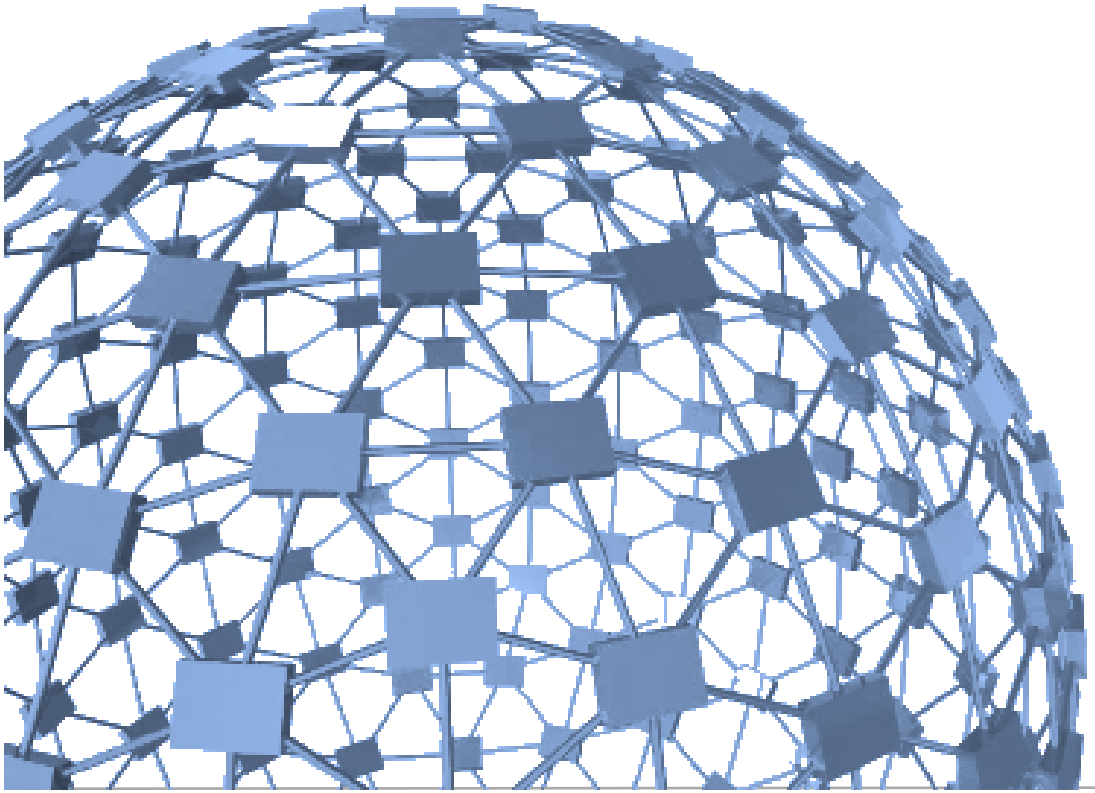
I-SPY 2 and I-SPY 3 TRIALS Drug Development Paradigm : A Breast Cancer Demonstration



Laura Esserman MD MBA

Better Health, Better Science

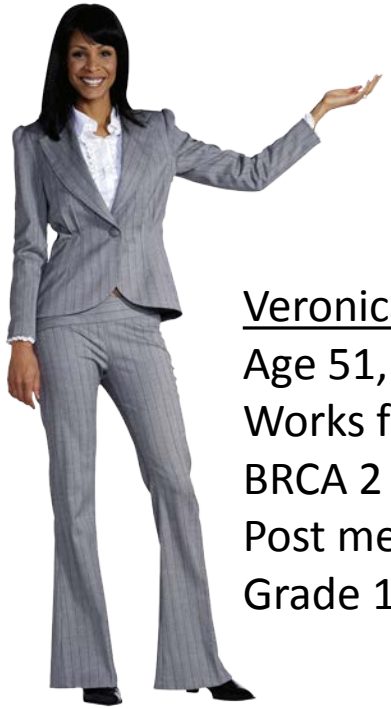
October 27, 2015

The Right Drug .
The Right Patient.
The Right Time. Now.

Precision Medicine is the art of . . . .

Tailoring Care to Biology, Patient Preference, and Clinical Performance

Two People Who Seem Similar, Are Not . . .



Veronica
Age 51, 1 cm tumor
Works for Walmart
BRCA 2 carrier
Post menopausal
Grade 1 ER+ tumor

Kim
Age 51, 1 cm tumor
Self employed consultant
Recently divorced, single mom
Pre menopausal
Grade 3 triple negative tumor
Positive nodes

The Problem for Patients, Companies

- *30-50% of women with breast cancer still die of their disease*
- *It takes 10-15 years for new oncology drugs to reach patients*
  - *And over $2.7 billion*
  - *Access depends on where in the world you live*
- *Many new therapeutic options- little chance to rapidly get them to patients*
- *Blockbuster approach unlikely to be successful*
  - *Cancer is a subset of diseases*
- *70-90% of phase 3 trials fail*

We HAVE to do better . . .

