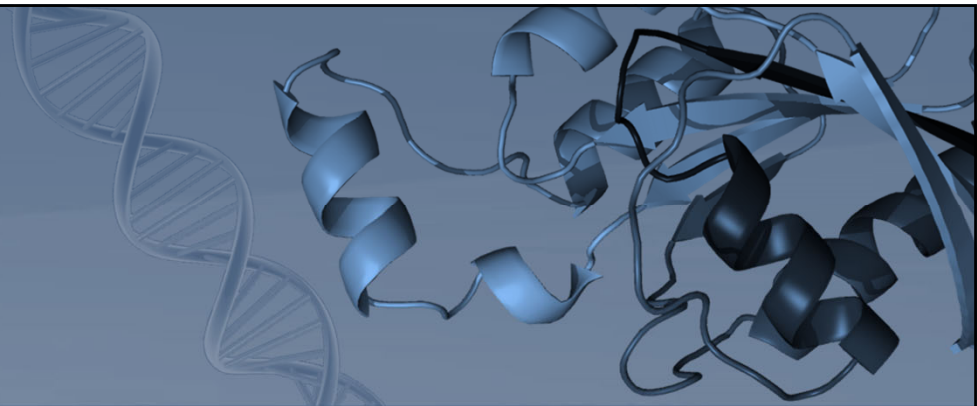




OFFICE OF CANCER CLINICAL
PROTEOMICS RESEARCH



CPTAC Overview:

NEW OPPORTUNITIES IN CANCER BIOLOGY AND PRECISION MEDICINE

Chris Kinsinger, PhD

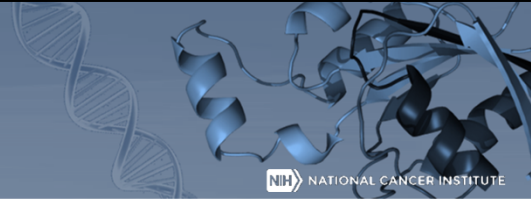
Program Director

Office of Cancer Clinical Proteomics Research



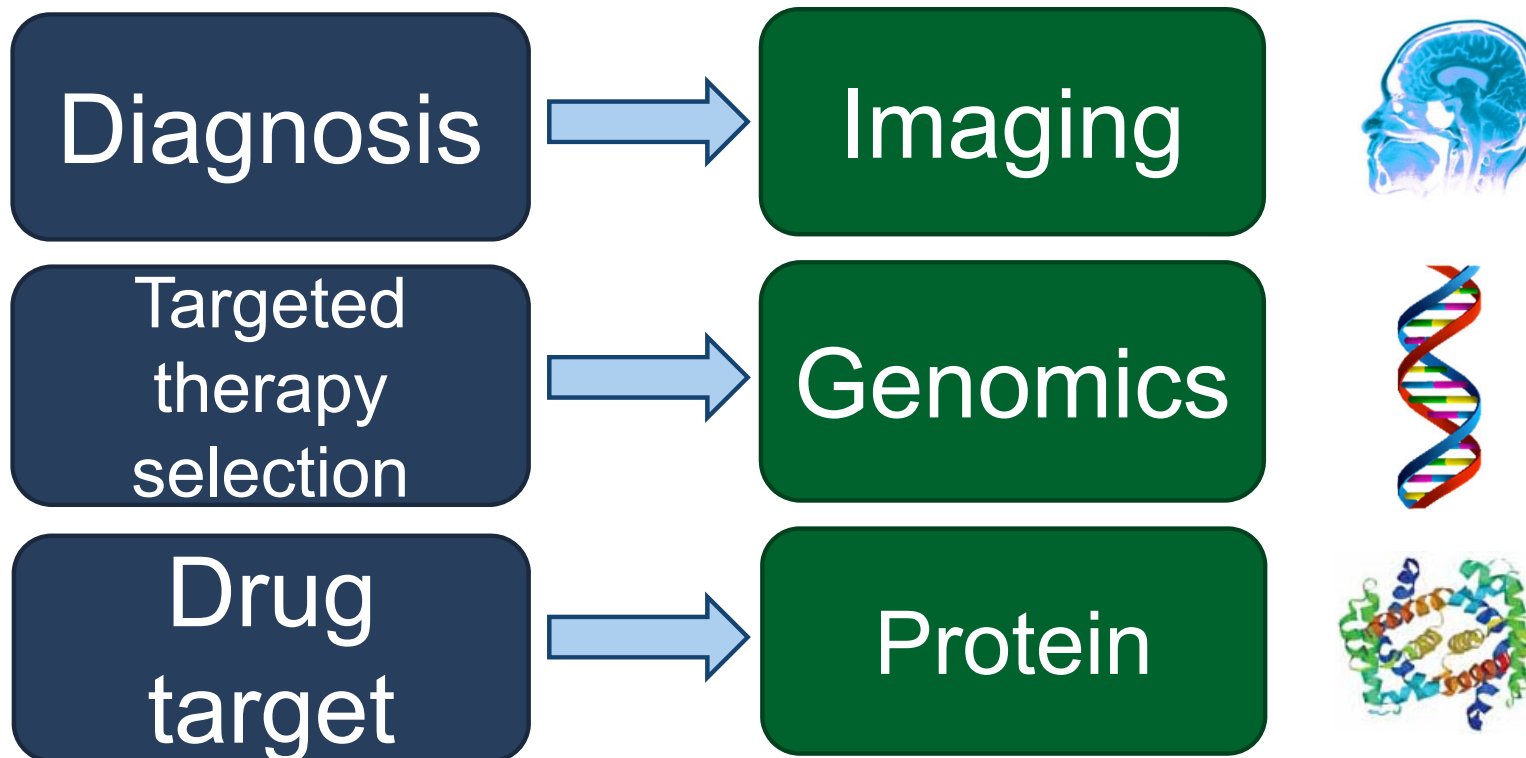
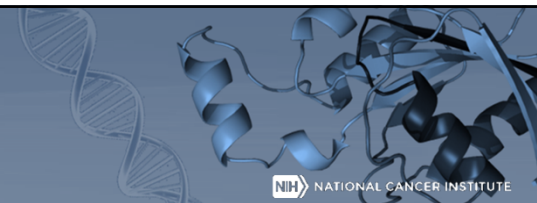
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CANCER
INSTITUTE

