Opportunities and Challenges in the Validation and Implementation of Novel Screening Techniques

Session 3

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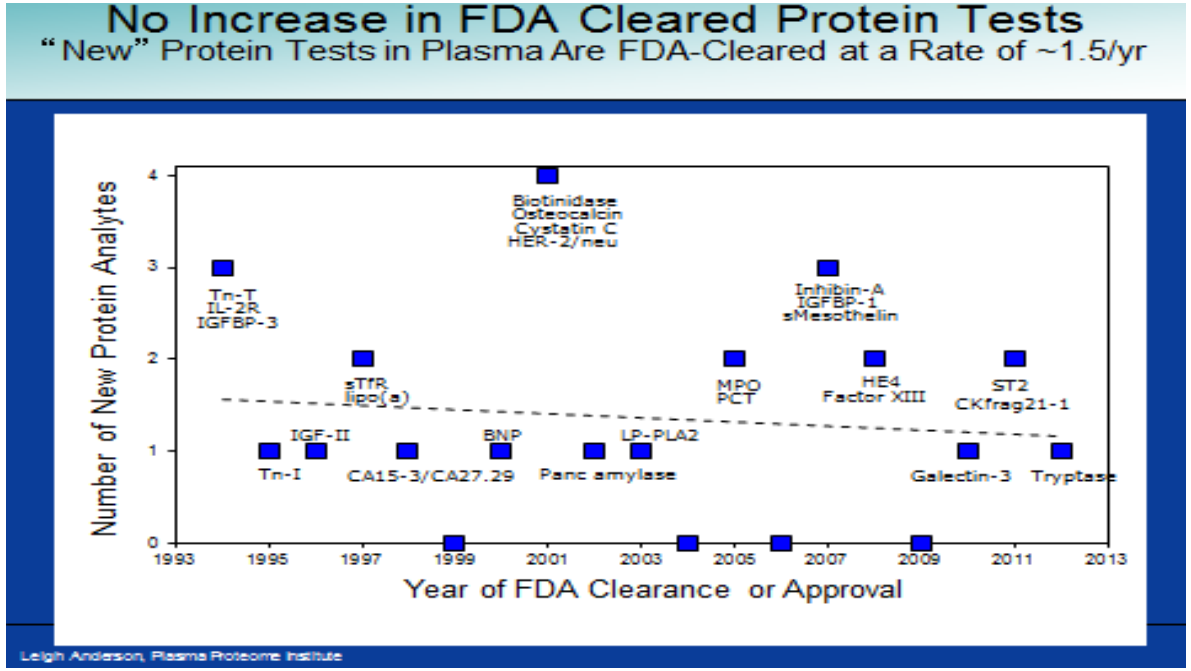
State of the Science in Biomarker Research

- More than 60,000 papers on cancer biomarkers each year (2019 Medline Search)
- Around 4000–5000 on biomarkers for early detection
- 99% claims >90% sensitivity and specificity
- But very few, if any, get through regulatory approval



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
  - Absence of analytical chemistry
  - 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

Successful Discovery and Validation of Biomarkers for Early Cancer Detection Requires and Integrated, Collaborative Approach

