Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

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International Multi-Center Natural History Study of Newly Diagnosed NF1-Associated Non-Optic Pathway Glioma

Chelsea Kotch, MD MSCE and Michael Fisher, MD

Sponsor: Gilbert Family Foundation

Children's Hospital of Philadelphia®

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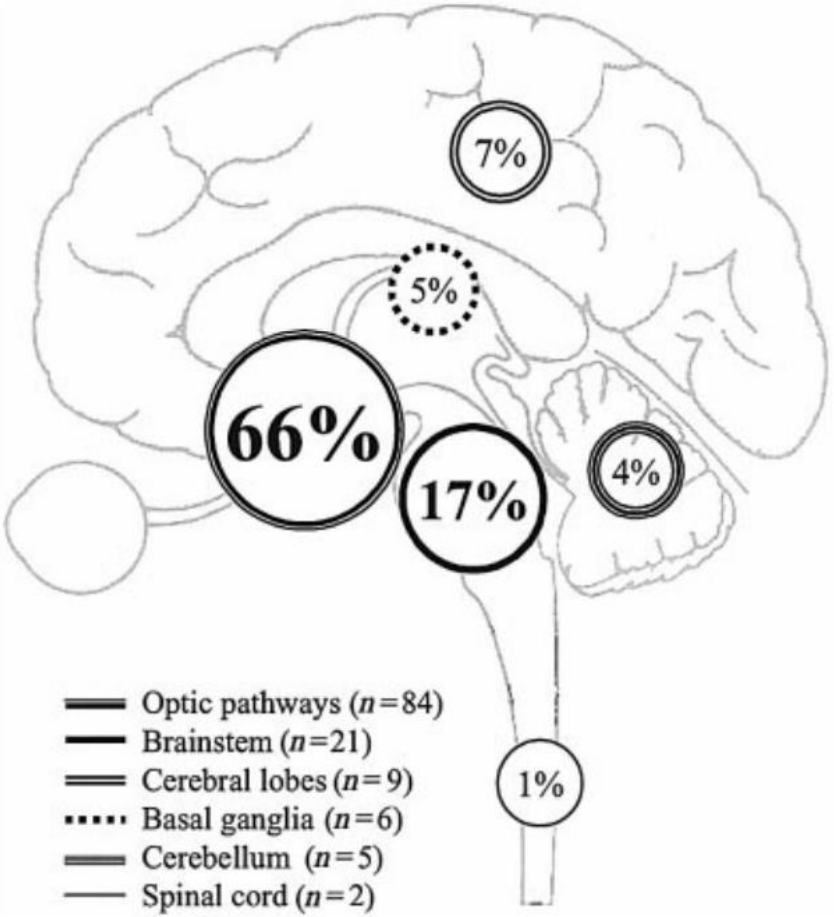
Neurofibromatosis Type 1-Associated Non-Optic Pathway Low-Grade Glioma

- Up to 1/3 of NF1-LGG occur extrinsic to the optic pathway
- Natural history of non-OPG NF1-LGG is relatively unknown
- No evidence-based guidelines for imaging surveillance or initiation of therapy for non-OPG NF1-LGG
- Prospective studies required to develop guidelines for surveillance and treatment



Guillamo et al (2003)

Unanswered Questions for Non-OPG NF1-LGG

- What is the natural history of these tumors?
- Are there prognostic factors for outcome (e.g., age, location, histology, molecular alterations)?
- When and how should we treat these tumors?
  - Should we treat like NF1-OPG i.e., for objective functional deficits?
  - Should we use targeted therapy?
- What is the impact on quality of life?
  - Functional, seizure, pain?

Study Overview

- Prospective, observational study
- Enroll at least 250 children, ≤ 18 years of age, with NF1 and newly diagnosed treatment-naïve low grade non-optic NF1-glioma
  - Also enrolling sample of newly diagnosed NF1-HGG (goal >20 subjects)
- Follow actively through at least 25 years of age (ideally life-long)
- Regular surveillance MRI and oncology/NF1 medical evaluations, in addition to QOL/functional assessments
- Optional studies: neurocognitive/social skills, banking of biological specimens for future research

Main Objectives

- To determine prognostic factors for tumor progression and need for treatment in non-OPG NF1-LGG
- For the subset of tumors that undergo treatment, to determine prognostic factors for treatment outcomes

