Conference on Clinical Cancer Research

September 26, 2008

The Hotel Palomar

Washington, DC

ENGELBERG CENTER for Health Care Reform at BROOKINGS

Conference on Clinical Cancer Research

Friday, September 26, 2008 • Hotel Palomar, Washington, DC

8:40 – 9:00 **Welcome**
Mark McClellan, MD, PhD, Engelberg Center for Health Care Reform at Brookings
John Niederhuber, MD, National Cancer Institute (NCI)

9:00 – 10:20 **Panel 1 – Data Submission Standards and Evidence Requirements**
Moderator: Richard Schilsky, MD, University of Chicago Medical Center
- Jeffrey Abrams, MD, National Cancer Institute
- Gwen Fyfe, MD, Genentech
- Robert Erwin, Marti Nelson Cancer Foundation
- Janet Woodcock, MD, Food and Drug Administration (FDA)

Audience Questions and Comments

10:20 – 10:35 **Break**

10:35 – 11:55 **Panel 2 – Improved Insights into Effects of Cancer Therapies**
Moderator: Raymond DuBois, MD, M.D. Anderson Cancer Center
- Jim Doroshow, MD, FACP, NCI
- Debasish Roychowdhury, MD, GlaxoSmithKline
- Richard Pazdur, MD, FDA
- Donald Berry, PhD, M.D. Anderson Cancer Center
- Nancy Roach, C3: Colorectal Cancer Coalition

Audience Questions and Comments

12:10 – 1:10 **Lunch, Keynote Remarks**
Andrew C. von Eschenbach, MD, FDA Commissioner

1:25 – 2:45 **Panel 3 – Co-Development of Diagnostics & Therapeutics**
Moderator: Daniel Hayes, MD, University of Michigan
- Raymond Woosley, MD, PhD, C-Path Institute
- Steven Gutman, MD, FDA
- Richard Simon, DSc, National Cancer Institute
- Richard Frank, MD, PhD, GE Healthcare
- Nancy Roach, C3: Colorectal Cancer Coalition

Audience Questions and Comments

2:45 – 3:00 **Break**

3:00 – 4:00 **Panel 4 – Vision for the Future of FDA**
Moderator: Robert Young, MD, Fox Chase Cancer Center
- Mark McClellan, MD, PhD, Engelberg Center at Brookings
- Anna Barker, PhD, NCI
- David Kessler, MD, Former FDA Commissioner
- David Epstein, MD, Novartis
- Ellen Sigal, PhD, Friends of Cancer Research

Audience Questions and Comments

4:00 – 4:30 **Final Questions & Closing Comments**
Mark McClellan

AACR CENTENNIAL 1907 - 2007 American Association for Cancer Research

ASCO American Society of Clinical Oncology

FRIENDS of CANCER RESEARCH

Conference on Clinical Cancer Research

Welcoming Remarks

September 26, 2008
The Hotel Palomar
Washington, DC

National Cancer Institute

Facilitating Patient-Centered Cancer Research

Dr. John E. Niederhuber

Director, National Cancer Institute

Brookings Conference on Clinical Cancer Research

September 26, 2008

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

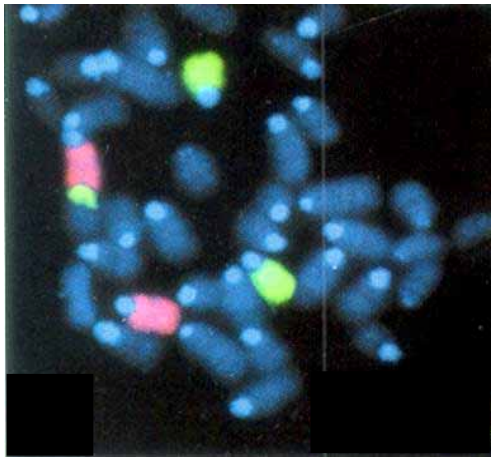
Facilitating Patient-Centered Cancer Research

Changing how we get the latest therapies to cancer patients is not a goal.

It is a necessity.

Cancer: A Disease of the Genes

- Biological significance of understanding genomic changes in cancer:
  - Copy number
  - Expression (regulation of)
  - Regulation of translation
  - Mutations

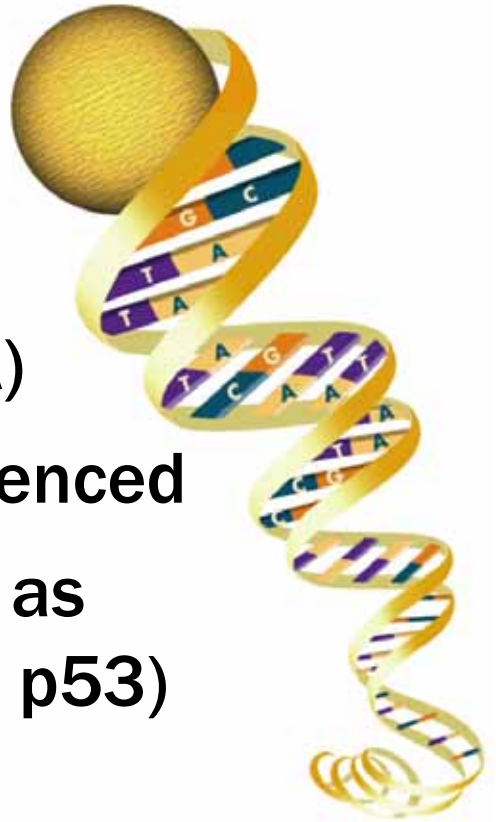


- Approaching a comprehensive “catalogue”