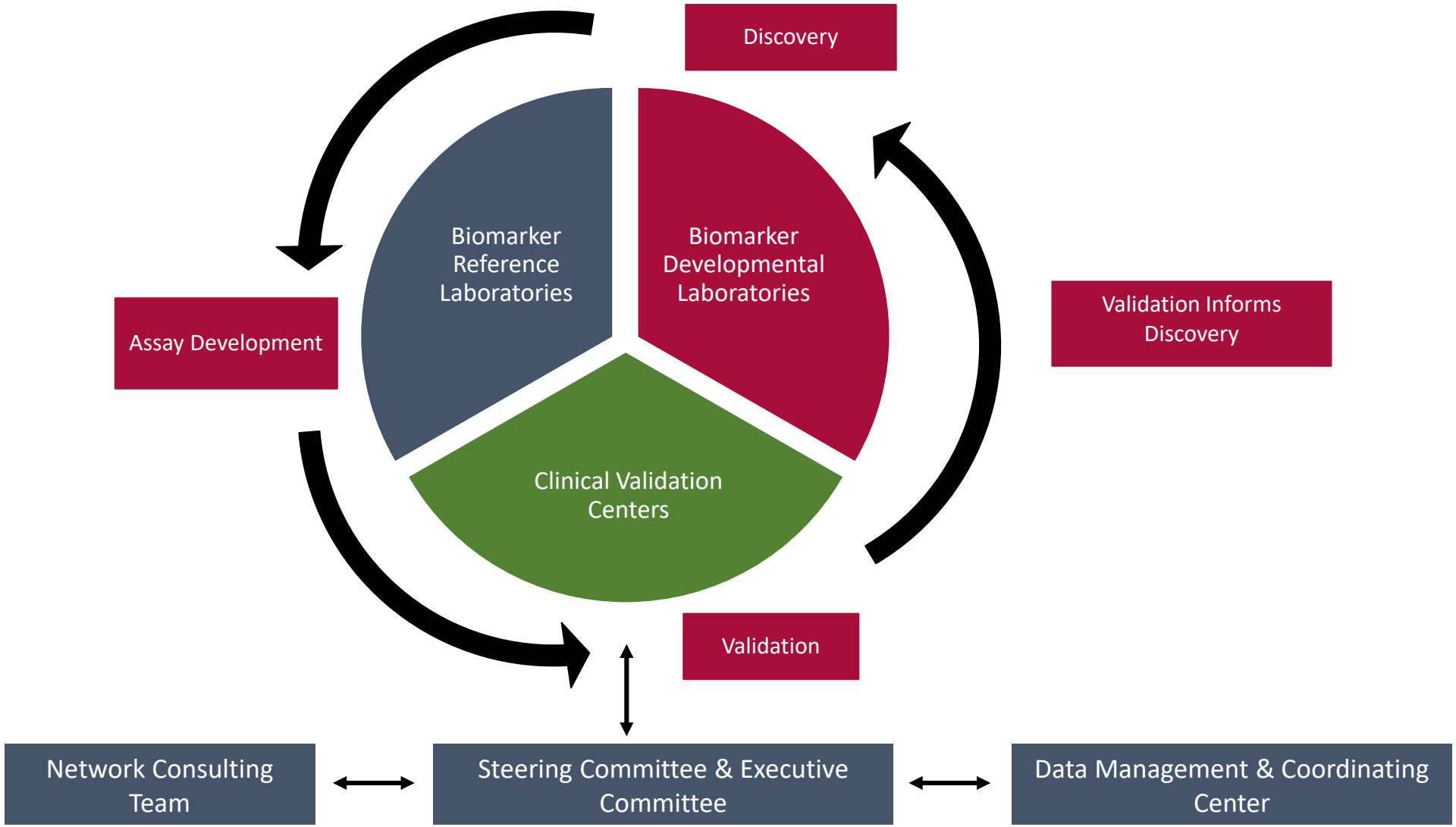
Individual Grants

- Many biomarkers are reported
- Often with unrealistic performance
- Fail to replicate in independent biospecimens
- Use limited number of biospecimens
- Use late stage cancers
- Often yield biomarkers that result from overfitting.
- An extraordinary number of one hit wonders.

Integrated, Collaborative Structure, e.g. EDRN

- Moderate number of biomarkers are reported
  - Bad markers are down selected before reporting
  - Reported performance is more realistic
  - Markers perform well in independent samples.
- Use larger numbers of biospecimens
- Use samples from early stage cancers
- Samples collected from multiple sites to reduce bias
- Markers routinely tested in independent cohorts
- The same samples are used to test to multiple markers
  - Enables combinations of markers
  - Saves time and money

Early Detection Research Network: A Collaborative Community on Biomarker Research



