MOLECULAR PATHOLOGY OF PEDIATRIC AND RARE TUMORS

Alanna Church, MD
Associate Director, Laboratory for Molecular Pediatric Pathology (LaMPP)
September 14, 2021

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Boston Children's Hospital
Until every child is well™

DANA-FARBER CANCER INSTITUTE

CHALLENGES AND OPPORTUNITIES IN MOLECULAR DIAGNOSTICS FOR PEDIATRIC CANCERS

- The pediatric cancer genome is different than its adult counterpart
- High likelihood that a child with cancer has an associated germline predisposition
- Each tumor type is rare, such that clinical associations are difficult to make
- Patients have limited access to clinical trials
- Tiny biopsies
- Difficult reimbursement

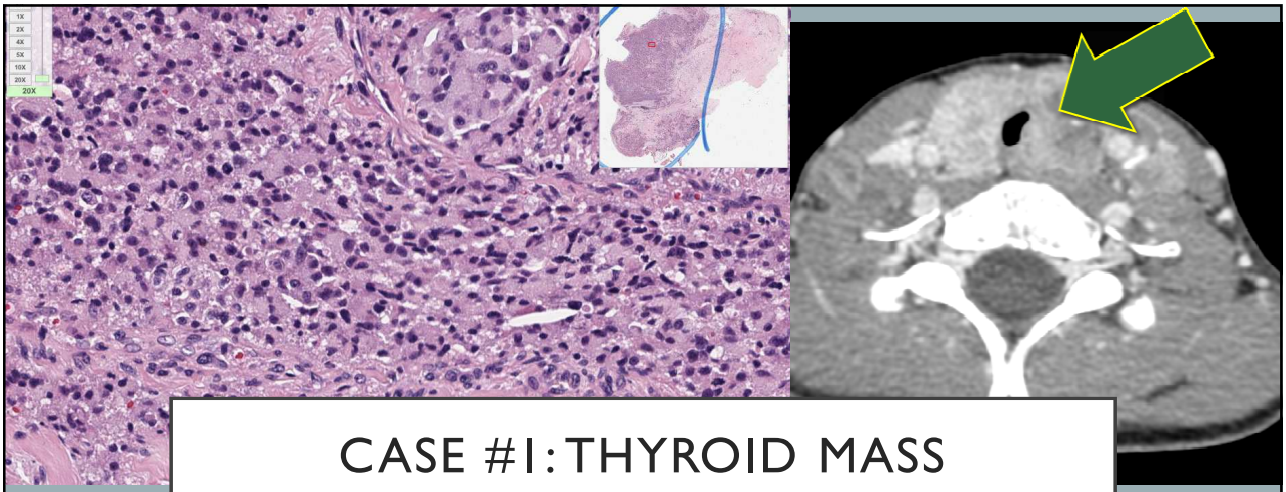
INCIDENCE AND MORTALITY OF PEDIATRIC CANCERS

Pediatric cancers represent 1% of all new cancers diagnosed in the US

The second leading cause of death (following accidents) in children ages 5-14

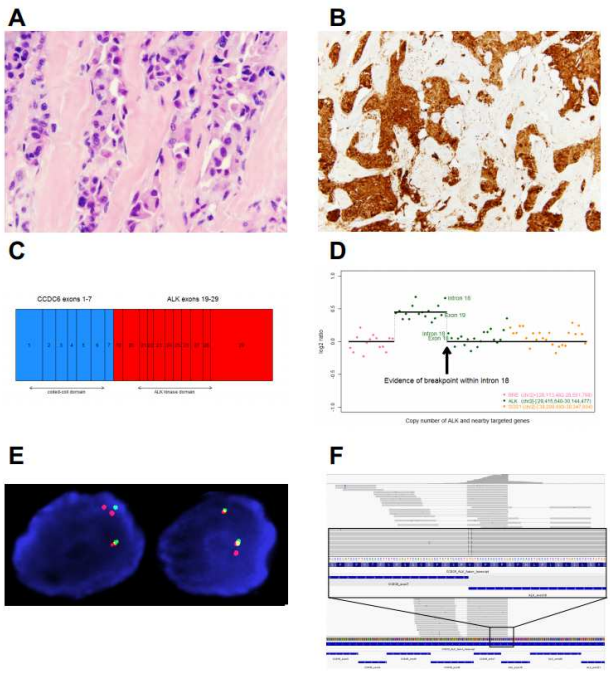
~1 in 285 children in the US will be diagnosed with cancer before the age of 20

