NCI Director's Report

Norman E. Sharpless, M.D.

March 20, 2018

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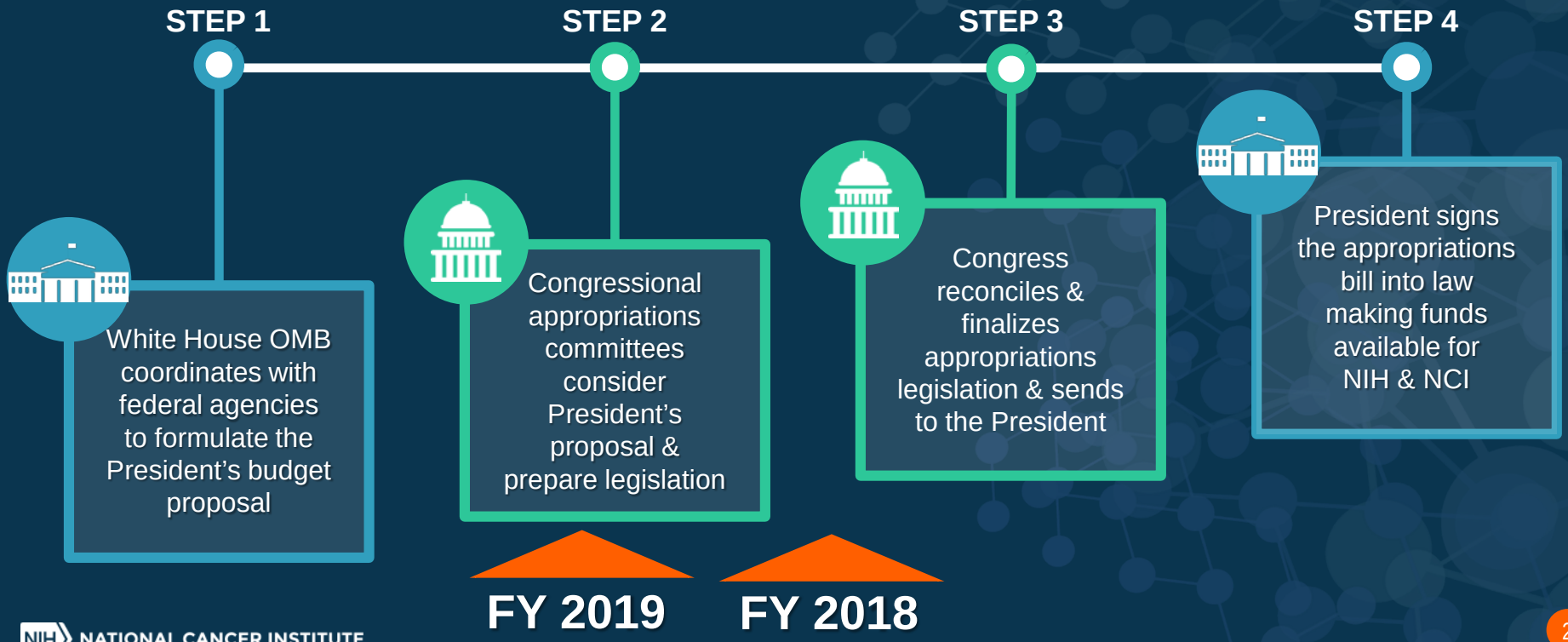
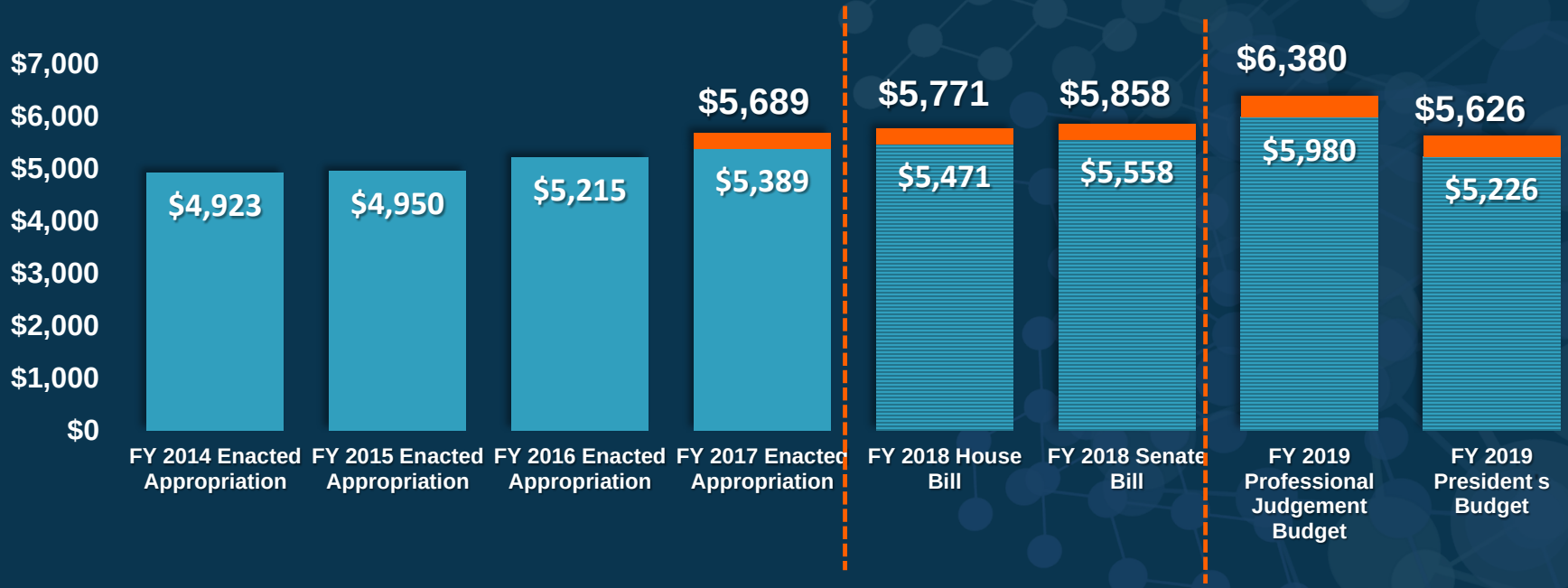
Appropriations Outlook