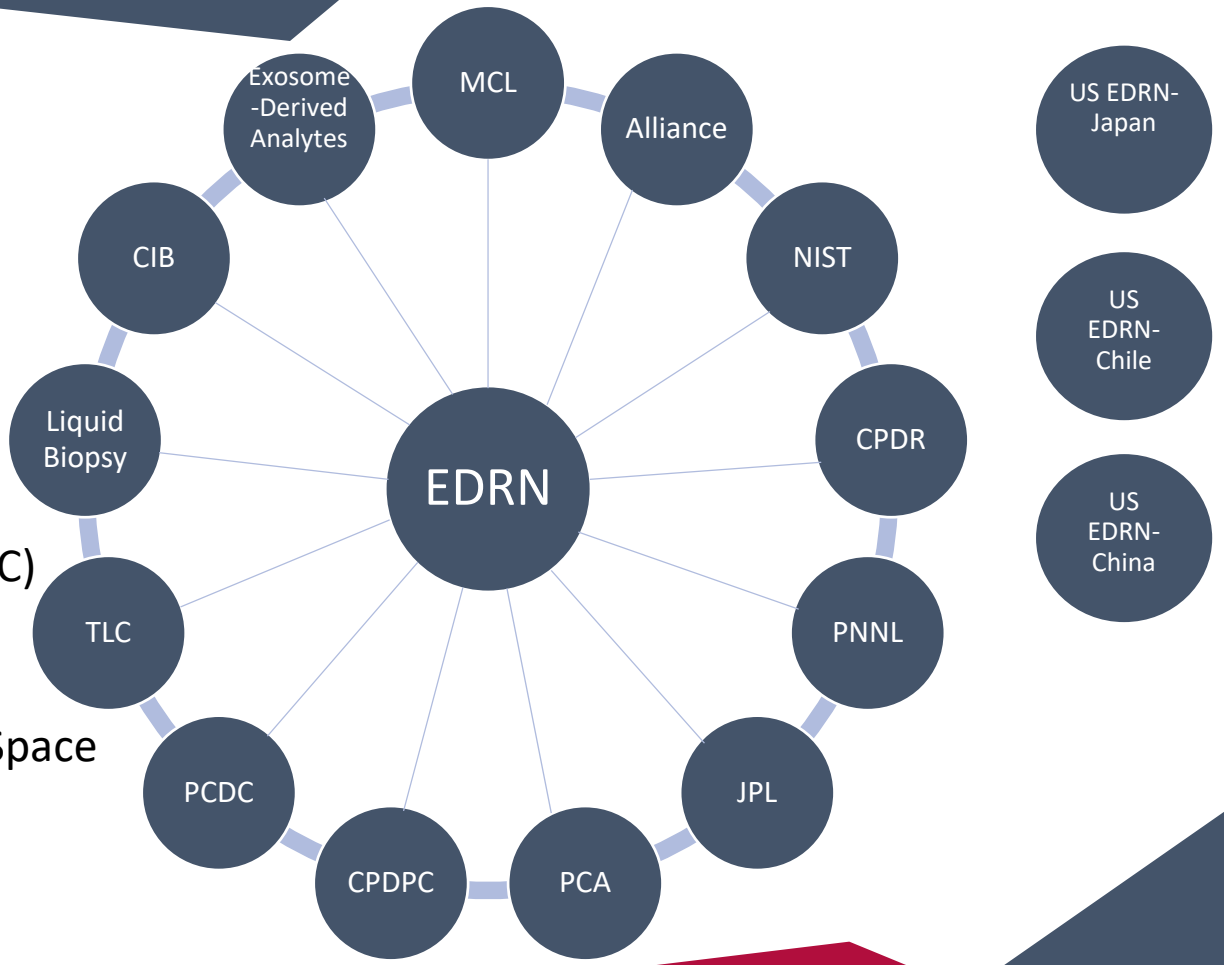
EDRN Serves as a HUB to Many Sister Programs (HUB and Spokes)

Programs

- *Early Detection Research Network* (EDRN)
- Molecular and Cellular Characterization of Screen-Detected Lesions (MCL)
- Alliance of Glycobiologists for Cancer
- Exosome-Derived Analytes for Cancer
- Consortium for Imaging and Biomarkers (CIB)
- Liquid Biopsy for Early Cancer Assessment
- Translational Liver Cancer (TLC) Consortium