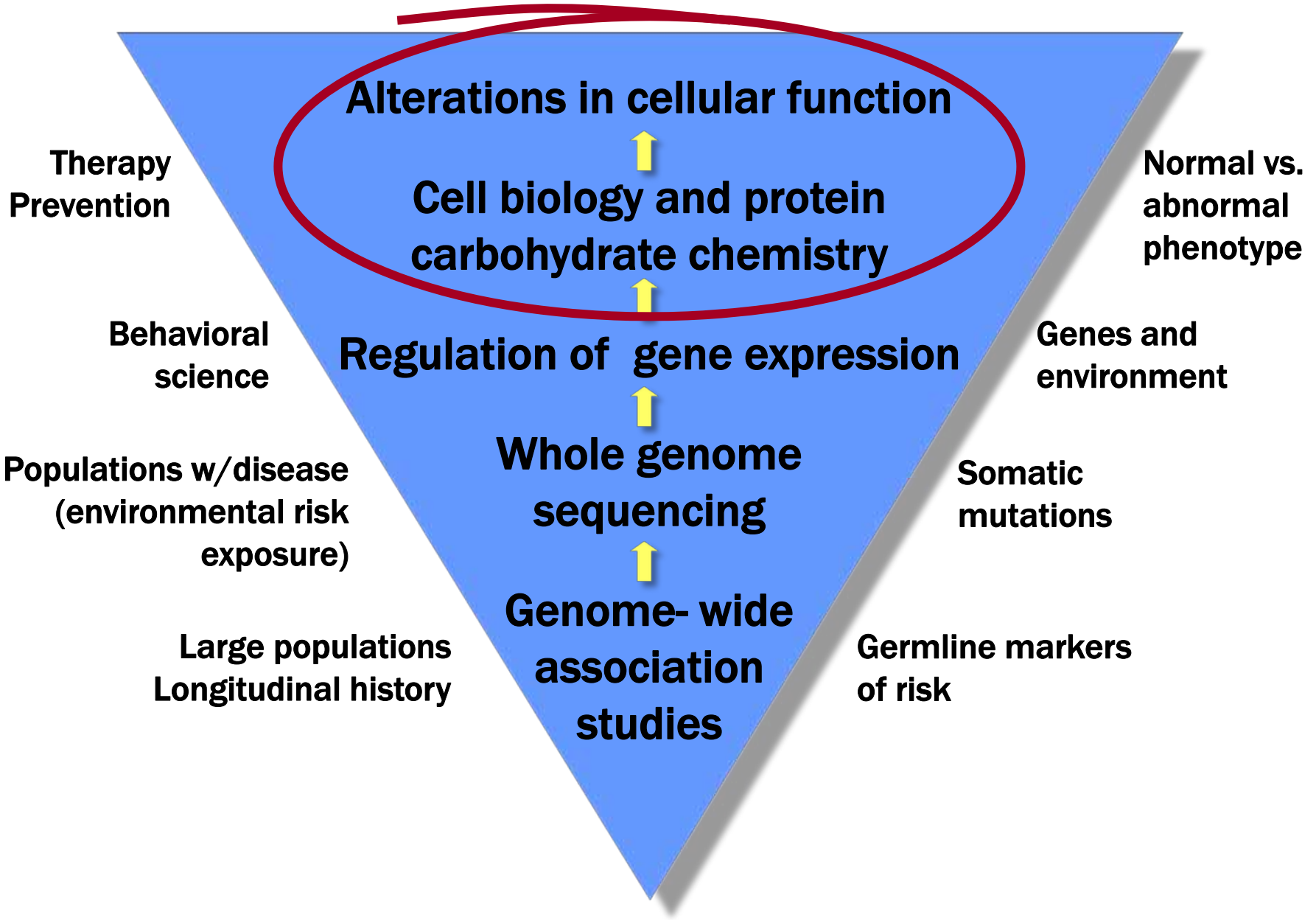
Novel, next-generation DNA sequencing technologies will enable full genomes to be sequenced nearly in real time.

The Cancer Genome Atlas

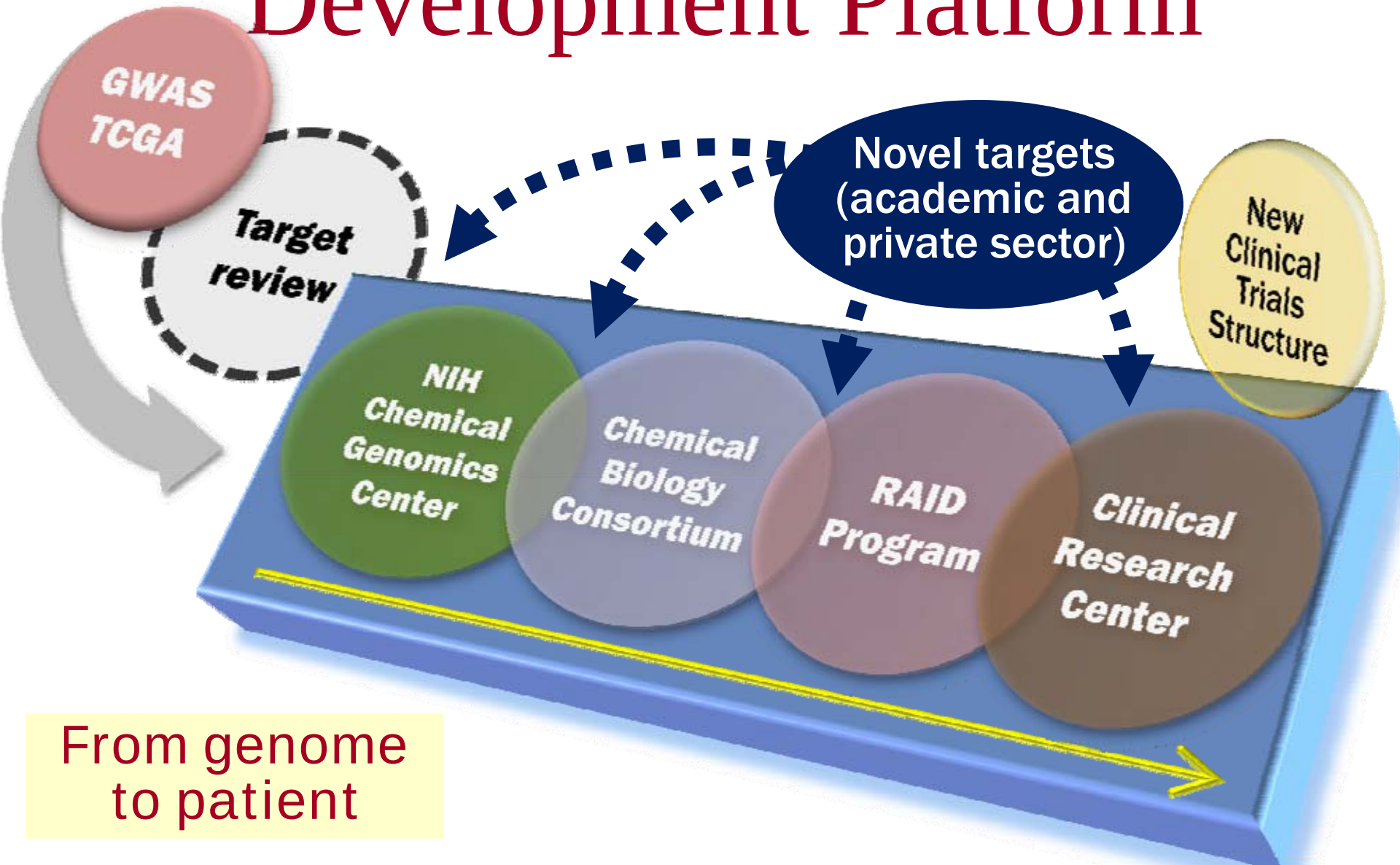
- Pilot includes glioblastoma, ovarian and lung cancers
- Glioblastoma (all tissue must have 80% tumor and matched normal DNA)
  - >200 tissues analyzed; >100 sequenced
  - Identified NF1, Erbb2, and PIK3R1 as highly associated with GBM (EGFR, p53)
  - At least 4 subtypes emerging
- Beginning to analyze ovarian and lung
- Newer sequencing technology being applied



