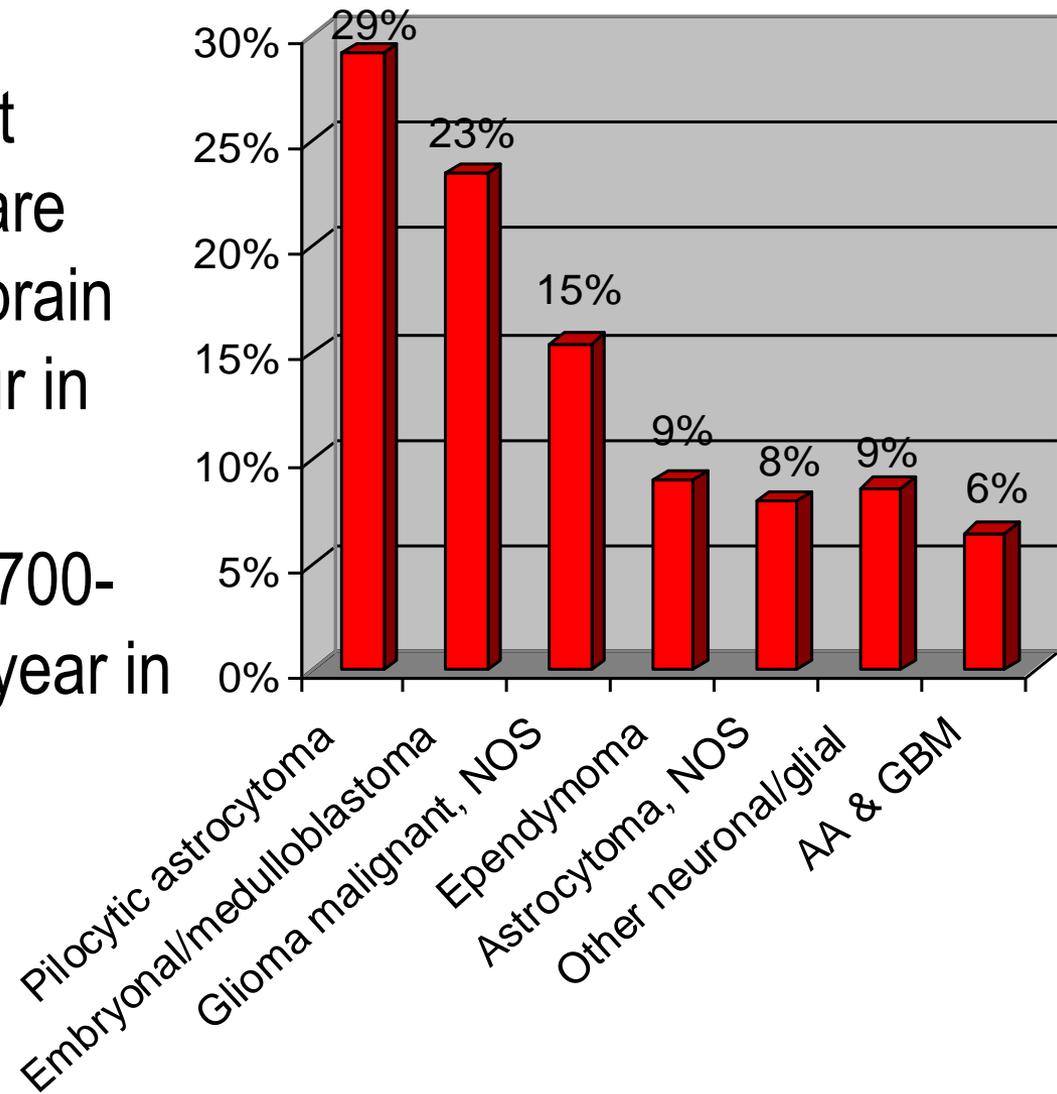


# Concept Proposal for Pediatric Brain Tumor Consortium RFA Reissuance

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March 2008

# Childhood Brain Tumors

- Childhood brain tumors represent histologies that are distinctive from brain tumors that occur in adults.
- Approximately 2700-2800 cases per year in 0-19 year group



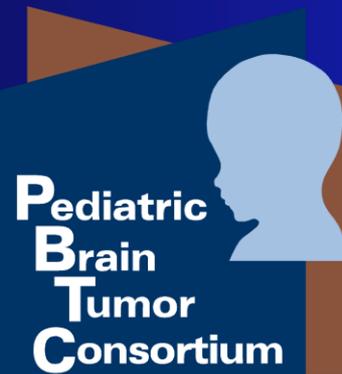
# Childhood Brain Tumors: Remaining Challenges

