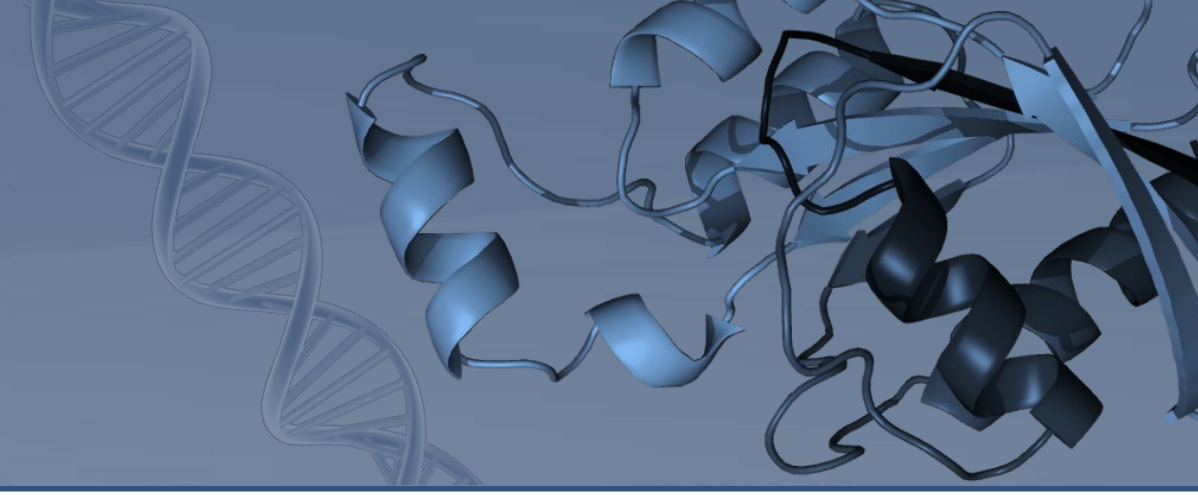


OFFICE OF CANCER CLINICAL PROTEOMICS RESEARCH

CPTAC Overview:

NEW OPPORTUNITIES IN CANCER BIOLOGY AND PRECISION MEDICINE

Chris Kinsinger, PhD

Program Director

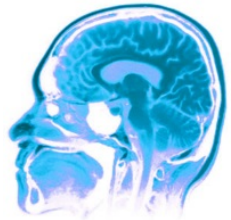
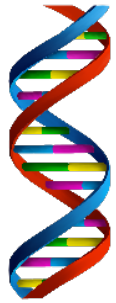
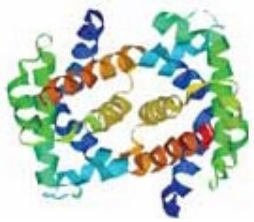
Office of Cancer Clinical Proteomics Research