Functional Genomics

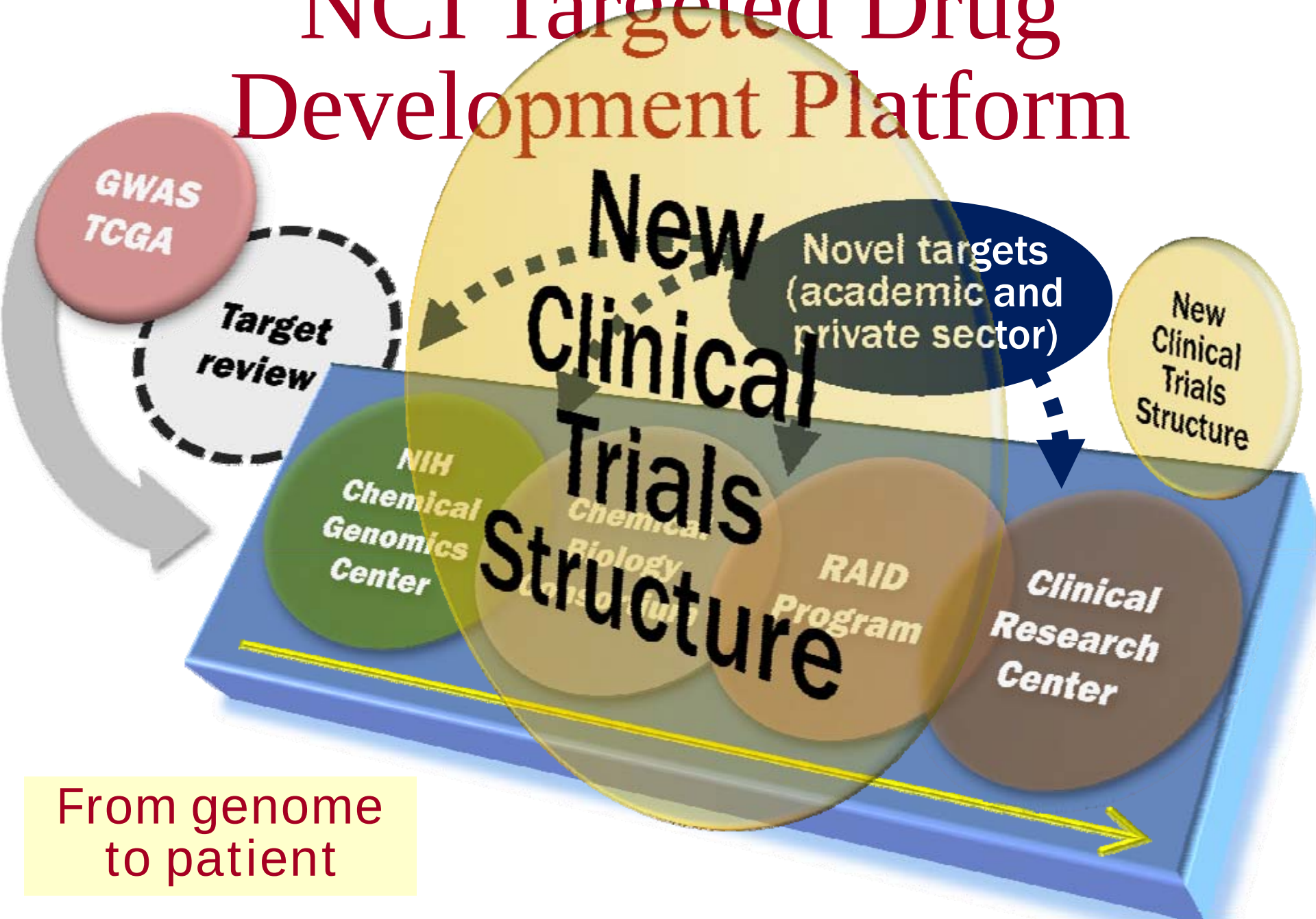


NCI Targeted Drug Development Platform



From genome to patient

NCI Targeted Drug Development Platform



From genome to patient

Translational Science: The Paradigm Shift

The 20th Century Paradigm:

Organ site-based, single agent based trials

- Reactive
- Based on gross differences
- Toxic (MTD/DLT)
- Emerging resistance
- Poor life quality

Research
- Human genome
- Genomics
- Proteomics
- Immunology
- Mechanisms
- Rational design

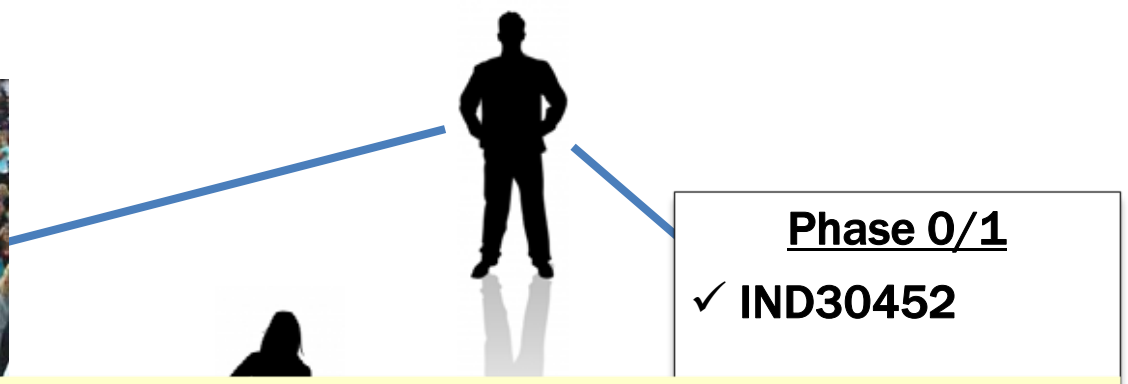
The New Paradigm:

Multiple, highly targeted agents matched to molecularly selected patients

- Proactive
- Rational/targeted
- Less toxicity
- Biomarker endpoints (subcellular target imaging)
- Significant savings of cost and time

Solutions for the Individual

Science and technology



- It takes too long to start a trial
- Cancer drugs cost too much
- Healthcare costs are out of control
- We must provide equal access to the latest science

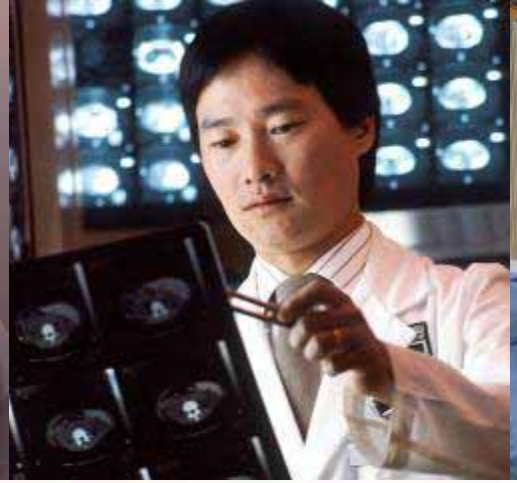
Challenges

1. Time to get a trial up and running
2. Standardized data collection tools
3. Intellectual property
4. Restraint of trade
5. Transparency in translational research

Life Sciences Consortium

"The Department of Justice announced today that it will not oppose a proposal by the CEO Roundtable on Cancer to develop and publicize model contract language for clinical trials of potential new cancer treatments."

