CENTER FOR CANCER RESEARCH

Connecting the Cancer Community

Congressional Childhood Cancer Caucus

3rd Annual Summit ▪ September 20, 2012

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Pediatric Oncology Branch, Center for Cancer Research

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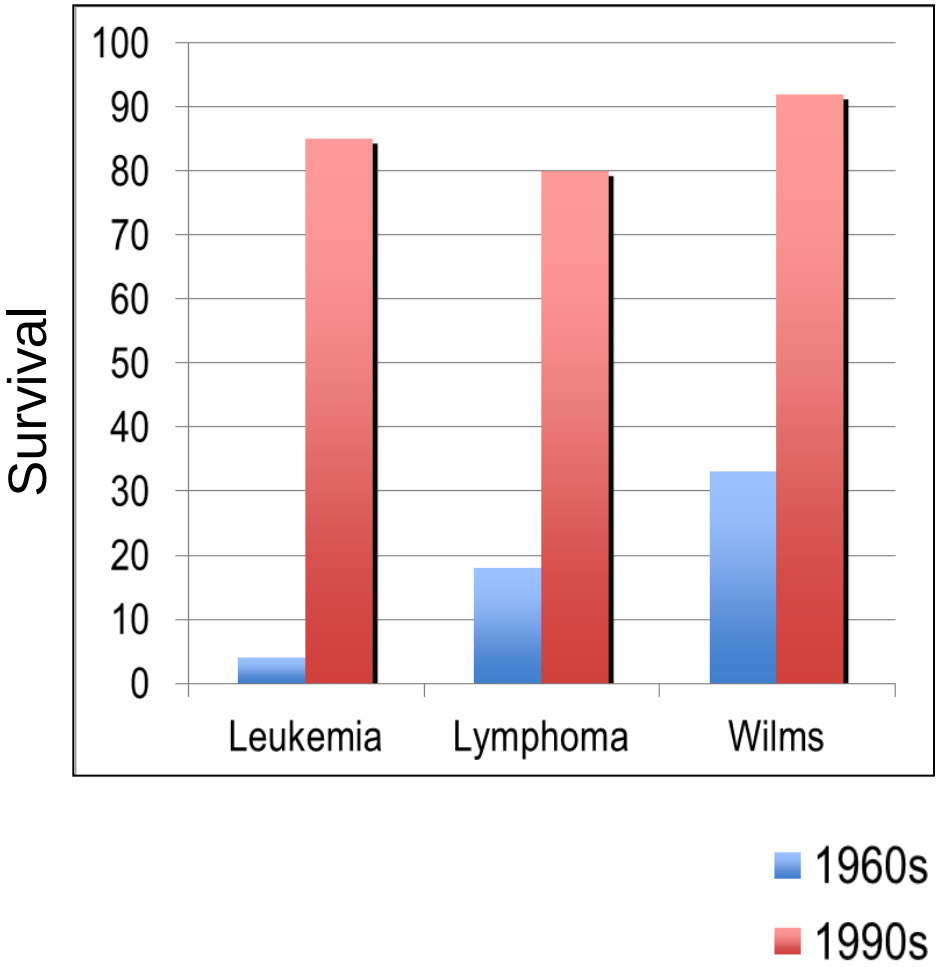
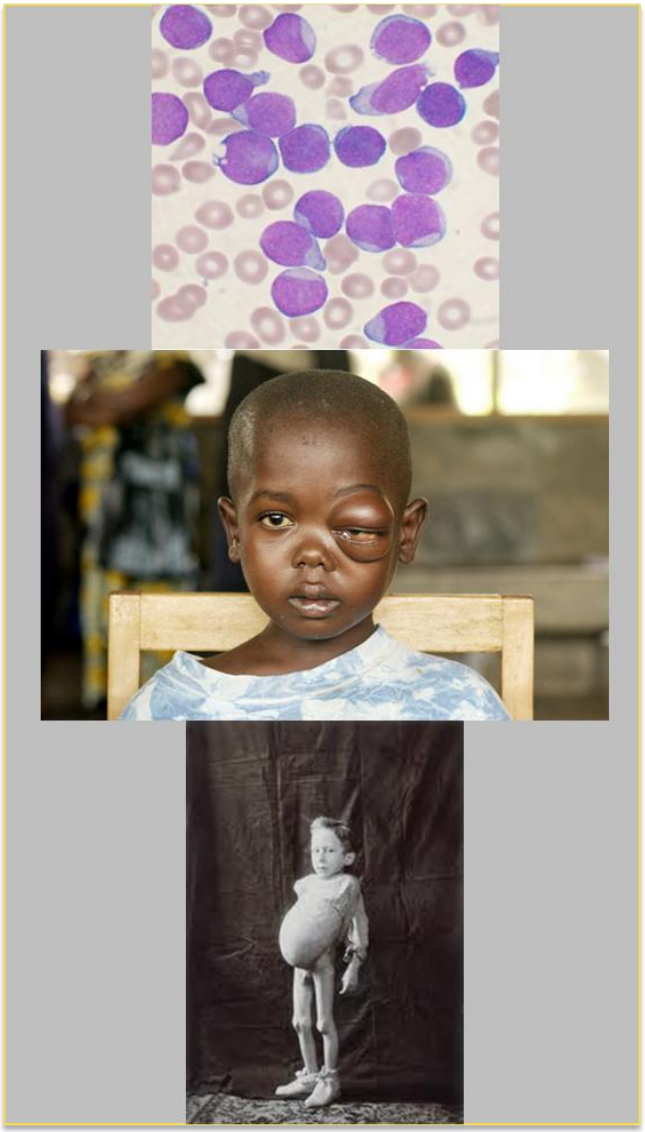
Childhood cancer: The beginning of a modern medical success story