NCI Appropriations FY 2014-2019 (in millions)



Source: NCI Office of Budget and Finance

RPG Pool Trends

	FY2013	FY2014	FY2015	FY2016	FY2017
Number of R01 Applications	4003	3847	4550	4758	5263
Number of R01 Awards	582	578	623	650	650
Success rate (%)	15%	15%	14%	14%	12%
Non-competing support (%)	94%	97%	100%	100%	100%
Total RPG ($B)	1.854	1.858	1.927	1.967	2.070

Intergovernmental Affairs

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Collaborating with FDA and CMS

Scott Gottlieb
Commissioner of FDA

- Oncology Center of Excellence
- Joint Training
- Data Sharing
- Compliance advice on cell manufacture

Seema Verma
Director, CMS

- Help with NGS coverage decision
- Data Sharing
- Discussions over enhanced coverage of clinical trials

Collaborating with DoD and VA

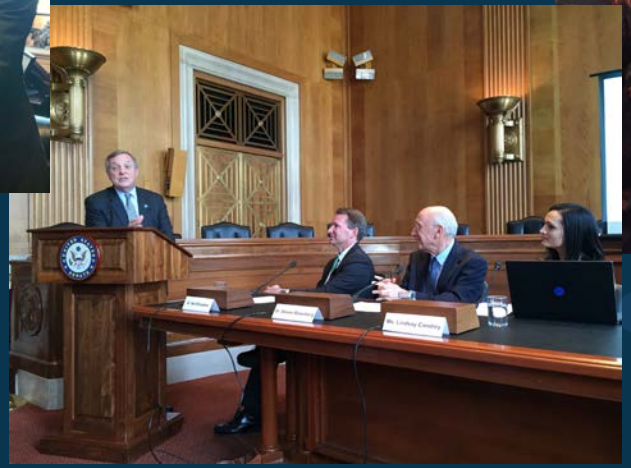
Interactions with HHS

Alex M. Azar II
Secretary, HHS

Eric D. Hargan
Deputy Secretary, HHS

Admiral Brett P. Giroir, M.D.
Assistant Secretary for Health

Congressional Outreach



President's Cancer Panel Report
March 2018

Updates

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Early Stage Investigators

Method to Extend Research in Time

R37 Award

NCI recognizes that Early Stage Investigators (ESI) face challenges.

In addition to increased ESI payline, NCI is announcing its new use of the MERIT Award in 2018.

The award gives eligible investigators applying for first R01 the opportunity to obtain up to seven years of grant funding (5+2)

This will provide critical time for ESIs to launch their careers and become more established before attempting renewal.

Global Health Working Group

Global Health

- Deborah Bruner, RN, PhD
  Emory University
- Satish Gopal, MD
  UNC Chapel Hill

Sample questions

1. Balance of functions for CGH (representational vs. research)?
2. Portfolio analysis?
3. How to set priorities for NCI given the tremendous international burden of cancer?

SBIR / STTR Working Group

SBIR / STTR

- Elizabeth Jaffee, MD
  Johns Hopkins University
- Mel Billingsley, PhD
  Pennsylvania State University

Sample questions

1. Are award sizes for the different phases of funding for SBIR/STTR appropriate?
2. How to improve review?
3. What resources in addition to funding should SBIR provide?
4. How to speed delivery of funds to small companies?

Informatics Working Group

Informatics

- Mia Levy, MD
  Vanderbilt University
- Charles Sawyers, MD
  Memorial Sloan Kettering Cancer Center

- Provide input into the role of the CBIIT director, focusing particularly on whether the duties of a chief information officer should be separate
- Advise on expanding funding opportunities for data science and bioinformatics research across the NCI research portfolio and building a cancer-focused data science and bioinformatics workforce
- Provide guidance for improving data sharing to maximize the impact of cancer research on patients