Department of Justice press release
Wednesday Sept. 17, 2008



Patients & Families

www.cancer.gov

NCI at a Glance

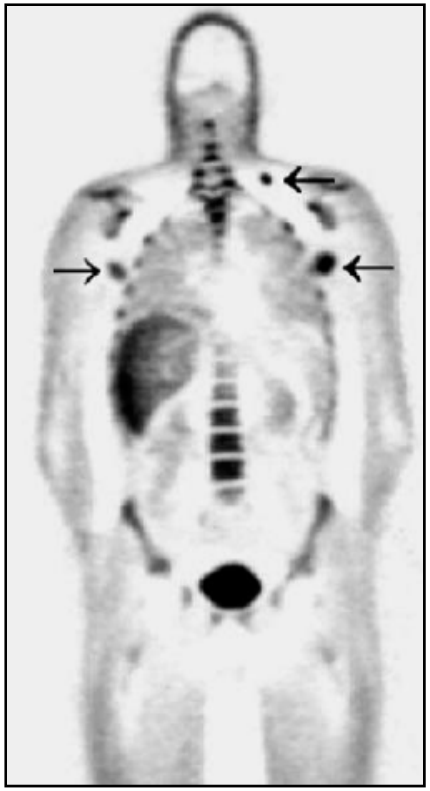
- World's largest cancer research institution
- Authorized by Congress in 1937
- FY2008 budget $4.8 billion
  - 82% goes to support investigators
- Supports 5,400 total extramural grants
- Supports over 1,300 clinical trials a year
- Total workforce: about 6,000
- 260 tenure-track scientists
- 1,100 fellows in training at NCI

Cancer as a Model

Of studying disease:

- **Macular degeneration**
- **Diabetes**
- **Heart disease**
- **Alzheimer's**
- **HIV/AIDS**

Cancer as a Model



Of healthcare:

- Interdisciplinary clinical care teams
- Community-based research for delivery of services
- Bioinformatics/electronic medical records
- Preventative approaches/behavioral science

Cancer as a Model

Of conducting clinical trials:

- **Cancer Centers Program**
- **Cooperative Groups**
- **Community Clinical Trials Programs**
- **NIH Clinical Research Center**

Opportunities in Science

- Transcriptional regulation
- Epigenetics
- MicroRNA — translational regulation
- Germline differences in predicting risk
- Whole tumor sequencing to indentify somatic changes involved in cancer
- Biomarker discovery
- Tumor microenvironment and new targets

Involving the Physical Sciences in Cancer Research

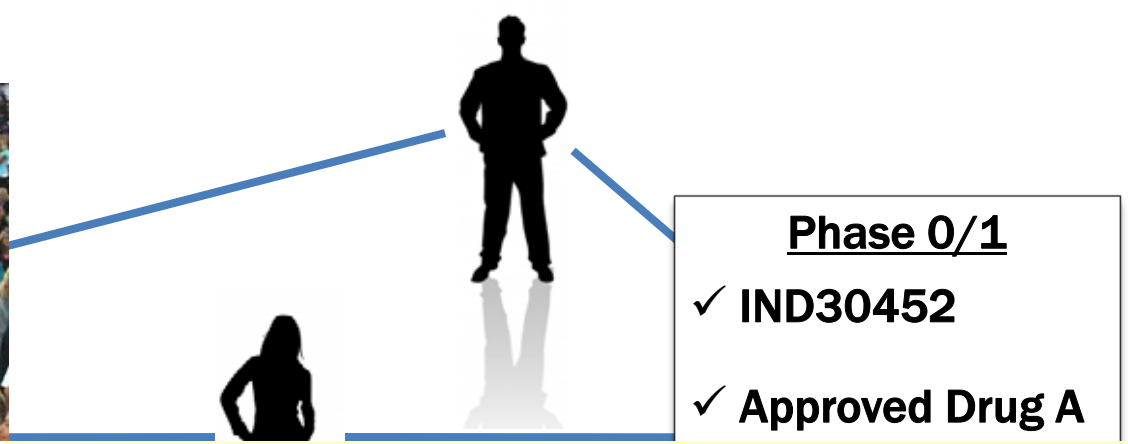
- We lack a field of Theoretical Cancer Biology
- Tumor cell complexity in association with the microenvironment requires mathematical models (cell communication, metastasis)
- Impact of basic physical principles and laws on cancer (mechanical forces, energy and energy transfer, cell shape, dimensions of time)
- The role of tumor cell evolution

The Cancer Genome Atlas (TCGA)

- To assess the value of large-scale multi-dimensional analysis of the molecular characteristics present in human cancer
- To provide integrative analysis (pathways) of:
  - nucleotide sequence
  - DNA copy number
  - gene expression
  - DNA methylation

Solutions for the Individual

Science and technology



- Time
- Expense (cancer drugs too costly)
- Healthcare costs out of control
- Equal access to the latest science

NCI Clinical Trials System: Current Status

- System is inefficient, time consuming, and under-funded
- In an era of targeted therapy, the system is geared toward the testing of non-specific regimens
  - Lacks the capacity to highly characterize each patient and carefully match that patient profile to targeted therapeutic combinations

NCI Clinical Trials System: Challenges

Not Drug Development but Therapeutic Solutions

- Design a trials structure that:
  - **can obtain drug approval and demonstrate safety and benefit**
  - **has the ability to incorporate multiple, specifically targeted agents optimally matched to the patient**
- **Must seek short term, long term, and regulatory solutions**

Some Thoughts in Conclusion

- Will completely change diagnosis of disease and therapy
- There will be great opportunities for prevention to extend life
- Therapy highly personalized and developed as treatment solutions
- Rapidly advancing technology will transform the conduct of science

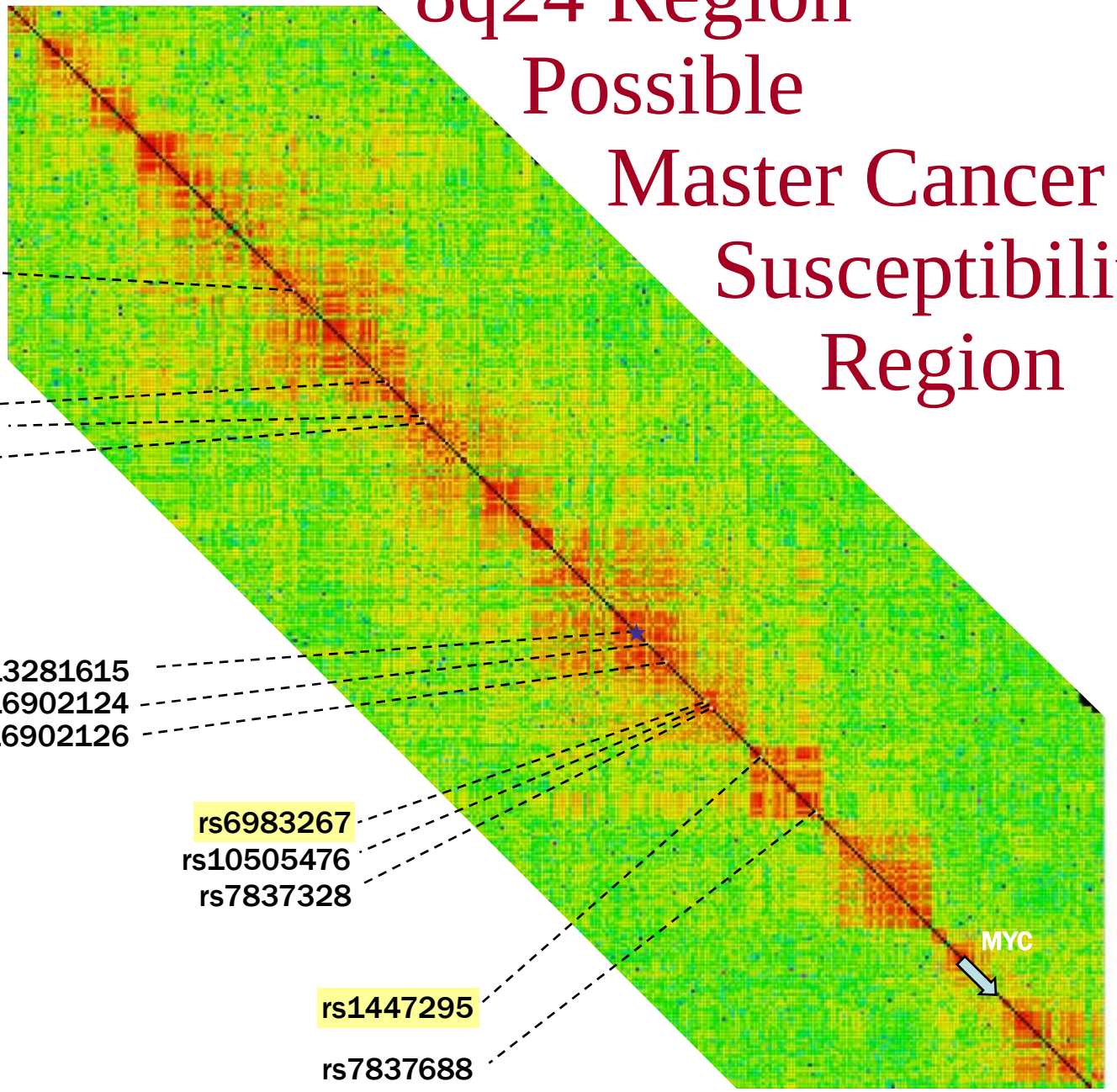
NCI is a catalyst for driving science forward to benefit patients

