NCI's Precision Medicine Trials

Lyndsay N. Harris, M.D.
National Cancer Institute

March 7, 2023

National Academies of Sciences, Engineering, and Medicine
Incorporating Integrated Diagnostics into Precision Oncology Care: A Workshop

NIH NATIONAL CANCER INSTITUTE

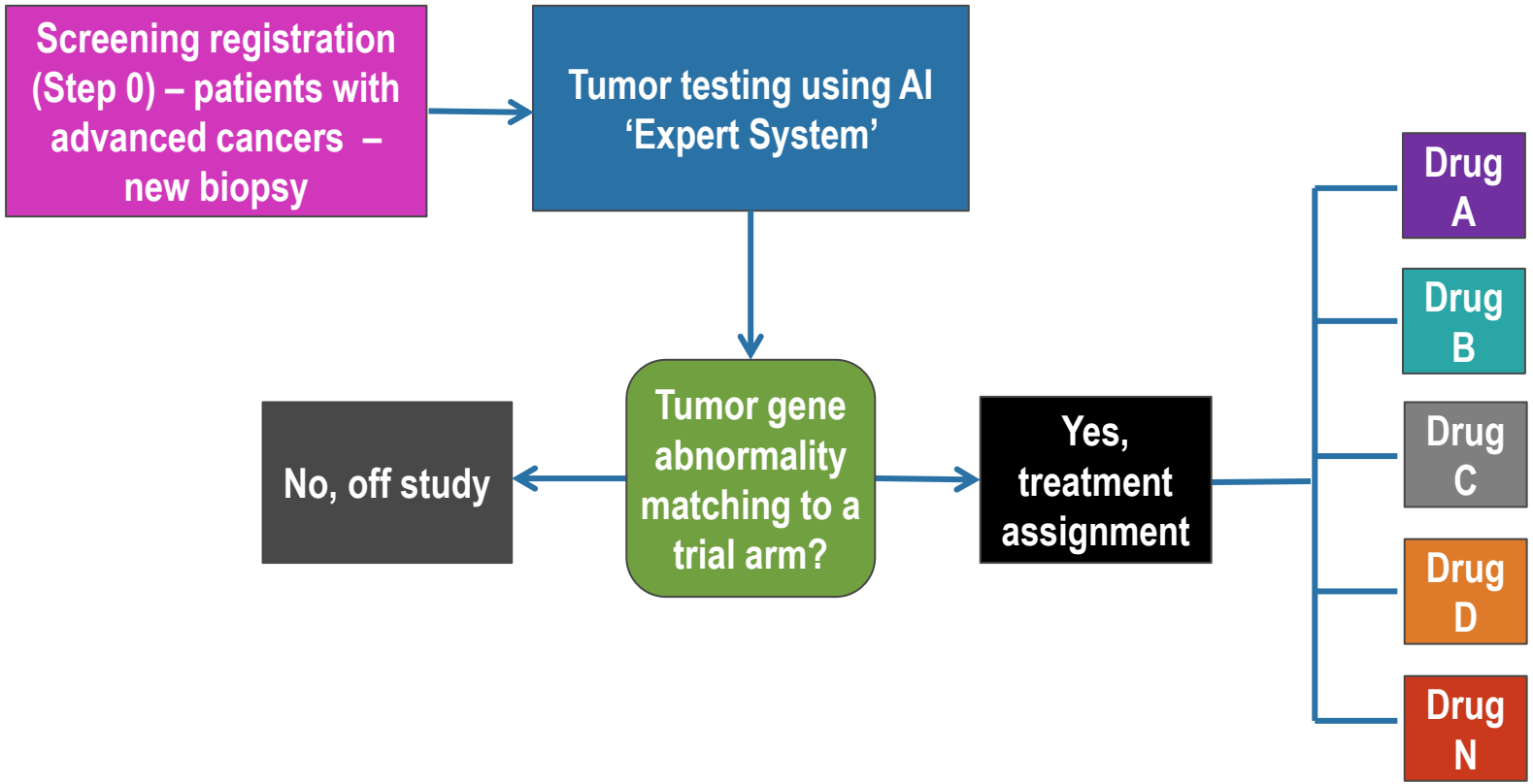
What is NCI-MATCH?

NCI-MATCH is a precision medicine trial that explores treating patients based on the **molecular profiles of their tumors**

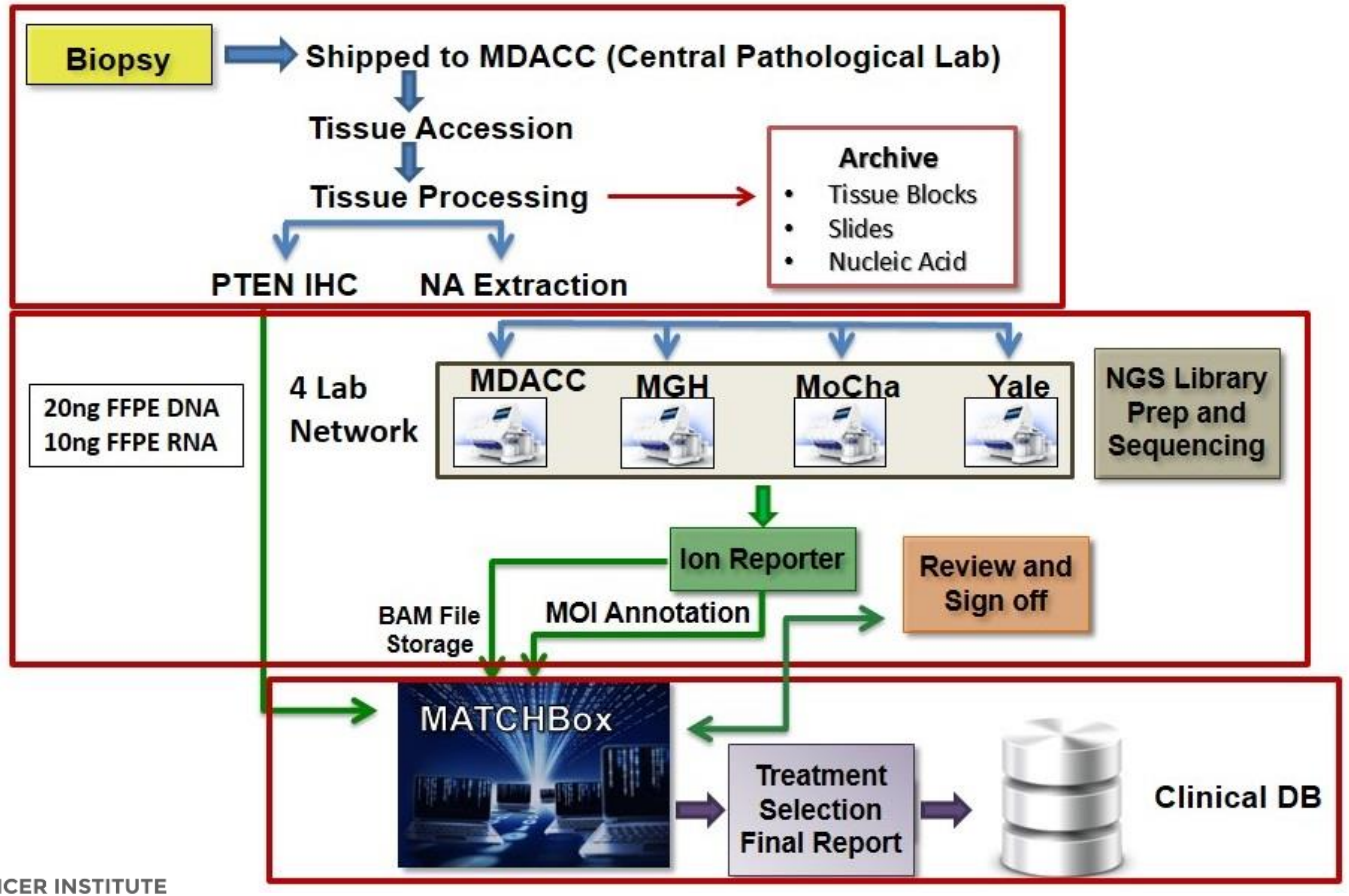
NCI-MATCH is for adults with:

