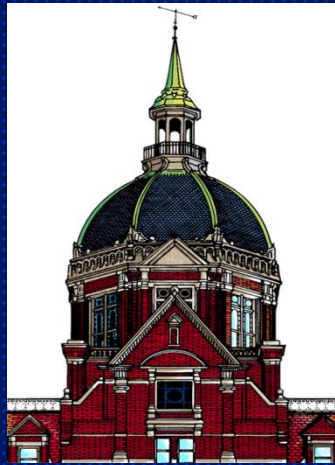
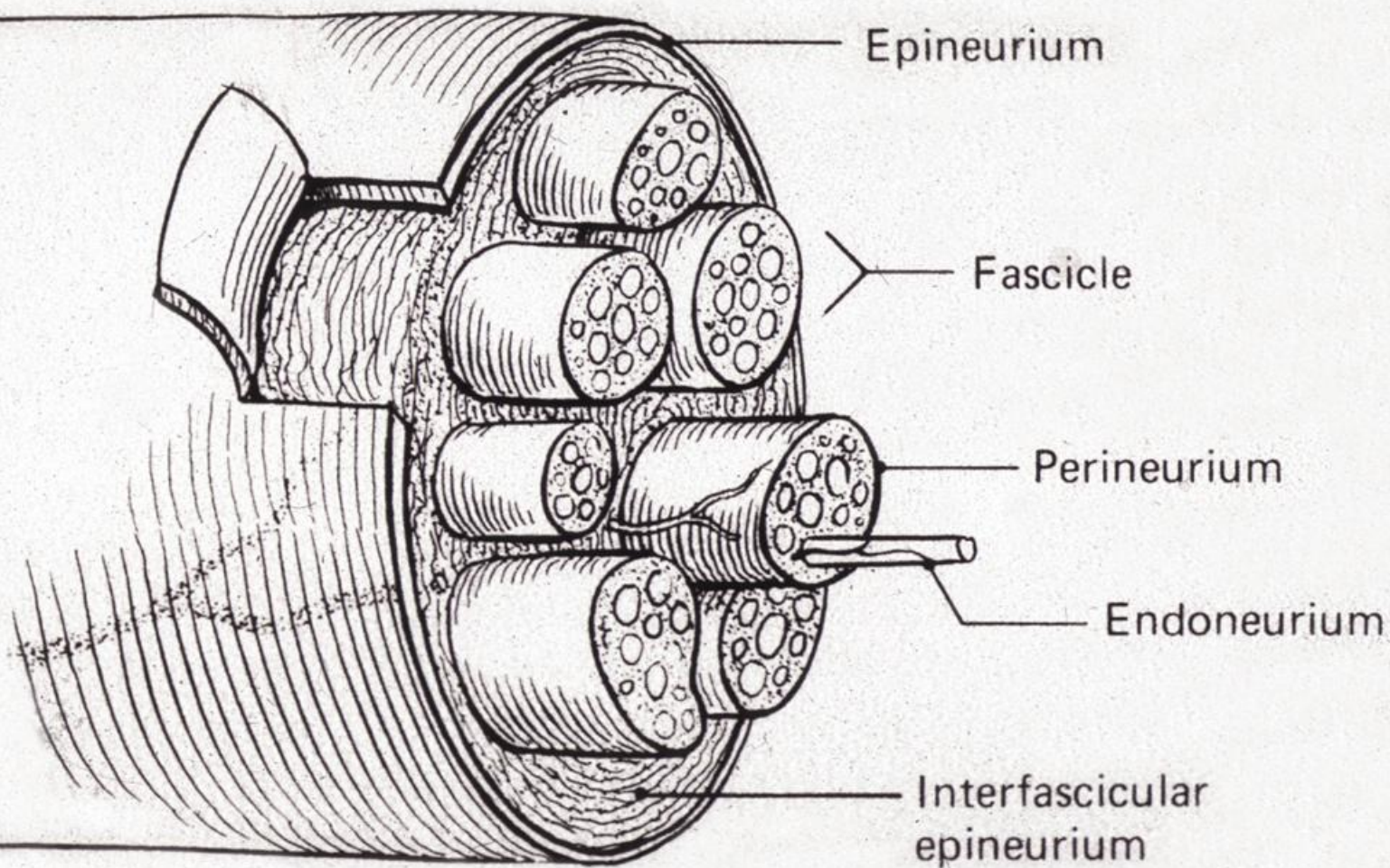


Peripheral Nerve Tumors





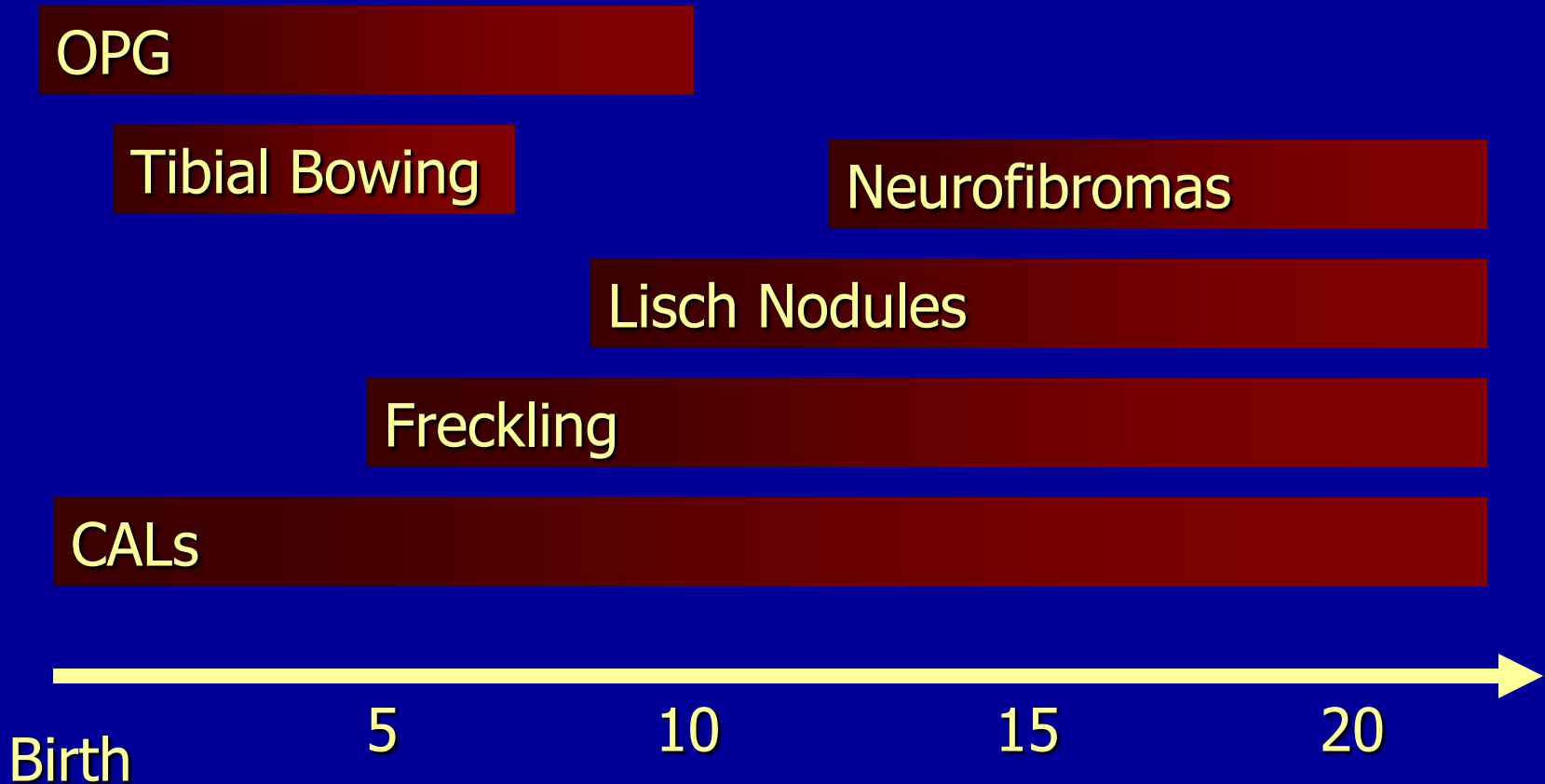
Neurofibromatosis Type 1 (NF1)