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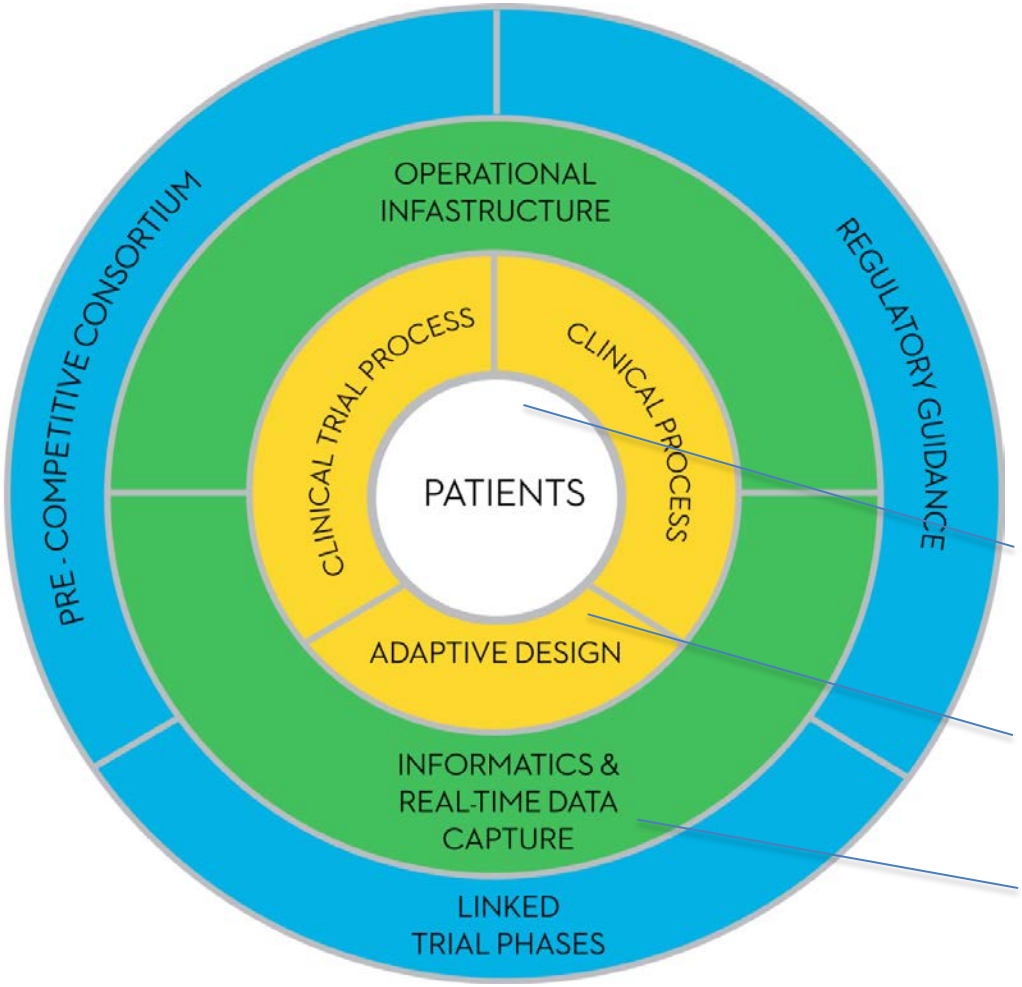
Solution: Re-Engineer and Start at the Point of Care



Clinical Process Re-engineering

Structural

Alignment

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Optimize the Clinical Care Process