- Solid tumors (including rare tumors), lymphomas, and myeloma
- Tumors that no longer respond to standard treatment

NCI-MATCH Screening (Step 0) Overall Design



NCI-MATCH Integrated Workflow



Levels of Evidence for Target Selection in NCI-MATCH

- **Level 1**: Gene variant credentialed for selection of an approved drug
- **Level 2a**: Variant is eligibility criteria for an ongoing clinical trial for that drug
- **Level 2b**: Variant identified in an N of one response(s)
- **Level 3**: Preclinical inferential data
  - Models with variant respond; without variant do not
  - Gain of function mutation demonstrated in preclinical model
  - Loss of function (tumor suppressor genes or pathway inhibitor, e.g,. NF1); stop codon or demonstrated loss of function in pre-clinical model

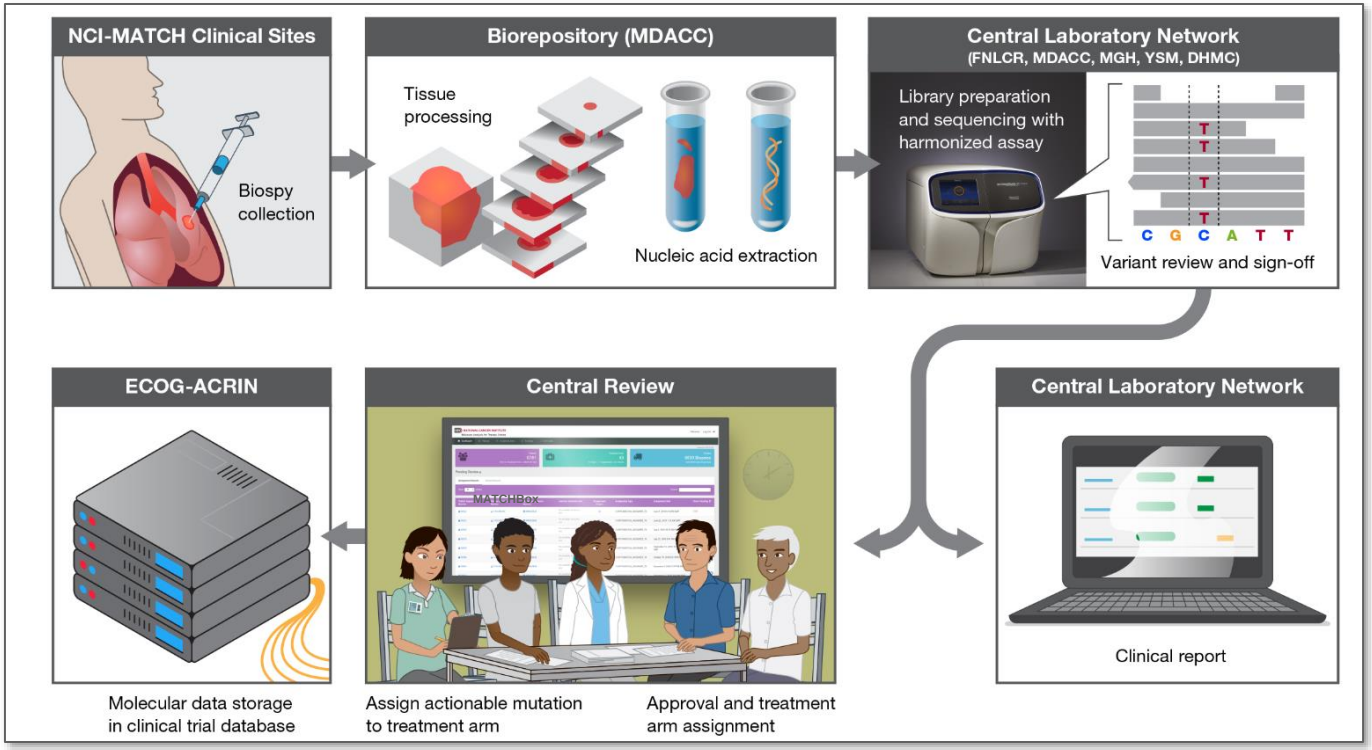
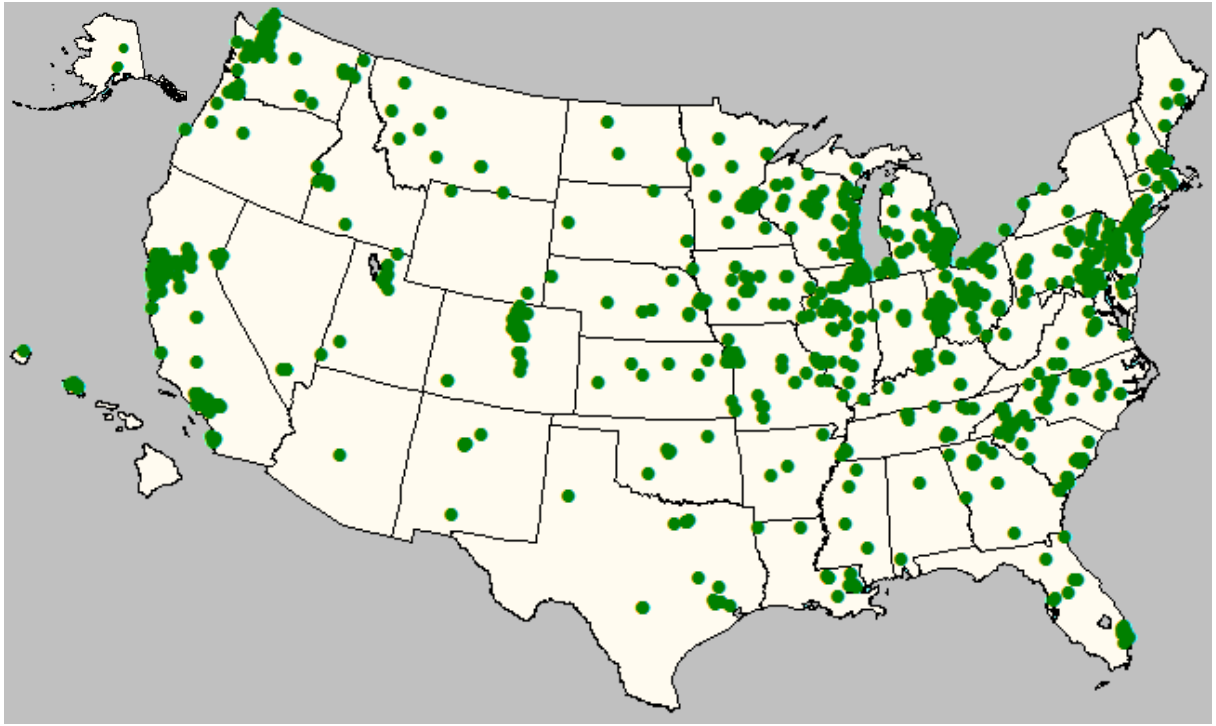