American Cancer Society: Cancer Facts and Figures 2014

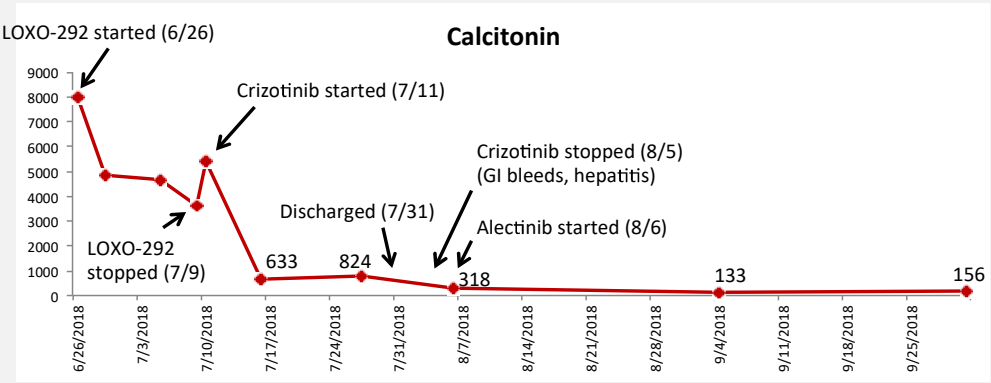


CASE #1: THYROID MASS OBSTRUCTING AIRWAY

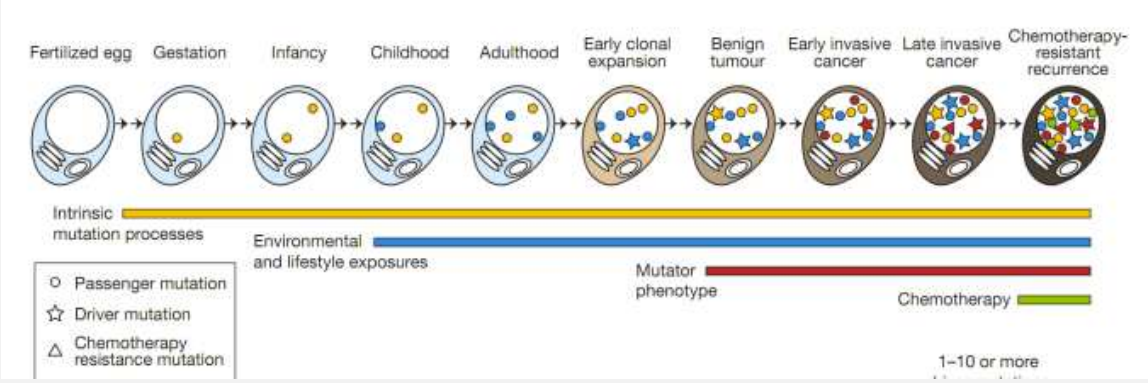
ALK FUSION DETECTED



Hillier K, et al. Thyroid 29 (11), 1704-1707

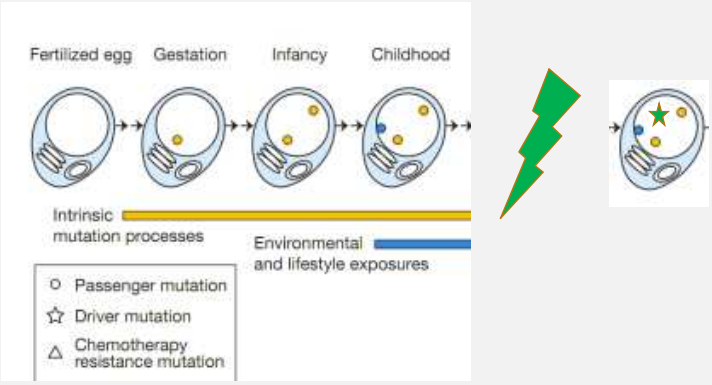


IMPROVEMENT WITH TARGETED TREATMENT