- Incidence: 1/3,500 births
 - About 13 new babies born each year in Baltimore
 - 383 patients known to our clinic
- ~50% of cases are *de novo*
- Autosomal dominant
 - Symptoms within a family can vary widely
- Gene is neurofibromin on 17q11.2
 - Tumor suppressor gene
- Molecular testing available
 - Detects greater than 95% of mutations in individuals meeting NIH criteria

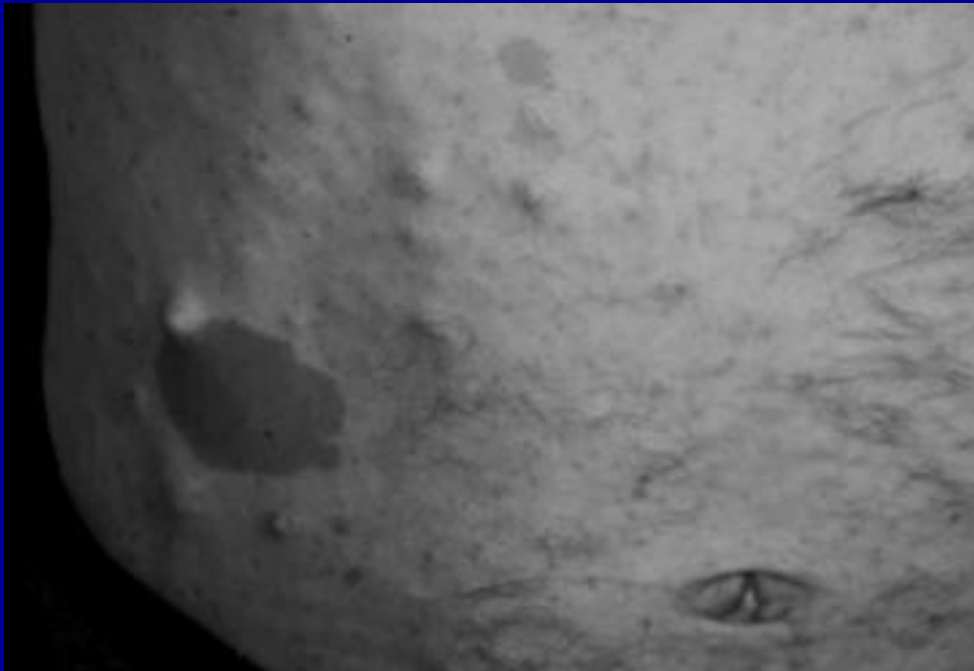
NIH Criteria

- *Two or more of the following need to be present*
- Cafe-au-lait spots
 - 6 or more
 - ≥ 5 mm child (~ dime), ≥ 15 mm adult (~quarter)
- Axillary or inguinal freckling
- Lisch nodules (iris hamartomas)
 - 2 or more
- Optic glioma
- 2 or more neurofibromas OR 1 plexiform neurofibroma
- Distinctive bone lesions
 - I.e. sphenoid dysplasia, tibial pseudoarthrosis
- 1st degree relative with NF1

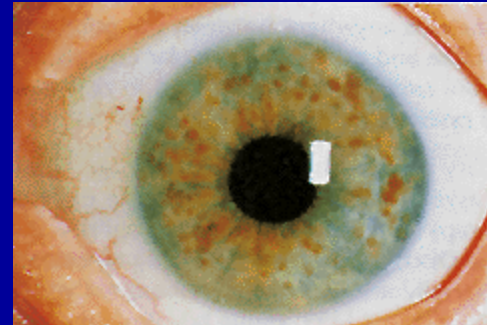
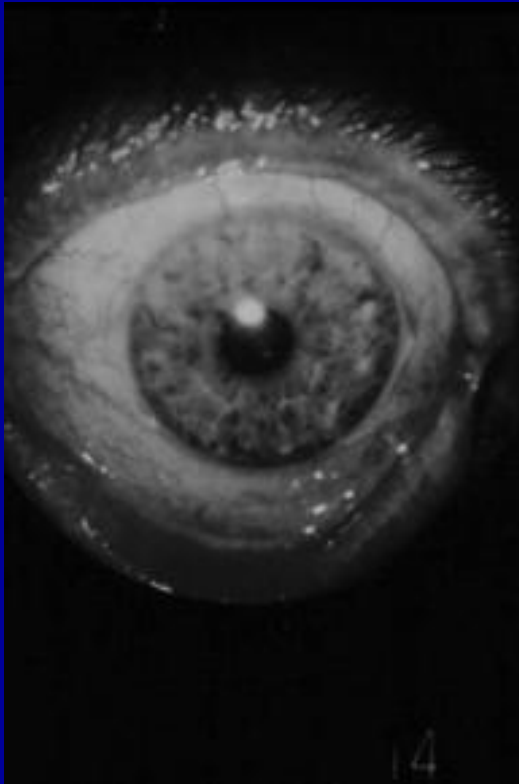
Age of Onset