FIGURE 1. NCI-MATCH test workflow for the first ~6000 patients screened. Each patient tested through the central laboratory network had their sequencing results compiled into a clinical report that was sent to the treating physician at the clinical site. Sequencing results were also uploaded by the network laboratory into **MATCHBox, a rules engine that assigned eligible patients to a treatment arm**. All treatment assignments were reviewed by a group of clinical and scientific experts before final sign-off. MDACC indicates MD Anderson Cancer Center; FNLCR, Frederick National Laboratory for Cancer Research; MGH, Massachusetts General Hospital; YSM, Yale University School of Medicine; DHMC, Dartmouth Hitchcock Medical Center; ECOG-ACRIN, Eastern Cooperative Oncology Group (ECOG) and the American College of Radiology Imaging Network (ACRIN).

NCI-MATCH's ~1,100 Trial Locations Nationwide



In every state, the District of Columbia, and Puerto Rico

NCI-MATCH Central Screening Summary

No. registered for screening	No. with samples Submitted	No. with testing complete	No. assigned To Rx	No. enrolled On Rx
6,396	5,961	5,558	992	**689**

As of 02/18/2018

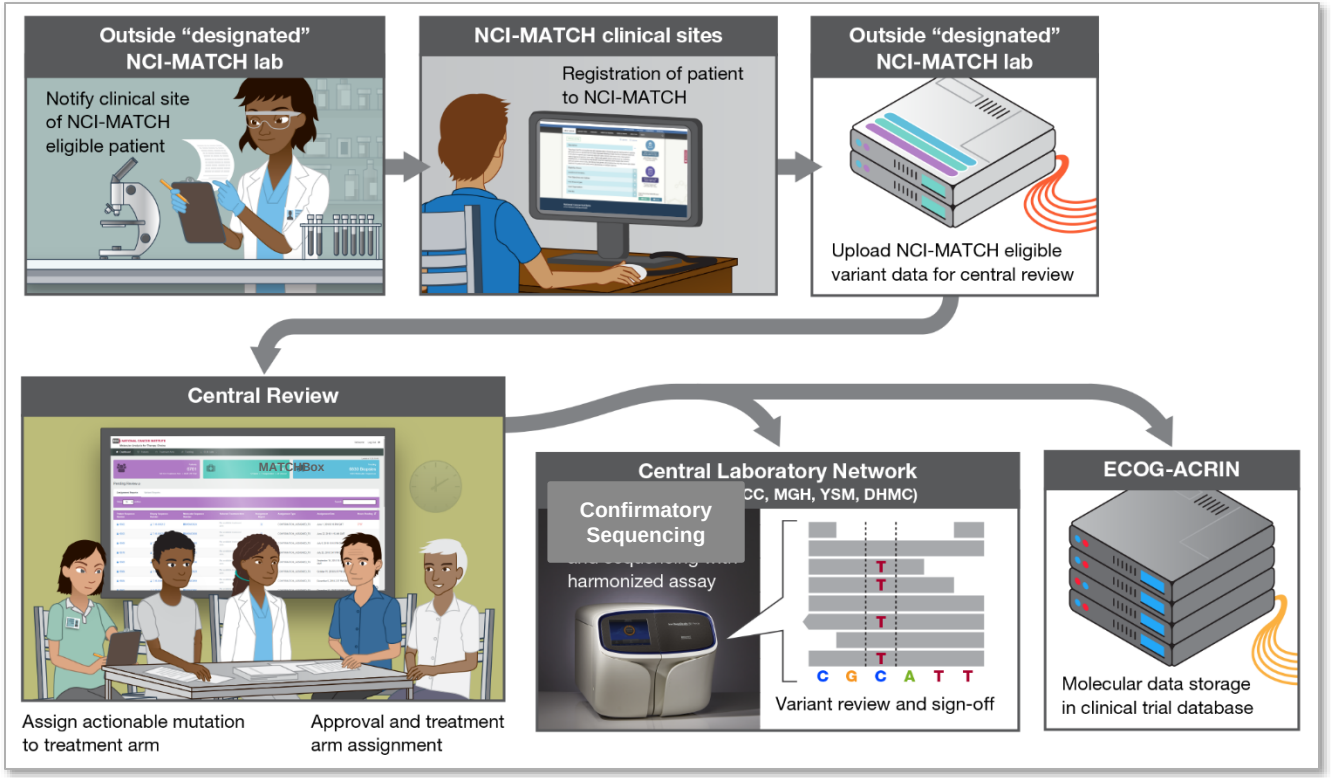


FIGURE 2. NCI-MATCH test workflow for the designated laboratory network. The designated lab reviews test reports and notifies NCI-MATCH clinical sites of patients potentially eligible for NCI-MATCH. If the patient is registered by the clinical site, the designated lab receives an email notification to upload the patient's variant data for **MATCHBox review**. After the patient is assigned to treatment, a specimen is also sent to the central laboratory network for confirmation of the actionable variant identified by the designated lab.