Outline

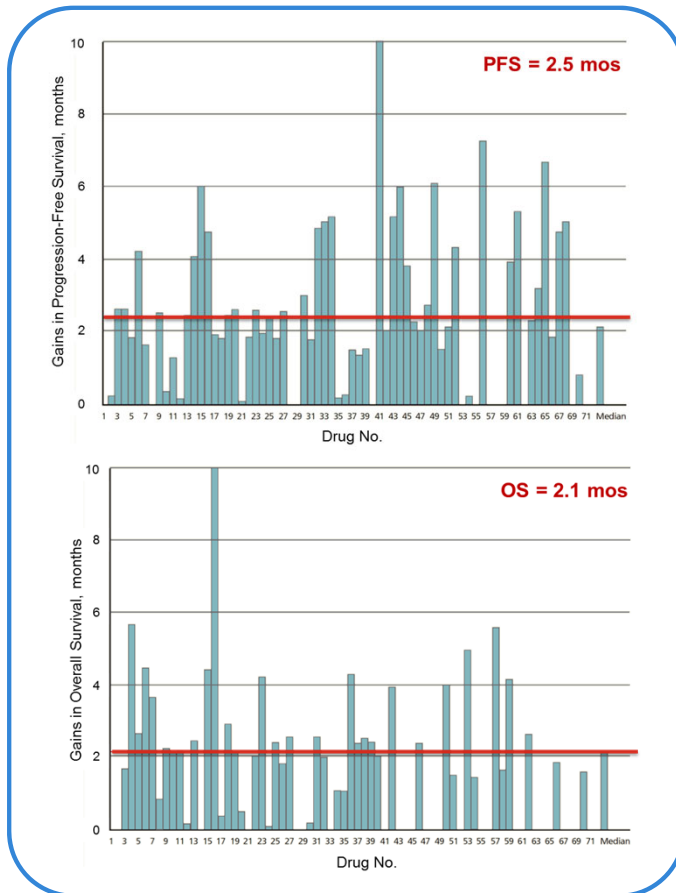
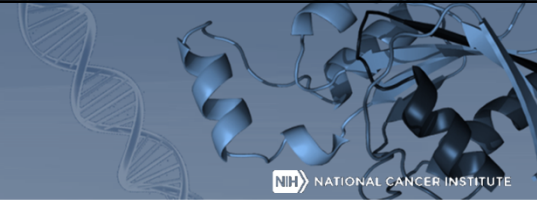


- Motivation
- Examples of proteogenomic integration
- Pipeline
- Replication

Omics in cancer care today



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

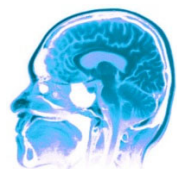
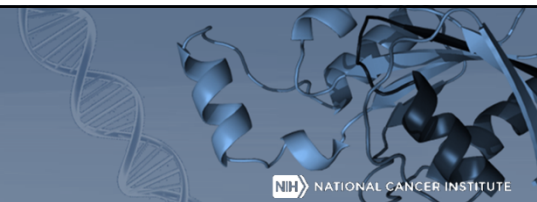
PFS: 2.5 mos