NIH NATIONAL CANCER INSTITUTE

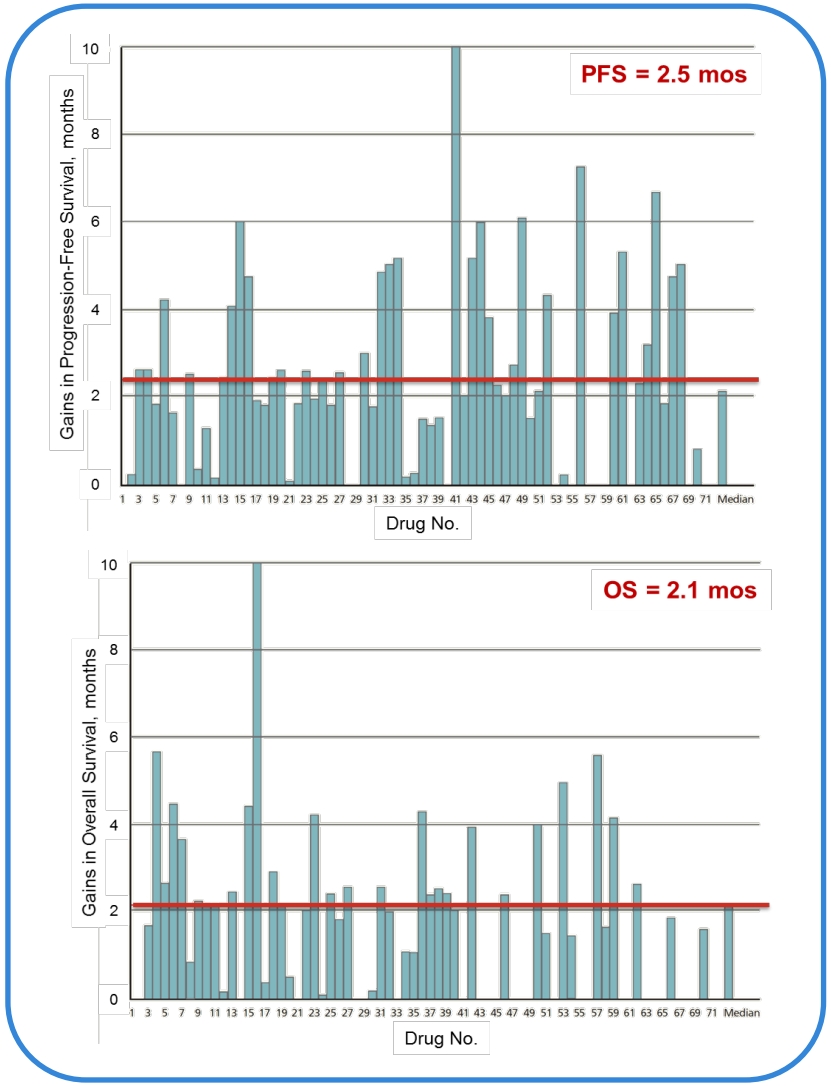
Outline

- 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

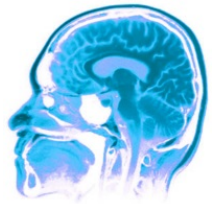
PFS: 2.5 mos

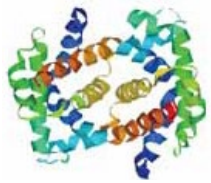
OS: 2.1 mos

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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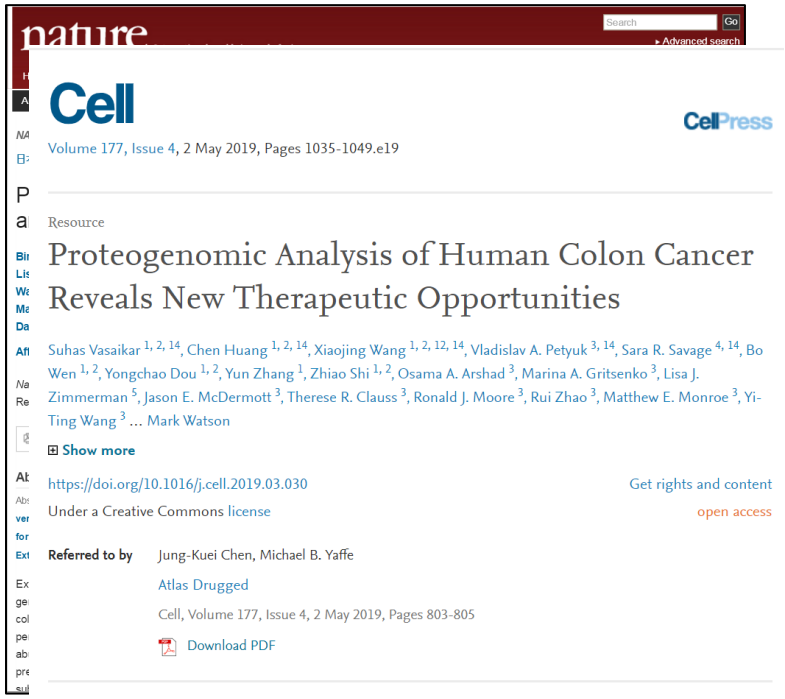
CPTAC Data Portal