"The…National Cancer Institute shall coordinate all of the activities of the National Institutes of Health relating to cancer with the National Cancer Program."

The National Cancer Act of 1971

- Industry
- Pharma
- Biotechnology
- Advocacy Organizations
- Professional Societies
- Philanthropy/Foundations
- Universities
- NCI Cancer Centers
- NCI NCCCP
- NCI CCOPs

8q24 Region Possible Master Cancer Susceptibility Region



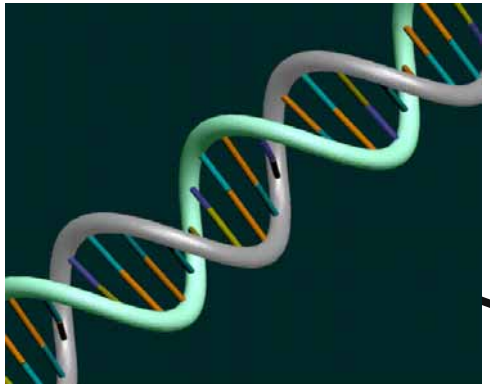
Region 2
Prostate only

Breast only

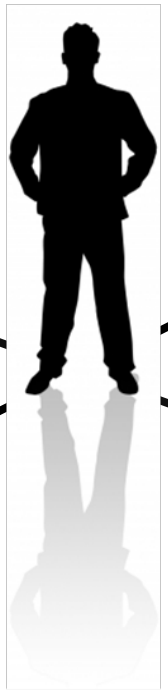
Region 3
Prostate & Colon

Region 1
Prostate only

Treatment Selection and Efficacy



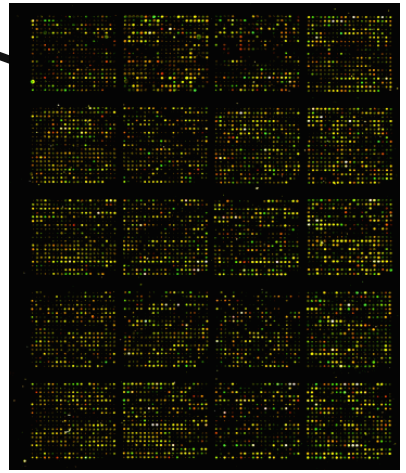
- Methylated DNA
- Serum analytes
- Biomarkers



