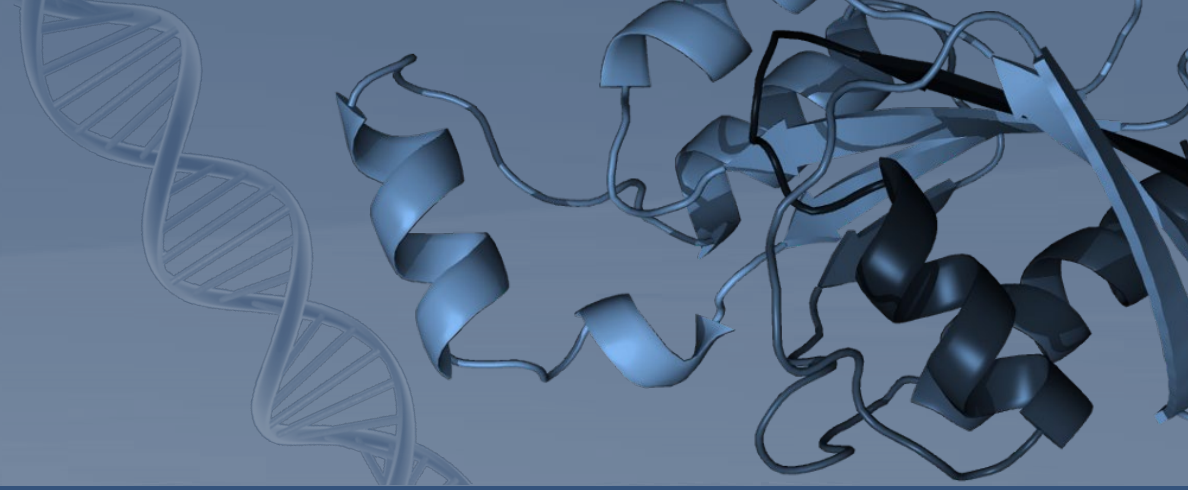




OFFICE OF CANCER CLINICAL
PROTEOMICS RESEARCH



CPTAC Overview:

NEW OPPORTUNITIES IN CANCER BIOLOGY AND PRECISION MEDICINE

Chris Kinsinger, PhD

Program Director

Office of Cancer Clinical Proteomics Research



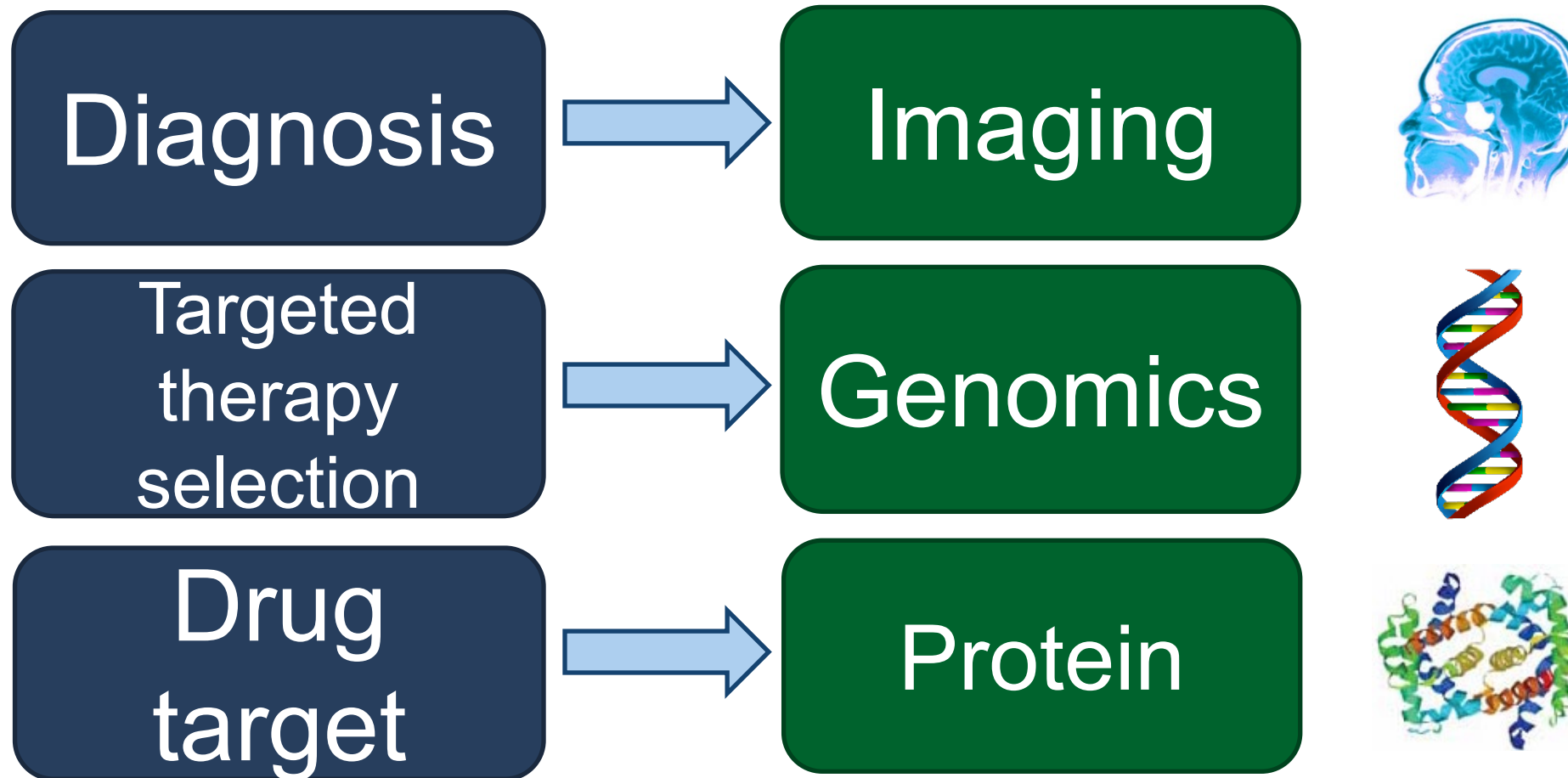
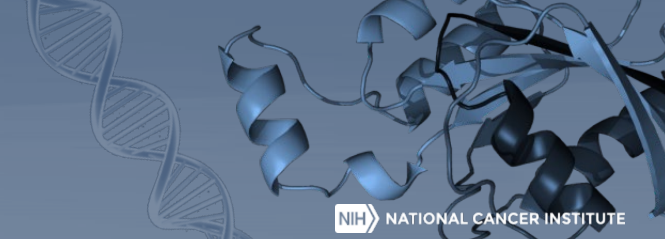
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Outline

