Conference on Clinical Cancer Research

October 20, 2010 ~ Washington, DC

Using Patient-Initiated Study Participation in the Development of Evidence for Personalized Cancer Therapy

Stephen Friend

President, Co-Founder and Director

Sage Bionetworks

Need for Considering New Trial Strategies

- On average only ¼ of cancer patients receiving an approved cancer drug regimen will gain a significant benefit from that treatment.
- Despite this lack of effectiveness of current therapies, they are considered “standards of care.”
- The ¾ of patients receiving these approved therapies with minimal benefit often suffer toxicities, and always have the consequence of delayed effective therapy.
- A significant component of this reality stems from the fact that many approved first line therapies were evaluated years to decades ago assuming a relative homogeneity in patient subtypes.

New Powerful Tools Can Detect Patient Subpopulations with Different Responses

- Recently developed powerful genomic and molecular tools can sub-classify tumors
- Traditional biomarkers (e.g., for receptors- HER2) and emerging molecular markers now can allow identification of tumor subtypes from genome wide molecular analyses
- These subpopulations may have different prognoses and responses to therapy

Post-Approval Non-Responder Studies

- A prospective study of a marketed drug, in which genomic data from biospecimens are used to identify biomarkers predictive of clinical outcomes.
- Objective is to identify biomarkers that reliably predict patients unlikely to benefit, and to use such data to support revision of the approved drug label and a change in standard of care.
- Many investigational drugs in clinical trials now are accompanied by molecular signatures that identify responder sub-populations.

Opportunity to Identify Subpopulations of Responders/Non-Responders

- Many investigational drugs in clinical trials now are accompanied by molecular signatures that identify responder sub-populations
- Powerful opportunity to identify sub-populations of patients not responding to existing approved cancer treatment regimens
  - Avoid delays in effective therapy
  - Opportunity to receive new selective therapies not added onto existing non-selective regimens
  - Avoid costs and toxicities of drugs with unlikely benefit

Sage Bionetworks Non-Responder Project

- Studies are being planned to identify predictive markers of non-response to standard of care cancer therapies
- Several candidate tumors have been proposed for study, with an initial pilot in AML. These include lung cancer, breast cancer, ovarian cancer, and multiple myeloma

Patient-Initiated Study Participation

- A model in which patients are engaged and recruited directly by the sponsor of an IRB-approved study, and patients in turn drive the participation of their physicians and other health care providers to facilitate collection of required data and/or tissue samples.

Why Consider Patient-Initiated Study Participation?

- Potential benefits from trials/cohort studies enabling patient-initiated study participation:
  - Large patient sample sizes
  - Participation and robust patient consents
  - Long term scalability

Goal of the Panel

- Take a specific example of patient-initiated study participation in the setting of metastatic non-small cell lung cancer
- Examine study design and related considerations, with special attention to:
  a) Feasibility of designing a prospective study featuring patient-initiated participation
  b) Evidentiary standards and other factors influencing how actionable resulting data would be to support regulatory approval of label changes

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* Views expressed are the author's professional views and not necessarily those of the U.S. FDA

Trial Design Principles

- Study design should have the ability to address the primary study objective
- Study objective(s) should be clearly laid out, e.g., identify molecular signatures associated with non-response to chemotherapy
- Study results, depending on the study design, should be interpretable

Study Designs Commonly Seen

- Prospective adequate & well-controlled
  - Placebo-control, active-control, add-on
  - May be stratified by biomarker status
- Prospective (adaptive) enrichment
- Retrospective case-control with single-arm

- The proposal: prospective cohort with defined predictor(s) to identify non-responder

Potential Explanations of Treatment Effect Seen in an Approved Drug

- Variability within clinical expectation of a homogeneous patient population
- Variability due to heterogeneity at molecular, genomic or genetic level that is either prognostic and/or predictive of therapy

Scientific Consideration of
Post-Approval Non-Responder Study with Patient Initiated Study Participation

- A prospective study of a marketed drug with biospecimens prospectively collected following patient consents
- Use genomic data to identify biomarkers that can reliably predict patients unlikely to benefit
- Such data may be considered to support revision of the approved drug label and a change in standard of care
- The sponsorship should be different from those industry-sponsored trials with appropriate governance structure, in principle, with no financial and scientific conflict of interests
- The study should be attentive to potential bias due to patient accrual, trial conduct and analysis interpretation if restrict label only in patient subset

Regulatory Considerations

Post-Marketing Study to Justify Label Revision

- Level of scientific rigor differs depending on study design
- Single arm study can address association of biomarker and clinical outcome, absent of comparative evidence
- Efficacy vs toxicity may bear different evidential criteria

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Richard L. Schilsky, M.D.