OS: 2.1 mos

Solid tumors

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

Opportunity for Big Data



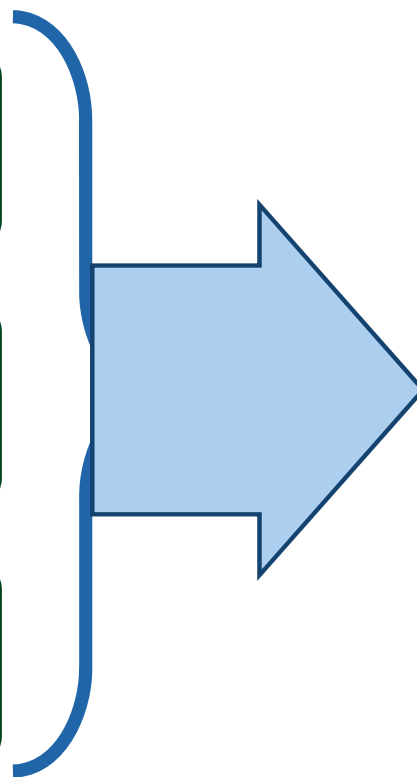
Imaging



Genomics

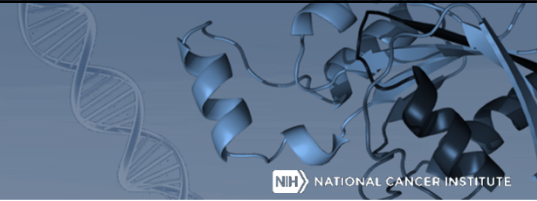


Proteomics



Improved
Prevention,
Diagnosis,
Treatment

CPTAC Research Question



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

Flagship Characterization Studies

NIH NATIONAL CANCER INSTITUTE



Colorectal Cancer

Breast Cancer

Ovarian Cancer

Cell
Volume 177, Issue 4, 2 May 2019, Pages 1035-1049.e19

Resource

Proteogenomic Analysis of Human Colon Cancer Reveals New Therapeutic Opportunities

Suhas Vasaikar^{1,2,14}, Chen Huang^{1,2,14}, Xiaojing Wang^{1,2,12,14}, Vladislav A. Petyuk^{3,14}, Sara R. Savage^{4,14}, Bo Wen^{1,2}, Yongchao Dou^{1,2}, Yun Zhang¹, Zhao Shi^{1,2}, Osama A. Arshad³, Marina A. Gritsenko³, Lisa J. Zimmerman³, Jason E. McDermott³, Therese R. Clauss³, Ronald J. Moore³, Rui Zhao³, Matthew E. Monroe³, Yi-Ting Wang³, ... Mark Watson

<https://doi.org/10.1016/j.cell.2019.03.030>

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Referred to by: Jung-Kuei Chen, Michael B. Yaffe

Atlas Drugged

Cell, Volume 177, Issue 4, 2 May 2019, Pages 803-805

Download PDF

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

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

nature
International weekly journal of science

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Current Issue > Articles > Article

Proteogenomics connects somatic mutations to signalling in breast cancer

Philipp Mertins, D. R. Mani, Kelly V. Ruggles, Michael A. Gillette, Karl R. Clauser, Pei Wang, Xianrong Wang, Jana W. Cui, Song Cao, Francesca Petralia, Emily Kawaller, Filip Mundt, Karsten Krug, Zhidong Tu, Jonathan T. Lee, Michael L. Gatta, Matthew Wilkerson, Charles M. Perou, Venkata Yellapantula, Kuan-In Huang, Chenwei Lin, Michael D. McLellan, Ping Yan, Sherri R. Davies, R. Reid Townsend & et al.

Affiliations | Contributions | Corresponding authors

Nature 534, 55–62 (02 June 2016) | doi:10.1038/nature18003
Received 02 July 2015 | Accepted 13 April 2016 | Published online 25 May 2016

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Abstract

Introduction - Proteogenomic analysis of TCGA samples - Copy number alterations - Clustering and network analyses - Phospho markers in PFK3A- and TP53-mutated tumours - Kinase gene amplification and subtype-specific activation - Discussion - References - Acknowledgements - Author information - Extended data figures and tables - Supplementary information

Somatic mutations have been extensively characterized in breast cancer, but the effects of these genetic alterations on the proteomic landscape remain poorly understood. Here we describe quantitative mass-spectrometry-based proteomic and phosphoproteomic analyses of 105 genomically annotated breast cancers, of which 77 provided high-quality data. Integrated analyses provided insights into the somatic cancer genome including the consequences of chromosomal loss, such as the 5q deletion characteristic of basal-like breast cancer. Interrogation of the 5q transcriptome against the library of Integrated Network-based Cellular Signatures connected loss

Editor's summary

This large-scale collaborative study describes quantitative mass spectrometry-based proteomic and phosphoproteomic analyses of 105 breast cancer samples from the Cancer Genome Atlas (TCGA), represent...