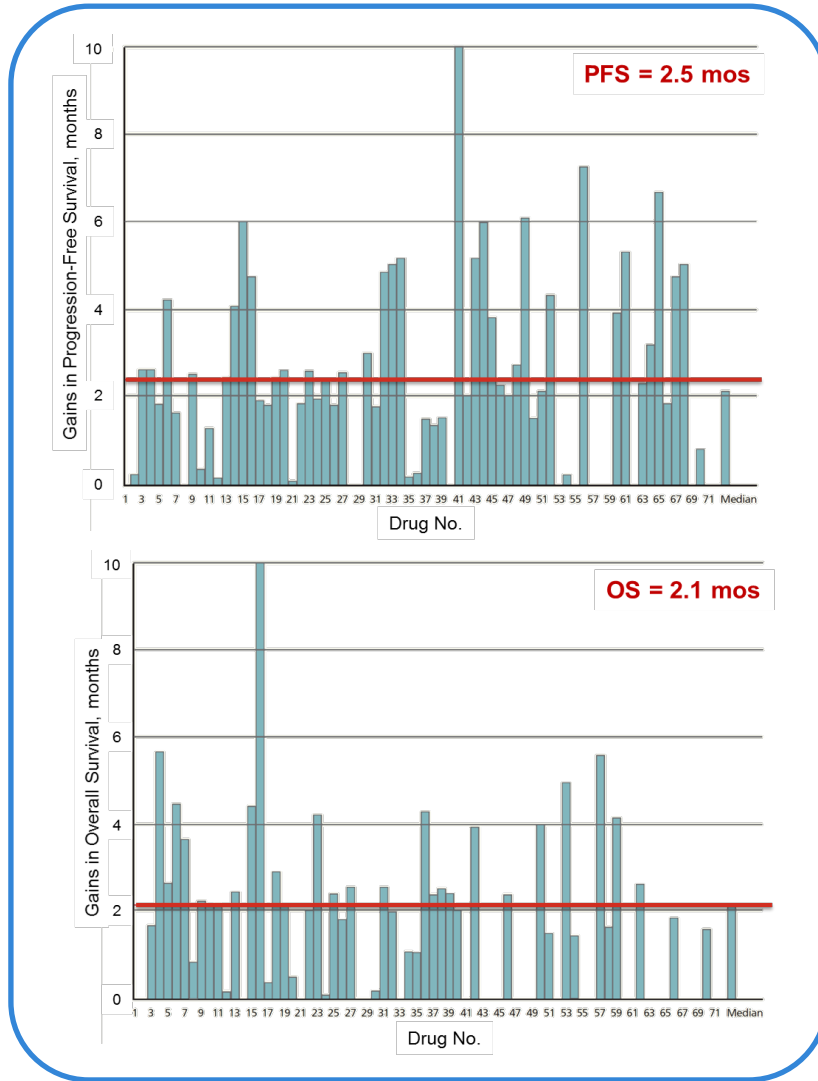


- Motivation
- Examples of proteogenomic integration
- Pipeline
- Replication

Omics in cancer care today



Drugs approved by FDA for advanced cancer

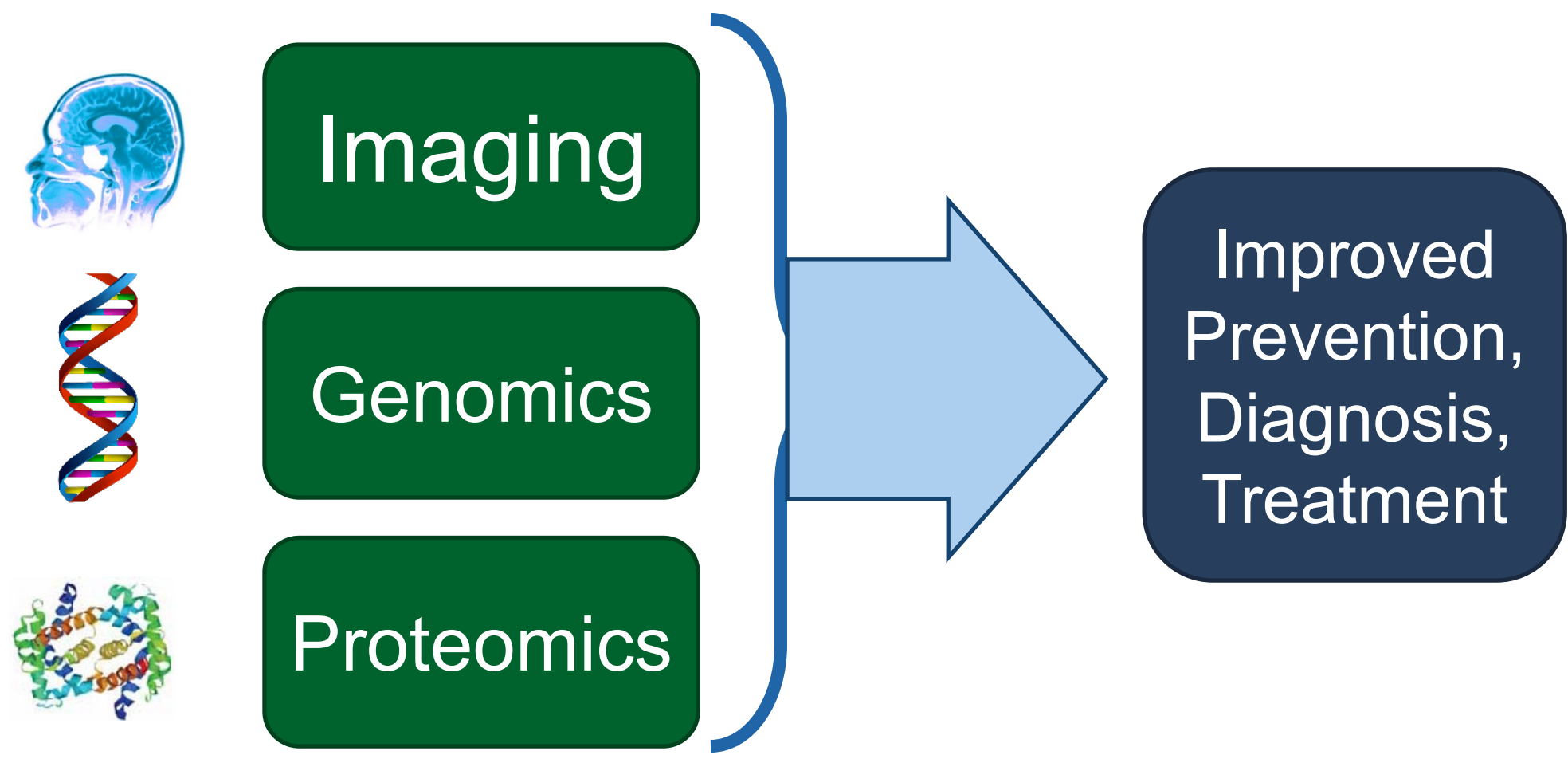


Gains in overall survival for the 71 drugs approved by FDA from 2002 to 2014 for advanced cancer

PFS: 2.5 mos

OS: 2.1 mos

Opportunity for Big Data



CPTAC Research Question



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

Flagship Characterization Studies



Colorectal Cancer

nature
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. Zimmerman⁵, 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
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Breast Cancer

nature
International weekly journal of science
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日本語要約
Proteogenomics connects somatic mutations to signalling in breast cancer
Philipp Mertins, D. R. Mani, Kelly V. Ruggles, Michael A. Gillette, Kari R. Clauser, Pei Wang, Xianlong Wang, Jana W. Qiao, Song Cao, Francesca Petralia, Emily Kawaler, Filip Mundt, Karsten Krug, Zhidong Tu, Jonathan T. Lei, Michael L. Gatz, Matthew Wilkerson, Charles M. Perou, Venkata Yellapantula, Kuan-lin 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
PDF | Citation | Reprints | Rights & permissions | Article metrics
Abstract
Introduction · Proteogenomic analysis of TCGA samples · Copy number alterations · Clustering and network analyses · Phosphite markers in *PIK3CA*- 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 trans-effects against the Library of Integrated Network-based Cellular Signatures (LINC) revealed