Colorectal Cancer

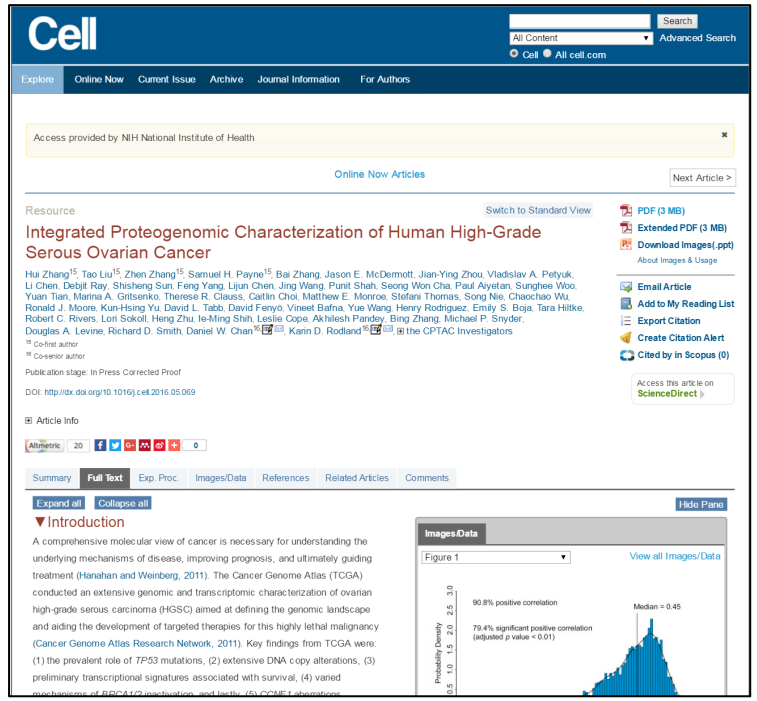


Zhang B, *Nature* 513, 382–387 (18 Sept 2014)