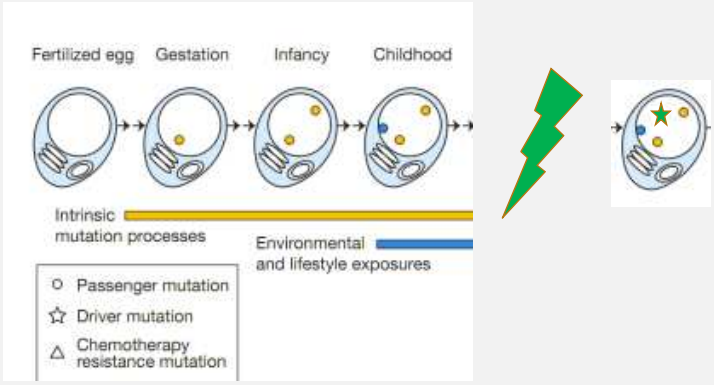
CANCER GENOME

Nature. 2009;458: 719-24



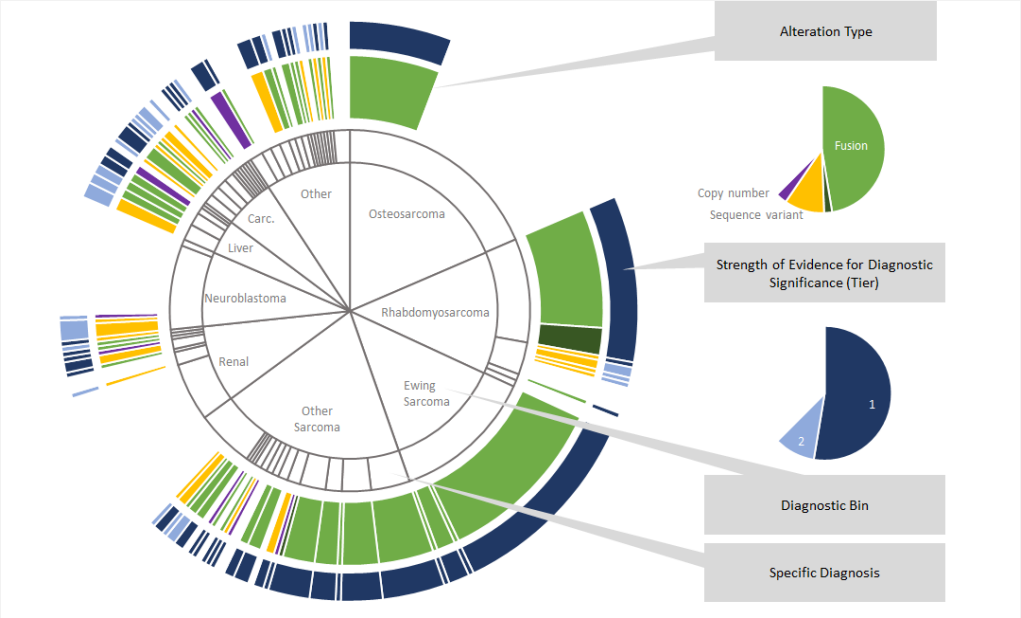
PEDIATRIC CANCER GENOME

Nature. 2009;458: 719-24

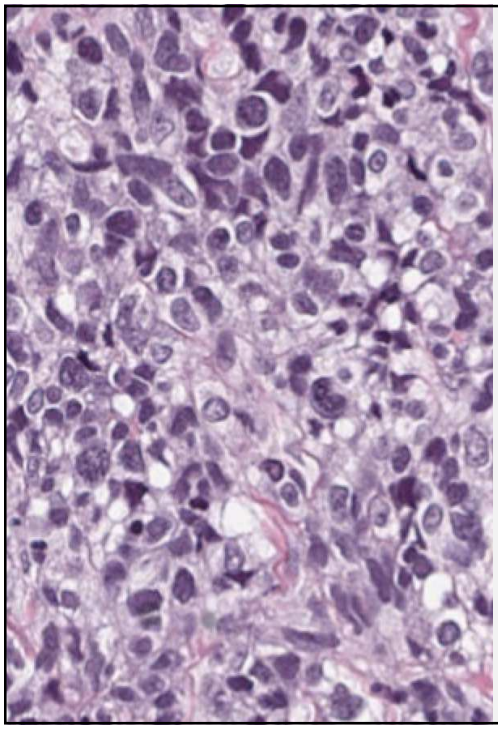


SARCOMA GENOME

Nature. 2009;458: 719-24



Church AJ, et al. ASCO Annual Meeting, 2021. Journal of Clinical Oncology 39 (15_suppl), 10005-10005

