BSA meeting, March 29, 2022

Concept for Renewal of Cancer Immune Monitoring and Analysis Centers (CIMACs) (U24) and Cancer Immunologic Data Center (CIDC) (U24) Network

Cancer Moonshot Blue Ribbon Panel Recommendation D: "Build a national cancer data ecosystem"

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CIMAC-CIDC Immuno-Oncology Biomarker Network

Biomarkers are critical to guide personalized immunotherapy choices for patients.

Challenges of biomarker research:

- Need for **innovative multimodal approaches** to address the complexity of the tumor-immune system interface and treatment modalities.
- Need for standardized and **harmonized assays** to address assay performance variables between laboratories resulting in high data variability and poor reproducibility.
- Need for **clinical outcome data** and access to multiple clinical trials.
- Need for centralized **bioinformatic pipelines** for data analysis.
- Need for **databases** that integrate molecular and cellular data with clinical outcomes.

History of CIMAC-CIDC Network

- **Project Period:** Sept 30, 2017 – Mid-2022 (Mid-2023 with NCE)
- **CIMACs U24:** RFA-CA-17-005
- **CIDC U24:** RFA-CA-17-006

- **Partnership for Accelerating Cancer Therapies (PACT)**
  - 5-year Public-Private Partnership between CIMAC-CIDC and 12 pharmaceutical companies through FNIH.
  - PACT joined CIMAC-CIDC in 2018 and provided support for:
    - Clinical trials portfolio
    - CIDC database
    - Specimen tracking system
    - Project management
  - Future PACT support remains to be determined.

Cancer Immunotherapy Monitoring Network – Goals and Objectives

Scientific goals:

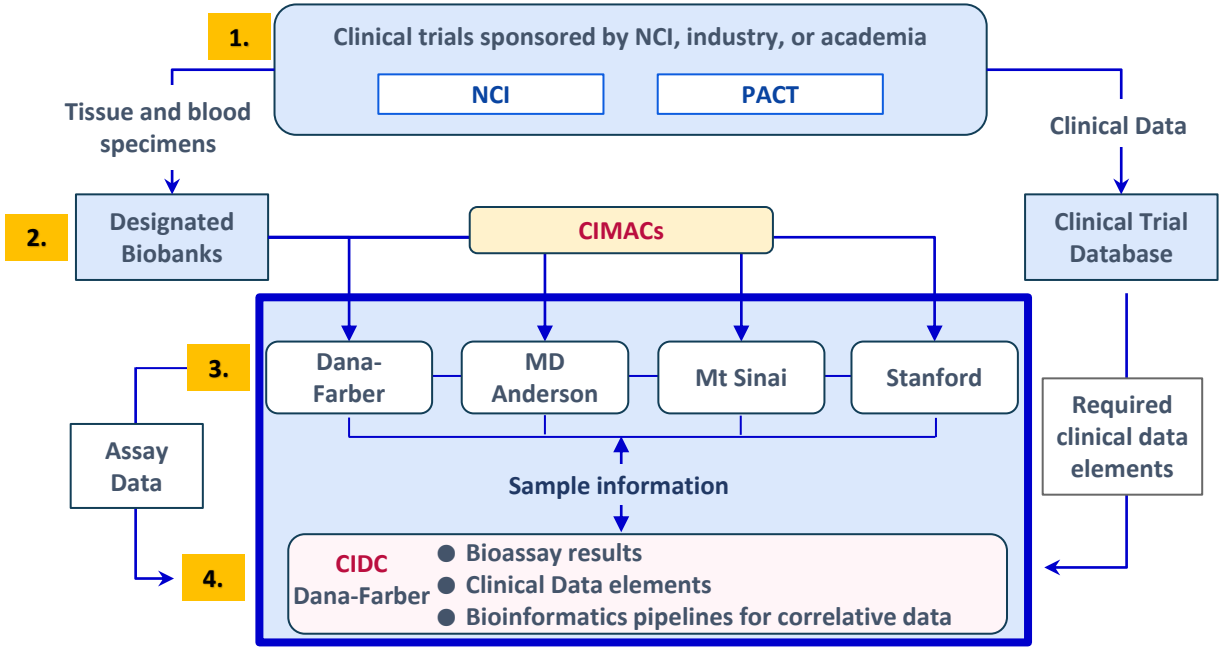
1. Enhance **mechanistic understanding** of action of immunotherapy agents and combinations in clinical trials.
2. Accelerate identification of clinically impactful **biomarkers of response, resistance, and adverse events** for development of precision cancer treatment.