Professor of Medicine

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Principles of the SAGE Non-Responder Project

- The treatment under investigation should have substantial response and non-response rates (>20 percent in either group).
- The disease must have clear, robust definitions of response and non-response that are clinically important. (A non-response biomarker should have the potential to change clinical practice.)
- Routine clinical management of the disease guarantees access to high quality tissue specimens.
- The non-response group should ideally be defined as patients refractory to treatment rather than those who respond then relapse early.

NSCLC Study Objectives

- Determine the feasibility of patient-initiated study enrollment
- Determine success rate for collection of evaluable normal tissue and tumor specimens
- Identify molecular signatures associated with non-response to chemotherapy
- Develop data to support regulatory approval of drug label change

NSCLC Study Design

- Single arm, prospective registry
- Metastatic NSCLC appropriate for first-line platinum-based doublet chemotherapy
- Core needle biopsy feasible and safe
- Measurable disease by RECIST criteria
- Estimated rate of non-response: 50%
- Collect OS

NSCLC Study Schema

Patient awareness of study via web, advocacy organizations, physician, other

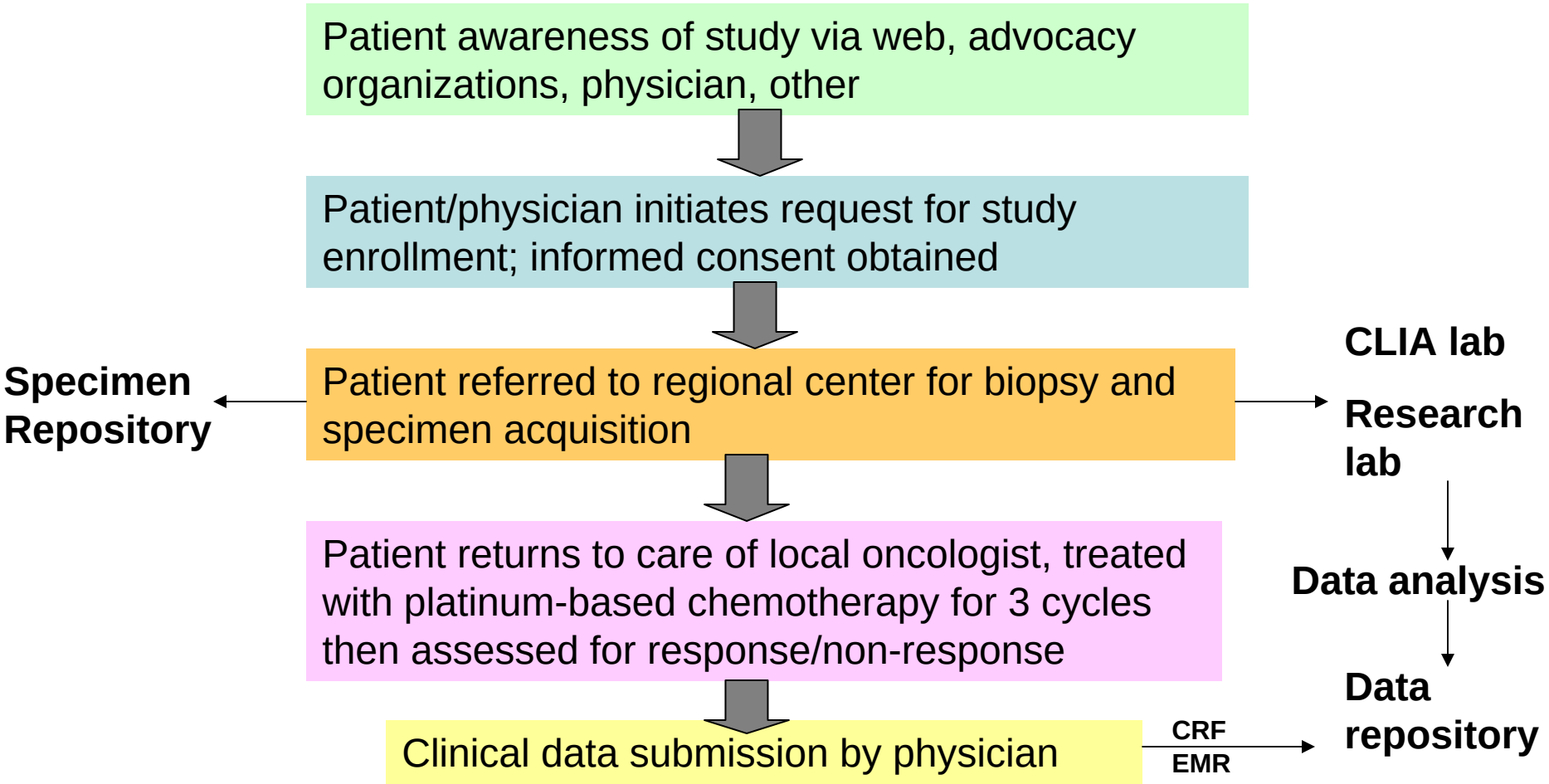
Patient/physician initiates request for study enrollment; informed consent obtained