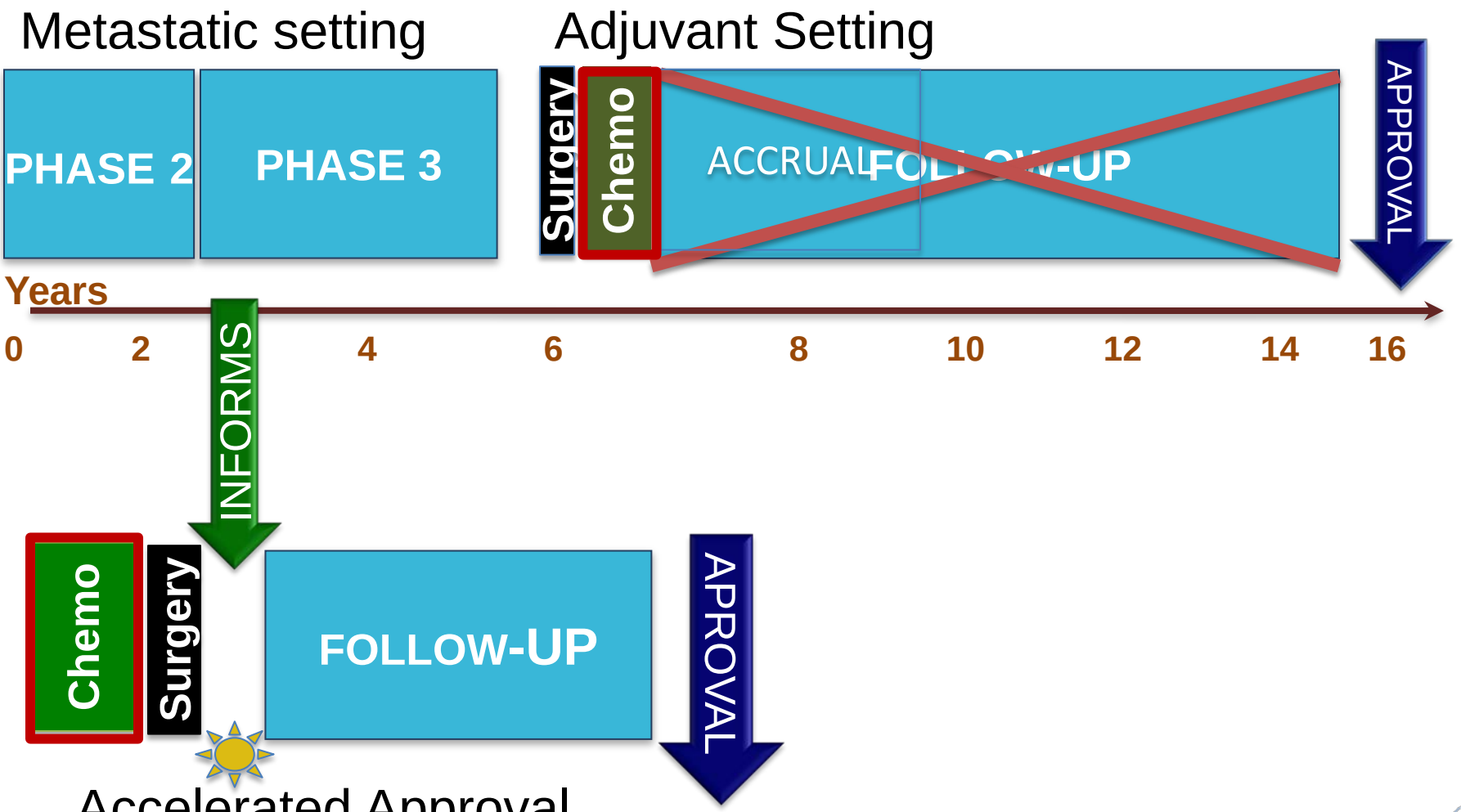
Women at Risk for Systemic Recurrence

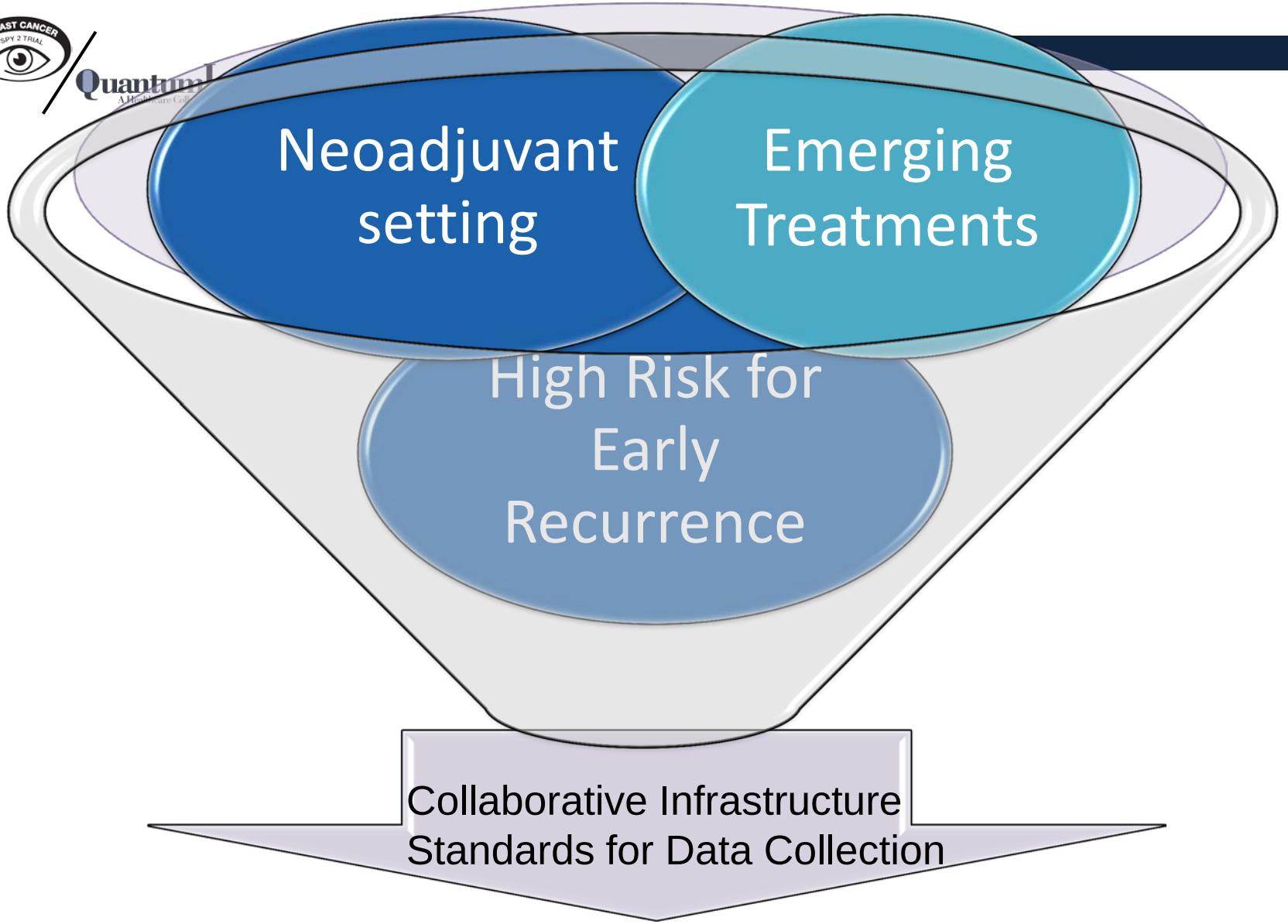
- Larger tumors, node positive, chemotherapy indicated (25%)
- Will not be cured with surgery alone

- Order of surgery, systemic therapy has no impact on survival outcomes

- Neoadjuvant approach is an opportunity
  - Downstage tumors, refine local therapy options
  - Better understand response to therapy, prognosis
  - Accelerate targeted drug development to improve outcomes in highest risk women

What Conditions Could Enable Dramatic Improvements in Knowledge Turns? *What scenarios can take real time off the clock?*





I-SPY 2

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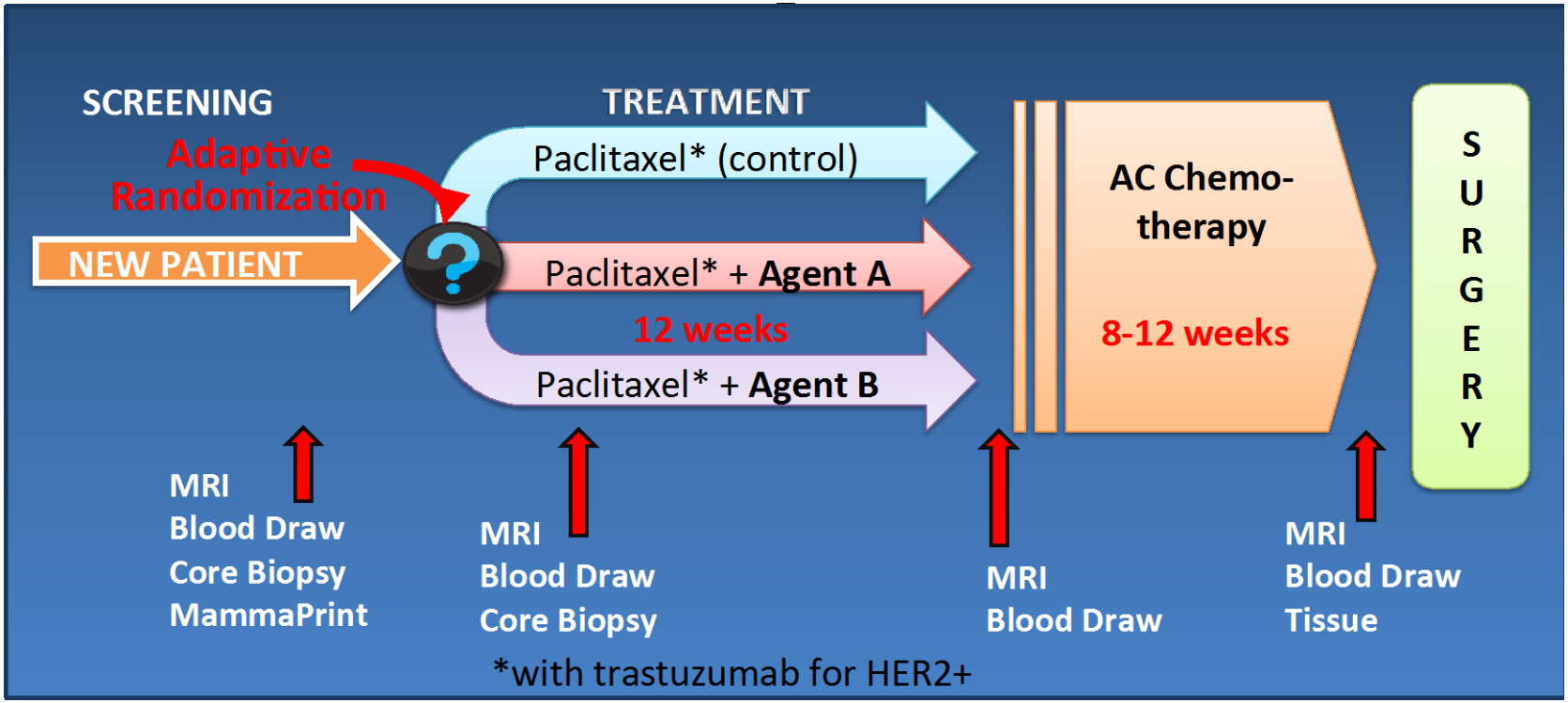
I-SPY 2 TRIAL Schema