Courtesy: John Maris

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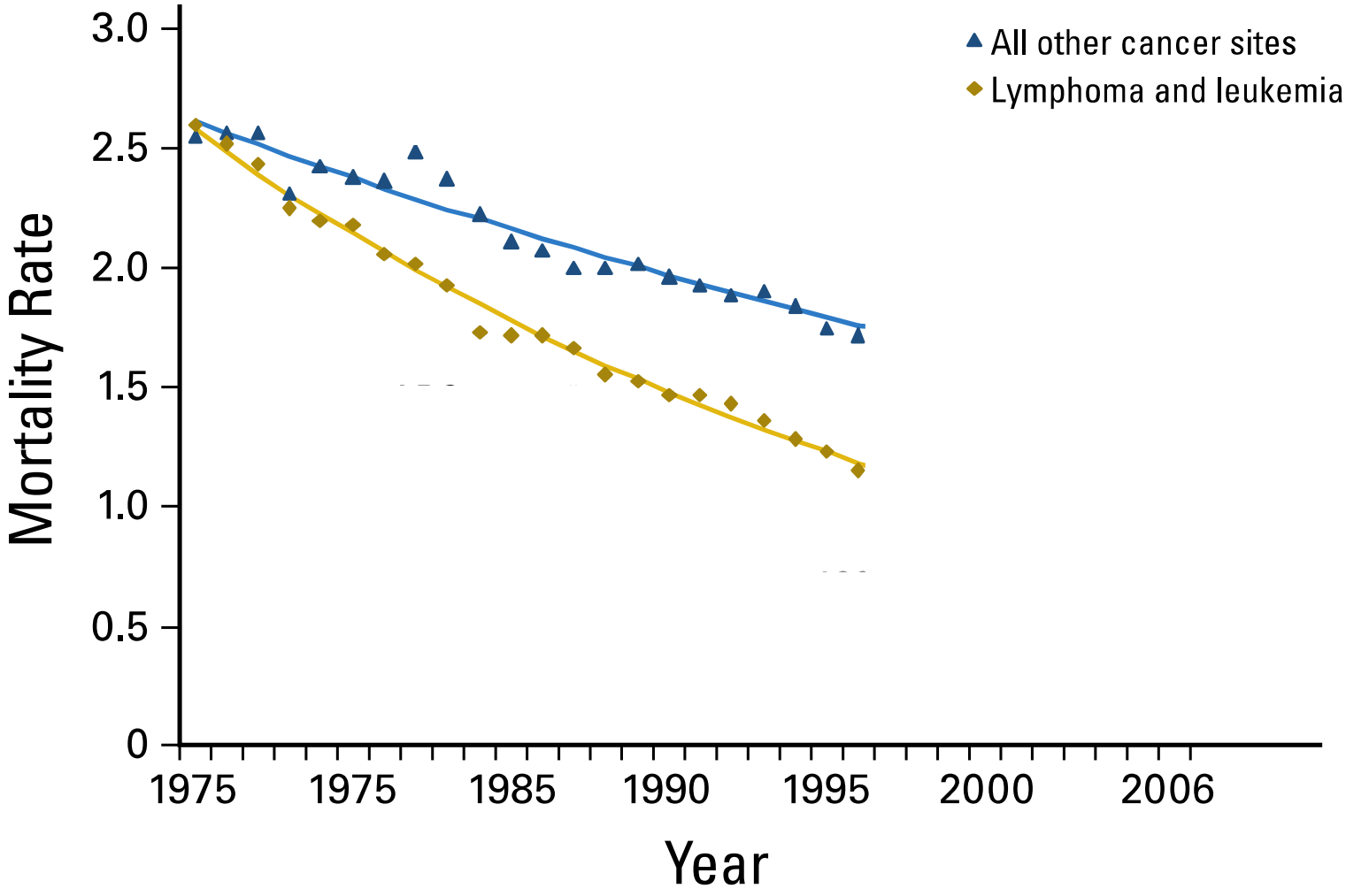
Success rate attributed to careful NCI funded empirical (observational) clinical efficacy trials



Courtesy: Malcolm Smith

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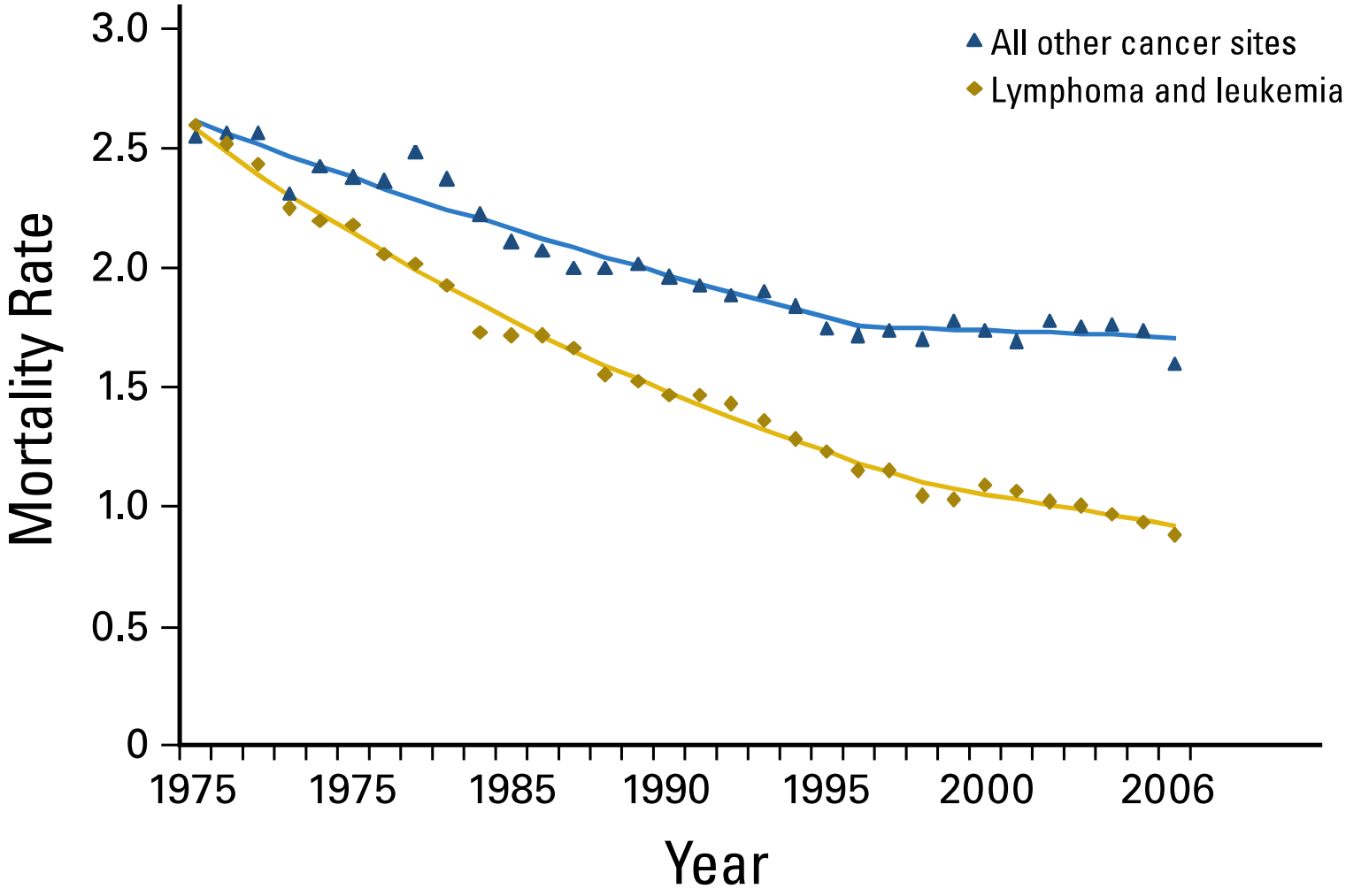
However in the past 16 years no improvement in mortality rates despite increased intensity of treatment