Cancer Moonshot

April 2017

Cancer Moonshot Implementation Teams Developed Scientific Proposals

May 2017

NCI Scientific Program Leaders reviewed and recommended

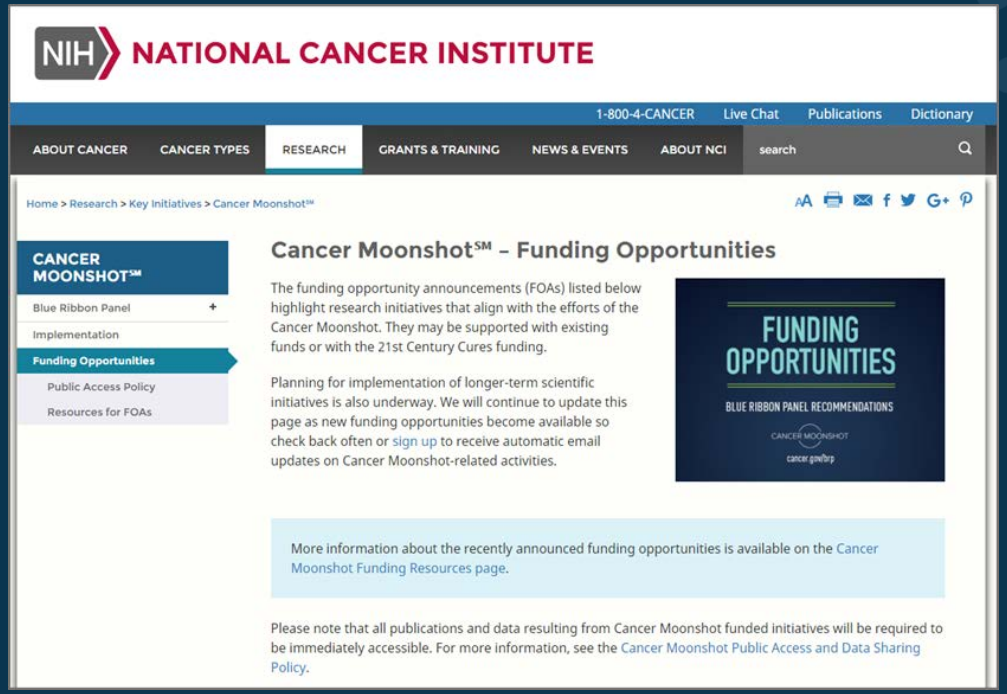
June 2017

NCI Board of Scientific Advisors reviewed and recommended

Oct 2017
ongoing

FY 2018 FOAs Released

Cancer Moonshot FOAs



- Close to **50** Funding Opportunity Announcements to date and more to come
- **6** intramural initiatives
- Requirements related to data sharing and health disparities/ underserved populations

Partnership for Accelerating Cancer Therapies (PACT)

National Cancer Institute - Division of Cancer Treatment & Diagnosis

Cancer Immune Monitoring Analysis Centers (CIMACs)

- Dana-Farber
- Stanford
- Mount Sinai
- MD Anderson

Cancer Immunologic Data Commons (CIDC)

- Dana-Farber Cancer Institute

- AbbVie
- Amgen
- Boehringer Ingelheim
- BMS
- Celgene
- Genentech
- Gilead
- GSK
- Janssen
- Novartis
- Pfizer
- Sanofi

Two New Immunotherapy Networks

ADULT CANCERS

Immuno-Oncology Translational Network

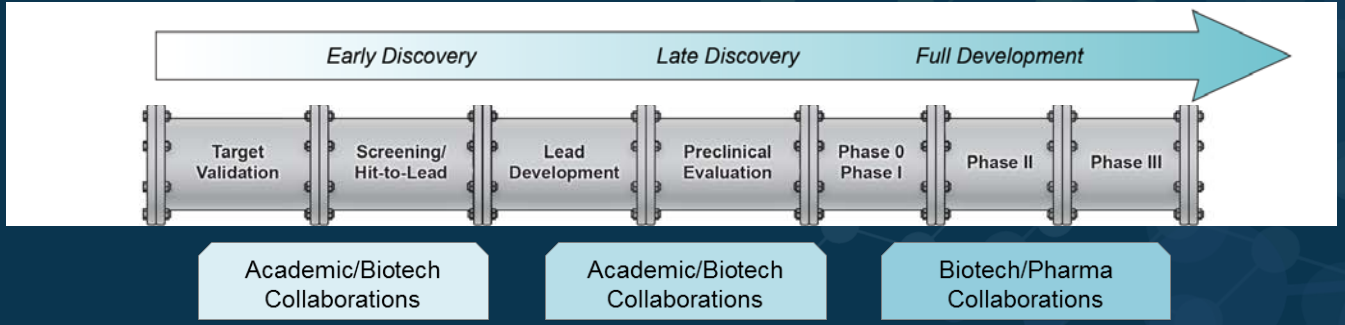
(IOTN, U01)

PEDIATRIC CANCERS

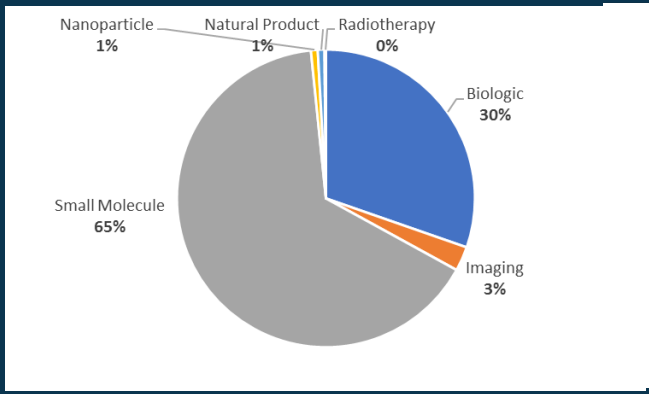
Pediatric Immunotherapy Discovery and Development Network

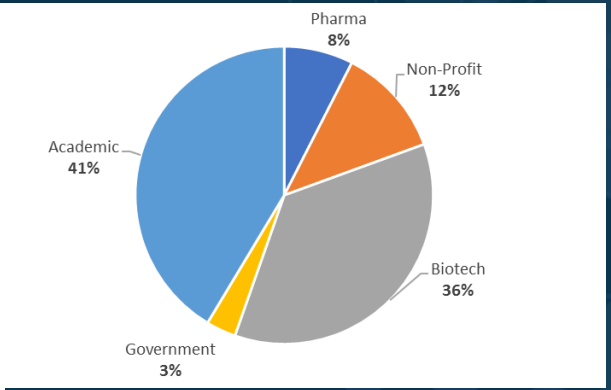
(PIDDN, U54)