- Pancreatic Cancer Detection Consortium (PCDC)
- Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC)
- Pre-Cancer Atlas (PCA)-Cancer Moonshot Program

Inter-Agency Agreements (IAA)

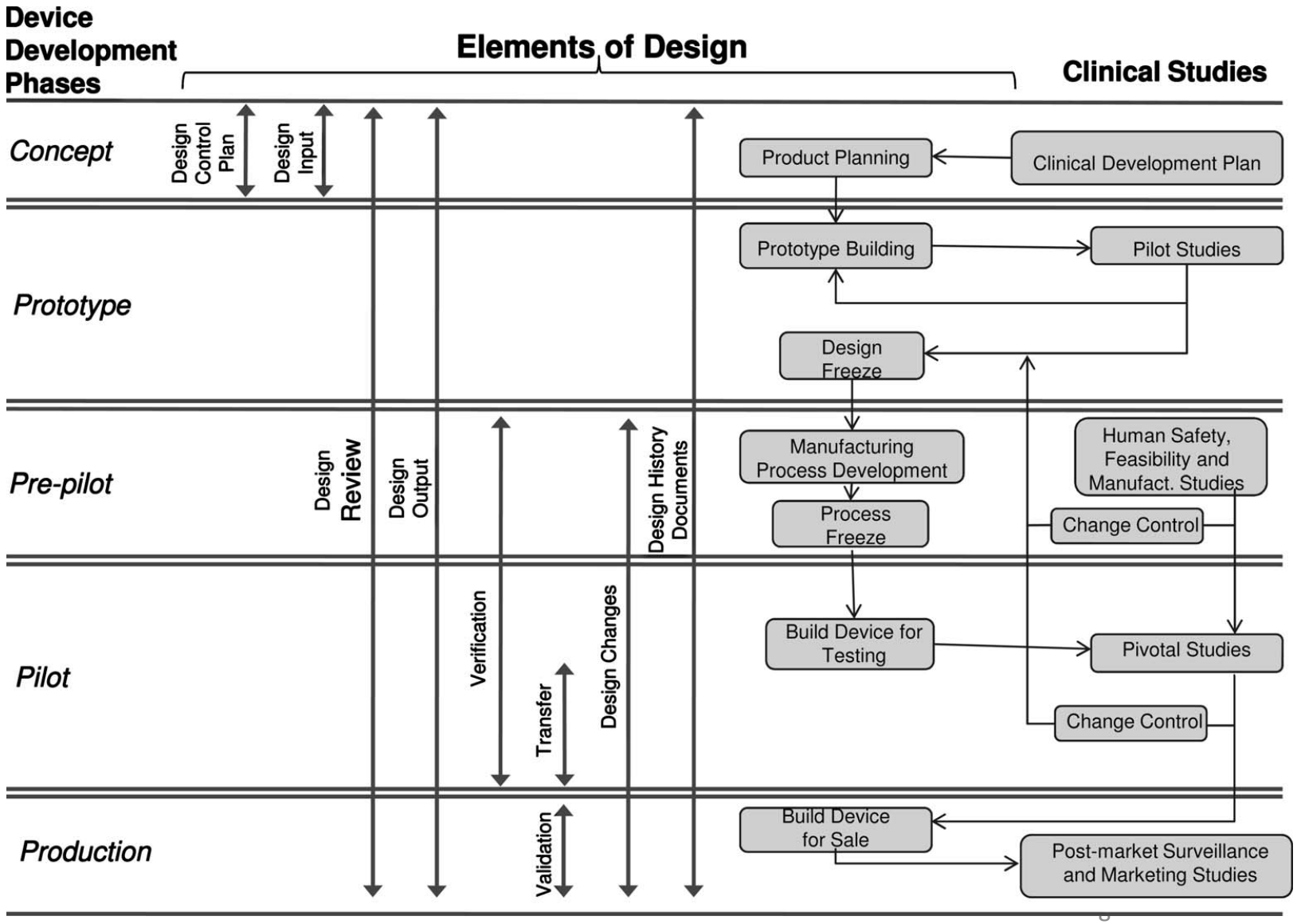
- Jet Propulsion Laboratory (JPL) / National Aeronautics and Space Administration (NASA)
- National Institute of Standards and Technology (NIST)
- Pacific Northwest National Laboratory (PNNL)
- Center for Prostate Disease Research (CPDR)