Courtesy: Malcolm Smith

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NCI Center for Cancer Research (CCR):
Performing State-of-the-Art Translational Research

- CCR is home to approximately 250 principal investigators and clinicians working in intramural research at NCI
- Over 50 branches and laboratories, including the pediatric oncology branch (POB)
- The POB has 12 Clinical Programs, and 12 Scientific Programs – including the Oncogenomics Section:
  - **Leverage the power of genomics to improve outcomes for pediatric patients with cancer**
  - **Refractory solid tumors including Neuroblastoma and Rhabdomyosarcoma**
  - **Goals include identifying and validating new diagnostic and prognostic biomarkers and targets; public release of data to stimulate collaborative research; and technology development**
  - **Rapid translation to patients**

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NCI-Supported Childhood Cancer Research

- Children's Oncology Group (COG)
- COG Phase 1 / Pilot Consortium
- NCI Intramural Program – CCR –POB
- Pediatric Brain Tumor Consortium (PBTC)
- Childhood Cancer Survivorship Study (CCSS)
- The Therapeutically Applicable Research to Generate Effective Treatments (TARGET) Initiative
- The Pediatric Preclinical Testing Program (PPTP)
- Investigator-initiated research projects
- Other research

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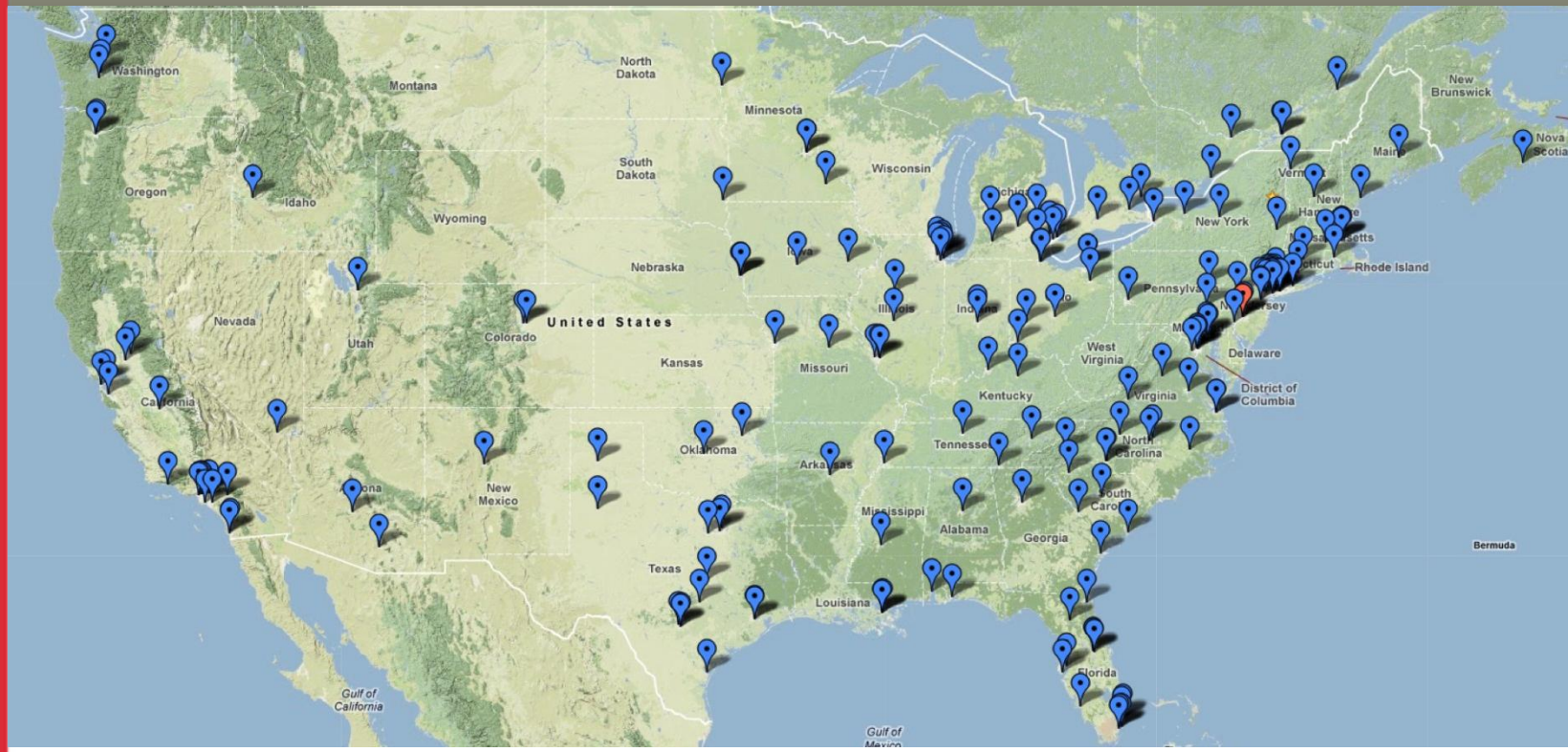
NCI supported Children's Oncology Group



- More than 200 translational clinical/research sites throughout United States
- 90% of children with cancer are treated at COG institutions
- International collaborations
- Ensures uniformity of treatment for children with cancer

Courtesy of Peter Adamson, COG

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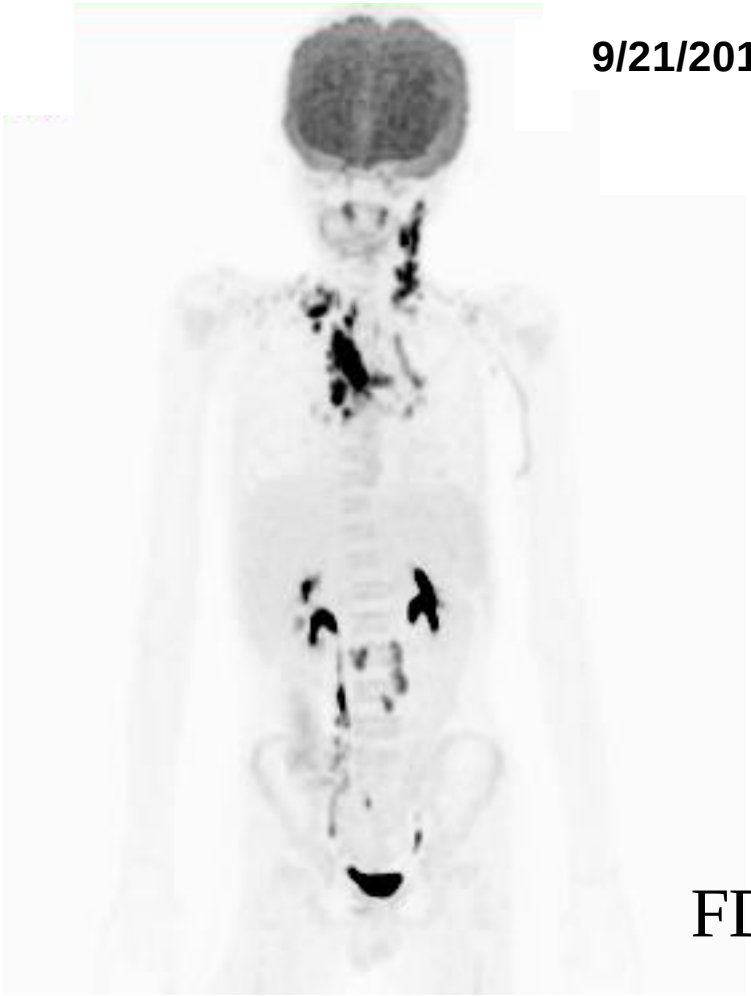
Other Research – Benefits Pediatric Cancer Research Examples:

- Forget cancer type. Think genes and pathways
- Example: lung, breast, or other cancers have recently discovered mutations that drive the cancer (including ALK, EGFR, BRAF, MEK, and HER2)
- Cancer cells are “addicted” to these driver mutations irrespective of the cancer type
- Use these findings to inform research, including potential treatment approaches, for pediatric and other cancers with the same drivers.
- Pediatric cancer example: Crizotinib used in lung cancers investigated for its use in neuroblastoma and anaplastic large-cell lymphoma with ALK mutations. *(Children’s Oncology Group Phase I/Pilot Consortium Trial, COG-ADVL0912/NCT00939770)*

Case History 1: 11 year old NPM-ALK positive ALCL, multiply relapsed after combination chemotherapy. Treated with crizotinib small molecule ALK-inhibitor

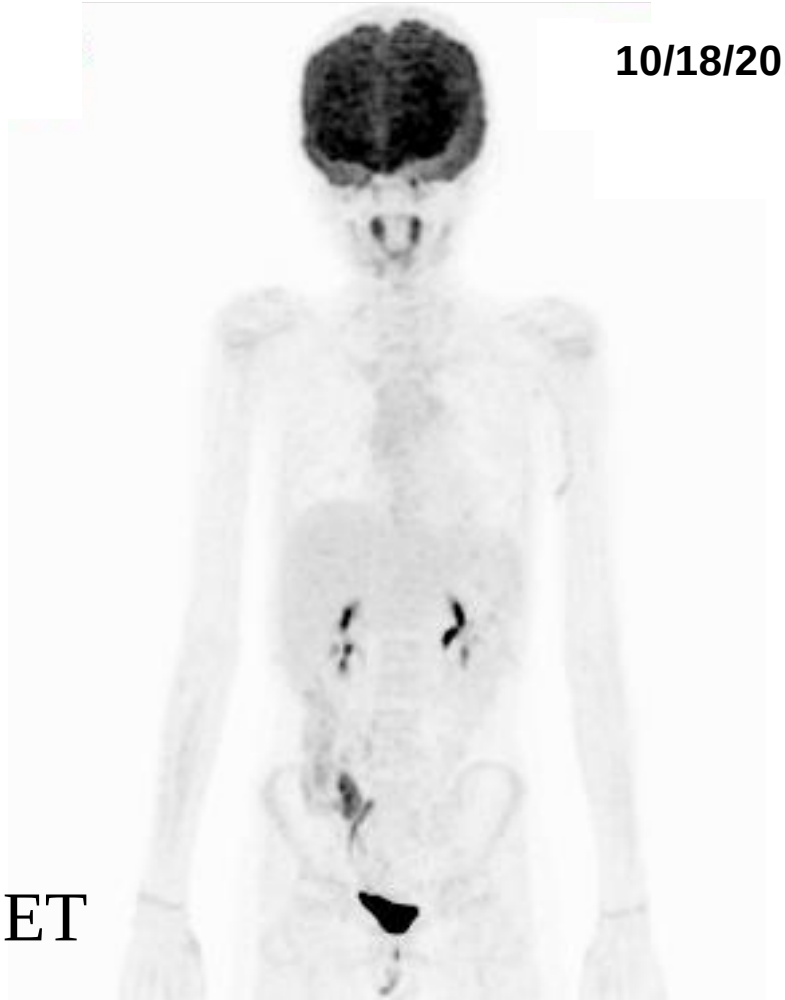
Pre-Cycle 1

9/21/2010



Post-Cycle 1 (CR)

10/18/2010



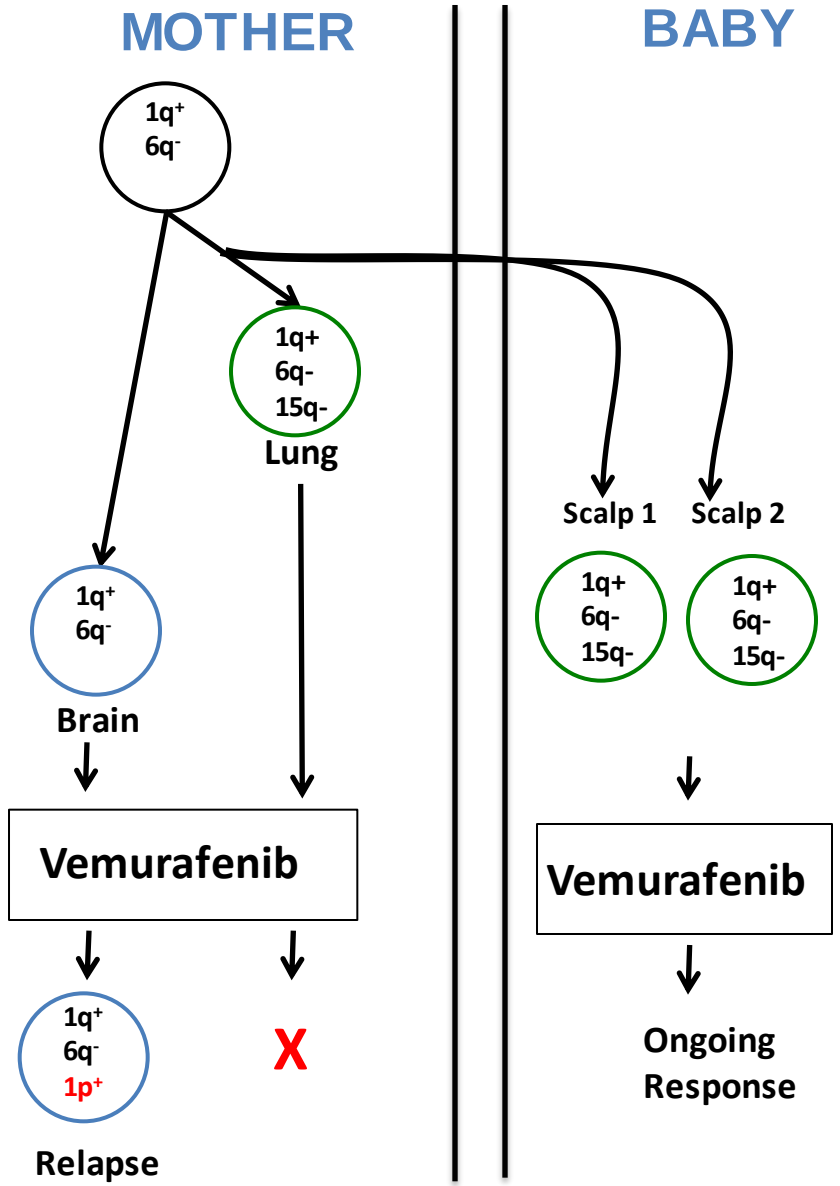
FDG-PET

Courtesy of Brigitte Widemann, MD, Alan S. Wayne, MD (POB)

