

NF Clinic Network and NF Clinical Trials Consortium

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For Mark Ebel – Duke is top this year! Let's keep it all in the ACC.

NF Clinic Network

- Assimilate expertise for rare manifestations
- Provide anticipatory guidance
- Collect outcomes data to establish best practices
- Standard of care protocols may have better coverage from insurers
- Link to sites for clinical trials

Anticipatory Guidance - toddlers

- Tibial bowing
- Optic pathway tumor
- Coordination and speech
- Plexiform neurofibromas

Anticipatory Guidance - childhood

- School readiness – learning disabilities
- Scoliosis
- Growth issues
- Plexiform neurofibroma

Anticipatory Guidance - adolescence

- Dermal neurofibromas
- Plexiform neurofibroma
- Psychosocial
- Puberty
- Transition

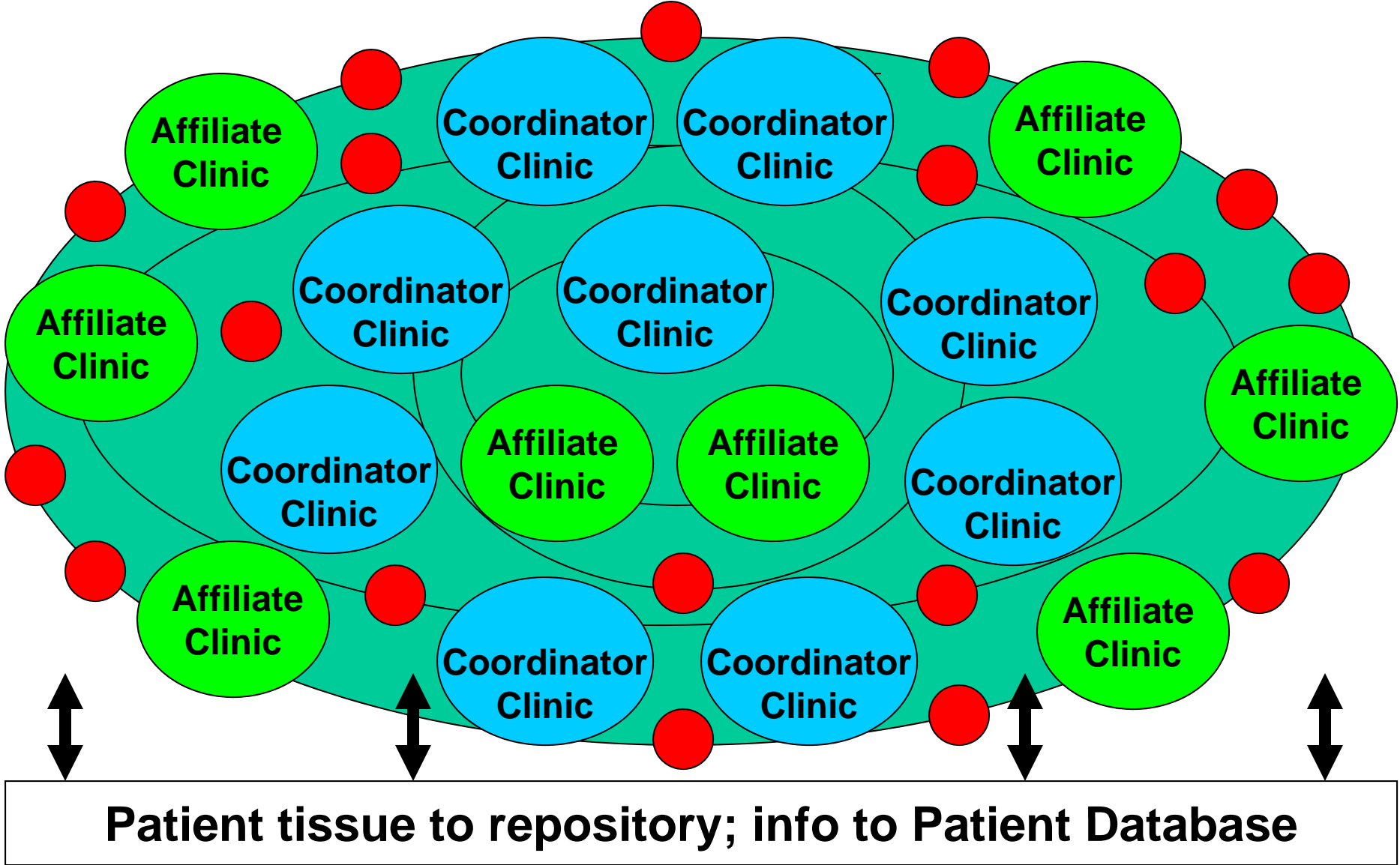
Anticipatory Guidance - adults

- Malignant peripheral nerve sheath tumors (MPNSTs)
- Psychosocial
- Dermal neurofibromas
- Pain
- Reproductive decisions

