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Sudhir Srivastava, Ph.D., M.P.H., National Cancer Institute

35th EDRN Steering Committee Meeting (Virtual)

NIH NATIONAL CANCER INSTITUTE

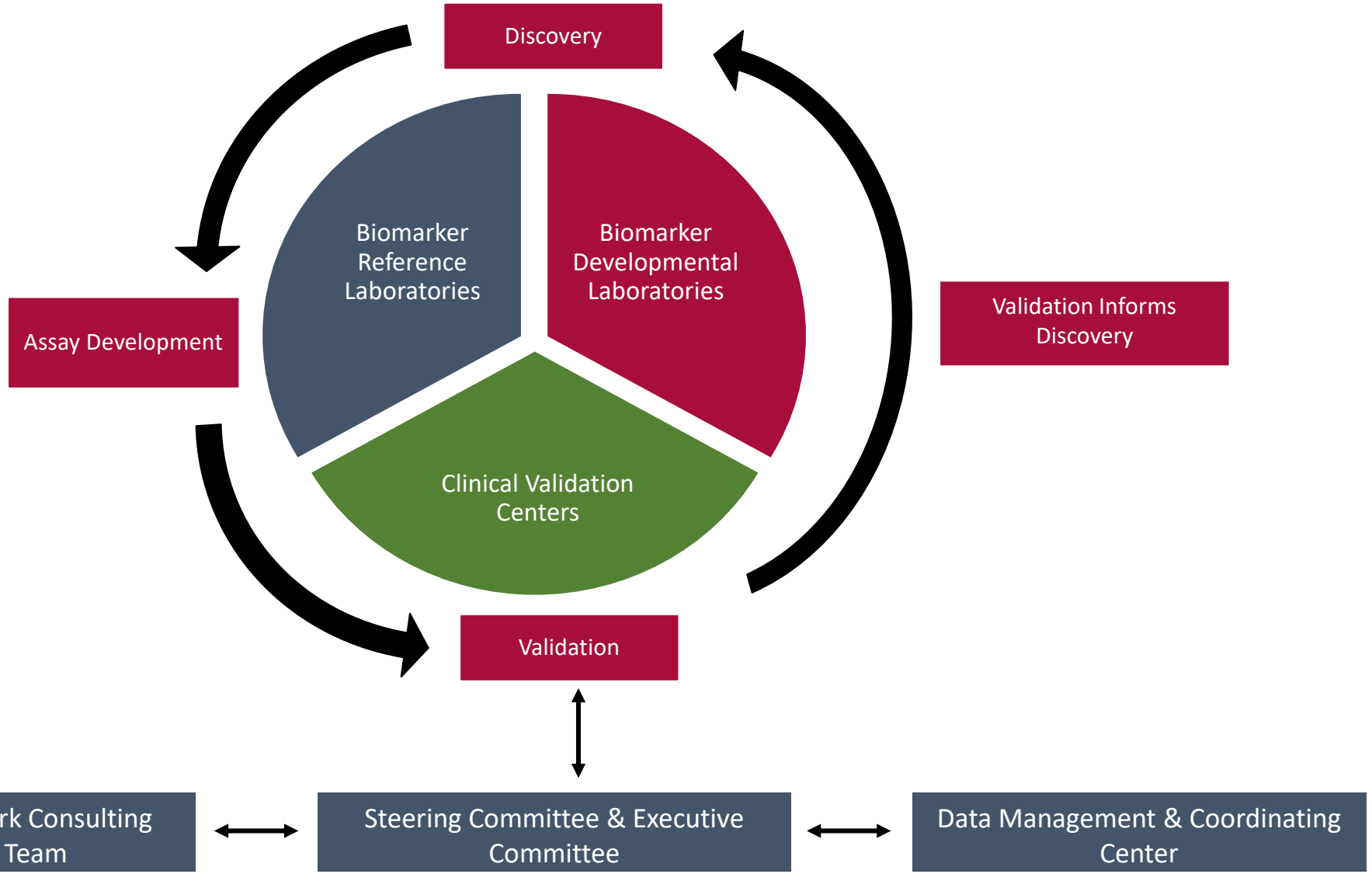
June 30–July 1, 2020

Early Detection Research Network (EDRN): Program Objectives

An investigator-initiated infrastructure to:

- Support the development and validation of early detection biomarkers and markers of progression
- Interaction among academic, clinical and industrial leaders
- Standardize biomarker validation criteria
- Develop quality assurance in biomarker measurement
- Bring biomarkers to clinical use

