Enabling Precompetitive Collaboration: The I-SPY TRIAL Process

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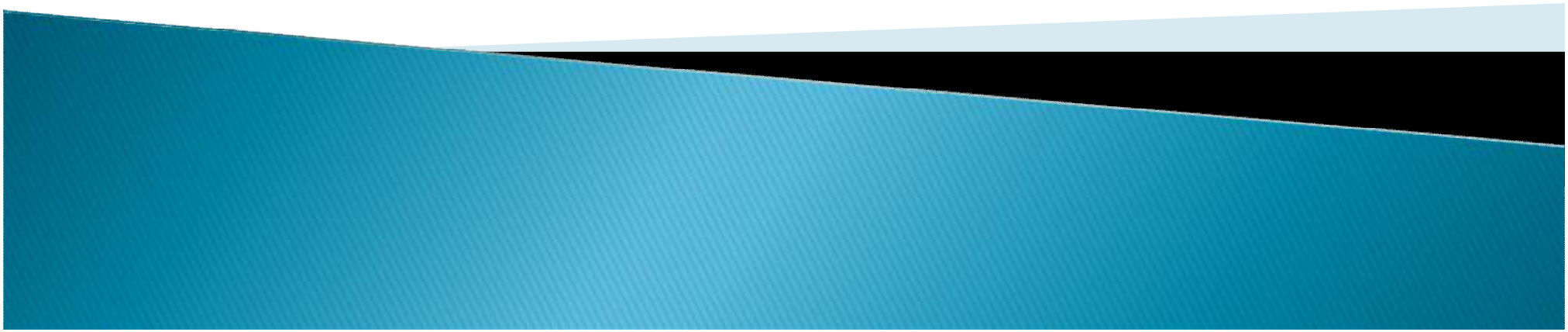

Knowledge Turns:
Indicators of time it takes for an experiment to proceed from hypothesis **è** result **è** new hypothesis **è** new result

COMMENTARY

Efficiency in the Health Care Industries
A View From the Outside

Andrew S. Grove, PhD

THE HEALTH SCIENCE/HEALTH CARE INDUSTRY AND THE microchip industry are similar in some important ways: both are populated by extremely dedicated and

Knowledge Turn for Metastatic **è** Adjuvant **è** Practice: **20 years**

Knowledge Turn for Neoadjuvant Phase 2 **è** Phase 3 **è** Practice: **2-3 years**

services.

To be sure, there are additional fundamental differences between the 2 industries. One industry deals with the well-defined world of silicon, the other with living human beings. Humans are incredibly complex biological systems, and working with them has to be subject to safety, legal, and ethical concerns. Nevertheless, it is helpful to mine this comparison for every measure of learning that can be found.

plex experiment. The test chips are monitored as an experiment progresses. If they show negative results, the experiment is stopped, the information is recorded, and a new experiment is started.

This concept is also well known in the health sciences. It is embodied in the practice of futility studies, which

The difference is this: whereas the surrogate "end point" in the case of microchip development—the test chip failure—is well defined, its equivalent in the health sciences is usually not. Most clinical trials fall back on an end point that compares the extent by which a new drug or therapy extends life as compared with the current standard treatment. Reaching this end point usually takes a long time; thus, knowledge turns are slow. In many instances, a scientist's career can continue only through 2 or 3 such turns. The re-

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More Efficient Clinical Trial Processes Required

Inefficient clinical trials account for a majority of the time and cost associated with the failures of the current system

- Reduce time to conclusive results/Accelerate learning
- Reduce patients/volunteers required
- Reduce cost of conducting trials
- Increase collaboration/Data sharing

Design Trials with the Future in Mind

Principle	Solution
Test agents where they matter most	•Neoadjuvant setting, poor prognosis cancers •Integrate advocates into trial planning
Rapidly learn to tailor agents	•Adaptive Design •Neoadjuvant therapy •Integration of biomarkers, imaging
Optimize Phase 3 trials	•Graduate drugs with predicted probability of success in Phase 3 trials for given biomarker profile
Drive Organizational Efficiency	•Adaptive Design •Master IND •Test drugs by class, across many companies •Shared cost of profiling •Financial support separated from drug supply •Shared IT Infrastructure, caBIG
Use Team Approach	•Democratize access to data •Share credit and opportunity •Collaborative process for development

CALGB INTERSPORE ACRIN NCICB

CALGB 150012/150007 and ACRIN 6657

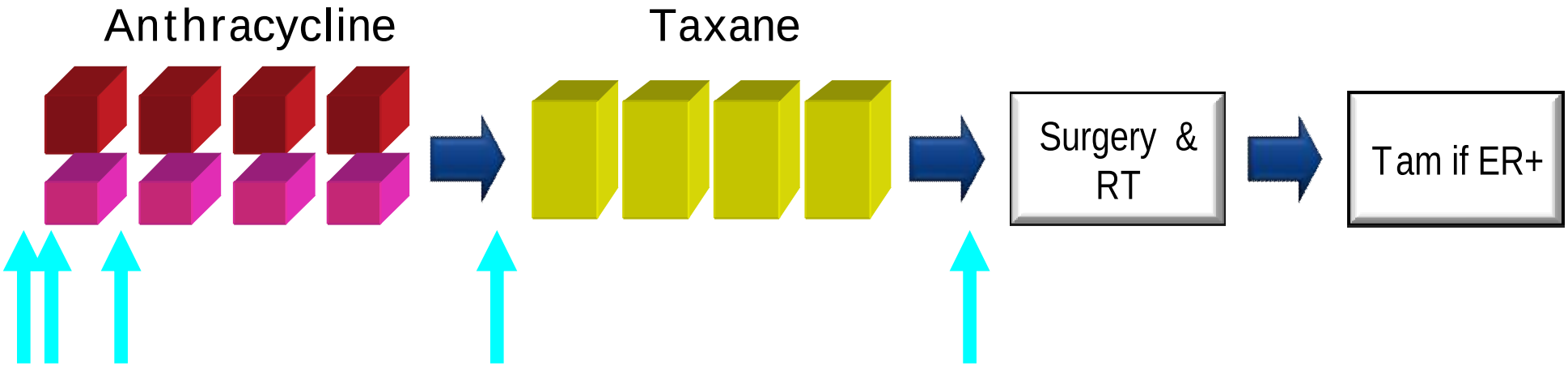
Investigation of
Serial studies to
Predict
Your
Therapeutic
Response with
Imaging and Molecular
Ana-
Lysis

I SPY WITH MY LITTLE EYE ... A BIO-MARKER BEGINING WITH X...