Patient referred to regional center for biopsy and specimen acquisition

Patient returns to care of local oncologist, treated with platinum-based chemotherapy for 3 cycles then assessed for response/non-response

Clinical data submission by physician

NSCLC Study Schema



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Laurie Fenton Ambrose

President & CEO

Lung Cancer Alliance

Feasibility of Patient-Initiated Study Participation: Patient Perspective

- Yes, it is feasible. Patients and families can be highly motivated to accelerate research into discoveries.
- Paper reflects examples including LCA's own experience with the lung cancer community vis-à-vis "Give A Scan."
- Give A Scan goal -- to accelerate imaging research and software development so imaging can be a more accurate "quantitative biomarker" and thus expedite improvements in the early diagnosis and treatment of lung cancer.

Principles That Guided Give A Scan

- Database should be made available to all researchers.
- Patient privacy would be maintained at highest level possible.
- Patients should bear no cost.
- LCA would neither buy nor sell scans or data.
- LCA would not be directly involved in research.
- Patients would be advised upfront that research may lead to commercialization.
- Governance practices and policies observed – Advisory Board created.

Translate Experience to Non-Responder Project Using Patient-Initiated Study Participation for NSCLC

- Would patients be willing to donate specimens? Yes.
- Can principles be established to guide the study process? Yes.
- Are there additional challenges? Yes.
- Can they be overcome? Yes.

Patient Considerations and Challenges

- Timing will influence patients' receptivity to messages about study participation.
- At diagnosis -- very difficult time to ask patients to consider this.
- Only way to acquire tumor tissue is biopsy or surgery.
- Most patients are not being biopsied as standard of care at this stage (rather being diagnosed by CT scans or PET/CT to assess tumor growth over time).
- Surgery is not an option in these patients.
- Overall challenging time to discuss study that has risk, might cause harm, and could potentially cost money.

How to Maximize the Opportunity to Collect Tumor Tissue

- Cover the cost of the biopsy and genetic assays for the tumor.
- Encourage CMS to cover new tools, such as Electromagnetic Navigation Bronchoscopy (ENB) that help facilitate biopsies and can reach peripheral tumors bronchoscopes cannot.
- Partner with researchers who are recruiting individuals at high risk for lung cancer for CT screening.
  - Maximizing potential of diagnosing early stage operable lung cancer.
  - Patients already amendable to study participation.
  - Patients have more time to process and digest information.
  - Patients are more motivated to participate.

Comment About Lung Cancer Community

- The lung cancer community recognizes that very little is being done to sufficiently support them.
- They know that little if any research has been funded.
- They are angry.
- They want to do what they can to advance better outcomes – and if approached at the right time – with the right plan of engagement I believe they would participate.

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Jamie Freedman

Vice President, R&D

GlaxoSmithKline

Patient-Initiated Samples

"An open-label, trial with a marketed drug, in which genomic data from biospecimens will identify biomarkers predictive of clinical outcome"

Patients motivated to provide their tissues in the context of a clinical trial to better define how a drug should be used to treat future patients with the same disease.