EDRN: Organizational and Operational Structure



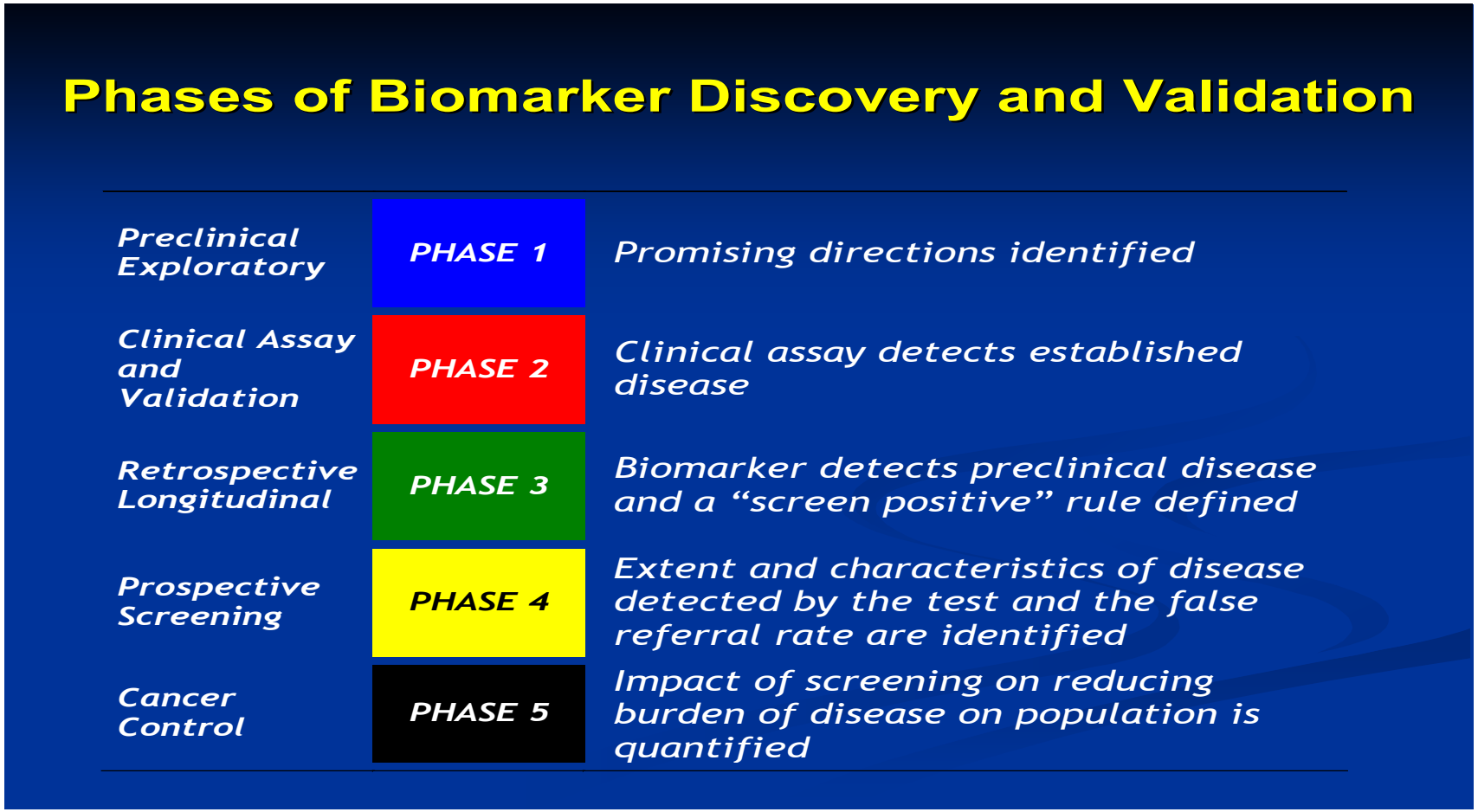
State-of-the-Cancer Biomarkers: "Water, water everywhere, and not a drop to drink"

- Most studies fail to use biomarker science
  - Poor study design
  - Lack of appropriate specimens and reagents
  - Lack of quality control of preanalytical variables
  - Inappropriate statistical methods
  - Bias, chance and overfitting
  - Incomplete protocol reporting
- Biology of early disease not well explored
- Unintentional selective reporting
- Lack of collaboration
  - It takes a multidisciplinary village

Lack of Collaboration

EDRN-Led Rigor and Reproducibility Criteria: Study Designs for Biomarker Development