Café-au-lait spots and Axillary Freckling



Iris Lisch nodules

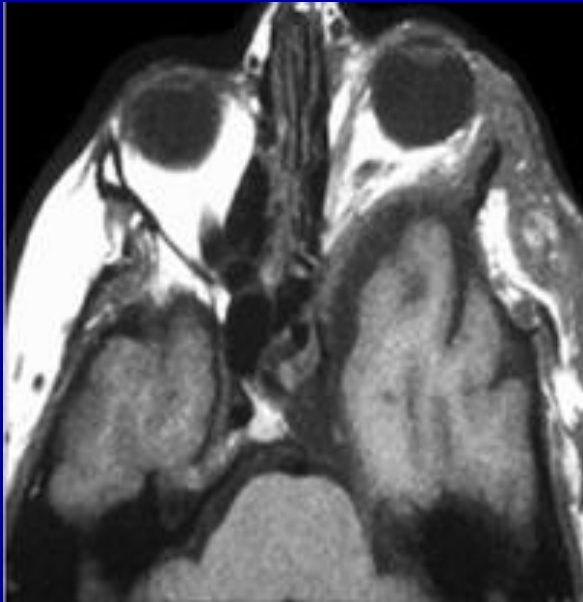


Bony Abnormalities in NF1

- Bone dysplasia and remodeling
 - Macrocephaly
 - Craniofacial dysplasia
 - sphenoid winging
 - Vertebrae (scalloping, scoliosis)
 - Pseudoarthrosis
 - especially congenital
 - Bowing valgum/varum



Sphenoid dysplasia



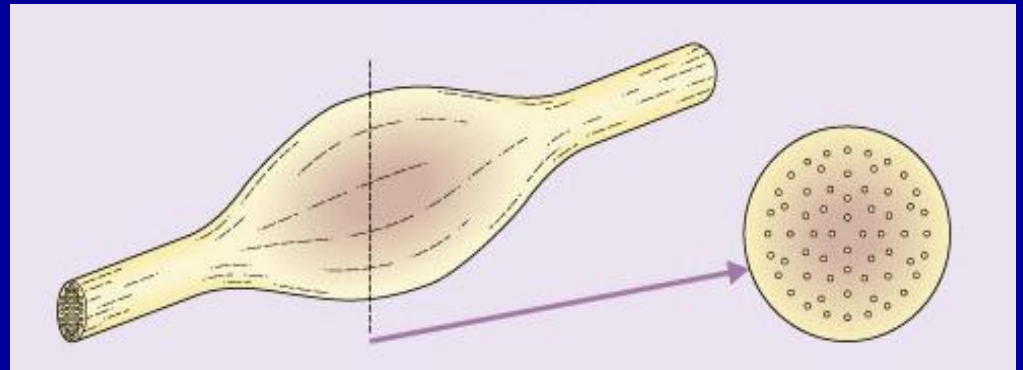
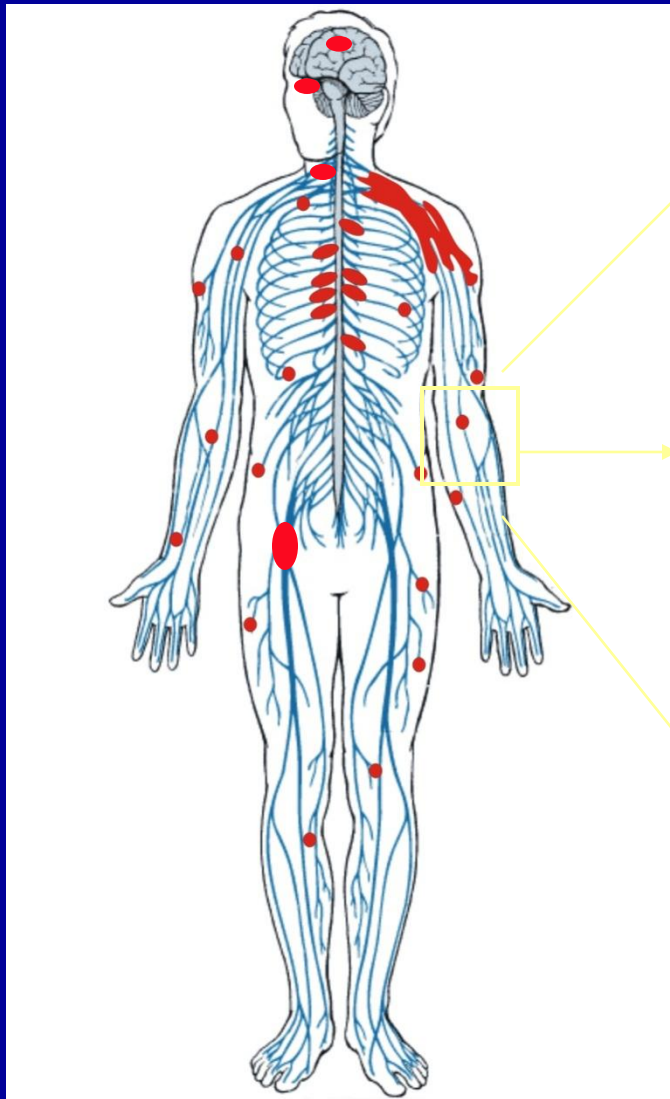
Neoplasms associated with NF1