NCI Experimental Therapeutics (NExT) Pipeline



Projects enter the pipeline on a competitive basis at any stage of the pipeline
Since inception in 2009 NExT has received over 650 applications





NExT Pipeline

Artemis Endonuclease inhibitor
AAA ATPase p97 inhibitor
Taspase1 inhibitor
WDR5-MLL1 inhibitor
LDHA inhibitor
SHP2 inhibitor
PHGDH inhibitor

MCL1 Inhibitor
Mutant IDH1 inhibitor

DNMT1 Inhibitors (TdCyd)
11-1F4 mAb Amyloidosis
Endoxifen
Mer Kinase Inhibitors
NIR Fluorophore
EGFR Panitumumab
LUM015

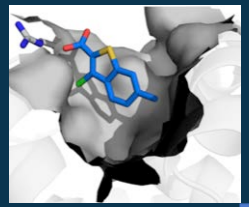
Target Validation
Exploratory Screen Development
Screening/Hit-to-Lead
Lead Development

Candidate Selection

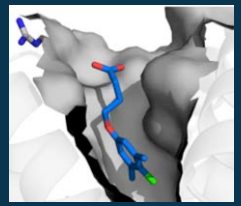
Clinical Trials
Phase 0
Phase 1
Phase 2
Phase 3

Mcl-1 Inhibitor Discovery by Fragment-Based Methods & Structure-Based Design

Hit to Lead | **Lead Optimization** | ***In vivo* Optimization**

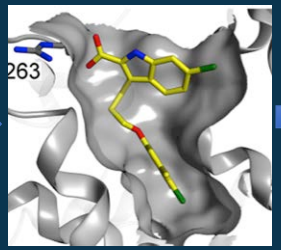


K_i 131 µM



K_i 60 µM

Fragment hits



Mcl 1 K_i 55 nM

Structure guided fragment merging

> 200,000x improvement in affinity for target

Mcl 1 K_i 23 nM

Binding interface Expansion

Mcl 1 K_i 0.39 nM
H929 GI_{50} = 1.2 µM

Structure guided Tethering

Mcl 1 K_i <0.3 nM
H929 GI_{50} = <0.3 µM

Med. Chem. Optimization

Likely candidate profile

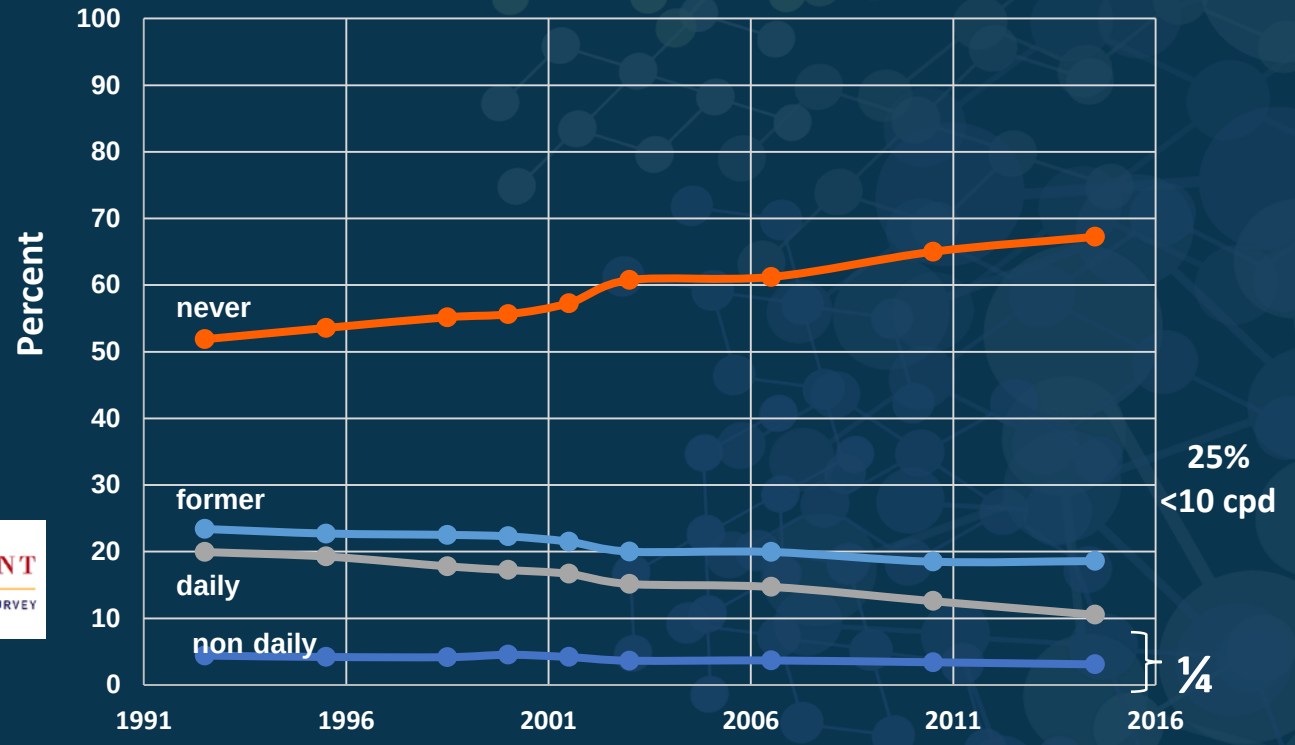
- ✓ K_i < 0.3 nM to Mcl-1
- ✓ Cellular IC_{50} < 100 nM
- ✓ Oral bioavailability
- ✓ Robust pharmacodynamic response

Current work focused on identification of clinical candidate by profiling compounds for *in vivo* efficacy and therapeutic window.