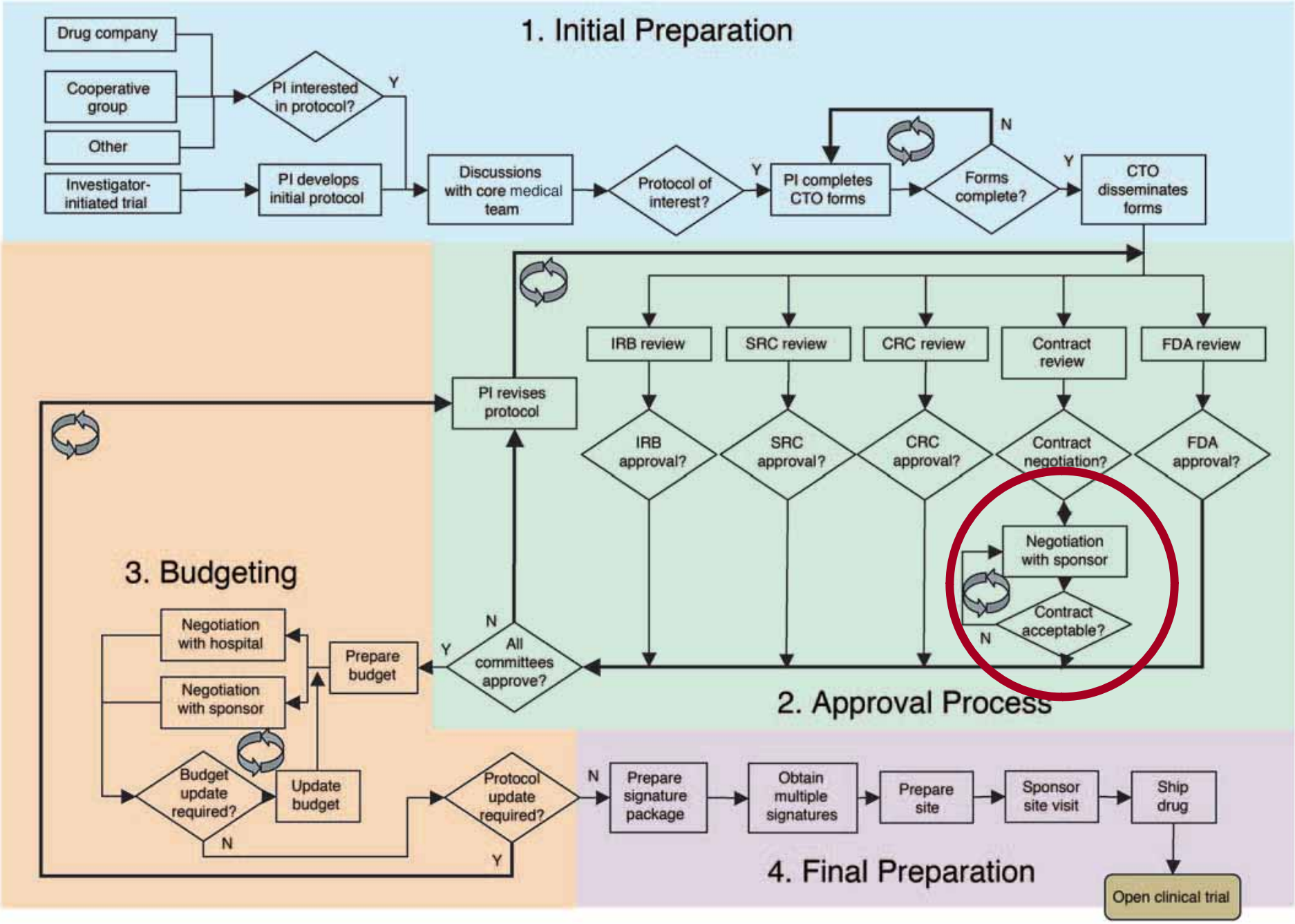
- Imaging

REMBRANDT

- Correlative data analysis
  - Repository of Molecular Brain Neoplasia Data



- Microarrays


1. Initial Preparation
Drug company
Cooperative group
Other
Investigator-initiated trial
PI interested in protocol?
Y
PI develops initial protocol
Discussions with core medical team
Protocol of interest?
Y
PI completes CTO forms
Forms complete?
N
Y
CTO disseminates forms
IRB review
SRC review
CRC review
Contract review
FDA review
PI revises protocol
IRB approval?
SRC approval?
CRC approval?
Contract negotiation?
FDA approval?
Negotiation with sponsor
Contract acceptable?
N
2. Approval Process
3. Budgeting
Negotiation with hospital
Negotiation with sponsor
Prepare budget
N
All committees approve?
Y
Budget update required?
Update budget
N
Protocol update required?
Y
N
Prepare signature package
Obtain multiple signatures
Prepare site
Sponsor site visit
Ship drug
4. Final Preparation
Open clinical trial

Conference on Clinical Cancer Research

Panel 1: Data Submission Standards and Evidence Requirements

September 26, 2008

The Hotel Palomar

Washington, DC

Panel 1: Data Submission Standards

Richard L. Schilsky, M.D.
Professor of Medicine
University of Chicago
Chairman, Cancer and Leukemia Group B
President, American Society of Clinical Oncology

Panel Members

- Jeffrey Abrams, M.D., Assoc. Director, Cancer Therapy Evaluation Program, NCI
- Robert Erwin, President, Marti Nelson Cancer Foundation
- Gwen Fyfe, M.D., Senior Staff Scientist, Genentech
- Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, FDA

What are we talking about?

- Minimum data set necessary to support a claim of safety and effectiveness for an NDA (BLA) or sNDA (sBLA)
- Data required to permit appropriate labeling and to inform clinical use
- Focus on data to assess safety, particularly toxicity grading/reporting, SAEs
- Documentation of non-protocol therapy, con meds, follow on therapy also discussed

What are we talking about?

- Nature, extent, frequency, format of reporting
- % of study population necessary for informative data capture
- Level of detail required in documentation, e.g., toxicity on/off dates or ability to deliver therapy on time? All con meds or specific drug classes?, etc.

Why is this important?

- Insure adequate data collection to inform regulatory and clinical decisions
- Focus on what is important
- Reduce data collection burden to increase likelihood that critical data is complete/accurate
- Reduce cost
- Enhance physician participation in clinical trials
- Harmonize data collection standards across regulatory agencies

Tradeoffs

- Accuracy/cost vs. precision/completeness
- Data used in review/labeling vs. data collected
- Risk of missing previously unknown AE vs. precision of quantifying risk to patients
- Efficiency of trial conduct vs. comprehensiveness of database

What do we need?

- Common data elements
- Consensus on type/ frequency/format of data collection
- Standard data collection tools
- Electronic data submission

Principles

- Collect necessary data to inform regulatory review, labeling and clinical use
- Use the data collected; don’t collect data not used
- Data collection for new drug applications should remain comprehensive
- Data collection requirements for supplemental applications will vary based on:

-safety database/known pharmacology and drug interactions

-similarity of study population/intended use

-similarity of regimen to that already approved

-whether supplemental application follows initial full or accelerated approval

Drug Safety in the context of supplemental approvals: what data are informative?

Gwen Fyfe, MD

Genentech

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For a supplemental approval much is already known about the safety profile

- Kinds and severity (Grade 1-4) of adverse events seen in prior randomized controlled Phase III trials
- Impact on bone marrow, liver and renal function
- Time course of adverse adverse events relative to treatment cycles
- Sense of cumulative toxicity
- Some likelihood of drug:drug interactions
  - Pharmacokinetic
  - Pharmacodynamic

What is not always known about safety at the beginning of a supplemental Phase III

- Disease, line of treatment or chemotherapy-specific safety events
  - Safety in subpopulations in specific context: ethnicity, impaired organ function, elderly
- Rare safety events

How much new data will be informative?

A Clinical Example…..

- Mrs. Jones
  - 66 year old white female with newly diagnosed metastatic breast cancer
  - Enrolls in RCT of chemo +/- approved biologic being evaluated for the first time in breast cancer
    - Randomized to oral 5-FU plus investigational agent
    - She will be seen every 3 weeks at trial site and followed by her local physician during cycles

A Clinical Example…..

- Following her first cycle of chemotherapy + investigational agent, Mrs. Jones experienced a number of treatment-emergent adverse events
  - In first week:
    - Severe nausea and vomiting and fatigue
    - Mild/moderate diarrhea and dehydration and asthenia
    - Mild sore throat, brief episode of dizziness, occasional abdominal pain, poor appetite
    - Most of these symptoms substantially improved over 7 days
  - Mild skin rash persisted for entire cycle
  - Her pre-existing hypertension sl worsened (asymptomatic)
  - All 'expected' in context of chemo and investigational agent

What will she remember 3 weeks later?

NCI CTC grading

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Fatigue (asthenia, lethargy, malaise)	Fatigue	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	—
Nausea	Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
Vomiting	Vomiting	1 episode in 24 hrs	2 – 5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life-threatening consequences	Death
Diarrhea	Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated <24hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Life-threatening consequences (e.g., hemodynamic collapse)	Death
REMARK: Diarrhea includes diarrhea of small bowel or colonic origin, and/or ostomy diarrhea. **ALSO CONSIDER**: Dehydration; Hypotension.						
Dehydration	Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids indicated ≥24 hrs	Life-threatening consequences (eg., hemodynamic collapse)	Death
ALSO CONSIDER: Diarrhea; Hypotension; Vomiting.						
Dysphagia (difficulty swallowing)	Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing (e.g., altered dietary habits, oral supplements); IV fluids indicated <24 hrs	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life-threatening consequences (e.g., obstruction, perforation)	Death
REMARK: Dysphagia (difficulty swallowing) is to be used for swallowing difficulty from oral, pharyngeal, esophageal, or neurologic origin. Dysphagia requiring dilation is graded as Stricture/stenosis (including anastomotic), GI – Select. **ALSO CONSIDER**: Dehydration; Esophagitis.						

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What will be reported if all adverse event data are collected?

- Mrs Jones experienced:
  - 3 grade 3/4 adverse events (24 fields)
  - 9 grade 1/2 adverse events (72 fields)
  - All resolved without sequelae
  - All will need to be re-entered if they occur in subsequent cycles
  - If she receives 5 more cycles with the same or more AEs, 120 more grade 3/4 data fields and a minimum of 360 more grade 1/2 AE data fields

Will Mrs. Jones remember that she had all of these adverse events and what would be lost if these events were not reported?