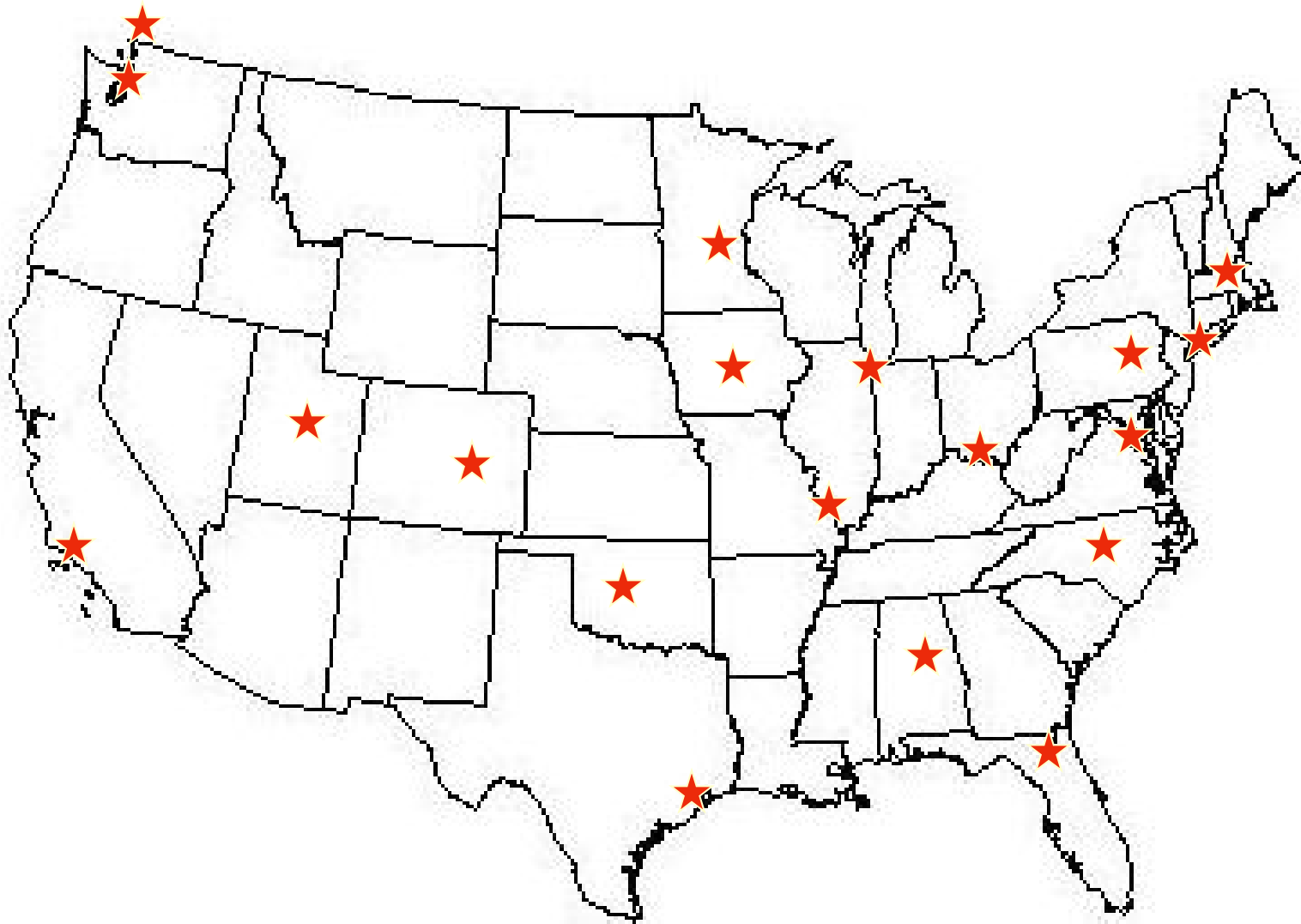
Affiliate Clinic Application

- Self-reported information
- Submitted by applicant clinic director
- Demonstration of integrated and multidisciplinary care at the institution
- Institutional support
- Applications reviewed quarterly by CCAB and recommendations passed forward to the CTF Board of Directors

CTF NF Clinic Network - GOAL FOR March 2008



 *Regional Physicians: Small, Non-Member Clinics*



NF Clinic Network - care guidelines from outcomes and potential clinical trials

CTF Sponsorship of NF Clinics

- Providing up to \$5,000 for activities associated with the clinic
 - Educational symposia
 - Coordination of clinical care
 - Travel to symposia
- Development and implementation of registry
- Provision of a listserve for member clinics

Clinical Trials

- Definition of terms
- Goals of trials
- Protocol development
- Human subject protections
- Recruitment and enrollment
- Endpoints
- Transition to standard of care

Endpoints

- Determined by team of experts
- Measurable objective values
- Duration
- Stopping rules
- Primary versus secondary

Transition to Standard of Care

- End trial – consider extension trial while data is still being analyzed
- Time to peer review and acceptance in the medical community
- Additional trials as needed
- Adjustments as recommended through results review

Examples of NF1 Clinical Trials

- Observational – Natural History
- Quality of Life
- Treatment
 - Safety (phase I)
 - Effectiveness (phase II)
 - Open-label
 - Placebo-controlled