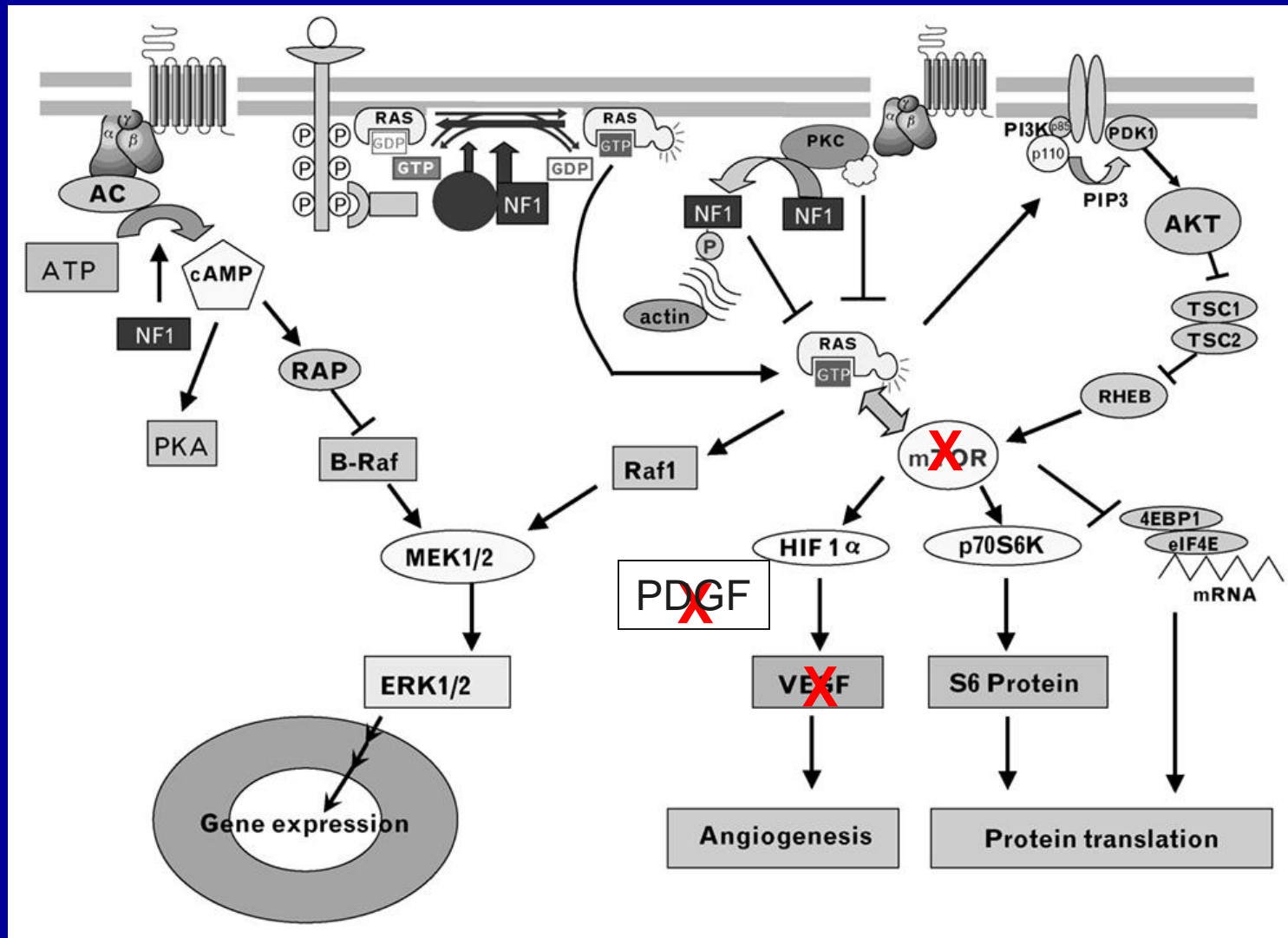
- Neurofibromas
- Plexiform neurofibromas
 - Can involve multiple fascicles
 - 30% of NF1 patients
- Optic pathway gliomas
- Malignant peripheral nerve sheath tumors
 - Is in the family of sarcoma
 - About 8-13% lifetime risk for people with NF1

Optic Pathway Glioma



Neurofibromas in NF1





NF1: Open Clinical Trials

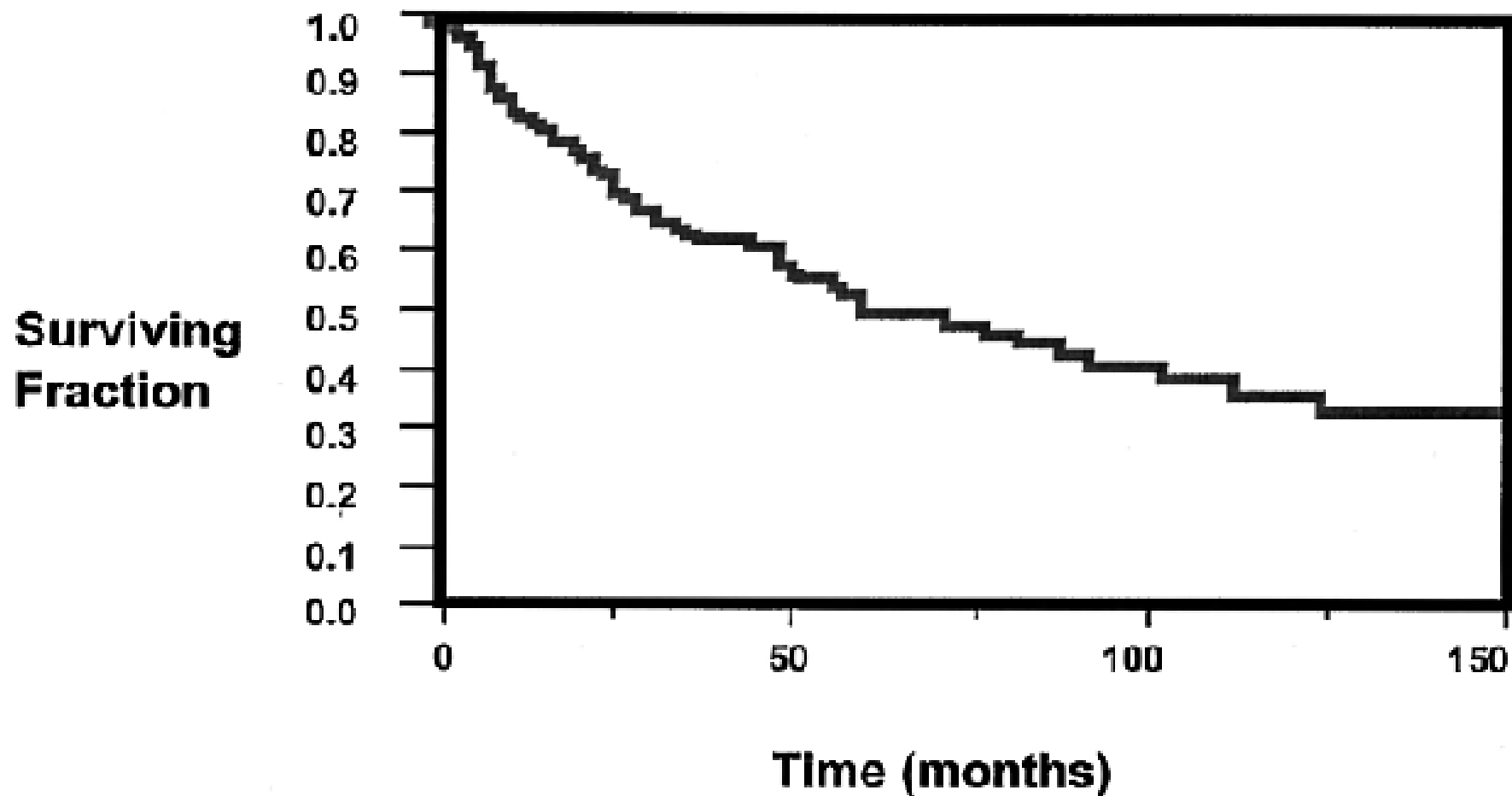
Drug	Target	Indication	Age	Phase	Status
Weekly Vinblastine		LGG	1 to 18 years	II	Recruiting
Carboplatin +Vinblastine		LGG	Children (up to 21)	I	Recruiting
Anti-Neoplastin		LGG	6 to 17	II	Recruiting
Pirfenidone	Fibrosis/TGFb	Plexiform neurofibromas	Children (3-21)	II	Recruiting
PEG-Interferon α -2b	JAK/STAT	Plexiform neurofibromas	Children (1-21)	II	Recruiting
Methotrexate + Vinblastine		Plexiform neurofibromas	Children	II	Recruiting
Sorafenib	RAF Kinase	Plexiform neurofibromas	Children (3-18)	I	Recruiting
Tipifarnib (Zarnestra)	Farnesyl protein transferase	Plexiform neurofibromas	Children (3 to 25)	II	Recruiting
ADZ2171 (cediranib)	VEGF, PDGFA and b	Plexiform neurofibromas	Adults	II	Recruiting
Sirolimus/Rapamycin	mTOR	Plexiform neurofibromas	Children/Adult (3-75)	II	Recruiting
Neo-adjuvant Chemo	Dividing cells	MPNST	Children/Adult	II	Recruiting
Imatinib	Bcr-abl C-kit PDGF-R	MPNST	Adult	II	Recruiting
Lovastatin	HMG CoA Reductase	Cognitive Deficits	Adult	I	Recruiting
Ranibizumab (Lucentis)	VEGF-A	Cutaneous Neurofibromas	Adult	0	Recruiting