Ovarian Cancer

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Integrated Proteogenomic Characterization of Human High-Grade Serous Ovarian Cancer
Hui Zhang¹⁵, Tao Liu¹⁵, Zhen Zhang¹⁵, Samuel H. Payne¹⁵, Bai Zhang, Jason E. McDermott, Jian-Ying Zhou, Vladislav A. Petyuk, Li Chen, Deji Ray, Shisheng Sun, Feng Yang, Lijun Chen, Jing Wang, Punet Shah, Seong Won Cha, Paul Aiyetan, Sunghae Woo, Yuan Tian, Marina A. Gritsenko, Therese R. Clauss, Caitlin Choi, Matthew E. Monroe, Stefani Thomas, Song Nie, Chaochao Wu, Ronald J. Moore, Kun-Hang Yu, David L. Tabb, David Ferry, Vineet Bafna, Yue Wang, Henry Rodriguez, Emily S. Boja, Tara Hillke, Robert C. Rivers, Lori Sokoll, Heng Zhu, Le-Ming Shi, Leslie Coors, Akhilesh Pandey, Bing Zhang, Michael P. Snyder, Douglas A. Levine, Richard D. Smith, Daniel W. Chan¹⁶, Karin D. Rodland¹⁶ et al. the CPTAC Investigators
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Cosenior author
Publication stage: In Press Corrected Proof
DOI: [http://dx.doi.org/10.1016/j.cell.2016.05.069](https://doi.org/10.1016/j.cell.2016.05.069)
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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) *CCNE1* alterations.

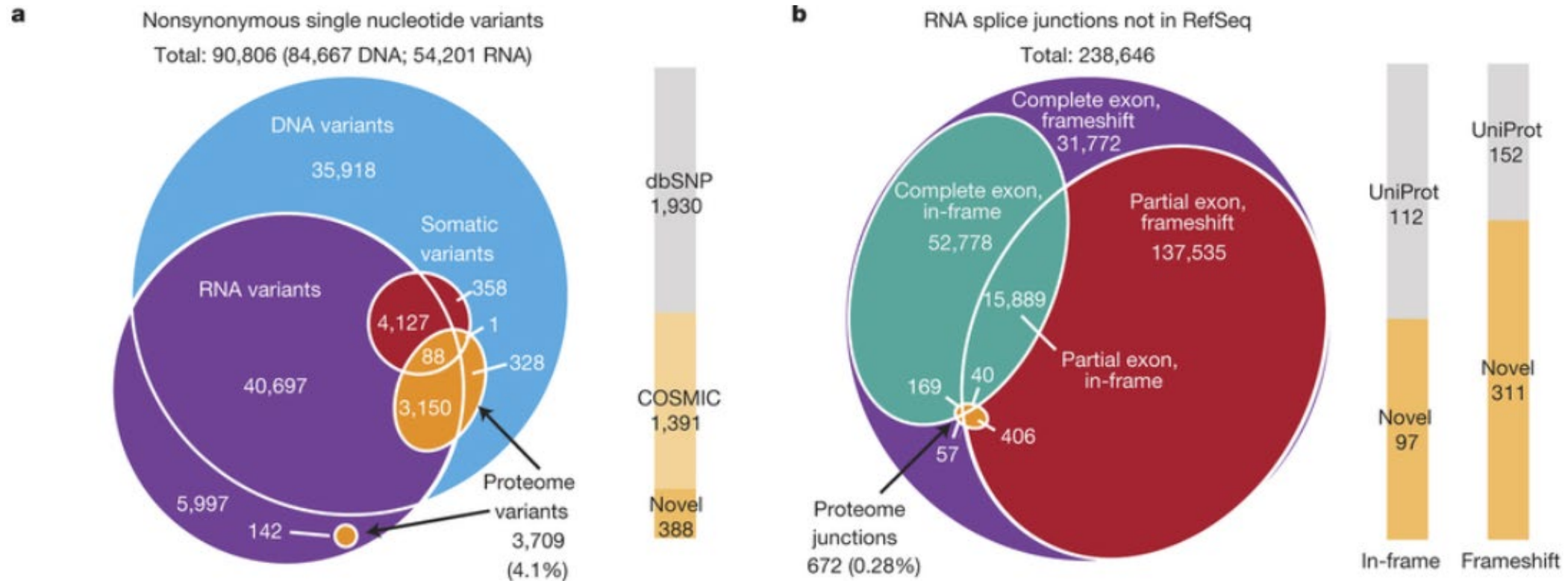
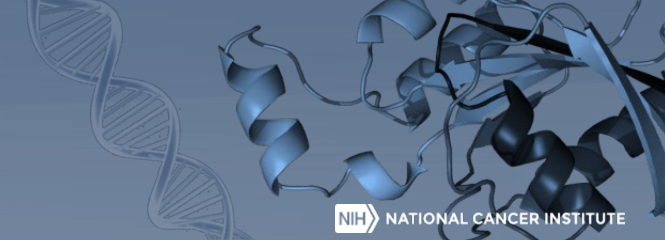
Zhang B, *Nature* 513, 382–387 (18 Sept 2014)

