U.S. FOOD & DRUG ADMINISTRATION

Cancer Drug Development and Access to Precision Medicine for Children with Cancer

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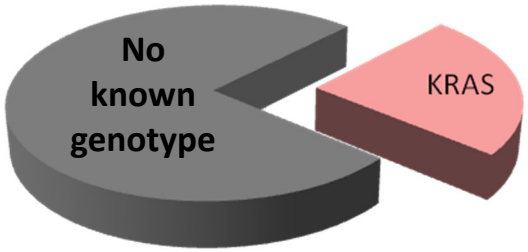
Cancer Drug Development for Children and Adolescents

- Well recognized, long-standing challenges- biologic, societal, economic
- **Widely leverages adult drug discovery/development- limited opportunities for extrapolation and limited pre-clinical testing in pediatric models**
- **Impact of legislative initiatives which support pediatric drug development has been markedly less obvious in Oncology than in other clinical areas.**
- Accepted off label use as part of standard of care and clinical research- delayed pediatric evaluations
- Improved outcomes **resulting from collaborative research** for children with cancer lead to misperception of the unmet clinical need for new drugs.
- **Unique practice model- integration of clinical research and management provides obvious opportunity to facilitate drug development**.
- **Lag in evolution of cancer drug development paradigm in pediatrics**

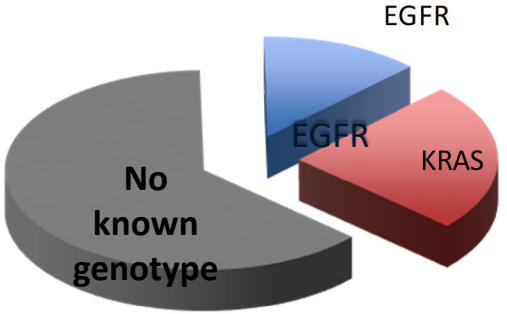
Evolving Landscape of Oncology Drug Development

- Evolutionary Paradigm shift: Human genome (2003) – wide-spread availability of NGS
- Genomic and proteomic interrogation of individual cancers screened for specific molecular abnormalities for which “highly specific” targeted agents are developed
- Resulted in the creation of multiple rare subsets(defined by molecular phenotype) of previously common cancers and reconsideration of taxonomy
- Transformative: NSCLC, Melanoma, Myeloma, AML
- Tissue/histology agnostic development

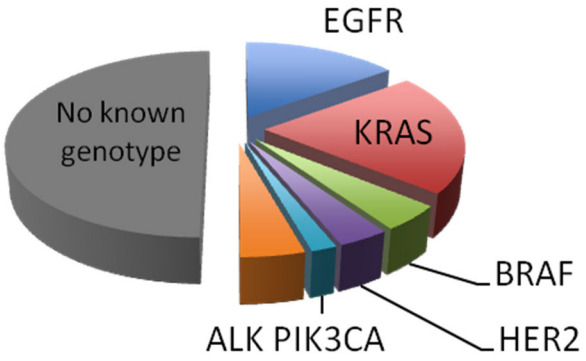
Evolution of Identification of Genomic Alterations in Lung Adenocarcinoma



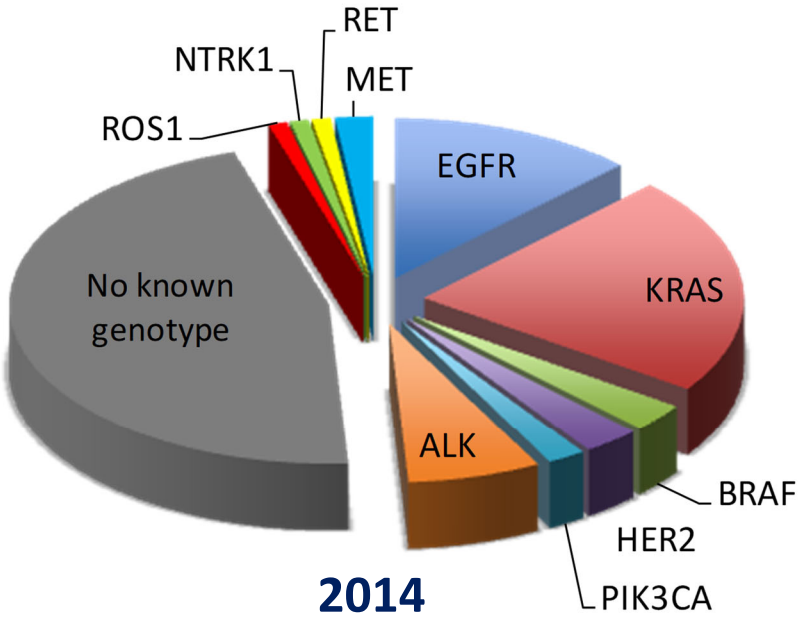
1984 - 2003



2004



2009



2014

Precision Medicine and Oncology Drug Development

- Precision oncology requires novel study platforms for evaluating new targeted therapies
  - Multiple new targeted agents (including same in class)
  - Platform studies: Master Protocols
  - Combinations
  - Standard control arms
  - Centralized biomarker platforms
  - Efficiency in setting of small populations (rare subsets)
  - **Expansion cohorts including adolescents and children**
- Precision cancer medicine: **targeted therapy** selection by identifying **key gene variants.**