Sorting It Out.....

Feature	NF1	NF2	Schwan.
Café-au-lait	X		
Freckling	X		
Dermal NF	X		
Internal NF	X	X	
Schwannoma		X	X (not vestibular)
Glioma	X (optic pathway)	X	
Meningioma		X	

Malignant Peripheral Nerve Sheath Tumors (MPNST)

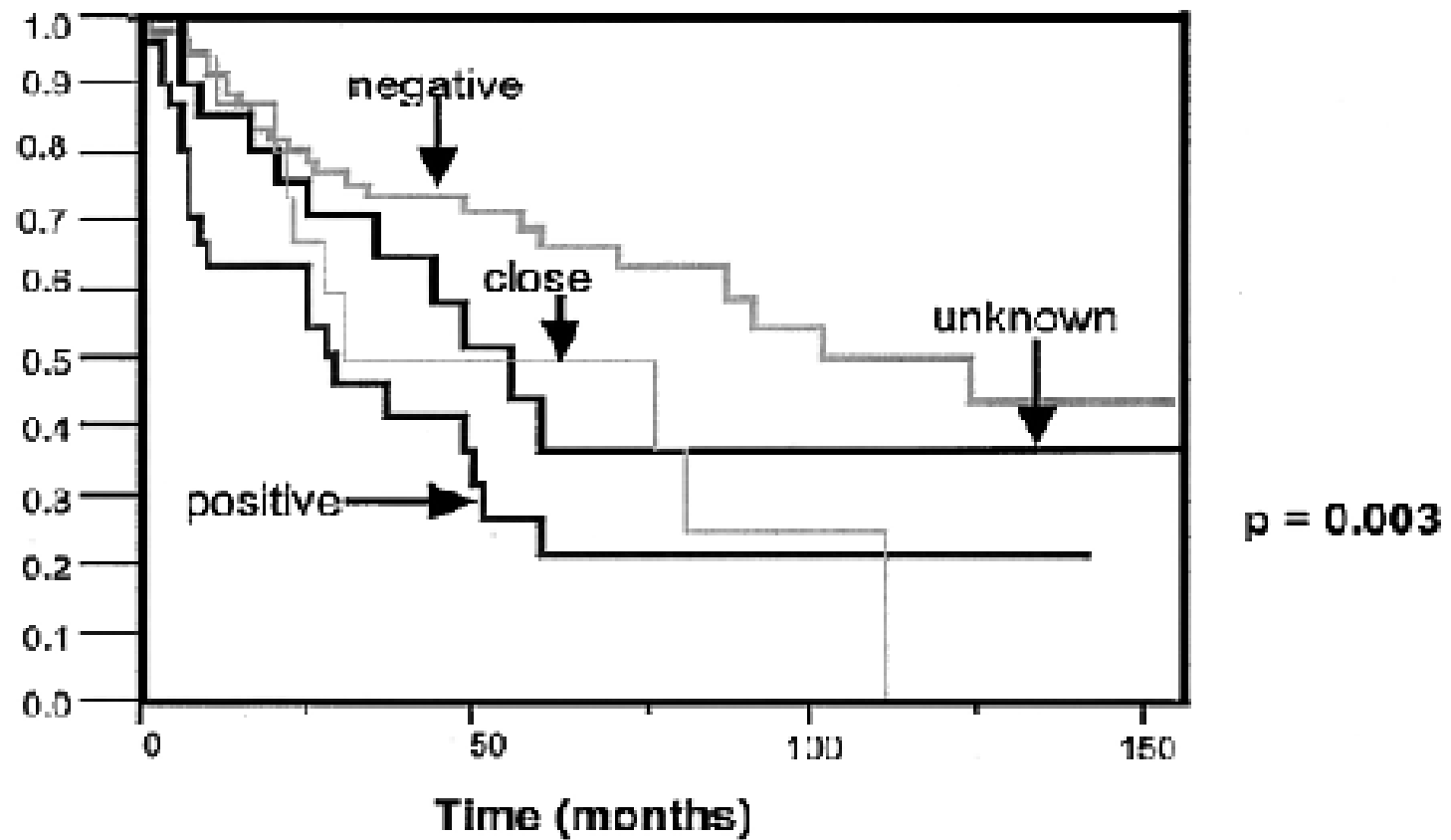
- NF1 lifetime risk of malignancy: 15-20%
 - MPNST accounts for most of this risk (5-12%)
 - Remainder:
 - Malignant gliomas
 - Increased risk of leukemia, breast cancer, ?others
- Aggressive and generally fatal.
- 5 year EFS 19%, overall Survival 28%
- Usually present with rapid, painful growth of a preexisting nodule within a plexiform neurofibroma.
- Resistant to chemotherapy and radiation
 - Best chance for cure is complete resection with wide margin.