Outcomes of the initial 13/27 substudies in NCI-MATCH representing 71% of all activated arms (n=38) in the trial

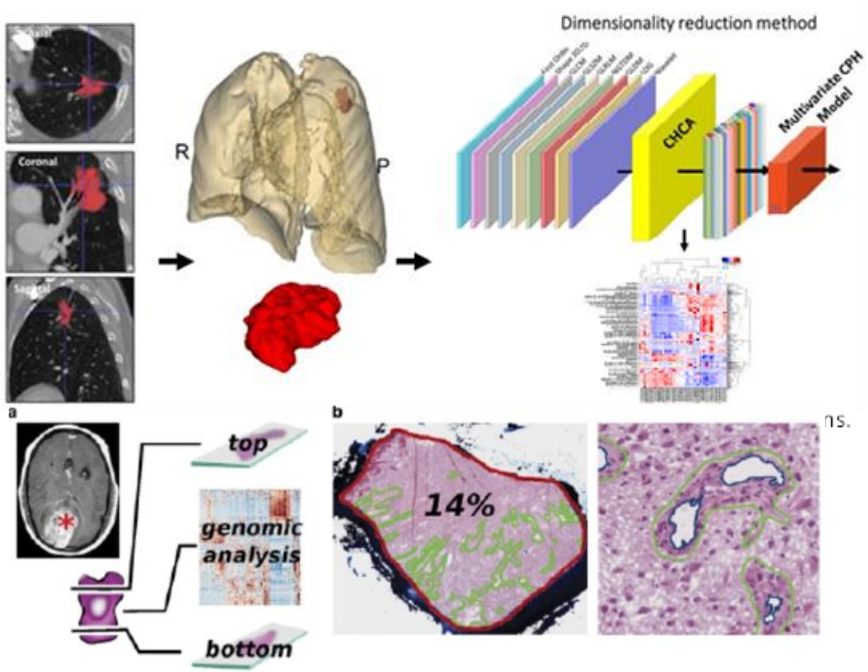
Eligible, treated, and variant Confirmed by MATCH assay

Arm	Molecular Aberration	Treatment	Total enrolled	N evaluable	No. of responses (%)	6-month PFS	Ref #	Met Endpoint?
A	EGFR activating mutations	afatinib	19	14	1 (7.1%)	8.9%	10	No
B	HER2 activating mutations	afatinib	40	37	1 (2.7%)	12.0%	11	No
F	ALK fusions	**crizotinib**	5	4	**2 (50.0%)**	**25.0%**	12	**Yes**
G	ROS1 fusions	crizotinib	4	4	1 (25.0%)	50.0%	12	No
H	BRAF V600E or V600K mutations	Dabrafenib / trametinib	35	29	**11 (37.9%)**	**68.4%**	13	**Yes**
I	PIK3CA mutation / without RAS mutation or PTEN loss	taselisib	70	61	0.0%	19.9%	14	No
J	HER2 amplification	Trastuzumab / pertuzumab	35	25	3 (12.0%)	25.3%	15	No
K2	FGFR mutation/fusion	**erdafitinib**	35	21	**3 (14.3%)**	36.8%	16	**Yes***
M	TSC1 or TSC2 mutations	TAK-228	49	34	5 (14.7%)	28.7%	17	No
N	PTEN aberration with + expression on IHC	GSK2636771	24	22	0.0%	4.8%	18	No
P	PTEN loss by IHC	GSK2636771	35	32	0.0%	3.3%	18	No
Q	HER2 amplification	ado-trastuzumab emtasine	38	36	2 (5.6%)	23.6%	19	No
R	BRAF fusions / non-V600 mutations	trametinib	35	32	1 (3.0%)	17.0%	20	No

Radiomic, Pathomic and Genomic Features in NCI-MATCH

Studies collected on Screened Subjects
(Not assigned to therapy)

	Pre-enrollment / Biopsy	
	Subjects	Studies Collected
	5091	**10996**
CT	4620	8469
US	901	1031
PET	677	803
MR	379	524
NM	56	59
NU	40	56
XR	35	54
Grand Total	**5091**	**10996**



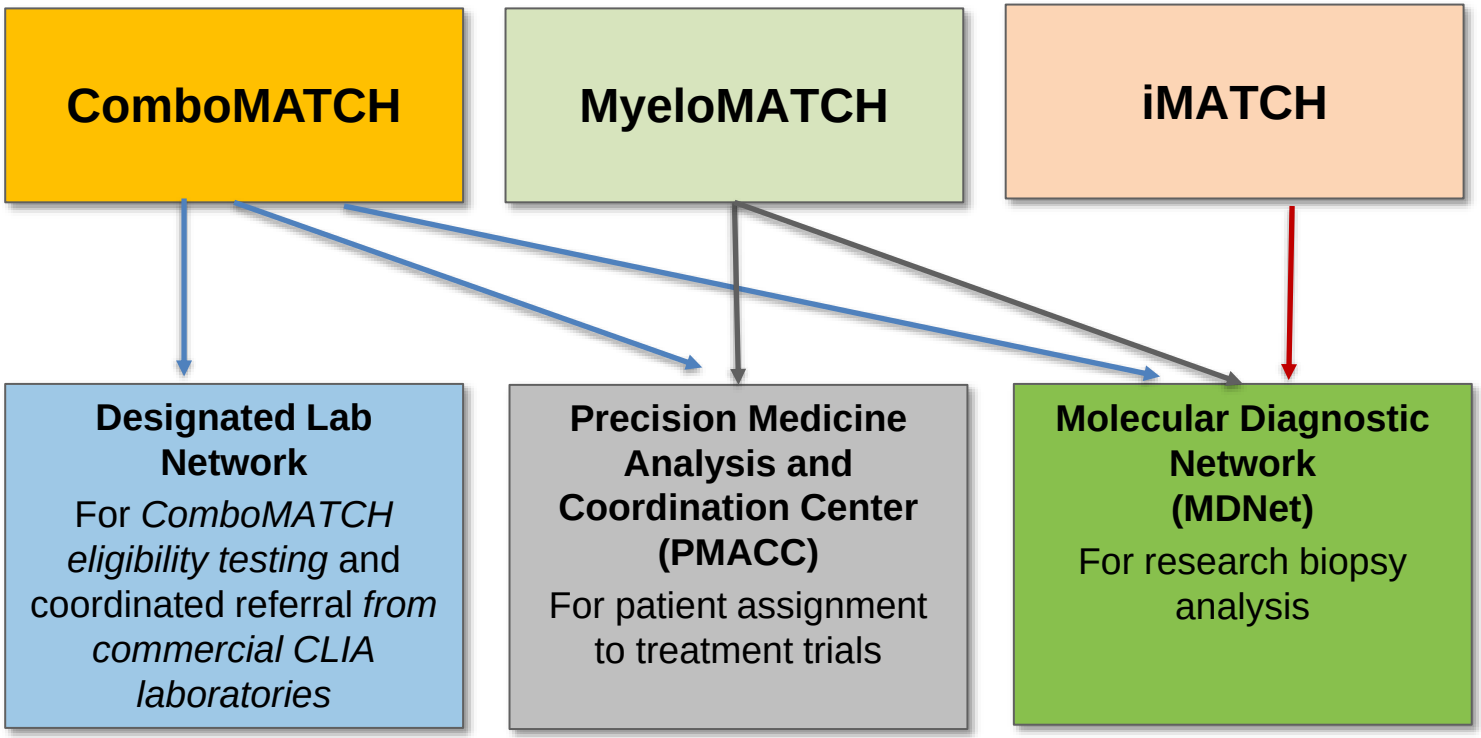
Socio-economic and environmental factors often associated with health disparities (“disparity correlates”)