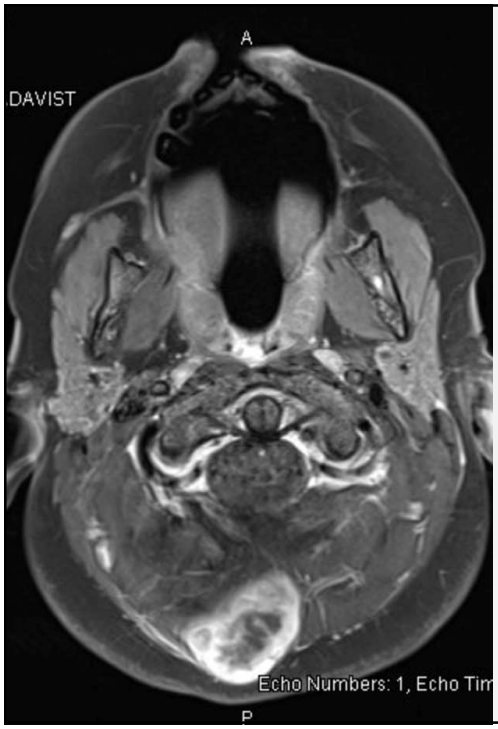


CASE #2

- 2-year-old girl with a bump on her scalp
- Biopsy showed a high-grade lesion with rhabdomyosarcomatous features, consistent with embryonal rhabdomyosarcoma with anaplasia

- Tumor DNA sequencing panel identified a variant:
- TP53 c.818G>A (p.R273H), exon 8 - in 86% of 220 reads

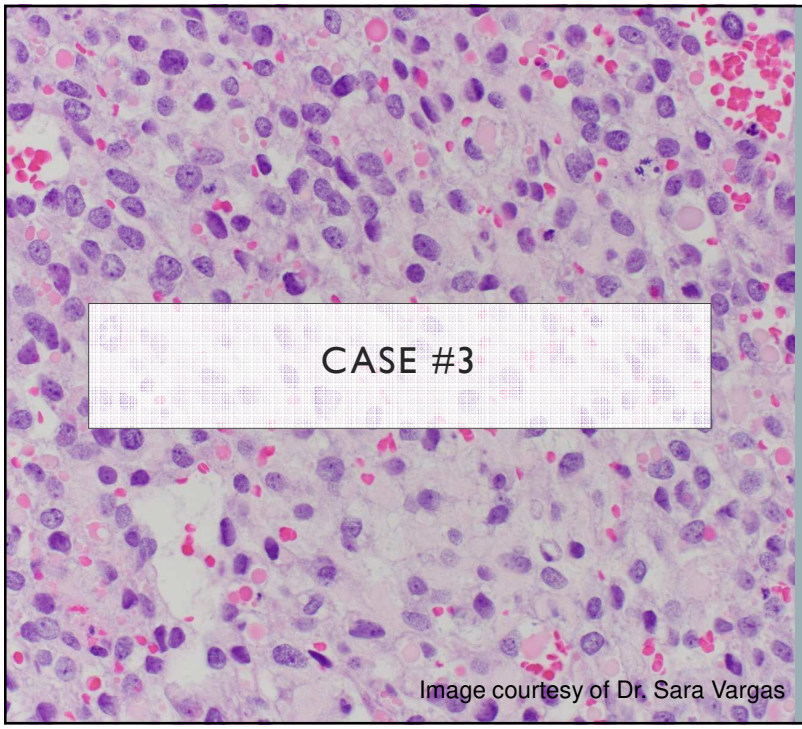
with thanks to S. Vargas



CASE #2

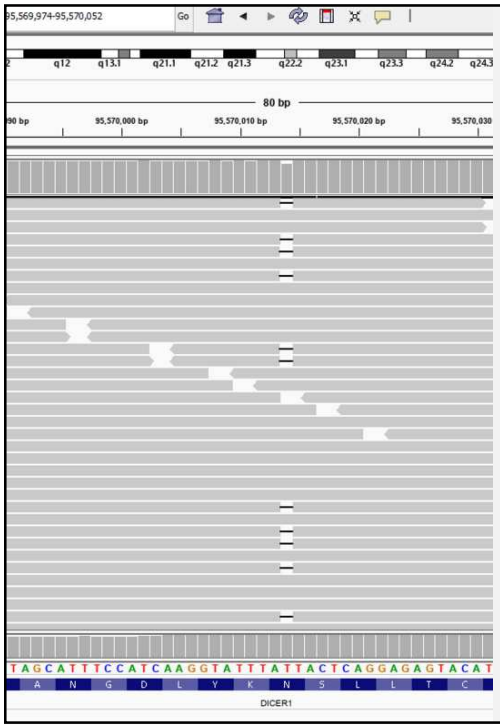
- Lesion was infiltrating into her brain
- The TP53 variant was confirmed to be germline with LOH in the tumor
- She was diagnosed with Li Fraumeni syndrome
- She is doing well, now off-therapy and undergoingLFS surveillance