Authors with Loop profiles

D. R. Mani

MICHAEL MCLELLAN

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Editors' pick

Image credit: L. Bourouiba/The Fluid Dynamics of Disease Transmission Laboratory/MT

A sneeze as you've never seen it before: Mathematician Lydia Bourouiba uses high-speed video to find out how far and how fast it goes.

Science jobs | Science events

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

Cell

Access provided by NIH National Institute of Health

Online Now Articles

Integrated Proteogenomic Characterization of Human High-Grade Serous Ovarian Cancer

Hui Zhang^{1,2}, Tao Liu^{1,2}, Zhen Zhang^{1,2}, Samuel H. Payne^{1,2}, Bai Zhang, Jason E. McDermott, Jian-Ying Zhou, Vladislav A. Petyuk, Li Chen, Daxin Ray, Shaoheng Sun, Feng Yang, Lian Chen, Jing Wang, Punit Shah, Seong Won Cho, Paul Ayerlin, Sunghee Woo, Yanyan Tian, Mariana A. Gritsenko, Therese R. Clauss, Gailin Chai, Matthew E. Monroe, Stefan Thomas, Song Nie, Chaochao Wu, Robert J. Moore, Kun-Hong Yu, David L. Tabb, David Ferris, Vinod Balva, Yue Wang, Henry Rodriguez, Emily S. Book, Tara Hillis, Robert C. Rivers, Lori Sokoll, Heng Zhu, Le-Ming Shah, Leslie Coppe, Akhlesh Pandey, Bing Zhang, Michael P. Snyder, Douglas A. Levine, Richard D. Smith, Daniel W. Chan, ... Keen D. Rodland & et al. as the CPTAC Investigators

Publication stage: In Press, Corrected Proof

DOI: <https://doi.org/10.1016/j.cell.2016.06.059>

Article Info

Summary | Full Text | Exp. Proc. | Images/Data | References | Related Articles | Comments

Introduction

A comprehensive molecular view of cancer is necessary for understanding the underlying mechanisms of disease, improving prognosis, and ultimately guiding treatment (Hanahan and Weinberg, 2011). The Cancer Genome Atlas (TCGA) conducted an extensive genomic and transcriptomic characterization of ovarian high-grade serous carcinoma (HGSC) aimed at defining the genomic landscape and aiding the development of targeted therapies for this highly lethal malignancy (Cancer Genome Atlas Research Network, 2011). Key findings from TCGA were (1) the prevalent role of TP53 mutations, (2) extensive DNA copy alterations, (3) preliminary transcriptional signatures associated with survival, (4) varied mechanisms of BRCA1/2 inactivation, and (5) CNV/CPV alterations.