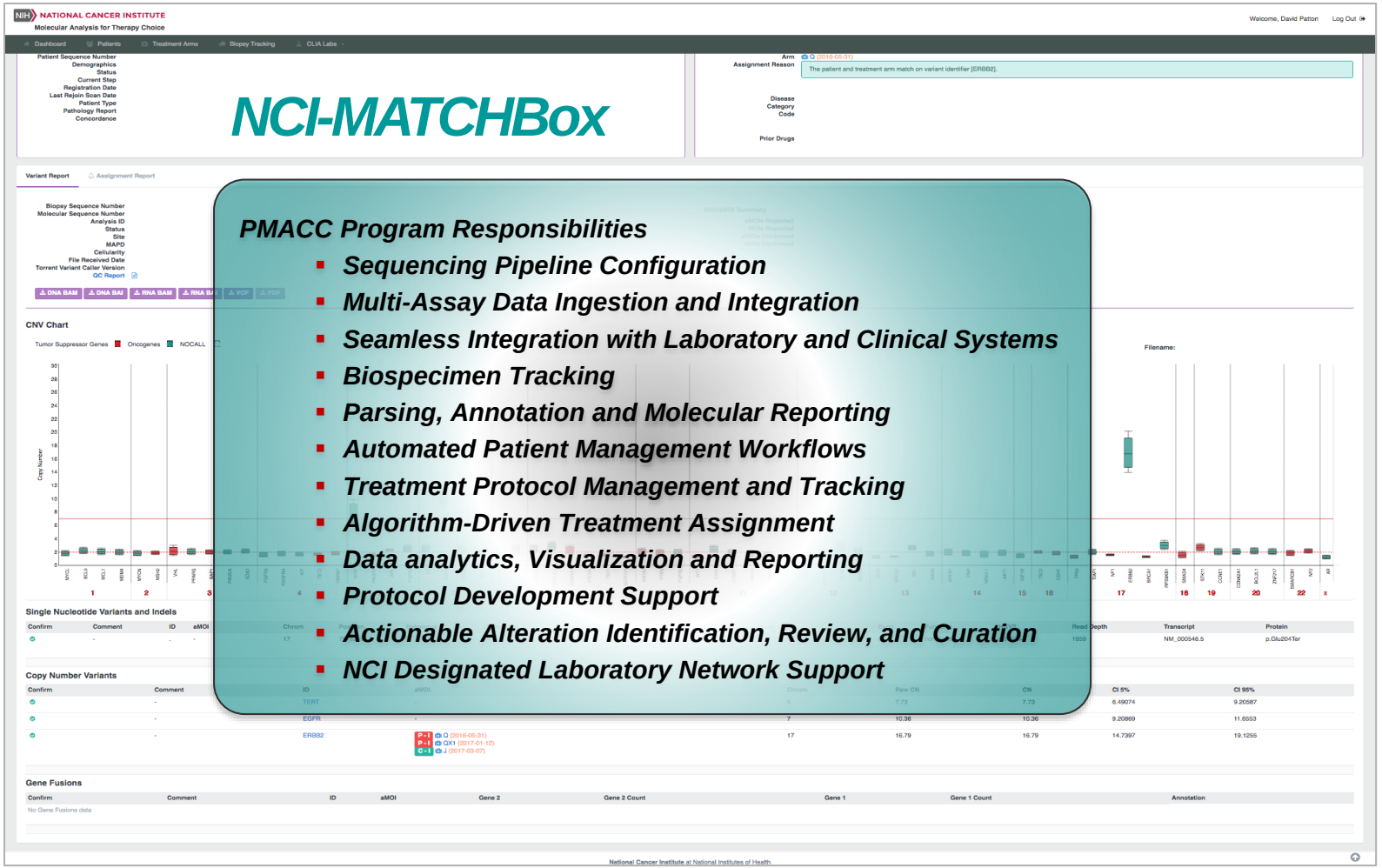
- Healthcare access
  - Payment method (Uninsured, Medicare/Medicaid, Private insurance)
  - Enrolling institution type (NCORP, LAPS, Other Main, Affiliate, Other)
  - Distance from home to clinical site (calculated from home and enrolling institution zip codes)
- Neighborhood-based (derived from home zip codes)
  - Metrics reflecting structural racism and discrimination (focusing on Black race)
  - Socio-economic status
    - Yost SES index
    - AHRQ SES index
  - Rurality (rural-urban continuum)

Disparity correlates and their association with tumor and clinical characteristics

- What is the distribution of disparity correlates across the NCI-MATCH cohort, and how do they associate with one another and with sex, age, race, and ethnicity?
- Are patient clinical condition (e.g., weight loss, performance status), time since metastatic diagnosis, and treatment history at study entry associated with disparity correlates?
- Do potentially modifiable cancer risk factors such as BMI or smoking differ by disparity correlates?
- Are tumor molecular characteristics associated with disparity correlates?
  - If associated, are the differential molecular characteristics known to have implications for prognosis or do they suggest different actionability for treatment selection?
  - If associated, are the associations wholly or partially explained through sex, age, race, and ethnicity?