Finding an NF1-Related Trial

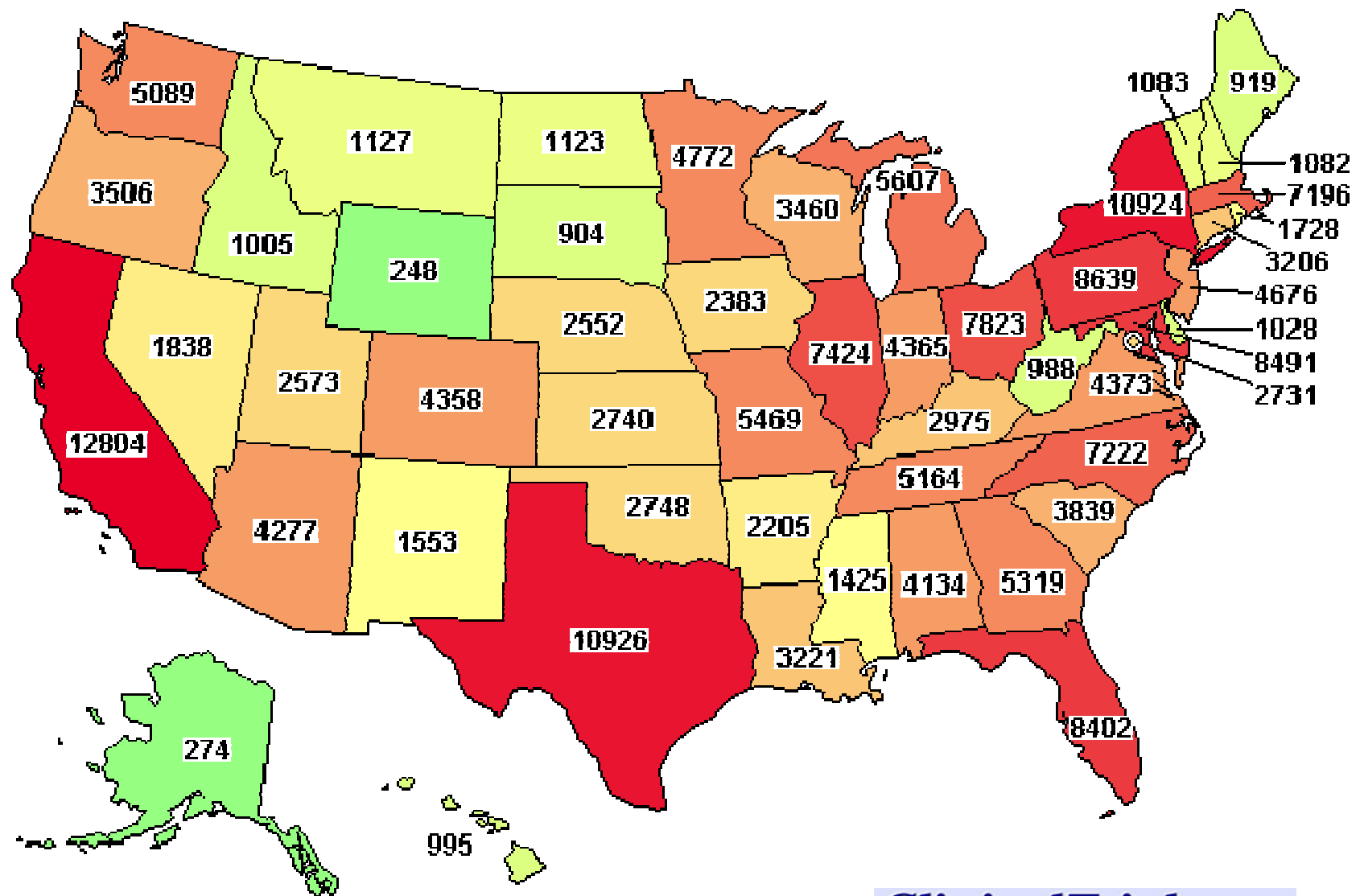


Many links to get to this web site – including CTF.org



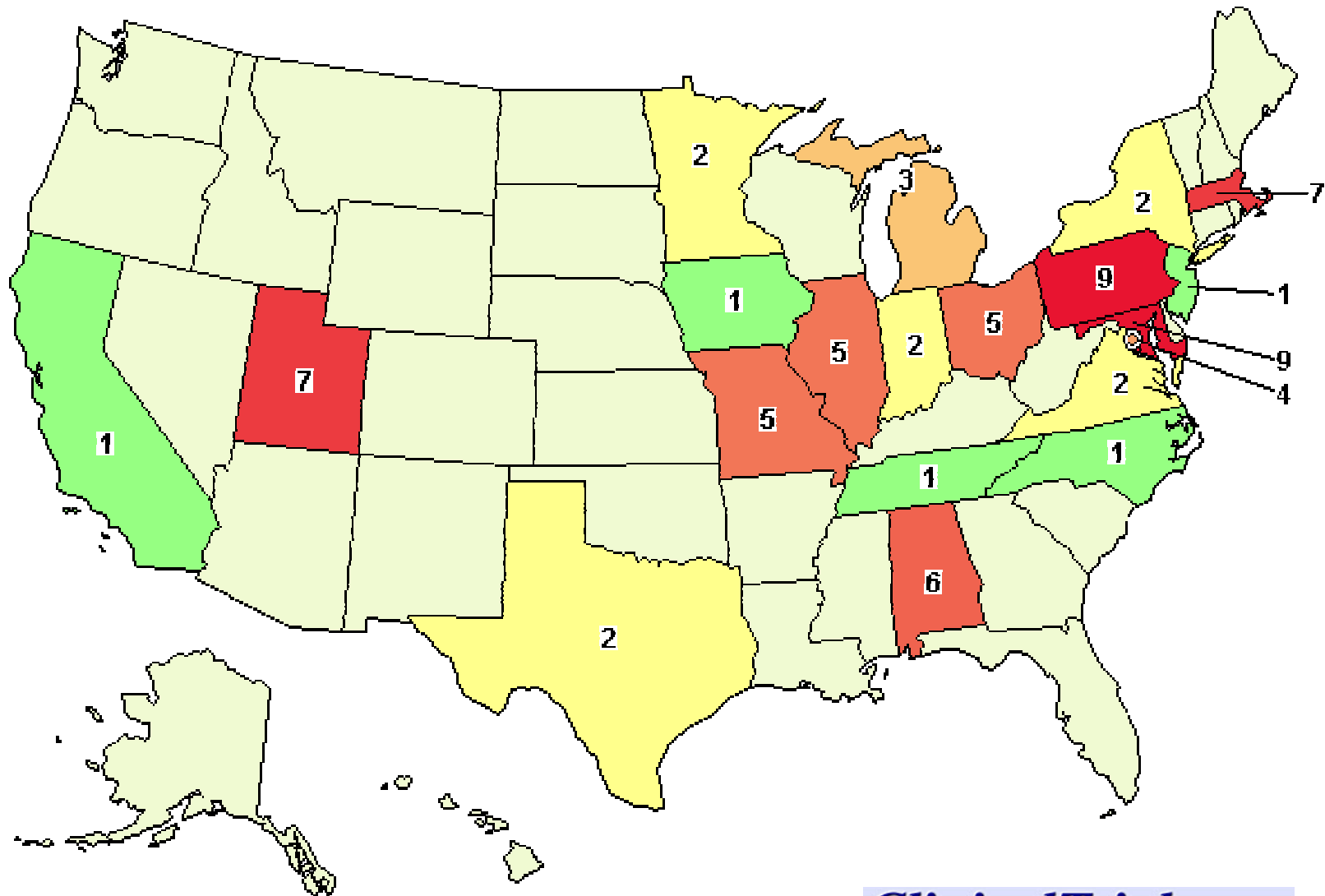
- ClinicalTrials.gov currently has 87,939 trials with locations in 172 countries
- 47 Clinical trials listed for NF1
 - 36 specific for NF1
 - 26 recruiting phase
 - 8 categories
 - Dermal neurofibromas, plexiform neurofibromas
 - Malignant peripheral nerve sheath tumors
 - Bone studies
 - ADHD, Reading, QoL, Imaging

Map of All US Studies in ClinicalTrials.gov



Map of 25 studies found by search of:
Type 1"

Open Studies | "Neurofibromatosis



Found 25 studies with search of: **Open Studies | "Neurofibromatosis Type 1"**

1 Recruiting A Randomized Placebo-Controlled Study of Lovastatin in Children With Neurofibromatosis Type 1

2 Recruiting Multi-Center Project: Spinal Abnormalities in Neurofibromatosis Type 1 (NF1) Patients
Condition: Neurofibromatosis Type 1

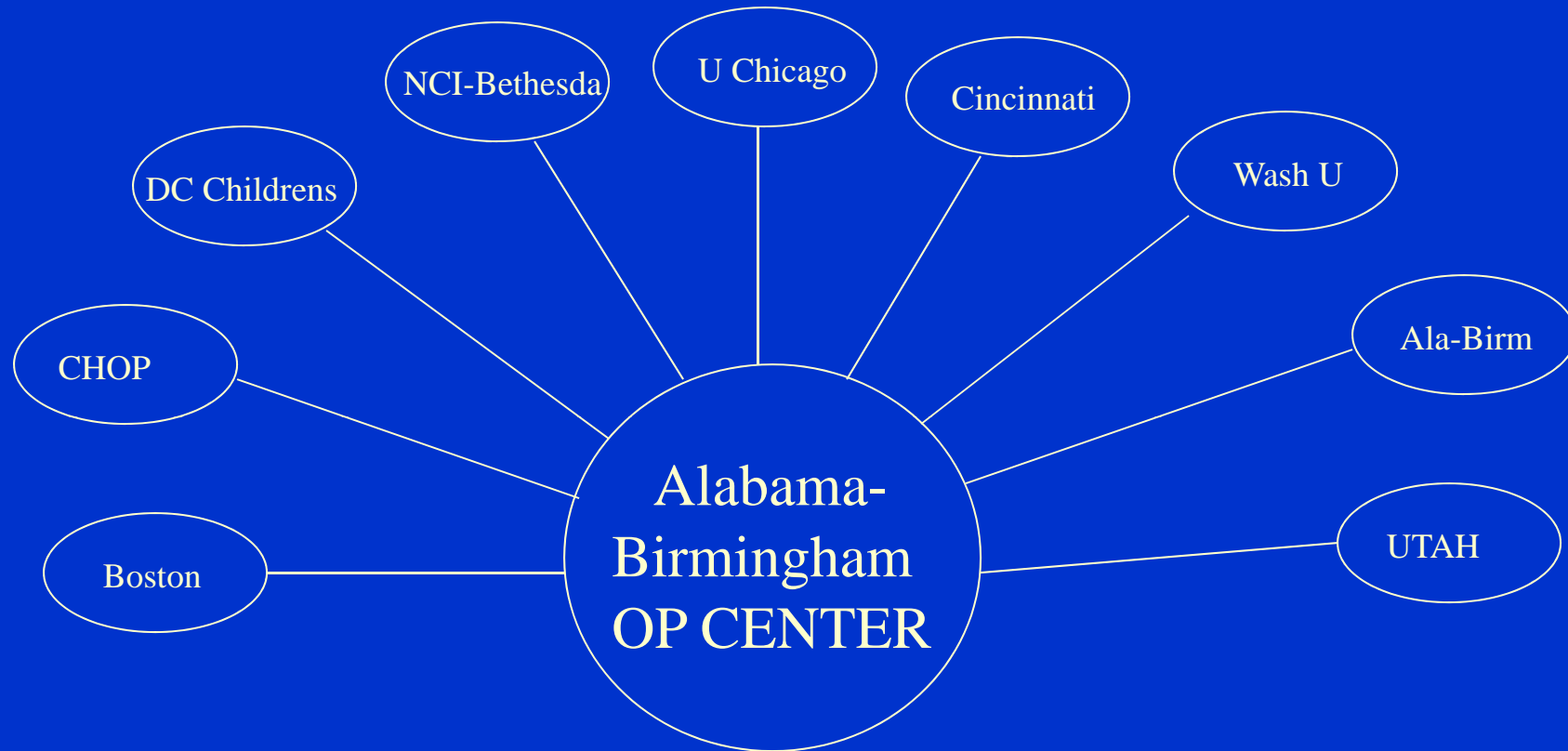
3 Recruiting Sirolimus in Treating Patients With Neurofibromatosis Type 1 and Plexiform Neurofibromas That Cannot Be Removed by Surgery