Leads feature

- K_i < 0.3 nM to Mcl-1
- IC_{50} < 300 nM in multiple cancer cell-lines
- Target-based on-mechanism activity (Caspase activation, JC-1/BH3 profiling, co-IP, multiplex PD apoptosis assays)
- Good PK properties

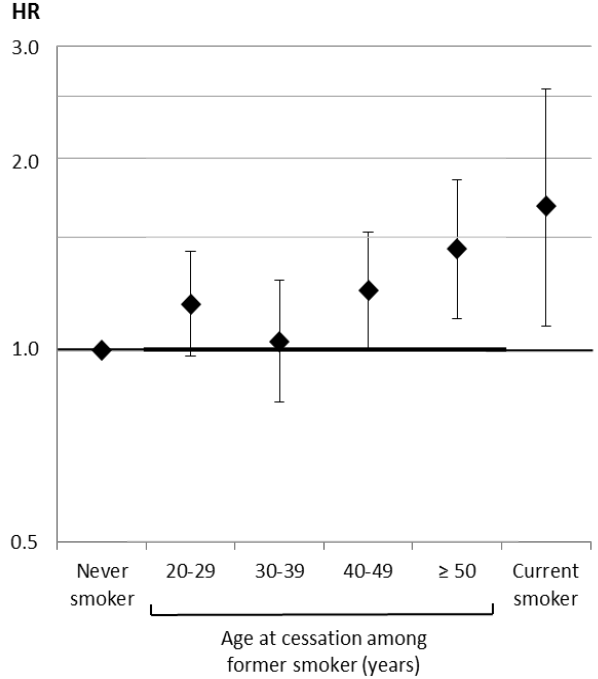
Cigarette use in the United States



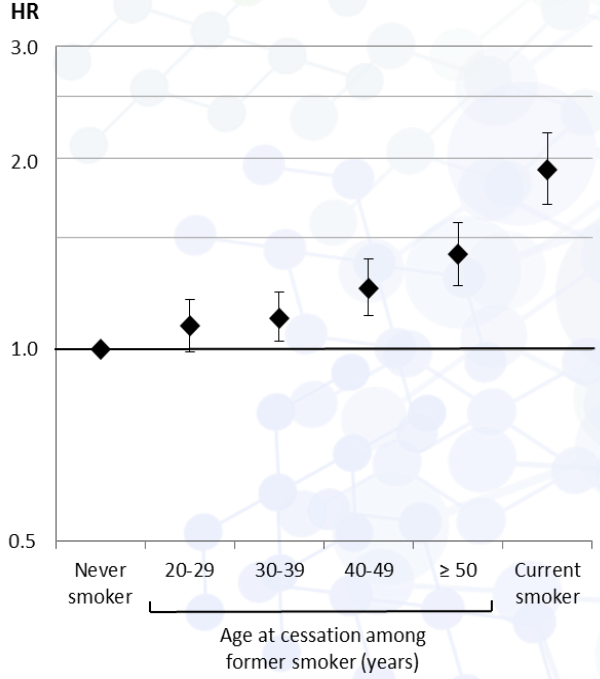
TOBACCO USE SUPPLEMENT
CURRENT POPULATION SURVEY

Lifelong consistent low-intensity smokers had increased risk of mortality vs. never-smokers

Consistent smokers of <1 CPD



Consistent smokers of 1-10 CPD



Inoue Choi et al, *JAMA Internal Medicine*, 2017

Rural Cancer Control Update

BACKGROUND

- 14-19% of the US population lives in non-metropolitan (rural) counties
- Notable challenges, compared to urban areas:
  - Higher poverty
  - Lower educational attainment
  - Higher proportion of elderly individuals
  - Lower access to health services
  - Higher rates of behavioral risk factors (tobacco use, obesity)

Rural Cancer Control Update
Planning & Engagement Efforts

- Rural Cancer Control Workshop, Memphis, May 4-5, 2017
- HRSA/NCI/CDC Webinar, Aug 30, 2017
- Understanding Definitions of Rural/Rurality, Oct 27, 2017
- National Academy Workshop on Small Populations, Jan 18-19, 2018
- Rural Health Policy Institute, Feb 6-8, 2018
- National Rural Health Assoc. Annual Meeting, May 8-11, 2018

Save the Date

Accelerating Research in Rural Cancer Control

Conference

May 30-31, 2018

Natcher Conference Center
National Institutes of Health | Bethesda, Maryland

Program Committee Chair: Robin Vanderpool, University of Kentucky

https://cancercontrol.cancer.gov/research-emphasis/meetings/arcc-meeting.html.

