CPTAC Overview:

NEW OPPORTUNITIES IN CANCER BIOLOGY AND PRECISION MEDICINE

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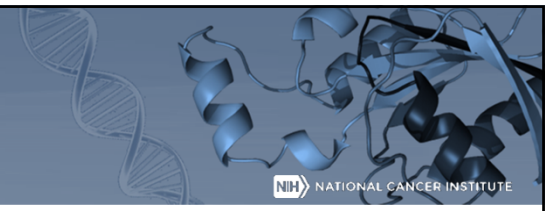
Office of Cancer Clinical Proteomics Research

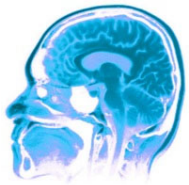
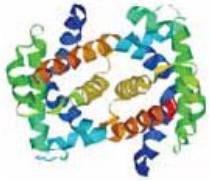
NIH NATIONAL CANCER INSTITUTE

Outline

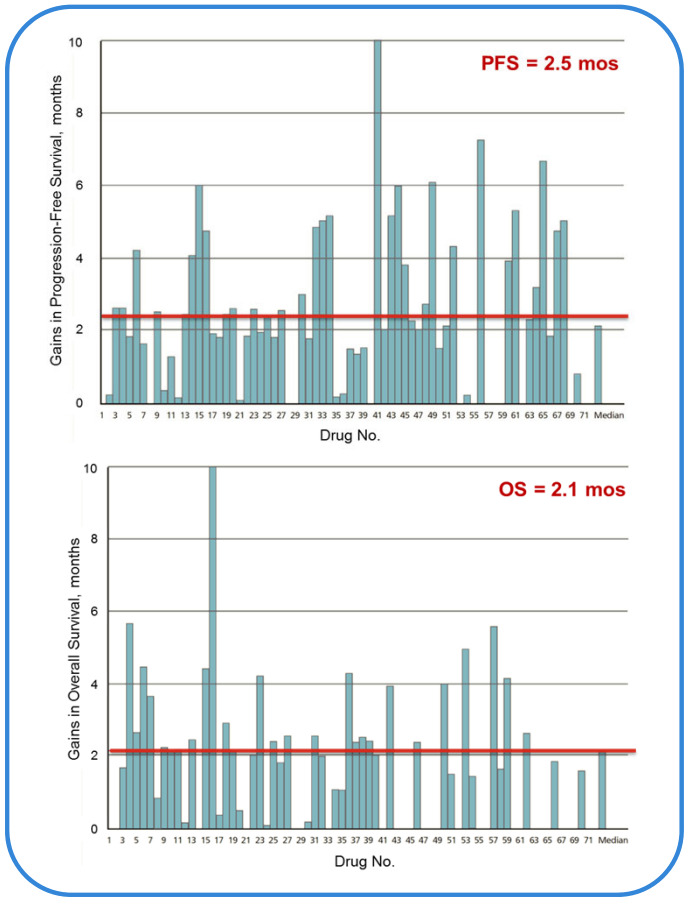


- Motivation
- Examples of proteogenomic integration
- Pipeline
- Replication

Omics in cancer care today

Diagnosis	→ Imaging	
Targeted therapy selection	→ Genomics	
Drug target	→ Protein	

Drugs approved by FDA for advanced cancer



Gains in overall survival for the 71 drugs approved by FDA from 2002 to 2014 for advanced cancer

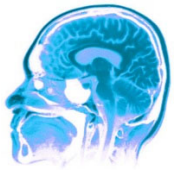
PFS: 2.5 mos

OS: 2.1 mos

Solid tumors

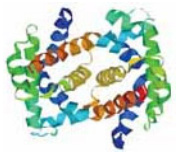
Fojo et al. *JAMA Otolaryngol Head Neck Surg.* 2014;140:1225-1236.