Other reporting systems exist to capture medically important adverse events*

- All treatment discontinuations and dose modifications
- “Serious” adverse event collection is in addition to graded AE collection (FDA Guidance, Part 314.80)
  - Death
  - Life-threatening
  - Hospitalization
  - Requires intervention to prevent permanent impairment or damage
  - Disability or congenital anomaly
- These ‘serious’ events trigger collection of substantial history relating to all aspects of above at the time of the event
- If ‘unexpected’ in the context of the known toxicity of the regimen, this must be reported within 15 days

**Will be collected in all patients*

The following different approaches to assessing information loss from subset collection of AE data suggests that minimal information will be lost

Example 1: does more safety data provide greater certainty?

95% Confidence intervals (+/-) as a function of patient number

Expected Rate (%) of Adverse Event	Number of Patients Analyzed per treatment arm			
	100	200	400	800
5	4.3	3.0	2.1	1.5
10	5.9	4.2	2.9	2.1
20	7.8	5.5	3.9	2.8
30	9.0	6.5	4.5	3.2
40	9.6	6.8	4.8	3.4
50	9.8	6.9	4.9	3.5

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Example 2

- If an AE rate in a treatment group is truly 5%, what is the chance that it will be observed at a rate of 1% or greater in a treatment group?

N per treatment group	P(observed AE rate >= 1%)
100	99.4%
150	99.6%
200	>99.9%
250	>99.9%

Therefore, even 100 patients is adequate to observe a 1% or greater event rate for an AE with a true event rate of 5%

Example 3 :

Using modeling to assess what could we miss with subsets of grade 3/4 events from Avastin Phase III trials

- Simulation based on Avastin NSCLC trial of gem/cis +/- Avastin, n~=650 patients
- Collection of SAEs, AEs→DC, AEs→dose change (all patients) in 2% excess identifies:
  - Neutropenia, Thrombocytopenia, Epistaxis, and Hypertension
- Analysis w all Grade 3/4 Aes in 2% excess adds:
  - Vomiting, Nausea, Asthenia, Weight loss, and Proteinuria

How often are these latter events identified in the simulated subsets?

What could we miss with subset of grade 3/4 events? Results of NSCLC simulation

AEs potentially missed in subset	Full Trial--Diff in %s	AE detected in this percentage of 1000 subsamples			
		100 patients per arm	150 patients per arm	200 patients per arm	250 patients per arm
Vomiting	5.4	90	97	99	100
Nausea	2.7	68	69	74	80
Asthenia	2.1	61	61	60	62
Weight decreased	2.1	63	62	63	67
Proteinuria	2.1	67	69	73	76

- AEs w ~5% or greater excess are observed in most subsets
- AEs w ~2% excess are missed ~25 to 40% of time
  - Such events present in substudy, but delta smaller than 2%

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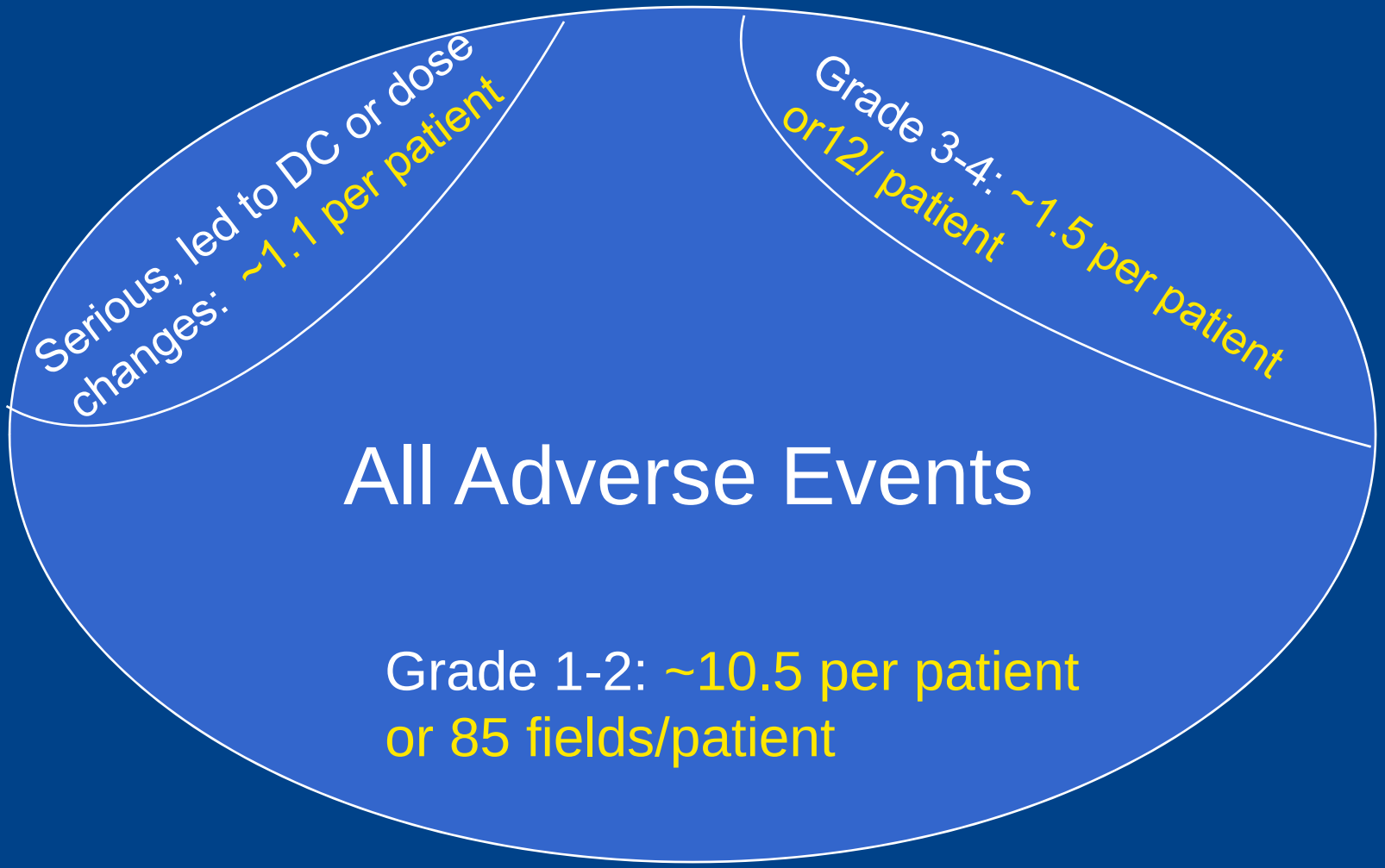
What is saved?



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Based on Avastin studies AVF2107g, AVF2119g, and AVAIL

What might be lost?