Breast Cancer

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

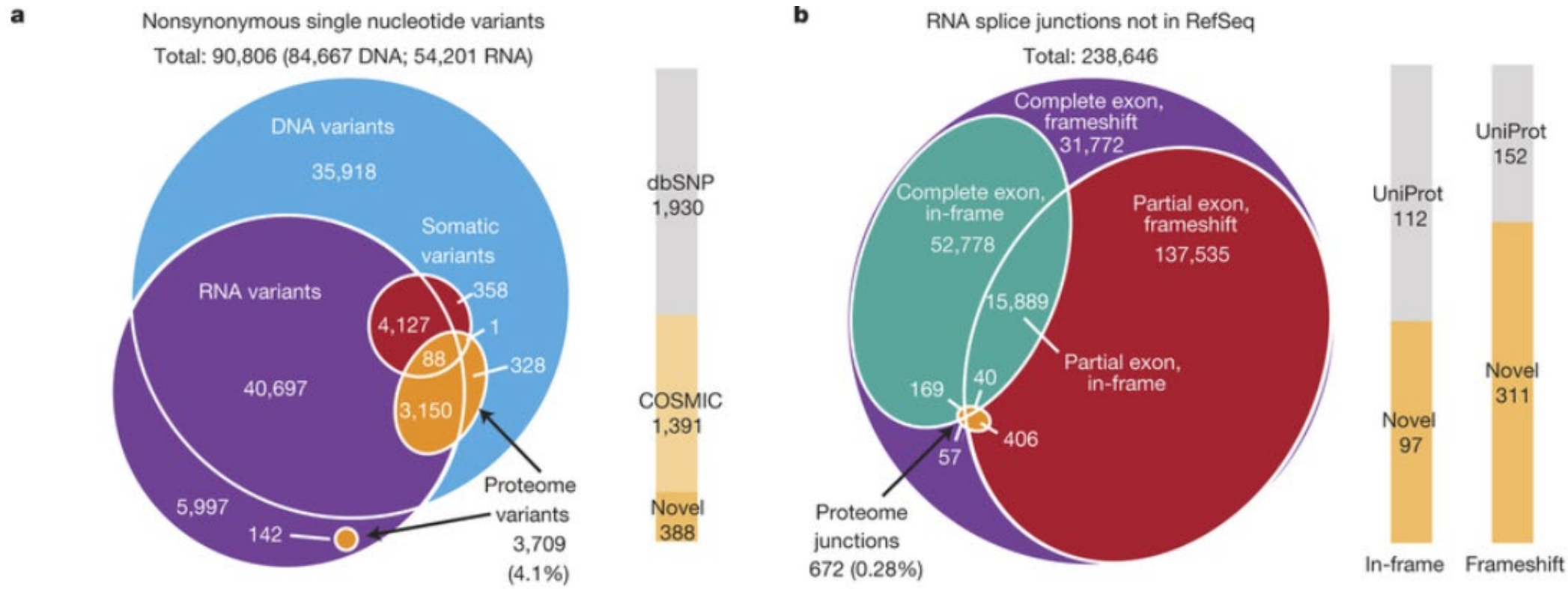
Ovarian Cancer



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

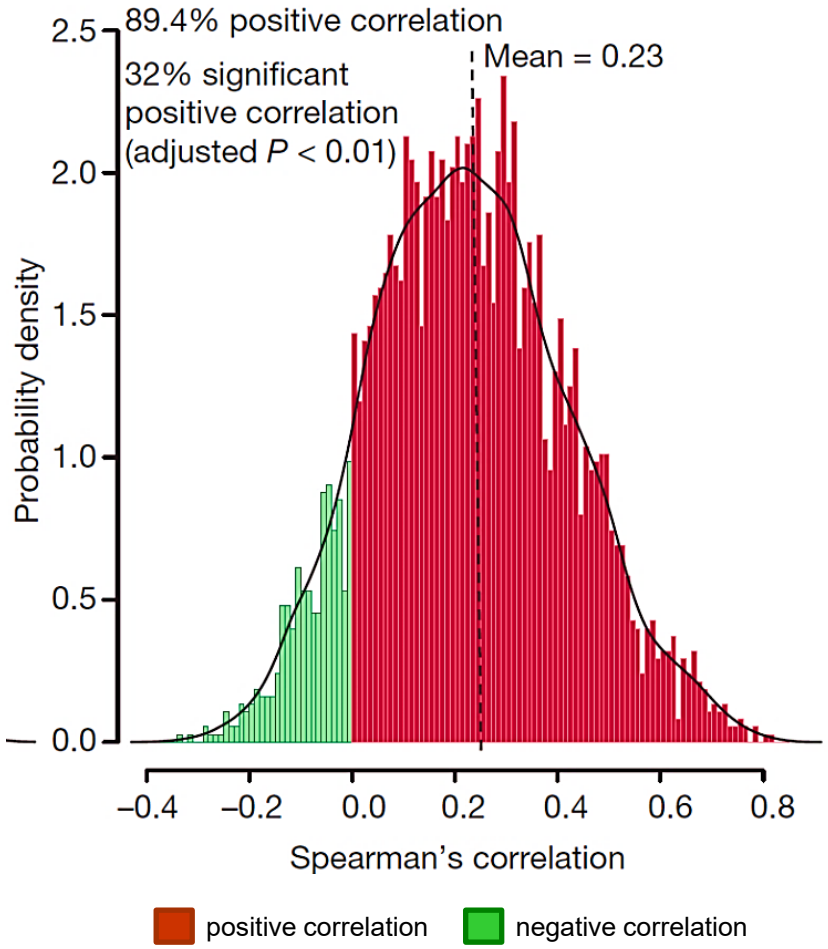


- Most single amino acid variants previously reported
- Few splice junctions detected, but many are novel