Opportunity for Big Data



Imaging

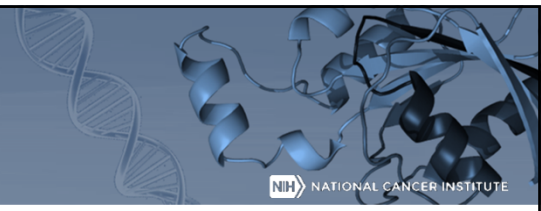
Genomics



Proteomics

Improved Prevention, Diagnosis, Treatment

CPTAC Research Question



Can proteomics help predict which patients will respond to targeted therapies?

Flagship Characterization Studies

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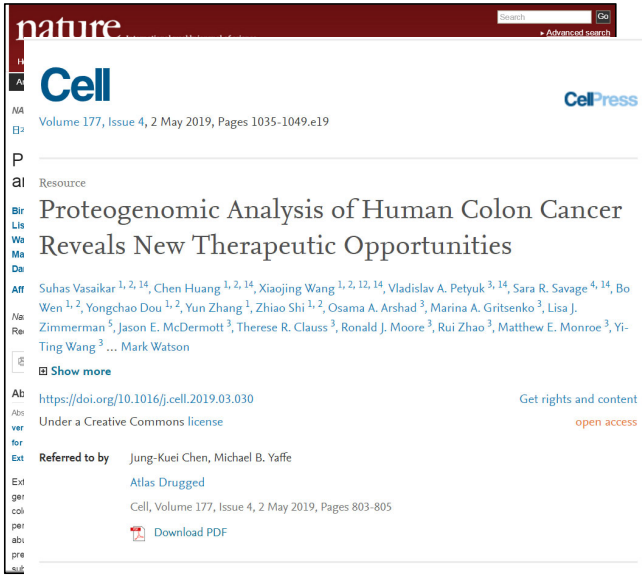
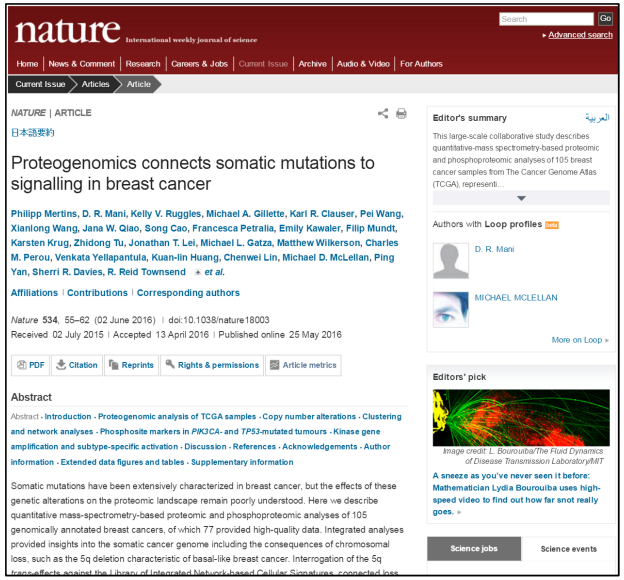
CPTAC Data Portal

Colorectal Cancer



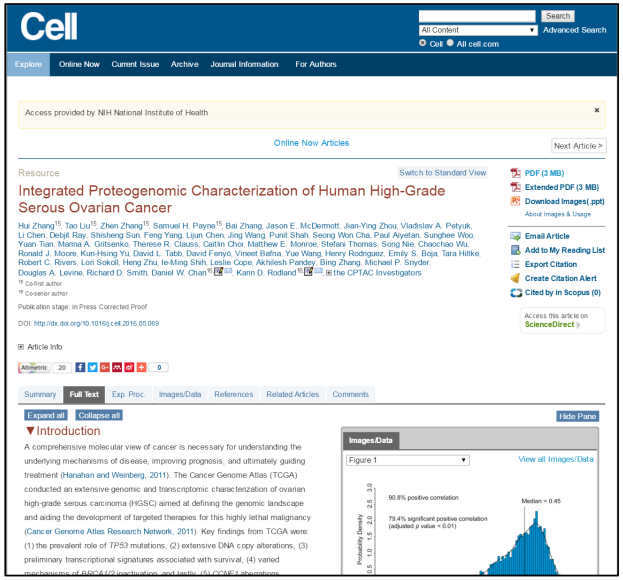
Zhang B, *Nature* 513, 382–387 (18 Sept 2014)