NCI-MATCH

Molecular Analysis for Therapy Choice

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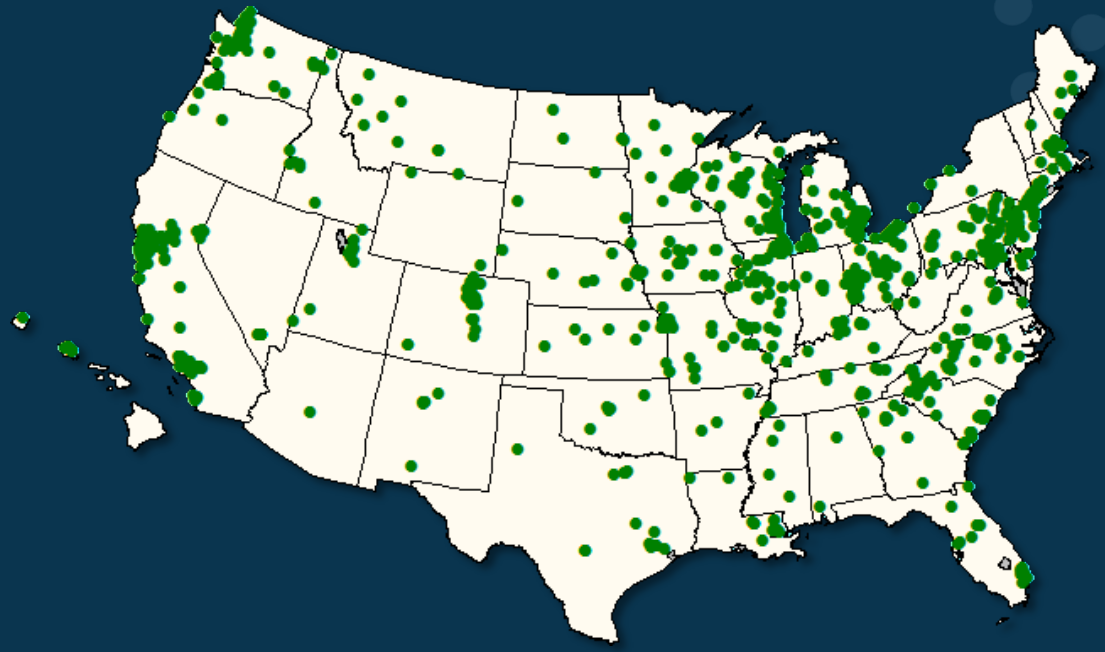
NCI Molecular Analysis for Therapy Choice (NCI-MATCH)



- Precision medicine trial to explore treating patients based on the molecular profiles of their tumors
- **1,089** sites in U.S. across NCTN and NCORP

NCI Molecular Analysis for Therapy Choice (NCI-MATCH)

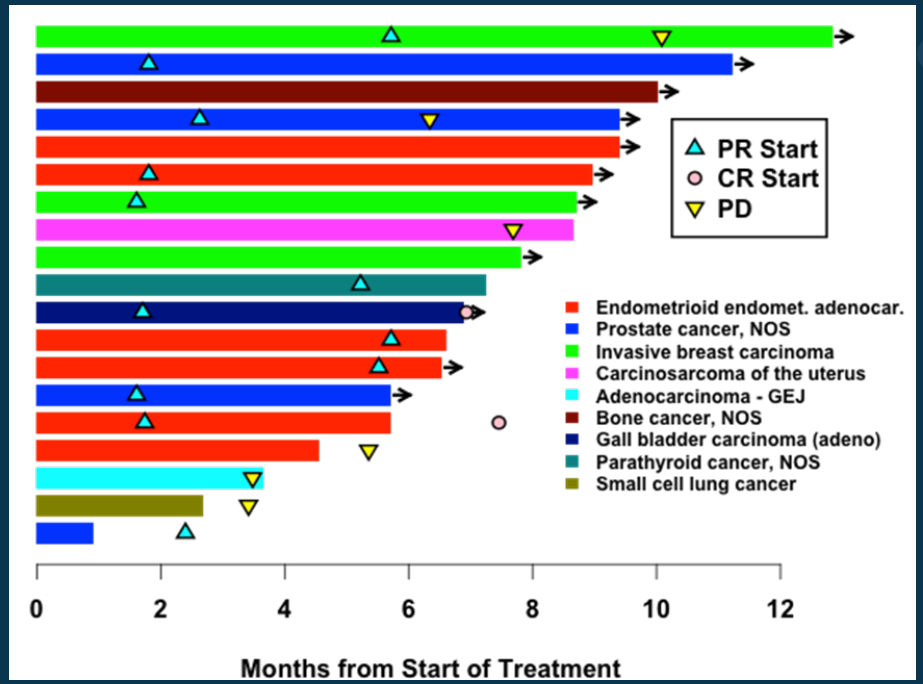
Rare Variant Initiative:

- Patients with low frequency mutations (< 2%) where well qualified drugs/targets available
- Foundation Medicine, Caris Life Sciences, MDACC, MSKCC will notify treating physician at any of the MATCH sites when results of their NGS panel would make patient eligible for a MATCH treatment arm
- Results verified centrally by NCI-MATCH Oncomine® assay
- RFP from other NGS providers posted August 2017 and received January 2018 to broaden the base of patients available to enroll in precision oncology studies

NCI Molecular Analysis for Therapy Choice (NCI-MATCH)