Objectives of the FOA:

1. Establish a **biomarker infrastructure** to address scientific issues for NCI immunotherapy trials.
2. Provide **comprehensive immune profiling** using state-of-the-art platforms.
3. Provide quality control through **harmonization** of assays facilitating comparison of data across clinical trial sites.
4. Develop **bioinformatics pipelines** for within- and cross-trial analysis.
5. Establish a **database of clinically annotated biomarkers**.
6. Facilitate **sharing** data and guidelines to address assay performance variables with the research community.

Current Status and Future Goals

CIMAC-CIDC Network Accomplishments: Organizational Structure



1. Clinical Trial Groups
2. Biobanks
3. CIMAC Laboratories
4. CIDC Data Coordination Center

Adapted from Chen et al. Network for Biomarker Immunoprofiling for Cancer Immunotherapy: CIMAC-CIDC, Clin Cancer Res 2021

CIMAC-CIDC Network Accomplishments: Assays and Standards

1. **Harmonization of Tier 1 Assays** to ensure comparability and data reporting across trials (*Clinical Cancer Research 2021)*
2. **Validation of all assays**, SOPs, and harmonization guidelines made available to the scientific community https://cimac-network.org/
3. **Specimen collection umbrella protocol** to minimize preanalytical variability and enhance accuracy of biomarker assays.
4. Standards to **monitor longitudinal assay performance**.

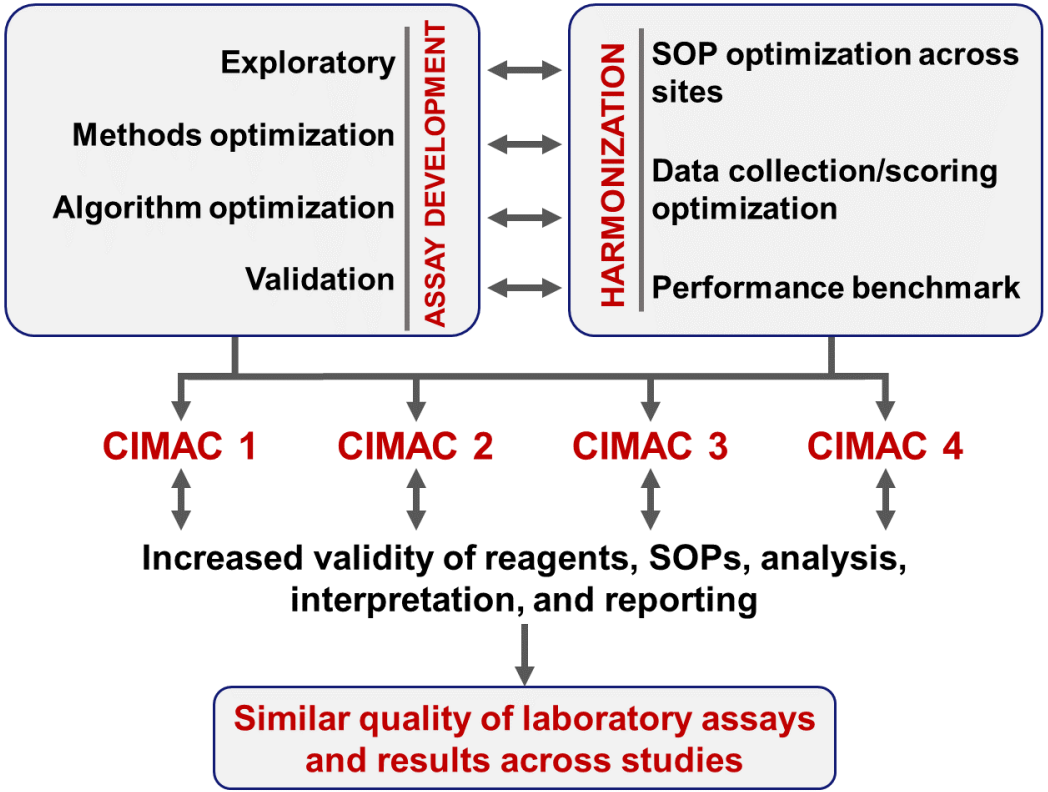
Tier 1 assays	Tier 2 assays	Tier 3 assays
• WES • RNA-seq / NanoString • CyTOF • mIHC/IF • Singleplex IHC • Olink	• TCR-seq • cfDNA • MIBI • Grand Serology ELISA • ATAC-seq • 16s microbiome sequencing	• scATAC-seq • scTCR-seq • scRNA-seq • CITE-seq • Spatial transcriptomics (Visium/GeoMx) • Spatial tissue imaging • ELISPOT • HLA tetramers