Case History 2: Trans-Placental Transfer of Melanoma. Treated with Vemurafenib small molecule BRAF-inhibitor

Clinical History

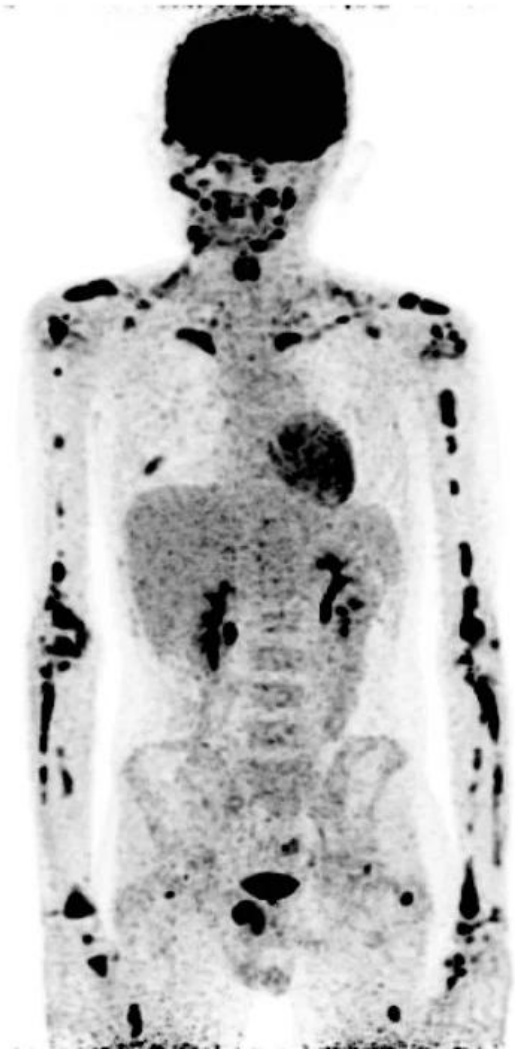
- During pregnancy mother develops metastatic melanoma with BRAF V600E mutation- declined therapy
- Within weeks of delivery the baby developed multiple skin lesions with BRAF V600E positive metastatic melanoma.
- Anti-BRAF V600E therapy (vemurafenib) treatment was initiated in mother after delivery.
- Baby was initiated on a modified vemurafenib protocol.
- Both mother and the baby demonstrated initial response to vemurafenib.
- While mother quickly relapsed and rapidly progressed the infant continues to respond.



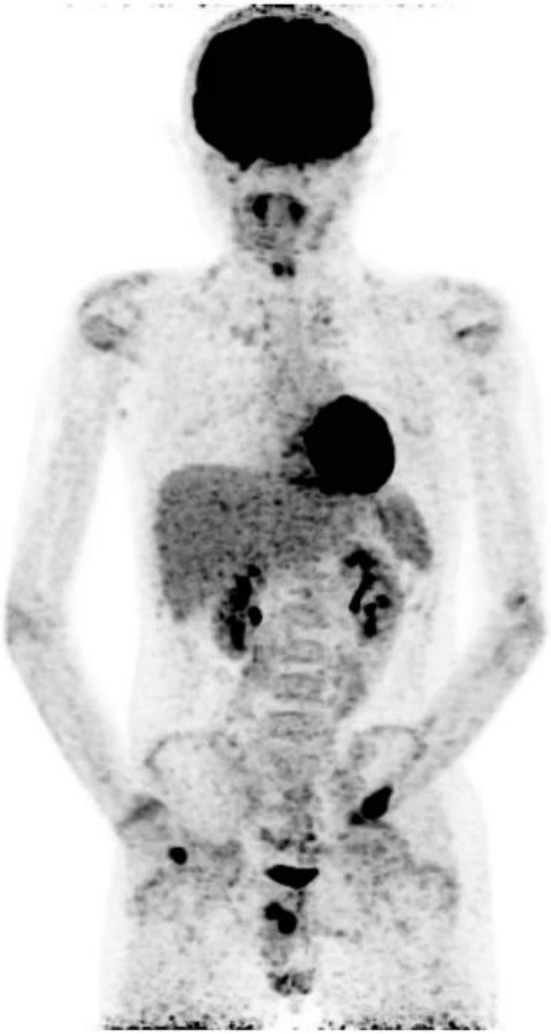
Courtesy Jeff Trent, TGen

Case History 3: 15yr male Post-Transplant "Lymphomatous" Relapse of ALL Treated with Anti-CD22 Immunotoxin Developed at the NCI

FDG-PET Scan



Pre



Cycle 2 Day 14

Courtesy of Alan S. Wayne, MD (POB)