Survival of patients with MPNST Wong et al, 1998



**Surviving
Fraction**



Survival of patients according to margins

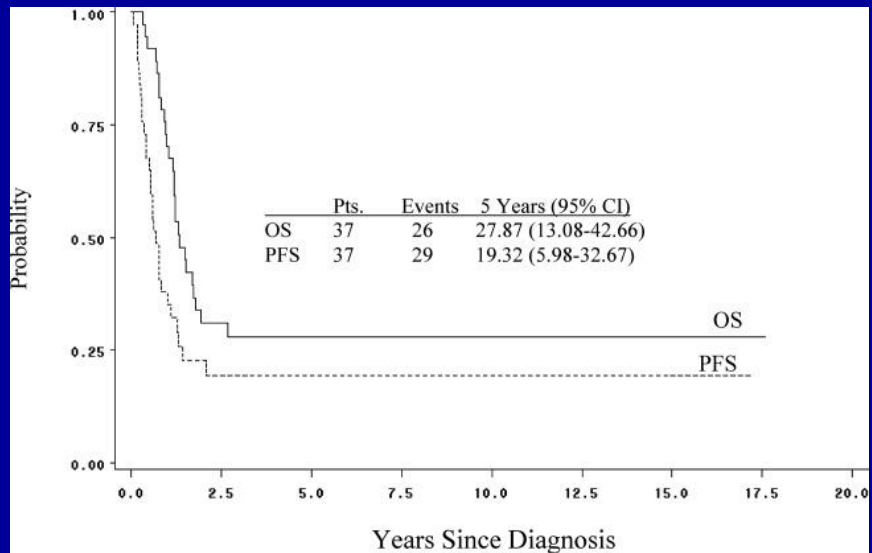
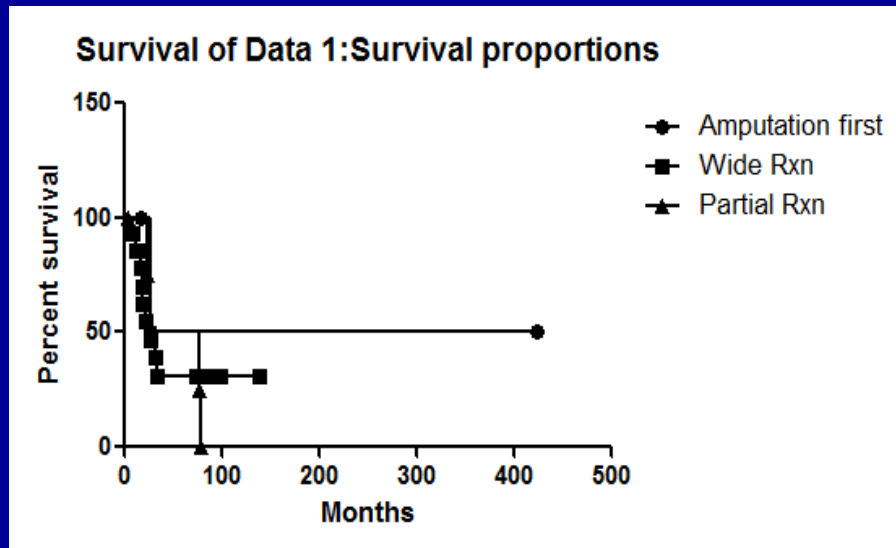
Wong et al, 1998



JHCNC Retrospective Review

- 33 patients with confirmed MPNST from 01/73-01/08
- 23 with complete records
- 14 (60%) had NF1
- NF1 mean age 30 years, sporadic mean age 44 years
- 16/23 cases male
- Time to diagnosis (TTD): 13-281 days
 - (mean NF1 TTD: 178 days, sporadic 91 days)

Does early amputation change survival?



Need more data.

Peripheral Nerve Tumor

The Biopsy??

- What is the indication for biopsy of a peripheral nerve sheath tumor?
 - Can differentiate a nerve sheath tumor from other pathology
 - Biopsy will increase risk of neurological deficit from surgery *Neurosurgery 66:833-840, 2010*
- What is the false positive / false negative for MPNST?
- Is there a role for open 4 quarter biopsy?



Project Narrative: *Circulating Tumor DNA as a Biomarker for Malignant Peripheral Nerve Sheath Tumors*