Assay Harmonization across CIMACs

Genomics harmonization: *Zeng Z et al. Cross-Site Concordance Evaluation of Tumor DNA and RNA Sequencing Platforms for the CIMAC-CIDC Network. Clin Cancer Res. 2021 Sep 15;27(18):5049-5061.*

CyTOF harmonization: *Sahaf B et al. Immune Profiling Mass Cytometry Assay Harmonization: Multicenter Experience from CIMAC-CIDC. Clin Cancer Res. 2021 Sep 15;27(18):5062-5071.*

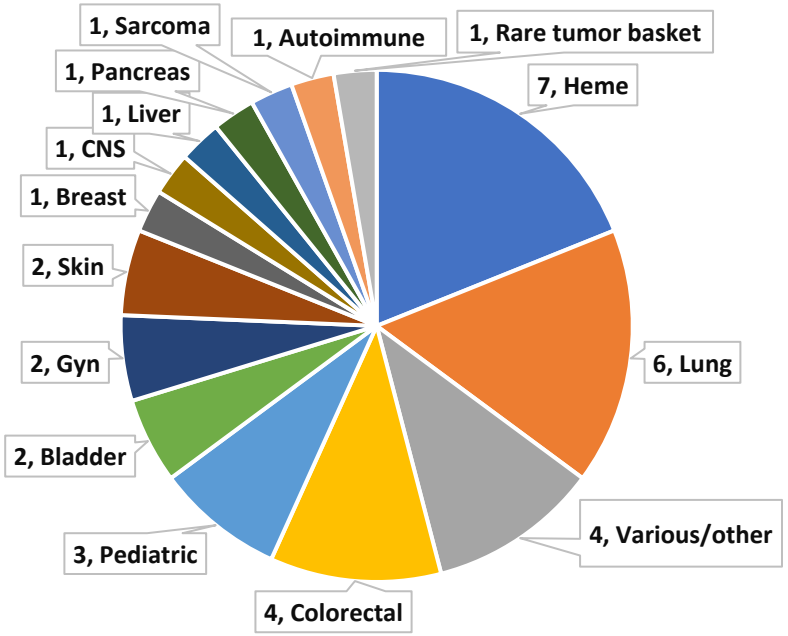
IHC/IF harmonization: *Akturk G et al. Multiplex Tissue Imaging Harmonization: A Multicenter Experience from CIMAC-CIDC Immuno-Oncology Biomarkers Network. Clin Cancer Res. 2021 Sep 15;27(18):5072-5083.*



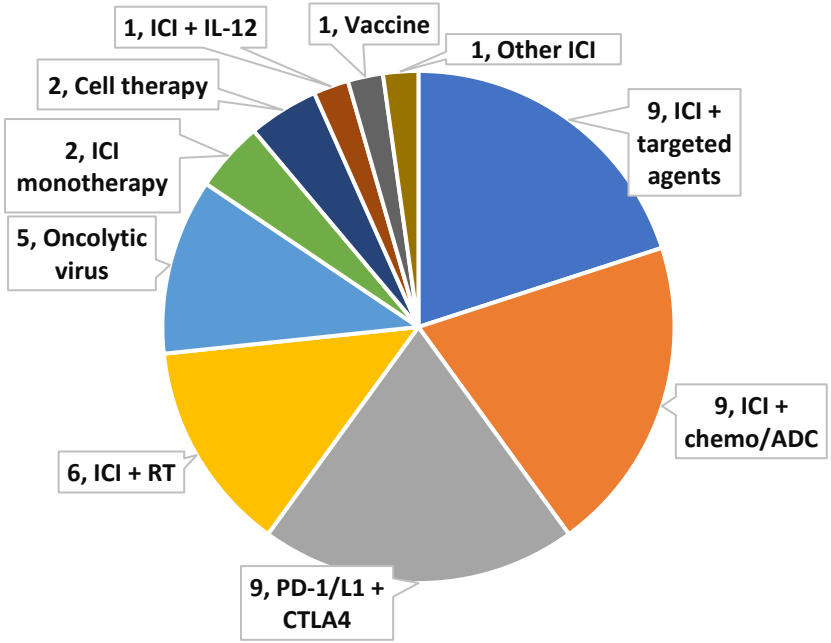
CIMAC-CIDC Network Accomplishments: Clinical Trial Collaborations