New NCI Precision Medicine Initiatives




NATIONAL CANCER INSTITUTE
Molecular Analysis for Therapy Choice
NCI-MATCHBox
PMACC Program Responsibilities
Sequencing Pipeline Configuration
Multi-Assay Data Ingestion and Integration
Seamless Integration with Laboratory and Clinical Systems
Biospecimen Tracking
Parsing, Annotation and Molecular Reporting
Automated Patient Management Workflows
Treatment Protocol Management and Tracking
Algorithm-Driven Treatment Assignment
Data analytics, Visualization and Reporting
Protocol Development Support
Actionable Alteration Identification, Review, and Curation
NCI Designated Laboratory Network Support

A Step-wise Approach to Precision Immunotherapy

Current

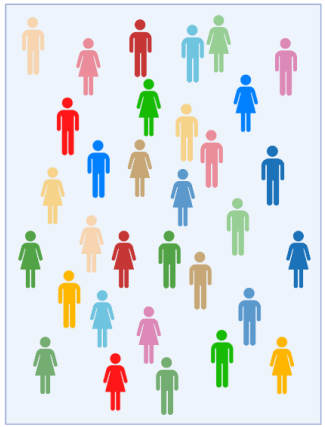
- No upfront patient/tumor characterization in most IO trials
- Retrospective correlative studies

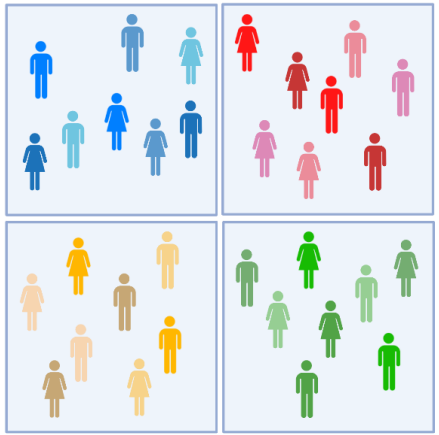
Proposal - iMATCH

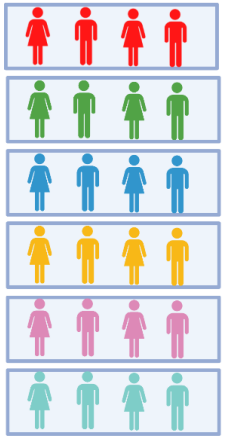
- Prospective use of available markers for therapeutic trials in pre-defined molecular strata
- Retrospective analysis with deep tumor/immune profiling