Images/Data

Figure 1

View all Images/Data

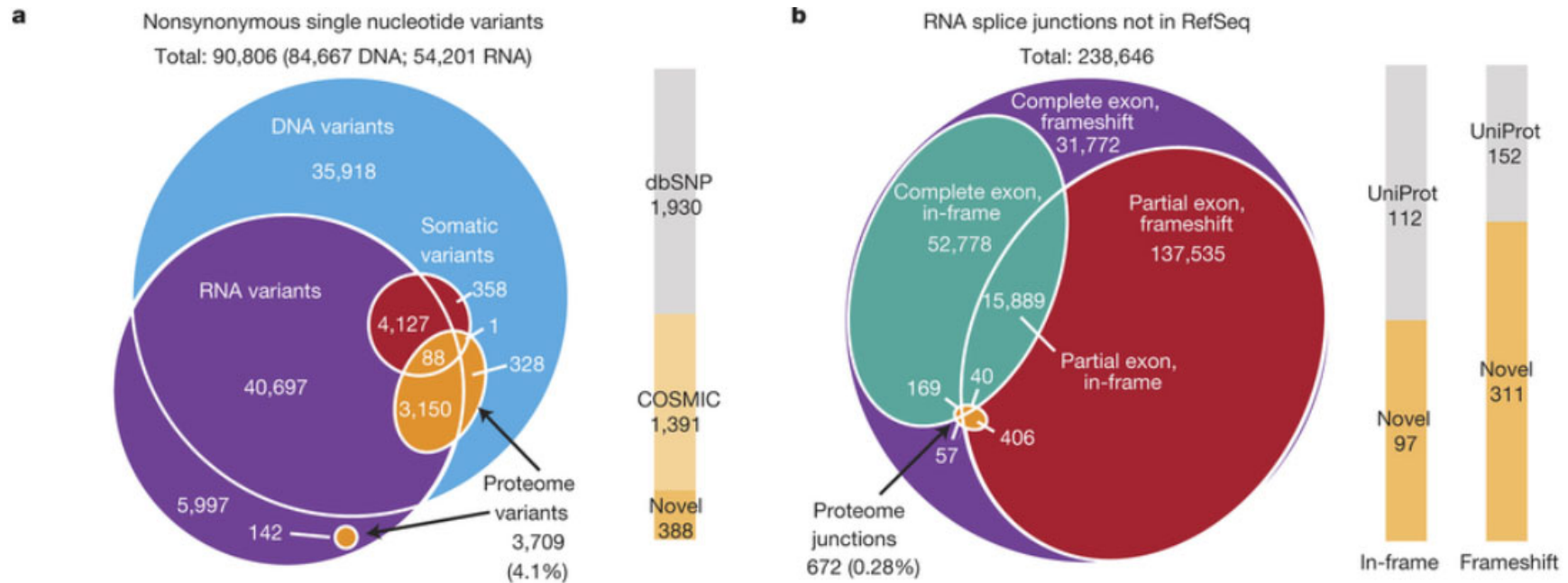
90.8% positive correlation

79.4% significant positive correlation (indicated in value < 0.01)

Median = 0.45

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

Proteogenomic mutation detection

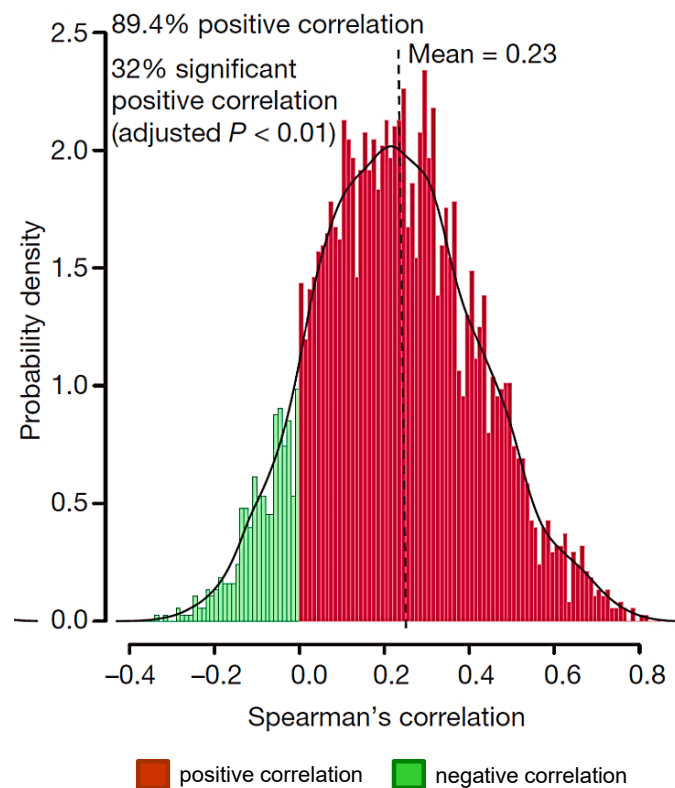


- Most single amino acid variants previously reported
- Few splice junctions detected, but many are novel

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**

Ovarian Cancer

(PROTEIN ABUNDANCE - new proteome subtype identified)