4 Recruiting NF1-Attention: Study of Children With Neurofibromatosis Type 1 Treated by Methylphenidate

5 Recruiting AZD2171 in Treating Patients With Neurofibromatosis Type 1 and Plexiform Neurofibroma and/or Neurofibroma Near the Spine (cediranib maleate)

- 6 Recruiting Sorafenib in Treating Young Patients With Neurofibromatosis Type 1 and Plexiform Neurofibromas That Cannot Be Removed by Surgery
- 7 Recruiting A Phase II Study of the mTOR Inhibitor Sirolimus in Neurofibromatosis Type 1 Related Plexiform Neurofibromas
- 8 Recruiting Natural History Study of Patients With Neurofibromatosis Type I
- 9 Recruiting PEG-Interferon Alfa-2b in Treating Young Patients With Unresectable Plexiform Neurofibromas Associated With Neurofibromatosis Type 1
- 10 Recruiting Study of Disease Severity in Adults With Neurofibromatosis Type 1 (NF1)

DOD-sponsored NF1 Consortium for Clinical Trials



TRIALS

Plexiform Neurofibroma
MPNST
Optic Nerve Pathway Tumors
Neurocognitive

CORES

Biology
Radiology
Administrative

As of Jan 2007

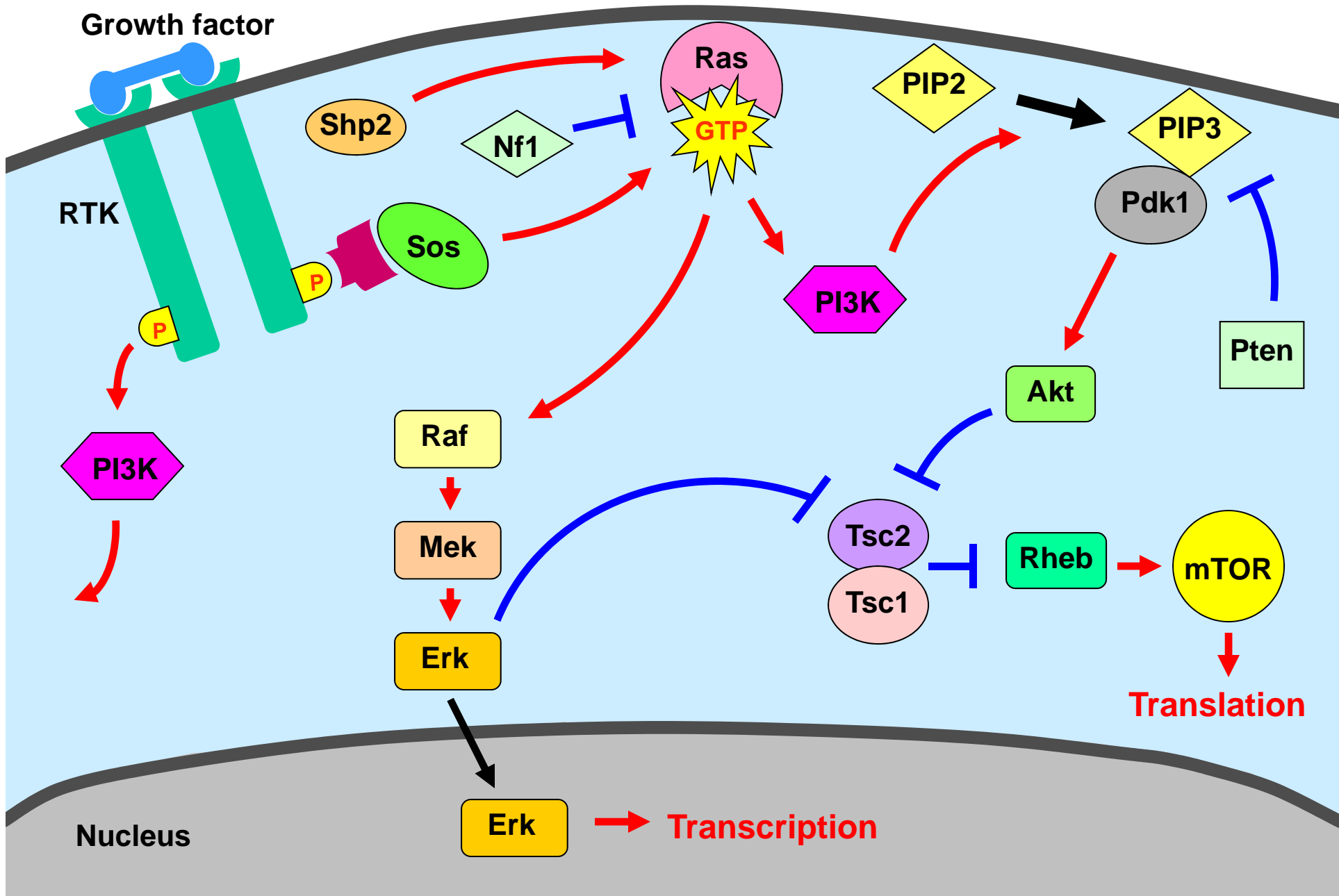
NF Clinical Trials Consortium

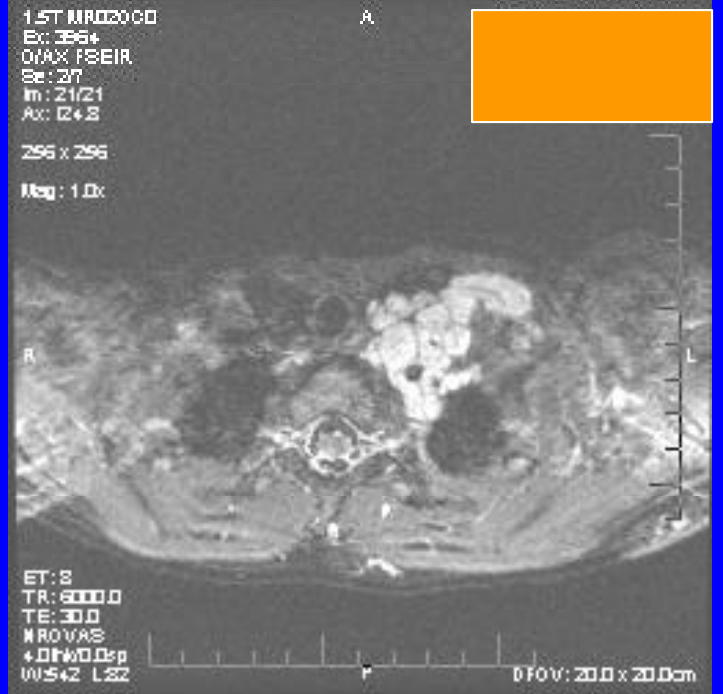
- Rapamycin for plexiform neurofibroma
- Lovastatin for cognitive impairment
- Rapamycin for recurrent CNS glioma
- Avastin/----- for non-responsive MPNST