- Devastating neuropsychological sequelae in some survivors
- No effective therapy for brain stem gliomas
- Ineffective therapy for high-grade gliomas
- Poor outcome for children with ependymoma unable to achieve complete resection
- Guarded outcome despite intensive therapy for children with disseminated medulloblastoma and for infants / young children with non-desmoplastic medulloblastoma

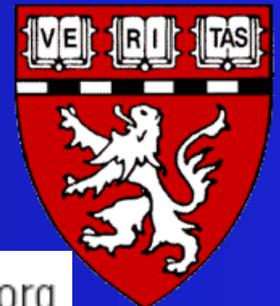
## Pediatric Brain Tumor Consortium (PBTC)

- The PBTC ([www.pbtc.org](http://www.pbtc.org)) formed by NCI in 1999 to evaluate new treatment approaches for children with brain tumors.
- Includes 10 academic centers and children's hospitals with high levels of expertise in the treatment of pediatric brain tumors.
- Operations and Biostatistics Center at SJCRH coordinates the Consortium's research efforts.
- Focus on introducing novel treatment strategies for children with brain tumors through phase 1 and phase 2 clinical trials.
- Relationship with COG to ensure that promising results can be further developed through COG.

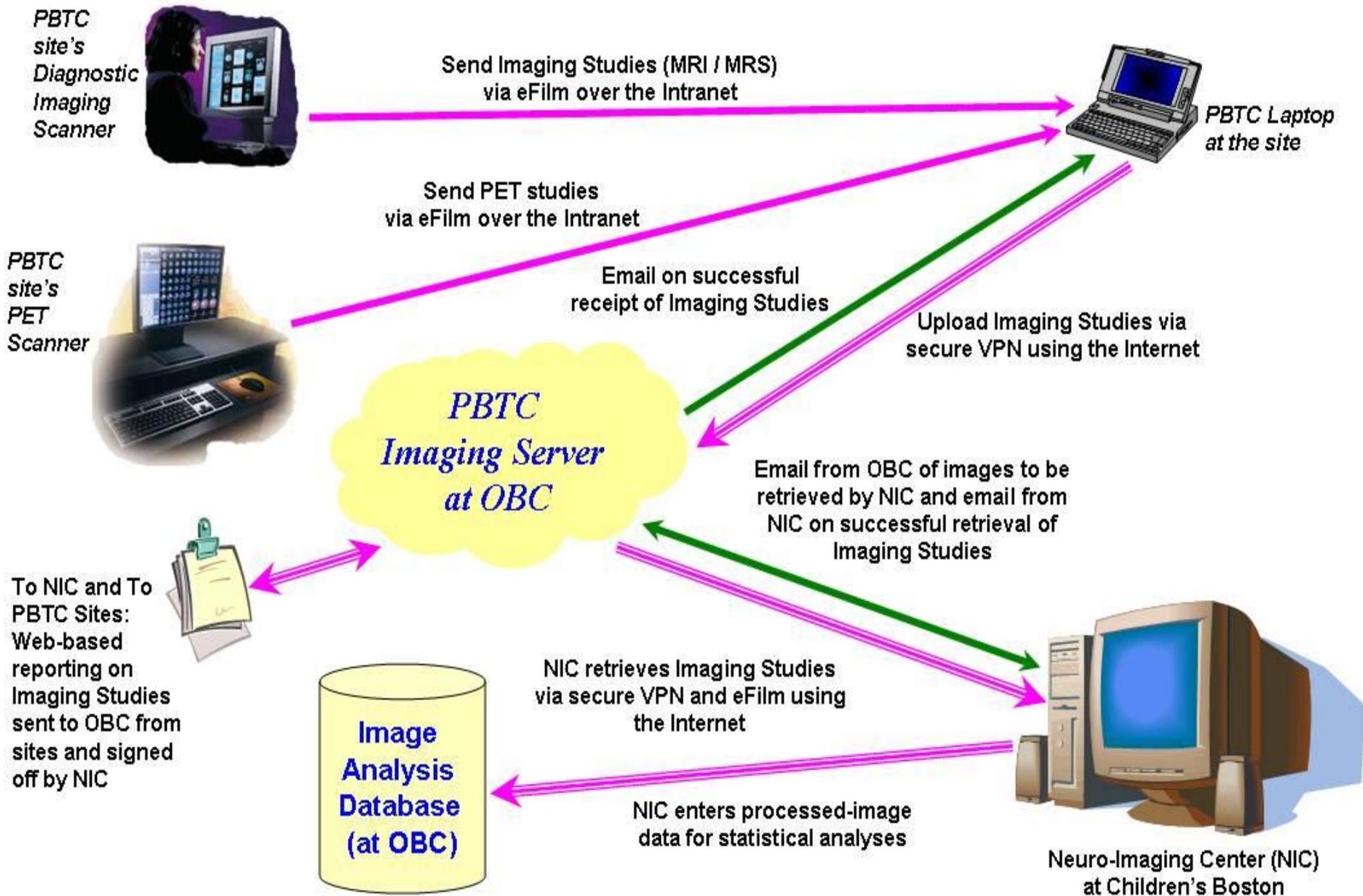
# PBTC Neuroimaging Center



Tina Young Poussaint, MD  
Children's Hospital Boston



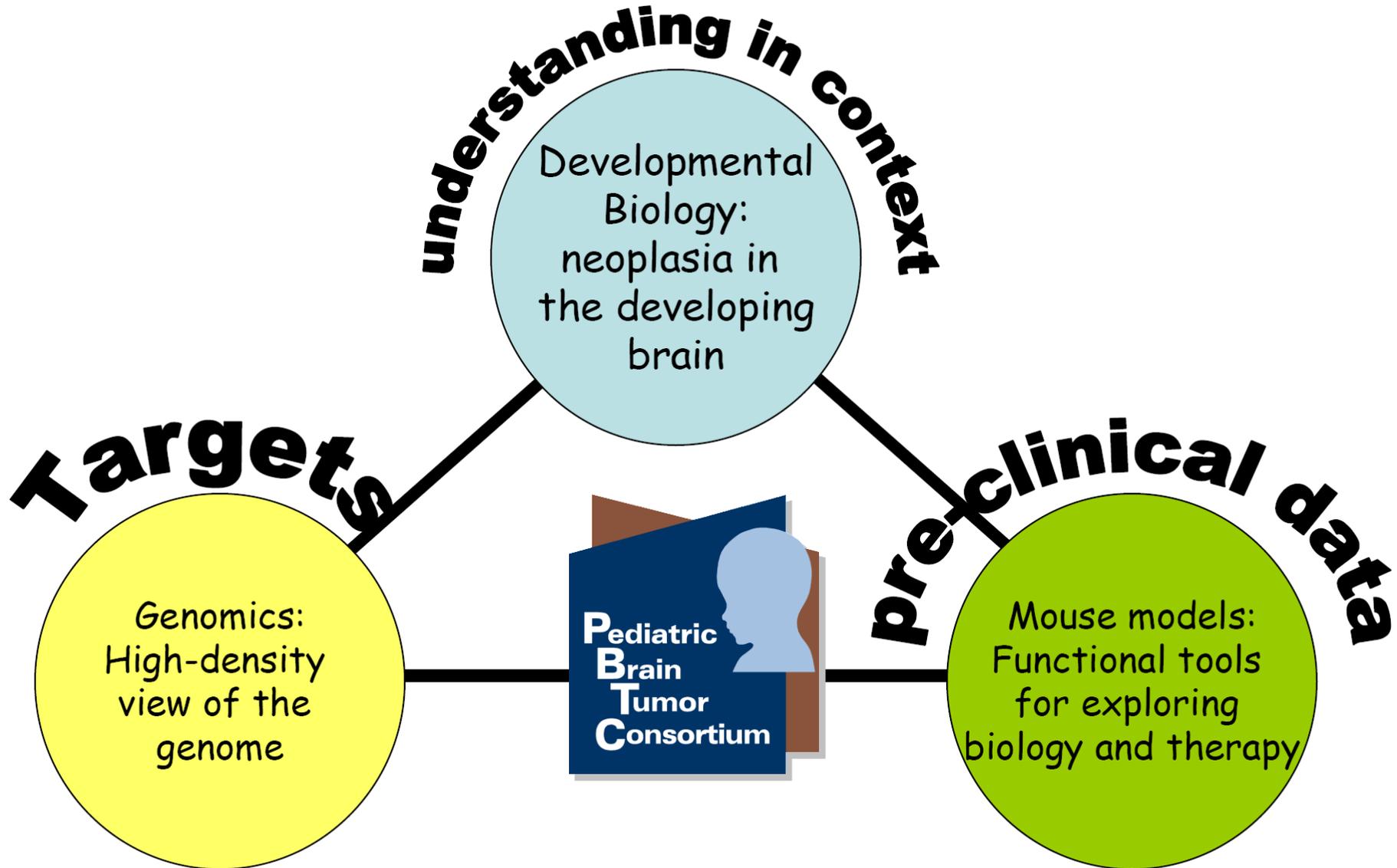
# PBTC Neuro-Imaging Transport /Archive System