Breast Cancer



Mertins P, et al, *Nature* 534, 55–62 (02 June 2016)

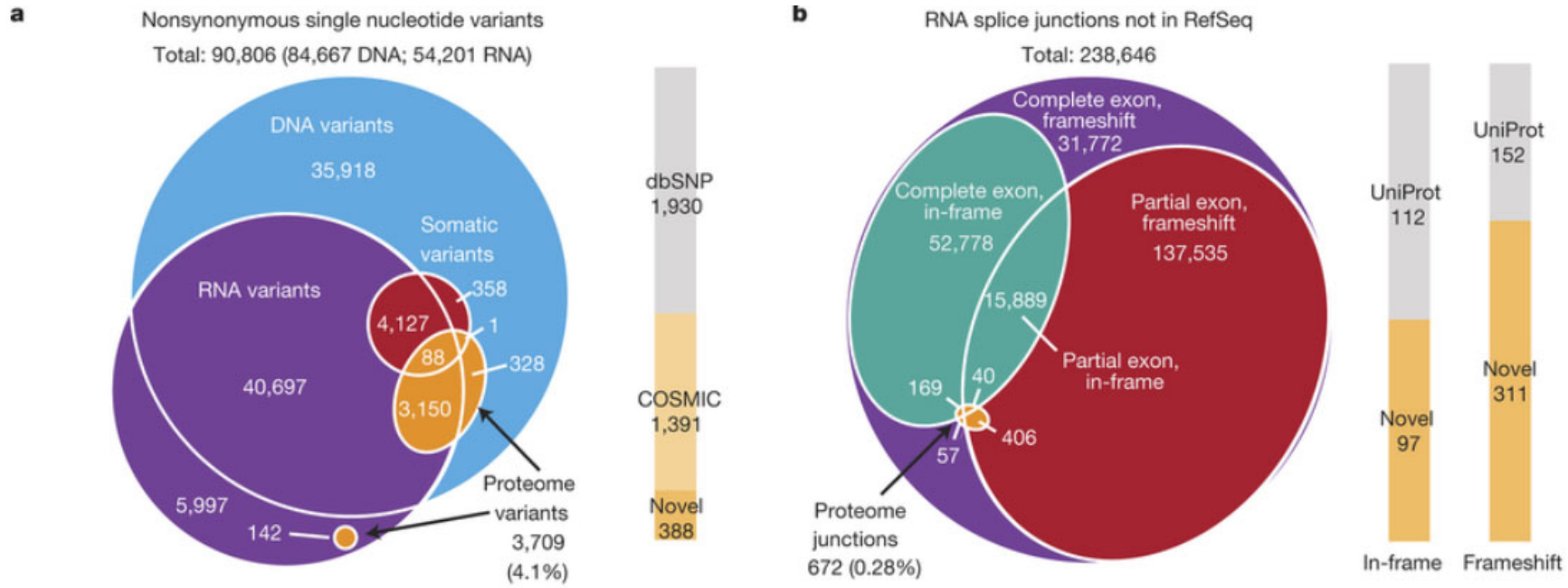
Ovarian Cancer



Zhang, H, et al, *Cell* 166(3):755-65 (28 Jul 2016)

Vasaikar S, et al, *Cell*, 177, 1035-49 (2 May 2019)