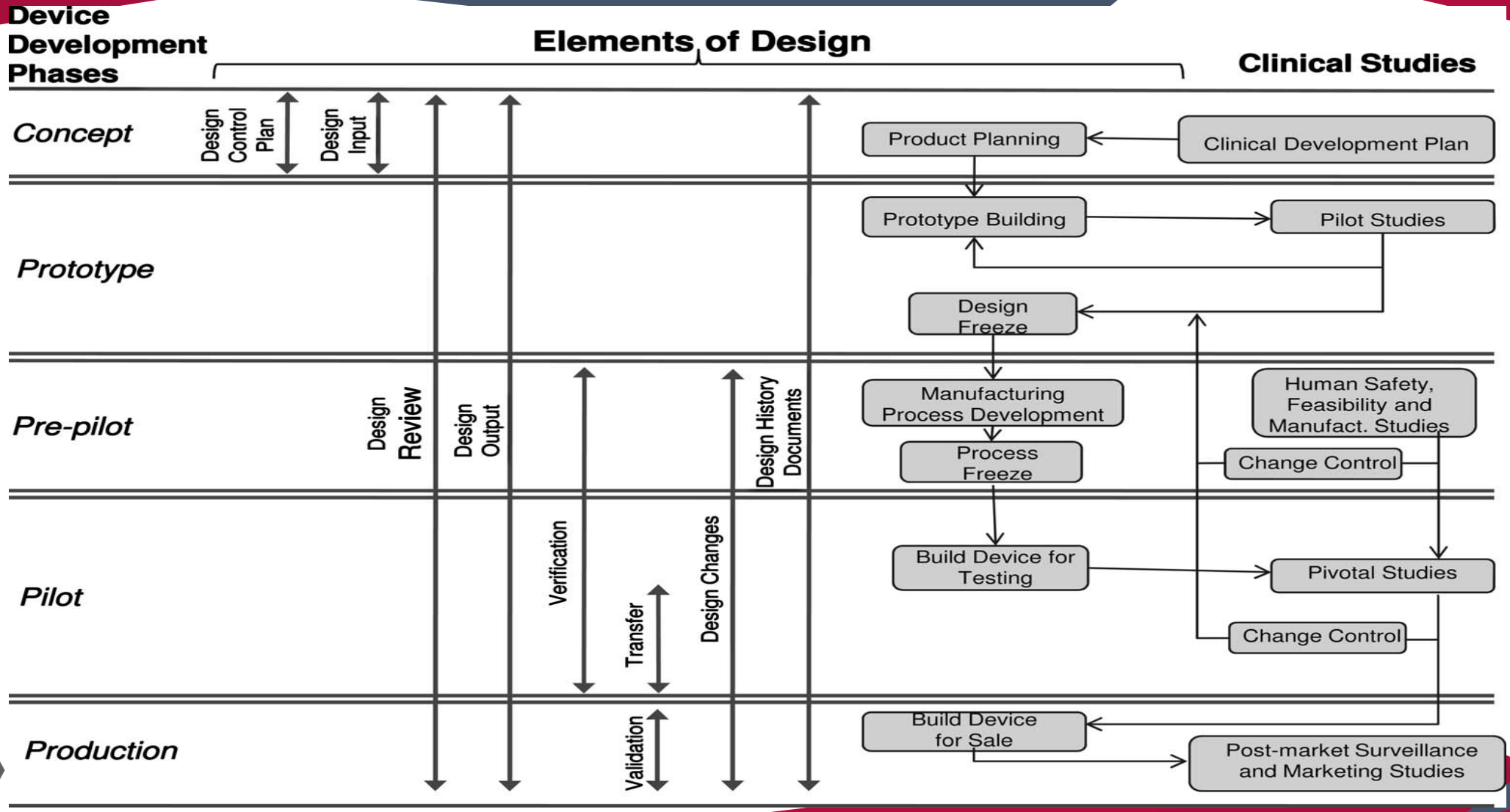
PRoBE Study Design:
Prospective-Specimen-Collection, **R**etro**s**pective-**B**linded-**E**valuation



Phases of Biomarker Development for Early Detection of Cancer
Margaret Sullivan Pepe et al.
J Natl Cancer Inst, Vol. 93, No. 14, July 18, 2001

Pivotal Evaluation of the Accuracy of a Biomarker Used for Classification or Prediction: Standards for Study Design
Margaret Sullivan Pepe et al.
J Natl Cancer Inst 2008; 100:1432-1438

Long Development Cycle of Diagnostic Devices
From Bench to Bedside



EDRN: Addressing the Challenges

- Scientists in the business of discovery
- Scientific laboratory experts to validate and standardize assays
- Clinician-scientists who:
  - Identify clinical applications for biomarkers
  - Determine the criteria for clinical success
  - Identify or develop reference sets for biomarker validation
  - Pursue formal prospective validation trials
- Biostatisticians who oversee process at every juncture
  - Data management
  - Biomarkers reaching milestones as they move from step to step
  - Quality assurance
- Infrastructure
  - Data management
  - Biorepositories

35th EDRN Meeting Topics

- Highlight of EsoCheck and EsoGuard
- Universal Cancer Screening
- SWOT Analysis, Organ by Organ
- Big Data and Biomarker Research
- International Partnership
- Industrial Collaborations

Discussion on Universal (Pan Cancer) Cancer Screening

- Paucity of single markers that have the prerequisite sensitivity and specificity to detect a particular cancer type (single organ screening);
- Potential efficiency of universal cancer screening (UCS) in detecting cancers originating from multiple organ sites using markers that are either specific for a cancer type or common for multiple cancers;
- Aggregate sample size provides better statistical power with screening for multiple cancers compared to single cancer screening.