I-SPY 1 Clinical Trial Backbone

CALGB 150007 / ACRIN 6657

Layered Imaging and Molecular Biomarker Studies Onto Standard Clinical Care

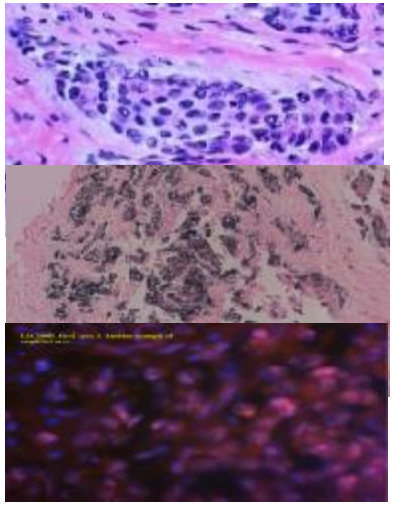


- Serial MRI Scans
- Serial Core Biopsies

I-SPY 1 Academic Collaboration

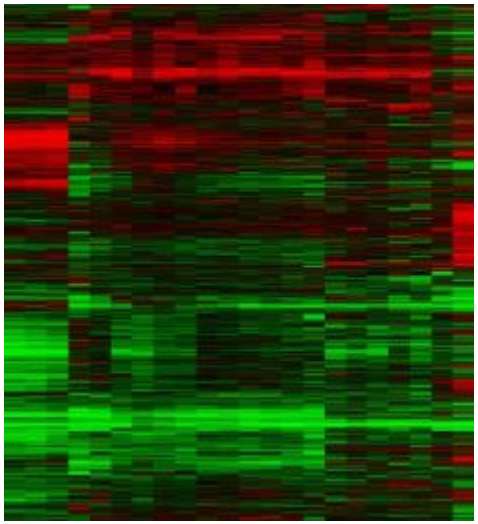
Tissue: Core or Surgical

H&E, IHC, FISH



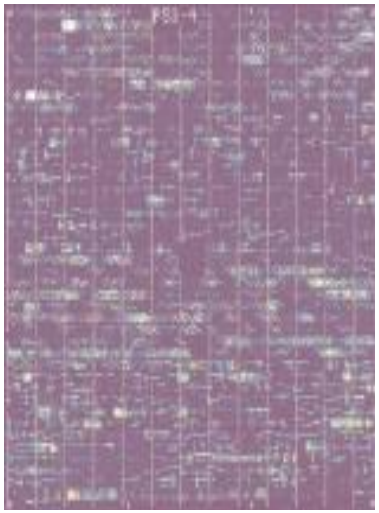
UNC, Penn

Expression Arrays



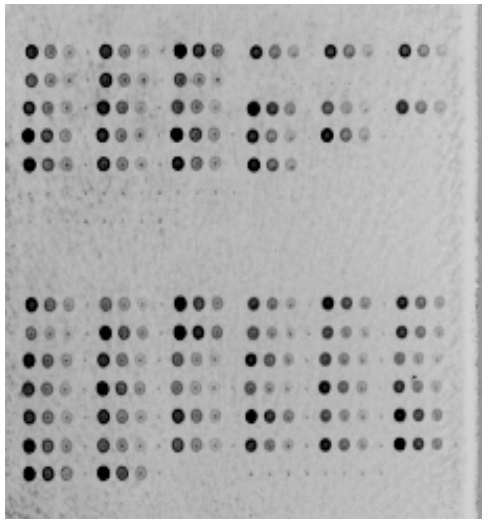
UNC, UCSF, NKI

p53 GeneChip



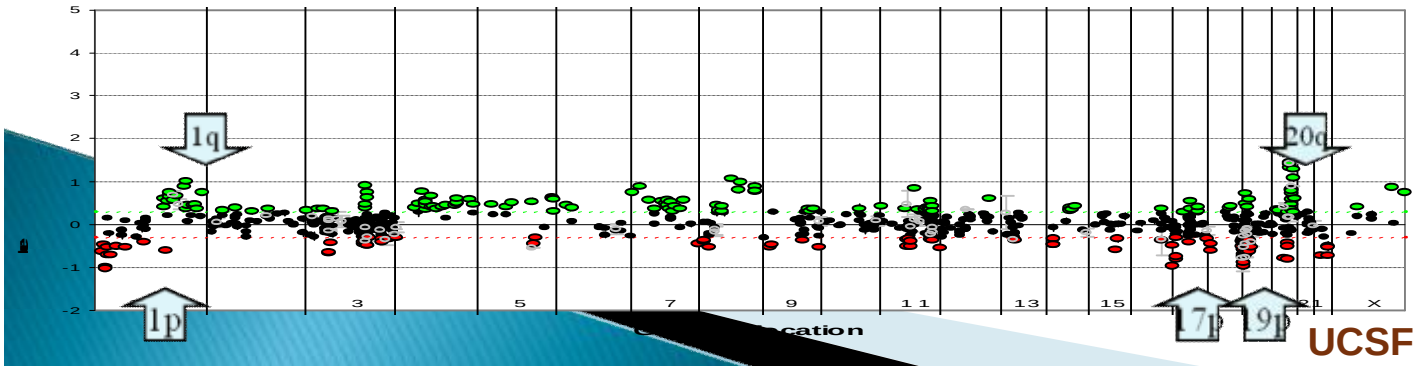
UNC

Protein Arrays (RPMA)