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

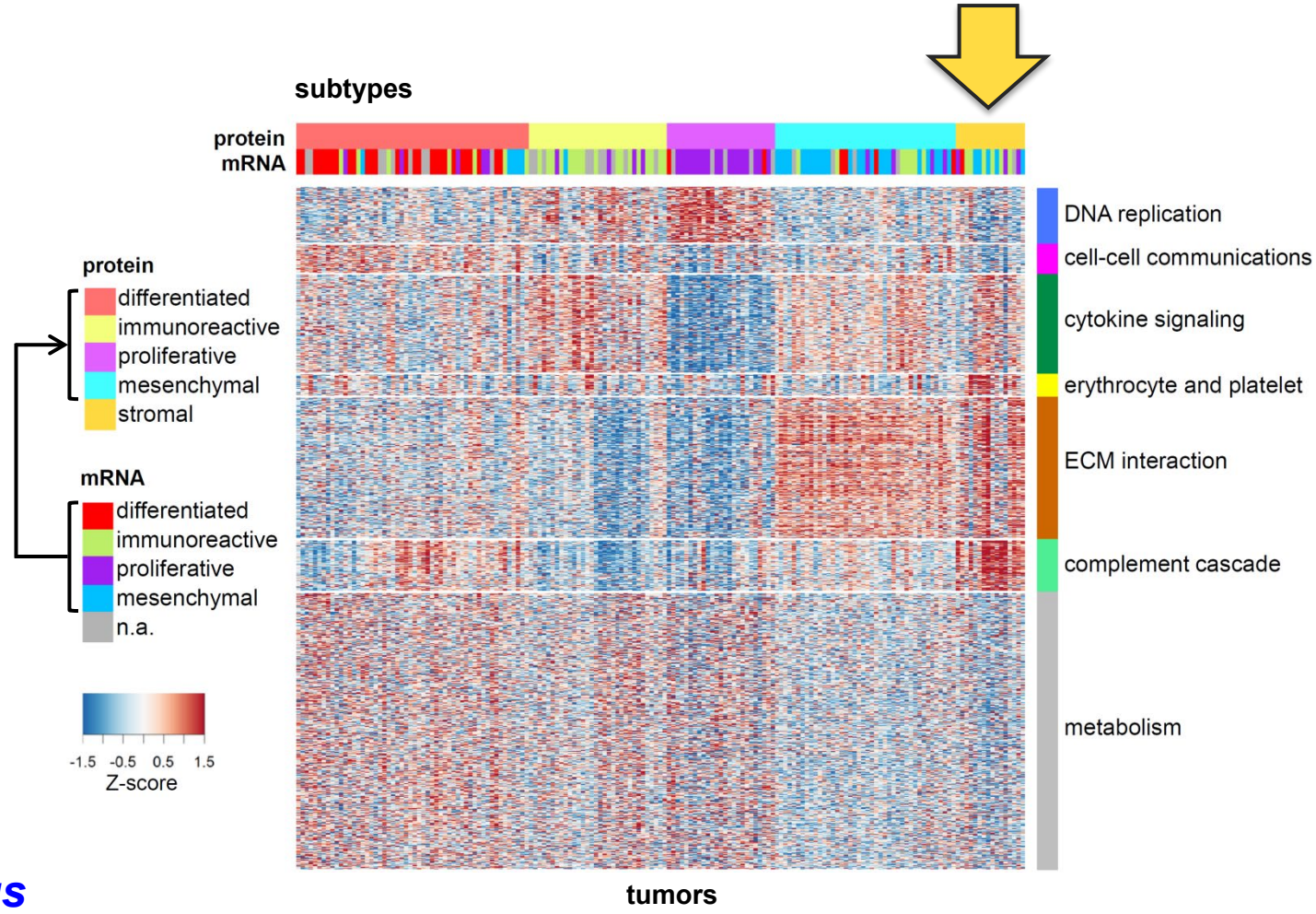
- ***Similarly poor correlations has also been shown for breast, ovarian and gastric cancers***

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)