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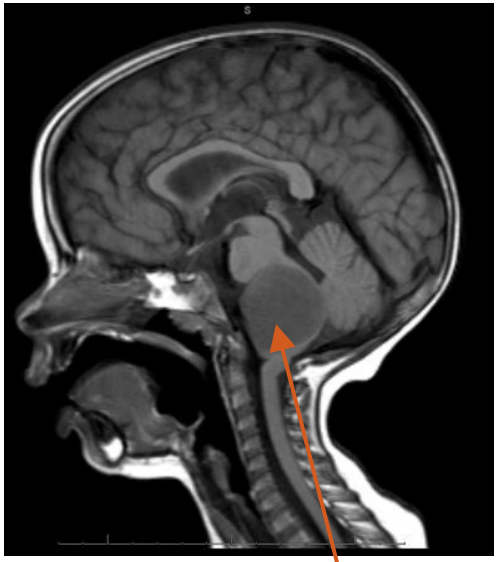
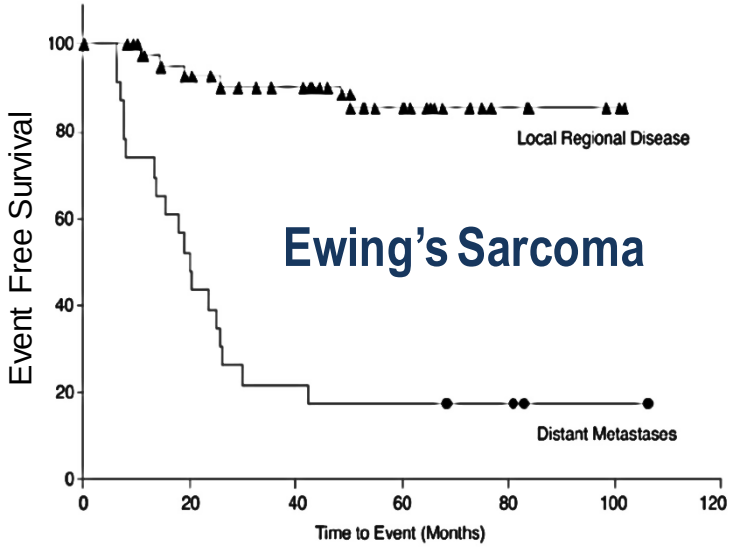
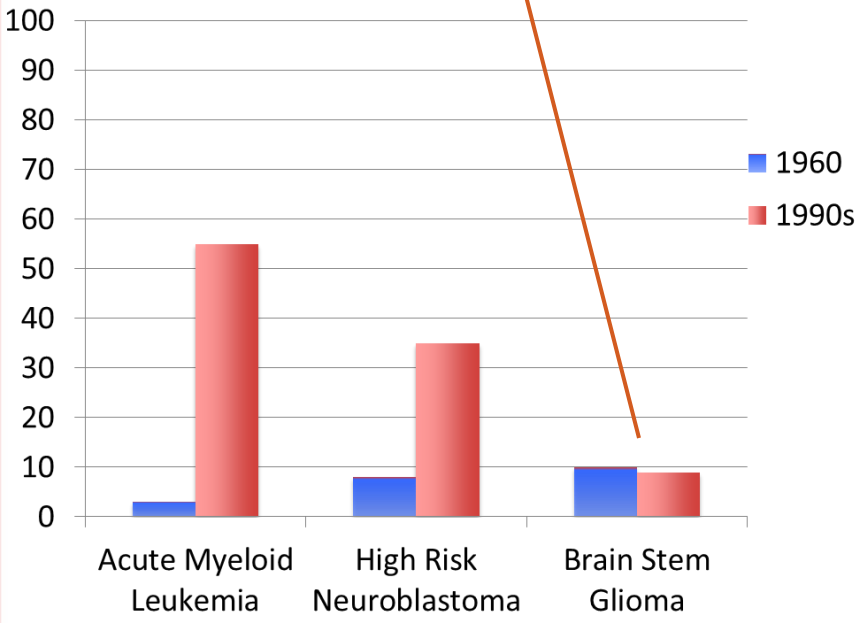
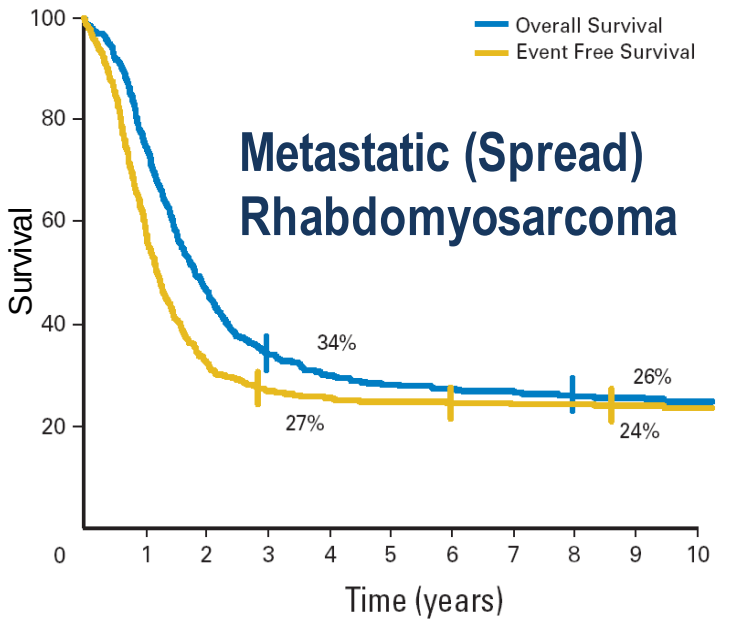
Certain cancers remain incurable- brain stem glioma
Cancer when spread remains incurable (<30% survive)









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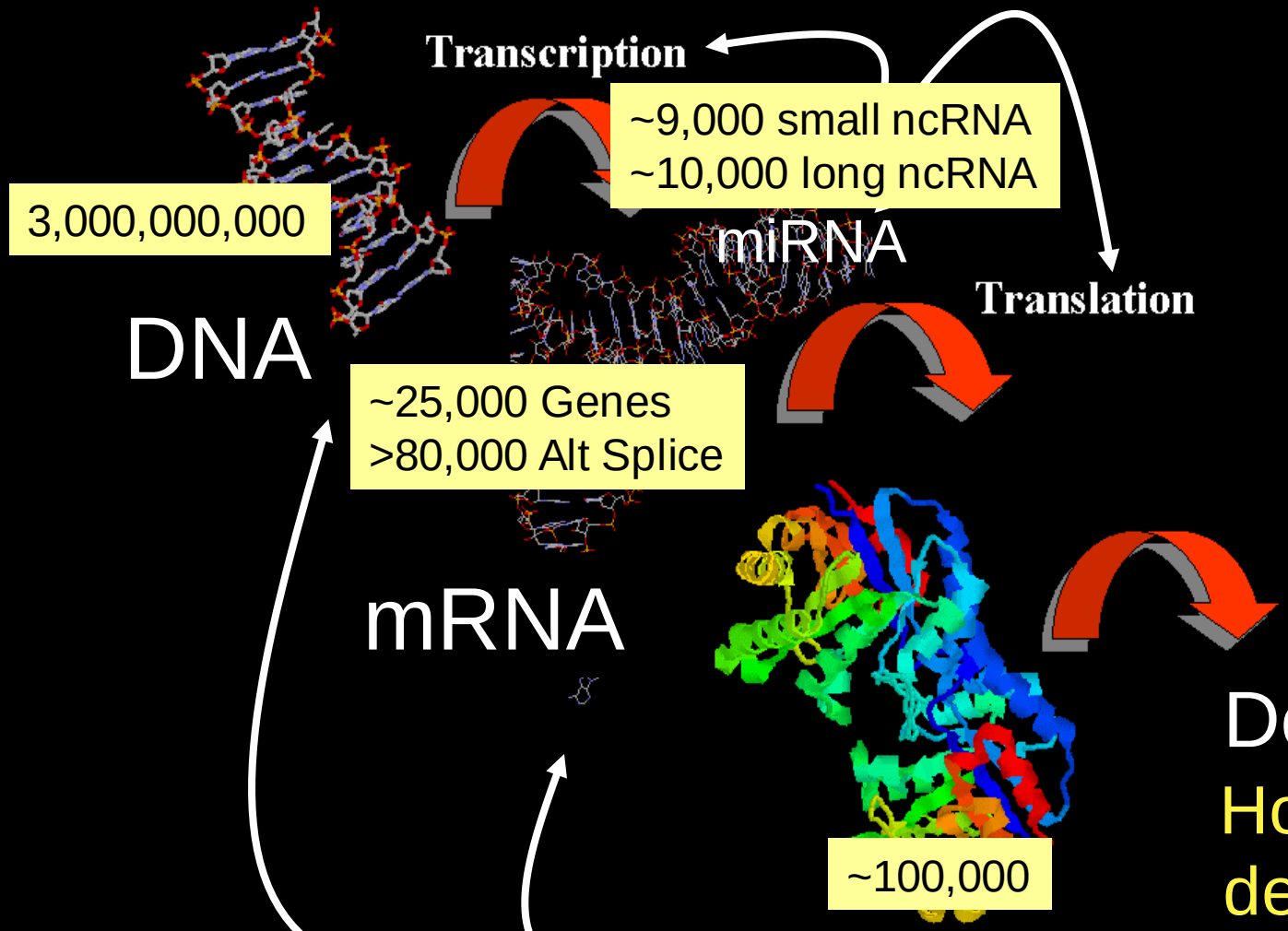
Challenges and Opportunities
Metastatic, Refractory and Recurrent Disease