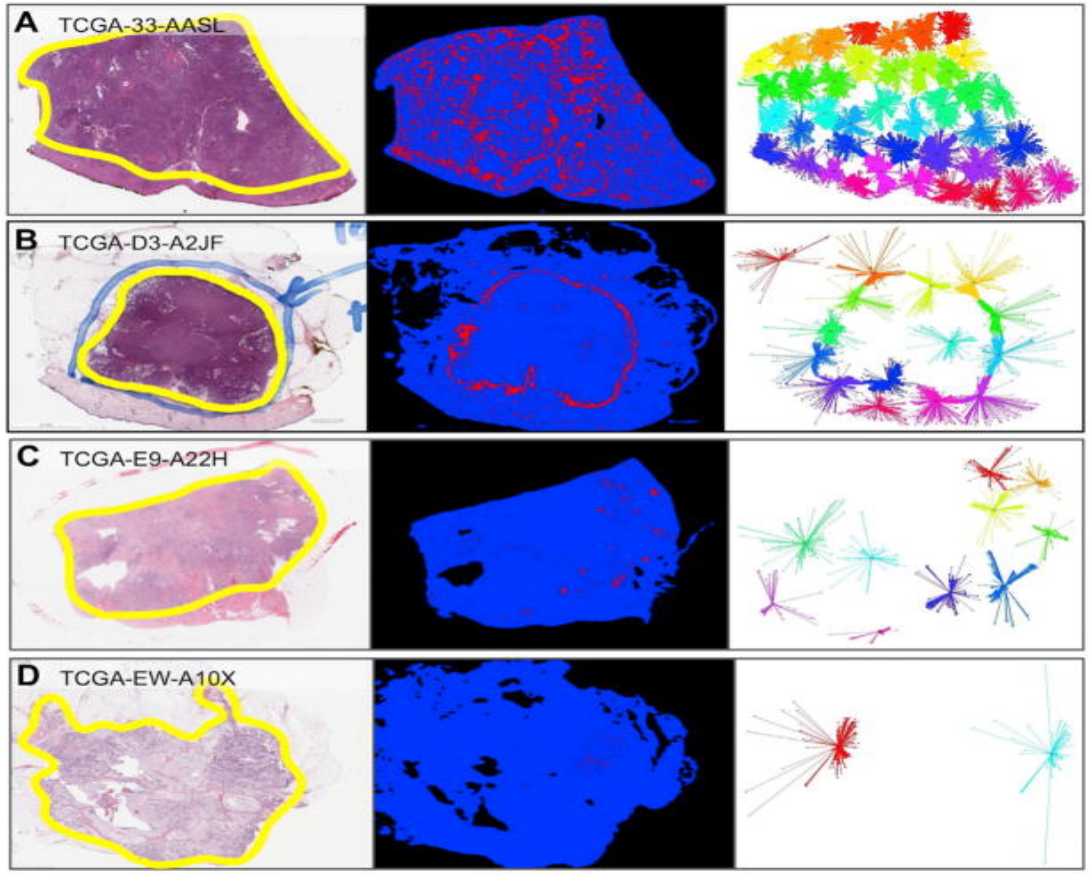
Biomarker Research Going Digital

In 2017, the authorization by the FDA for **digital pathology** in the US, the world's largest healthcare market, constitutes a **watershed moment** for the healthcare industry. ... **Digital pathology** enables them to view and diagnose **digital** images of surgical **pathology** slides prepared from biopsied and resectioned tissue.

Data science/systems approaches and modeling for the analysis, integration and interpretation of experimental data (genomics, epigenomics, proteomics, metabolomics, imaging etc.) to define “disease dynamics” in screen-detected early lesions

- Increasing trends toward digitizing histopathology, histochemistry along with imaging and molecular approaches to elucidate dynamic changes occurring during progressive disease
- Need for making a compendium of precancer images to study semantic and phenotypic features and apply radiomic tools to decipher distinct features of screen-detected and interval cancers
- Making data available to others for developing AI including Machine Learning Language (MLL) to develop rendition of hard-to-read early stage images for better interpretability and visualization