with thanks to J. Kamihara, and J. Schienda



11-year-old girl with a poorly differentiated ovarian tumor

Heterogeneous histology with areas of rhabdomyosarcomatous differentiation



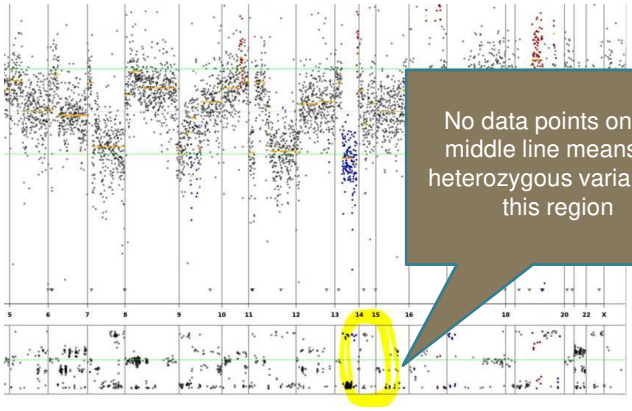
TUMOR-ONLY SEQUENCING USING A TARGETED CANCER PANEL

- Targeted DNA sequencing (447 genes), from a tumor sample with 80% tumor cellularity
- Sequence variants:
  - *DICER1* c.5425G>A p.G1809R, VAF = 80%
  - *DICER1* c.3179delA p.N1240Ifs*18, VAF = 10%

J, Kamihara et al. *Manuscript Under Review*

LOH ON CHR17

Where *DICER1* is located



DICER1-ASSOCIATED TUMORS

Germline variants in *DICER1* are association with cancer predisposition

DICER1-associated tumors include:

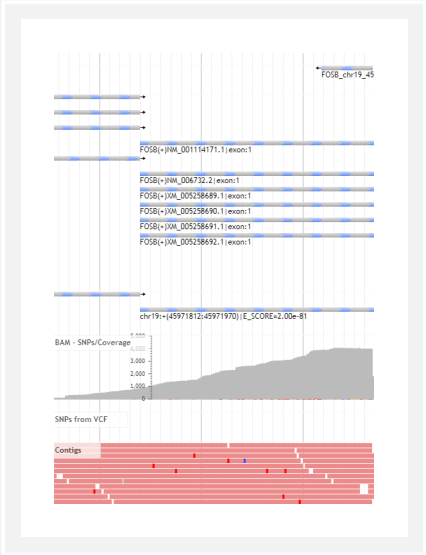
- pleuropulmonary blastoma (PPB)
- ovarian sex cord–stromal tumors, particularly Sertoli–Leydig cell tumor
- cystic nephroma
- renal sarcoma
- Wilms tumor
- Pineoblastoma
- Cilliary body medulloepithelioma
- Genitourinary rhabdomyosarcoma
- *DICER1*-associated CNS sarcoma

These tumors may also be associated with somatic only *DICER1* variants

CASE #4

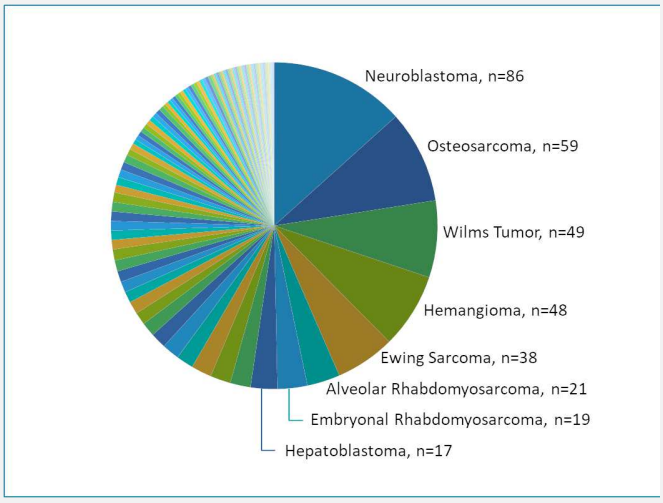
20yF with multiple lytic lesions in the pelvis and femur