Proteogenomic mutation detection

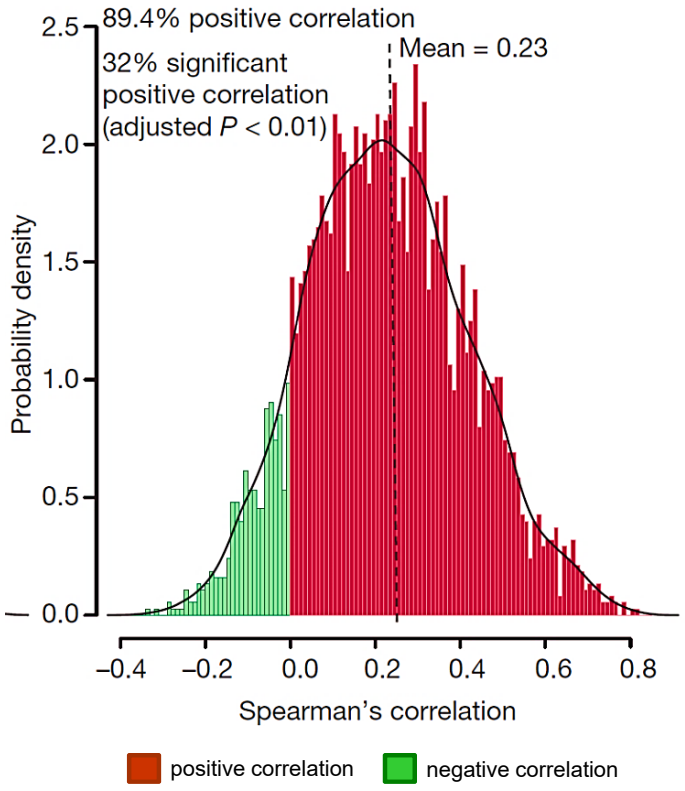


- Most single amino acid variants previously reported
- Few splice junctions detected, but many are novel

Mertins, et al. "Proteogenomics connects somatic mutations to signaling in breast cancer
Nature **2016,** doi:10.1038/nature18003

mRNA levels are poor indicators of abundance for many proteins

mRNA and protein abundance correlation for individual genes across all the tumors (samples)



Mean Correlation:

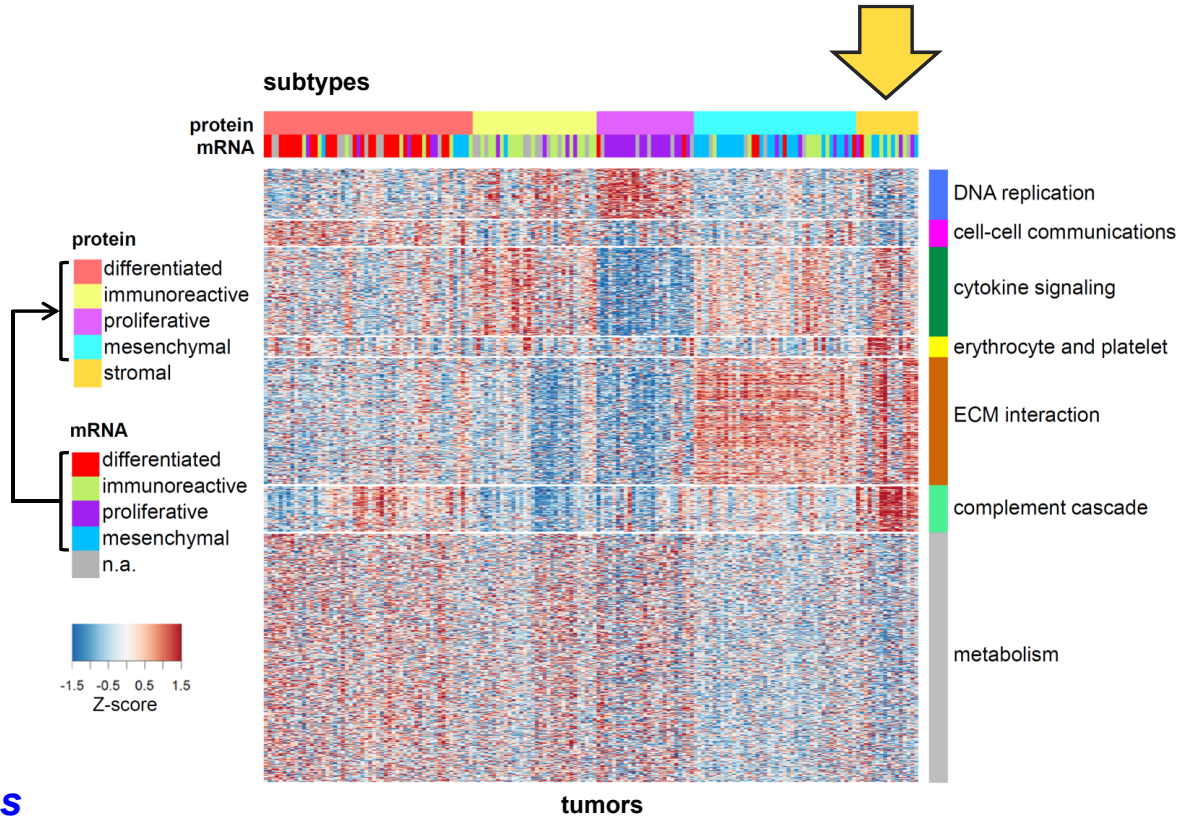
- within 0.47
- across 0.23

- ***Similarly poor correlations has also been shown for breast, ovarian and gastric cancers***

nature
2014 Jul 20; doi: 10.1038 / ***Nature*** 13438

Ovarian Cancer
(PROTEIN ABUNDANCE - new proteome subtype identified)

- **174 ovarian HGSC tumors**
  - Selection criteria:
    - Overall Survival (OS)
    - Homologous Recombination Deficiency status (HRD)
- **5 proteomic subtypes**
  (4 transcriptomic subtypes)
  - mRNA subtypes translate at protein level
  - New “stromal’ subtype emerged
- ***While interesting observations, no strong separation of OS and HRD status***



Cell 166(3):755-65 (28 Jul 2016)

Ovarian Cancer
(pathway activation correlates with overall survival)

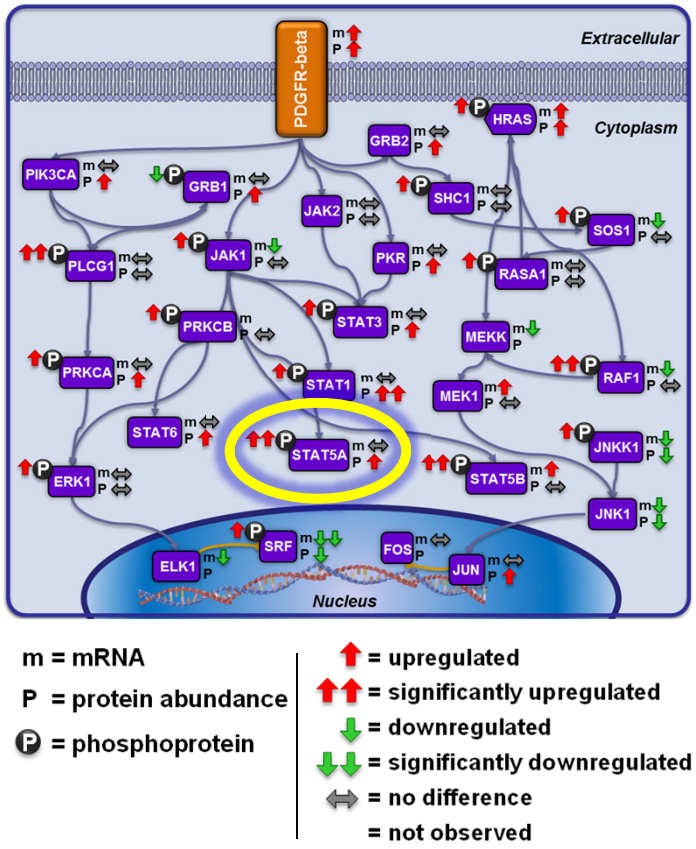
Network Data Exchange
[NCI Pathway Interaction Database]

(214 signaling pathways)

- Significantly upregulated pathways with short OS
  - Protein data (p<0.05)
  - Phosphorylation data (p<0.0001)
  - mRNA data (p<0.05)