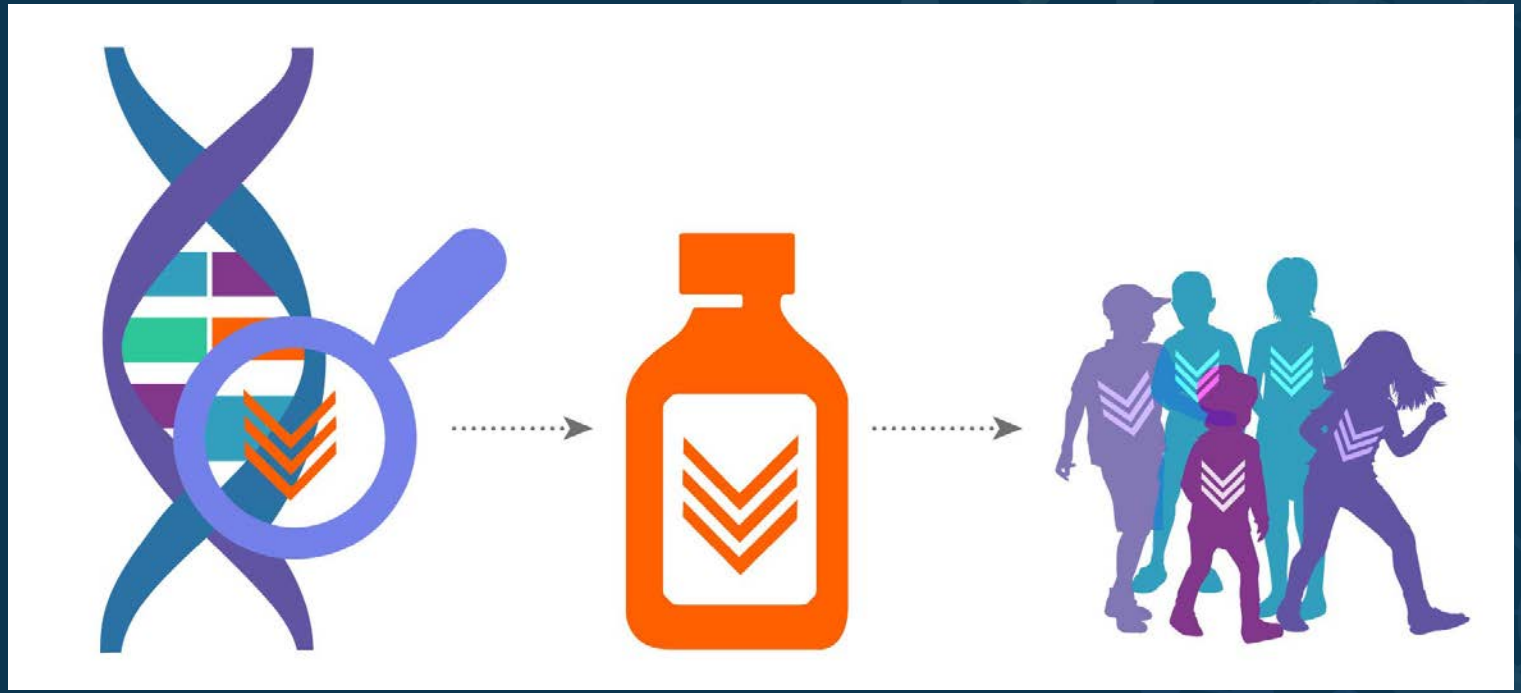
Time period	# enrolled	# first samples submitted	# first sample fail	# assay complete	# assigned to Rx	# enrolled on Rx
Total Pre Pause	794	739	116	645	54	27
Total Post Pause	5,602	5,222	428	4,913	938	662
Overall Total Screening Cohort	**6,396**	5,961	544	5,558	992	**689**
Total Outside Assay	104	59	3	102	88	71

First NCI-MATCH Efficacy Data: Nivolumab in MSI high cancers



- Median cycles 3.5 (range 1-13+ cycles)
- Median time to first response was 2.1 months (includes unconfirmed PRs)
- 6-Month PFS was 49% (95% CI: 32-67%)
- Median duration of response has not been reached (4-8+ months; 7/8 still under treatment at time of data cutoff)
- 11 patients remain on therapy at time of data cutoff

NCI-COG Pediatric MATCH

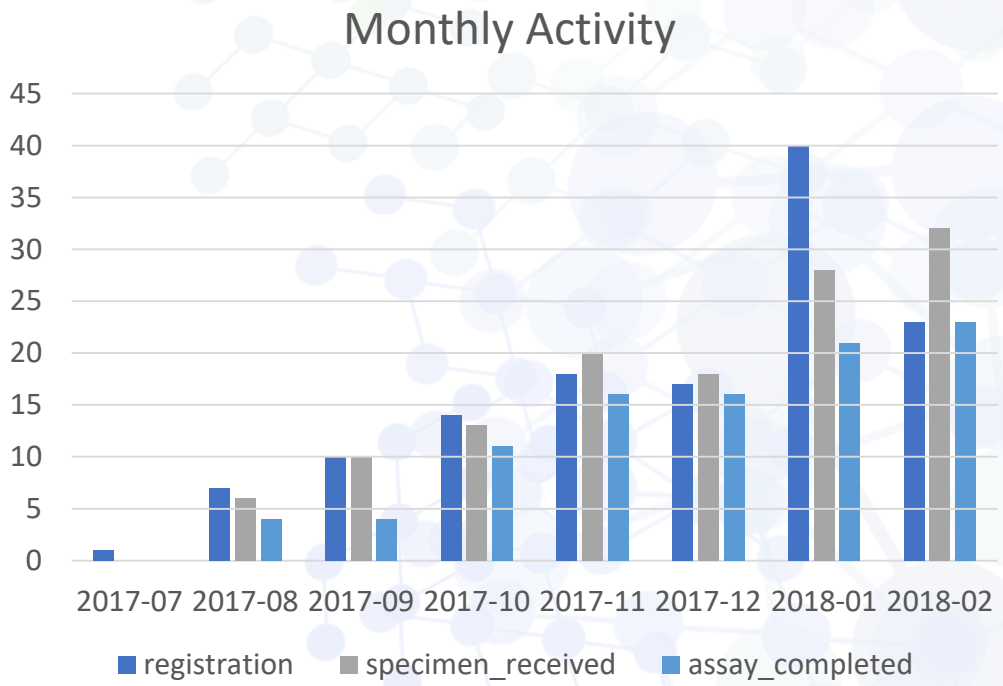


Pediatric MATCH
Active Therapeutic Arms

Arm	Agent Class	aMOI Frequency	Agent
APEC1621 A	Pan-TRK inhibitor	2-3%	Larotrectinib (LOXO-101)
APEC1621 B	FGFR inhibitor	2-3%	Erdafitinb
APEC1621 C	EZH2 inhibitor	2-3%	Tazemetostat
APEC1621 D	PI3K/mTOR inhibitor	5-10%	LY 3023414
APEC 1621 E	MEK inhibitor	10-20%	Selumetinib
APEC 1621 F	ALK inhibitor	2-3%	Ensartinib
APEC 1621 G	BRAF inhibitor	5%	Vemurafenib
APEC 1621 H	PARP inhibitor	2-3%	Olaparib