- **35 IO trials … 2,000+ patients**
- **NCI trial networks: NCTN, ETCTN, Ped-CITN, others**
- **Multiple diseases & modalities**

Diseases



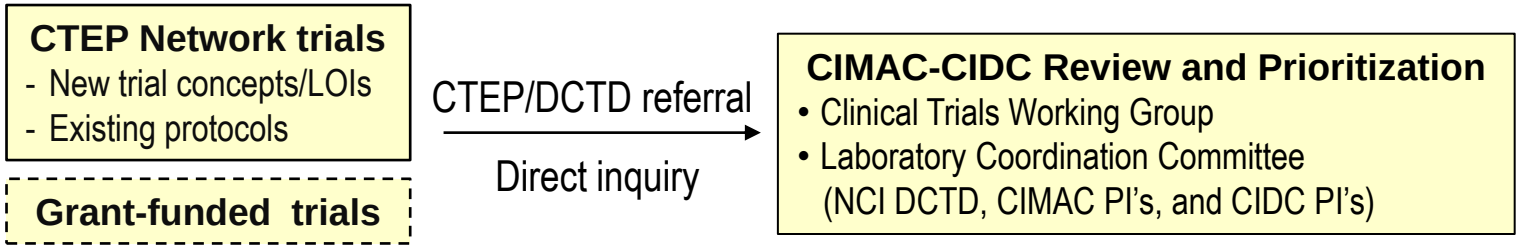
Modalities



How were trials selected for CIMAC-CIDC collaboration?

NCI U24-funded CIMAC-CIDC projects

1. **All NCI-funded IO trials** (CTEP networks or NCI grants) **are eligible** for CIMAC-CIDC.
2. Trial teams approach CIMAC-CIDC through **CTEP/DCTD recommendation or direct inquiry** (Intake process posted on the CIMAC-CIDC website).
3. **All proposals undergo a formal process involving NCI and CIMAC-CIDC investigators** for review and selection based on translational potential and Network priorities.



**All trials in the current portfolio are from CTEP: 17 ETCTN, 6 NCTN, 2 Ped-CITN, 1 ABTC*

PACT-funded CIMAC projects – *currently 9 trial collaborations*

- No restriction on the source of trials (Industry, NCI, or academia)
- Trial selected through the PACT review process (FNIH, Industry partners, and NCI staff).

CIMAC-CIDC Network Accomplishments: Clinical Trial Analyses

Data ingested in CIDC:

- 12 IO trials with biomarker & clinical data
- >5,100 specimens
- 9 bioinformatics pipelines

Clinical trials	**35 trials*** 2,000+ patients accrued
Published correlatives	**4 trials published** (**ETCTN:** 10021 CRC & NSCLC, 9204, 10026)
Correlatives completed/ manuscripts in preparation	**5 trials** (**NCTN:** S1400I, EAY131-Z1D, E4412, DART **NCI:** 14-C-0059)
Ongoing correlatives	**16 additional trials**

* ~10 trials may accrue/have specimens available beyond mid-2023.