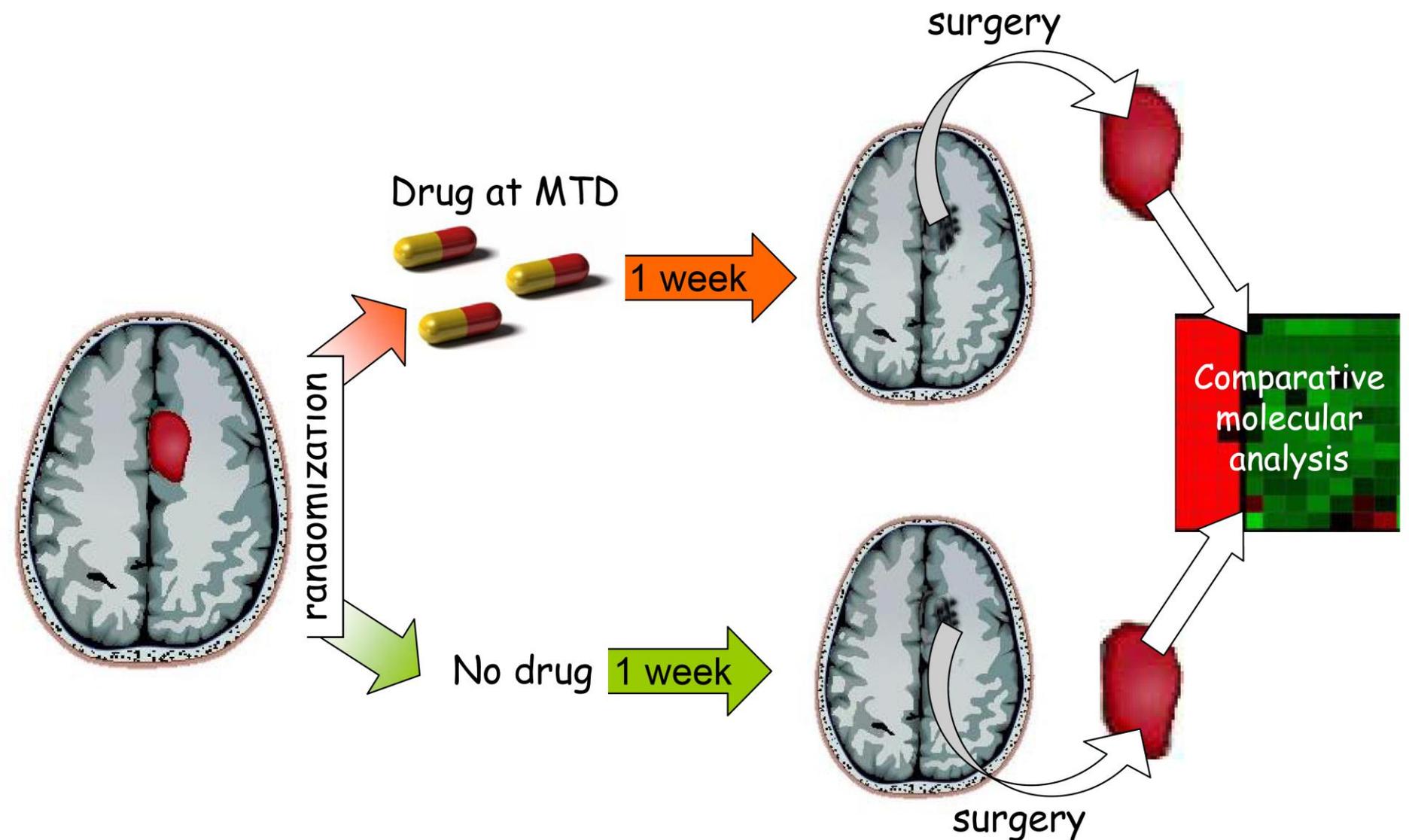


# PBTC Neuroimaging

- Developed Electronic Image Transfer System for MRI, MRS, Perfusion, Diffusion and PET studies.
- PBTC has completed and collected
  - 2,300 brain MRI studies,
  - 1,500 MR Perfusion studies,
  - 1,600 MR Diffusion studies,
  - 1200 MR Spectroscopy studies,
  - 895 spine MRI studies, and
  - 409 PET studies.
- PBTC has been involved in **caBIG Imaging Workspace** workshops and teleconferences and committed toward adopting caBIG GRID architecture and compliance to enable greater data interoperability.