Sample Collection

- Blood
  - Easily accessible, but limited information about actual disease (unless germline)
    - Pharmacogenomics
    - Proteomics
    - Circulating nucleic acids (surrogate for tumor)
- Tumor
  - Variable feasibility (depending on location)
  - Extensive information about disease
  - Predictive biomarkers

Predictive Biomarkers

- Aberrant drug target(s)
  - Activating mutation, amplification
  - Overexpression, methylation
- Aberrant pathways
  - Gene expression profiles (microarrays)
  - Proteomic profiles
- Polymorphisms
  - Single nucleotide, tandem repeats

Sample Storage

Frozen tumor

- Snap frozen
  - Via liquid nitrogen (~-80C)
  - Isopentene (~-50C)
  - In vial on dry ice
- OCT (optimal cutting temp medium) then liq N2

Fresh tumor

- RNA later; protein later

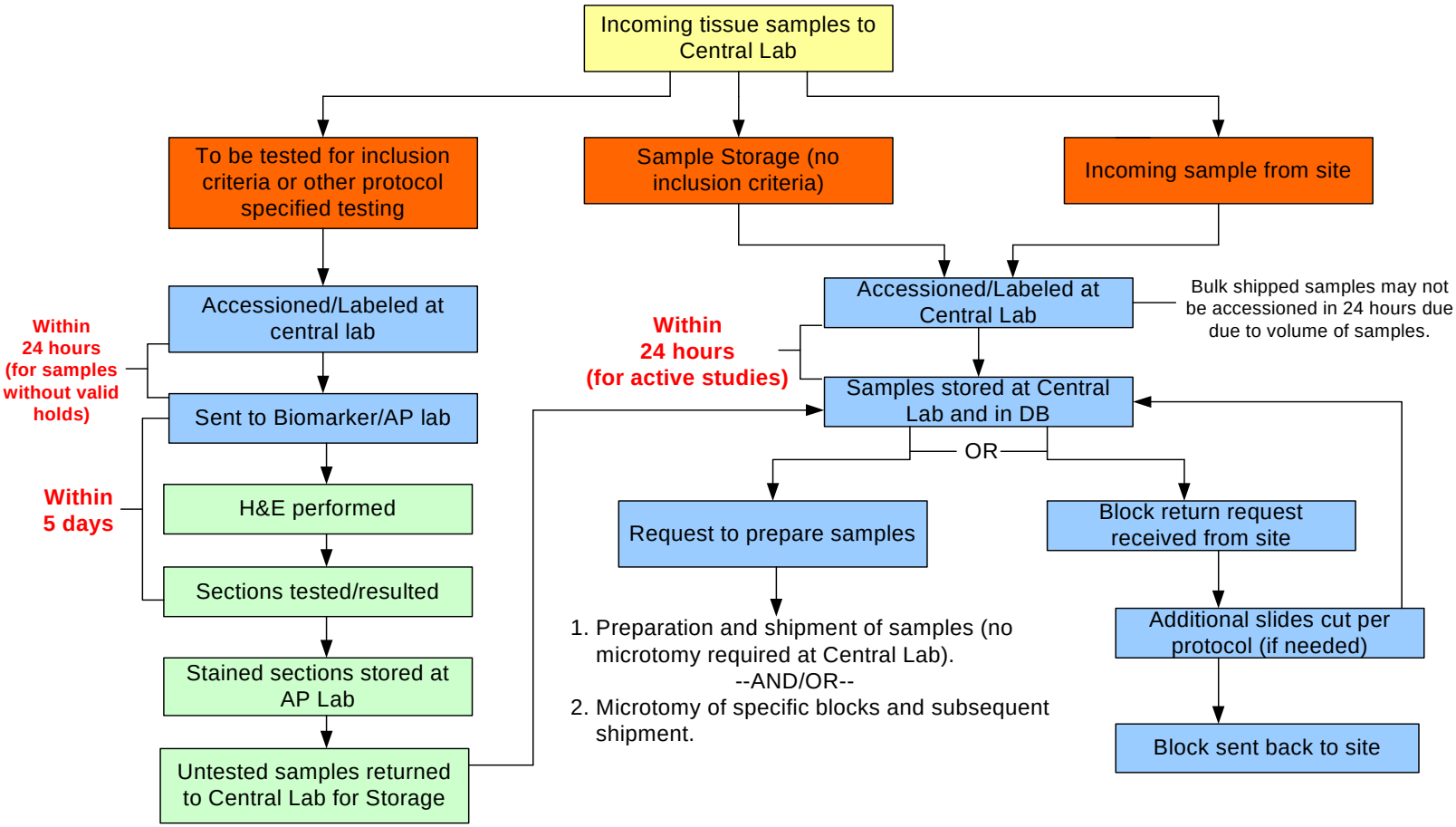
Fixed tumor

- FFPE
- Other fixatives

Pros/Cons

- Storage at -80C or colder; good preservation of nucleic acids; crush/freeze artifacts impact morphology
- OCT preserves morphology and histological assessments; can interfere with other assays
- RNA/protein later maintains integrity of RNA and protein for extraction only
- FFPE usual fixative; good for histology; IHC; impacts some assays by cross linking
- Specialized

Process Flow



Patient Protection

- Informed consents for open-access of patient data
- Patient privacy/protection
  - HIPAA
  - Anonymous coding
  - Double de-identification
  - Genetic Information Non-Discrimination Act
    - http://www.ginahelp.org/

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Ken Buetow, Ph.D.