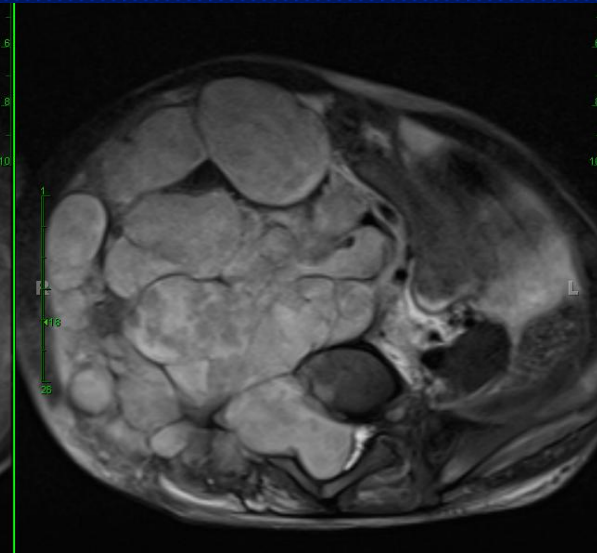
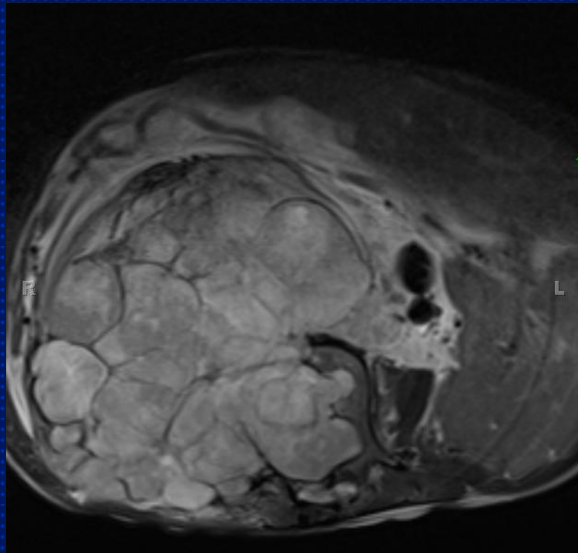
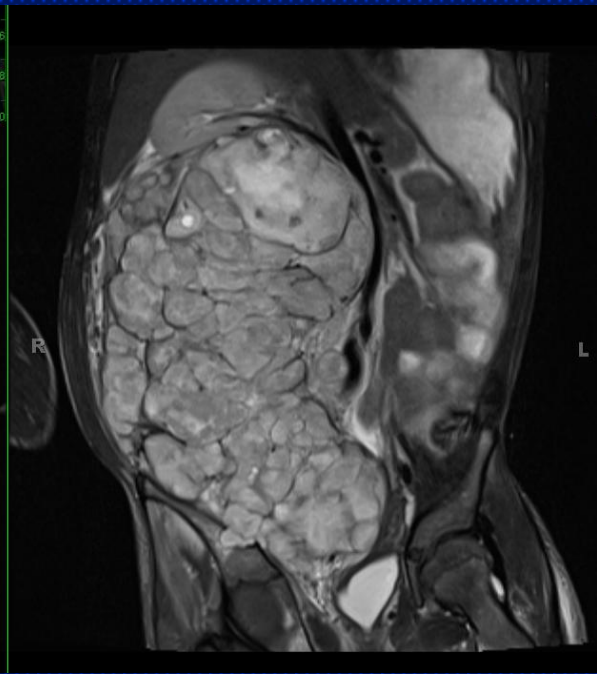
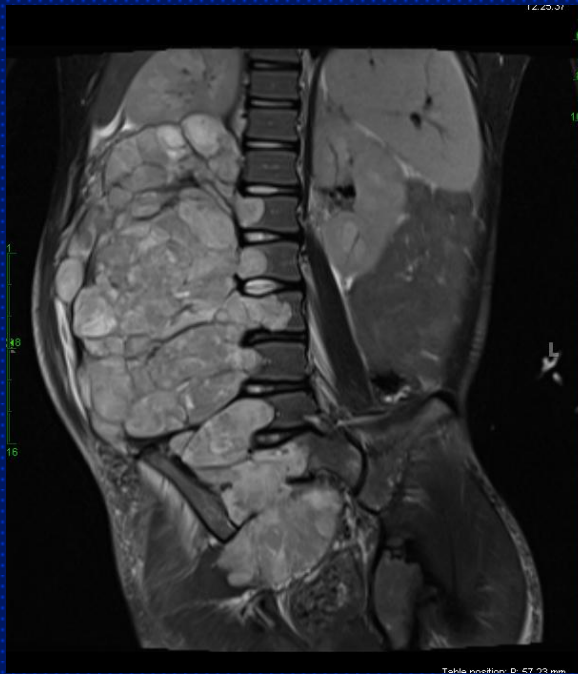
The goal for this project is to develop a novel blood based biomarker using circulating tumor DNA (ctDNA) in patients with malignant peripheral nerve sheath tumors (MPNSTs). It is known that tumor cells shed DNA into various body fluids, including urine, sputum and blood ^{1,2}. This DNA contains tumor specific genetic alterations or mutations, which can be utilized for diagnostic purposes. The mutations are only found within tumor cells, making ctDNA a very specific biomarker. We hope to apply this principle to MPNST and develop a PCR based assay that can be used to monitor disease burden within a patient as well as screen high risk individuals. The specific aims for this two year project are:

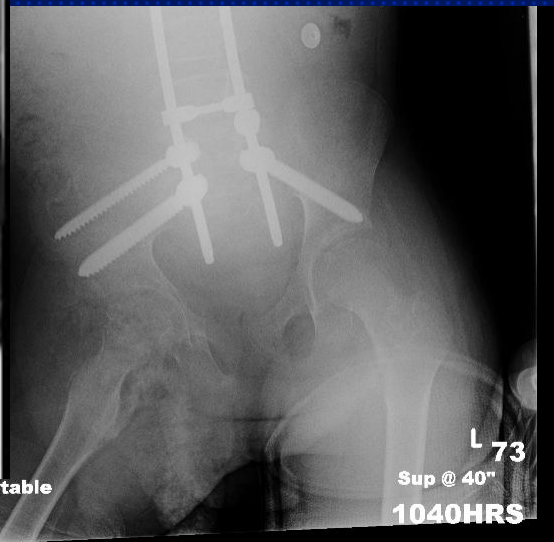
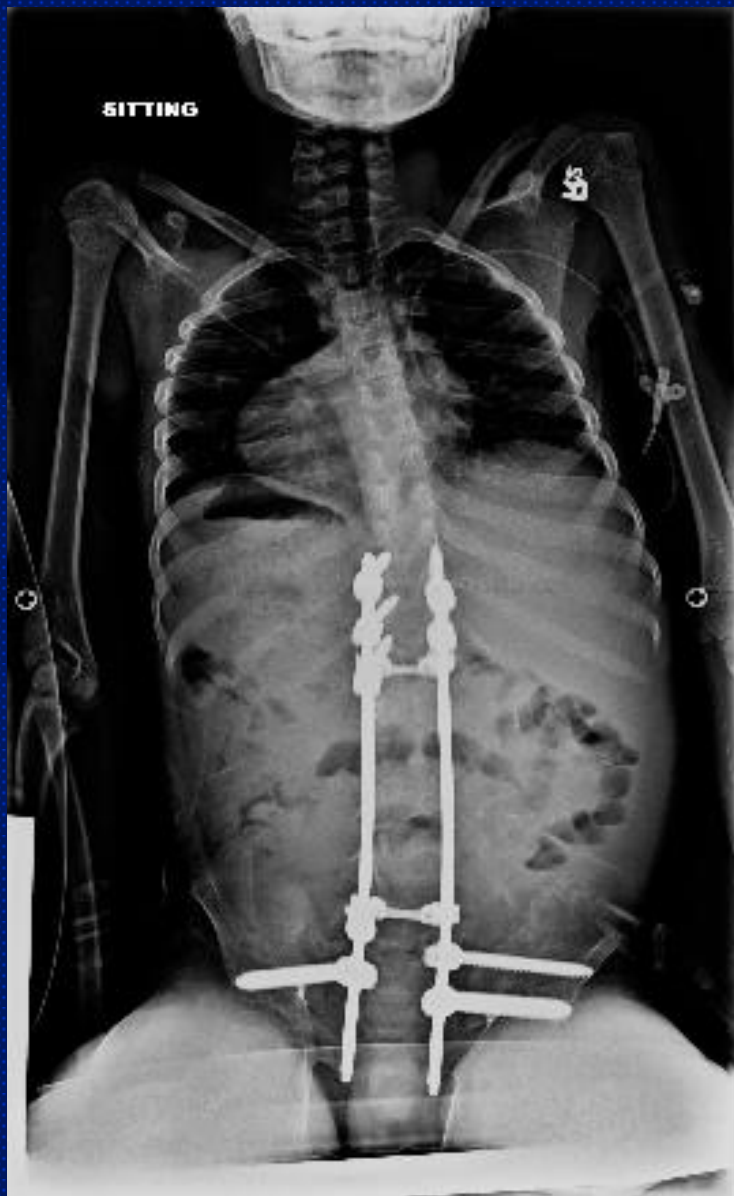
1. **Establish a MPNST matched tissue and blood repository.** Tumor tissue at the time of surgery or biopsy will be stored with matching white blood cells and plasma isolated from the patient's whole blood. Serial blood samples at clinically relevant time points will be drawn, processed and stored.
2. **Test the plasma of patients with MPNST for levels of ctDNA.** Specific mutations from each patient's tumor will be identified by direct sequencing of tumor DNA and those mutations will be queried for in the plasma using highly sensitive PCR based methodology.
3. **Test for the most common MPNST mutations in ctDNA as a screening modality for patients with NF1.** Most MPNSTs have somatic mutations in the NF1 gene and ~50% have mutations in TP53. Once we have shown that we can detect ctDNA in the plasma of patients with MPNST, we will prospectively collect blood from NF1 patients at serial time points. In the subset of patients that go on to develop a MPNST, we will test whether we can detect ctDNA from the tumor before it was diagnosed clinically.