GMU

CGH



UCSF

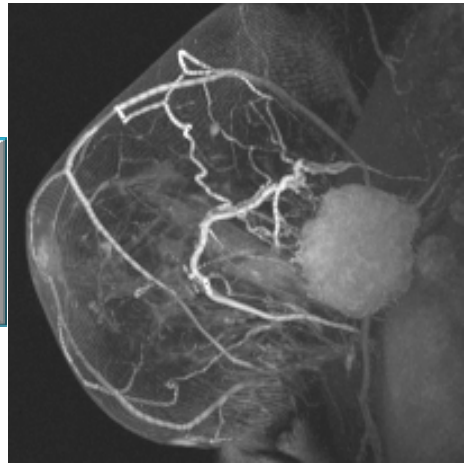
Serum

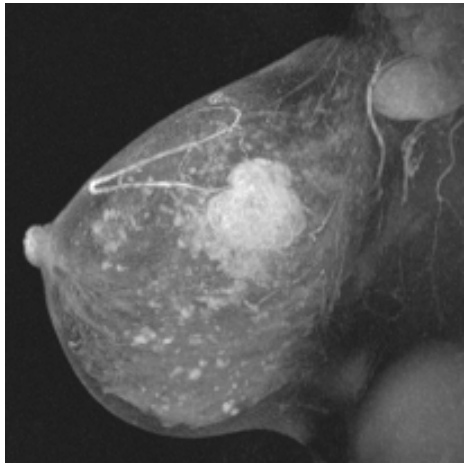
Id1 proteins
autoantibodies
phospho proteins

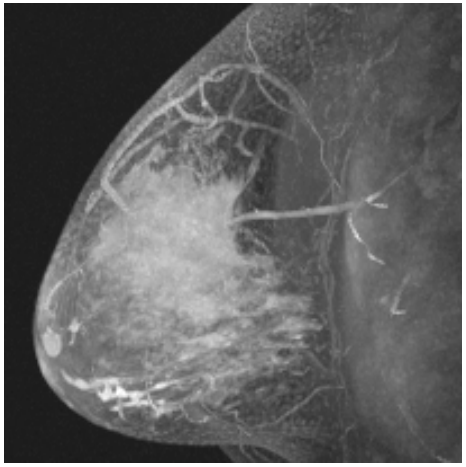
Quantitative and serial measurement of tumor response by MRI – ACRIN 6657