- **174 ovarian HGSC tumors**

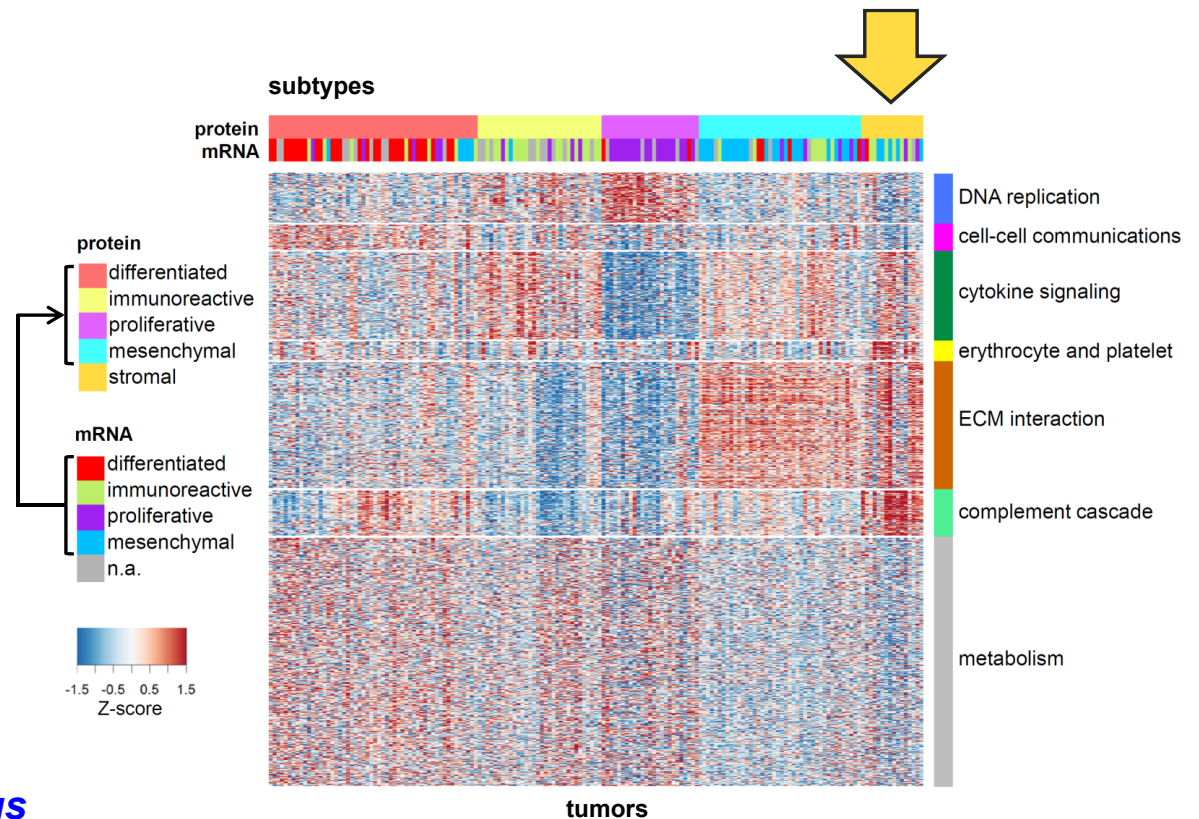
- Selection criteria:
 - Overall Survival (OS)
 - Homologous Recombination Deficiency status (HRD)

- **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*



Ovarian Cancer

(pathway activation correlates with overall survival)

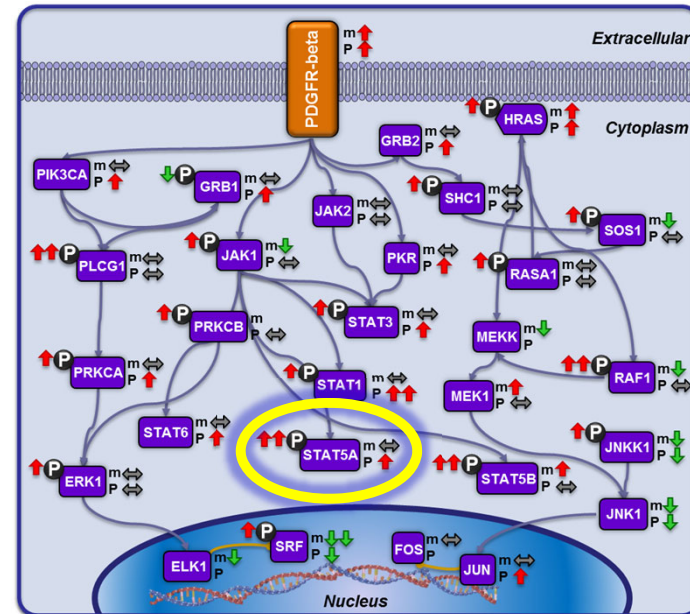
Network Data Exchange

[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

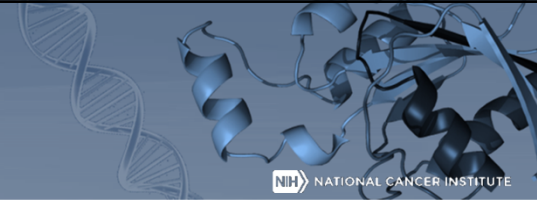


m = mRNA
 P = protein abundance
 P = phosphoprotein

↑ = upregulated
 ↑↑ = significantly upregulated
 ↓ = downregulated
 ↓↓ = significantly downregulated
 ↔ = no difference
 = not observed