Director, NCI Center for Biomedical Informatics and Information Technology

Clinical Information

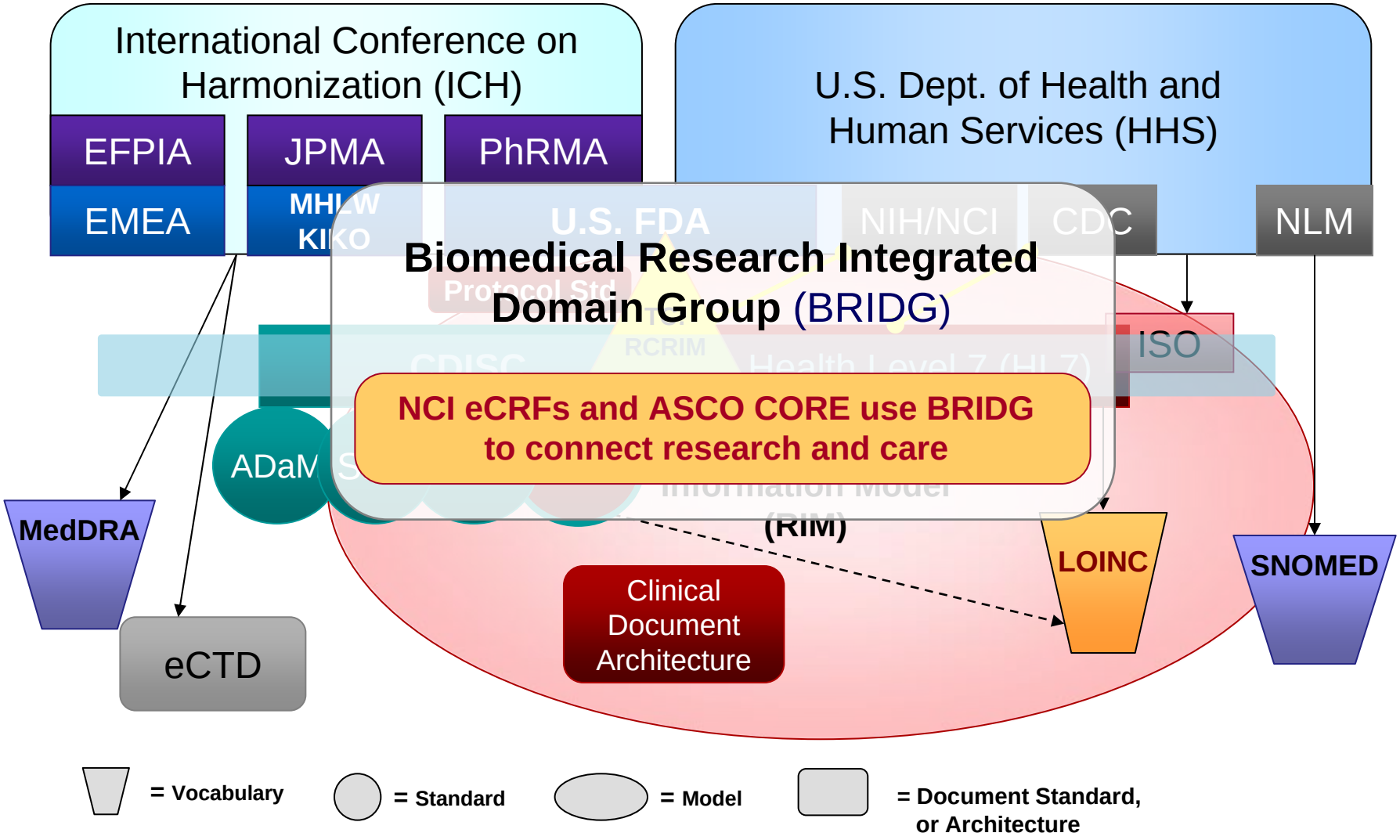
Clinical Research