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I-SPY 2 Mission: Change the Way We Test Promising New Drugs

- Test drugs where they matter most (Early stage)
- Use biomarker and imaging guidance,
- Use adaptive design
- Develop IT solutions where form→ function
  - collect data in real time, integrate care & research
- Leverage a precompetitive collaboration model

I-SPY 2 is a Standing Platform Trial with a Master Protocol

Using response-adaptive randomization

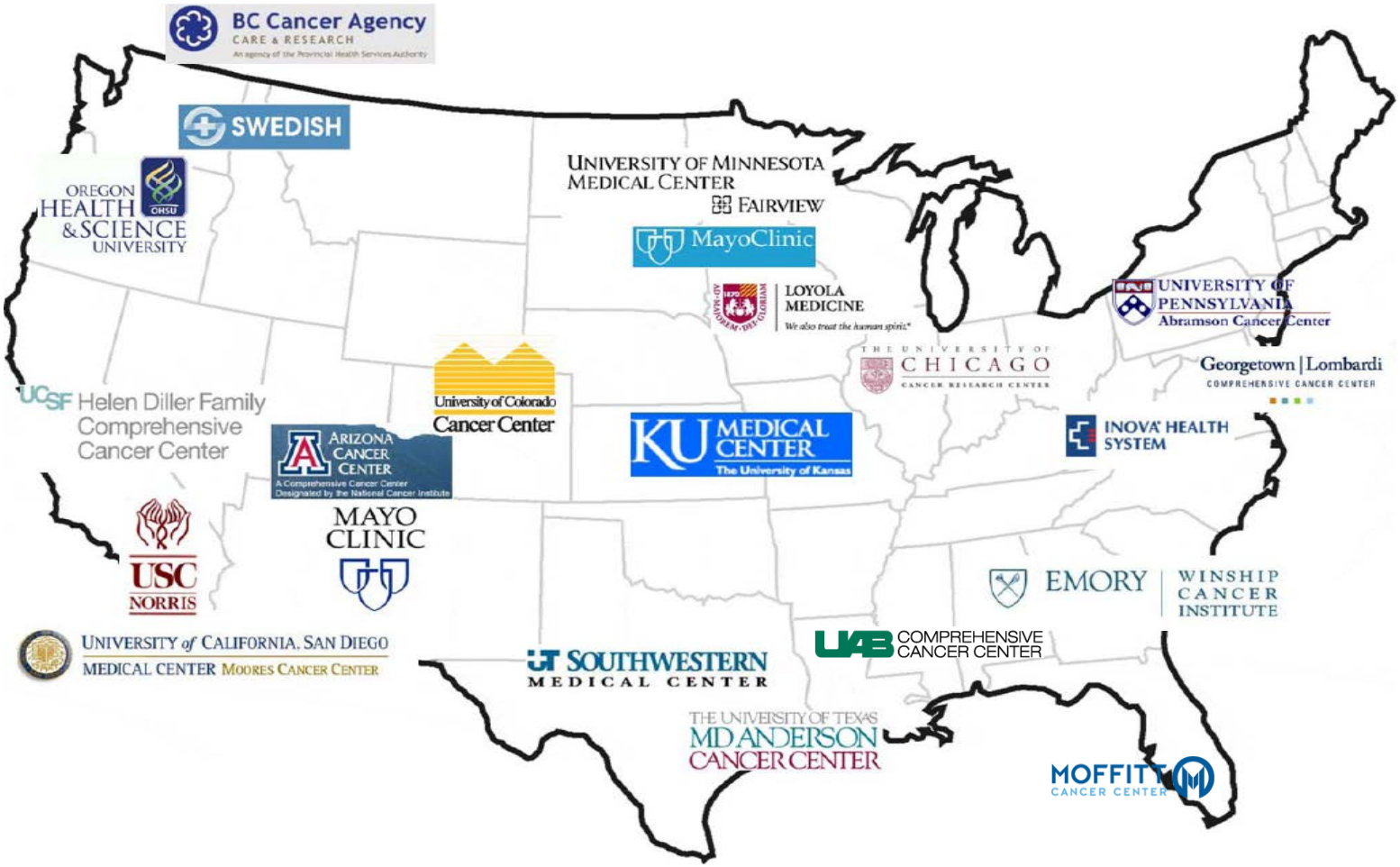
I-SPY 2: Designed to Optimize Success of Phase 3 Trials

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 & Master CTA •Test drugs by class, across many companies •Shared cost of profiling •Financial support separated from drug supply •Shared IT Infrastructure, caBIG •Protocol & ICF structure to minimize delays
Use Team Approach	•Democratize access to data •Share credit and opportunity •Collaborative process for development