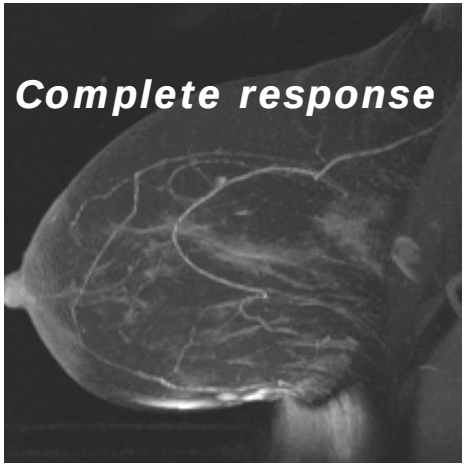
Pre Treatment

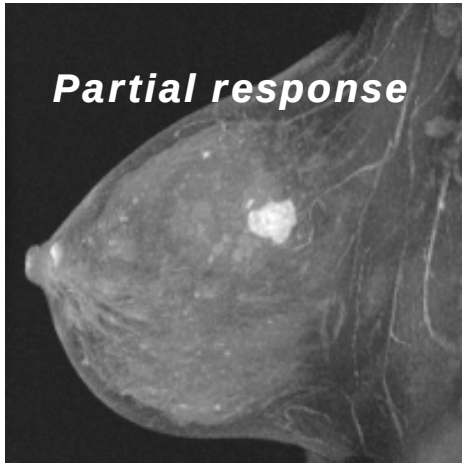
Post Treatment

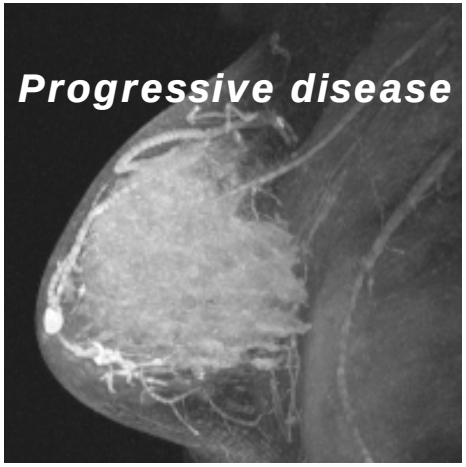












Barriers to Overcome in I-SPY 1

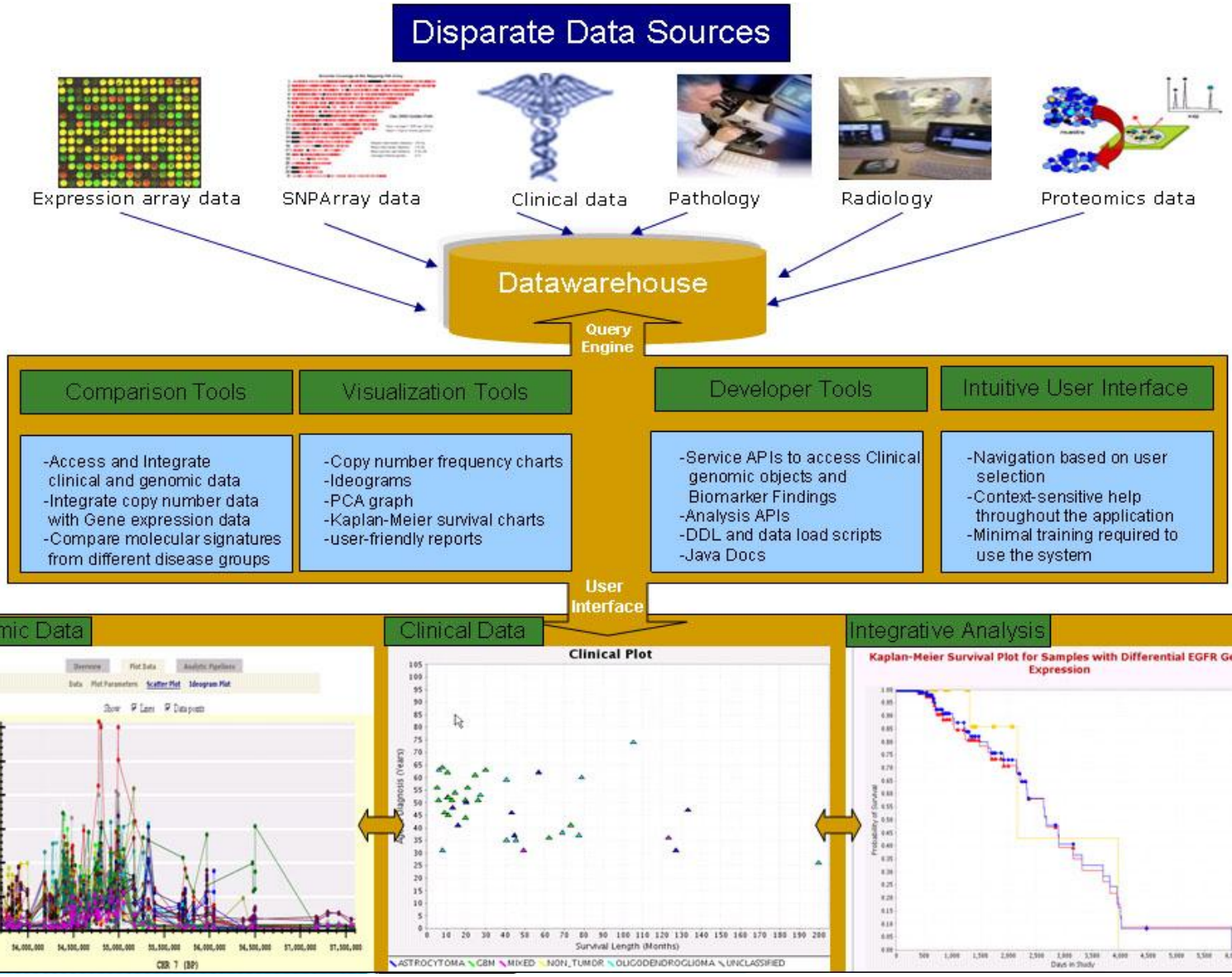
- Little motivation to share
  - Normal Process: Optimize assay of choice, present, and publish
  - Easier to stay within your field (easier to control)
  - Little credit for group science, collaboration
- Fear of allowing access to data (loss of control)
  - Fear process would corrupt data for final trial analysis
  - Trial design culture is around randomization, blinding, not allowing investigators or scientists to see data until data is mature (requires 3-6 yr product life cycle)
  - Correlative science, QI design is necessarily different

Implemented Solutions

Investigators and collaborators agreed to:

- Share data, biologic materials and analyses
  - Access granted with the expectation that all results would be annotated and added to database
- Release data after completion of trial and make accessible to the community
- Adhere to data standards
- Use common data elements to allow for easier integration of clinical, imaging, molecular results

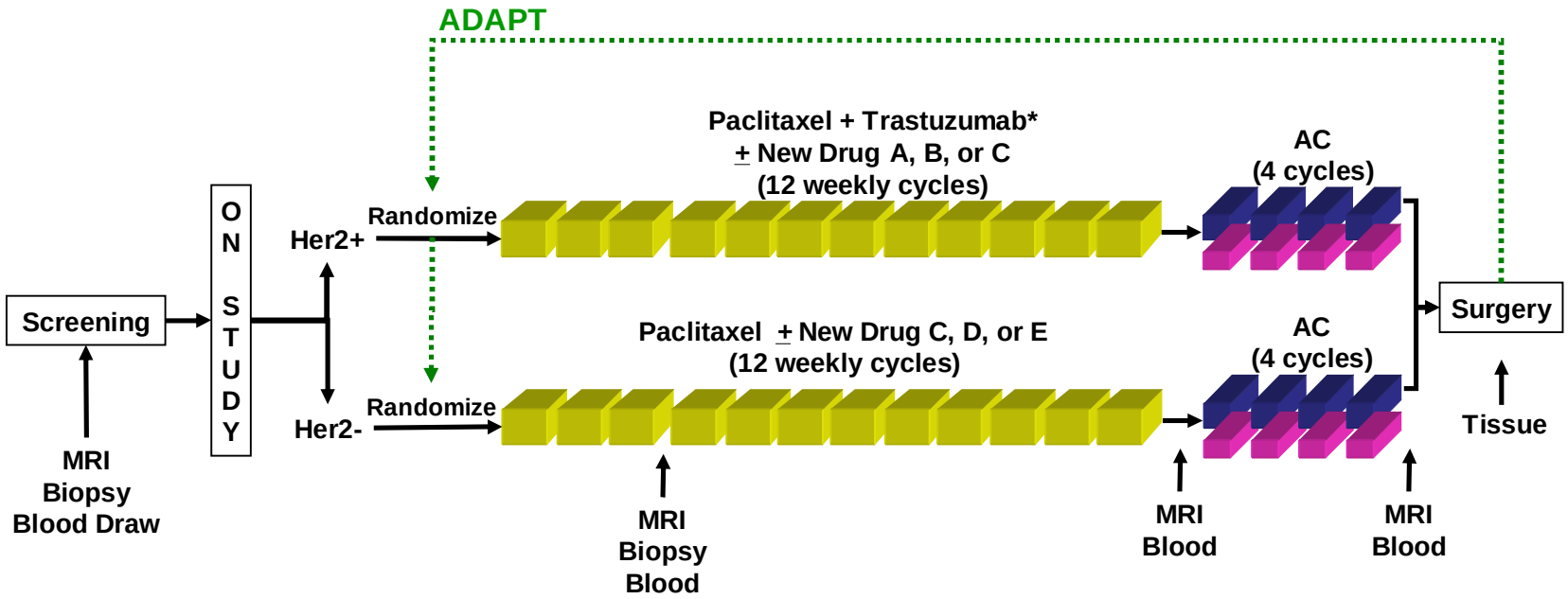
caINTEGRATOR 1 Built To Instantiate Data Sharing



I-SPY 2 Applies Findings, Infrastructure of I-SPY 1 to Testing of New Agents

- Introduction of phase 2 agents into the neoadjuvant setting in breast cancer
- Adaptive clinical trial design
- Process for rapid, focused clinical development of oncologic therapies and biomarkers
- High potential for both accelerating development of new therapies and benefiting patients