Challenges in Developing and Launching Diagnostics

- Cost $50M to $143M (in some cases substantially high; not including the Discovery Research) to develop diagnostics
- High-risk and low return on investment (short-term)
- Industry reluctant to invest in a long-term return-on-investment
- Discovery of biomarkers largely done in academia
- Funding for biomarker validation inadequate; validation proposals are not always hypothesis-driven and score poorly
- Validation requires more than a typical five-year funding cycle
- Long development cycle for technology and biomarkers
- IP Issues

Long Development Cycle



Courtsey of Mike Urdea

Public (Government) Support is Critical

- Cancer screening has huge potential society benefits (colon, cervices, breast, lung)
- The benefits are societal but diagnostic test has low benefit/cost ratio for industry
- Cancer screening test development → validation → clinical use is a long process requiring a team effort over a continuous long period
- EDRN is the first step to fill this unmet needs

Recently Approved Diagnostic Tests

Biomarker	Purpose	Year of Approval	EDRN Principal Investigator/ Industrial Partner
CancerSEEK	Universal cancer screening test	2018; FDA breakthrough device designation	Kinzler/Vogelstein/Thrive
Esoguard	ESOGuard will be used to detect, diagnose and manage patients with Barrett's esophagus	Pending	Sandy Markowitz, M.D., Ph.D.
%[-2]proPSA	Reduce the number of unnecessary initial biopsies during prostate cancer screening. Also, appears to be highly associated with increased risk of aggressive disease.	2012	Dan Chan, Ph.D./ Beckman Coulter
PCA3 (in urine)	Biopsy or re-biopsy decisions in patients at risk for prostate cancer.	2012	John Wei, M.D./ Gen-Probe
OVA1™ (5 analytes: CA 125, prealbumin, apolipoprotein A-1, beta2 microglobulin, transferrin)	Prediction of ovarian cancer risk in women with adnexal mass.	2009	Dan Chan, Ph.D./ Vermillion
OVA1™ Next Generation (commercial name Overa ; (5 analytes: CA 125, apolipoprotein A-1, transferrin, follicle-stimulating hormone, human epididymis protein 4)	Prediction of ovarian cancer risk in women with adnexal mass.	2016	Zhen Zhang, Ph.D./ Vermillion
Risk of Ovarian Malignancy (ROMA) algorithm with CA125 and HE4 blood tests for pelvic mass malignancies	Prediction of ovarian cancer risk in women with pelvic mass.	2011	Steve Skates, Ph.D./ Fujirebio Diagnostics
DCP and AFP-L3 – combined panel of markers	Risk assessment for development of hepatocellular carcinoma.	2011	Jorge Marrero, M.D./ Wako Diagnostics