I-SPY Milestones

- Demonstrated that pCR endpoints work better by subtype (I-SPY 1)
- Enlisted multiple pharma companies into same trial
- Developed I-SPY 2 infrastructure and team science approach
- Demonstration of the standing trial concept
  - multiple arms, single, evolving backbone and Master IND
- Successful use of Adaptive Randomization in a platform trial
- Graduation of 3 agents, with biomarker signatures
  - Neratanib (Puma Biotechnology) (Dec 4, 2013): HER2+ HR-
  - Veliparib (AbbVie) (Dec 13, 2013): HER2- HR- (triple negative)
  - MK-2206 (Merck) (May 29, 2015): HR-, HR-/HER2+, HER2+
- Accelerated Approval guidance issued by FDA
- I-SPY Phase 1 network and I-SPY 3 International Registration Trials

Participating Trial Sites: *17 Sites Open to Accrual: Screened >1600 (>30/month); Randomized >900*



I-SPY 2 Participating Organizations

Sponsor

QuantumLeap
A Healthcare Collaborative

Funders, Operations

QUINTILES

SAFEWAY
Ingredients for life.

UCSF
University of Califo
San Francisco

Novella
CLINICAL
Moving Potential. Forward.

FOUNDATION FOR THE National Institutes of Health
THE biomarkers CONSORTIUM

WILLIAM K. BOWES, JR. FOUNDATION

Investigational Agent Providers

abbvie

AMGEN

Genentech
A Member of the Roche Group

MERCK
Be well

Plexxikon

SYNTA
PHARMACEUTICALS®

Puma Biotechnology

Biomarker Device IT Providers

OREGON HEALTH & SCIENCE UNIVERSITY
OHSU

UCSF
University of California San Francisco

GEORGE MASON UNIVERSITY

BERKELEY LAB
LAWRENCE BERKELEY NATIONAL LABORATORY

salesforce

sentinelle MEDICAL

HOLOGIC
The Women's Health Company

agendia
coding cancer

THERANOSTICS HEALTH
The Partner of Choice for Personalized Medicine

FDA – Neoadjuvant Pathway for Accelerated Approval

Goal: get highly effective drugs to patients sooner

- Not a lesser standard or "easy" route to market for marginal drugs
- Target patients at high risk for recurrence and death
- Trials need to detect a large improvement in pathologic complete response (pCR)
- Choose drugs with high likelihood of meaningfully improving long-term outcomes

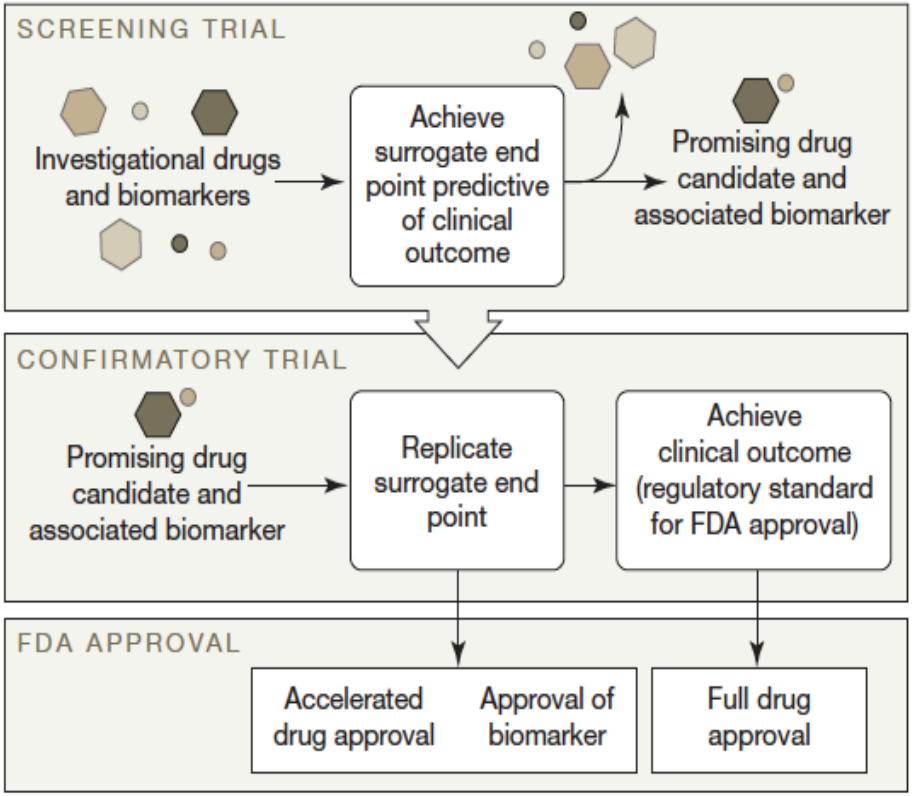
I-SPY 2 & I-SPY 3 as a Blueprint

I-SPY 2: Randomized phase II screening trial

- Identify new agents/biomarker combinations that improve pCR
- Standardize path assessment, including RCB
- Graduation threshold is 85% probability of success in subsequent Phase 3 trial