I-SPY 2 Adaptive Trial Outline



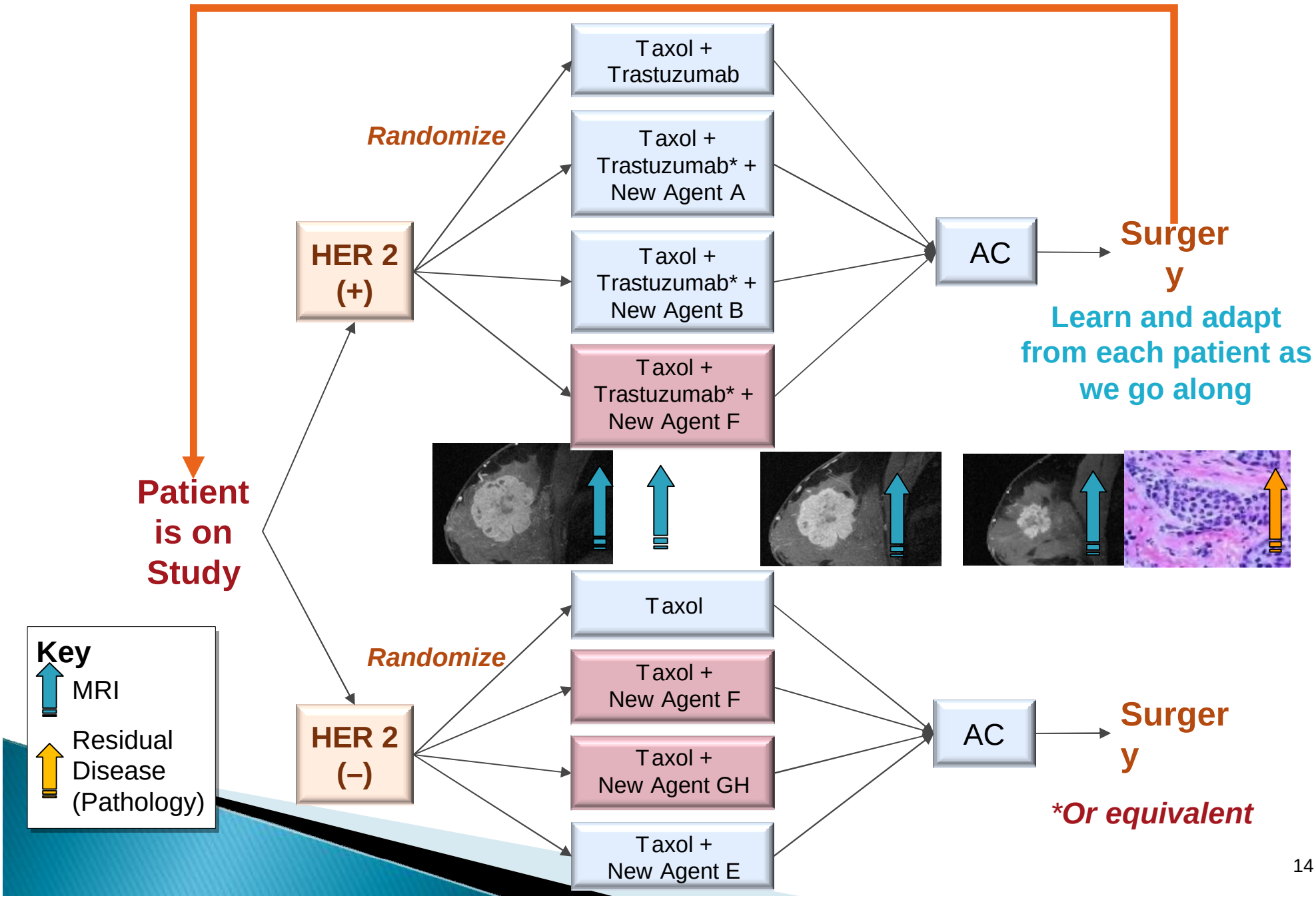
**New Drug may be used in place of Trastuzumab in Experimental Treatment Arm*

Accrual: Anticipate 800 patients over 3–4 years

Enroll: ~20 patients per month

Participating Sites: 15–20 across US and Canada

I-SPY 2 Adaptive Trial: Learn, Drop, Graduate, and Replace Agents Over Time



Advantages of Adaptive Design

- If the drug works better or worse than you think, you will learn that as the trial progresses
- Drugs can be dropped quickly if they are ineffective or harmful, or graduated sooner if they are clearly beneficial
- Smaller trials (usually), more accurate conclusions, better treatment of patients in the trial

Challenges

- Collaboration among multiple pharma and diagnostic companies, academia, and advocates
  - Each come to the table with strongly held views about what is critical to protect
  - Precompetitive agreement is ideal, but difficult to achieve
- Including multiple companies, but making each company feel like they have their own trial within a trial
- Who holds the IP makes or breaks the collaboration
  - FNIH in I-SPY 2 serves as trusted broker
  - New collaborations arising that were unanticipated

STAKEHOLDERS HAVE TO COME TOGETHER

I-SPY 2 Process Collaborative by Design

- Involve key stakeholders from inception
  - NCI, FDA, FNIH Biomarkers Consortium, Academic and Clinical Partners, Pharma, Biotech, IT, Advocates
- Involve new stakeholders as trial proceeds to approval
  - Preparation for IRB approval: 45 key stakeholders brought together for education and feedback
- Involve stakeholders from all sites
  - "Chaperones" for agents, biomarkers from trial investigators
  - Data in caINTEGRATOR 2 is open to all investigators

Master IND Accommodates Testing of Multiple agents, Organization Efficiency

- Eliminates need for new protocol each time an agent is added
- Enables approval as soon as an agent is “Tier 1” ready
- Provides pharmaceutical companies a pathway for rapid development, testing of promising agents
- Provides FDA with opportunity to test more efficient process of drug qualification
- Master IND to be held by FNIH