ACTB-FOSB fusion identified, consistent with pseudomyogenic hemangioendothelioma

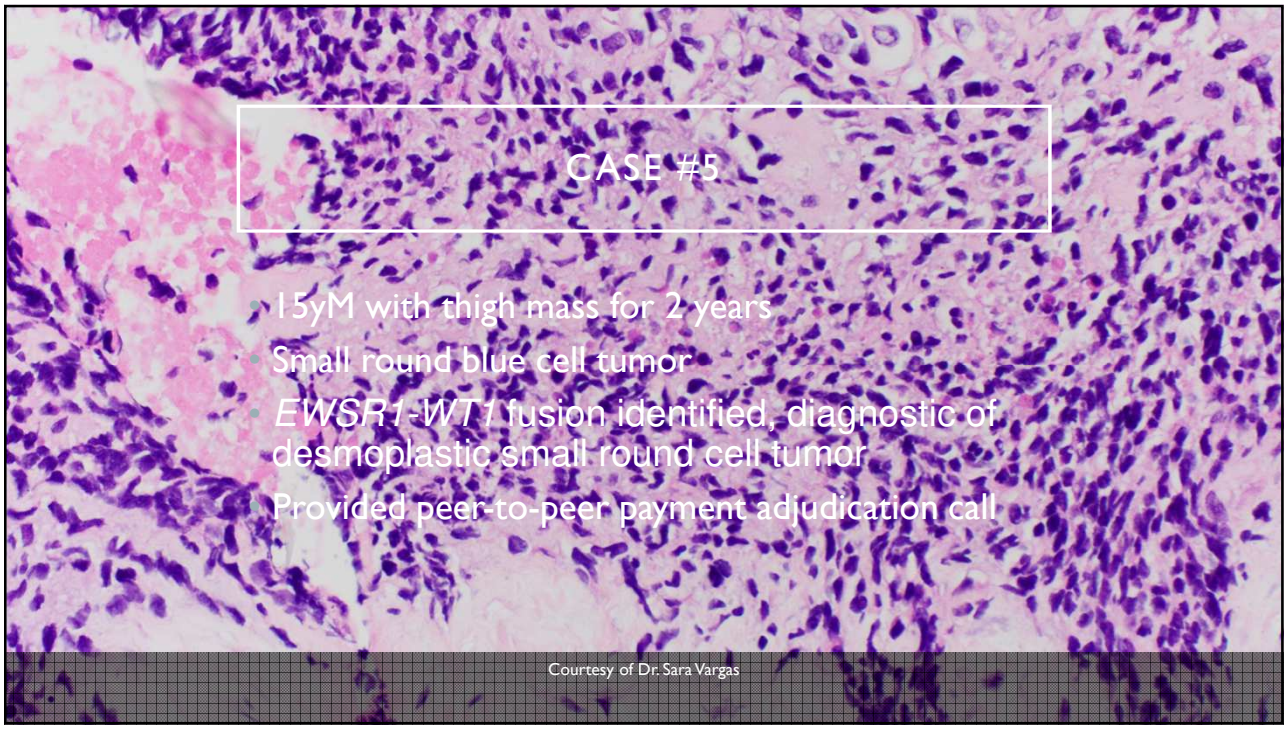


DIAGNOSES OF CONSENTED PATIENTS

- For 644 pediatric solid tumor patients consented to protocols requesting tissue:
  - 104 distinct diagnoses
  - 41 singular diagnoses



RS Pinches, et al., Pediatric Blood and Cancer. 2020 Jul 15;e28326.