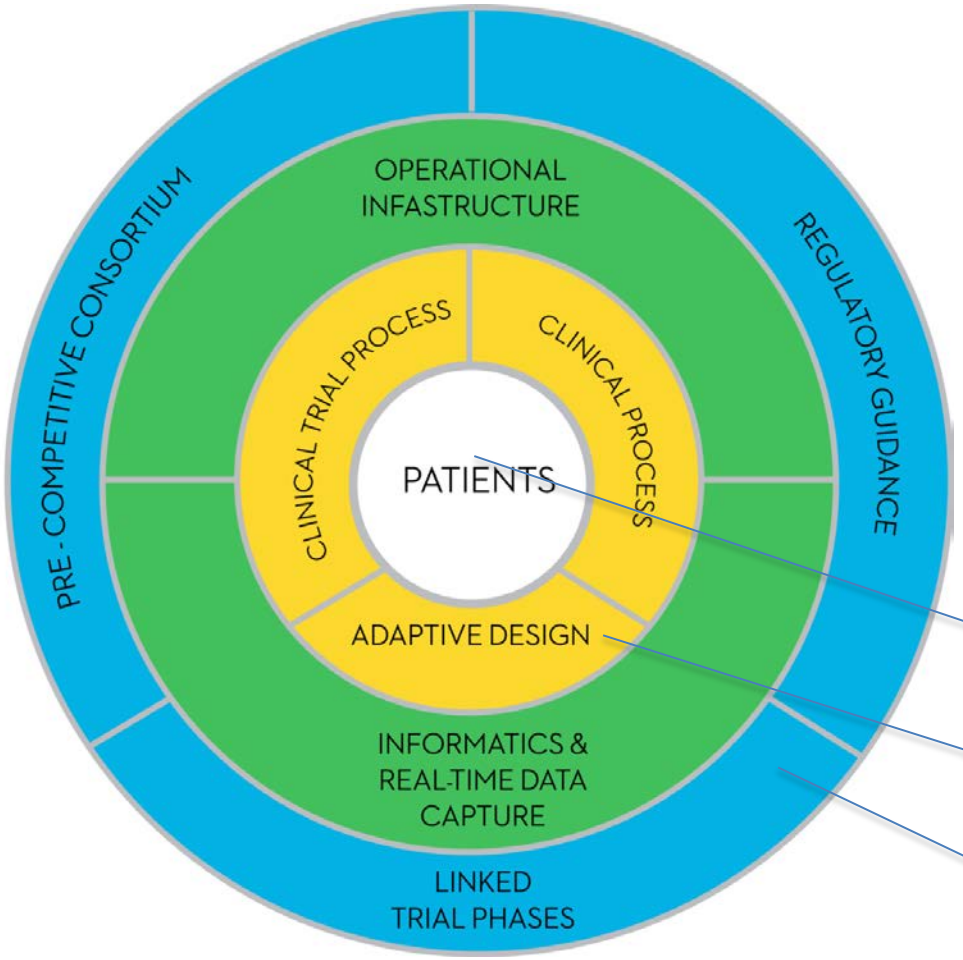
I-SPY 3: Randomized phase III confirmatory trial

- Validate I-SPY 2 biomarker- linked efficacy signals and create a fluid phase 2-3 platform
- Similar eligibility criteria as I-SPY 2 to allow confirmation in same patient population



Esserman & Woodcock, JAMA, 2011

A Framework to Accelerate Knowledge Turns



Linked trial phases could provide additional efficiency and further

Core

Structural

Alignment

The Right Drug .
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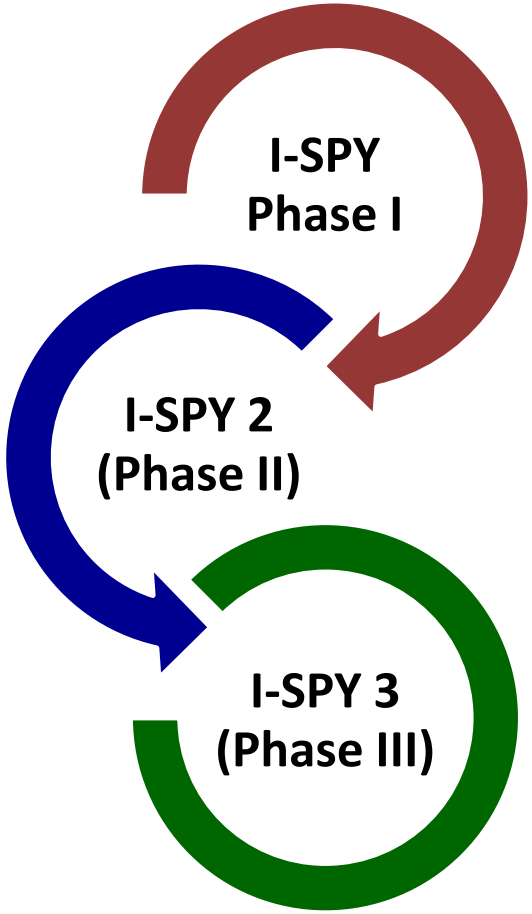
Time is Key . . .

- Get and keep the engine running
  - Invest in Key Centers that know how to identify the right patients (high risk)
  - Establish centers that put 50-80% of patients (instead of 5%) on trials for both phase 2 and phase 3
- Generate data from clinical systems in a way that it can be re-used
- Build automation and analytics into the trial data systems

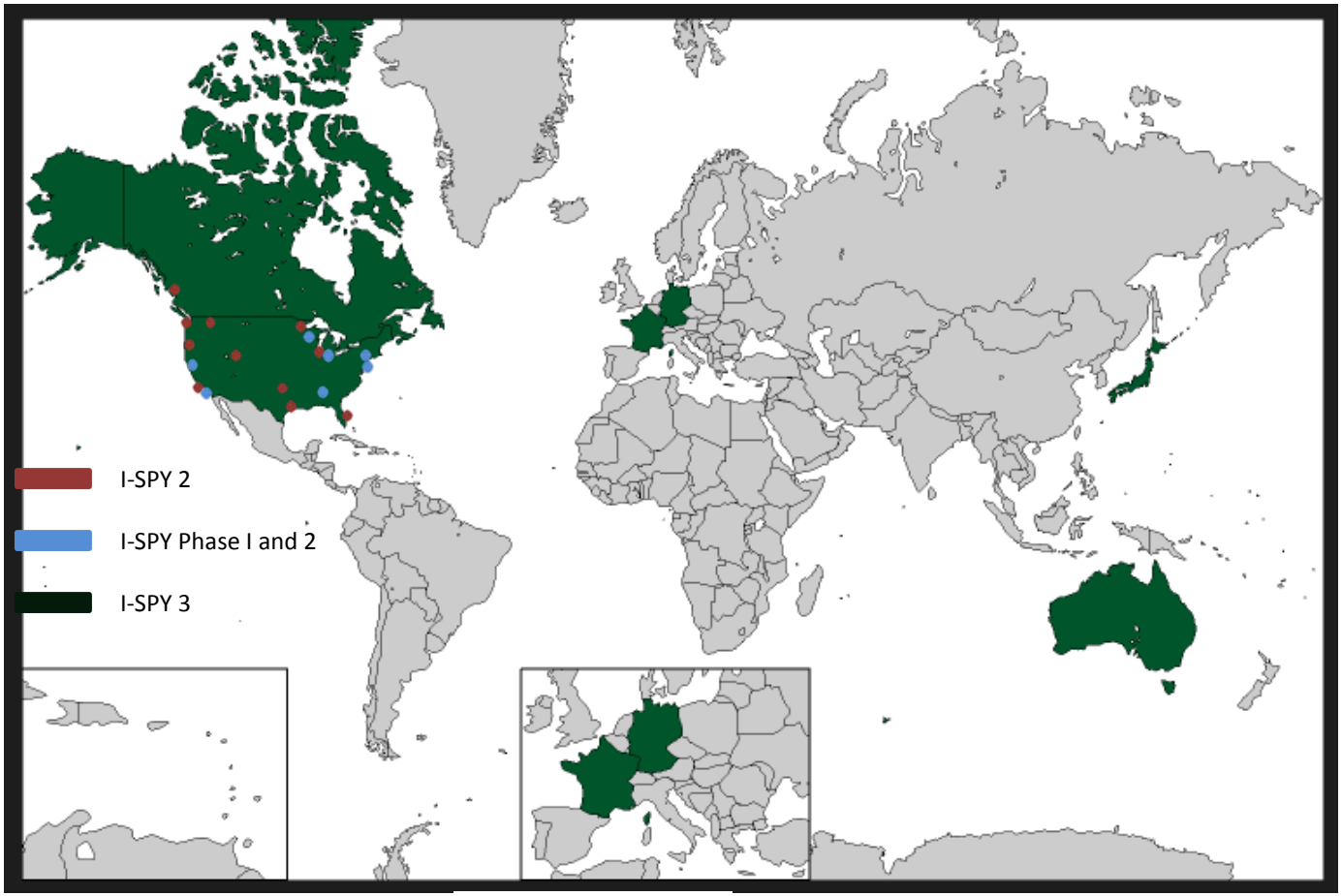
Goal: Decrease the time to 1 year instead of 3-5