Pediatric MATCH Enrollment

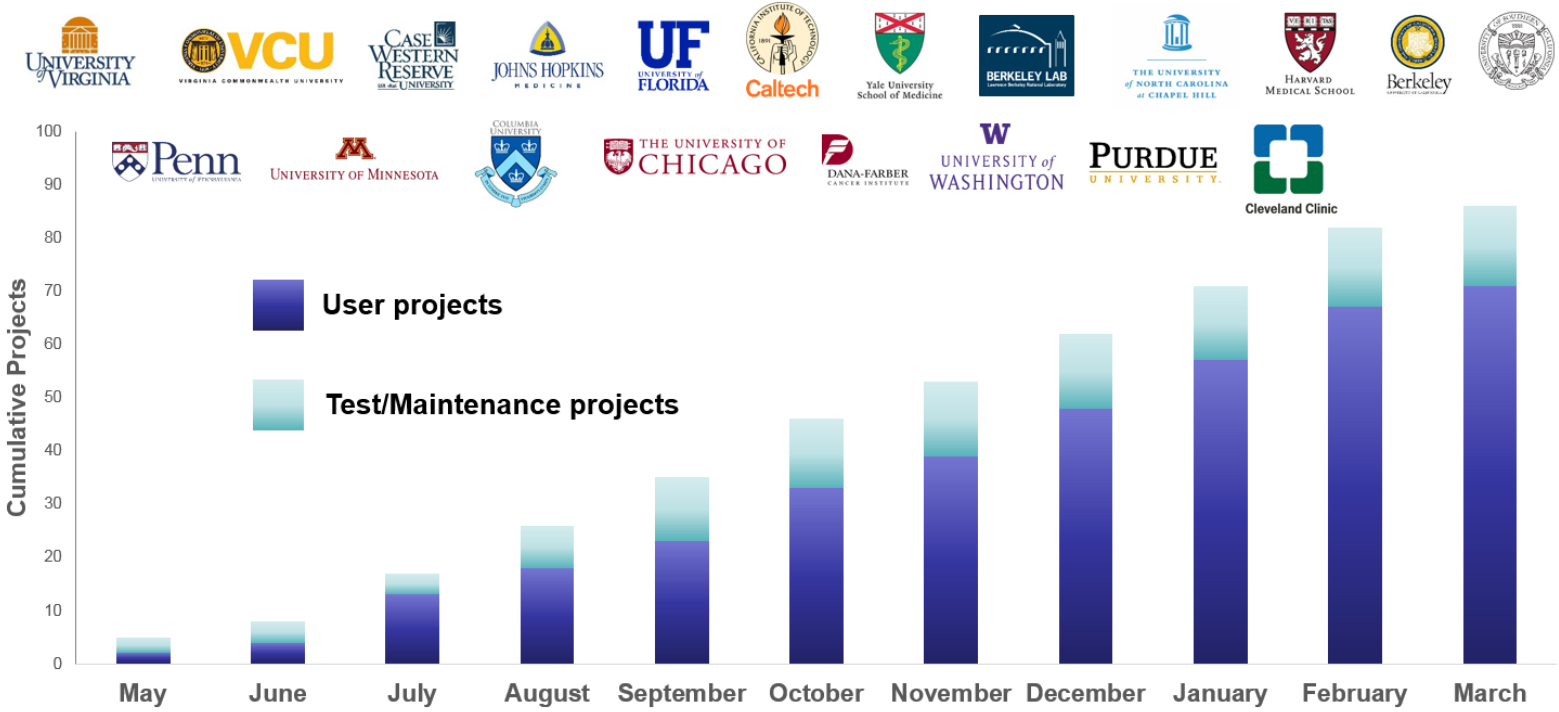
- First 131 patients:
  74 males, 57 females
  Age 1-21, median age 12 yrs
- 35% patients AYA
- Tumor sequencing completed on 94 patients
- At least one patient has matched to each of the treatment arms



National Cryo-EM Facility (NCEF) FNLCR

- **Mission**: **to address gap between need for cryo-EM and access to expensive instrumentation**
- Opened in May 2017 with one Titan Krios microscope. Second will be operational in Fall 2018.
- Addition of third microscope in 2019 if demand continues to grow.
- Advisory committee provides oversight on a biannual basis.
- Over 70 cancer-related projects from 20 institutions across US have been completed; feedback has been very positive.
- First user publication has just appeared in *Nature Communications.*

NCEF Usage Statistics



NCEF Personnel

Ethan Dmitrovsky
Lab Director, FNLCR

Sriram Subramaniam
FNLCR Cryo-EM
Program Advisor
(Founding Director, NCEF)

Dwight Nissley
Director, CRTP, FNLCR

Thomas Edwards
Microscopist, NCEF

Ulrich Baxa
Senior Microscopist,
NCEF

Helen Wang
Project Manager, NCEF

Matt Hutchison
IT Support, NCEF

Envisioning Key Focus Areas – *In progress*

We Must Always

ensure the health of the cancer research enterprise, and build our foundational knowledge.

We Must Continue

to leverage investments, further advancing our understanding and translation of our knowledge.

We Will

lead the nation's efforts to develop new approaches, technologies, and applications to change the meaning of a cancer diagnosis.

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