- Under review: rhBMP-2/intramedullary rod for tibial pseudarthrosis

Clinical Trial: Rapamycin therapy for plexiform neurofibromas

- Increase time to progression of inoperable progressive plexiform neurofibroma (29)
- Radiologic response of inoperable plexiform neurofibromas that are not progressive (12)
- Rapamycin at 0.8 mg/m² (BSA) b.i.d.
- Volumetric MRI





Neurofibromatosis (NF) Consortium

NF PROTOCOL 102

*A Phase II Study of the mTOR Inhibitor Sirolimus in
Neurofibromatosis Type 1 Related Plexiform Neurofibromas*

Sponsored by:

Department of Defense

USAMRMC

Office of the Congressionally Directed Medical Research Programs
(CDMRP)

Protocol Chairs

Brian Weiss, M.D., Chair

John Perentesis, M.D., Co-Chair

Brigitte Widemann, M.D., Co-Chair

Michael Fisher, M.D., Co-Chair

Bruce Korf, M.D., Ph.D., Co-Chair

Medical Monitor

Julie Park, M.D.

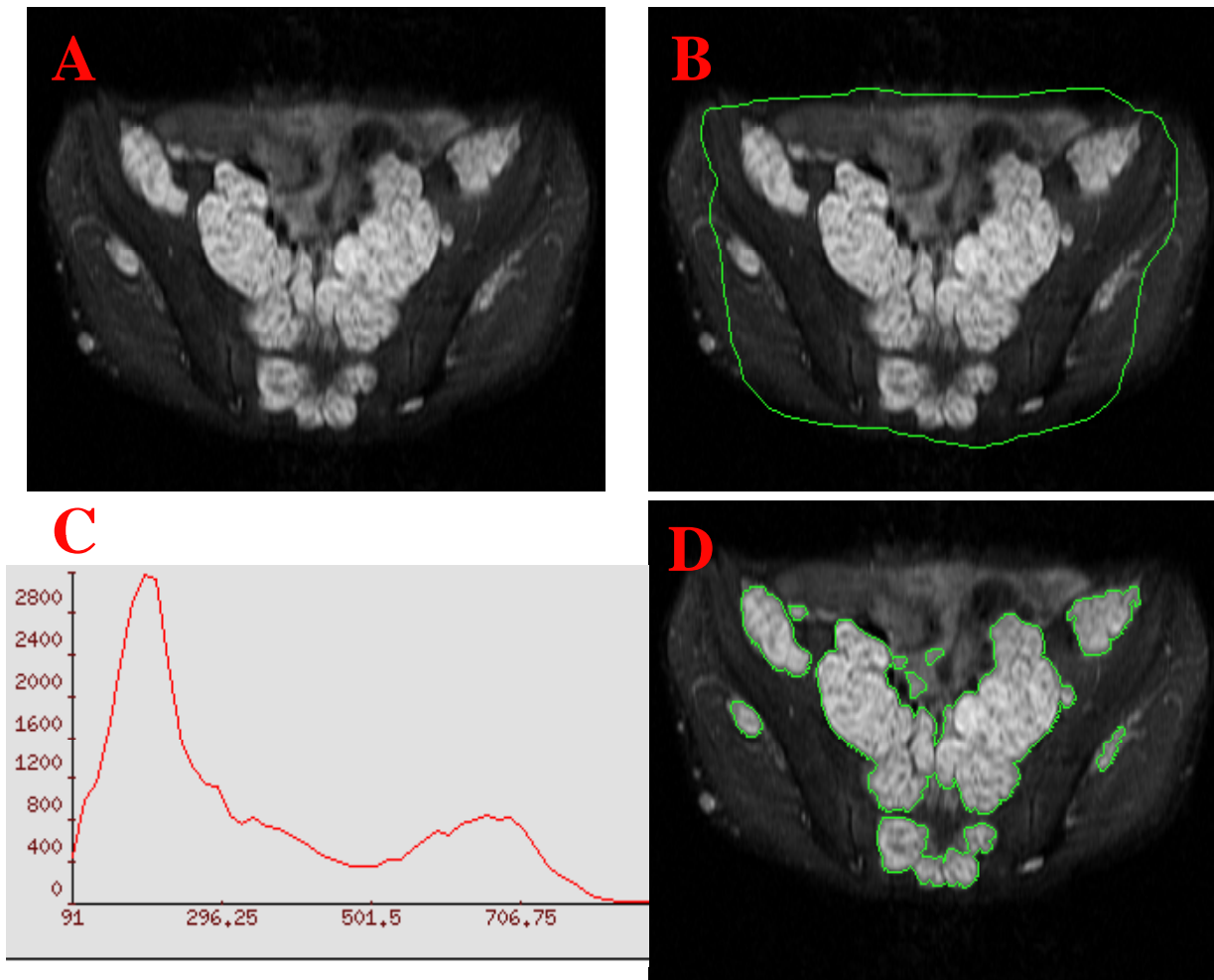
Phase II – Sirolimus and Plexiform Neurofibromas

Primary Aims

- To determine whether the mTOR inhibitor sirolimus, administered orally twice daily on a continuous dosing schedule (1 course = 28 days) using pharmacokinetically-guided dosing:
 - Increases time to disease progression based on volumetric MRI measurements in children and young adults with neurofibromatosis type 1 (NF1) and inoperable progressive plexiform neurofibromas (PN),
 - Results in objective radiographic responses based on volumetric MRI measurements in children and adults with NF1 and inoperable PN in the absence of documented radiographic progression at trial entry
- To evaluate the feasibility and toxicity of chronic sirolimus administration in this patient population.
- To characterize the pharmacokinetic profile of sirolimus when administered to this patient population.

Design: Phase II Sirolimus Trial

- Sirolimus oral solution will be administered orally BID on a continuous dosing schedule (28 days = 1 treatment course) with pharmacokinetically-guided dosing.
- Disease status will be evaluated using volumetric MRI analysis at regular intervals.
- The plasma pharmacokinetics and pharmacodynamics of sirolimus will be evaluated, as will pharmacogenetic polymorphisms and their influence on the metabolism of sirolimus in this patient population.
- Pain reduction and quality of life outcomes will also be assessed.
- Toxicity of chronic sirolimus administered will be evaluated using physical and laboratory evaluations.