CLIA-Approved Tests

Biomarker Assay	Purpose	EDRN Principal Investigator/ CLIA Laboratory
MiPS (Mi Prostate Score Urine test), Multiplex analysis of TMPRSS2:ERG gene fusion, PCA3 and serum PSA	Detection of prostate cancer	Arul Chinnaiyan, M.D., Ph.D./ Gen-Probe
IHC and FISH for TMPRSS2:ERG fusion	Detection of prostate cancer	Arul Chinnaiyan, M.D., Ph.D./ Roche
GSTP1 methylation	Decision making regarding repeat biopsies in prostate cancer	David Sidransky, M.D./ OncoMethylome
Mitochondrial deletion	Detection of prostate cancer	National Institute of Standards and Technology (NIST)*/ Mitomics
Proteomic panel	Detection of lung cancer	William Rom, M.D., M.P.H./ Celera
Aptamer-based markers	Detection of lung cancer	William Rom, M.D., M.P.H./ Somalogic
80-gene panel** **(This panel has been refined; Percepta®, a 23-gene classifier, is now available through Veracyte)	Detection of lung cancer	Avrum Spira, M.D., M.Sc./ Allegro/Veracyte
Vimentin methylation in stool	Detection of colon cancer	Sanford Markowitz, M.D., Ph.D./ LabCorp
Galectin-3 ligand	Detection of advanced adenomas and colon cancer	Robert Bresalier, M.D./ BG Medicine
GP73	Risk of hepatocellular carcinoma	Timothy Block, Ph.D./ Beckman Coulter
8-gene Panel for Barrett's Esophagus (BE)	Progression Prediction of BE	Stephen Meltzer, M.D./ Diagnovus
Blood-based proteomic assay (a panel of serum protein biomarkers and tumor-associated autoantibodies)	Detection of breast cancer in conjunction with mammography to reduce number of biopsies	Josh LaBaer, M.D., Ph.D./ Provista Diagnostics

*EDRN has an Interagency Agreement with U.S. Department of Commerce's NIST.

EDRN Maintains Integrity of Biomarker Research

- Maintain collaborative, comprehensive infrastructure and resources critical for biomarker discovery and validation; does not exist without EDRN
- Accelerate the development of biomarkers that will change practice – an important mission of the NCI
- Ensure data reproducibility and integrity; negative findings are as important as positive ones
  - Checks and balances for unsubstantiated claims and data reproducibility
  - Economy of scale compared to individual efforts

Does the Total Exceed the Sum of its Parts?

Prior to EDRN

- No SOPs for biosamples, reagents, methodologies, etc.
- No common data elements (data dictionary) to enable the development of common databases for biosample annotation
- Fragmented studies with convenience samples, not generalizable
- Lack of guidelines for biomarker discovery and validation

Now

- Network of integrated resources for supporting validation
- Checks and balances ensure good biomarkers are promoted without regard to pecuniary interests
- Provides infrastructure for promising markers to become medical tools
- Standard operating procedures for biosample collection and management.
- Developed roadmap for study designs for clinical verification and validation
- EDRN activities are not replicated within industry or academia

Collaborative Communities Are Needed!

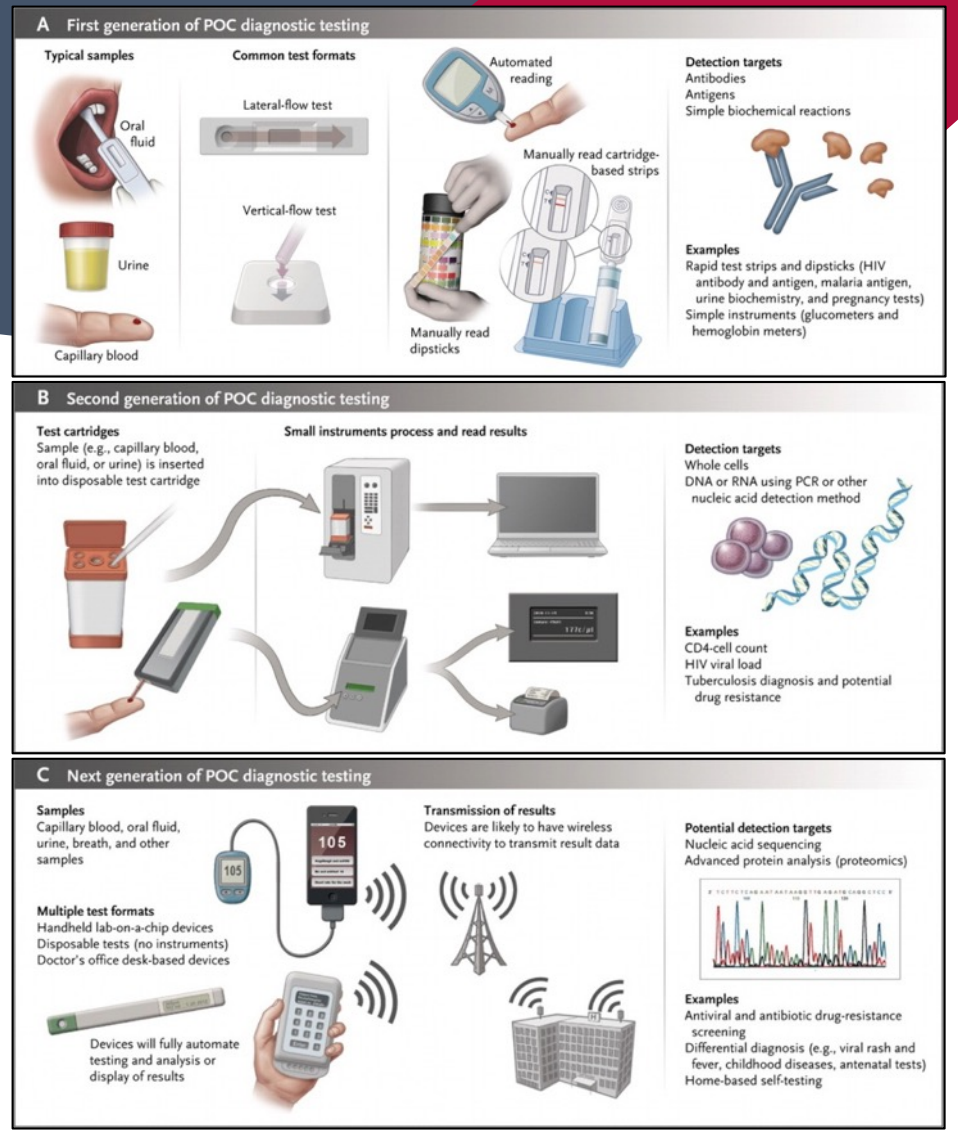
- Infrastructure (akin to National Clinical Trial Network), resources and integrated systems for new biomarker development and validation trials
- Collaboration and coordination required to maintain a network of multidisciplinary groups and institutions
- Adequate funding for conducting large scale, multi-institutional biomarker validation studies and maintain biorepositories as a national resource required
- Public-Private Partnership critical for accelerating progress