- We have reached the maximally tolerated dosage for the majority of standard chemotherapeutic drugs
- “Cure at a cost” and spontaneous and fatal toxicities at high dosage
- Drugs not available, not being developed, or withdrawn; no efficacy in adult cancers but activity in pediatric cancers e.g. IGF1R-R1507
- We need to systematically interrogate the genome of incurable pediatric solid tumors to identify genes that confer poor behavior - we need to “know the enemy” to develop effective treatments
- Treatment decisions need to be based on knowledge of which genes or pathways are active in an individual cancer
- The NCI is ideally placed to spearhead and coordinate these efforts

Omics Study of All of the Genes and Proteins will Identify all the Changes that Drive the Cancer



Determines

How a cancer develops and behaves

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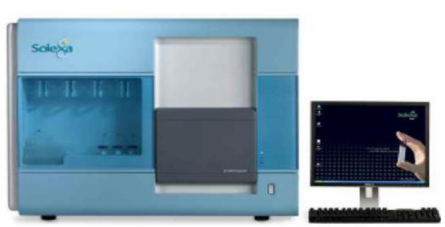
Next Generation Sequencing Technologies: Enabling rapid interrogation of the cancer genome to identify genes or pathways are active in an individual cancer

Roche / 454
Genome Sequencer FLX
Titanium



Illumina / GAII/HQ 2500
Whole Genome 48 hrs

PacBio RS
Ion Torrent

Life
Technologies
SOLiD v4

Life
Technologies
5500 XL

Life
Technologies
Ion Torrent

Life Technologies
Proton
1 Genome 2 hrs

Helicos
HeliScope

- Cost come down $3,000,000,000 to $6,000 per whole genome
- Time from 13 years to 2 days
- Projected $100 in less than 1 hour

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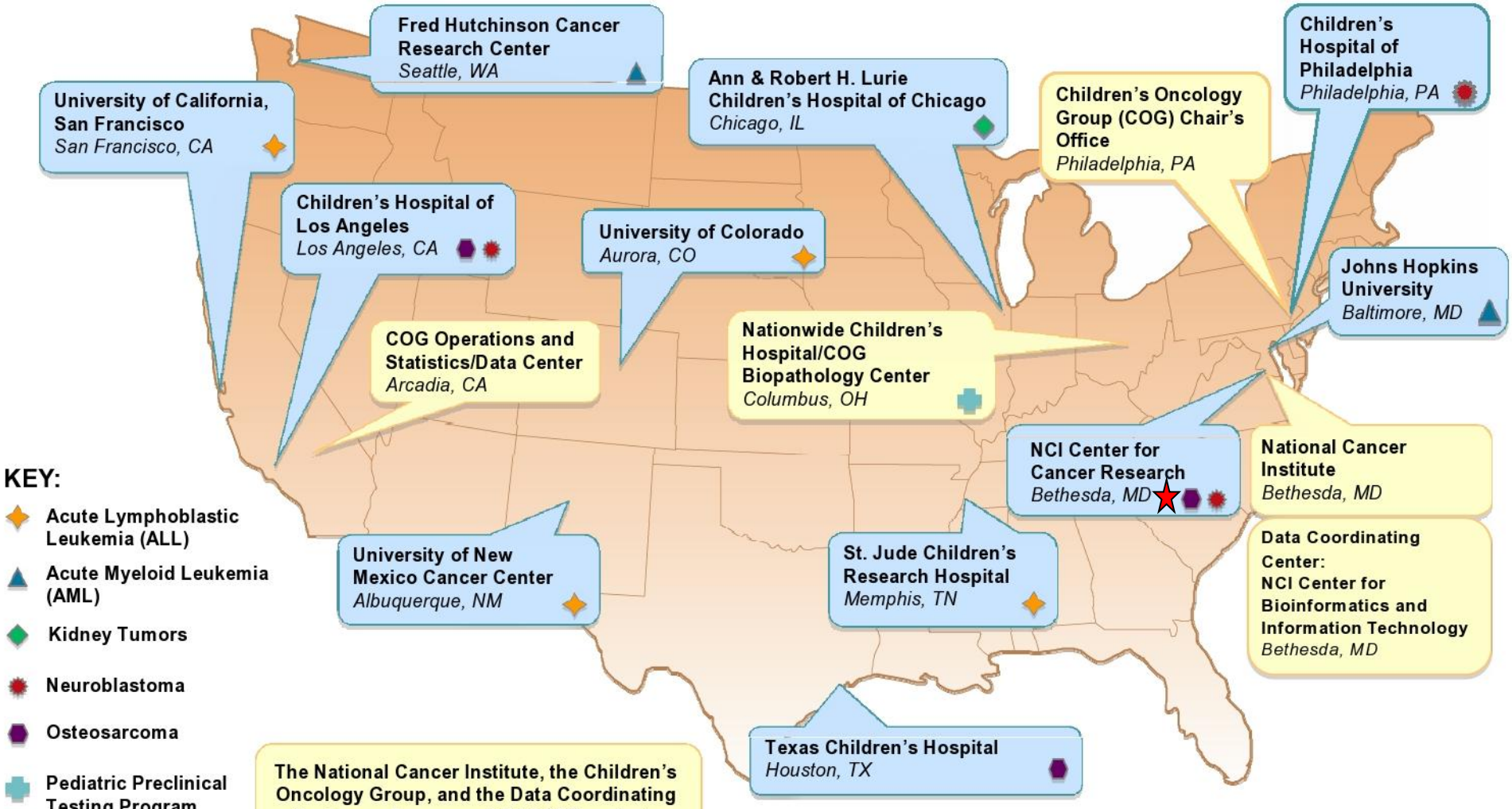
Applying this technology to childhood cancer research – NCI's TARGET Initiative