Transparent Agent Review Process

Pharmaceutical Company Focus Group

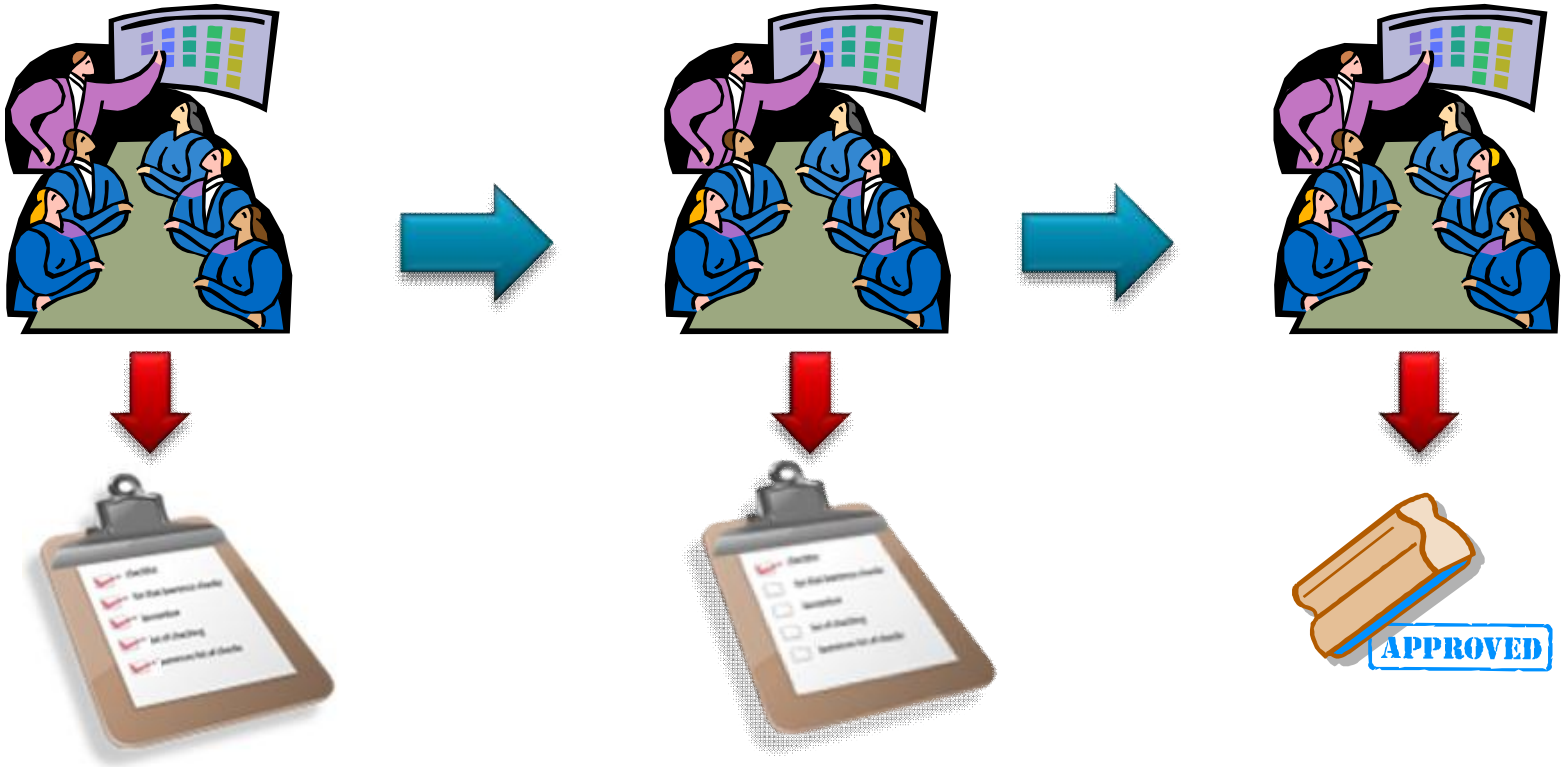
Produced broad list of candidate tier 1 and tier 2 agents

I-SPY 2 Internal Agent Review of Proposed Tier 1 Agents

Produced narrowed down list of tier 1 agents plus agents deferred to tier 2

I-SPY 2 Independent Agent Review of Proposed Tier 1 Agents

Produces approved list of tier 1 agents



Agents not included in tier 1 will be reviewed quarterly for addition to the trial pipeline

Change Linear Process of Contracts/IP to Team Approach

- Pharma
  - IP lawyers
  - Clinical Team Lead
  - Executive Leadership
  - Drug Supply
- FNIH
- Trial Leaders (contracts with sites, overall trial logistics)
- CRO
  - Distribution, FDA

Data Access and Publication Rules

- Access to Biomarkers (enrollment):
  - I-SPY 2 Internal Investigators
- Access to Drug Results, Qualifying Biomarkers when drug graduates:
  - Pharma, Drug Specific Chaperones
- Access to Exploratory Markers/ Platforms
  - 3 months for Internal Investigators
  - Simultaneous: I-SPY 2 Research Community

I-SPY 2 Informatics Infrastructure:TRANSCEND

Uses Common Tools, Enables Data Exchange for Adaptive Design Trials

Randomization Service

Patients randomized to novel treatment arm

Clinical Information System (Tolven eCHR)

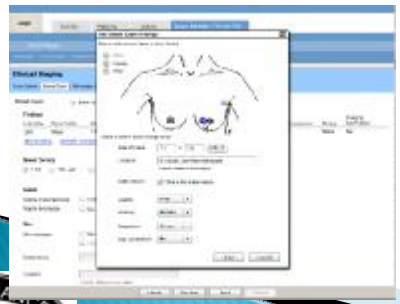
Eligibility is verified, patient is registered , clinical data is captured, tracks the patient schedule, identifies labs and allows them to be viewed/resulted

caINTEGRATOR

Investigators evaluate efficacy of treatment arms – as trial is underway

caXchange (Hub)