Histopathology and Histochemistry Digitization of Whole Mount Slides



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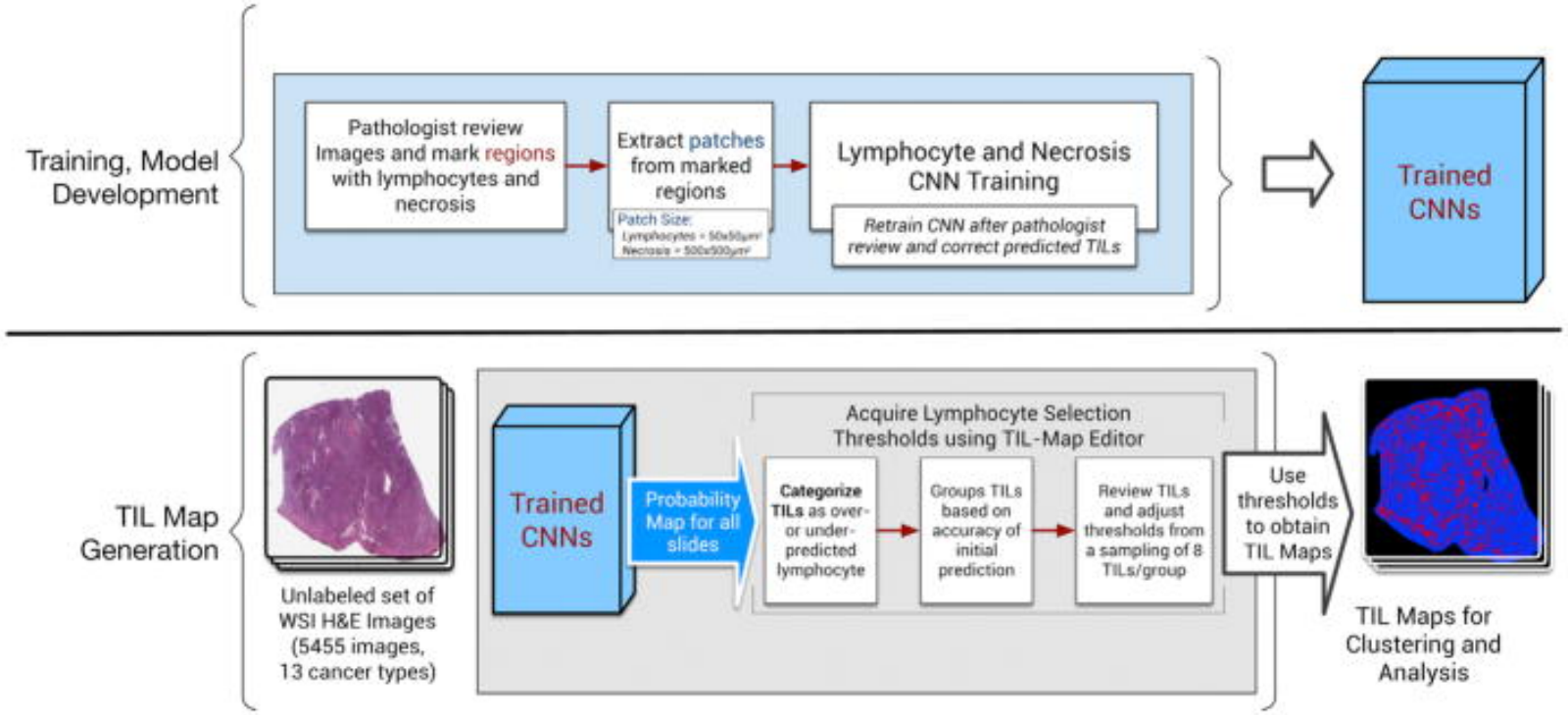
Participant Barcode	Study	Number of TIL Patches	TIL fraction	Number of TIL Clusters	Cluster Size Mean	Within-Cluster Dispersion Mean	Cluster Extent Mean	Ball Hall Index	Banfield Raftery Index	C Index	Determinant Ratio Index	Global Pattern
TCGA-33-AASL	LUSC	26245	20.6	40	656.1	293456	41.0	447	159518	0.015	2065.4	Brisk Diffuse
TCGA-D3-A2JF	SKCM	6832	4.9	18	379.6	238600	82.1	771	43456	0.022	790.0	Brisk Band-like
TCGA-E9-A22H	BRCA	1000	1.5	10	100.0	54876	51.9	560	6174	0.025	343.0	Non-Brisk Multifocal
TCGA-EW-A1OX	BRCA	285	0.1	2	142.5	430332	223.0	3093	2283	0.000	29.6	Non-Brisk Focal