Collaborative Community: Ability to Adapt Changing Landscape of Biomarker Science

- Ability to respond unforeseen clinical needs, e.g., indeterminate nodules epidemic (pancreas, lung, kidney, etc.) identified by highly sensitive technologies
- Changing regulatory requirements for biomarker qualifications (FDA) especially for multi-analyte tests
- Responding to regulatory needs
- Ability to respond to congressional directives on ‘recalcitrant cancers’, e.g. pancreas, liver and lung
- Ability to address overdiagnosis of cancers, a major public health issue, etc.

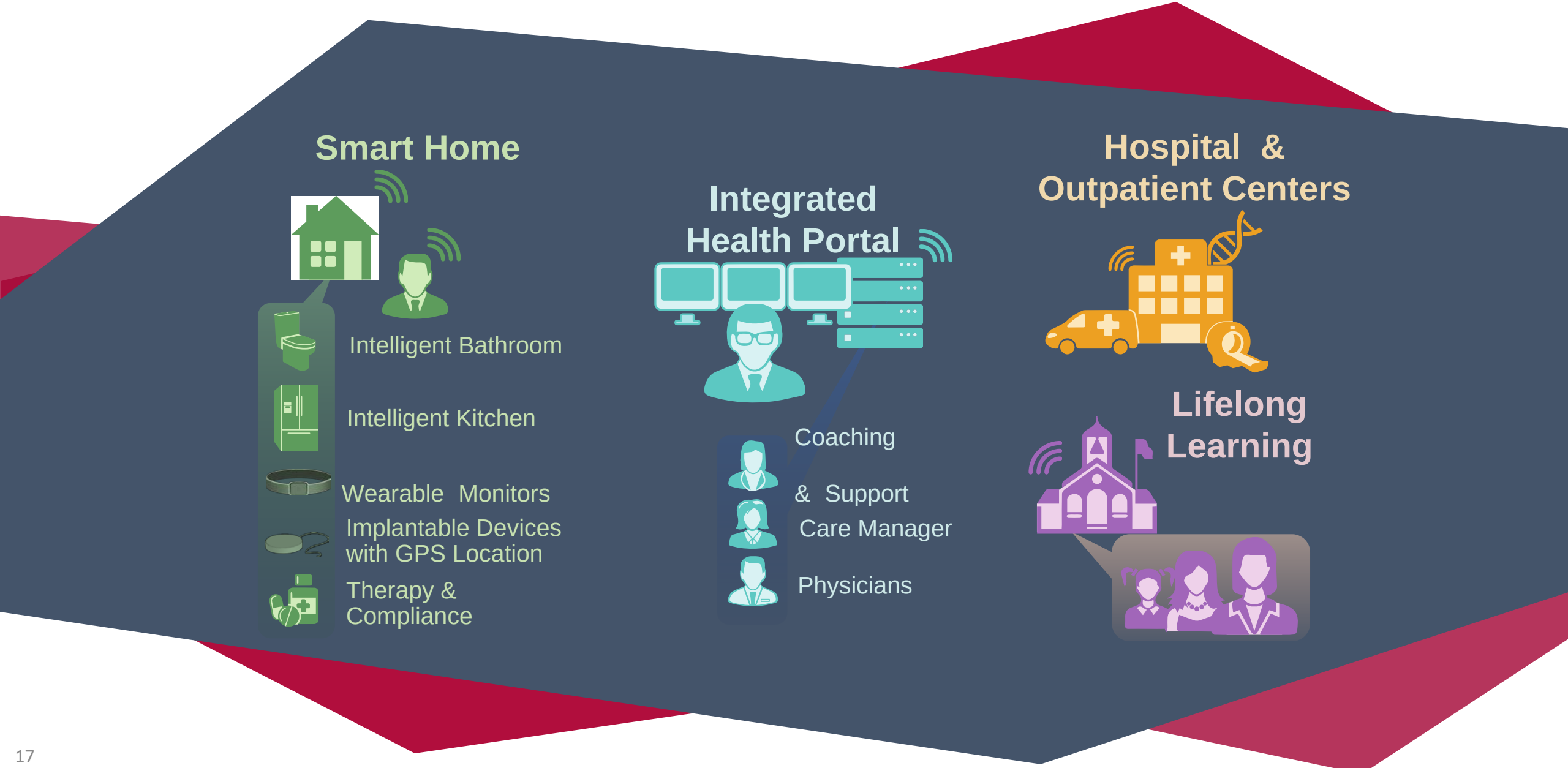
Trending…

- 1st Generation POCTs: relied on detection of common biomarkers, such as antibodies, antigens, and simple biochemical reactions.
- 2nd Generation POCTs: focused on more Liquid Biopsy, such as circulating nucleic acids and proteins and cell-surface markers, and took advantage of advances in microfluidics, microelectronics, and optics
- 3rd Generation POCTs:
  have begun to enable multiplexing and going after more sophisticated biomarkers.



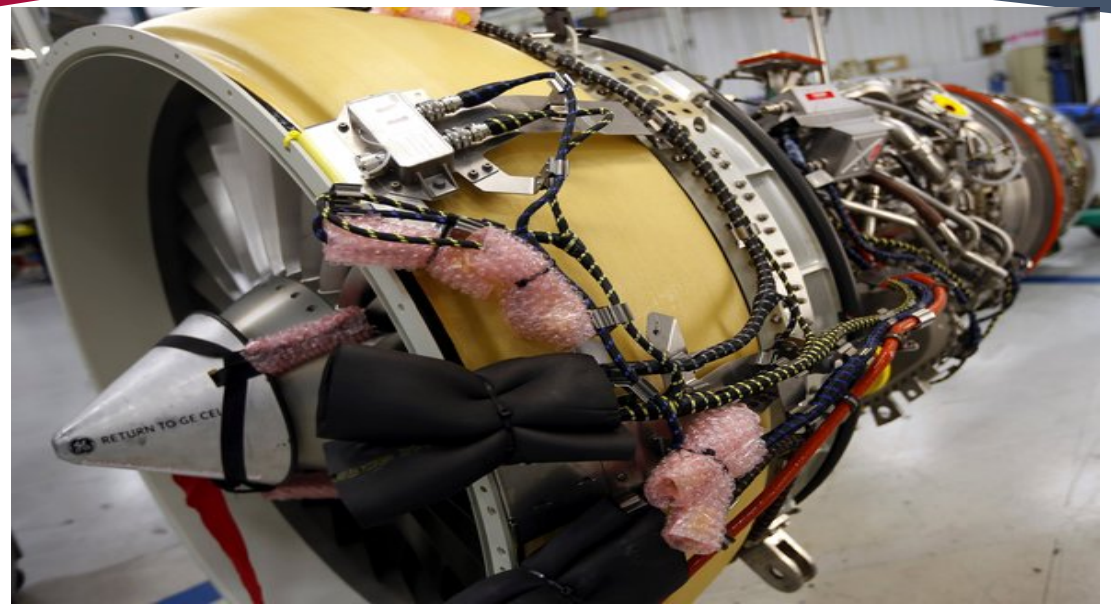
Jani V. Ilesh, June 13, 2013 N. Engl J Med

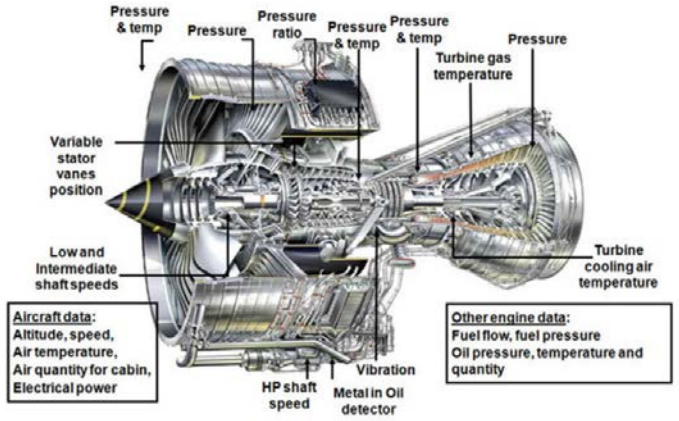
The Future: Precision Health



Courtesy of Sam Gambhir, M.D., Ph.D.