CIMAC-CIDC Network – High-Priority Scientific Objectives

1. **Enhance understanding of the evolution of tumor and tumor microenvironment, and mechanism of action of agents**
   - New targets, neoantigens, immuno-editing
   - Different classes of IO agents
   - Non-immunotherapy partners

2. **Develop multifactorial models and algorithms to inform combination therapy approaches**

3. **Identify clinically actionable biomarkers of response and resistance**
   - Biomarkers beyond PD-L1 and tumor mutation burden (TMB)

4. **Mechanisms and biomarkers of immune-related adverse events (irAEs)**
   - Synthetic cohorts with irAEs

5. **Biology and biomarkers for special populations**
   - Rare tumors and pediatric malignancies

CIMAC-CIDC Network – Scope and Future Goals

Capitalize on data and resources developed during current CIMAC-CIDC Network:

1. **An unprecedented infrastructure** for IO biomarkers testing across trials
2. **Assay and clinical data** from ~25 trials to be hosted in CIDC
3. **Specimens available from 10 trials** that accrue beyond mid-2023

New:

1. **Increase capacity for more IO trials in high-priority areas.**
   - 20+ trials, 2000+ patients
   - Including trials from NCI-funded investigators outside the NCI trial networks.
2. **Add novel assays for deep profiling to interrogate tumor and microenvironment.**
   - e.g., single-cell sequencing, spatial imaging, and spatial transcriptomics
3. **Enhance CIMAC and CIDC functionalities to integrate complex data and perform cross-trial analysis.**
   - Bioinformatic and machine learning methods
   - Build immunologic database

Cancer Immunologic Data Center (CIDC)

Correlative Sample Management System (CSMS)

Operations Center for Central Coordination

Cancer Immunologic Data Center (CIDC) Scope and Goals

Established bioinformatics and cloud-based IT infrastructure for the Network:

1. Data warehousing with security and access control
2. Collect specimen information via Correlative Sample Management System-CSMS
3. Ingest/QC assay and clinical data
4. Standardize and harmonize clinical data
5. Maintain data collaboration portal for correlative analyses
6. Deposit data into NCI data-sharing repositories

New:

1. Expand beyond current 9 bioinformatics pipelines/algorithms/tools
2. Support future cross-trial analyses and data sharing

Pipelines for:

1. RNA Seq
2. WES
3. NanoString
4. TCR-seq
5. CyTOF
6. Olink
7. ELISA
8. mIHC/mIF
9. Microbiome

Expand ongoing cross-trial analysis efforts

Establish clear CIDC data access rules/policies

- Consistent with various legal agreements

Harmonized clinical data standards

- CIDC-wide versus ad-hoc by project

Design cross-trial projects

- Availability of clinical data attributes across multiple trials
- Single versus multiple assay analysis
- Feasibility, review, and approval

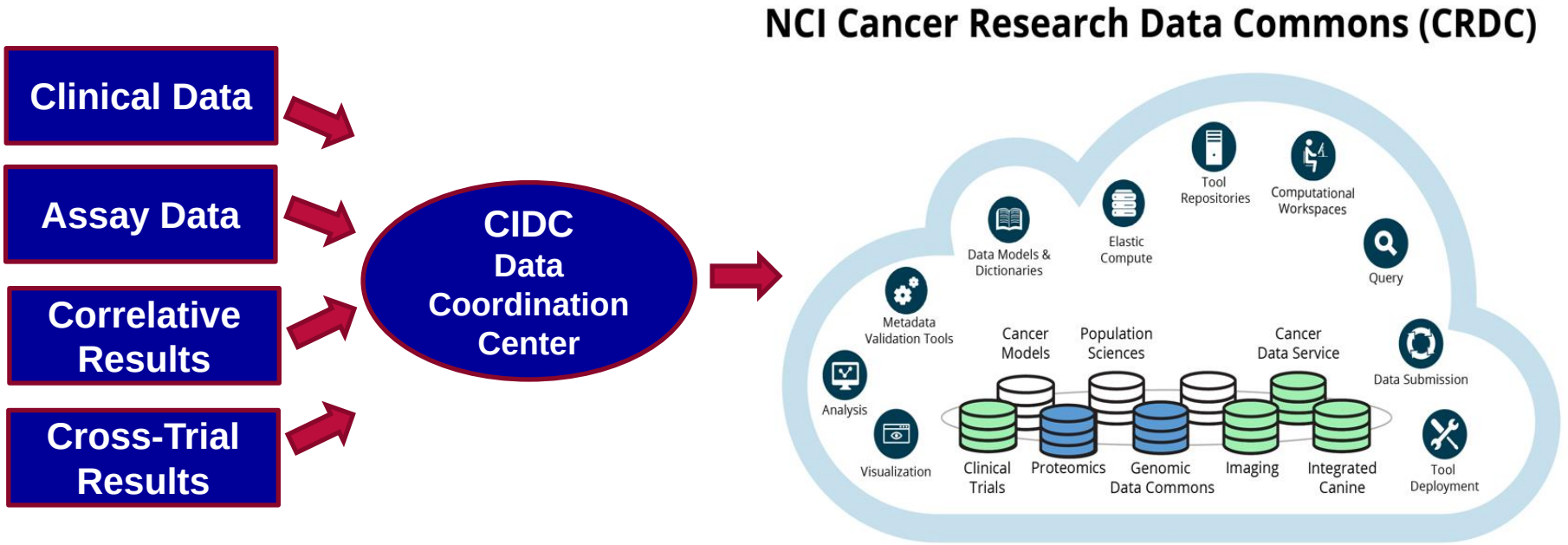
Assemble specialized teams to complete projects