Clinical Case 10

- 9 Year old male with multiple tumors in the abdomen and spine
- Has progressive weakness of the right lower
- Pain is 10/10 on heavy narcotic medication with patient somnolent

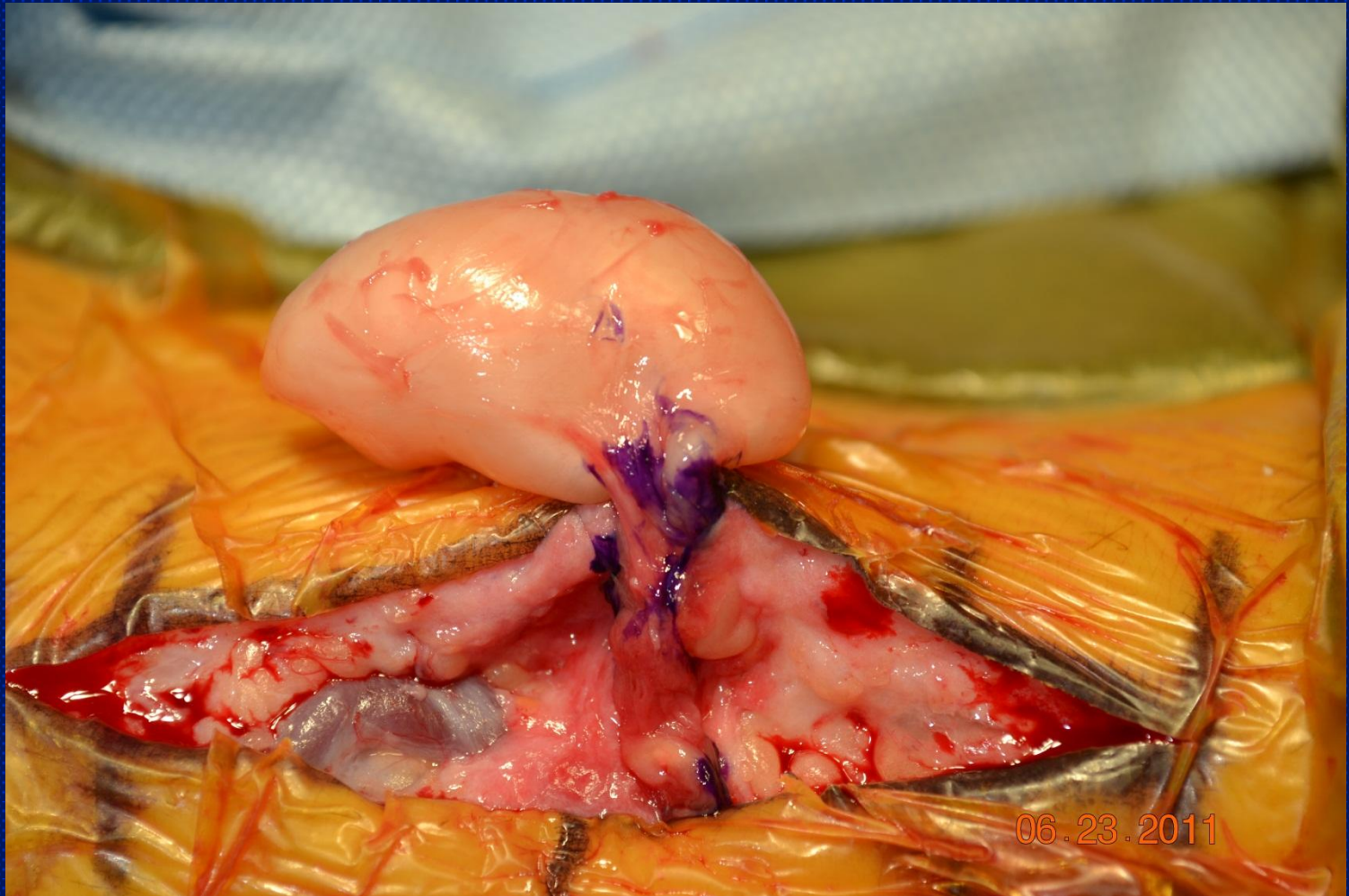




Johns Hopkins
January 24,











Conclusion

There are only two sorts of doctors: those who practice with their brains, and those who practice with their tongues.

SIR WILLIAM OSLER (1849 – 1919)

Johns Hopkins Professor Emeritus