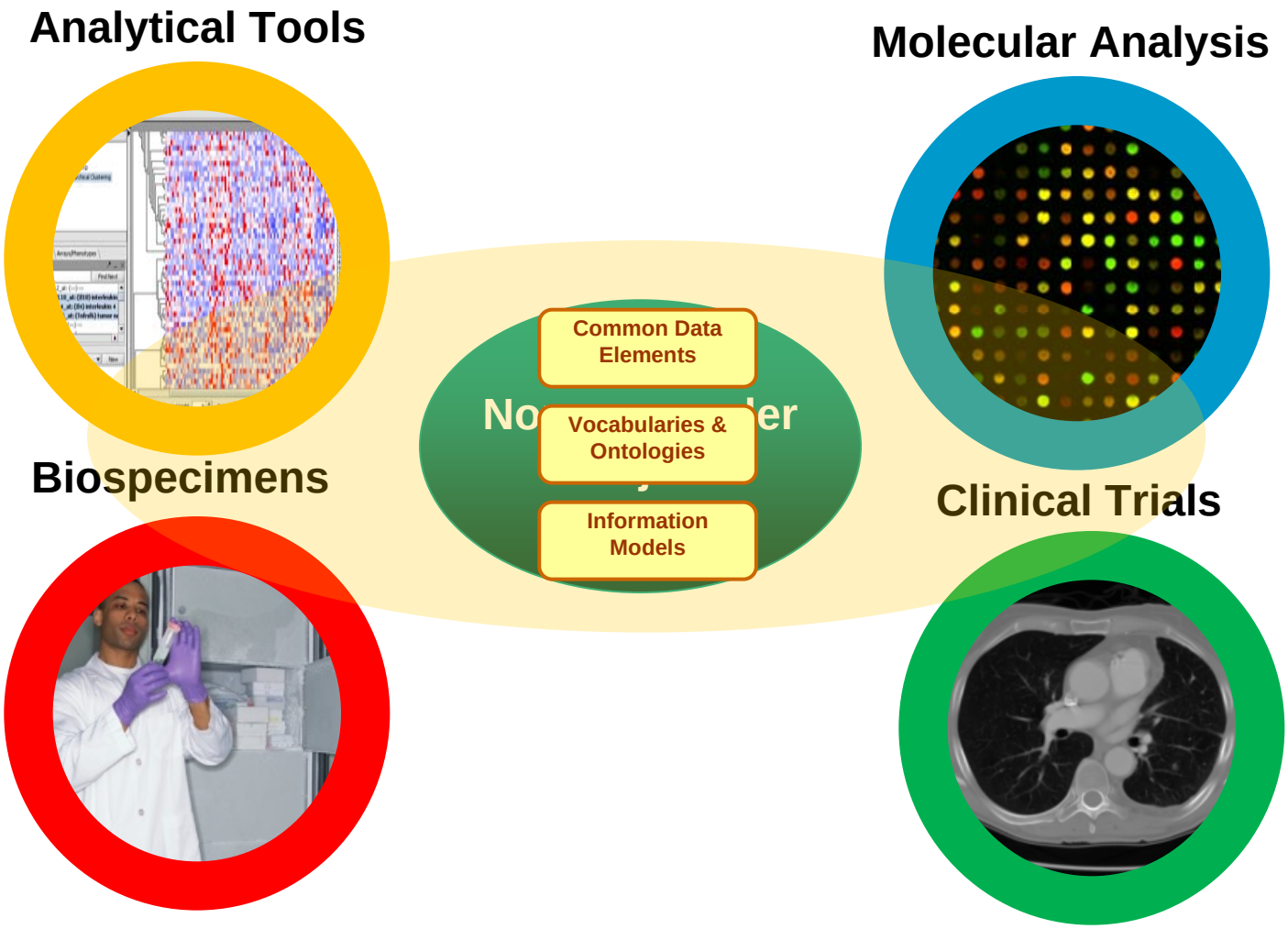
- Electronic Case Report Forms
  - Structured
  - Controlled vocabularies
  - Regulatory Standards
- Validated
- CDISC