- Identify the molecular changes that drive childhood cancers
- Includes acute lymphoblastic leukemia (ALL), neuroblastoma , acute myeloid leukemia (AML), osteosarcoma, and Wilms tumor (kidney)
- TARGET Collaborators –NCI intramural and extramural programs; Children's Oncology Group (COG), including at NCI-designated Cancer Centers
- CCR-POB-COG Cancer Genomes- Rhabdomyosarcoma
- Complements other genomics research, such as the Pediatric Cancer Genome Project (at NCI-designated cancer centers St. Jude and Washington University), and The Cancer Genome Atlas (NCI and the National Human Genome Research Institute, National Institutes of Health)

TARGET and CCR-POB-COG Pediatric Cancer Genomes
6 Cancer Types, 11 Institutes



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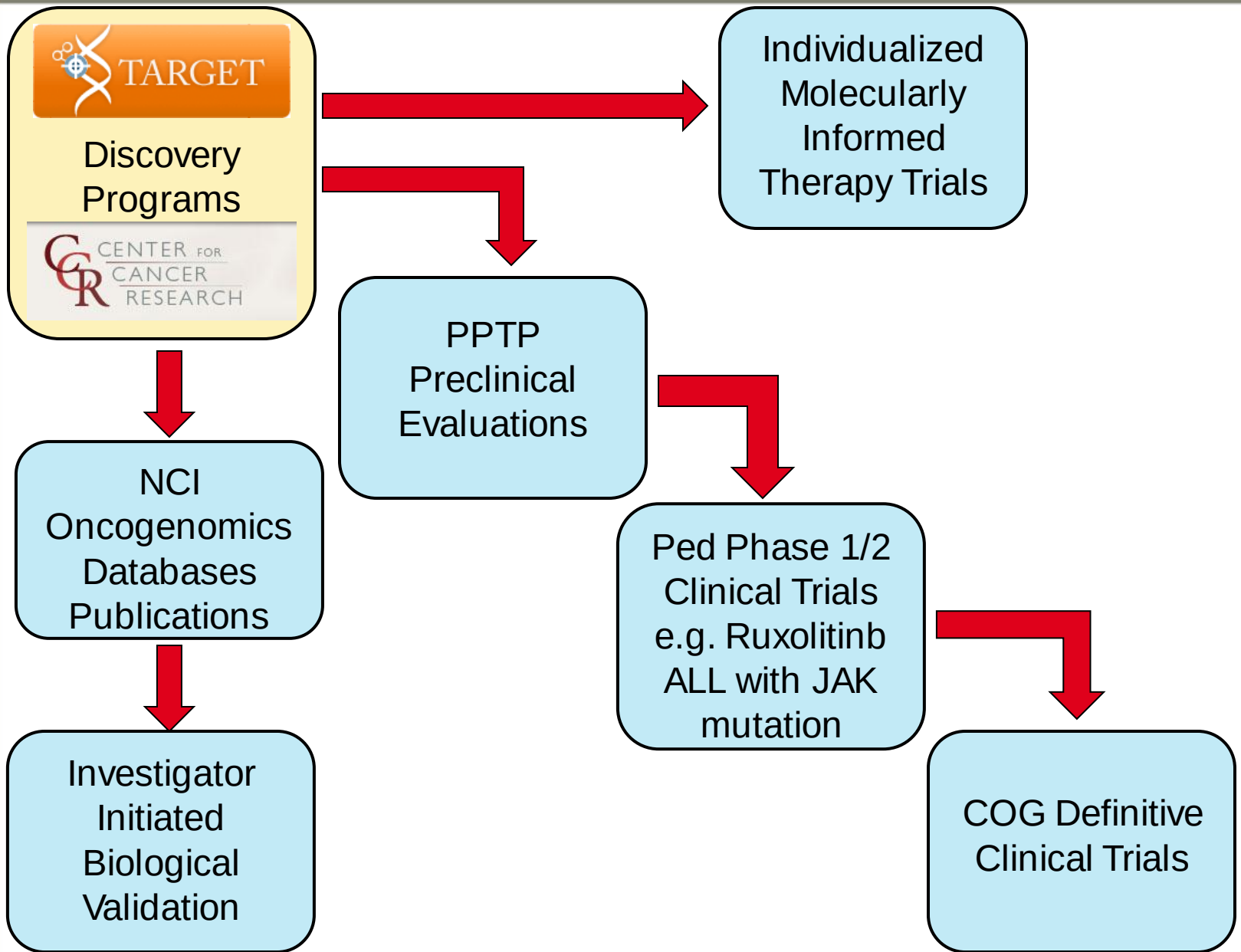
Strategy for Discovering Effective New Treatments for Children with Cancer



Current and Future Molecularly Informed Individualized Therapy Trials

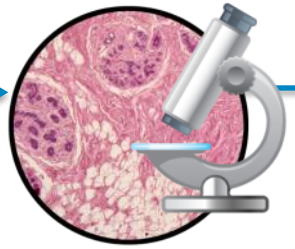
Delivering Precision Medicine for Refractory Pediatric Cancers

Collaboration NCI/Academia/Not-for-Profit/Charity/Industry

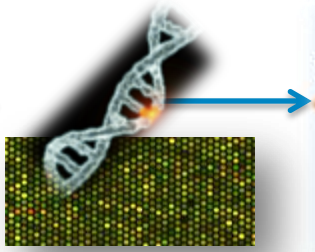
CCR/ COG/ TGen/ QuadW/ St. Baldrick's/ Intervention Insights/ Dell

14 days for individualized treatment

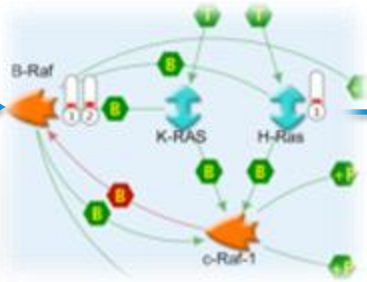
Patient / Physician diagnosis, treatment, ongoing management



Tumor Sample



Complete molecular characterization of the diseased tumor



Analytical tool for mapping patient data against database for recommended treatment

Integration of scientific & clinical evidence for future research

Courtesy: Jeff Trent TGen and Dell

Genomics Enabling Individualized Therapy-The Future for Pediatric Trials