Future

- True precision biomarkers for individual regimens/ combinations

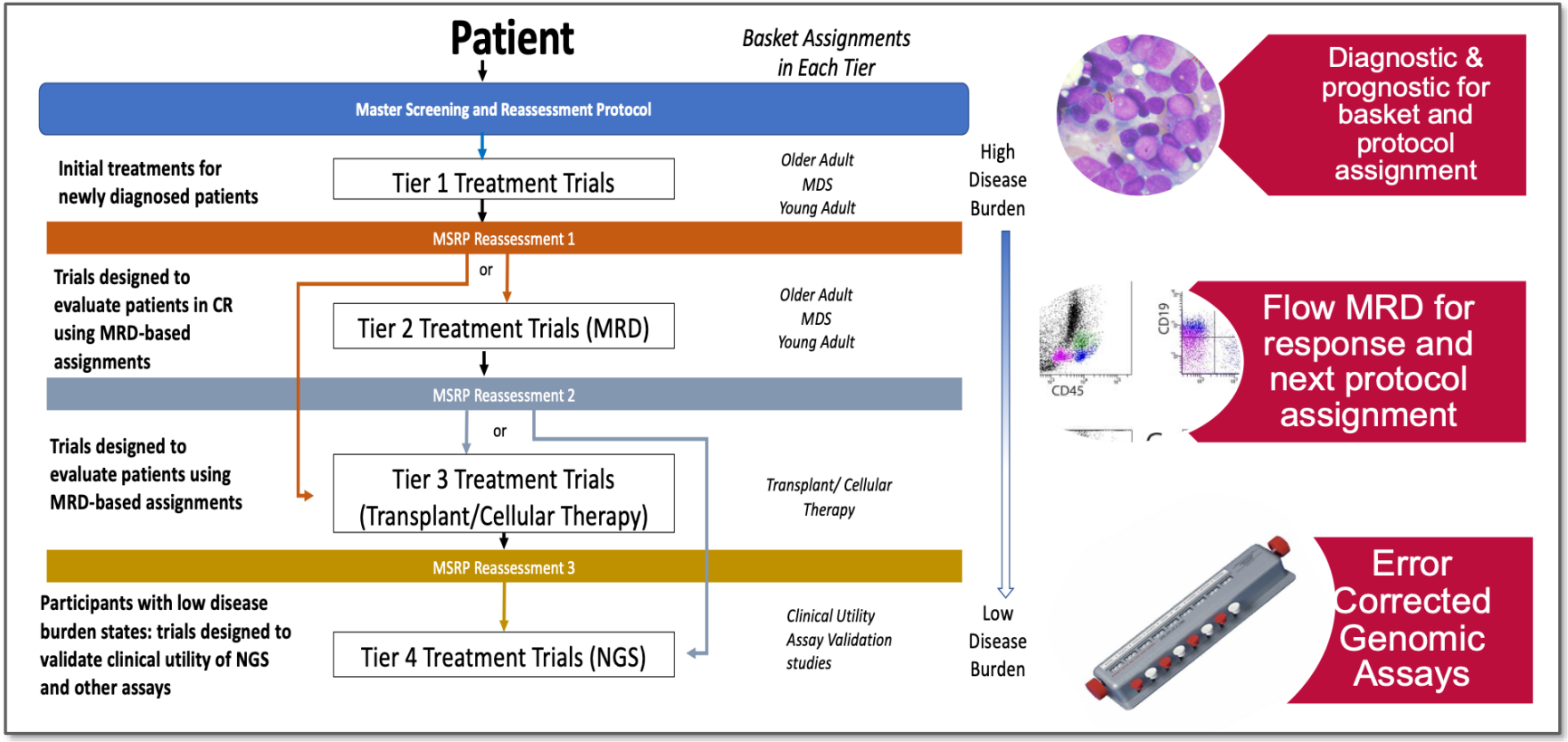




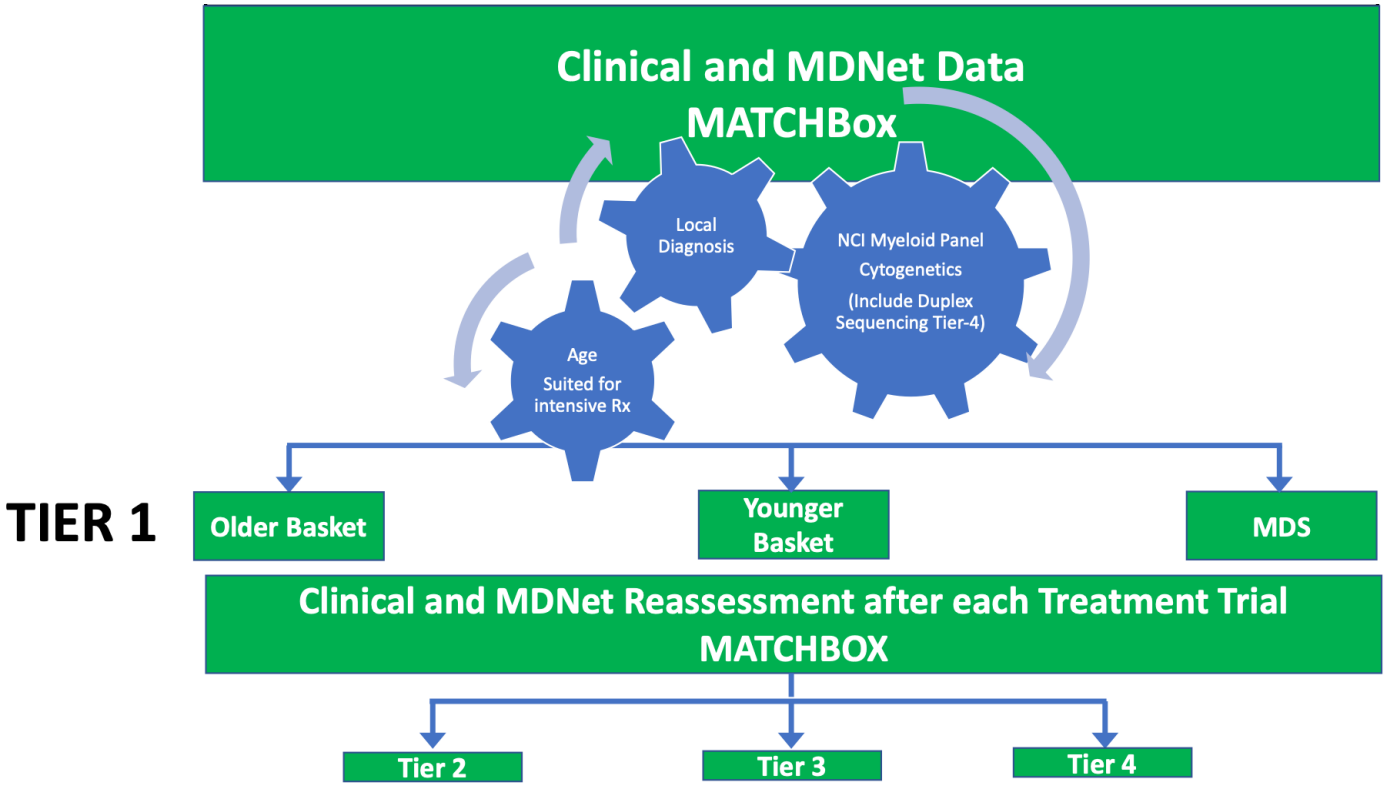


Graphics created with BioRender.com. Content adapted from Helen Chen, M.D.

Biomarkers in MyeloMATCH



Master Screening and Reassessment Protocol



Thank you!

www.cancer.gov

www.cancer.gov/espanol

1-800-4-CANCER

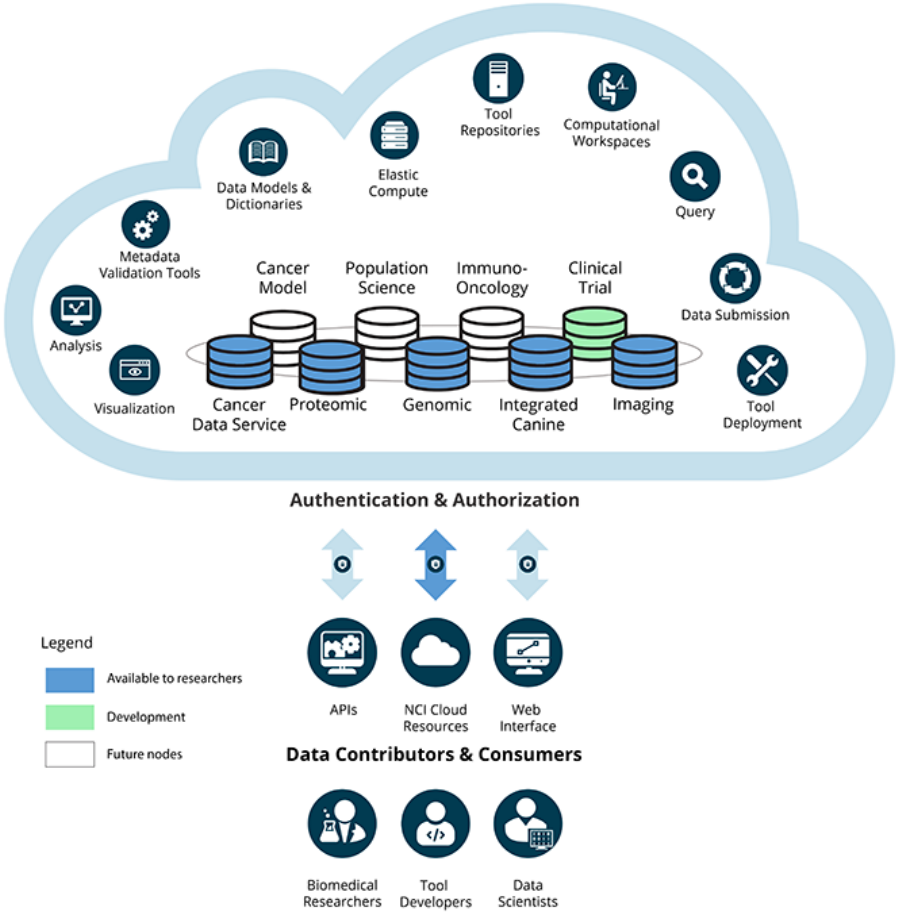
NCIinfo@nih.gov

@NCIDirector

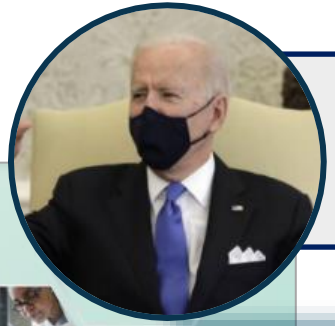
@TheNCI

Supplemental Slides

NCI Cancer Research Data Commons (CRDC)



Cancer Moonshot℠



"Let's end cancer as we know it. It's within our power to do it."
- President Joseph R. Biden