Adaptive Designs (Frequentist or Bayesian

- Allows for planned design modifications
- Modifications based on data accrued in the trial up to the interim time
- Un-blinded or blinded interim results
- Control probability of false positive rate for multiple options
- Control operational bias
- Assumes independent increments of information

Characteristics of an Ideal Master Protocol

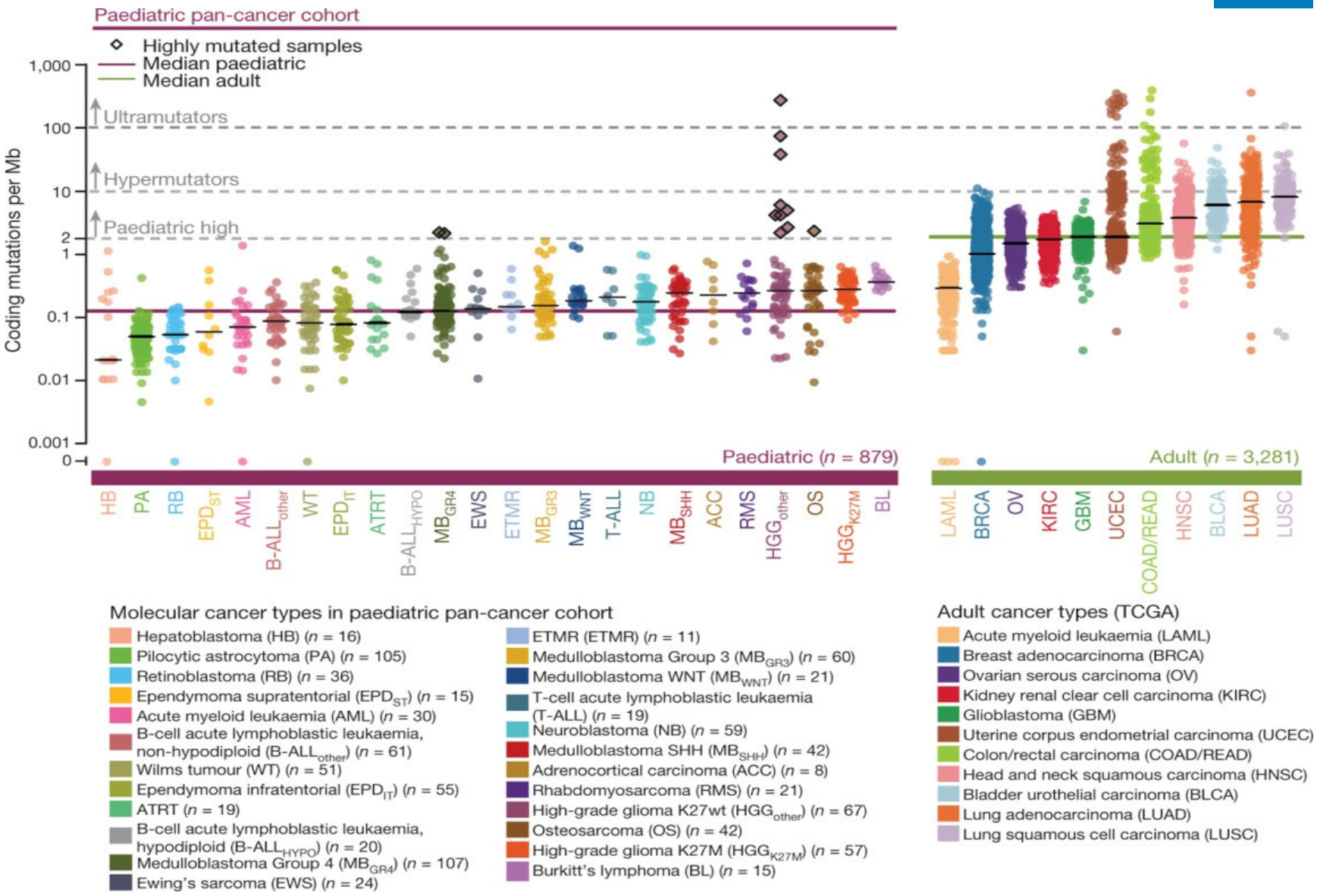
- Central governance structure
- Central IRB
- Central DSMC
- Central Independent Review Committee
- Central repository of data and specimens