Secondary Objectives

- To assess the impact of non-OPG NF1-LGG on quality of life and functional outcomes in patients
- To describe the risk of malignant transformation of pre-existing NF1-LGG in pediatric patients
- To determine the value of various imaging features in predicting subsequent tumor growth and/or imaging response for subset of participants undergoing treatment
- To perform comprehensive molecular tumor profiling of all non-optic pathway NF1-LGG requiring biopsy and all NF1-HGG
- To obtain blood, tumor tissue, and cerebrospinal fluid to be stored for future non-optic pathway NF1-LGG and HGG biological studies
- To acquire neurocognitive and social skills data to examine relationships between tumor development, treatment, and cognitive deficits, autism, or other developmental delays (NF1-LGG cohort)
- To determine prevalent treatment approaches and outcomes for NF1-HGG

Eligibility Criteria

Inclusion:

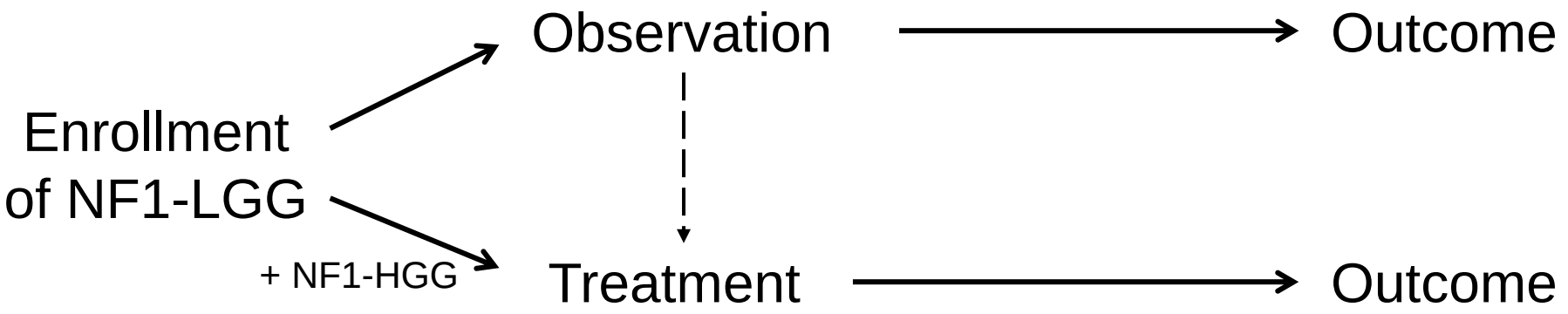
- Age ≤18 years with newly diagnosed non-OPG NF1-LGG or NF1-HGG
  - Newly diagnosed treatment-naïve probable non-OPG NF1-LGG (biopsy not required)
    - Diagnosis within 365 days of enrollment
    - Subjects with multiple target tumors (up to three) may be enrolled
    - Subjects may enroll if they are previously enrolled on the NF1-OPG Natural History study

Exclusion:

- Subjects with NF1-LGG will be excluded if previously received any tumor-directed therapy for target tumor or if they are presently receiving or have received systemic chemotherapy within 30 days of enrollment

Study Design

- Prospective observational clinical study
  - Goal N = 250
  - Participants followed at close intervals for a minimum of 5 years, but no end date of f/u
- Primary outcome measures = tumor progression and need for tumor-directed therapy at 1, 2 and 3 years



- MRI evaluation
  - At standardized time points (q 3-6 months)
- Neuro-Onc/NF visits assess treatment decisions
- All visits must be +/- 6 weeks from the expected time

Study Evaluations

- Baseline
  - Demographics: DOB, sex, NF1 inheritance type, race, ethnicity
  - Date of non-OPG Dx
  - MRI (standard anatomic MRI) and indication for MRI
  - Germline NF1 variant (if available)
  - Histopathologic and molecular data (if biopsy obtained)
  - Presence of other glioma (OPG), prior tumor-directed therapy (PN, OPG)
- Observation Arm
  - At 6*, 12, 24, 36, 48 months post Dx
  - Date of visit
  - MRI (standard anatomic MRI)
  - Medications (yearly)
  - Vineland (if motor deficit)
  - QOL

Study Evaluations

- Treatment Arm
  - q3 months while on treatment
  - MRI (standard anatomic MRI)
  - At treatment initiation
    - Reasons treatment is being initiated
    - Chemo agents and start date of chemo
  - Medications (yearly on treatment and at end of treatment)
  - QOL (yearly on treatment and at end of treatment)
- Post-Treatment Follow-up Arm
  - At 3, 6, 12, 18, 24, 30, 36, 48 months post Dx
  - MRI (standard anatomic MRI)
  - Medications (yearly)
  - QOL (yearly)
  - Vineland (yearly, as indicated)