Patient visits the Physician



Biopecimen Data Management System (caTISSUE)

biospecimens are tracked

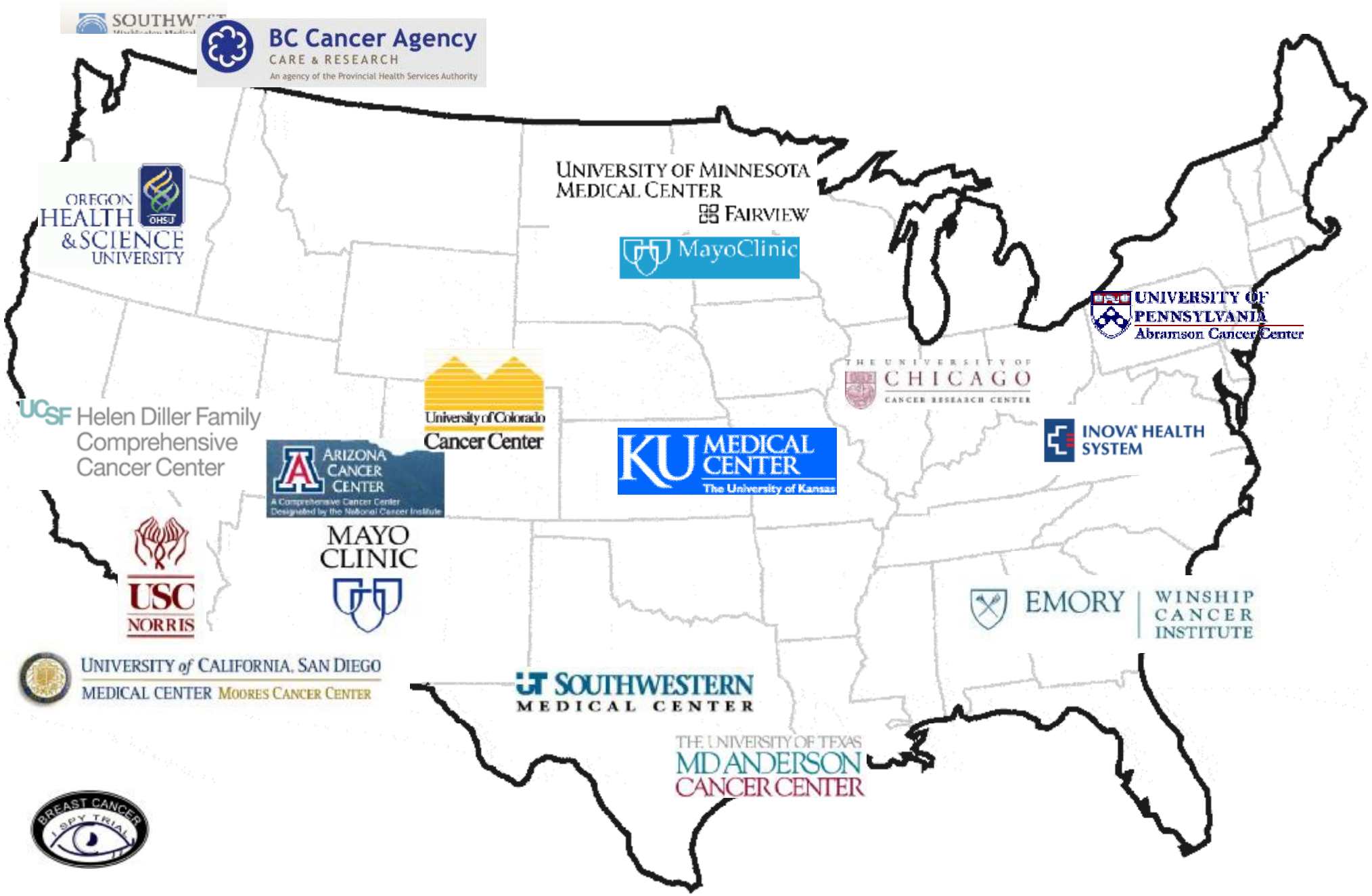
Cancer Adverse Event Reporting System (caAERS)

Identifies and tracks adverse events and any associated schedule changes

Precompetitive Dx Workshop

- Agree to have the I-SPY 2 Pharma and Diagnostics partners sit down together
- Understand role of FNIH as honest broker
- Move toward precompetitive agreement on biomarker standards by class as appropriate