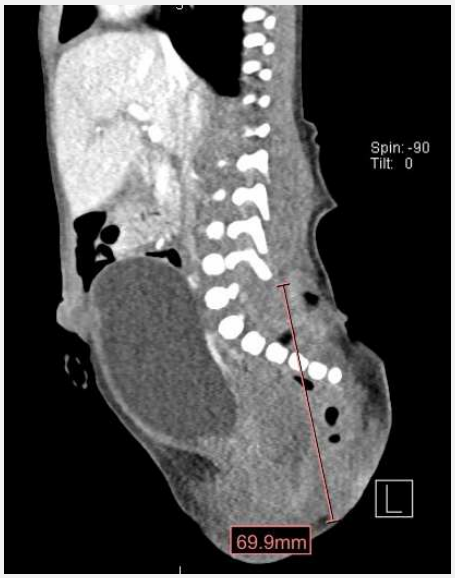


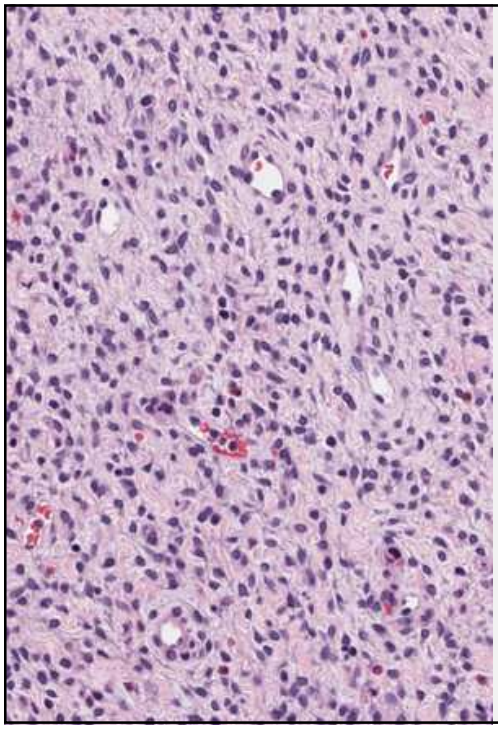
REIMBURSEMENT

- Working closely with our Billing Manager and with Patient Financial Services and payors to increase our reimbursement for in-house and sendout testing
- Collaborated with BCBS Massachusetts to create a pediatric cancer medical policy

CASE #6: BABY WITH A SPINAL MASS

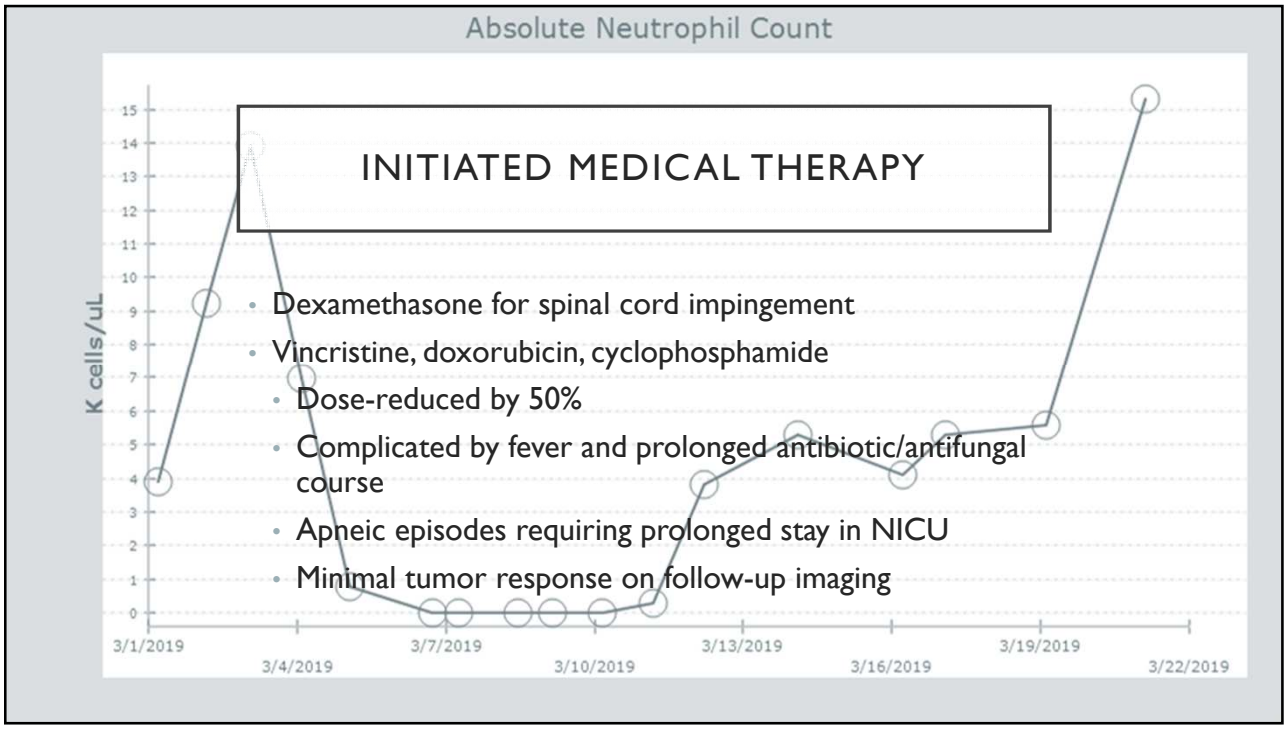
A 5-WEEK OLD GIRL WITH SPINAL DYSRAPHISM