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

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

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

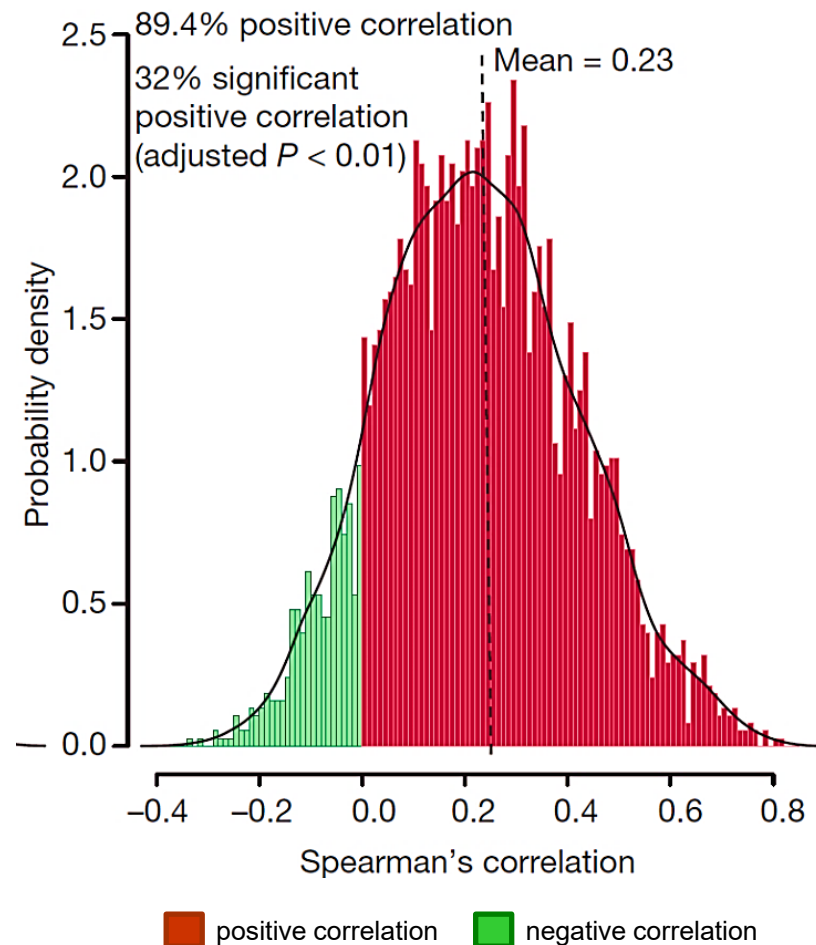
Proteogenomic mutation detection



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

mRNA levels are poor indicators of abundance for many proteins

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



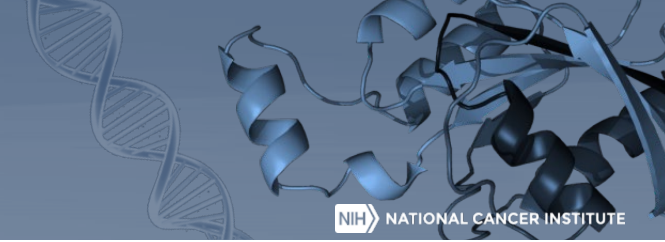
Mean Correlation:

- 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:

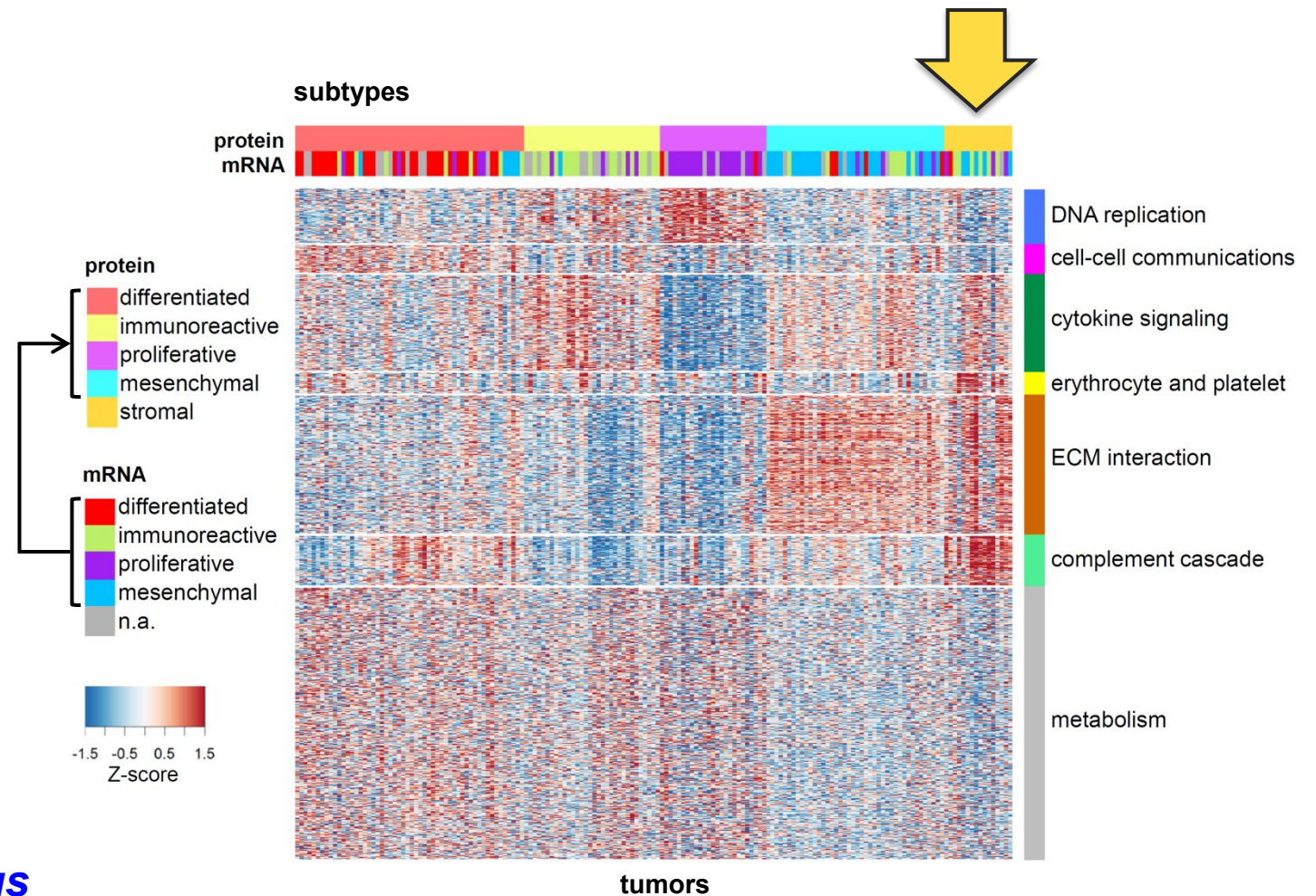
- Overall Survival (OS)
- Homologous Recombination Deficiency status (HRD)

- **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)

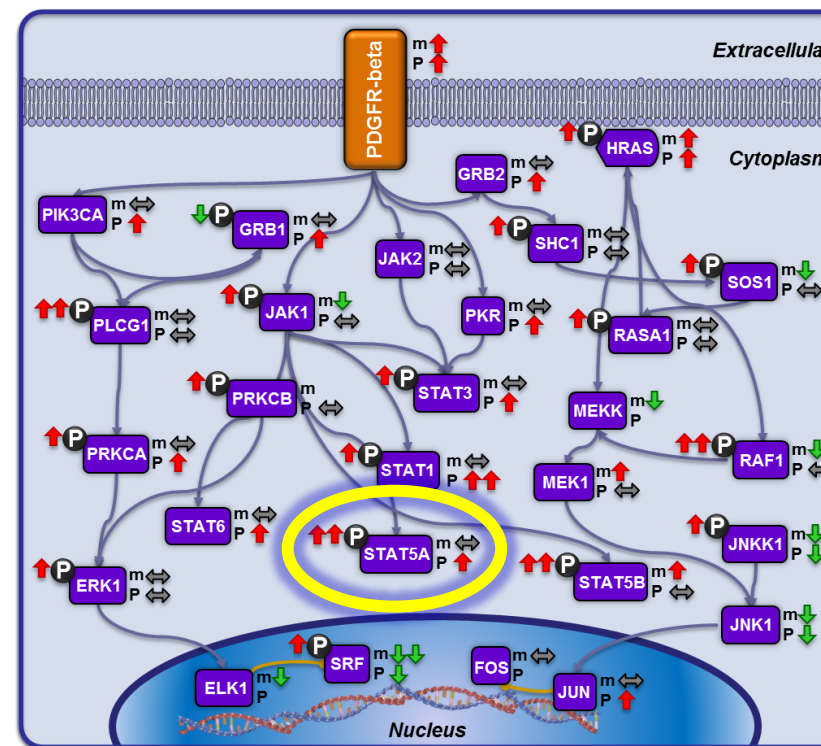
Network Data Exchange

[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)



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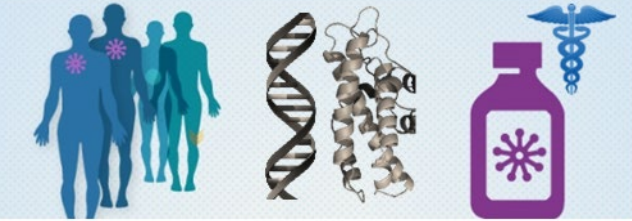
A. Proteome Characterization Centers