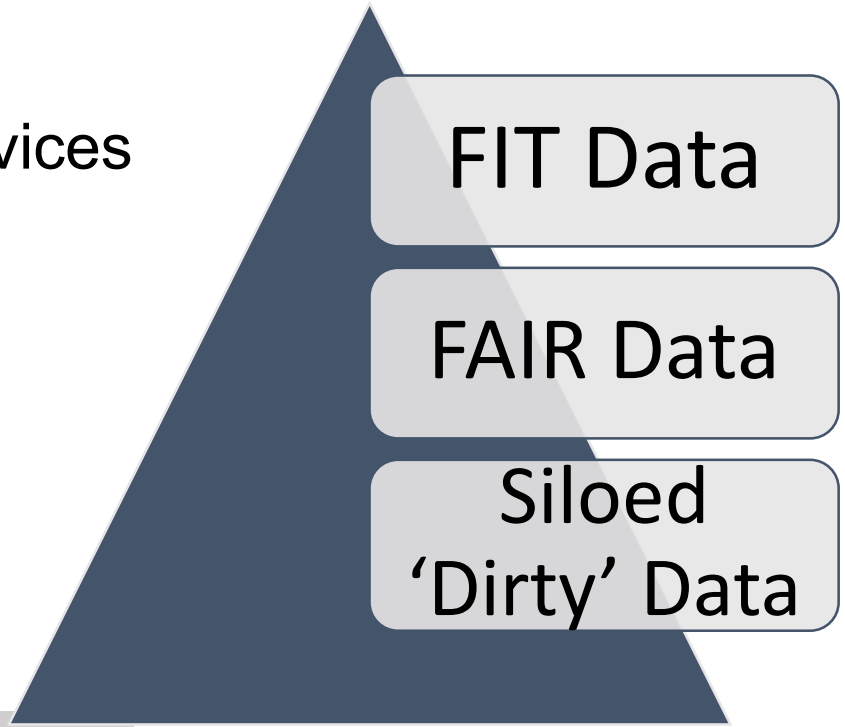
How Digitization Can Help Quantitative Analysis



EDRN Needs a Plan to Address BIG Data Challenges: *In silico Biomarker Discovery*

- Cancer Biomarker Data Commons Think Tank recommendation*
  - Open data sharing platform
  - Access to FIT (fit-for-purpose) datasets
  - Co-localized with analytical tools and services

- Cancer Biomarker Data Common
  - Build Interoperable Data Systems
  - Standardized Reporting to Minimize Selective Reporting, Chance, Bias
  - Reproducible and Sustainable Data



*NCI Cancer Biomarker Data Commons Think Tank, Bethesda, MD, 2018

Crowdsourcing and BIG Data in Biomarker Discovery and Validation

Enlarge Available Datasets	Solve Complex Problems	Leverage Multidisciplinary Expertise	Improve Patient Care	Compare with FDA-approved Technologies
Incent data sharing (open science), explore access to new data sources (PRO)	Develop and test novel methods (data integration, modeling, predictive analytics, etc.)	Identify SMEs, solicit help on key challenges (AI, machine learning, data reduction, selection bias, etc.)	Engage patients and stakeholders (23andMe, CrowdMed, advocacy, etc.)	Compare new ideas and technologies against FDA approved biomarkers (e.g., imaging)

Incentives to facilitate Crowdsourcing: Prizes, Publications, IP Ownership/Commercialization Support, Grants, Goodwill