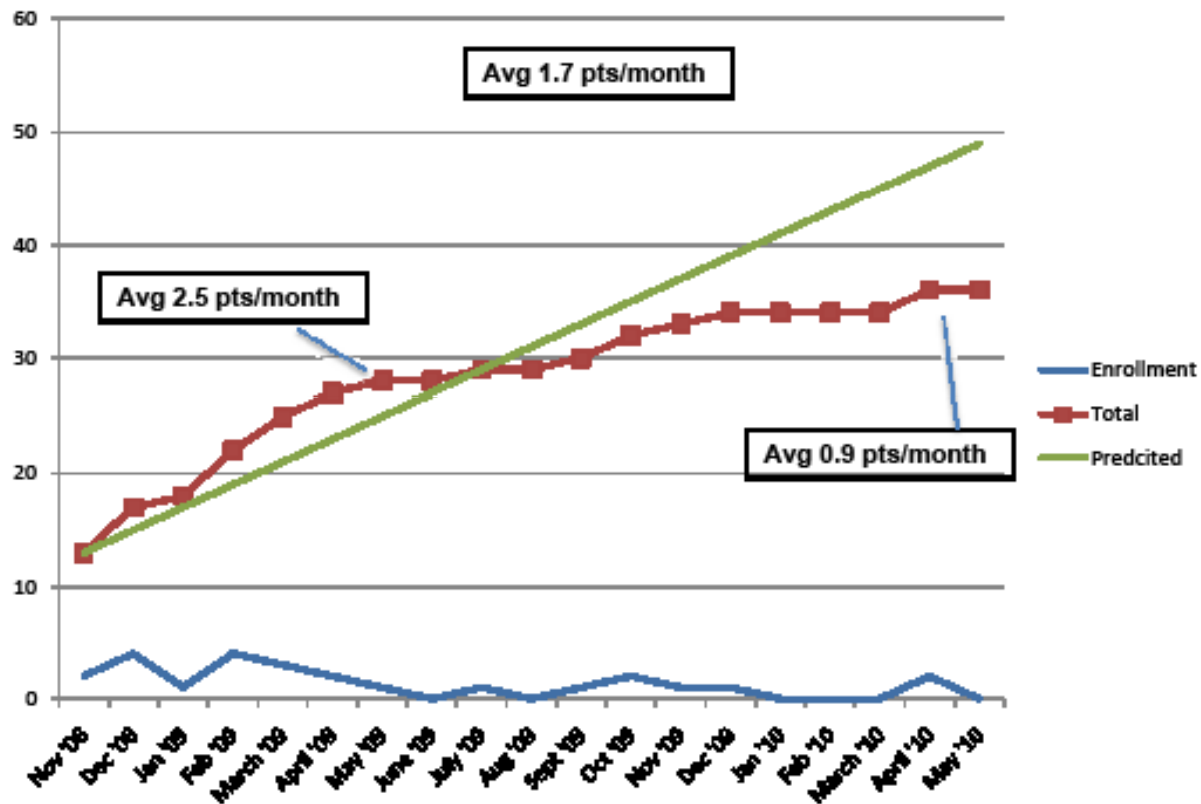
For each MR image (Figure 1A), the tumor is roughly outlined manually including a rim of low signal intensity normal tissue (Figure 1B). The program then performs a histogram analysis of signal intensity pixel by pixel and a threshold that distinguishes high signal intensity tumor from normal tissue is defined (Figure 1C). Tumor contours are then determined using a gradient image, connected component analysis and automatic edge following operation (Figure 1D).

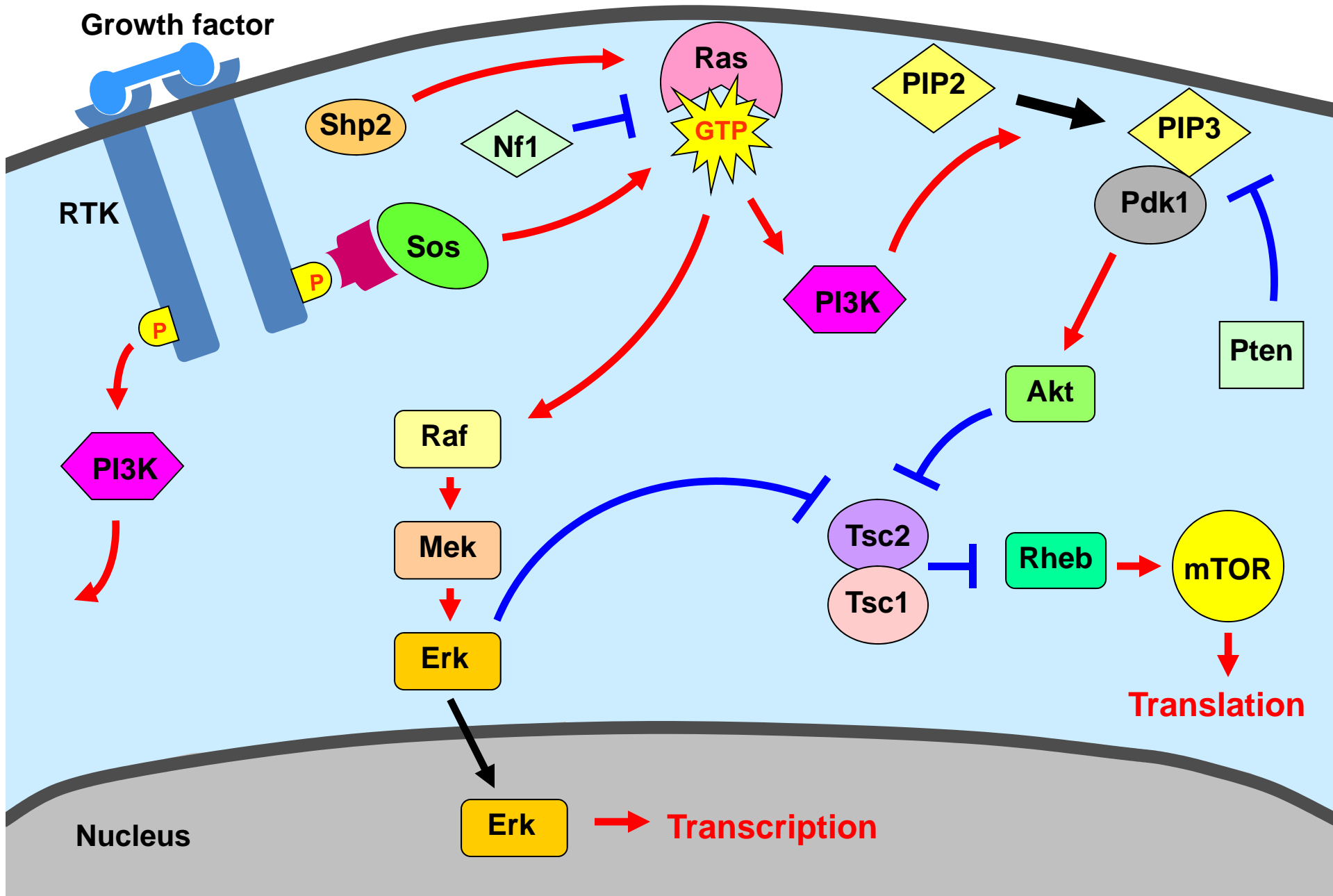
OVERVIEW

- Stratum 1 will evaluate TTP in progressive PN Patients may receive additional 4-week courses unless there is evidence of PD or unacceptable toxicity
- Stratum 2 will evaluate objective radiographic response in PNs that do not have documented progression at time of trial entry. Patients may receive up to a maximum of 6 courses (i.e. 24 weeks) unless there is evidence of objective response, tumor progression, or unacceptable toxicity.