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Network Data Exchange

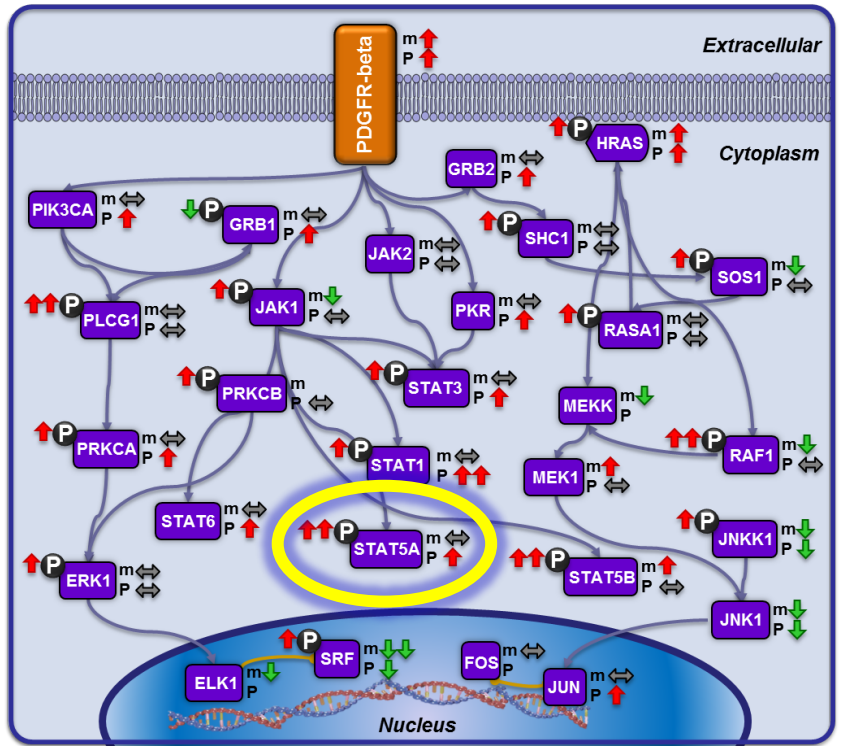
[NCI Pathway Interaction Database]

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

What's next for CPTAC (3.0)

(Programmatic Structure)

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A. Proteome Characterization Centers