Patient Diagnostics Analogy with Jet Engines & Sensors: Biomarkers and BIG Data

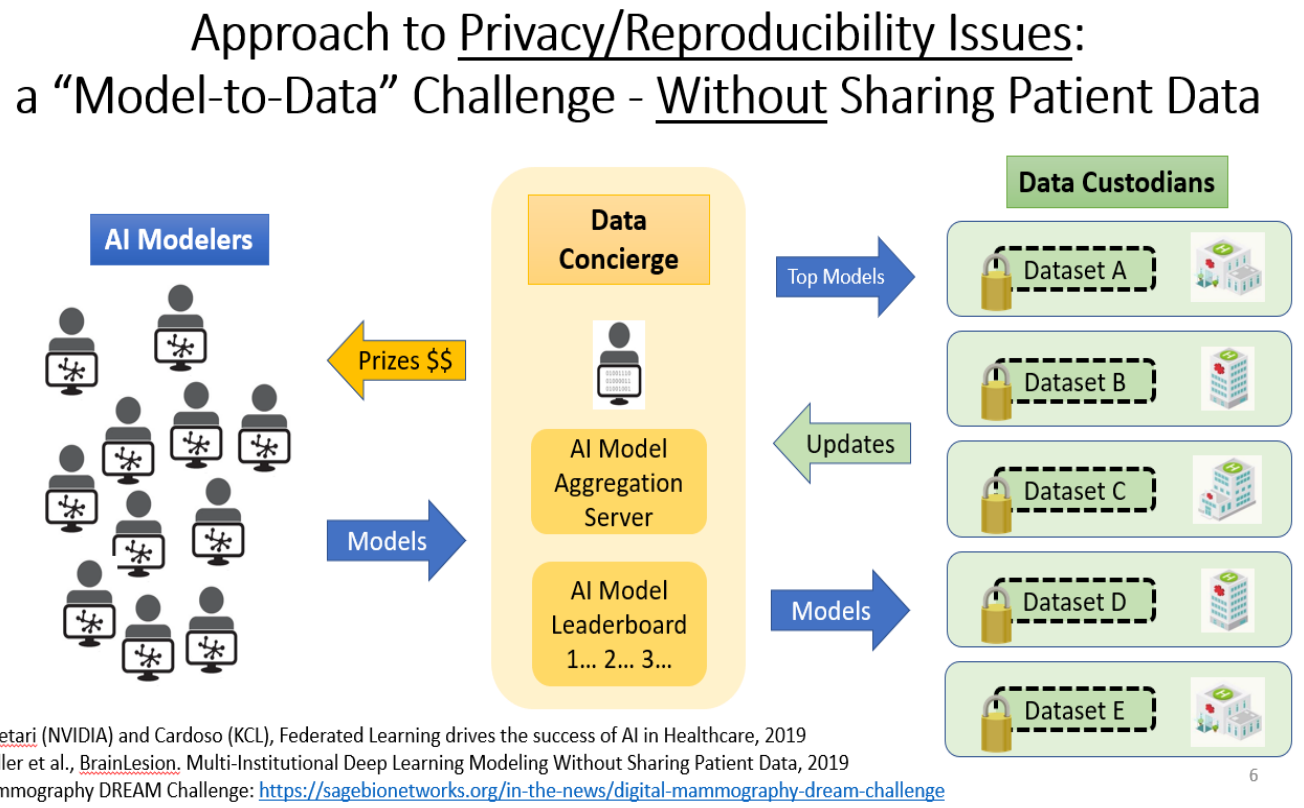




For example, a Boeing jet generates 10 terabytes of information per engine every 30 minutes of flight, according to Stephen Brobst, the CTO of **Teradata**. So for a single six-hour, cross-country flight from New York to Los Angeles on a twin-engine Boeing 737 — the plane used by many carriers on this route — the total amount of data generated would be a massive 240 terabytes of data. There are about 28,537 commercial flights in the sky in the United States on any given day. Using only commercial flights, a day's worth of sensor data quickly climbs into the petabyte scale — for a single day. Multiply that by weeks, months and years, and **the scale of sensor data gets massive.**

Biomarkers and BIG Data

- Multiplex data on biomarkers have accumulated faster than human can analyze.
- AI and Machine Learning tools are increasingly being used to deep dive into data (biochemical, molecular, and imaging) for analysis, interpretation and visualization.



Thank You!

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