CLOSED TO ACCRUAL

STOPN Stratum 1 Enrollment Nov '08-June '10





Lovastatin for Cognition

- Based on mouse studies – A. Silva
- Lovastatin decreases amount of ras attached to inner membrane
- Normal IQ
- Cognitive impairment demonstrated by CANTAB (computerized screen)
- Off medication for ADHD
- Placebo-controlled trial for 3 months

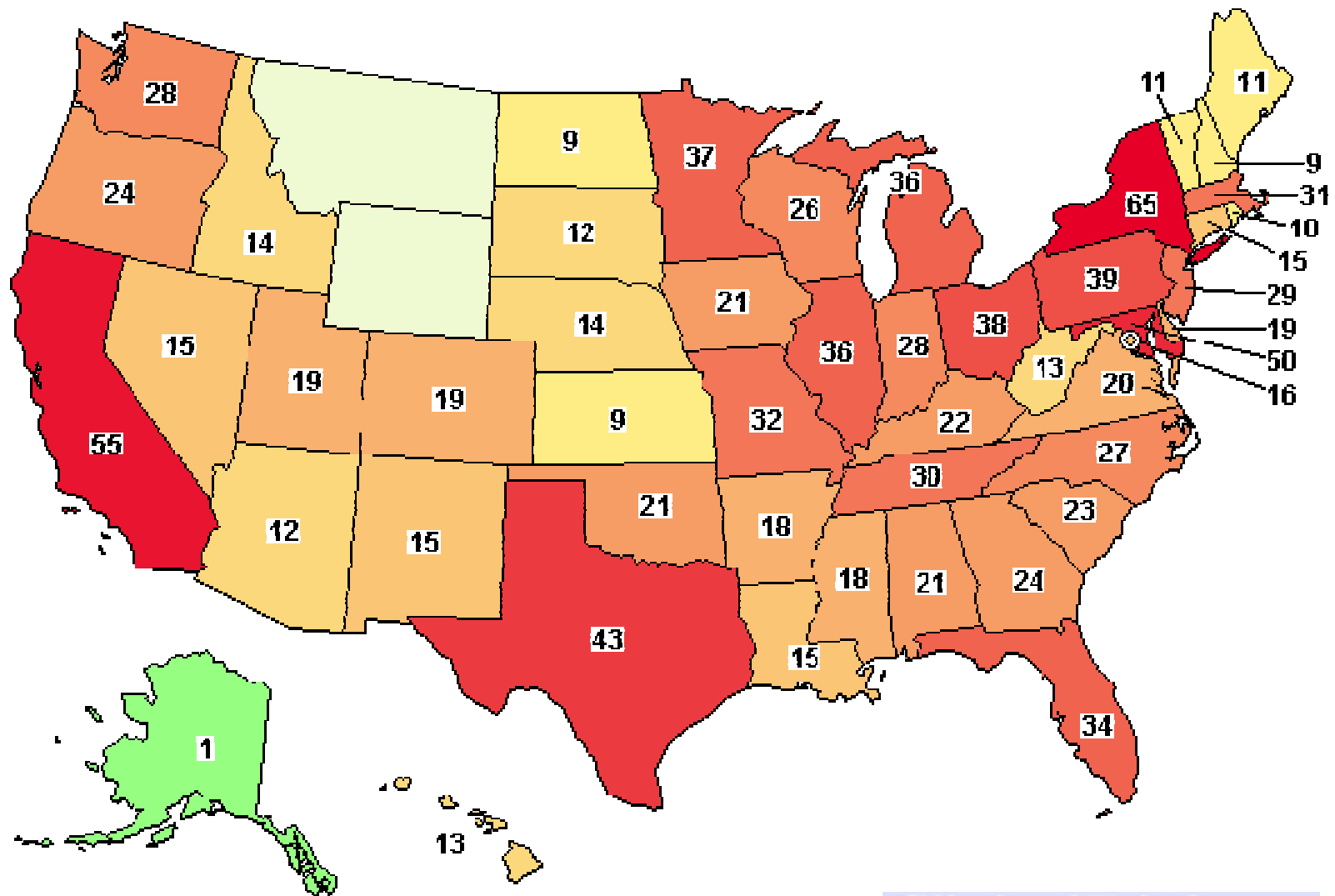
RAD001 (rapamycin) in Gliomas

- CNS glioma that progresses on standard chemotherapy
- Volumetric assessment is endpoint
- Lack of progression

MPNST

- Refractory to prior treatment
- Combination therapy with RAD001 plus VEGF inhibitor
- Assess volume as response to therapy
- NF1 and non-NF1

Found No studies when put in MPNST, but from a list of malignant selected a different term that yielded 254 studies with search of: **Open Studies | "Malignant Mesenchymal Tumor"**



Found 254 studies with search of: Open Studies | "Malignant Mesenchymal Tumor"

- 1 Recruiting A Five-Tier, Phase 2 Open-Label Study of IMC-A12 Administered as a Single Agent
Conditions: Ewing's Sarcoma / Peripheral Neuroectodermal Tumor (PNET); Rhabdomyosarcoma; Leiomyosarcoma; Adipocytic Sarcoma; Synovial Sarcoma
Intervention: Biological: IMC-A12
- 2 Recruiting Collection of Alveolar Soft Part Sarcoma and Blood Specimens for Research
Conditions: Alveolar Soft Part Sarcoma; Sarcoma Intervention:
- 3 Recruiting Sorafenib and Dacarbazine in Soft Tissue Sarcoma
Conditions: Sarcoma; Synovial Sarcoma; Leiomyosarcoma; **Malignant Peripheral Nerve Sheath Tumor** Intervention: Drug: Sorafenib and Dacarbazine

Many protocols are not designed for NF1 Population, but individuals with NF1 would not be excluded.