- Software engineers, bioinformaticians, clinicians, statisticians, and scientists

Example: Leveraging Tumor Immune Dysfunction and Exclusion Algorithm (TIDE)

- Identify gene expression signatures that differentiate responders from non-responders
- Identify immune modulation effect of drugs
- Identify new biomarkers across multiple trials

Facilitate Data Integration & Sharing



1. Standardize and harmonize clinical data with NCI Cancer Research Data Commons (CRDC) standards.
2. Manage submissions of data to NCI repositories for public data sharing.

Enhance Correlative Sample Management System (CSMS)

CSMS will provide specimen management across the Network (Contract)

Key functionalities accomplished: Funded by PACT

1. Sharing of specimen shipping manifests and redacted pathology reports
2. Standardized IDs, meta data, and demographics
3. Searchable landing page showing progress of individual projects

New: Support needed from NCI

1. System maintenance (security, operations & maintenance)
2. Training and coordination
3. System upgrades and help desk
4. Configure modules for new assays

New: Formalized Operations Center for Central Coordination

Need for central coordination was a lesson learned from current funding period **(Contract)**

Correlative study intake:

- Correlative study review & prioritization
- Cross-trial analysis proposal review

Assay performance review:

- Assay harmonization
- Assay validation
- Assay concordance monitoring

Strategic oversight:

- Monitor & track Network progress
- Assist NCI in prioritizing trials portfolio & scientific questions

Correlative study performance:

- "Kick off" calls for correlative studies
- Sample request letters
- Support clinical data model development
- HMTA processing

Administrative tasks:

- Data sharing facilitation
- Website to share resources with broader IO community
- Organize annual meetings
- Prepare progress reports
- Committee coordination

Note: CIDC is responsible for data coordination.

Budget

Budget Request for Renewal of CIMAC-CIDC Network

Awards	Mechanism	For 5 years	Per Year
4 CIMACs (academic)	Limited competition U24	$39.6 million	$7.92 million
1 CIDC	Limited competition U24	$14 million	$2.8 million
	U24 total	**$53.6 million**	**$10.72 million**
Operations Center	Contract	$3.5 million	$0.7 million
Specimen Management (CSMS)	Contract	$4.65 million	$0.93 million
	Contracts total	**$8.15 million**	**$1.63 million**
U24 + Contract grand total		**$61.75 million**	**$12.35 million**

2,000-2,300 patients analyzed

Budget above reflects support for the Network without supplemental funding from PACT.

Current funding period:

	U24 awards	Supplements	Total
4 CIMACs	$47.8M	$13M (PACT)	$60.8M
1 CIDC	$5.8M	$10M (PACT) + $1M (NCI)	$16.8M
Total	**$53.6M**	**$24M**	**$77.6M**

Questions from BSA subcommittee

Written responses were provided to questions from the BSA subcommittee: Discussed with BSA subcommittee and found to be satisfactory.

Responses to these questions provided to BSA.

Questions:

1. How does CIDC get incorporated into the overall program and what data will be captured? How will the database that has been generated advance toward an open source similar to, for example, TCGA?
2. Would the trials have been completed if not supported by the NCI?
3. Why not reissue the concept as an open competitive RFA instead of a limited competition?
4. What are the indicators to confirm that standardization and interoperability of assays has been achieved?
5. In terms of standardization, what are the expectations over the next five years?
6. How will the suggestions and recommendations identified by the evaluation panel be incorporated into the re-issue RFA?
7. What process is utilized to review the performance of awarded Centers?
8. What is the process for removing non-performing Centers?