- Study multiple drugs
  - Targeting more than one marker/tumor
  - More than one drug for one marker/tumor
- Study multiple markers
  - Overlapping expression of markers
- Leverage common control group (s)
- Flexibility to add/remove agents (Adaptive)

Opportunities for Pediatrics

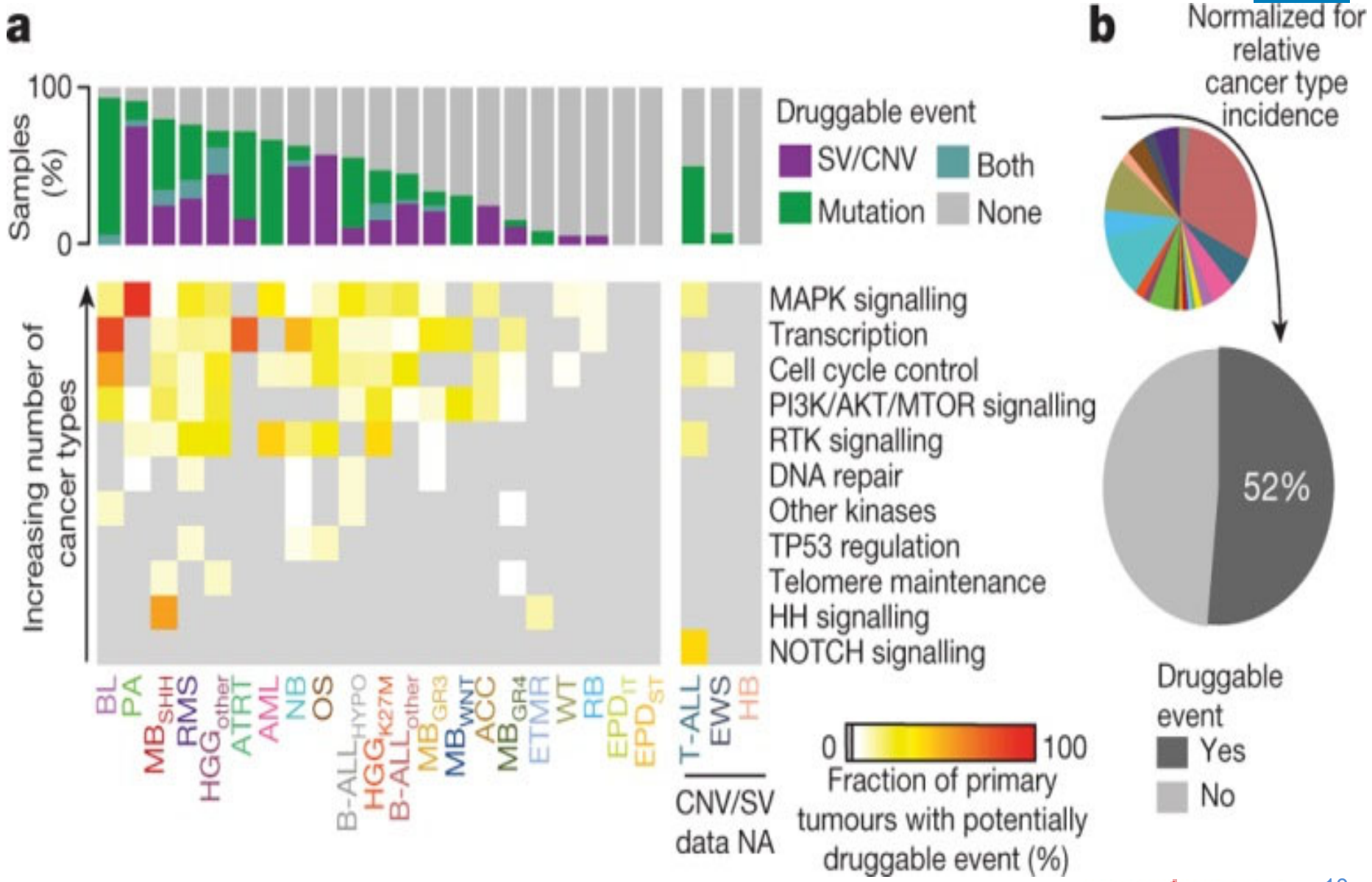
- Embryonal **solid tumors** with low mutation frequency
- Genetic and epigenetic evidence base for driver gene mutations differ between adult and pediatric cancers
- Multiple demonstrations of actionable gene aberrations in pediatric tumors provide suggest that inhibition of the same molecular targets may result in vulnerability of select childhood cancers
- Insufficient/delayed development opportunities for children require a paradigm shift in approaches to **early pediatric evaluation of potentially promising new agents**
- Paradigm shift necessitates amendment to current legislation to accelerate timelines.