- *Combining comprehensive proteomic, phosphoproteomic and transcriptomic analysis better elucidated the proteogenomic complexity of pathway activation not obtainable at the subtype level.*

*PDGFR pathway upregulation in TCGA **tumors** with short OS*



Cell 166(3):755-65 (28 Jul 2016)

What's next for CPTAC (3.0)

(Programmatic Structure)

A. Proteome Characterization Centers

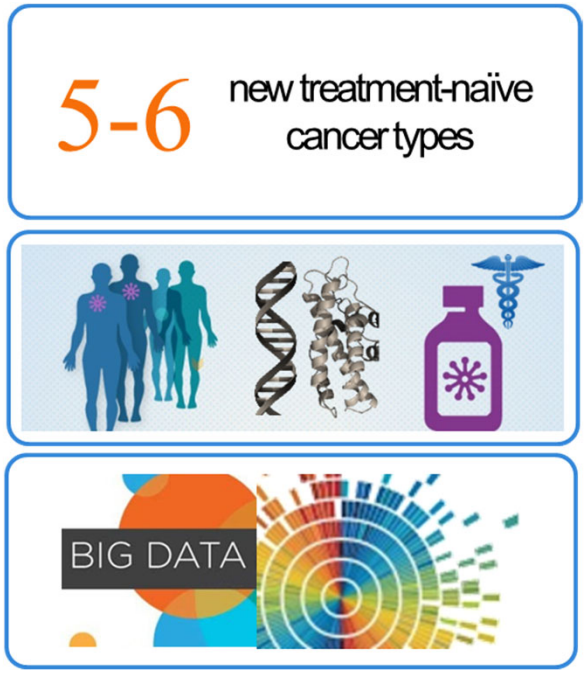
additional cancer types where questions remain on their proteogenomic complexity

B. Proteogenomic Translational Research Centers

research models and *NCI-sponsored clinical trials*

C. Proteogenomic Data Analysis Centers

develop innovative tools that process and integrate data across the entire proteom