Integrating and Linking Trial Phases



I-SPY Phase I: Patient safety trial	Safety testing of investigational agent in combination with standard of care 7 I-SPY 2 sites participating
I-SPY 2 (Phase II): Response Adaptive design	Response-adaptive randomization-Pts get combos more likely to benefit them 20 Sites in US and Canada (>1600 patients screened) 9 drugs /7 pharma partners so far
I-SPY 3 (Phase III): Accrual Adaptive Confirmatory trial	Confirmatory trial of promising drug/ biomarker pair from in I-SPY 2 or similar trials International collaboration (US, Canada, Europe , Australia, Japan , others)

I-SPY Program Footprint



Data Management Partners(evolving):

Novella CLINICAL
Moving Potential. Forward.

GBG
GERMAN BREAST GROUP

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I-SPY 3 Design

- **MASTER trial standing** platform: a fluid phase 2-3 for efficient validation of I-SPY 2 efficacy signals
- **Shared Control groups** as agents with same biomarker signatures enter trial
  - Promotes efficiency, minimizes impact on accrual as agents added
- **Data Plan** submitted as part of master protocol
  - Focus on efficiency and collection of data elements directly influencing efficacy and safety endpoints
  - Streamline data collection and monitoring **(one source/e-source)**
- **Open label** experimental arm administration
  - Improve patient safety and mitigate risk with preventive treatment of expected adverse events
  - Essential for harnessing efficiency of standing phase 3 concept

Opportunity created by the I-SPY 3 Consortium

- **Increase capacity** around the globe
  - Work collectively to enable effective drugs to get to women globally
  - Opportunity for regulatory harmonization, global drug registration
  - Advance integration of care and research

- **Promote adoption of standards** for data collection to enable:
  - A platform to improve the state of the art of breast care

    Centers of excellence, lower cost of trials

- **At the end of the trial,** better than when we started
  - Each site should have greater capacity for integrated research/care
  - Raise standards for all patients across the world
  - Proof of whether substantial increase in pCR leads to increased EFS

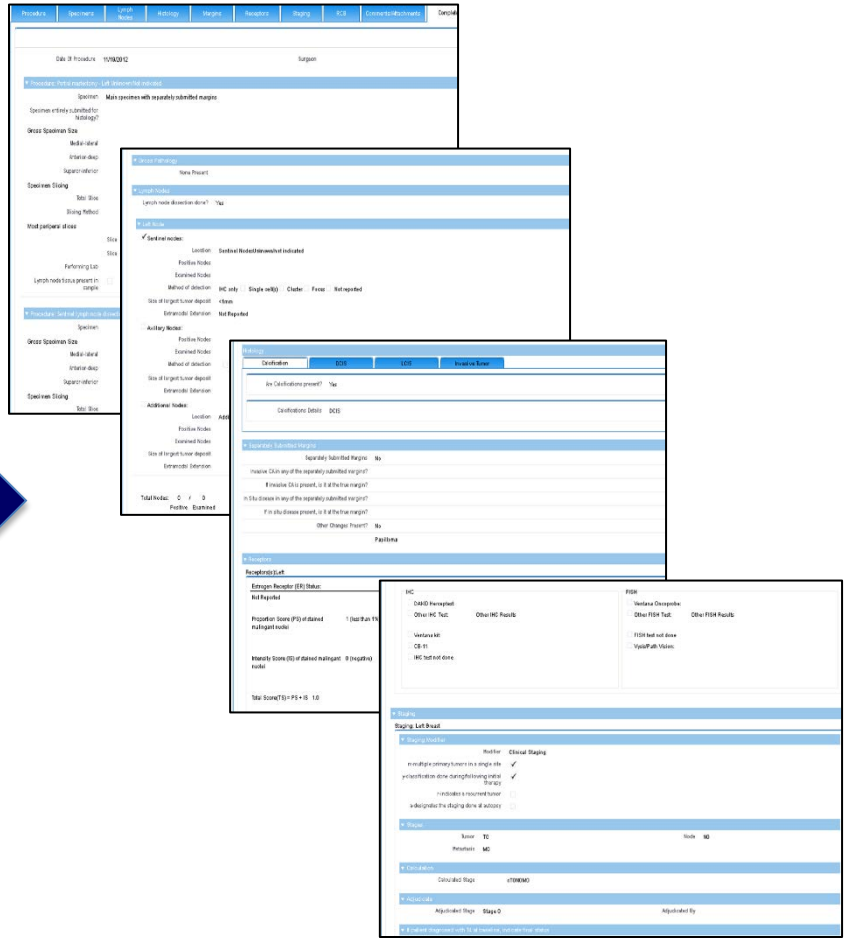
eSource/OneSource Data Collection

Others

SDC Standards

Enter the 'right' data once

Using dynamic XML-based checklists for data capture, rendering within the EHR



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Good quality clinical care, clinical trials, registries, quality improvement, researchers, scientists, payors, regulators and others all require the same data elements…

eSource Widget

Enter the 'right' data once
Using dynamic XML-based checklists for data capture, rendering using IHE RFD first (and later IHE SDC) standards