Clinical Care

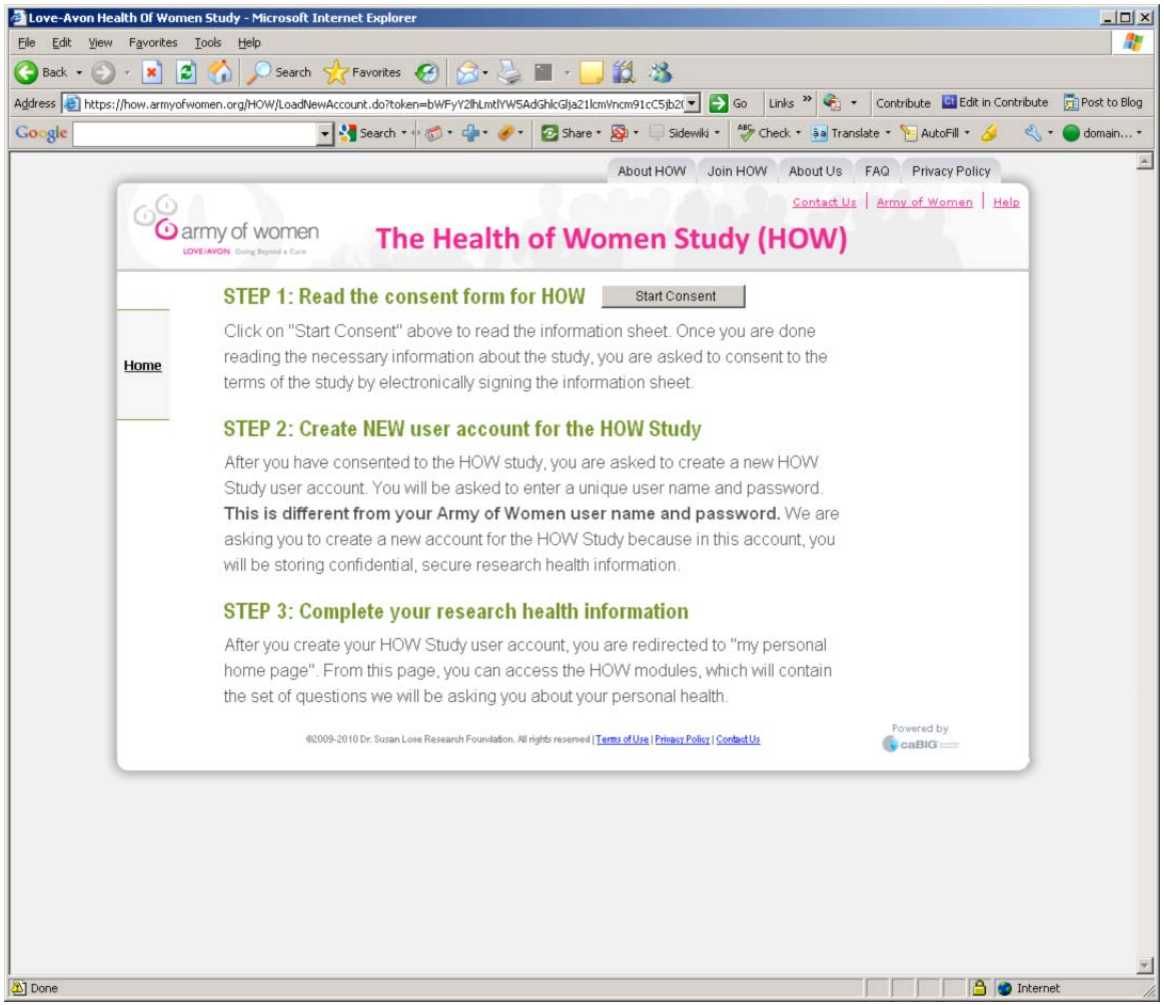
- Electronic Health Records
  - Largely unstructured
  - Free text
  - Health care standards
- Unmonitored
- HL7