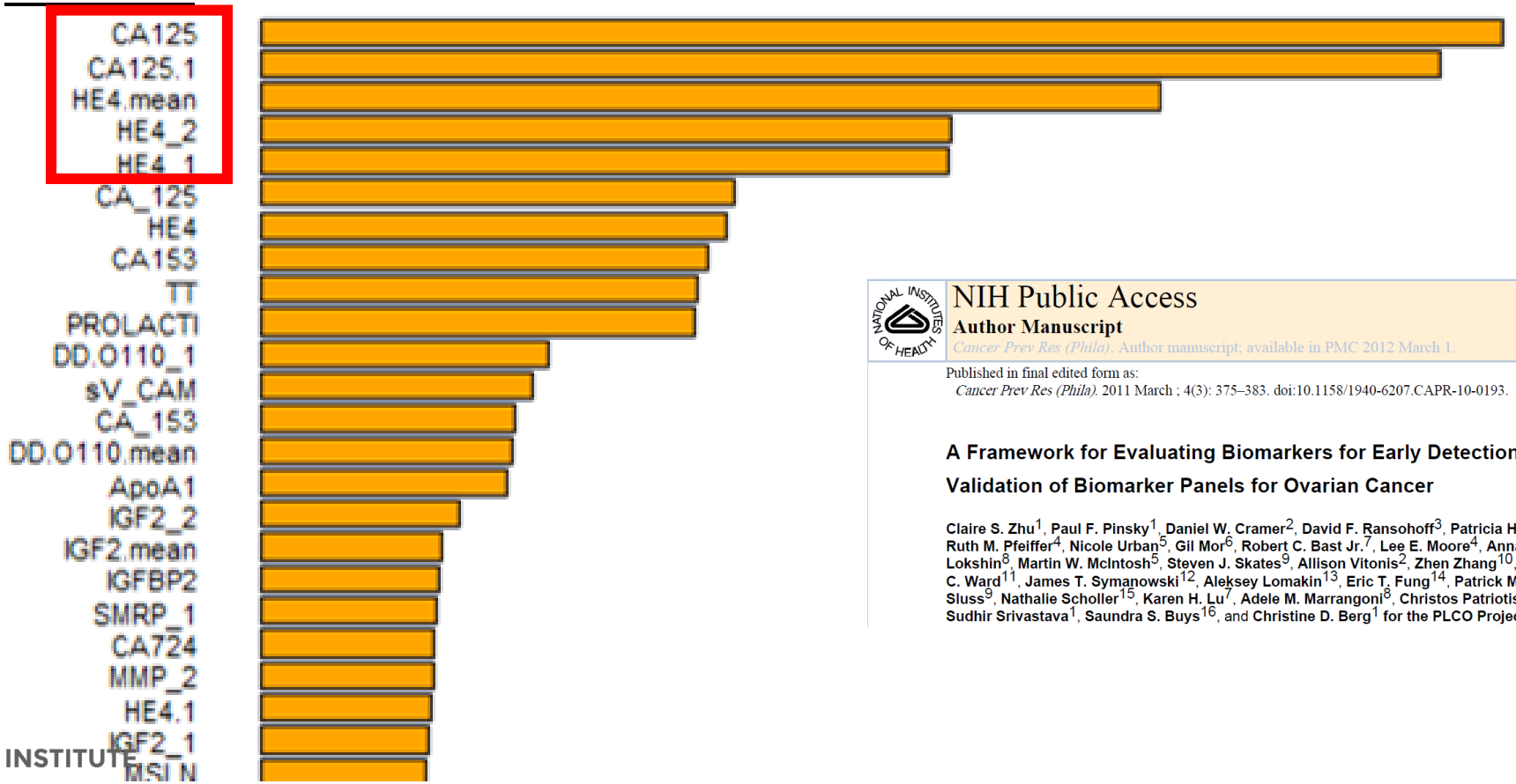
Source: Juergen Klenk, Jonathan Baba; See Deloitte posters for detail

Value of Data Science: Independent Validation Of Ovarian Cancer Biomarkers

FHCRC Model: CA125, HE4, HK11, B7-H4, DcR3, SMR, Spondin-2

Boston-NW Model: CA125, HE4, CA72.4, CA15.3, SMR

JPL Model:



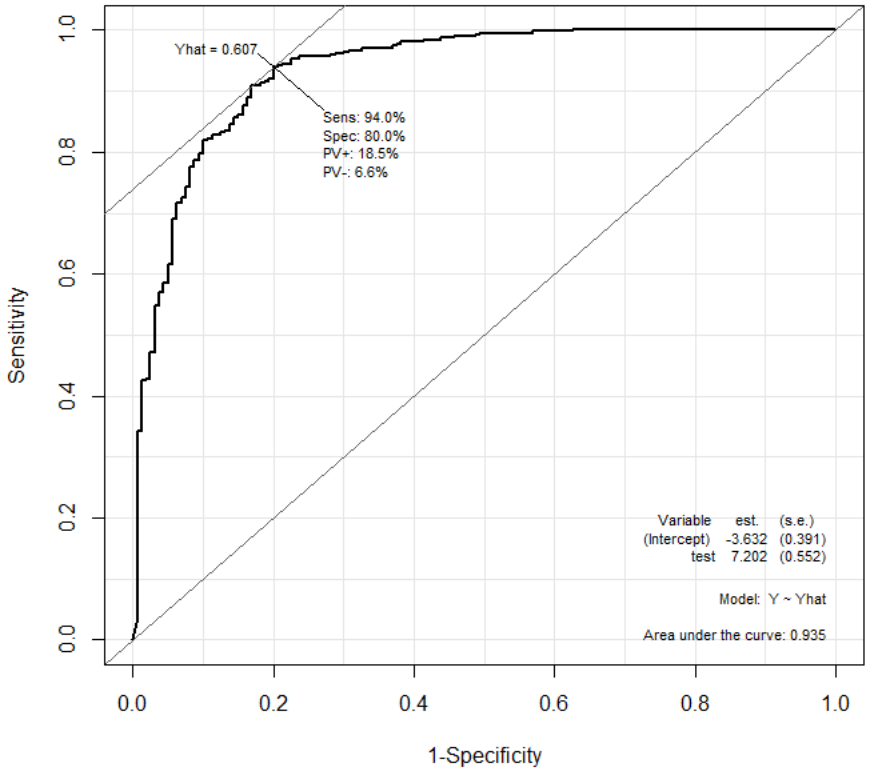
Published in final edited form as:
Cancer Prev Res (Phila). 2011 March ; 4(3): 375–383. doi:10.1158/1940-6207.CAPR-10-0193.