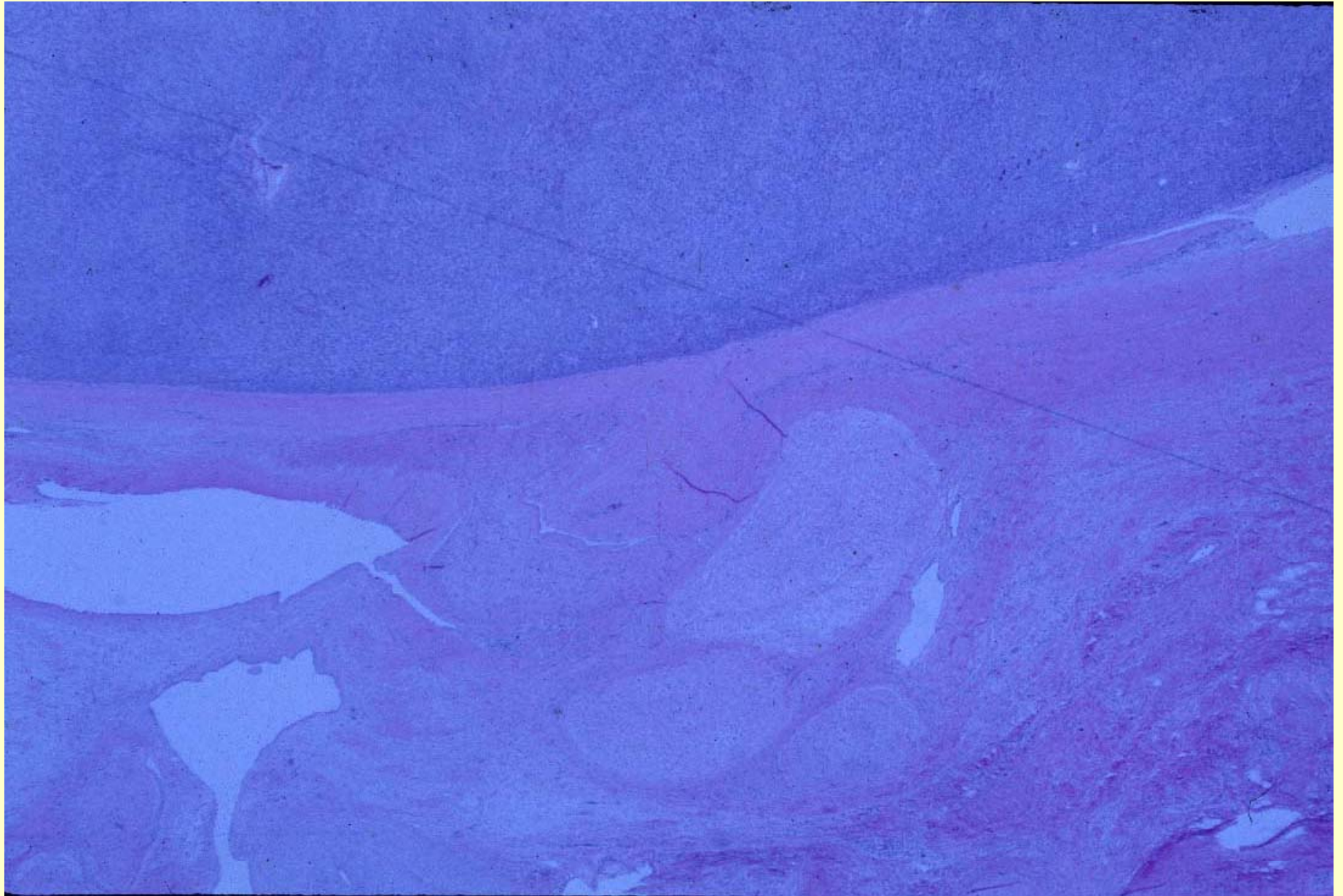
Caveats: Is the the drug dosing correct?
Is there something about NF1 that would cause someone to react differently?



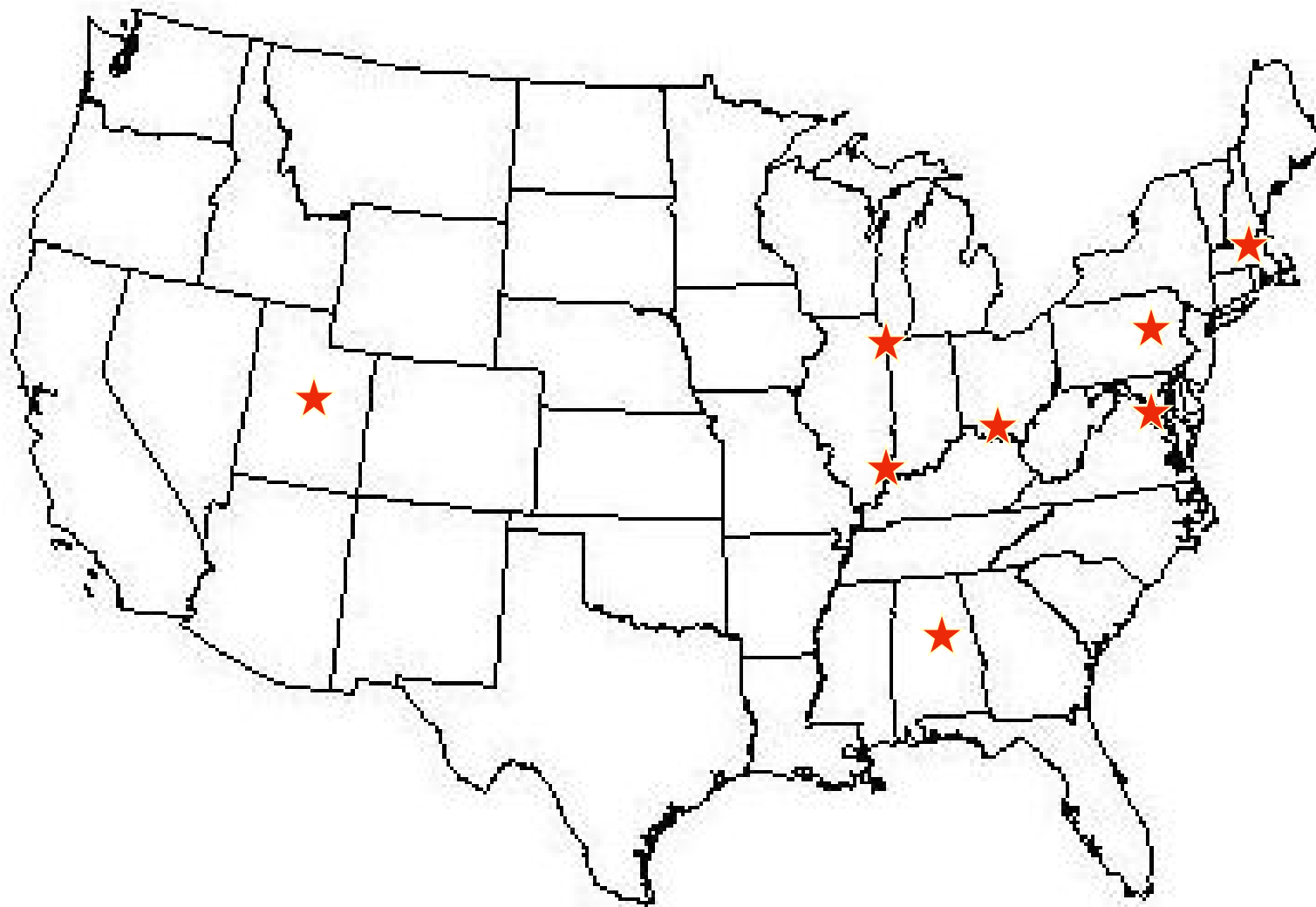
Find the site

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

AND GO FOR IT



MPNST: Malignant Peripheral Nerve Sheath Tumor



NF1 Consortium Sites for Clinical Trials

Thank you