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



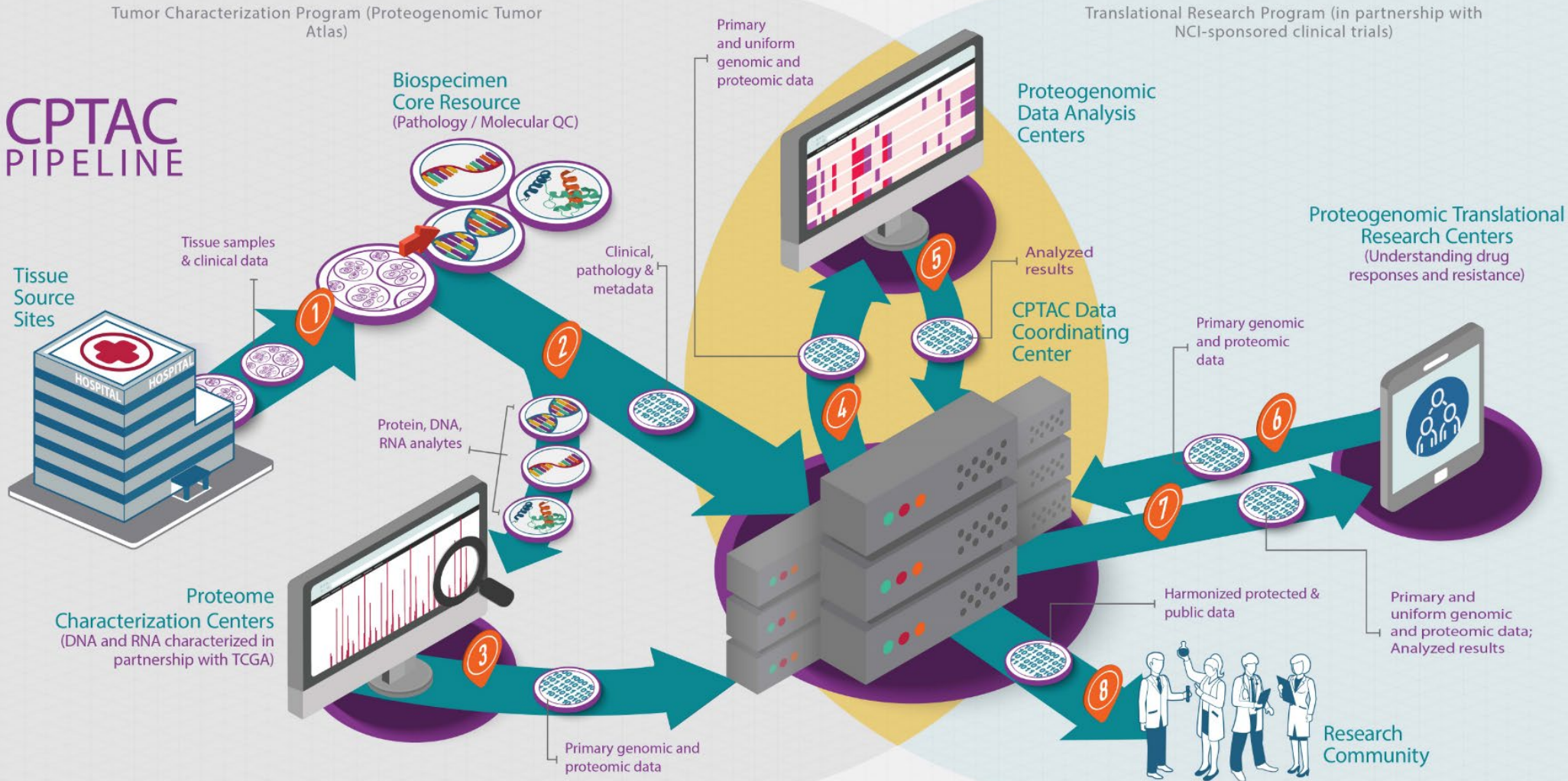
Public Resources:

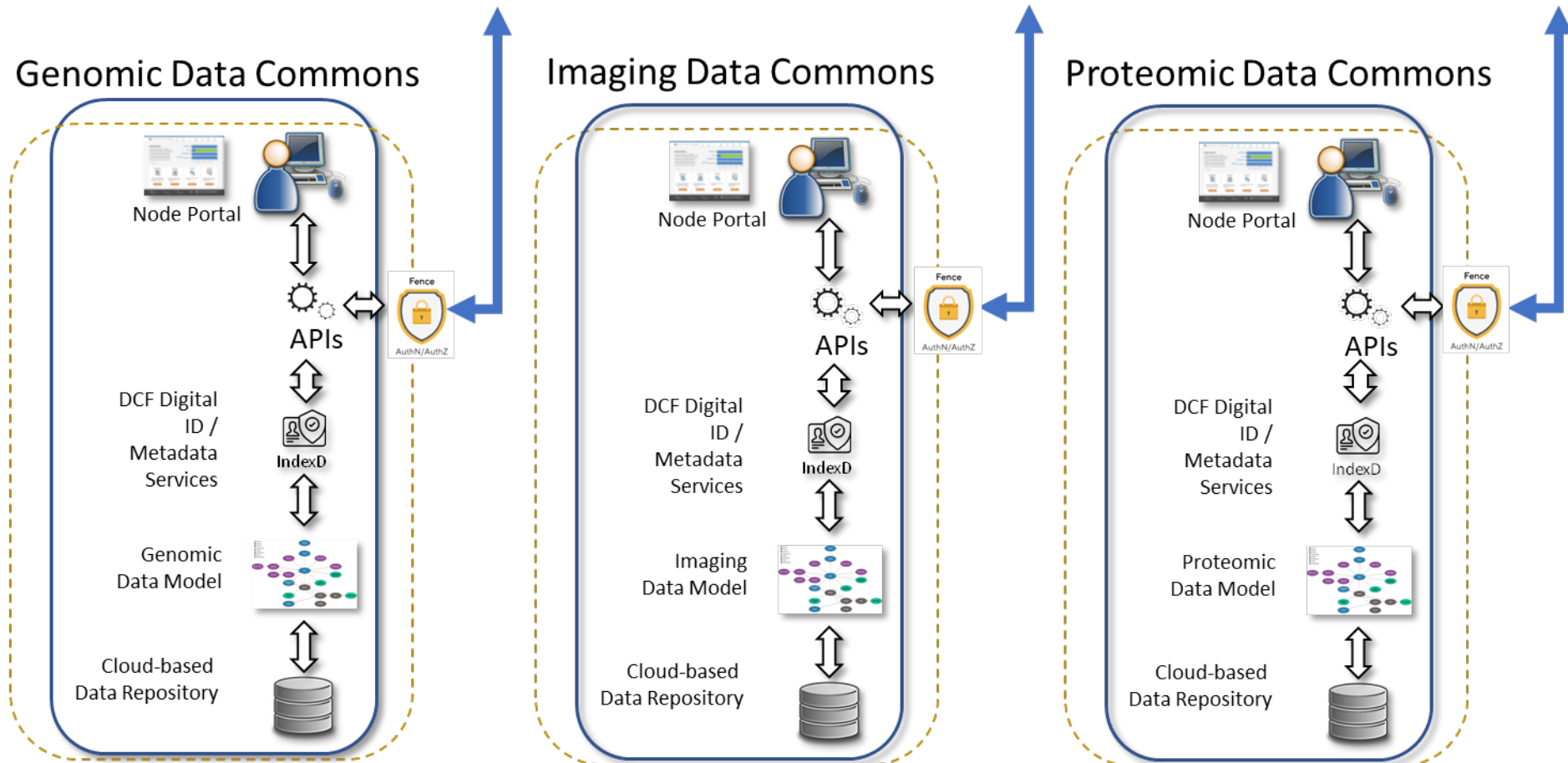
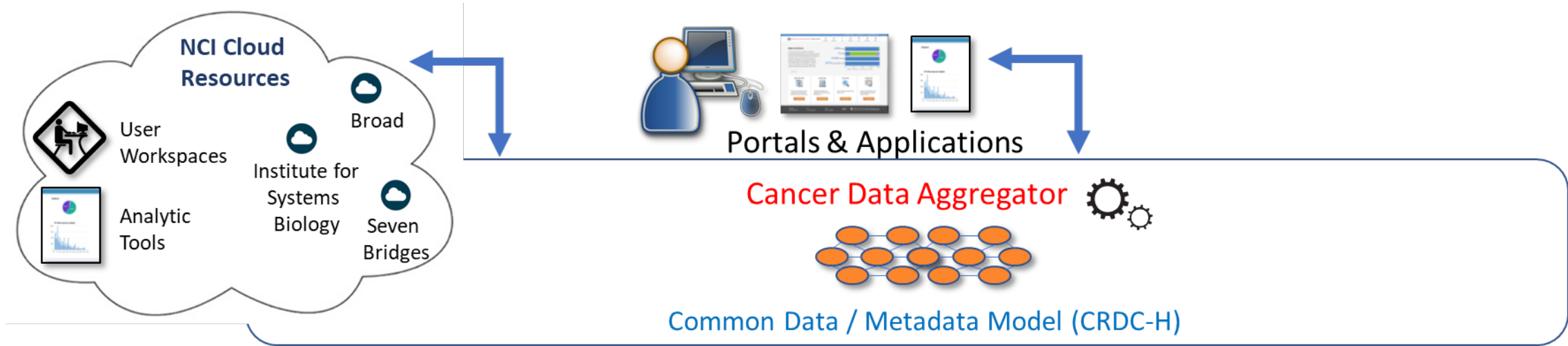
Data types: genomics (NCI GDC), proteomics (CPTAC Data Portal), imaging (NCI TCIA)

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

CPTAC workflow

CPTAC PIPELINE





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).



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 - Nathan Edwards
 - Peter McGarvey
- **Van Andel Research Institute**
 - Scott Jewell
 - Dan Rohrer
 - Dana Valley
 - Chelsea Peterson
 - Galen Hostetter
- **Tissue Source Sites**
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 - 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