CANCER MOONSHOT

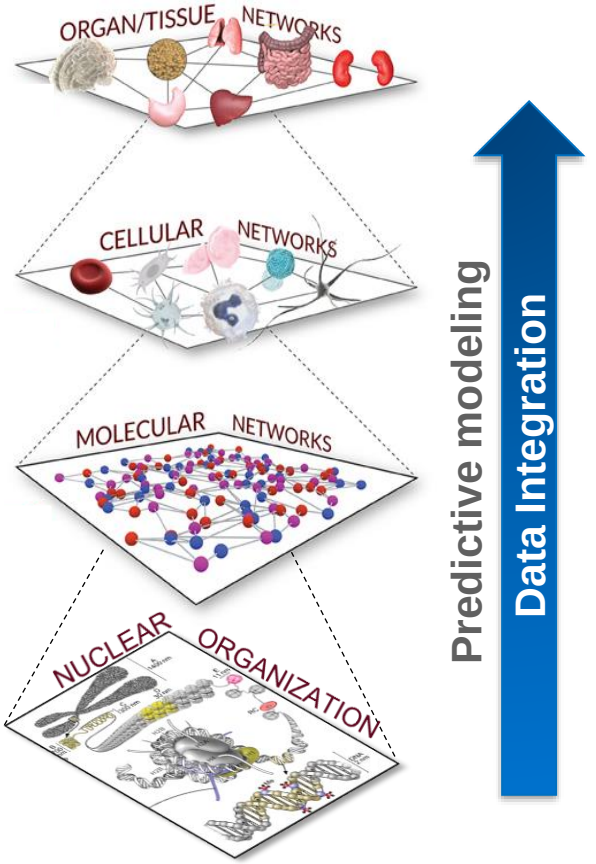
Cancer Moonshot℠:
Accelerate discovery, increase collaboration, and expand data sharing

In the Cancer Moonshot's first 4 years (2017-2021):

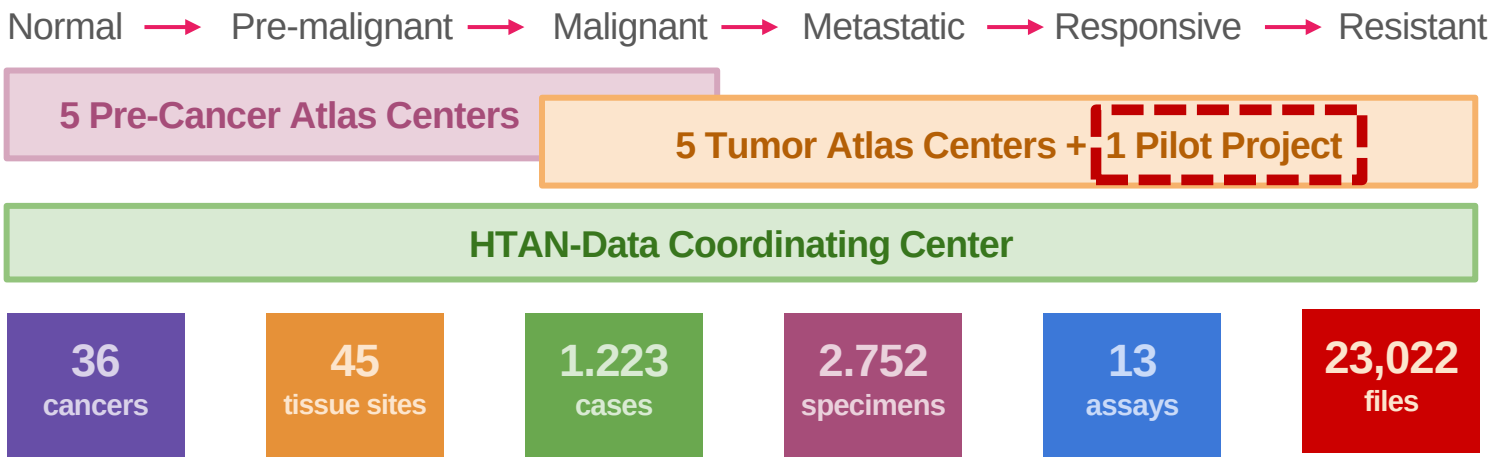
>2,000	49	>30
Publications	Clinical Trials	Patent Filings

Human Tumor Atlas Network (HTAN)

- Clinical imaging modalities (radiomics); circulating factors
- Histology; Highly multiplexed 2D and 3D imaging
- Metabolomics (Mass spec, MALDI imaging, etc.)
- Proteomics (many biochemical and imaging approaches)
- Transcriptomics (RNA-Seq, smFISH, etc.); Epigenomics (ATAC-Seq)
- Whole genome, whole exome, targeted DNA seq
- Chromatin conformation (4C, Hi-C, etc), EM imaging



NCI Human Tumor Atlas Network



The Human Tumor Atlas Network: Charting Tumor Transitions across Space and Time at Single-Cell Resolution. *Cell*. 2020. doi: 10.1016/j.cell.2020.03.053

Visit the HTAN Data Portal:

https://data.humantumoratlas.org/

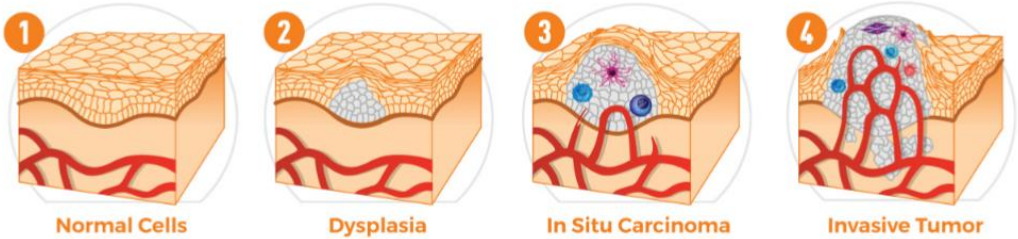
Current HTAN Atlases

Stanford CRC (FAP)

HTAPP CRC

Vanderbilt CRC (Spontaneous)

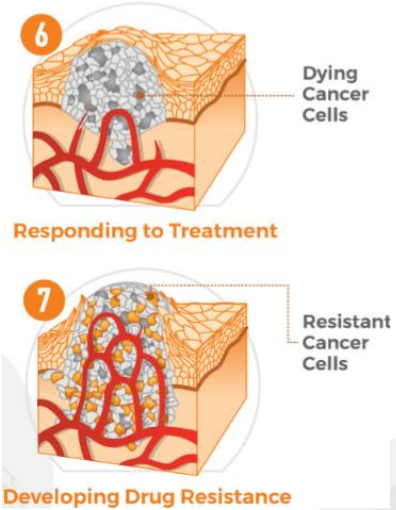
Trans-network project CRC



Harvard Melanoma

WUSTL Pancreas

CHOP Leukemia



Duke DCIS & Breast

OHSU Breast

Boston University Lung

MSKCC Lung