What's next for CPTAC (3.0)

(Programmatic Structure)



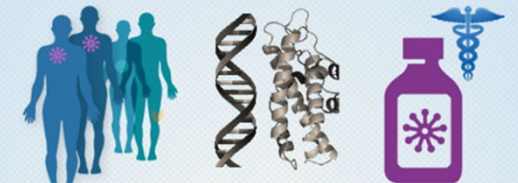
A. Proteome Characterization Centers

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

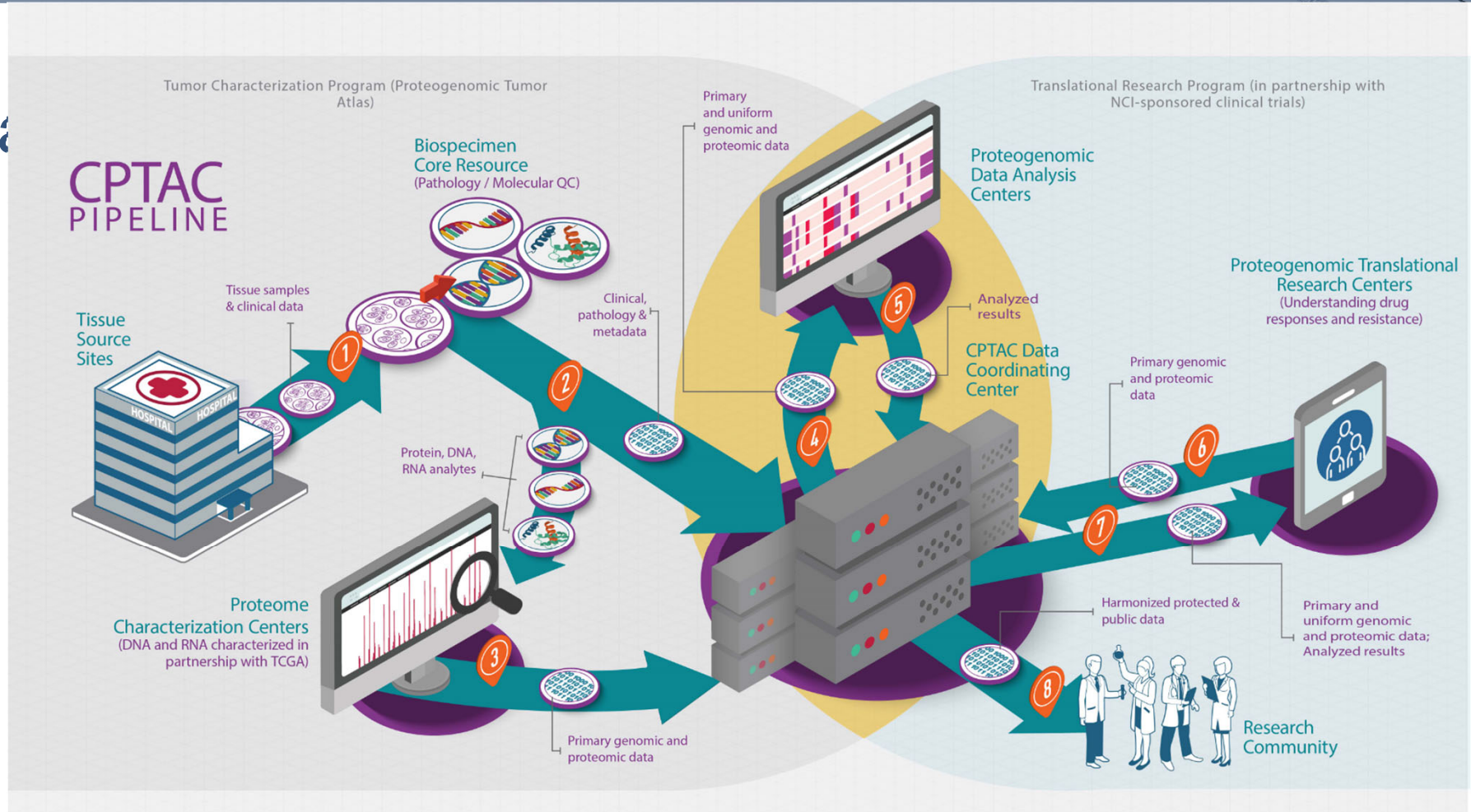


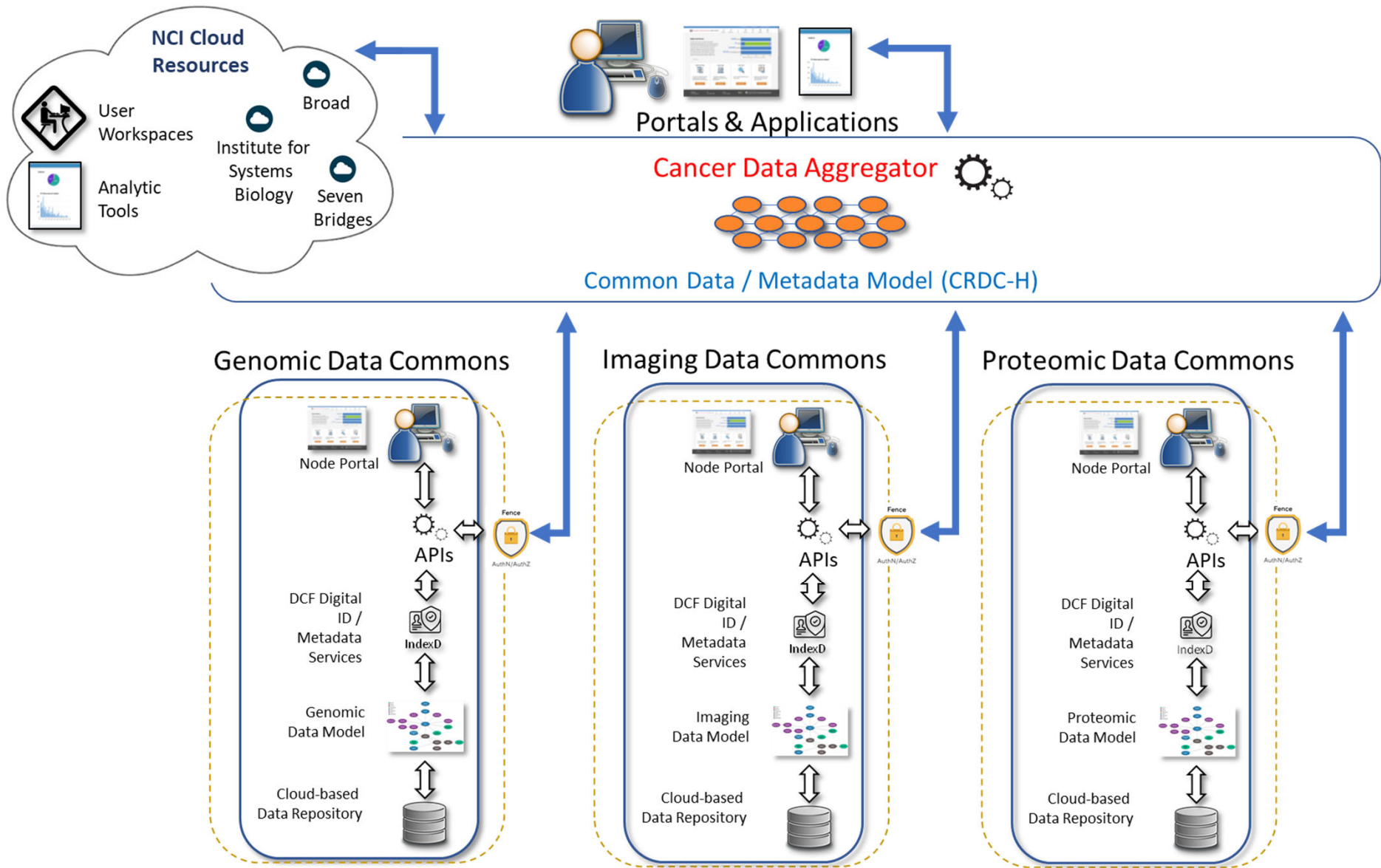
Public Resources:

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

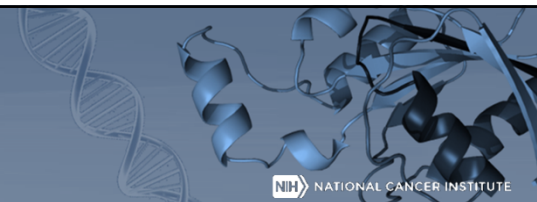
Assays: CPTAC Assay Portal; **Antibodies:** CPTAC Antibody Portal

CPTAC workflow





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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 - Melissa Borucki
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 - Mary Barcus
 - Gordon Whiteley
 - William Bocik
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 - Jonda Vance
 - Michael Schlatt
 - Iness Jeddi
 - Stephanie Kute
- **Vanderbilt**
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 - Biomatrix
 - IGC
 - ABS
 - IIMO
 - Beaumont
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 - University of California – San Diego
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