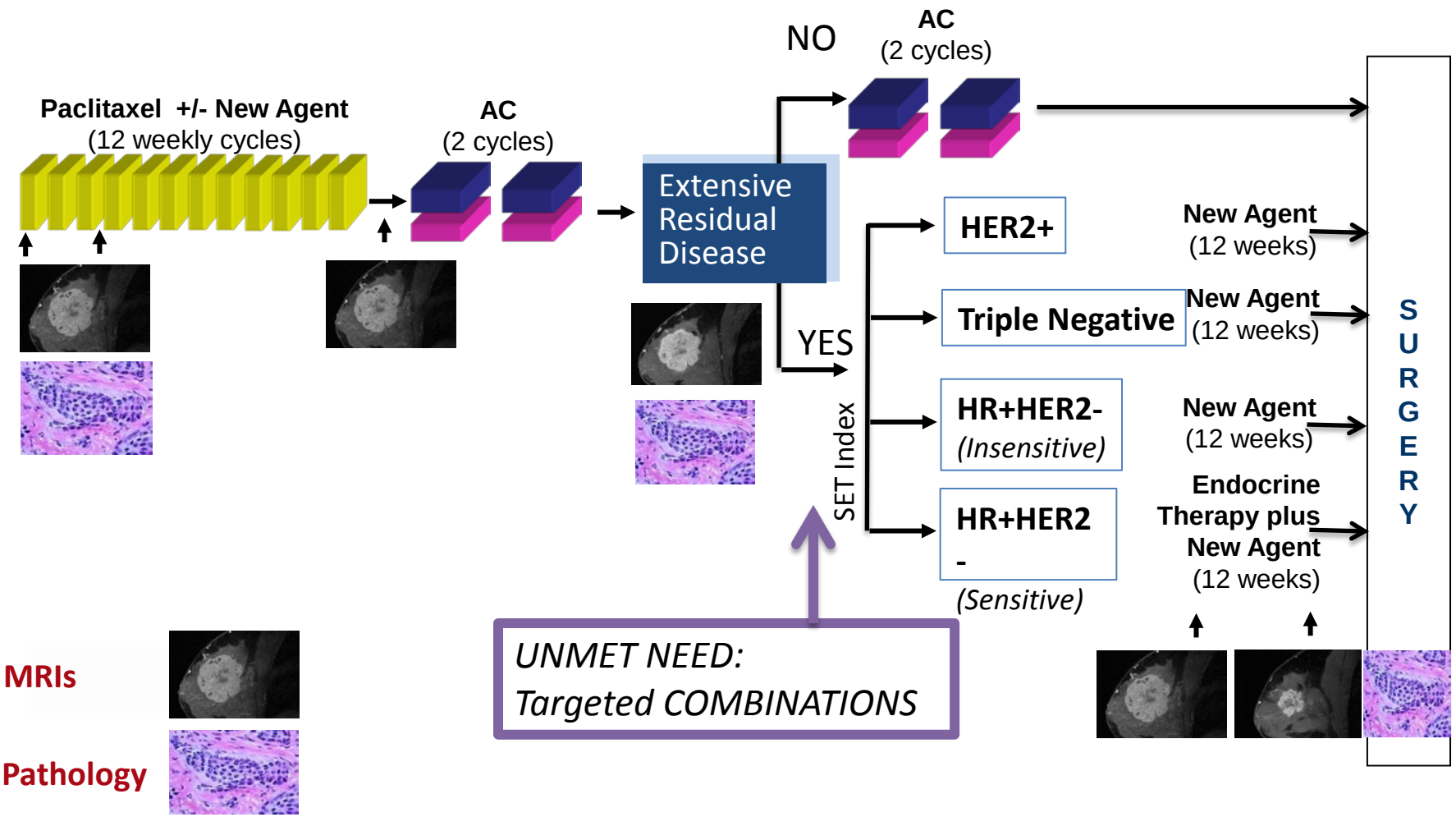
Use the 'right' data many times

Registries
Clinical Trials
Trial Matching
Regulators
Decision Support
Biomedical Research
Payors
Ancillary Patient Care Systems
Biopharma & Device Orgs
Home Care
Patient Engagement
Personalized Care
Clinical Efficiency

AHRQ
ACRO
FDA
PMDA
EMA
CDC
NIH
WISDOM
Athena

Possible Evolution→ I-SPY 2 PLUS:

Personalizing therapy for tumors resistant to chemotherapy



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I-SPY MORE

Goal:

- Extend the I-SPY model to other indications
  - Proliferate the acceleration of drug development and better integration of research into clinical care
- Aid other disease groups to establish their own master trial platforms
  - Utilize I-SPY “master trial” methodology and leanings
  - e.g., Myeloma, Glioblastoma, Parkinson’s, Alzheimer’s, and antimicrobial resistant infectious diseases

Force for Change: Quantum Leap, FNIH

Catalyst, Incubator, Change agent, Neutral convener

- Precompetitive Models
  - Educate
  - Promote Cultural change
  - Everyone has skin in the game . . .
- Data liquidity and embedded analytics
- New approaches for participant engagement


Data Gathering→Data Analysis→Action→ INTEGRATED PLAT
Hypothesis-→New Data→New Analysis→ New Hypothe
Get ready for a new kind of
Marc Benioff
Chairman & CEO
ACCELERATE
KNOWLEDGE TURNS

Tools

- Process Re-engineering
  - clinical care/research
- Innovative Design
  - Response adaptive randomization
- Regulatory Harmonization
- Technology
  - Data sharing, embedded analytics
  - Onesource (care→regulatory submission)
  - Patient Engagement
- Will to change