clinical information representation



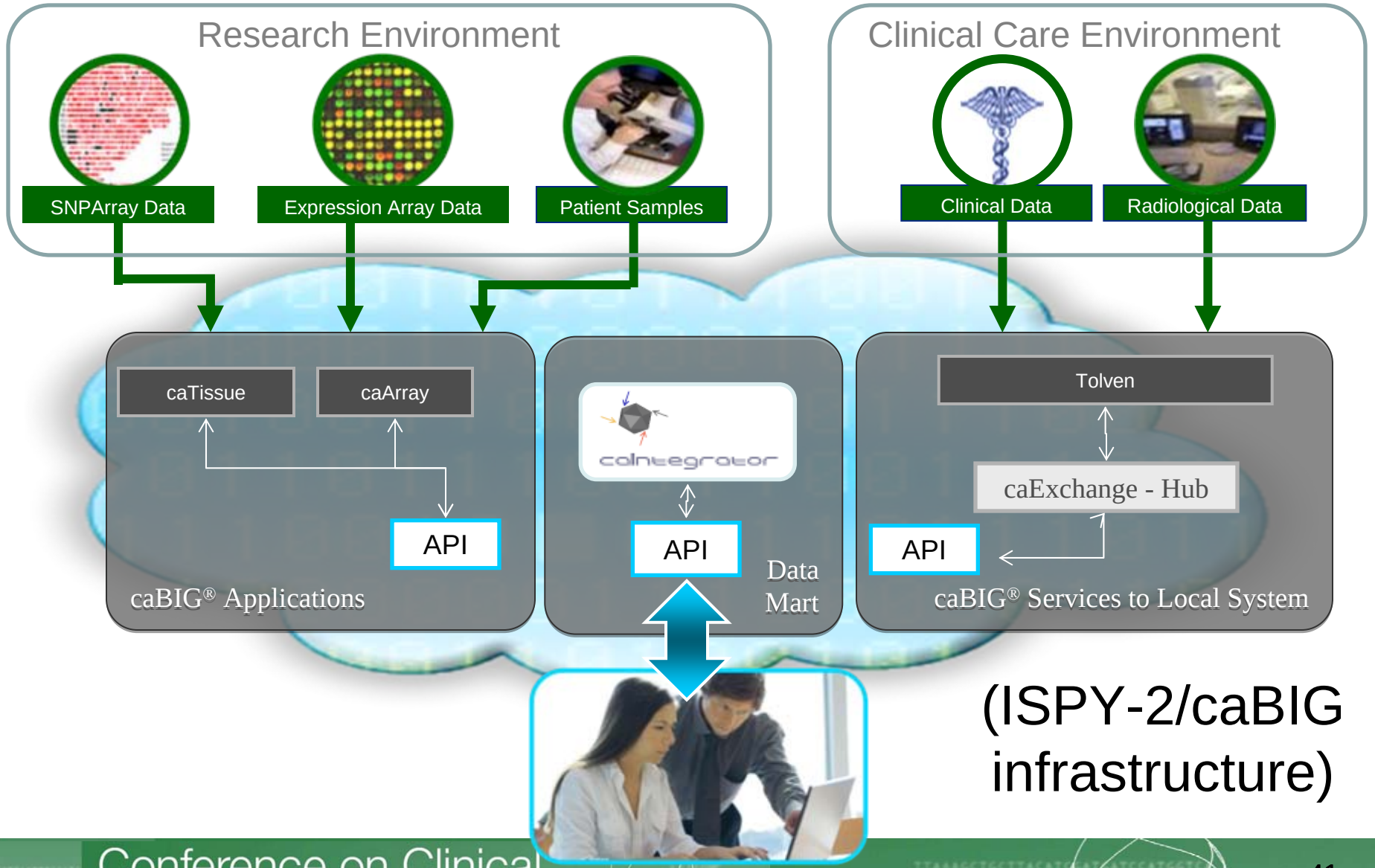

Analytical Tools
Molecular Analysis
Common Data Elements
Vocabularies & Ontologies
Information Models
Biospecimens
Clinical Trials

Patient-initiated Study Portal



(Army of Women – Health of Women Study)

NSCLC non-responder project



(ISPY-2/caBIG infrastructure)