A Framework for Evaluating Biomarkers for Early Detection: Validation of Biomarker Panels for Ovarian Cancer

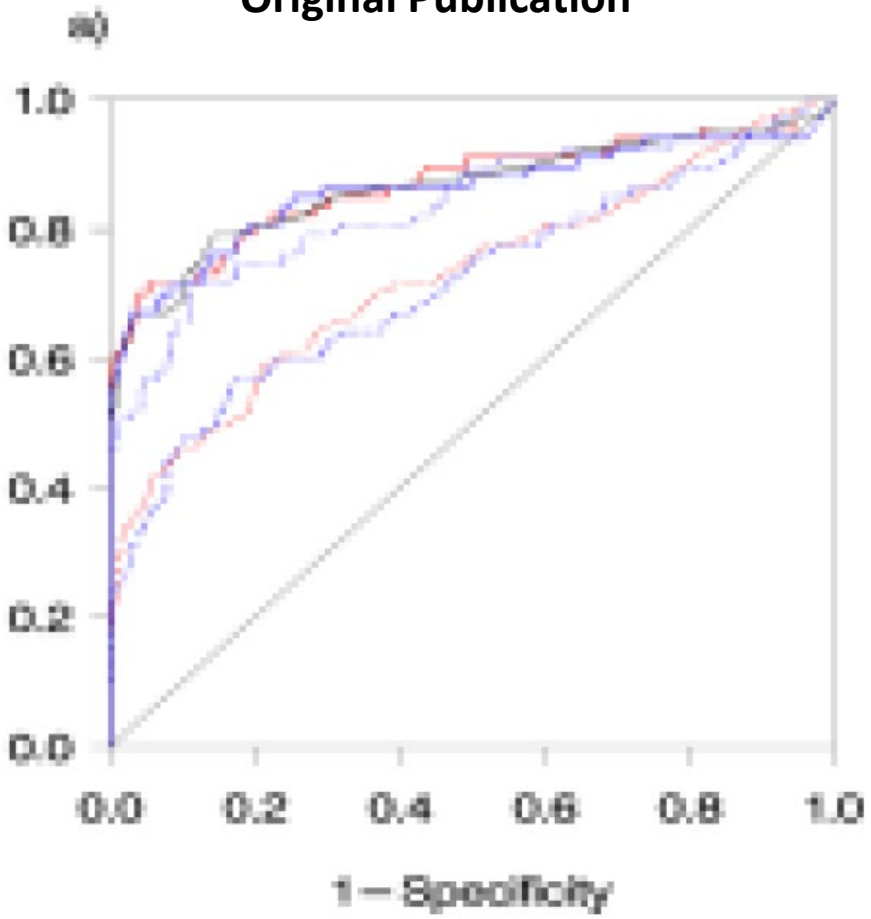
Claire S. Zhu[1], Paul F. Pinsky[1], Daniel W. Cramer[2], David F. Ransohoff[3], Patricia Hartge[4], Ruth M. Pfeiffer[4], Nicole Urban[5], Gil Mor[6], Robert C. Bast Jr.[7], Lee E. Moore[4], Anna E. Lokshin[8], Martin W. McIntosh[5], Steven J. Skates[9], Allison Vitonis[2], Zhen Zhang[10], David C. Ward[11], James T. Symanowski[12], Aleksey Lomakin[13], Eric T. Fung[14], Patrick M. Sluss[9], Nathalie Scholler[15], Karen H. Lu[7], Adele M. Marrangoni[8], Christos Patriotis[1], Sudhir Srivastava[1], Saundra S. Buys[16], and Christine D. Berg[1] for the PLCO Project Team

ROC curve

JPL Model: AUC = 0.935



Original Publication



Discussion on BIG Data and Digitizing Biomarker Research

- Short-term benefits
  - Standardization and access to high-value datasets
  - Standardization and access to statistical algorithms and other tools such as MLL
  - Incentive models for sharing of data, tools, expertise, biospecimens, etc. and for improving standard adoption
  - Evaluation of crowdsourcing-based approaches to stakeholder engagement in the NCI Data Commons efforts – community input
  - Early public-private collaborations
- Long-term benefits
  - Biomarkers for cancers with no screening tests available
  - Improved performance of existing tests
  - Optimal stakeholder engagement and talent distribution

Attendee Profile

- More than 250 registered
- Representations from Academia, Industry and Foundations
- Non-Government Funding Agencies: CR-UK, PanCAN, Kenner Family Research Foundation
- Advocacy Groups: PanCan, Kenner's Family Research Foundation, and others

Thank You!

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