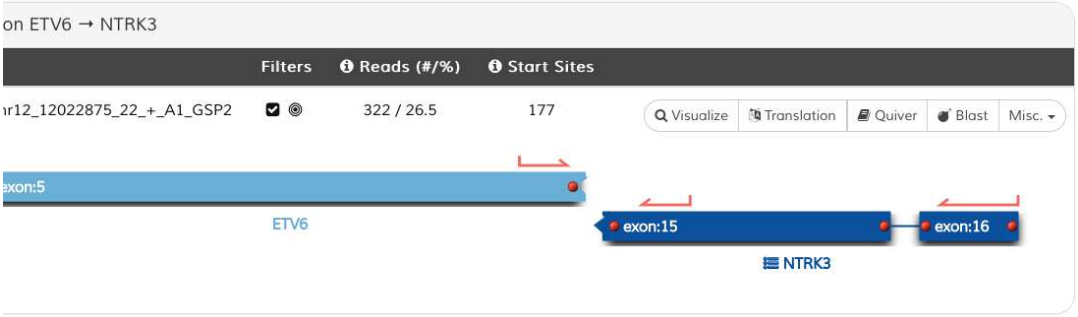
PRIMITIVE CELLULAR TUMOR WITH MULTILINEAGE DIFFERENTIATION

- Mesenchymal cells, spindle shaped
- Cystic structures reminiscent of infantile endocardium
- Smooth muscle, calcification, hemosiderosis, granulation-like tissue present
- CD34, desmin, S100, SMA, CD99, cyclinD-1, synaptophysin positive
- Faint staining for NTRK and BCOR (interpreted as negative)



INITIATED MEDICAL THERAPY

- Dexamethasone for spinal cord impingement
- Vincristine, doxorubicin, cyclophosphamide
  - Dose-reduced by 50%
  - Complicated by fever and prolonged antibiotic/antifungal course
  - Apneic episodes requiring prolonged stay in NICU
  - Minimal tumor response on follow-up imaging



ETV6-NTRK3 FUSION IDENTIFIED

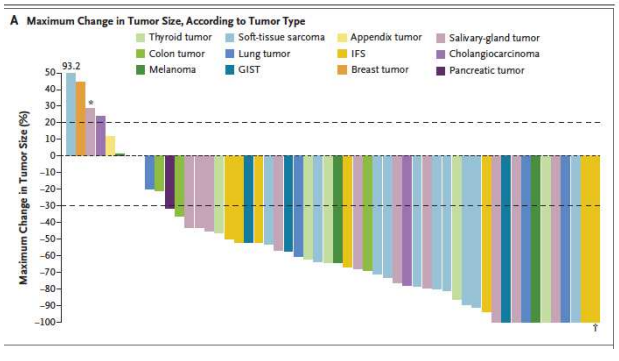
TARGETED THERAPY AVAILABLE

ORIGINAL ARTICLE

Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

A. Drilon, T.W. Laetsch, S. Kummar, S.G. DuBois, U.N. Lassen, G.D. Demetri, M. Nathenson, R.C. Doebele, A.F. Farago, A.S. Pappo, B. Turpin, A. Dowlati, M.S. Brose, L. Mascarenhas, N. Federman, J. Berlin, W.S. El-Deiry, C. Baik, J. Deeken, V. Boni, R. Nagasubramanian, M. Taylor, E.R. Rudzinski, F. Meric-Bernstam, D.P.S. Sohal, P.C. Ma, L.E. Raez, J.F. Hechtman, R. Benayed,

DANA-FARBER Boston Children's
CANCER AND BLOOD DISORDERS CENTER



RESPONSE ASSOCIATED WITH NTRK FUSION, ACROSS HISTOLOGIES

CHALLENGES AND OPPORTUNITIES IN MOLECULAR DIAGNOSTICS FOR PEDIATRIC CANCERS

- The pediatric cancer genome is different than its adult counterpart
- High likelihood that a child with cancer has an associated germline predisposition
- Each tumor type is rare, such that clinical associations are difficult to make
- Patients have limited access to clinical trials
- Tiny biopsies
- Difficult reimbursement

Boston Children's Hospital
Until every child is well®

Laboratory for Molecular Pediatric Pathology