additional cancer types where questions remain on their proteogenomic complexity

5-6 new treatment-naïve cancer types

B. Proteogenomic Translational Research Centers

research models and *NCI-sponsored clinical trials*

C. Proteogenomic Data Analysis Centers

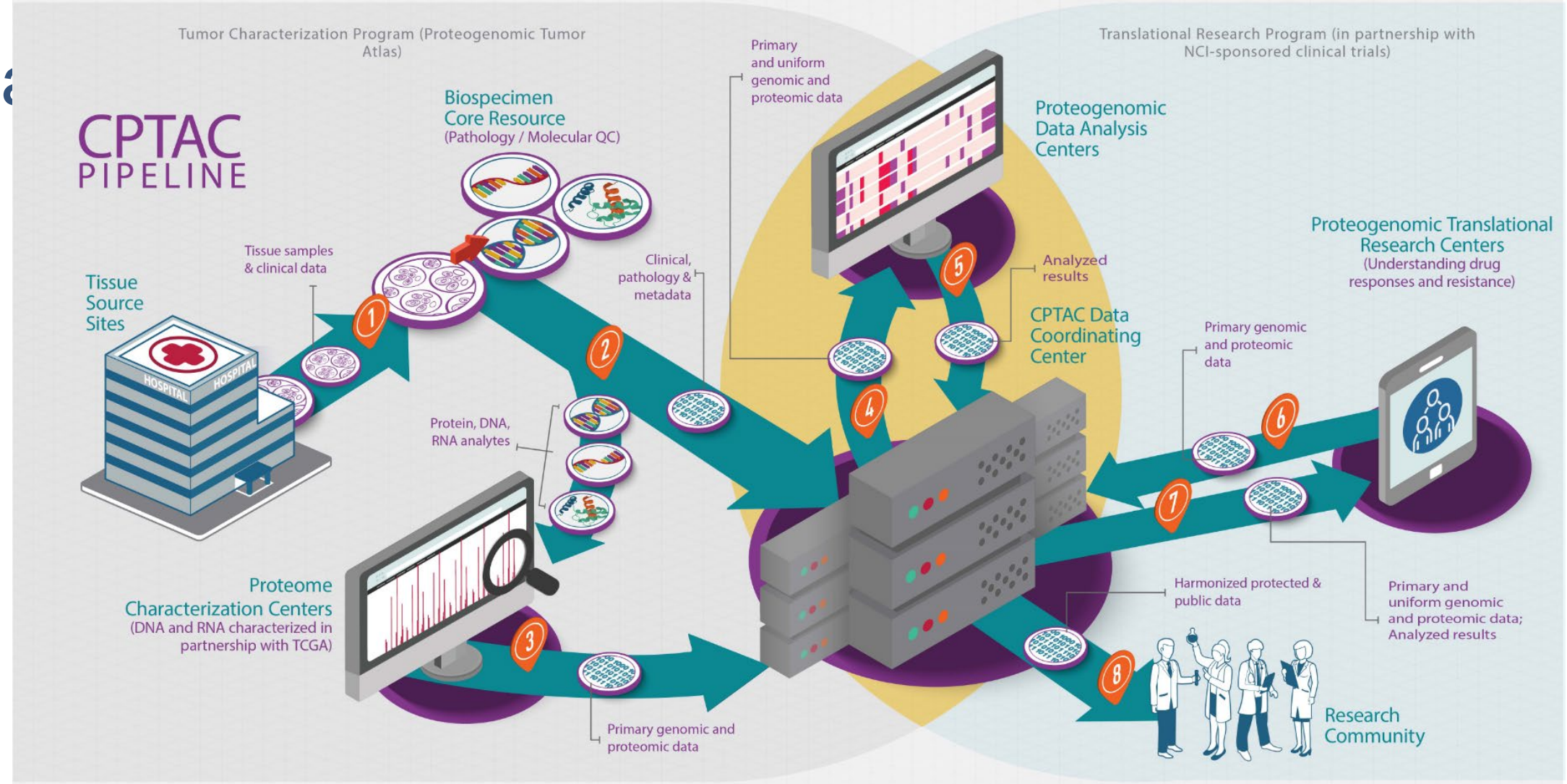
develop innovative tools that process and integrate data across the entire proteom