Somatic mutations in the pediatric pan-cancer cohort



S N Gröbner *et al. Nature* **555**, 321–327 (2018) doi:10.1038/nature25480

Potentially druggable events in pediatric cancers



S N Gröbner *et al. Nature* **555**, 321–327 (2018) doi:10.1038/nature25480

U.S. Legislation and Pediatric Drug Development

PREA

- Drugs and biologics
- **Mandatory** studies
- Requires studies **only on indication(s) under review**
- **Orphan indications exempt** from studies
- Pediatric studies must be labeled

BPCA

- Drugs and biologics
- **Voluntary** studies with incentive
- Studies relate to entire moiety and **may expand indications**
- Studies may be requested for orphan indications
- Pediatric studies must be labeled

RACE for Children Act: Changing the Paradigm

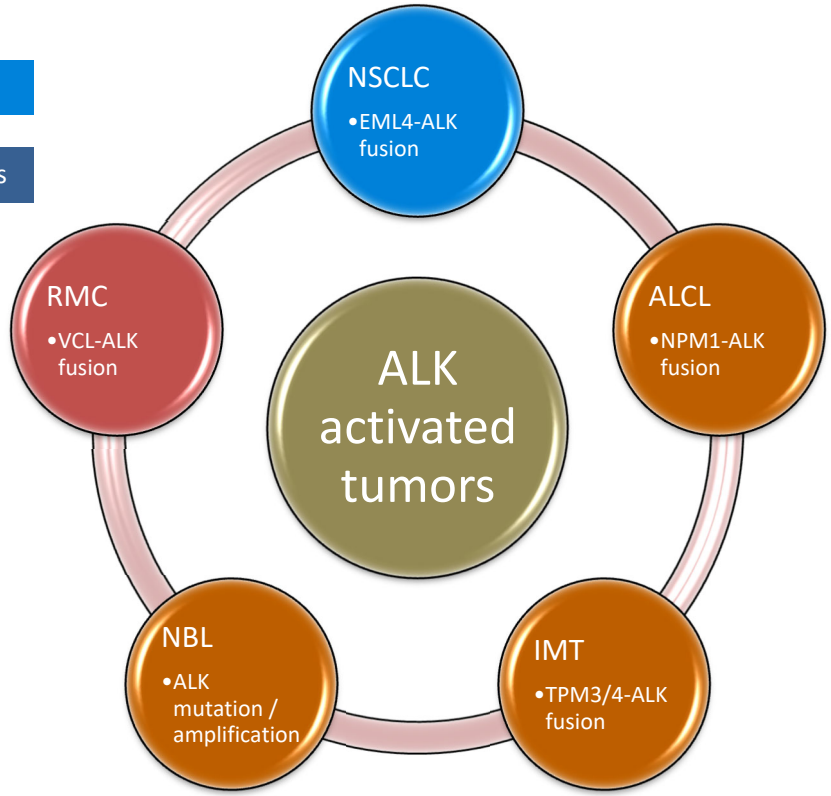
- Incorporated as Title V Sec. 504 of the **FDA Reauthorization Act (FDARA),** enacted August 18, 2017
- **Requires** evaluation of new molecularly targeted drugs and biologics "intended for the treatment of adult cancers and directed at a **molecular target** substantially relevant to the growth or progression of a pediatric cancer."
- Amends PREA: requirement for pediatric assessment based on MoA rather than clinical indication.
- **Molecularly targeted pediatric cancer investigation**: dosing, safety and **preliminary** efficacy to inform potential pediatric labeling."
- Elimination of **orphan exemption for pediatric studies** for cancer drugs directed at relevant molecular targets.

Pediatric Tumors are Different

…but not always

Adult tumor types

Pediatric tumor types



Children do not get NSCLC, but some pediatric tumors have ALK activation → targetability with ALK inhibitors?

NSCLC: non small cell lung cancer
RMC: renal medullary cancer
NBL: neuroblastoma
IMT: inflammatory myofibroblastic tumor
ALCL: anaplastic large cell lymphoma

Mano, AACR Cancer Discovery June, 2012,

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The Future

- Full implementation of FDARA Sec. 504- August, 2020
- Expansion of pediatric pre-clinical testing in progress
- Prioritization of which new targeted agents for pediatric assessment by Industry and academic investigator community
- Global coordination and collaboration