Despite Challenges I-SPY 2 To Open Late February 2010



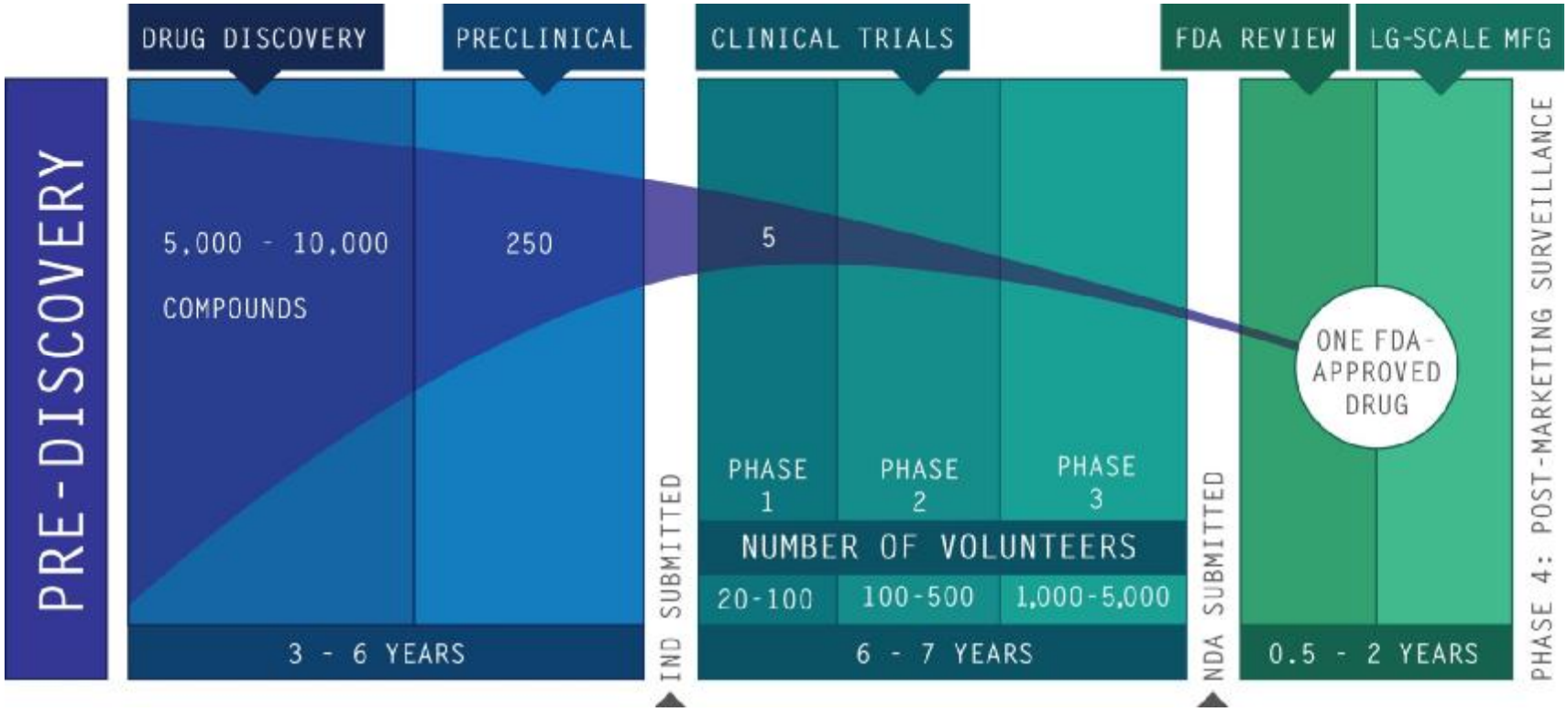
I-SPY 2 is a Paradigm Shift

- Uses adaptive design in neoadjuvant setting to allow efficient learning,
  - pCR is primary endpoint
- Biomarkers, imaging and pathology endpoints help drive trial
- Qualifies biomarkers as new agent classes are tested
  - Established/ Approved Biomarkers/ IDE Biomarkers
  - Qualifying Biomarkers
  - Exploratory Biomarkers
- Provides foundation of evidence for tailoring therapy
- Test Drugs by Class- allows industry to learn together

Value Proposition/Benefit for Partners in Public Private Partnership (PPP)

Patients	§ Opportunity to Drive Path to Personalized Treatment § Potentially More Effective Treatment/Management
FDA	§ Provides for Evidence-Based Regulatory Policy
Pharma	§ More Efficient Drug Development and Approval Path § Better Early Response Criteria
Device Industry	§ Larger Markets § Less Risk
CMS	§ Helps Define Reasonableness and Need
Academia/NCD	§ Better Clinical Data § More Effective Treatment/Management

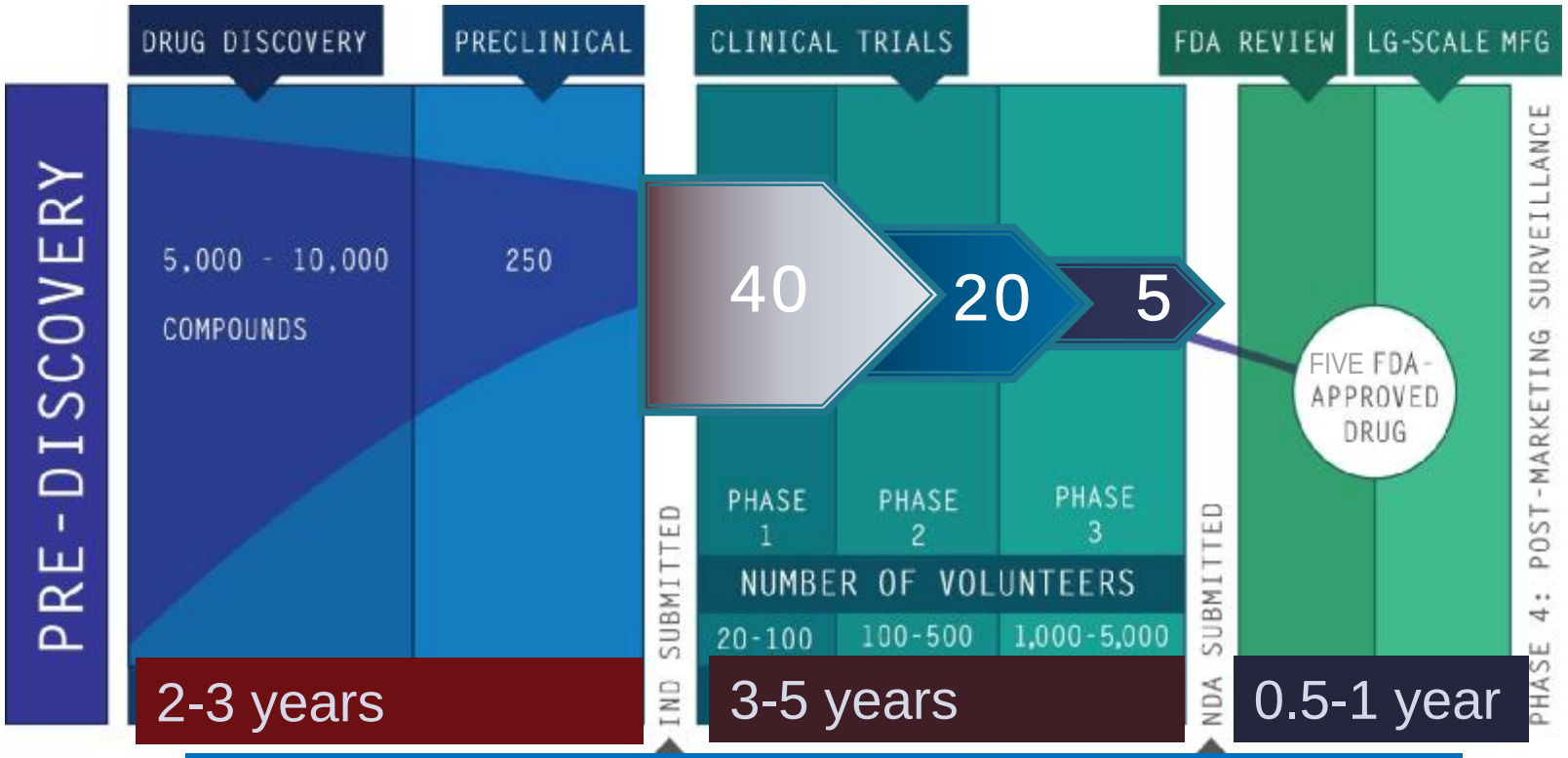
Drug Development – Current Model



One FDA-Approved Drug - Start to Finish

- 10- 15 Years
- 1,000 – 6,000 Volunteers
- $1 Billion

Drug Development – I-SPY 2 Model



- 5X More Products for 1/5 of the $$
- 25X Improvement
- ½ of the time, with ½ the volunteers
- 4X Improvement