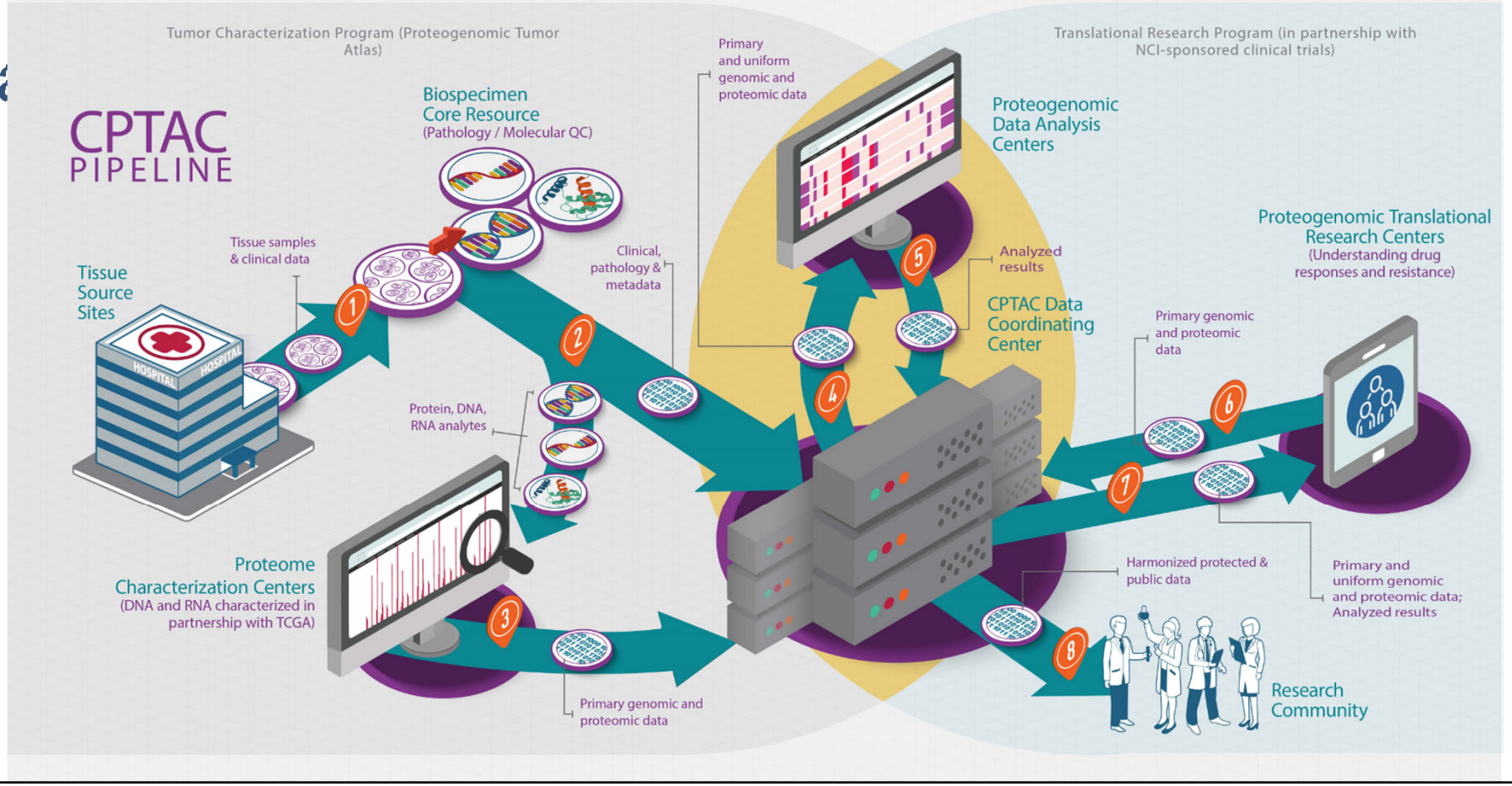


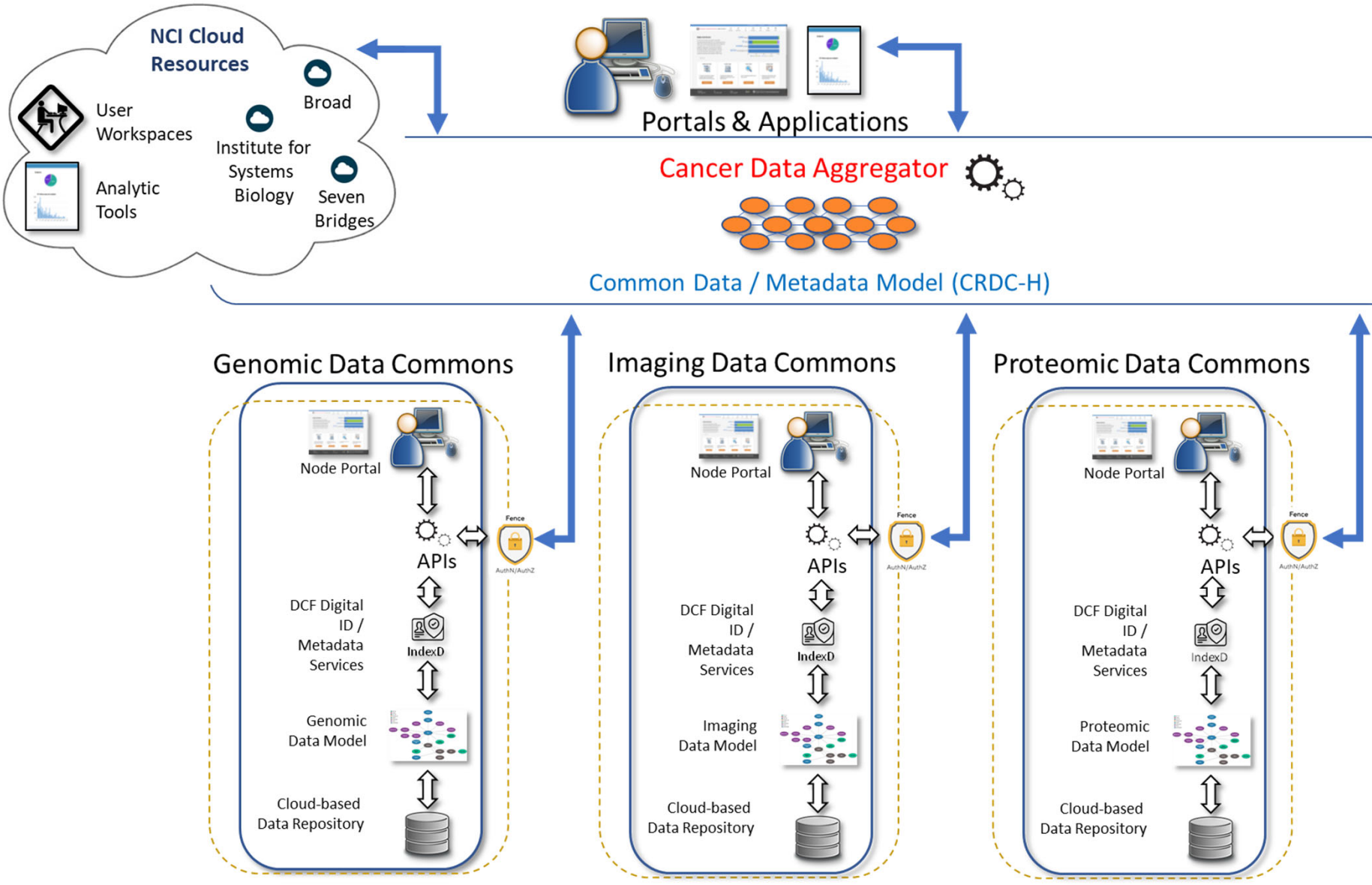
Public Resources:

Data types: genomics (NCI GDC), proteomics (CPTAC Data Portal), imaging (NCI TCIA)

Assays: CPTAC Assay Portal; ***Antibodies:*** CPTAC Antibody Portal

CPTAC workflow




NCI Cloud Resources
User Workspaces
Analytic Tools
Broad
Institute for Systems Biology
Seven Bridges
Portals & Applications
Cancer Data Aggregator
Common Data / Metadata Model (CRDC-H)
Genomic Data Commons
Imaging Data Commons
Proteomic Data Commons
Node Portal
APIs
DCF Digital ID / Metadata Services
IndexD
Genomic Data Model
Imaging Data Model
Proteomic Data Model
Cloud-based Data Repository
Fence
AuthN/AuthZ

Available data and where to get them

Tumor type	Proteomic	Genomic	Radiology
Breast	245	120	14
Kidney	120	110	43
Colorectal	197	197*	0
Ovary	286	177	28
Lung	111	111	23
Endometrial	104	101	42
Available at	https://cptac-data-portal.georgetown.edu/cptacPublic/	https://portal.gdc.cancer.gov/projects/CPTAC-3	https://wiki.cancerimagingarchive.net/display/Public/CPTAC+Imaging+Proteomics

* Raw genomics data from 110 cases are available at the Sequence Read Archive (SRA), BioProject ID: PRJNA514017 (ftp://ftp-trace.ncbi.nlm.nih.gov/sra/review/SRP178677_20190114_143443_27e795eb0f314edf0479737480ab0f2a).

Thank You

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  - Chelsea Peterson
  - Galen Hostetter
- Tissue Source Sites
  - Asterand
  - Global Bioclinical
  - Biomatrix
  - IGC
  - ABS
  - IIMO
  - Beaumont
  - Boston Medical Center
  - BioPartners
  - University of California – San Diego
  - Cedars-Sinai
  - Spectrum
  - Pittsburgh Cancer Center
  - BioOptions
  - Baylor
  - St. Joseph's
  - Washington University