Study Evaluations

- Long-term Follow-up Arm
  - At yearly intervals
  - Subject Status (alive, deceased, lost to follow up, treatment changes)
  - Tumor status (stable, progression, etc.)
  - Medications (yearly)
  - MRI (standard anatomic MRI)
  - QOL (yearly)
  - Vineland (as clinically indicated, yearly)
  - Qualitative functional outcomes (clinician assessment)

Vineland-3 Motor Scale

- Vineland Adaptive Behavior Scales
- Enables detection of change in motor function (fine and gross motor)
- Developed/validated for evaluation of motor functions in children 0–9 y.o.
  - Being used in all ages as each participants scores is compared to their own baseline score
- Multiple studies using
  - ACNS1831, ACNS1833, FIREFLY-1, LOGGIC/FIREFLY-2, NF1-OPG Nat Hx Study
- Challenge: Requires trained staff member
  - Verbal administration over the phone
  - Take ~30 minutes to complete
  - Important that the same parent complete the questionnaire at all sessions
  - We have selected as standard/best practice (align with FDA/EMA selection?)

Imaging Outcomes

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Series

Response assessment in paediatric low-grade glioma: recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group

Jason Fangusaro MD [a] [†] [✉], Prof Olaf Witt MD [c, †], Pablo Hernáiz Driever MD [d], Asim K Bag MD [e], Peter de Blank MD [f], Nadja Kadom MD [b], Lindsay Kilburn MD [g], Robert M Lober MD [h], Nathan J Robison [i], Prof Michael J Fisher MD [j], Prof Roger J Packer MD [k], Prof Tina Young Poussaint MD [l], Ludmila Papusha MD [n], Shivaram Avula FRCR [p], Alba A Brandes MD [q], Prof Eric Bouffet MD [r], Daniel Bowers MD [s], Anton Artemov MD [o], Prof Murali Chintagumpala MD [t], David Zurakowski PhD [m] ...Katherine E Warren MD [y]

Biological Specimens: Blood
(for participants who consent)

Observation Arm
- At baseline or first available study visit (ideally within 3 months of enrollment)
- At 36 months from enrollment

Treatment Arm
- Within 4 weeks prior to start of treatment
- Every 3 months on treatment (around time of MRI)
- Within 6 weeks of completion of treatment

Post Treatment Follow Up Arm
- Every 6-12 months (align with MRI)

Additional Time Points
- Any time NF1-LGG or NF1-HGG is biopsied
- Concerning radiographic change

Neurocognitive and Social Skills

(for participants who consent)

- At age 6, 12, and 18 years
- Domains to be assessed include attention, executive function, academic function, social/emotional/behavioral function
- Align with NF1-OPG study
- Length of testing is approximately 2 hours

Domain	Intellect/ Reasoning	Attention	Executive Function	Academics	Social-Emotional
Test Instrument *Blue = Performance based test* *Green = Symptom Questionnaire completed by parents*	Wechsler Abbreviated Scale of Intelligence (WASI-II)	DuPaul ADHD Rating Scale (ADHD-RS)	Behavior Rating Inventory of Executive Function (BRIEF-2)	Kaufman Test of Educational Achievement (KTEA)	Behavioral Assessment System for Children (BASC-2) Social Responsiveness Scale (SRS) Social Skills Improvement System (SSIS)

Regulatory Aspects

- Subjects may be enrolled once all eligibility requirements for the study have been met (including consent/assent).
- Subjects will be registered via the study electronic Redcap database using the study ID #’s from the site-specific Subject ID log
- Central eligibility review of diagnostic MRI
- Consent for ancillary studies and biology are optional
- Optional future use of data/specimens

Data Collection

- Data (coded) are entered into a password-protected RedCap database (at the data coordinating center at CHOP) by site investigator or CRC "prospectively"
- MRI studies are submitted electronically or on CD via FedEx/UPS to the CHOP DCC
- Biological specimens shipped to CHOP biorepository
  - Sample collection kits supplied by biorepository
  - Kits contain bar-coded tubes/cryovials, shipping materials, and pre-paid shipping label
  - Link between specimen and data
    - Specimen manifest labelled with subject's study #
    - Specimen #'s entered into the study RedCap database

Questions and Comments?