- The PBTC completed a pilot project to interface the PBTC with the National Cancer Image Archive (NCIA) with a goal of bringing the PBTC into the NCIA system in near future.

# Using Biology to Drive the PBTC's Research Agenda





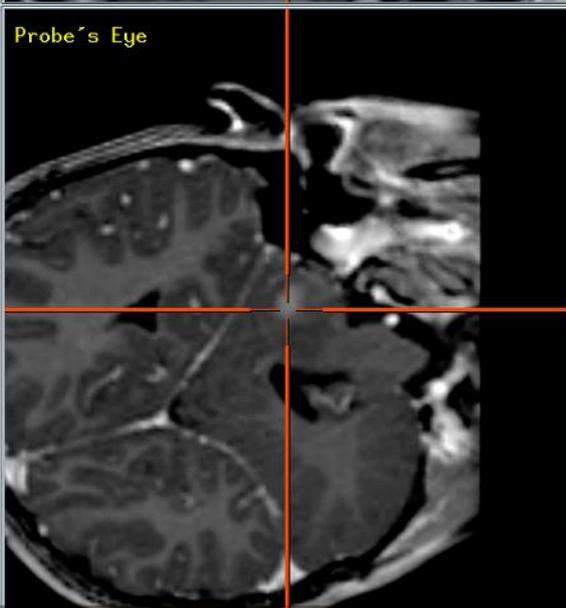
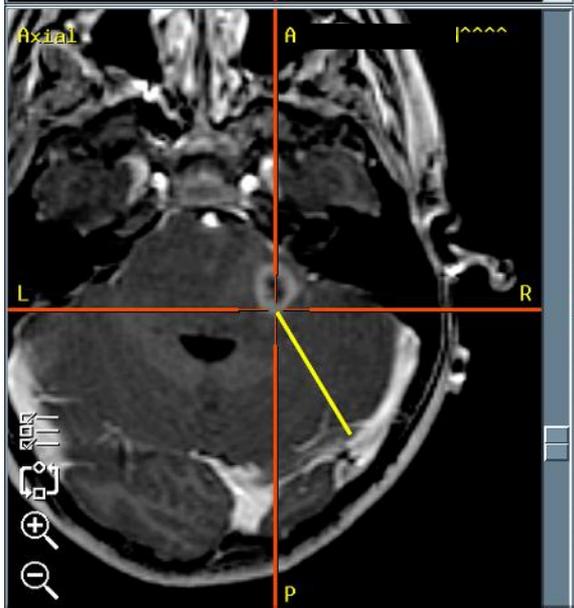
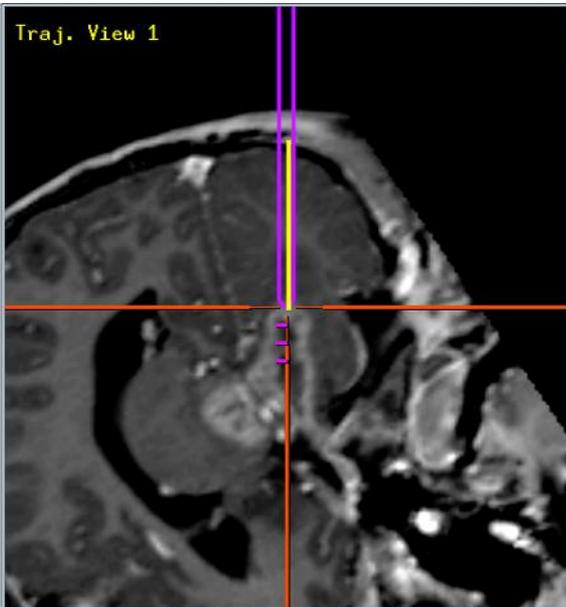
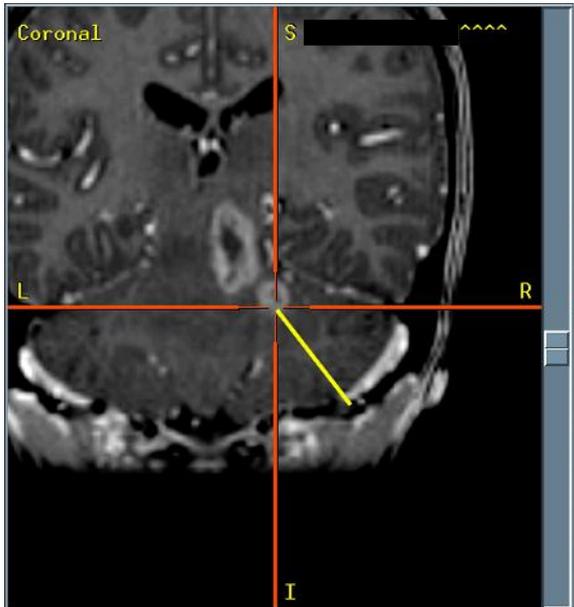
**Figure 4. Ongoing Molecular Phase within PBTC 016 clinical trial of Lapatinib.** Patients with residual medulloblastoma, ependymoma or HGG are randomized to receive drug at the MTD (or not) for the week prior to surgery. Comparative molecular analysis of excised tissue allows for direct assessment of drug activity within tumors in the brain.