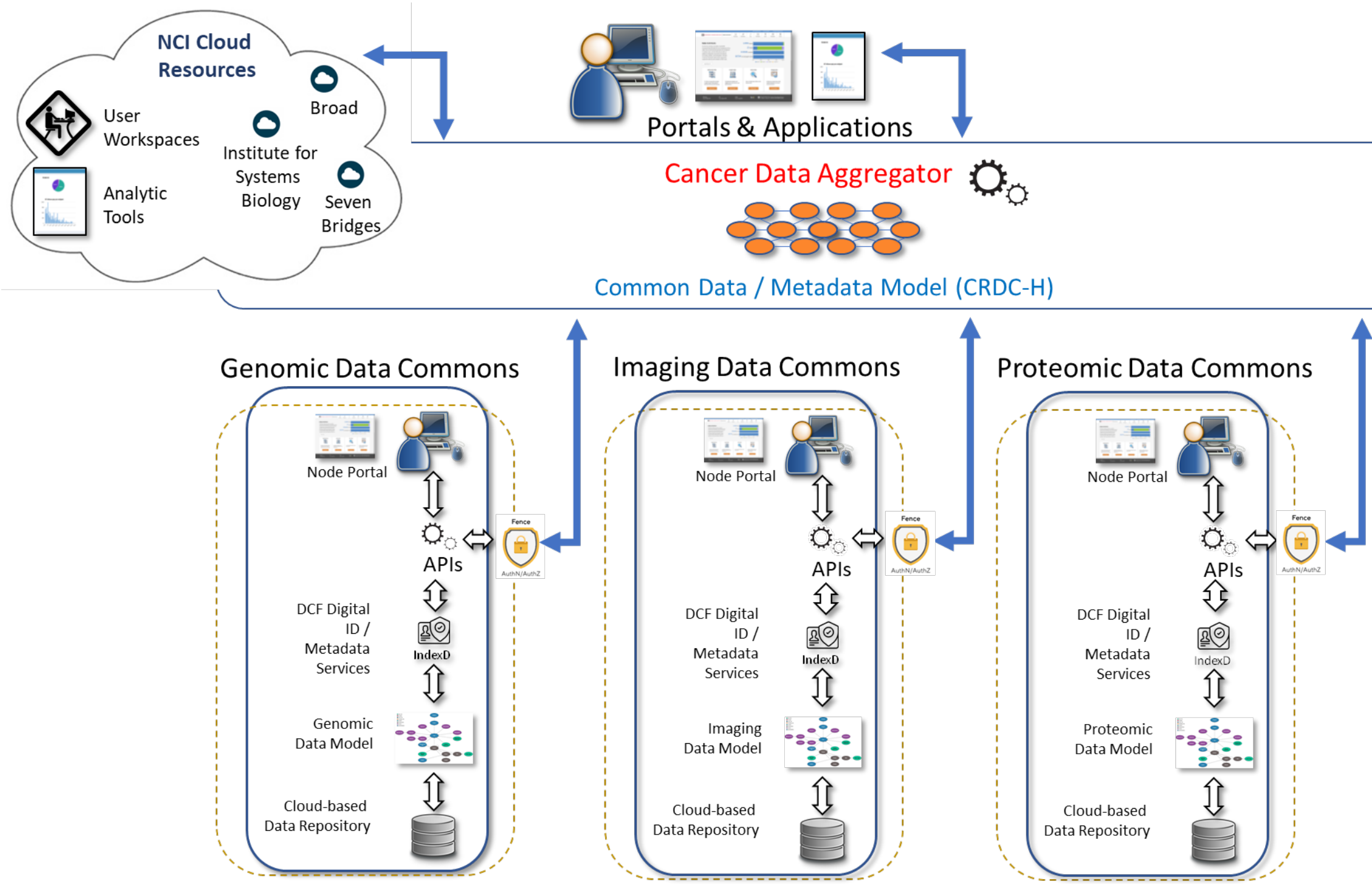
Public Resources:

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

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

Acknowledgments

- NCI
  - Henry Rodriguez
  - Emily Boja
  - Tara Hiltke
  - Mehdi Mesri
  - Etaria Omekwe
- Leidos
  - Linda Hannick
  - Kathy Terlesky
  - Maureen Dyer
  - Nancy Roche
  - Melissa Borucki
  - Kim Valentino
  - Jeff McLean
  - Tanya Krubit
  - Mathangi Thiagarajan
  - Mary Barcus
  - Gordon Whiteley
  - William Bocik
- Battelle
  - Laura Aume
  - Jonda Vance
  - Michael Schlatt
  - Iness Jeddi
  - Stephanie Kute
- Vanderbilt
  - Dan Liebler
  - Bing Zhang
  - Rob Slebos
  - Lisa Zimmerman
- Broad Institute
  - Steve Carr
  - Philipp Mertins
  - Michael Gillette
  - Karl Clauser
- Fred Hutchinsson Cancer Research Center
  - Amanda Paulovich
  - Jeff Whiteaker
  - Regine Schnoerr
- University of Washington
  - Andy Hoofnagle
- ESAC
  - Karen Ketchum
  - Ratna Thangudu
- Washington University – St. Louis
  - Reid Townsend
  - Sherri Davies
- Johns Hopkins
  - Dan Chan
  - Hui Zhang
  - Zhen Zhang
  - Stephanie Thomas
- Pacific Northwest National Lab
  - Dick Smith
  - Karin Rodland
  - Tao Liu
  - Sam Payne
  - Jason McDermott
- New York University
  - David Fenyo
- Columbia University
  - Andrea Califano
  - Aris Floratos
- The Ohio State University
  - Kun Huang
- National Institute of Standards and Technology
  - Steve Stein
  - Sandy Markey
- Spectragen-Informatics
  - Paul Rudnick
- Georgetown University
  - Nathan Edwards
  - Peter McGarvey
- Van Andel Research Institute
  - Scott Jewell
  - Dan Rohrer
  - Dana Valley
  - 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