# Applying Targeted Therapies to Specific Childhood Brain Tumor Populations

- Need patient populations selected for tumors with specific molecular characteristics.
- Medulloblastoma characterized by activation of -
  - The WNT pathway (e.g., through mutations of  $\beta$ -catenin and less commonly APC and axin), or
  - The Sonic Hedgehog (SHH) pathway. Activation of SHH pathway is primarily associated with inactivating mutations in *PTCH1* and the suppressor-of-fused (*SUFU*) gene and less commonly with activating mutations in the smoothened (*SMOH*) gene.
- Agents targeting the SHH pathway are under development by pharmaceutical sponsors.
- PBTC is well-positioned to conduct the initial first-in-children studies of such SHH pathway targeted agents in children with medulloblastoma whose tumors have SHH pathway activation.

# Brain Stem Glioma: Focus for the Future

- Brain stem gliomas (diffuse intrinsic) are resistant to virtually all tested therapeutics
- No progress with experimental agents, either alone or in combination with radiation therapy
- Little molecular data is available to guide development of new agents
- Frameless stereotactic biopsy of brain stem glioma lesions can now be performed with relative safety
- Molecular assays now require small amounts of tissue that can be obtained through stereotactic biopsies
- PBTC can play central role in safely reintroducing brain stem biopsy for research purposes and potentially to guide treatment



StealthStation<sup>®</sup>  
TREATMENT GUIDANCE PLATFORM

PreOp Setup Navigate Finish

- ◇ Check draping checkpoint
- ◇ Establish accuracy checkpoint
- ◇ Set up touchpad (opt)
- ◆ Navigate

The system is ready for navigation.

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Plan 1

Rename... On

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Store entry Store target

Re-align

Select probe...

Guide Frame-DT

Cranial Arc

Back Next

Undo View System Snap Exit

# Plan for Continuation of PBTC

- Plan for continuation of PBTC using current configuration via the “letter RFA” mechanism
- Suggested changes:
  - Required recompetition of a subset of PBTC member institutions twice during award period
  - Specified focus on brain stem gliomas
- Year 1 of new award reduced to \$2.0 million due to NCI budget constraints
  - FY2008 (Year 10) committed total costs are \$2,559,826
  - Attempts to cover deficit:
    - Co-sponsorship approved by NINDS (\$200K / yr)
    - Seeking additional funds from non-NCI sources
    - May have to decrease work scope

# Proposed Evaluation Criteria

- Adequate clinical trial development (3-4 / year) with appropriate protocol development timelines and patient accrual (110-125 / year).
- Appropriate incorporation of PK and translational biology studies into Consortium trials.
- Incorporation of state-of-the-art imaging studies into the Consortium trials.
- Incorporation of neurosurgical expertise into Consortium trials.
- Use of caBIG compatible systems for the management of PBTC clinical and imaging data.
- Timely presentation and publication of results.
- Appropriate interactions with other brain tumor research programs.
- Transition of new treatment approaches studied by the PBTC to the COG Brain Tumor Committee.