- Supplemental trials will be interpreted in the context of prior AE knowledge from RCTs of all SAEs & grade 1-4 AEs
- Likely toxicities based on the biology of the agent and its AE profile will allow focus on the 'right' AEs
- While…
  - Grade 3/4 events in 'apparent' 2% excess could be missed almost 50% of time
  - And Grade 1/2 events in 'apparent' 5% excess could be missed almost half the time
- …..it seems unlikely that important safety data will be missed

Panel 1: Data Submission Standards

Jeffrey S. Abrams, M.D.
Associate Director, Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute

Table 1: Standard practices for data collection when little prior data available

Data Type	Scope of Collection
Eligibility	Collect major inclusion/exclusion criteria (e.g. PS, disease or treatment characteristics) as individual yes/no boxes and remaining eligibility as a single yes/no on a case report form (CRF); do not collect source data (e.g. labs, scans)
On Study Form	Collect all relevant patient and baseline characteristics
Medical History	Collect targeted baseline medical history in checkbox format (e.g. diabetes, hypertension requiring treatment, history of myocardial infarction)
Physical Exam	Variable: (ranges from all to none)
Lab Findings	Varies: from all routine laboratory values at baseline and during treatment to subset, and via central lab vs. site laboratory
Disease Measurement	Collect all tumor assessment measurements at all time points
Treatment	Collect actual dose and treatment date or reason for modification, delay, hold, or discontinuation.
Vital Signs	Collect routine vital signs. Collect weight/height or body surface area (BSA) on initial Treatment page. If a change from the initial dose, a reason (weight change, toxicity, protocol specified, etc.) must be provided.
Non-Protocol Therapy (NPT)	Collect all NPT (but not doses), including start and stop date (month/year), until first progression (Need to clearly define what therapies are included)
Concomitant Medications	Collect all concomitant medications at baseline by name; practices vary from all start and start and stop dates, to by cycle,
Toxicity	Collect deaths, Grade 3/4 toxicity, serious AEs, AEs leading to discontinuation of treatment. For grades 1-2, practices range from collection of all grades with start and stop dates, to all grades by cycle, to collection of grades 1-2 in a subset
Long Term FU	First treatment initiated after disease progression; dose and duration of treatment not needed

Table 2: Data Collection (Secondary Indications or where substantial data exist)

Data Type	Scope of Collection
Eligibility	Collect major inclusion/exclusion criteria (e.g. PS, disease or treatment characteristics) as individual yes/no boxes and remaining eligibility as a single yes/no on a case report form (CRF) ; do not collect source data (e.g. labs, scans)
On Study Form	Collect all relevant patient and baseline characteristics
Medical History	Collect targeted baseline medical history in checkbox format (e.g. diabetes, hypertension requiring treatment, history of myocardial infarction)
Physical Exam	Do not record physical exam on CRF
Lab Findings	Do not collect routine laboratory values (except in the case when they are eligibility criteria or where certain targeted laboratory data are important) at baseline or during treatment except as adverse events. However, if there is a lab-related serious adverse event (SAE), the SAE should include whether the patient's initial value was normal, prior treatment values that were abnormal and related history
Disease Measurement	Collect all tumor assessment measurements at all time points
Treatment	Collect actual dose and treatment date or reason for modification, delay, hold, or discontinuation.
Vital Signs	Do not collect routinely except where certain targeted vital signs are important. Collect weight/height or body surface area (BSA) on initial Treatment page. If there is a change from the initial dose, a reason (weight change, toxicity, protocol specified, etc.) must be provided.
Non-Protocol Therapy (NPT)	Collect all NPT (but not doses), including start and stop date (month/year), until first progression (Need to clearly define what therapies are included)
Concomitant Medications	*Needs further discussion* **Current proposal:** Collect targeted concomitant medications by specific name based on safety profile of drug. Collect at baseline and when a SAE occurs.
Toxicity	*Needs further discussion* **Current proposal:** Collect deaths, targeted AEs, serious AEs, AEs leading to the discontinuation of treatment; collect grades 3-4 events by cycle at subset of sites (or patients)
Long Term FU	First treatment initiated after disease progression; dose and duration of treatment not needed

Issues for Data Collection in Cancer Drug Trials Intended for Regulatory Submission

Janet Woodcock

Director, CDER, FDA

Trade-offs in Data Collection: Benefits of Various Approaches

- Extensive data collection
  - Opportunity to learn most from each volunteer
  - Robust data set for subsequent analysis
    - Timecourse of adverse event development
    - Extent of subclinical laboratory abnormalities
    - Patient characteristics leading to poor outcome
  - May provide ability to salvage trial
  - Better understanding of drug effects
- Minimal data collection
  - Efficiently generate key results
  - Data quality may be higher—more focus on what is important
  - Save time, costs, volunteers

Trade-Offs in Data Collection: Liabilities of Approaches

- Extensive data collection
  - Compilation of large amounts of unimportant data (e.g., concomitant meds)
  - Degrade quality of key data elements
  - Increase costs, time
- Minimal data collection
  - May miss data elements that end up being critical if trial results are not what is hoped
  - Miss opportunity for modern safety analysis
  - Must less robust understanding of everything that happened in that trial

Factors Influencing Data Collection

- Priors: how much is known about drug already?
- For an already marketed drug:
  - How much data are available from previous trials; from marketing experience?
  - How different is the new patient population being studied?
  - What is the indication? Adjuvant? Advanced disease?
  - What other drugs are in the regimen? How well understood are they?

Suggested Approach

- For NMEs, collect “full” data on all patients in the trials intended for registration
- For marketed drugs, develop a decision tree that takes into account important factors in tailoring amount of data collected to the need for information in that setting
- This would represent a refinement of FDA’s existing guidance on collection of data in cancer clinical trials

Conference on Clinical Cancer Research

Panel 2: Improved Insights into Effects of Cancer Therapies

September 26, 2008
The Hotel Palomar
Washington, DC

Panel 2: Improved Insights into Effects of Cancer Therapies

Raymond DuBois, MD, PHD
Provost, Executive Vice President
University of Texas, MD Anderson Cancer Center

September 26, 2008

Panel Members

- **James Doroshow, MD, FACP** - Director, Division of Cancer Treatment and Diagnosis, NCI
- **Debasish Roychowdhury, MD -** Vice President, Global Clinical Development, Oncology, GlaxoSmithKline
- **Richard Pazdur, MD** - Director, Office of Oncology Drug Products CDER, FDA
- **Donald Berry, PhD** - Head of the Division of Quantitative Sciences & Chair, Department of Biostatistics, MD Anderson Cancer Center
- **Nancy Roach** - Founder, C3: Colorectal Cancer Coalition

Panel 2 Topic

- Large clinical trials are currently conducted in order to detect small differences in outcomes.
- Relatively minor improvements in overall survival have raised questions about true “effectiveness” of a drug.
- This has made utilization and acceptance of endpoints other than overall survival, particularly progression-free survival, unclear.
- Panel Charge: Propose auditing procedures that can serve to help build confidence in PFS as an indicator of clinical benefit.

Why is this Important?

- Overall survival (OS) remains the single most agreed upon endpoint in cancer clinical trials
- OS demonstrates efficacy without potential bias that can accompany endpoints that require clinical judgment
- Use of OS as a primary endpoint slows the rate of development
  - Increased trial duration, especially in cancers where the standard of care continue to prolong survival
  - Delayed trials can prolong the review of newer agents that could provide needed treatment options
- Additional endpoints are needed to quickly detect efficacy or failure

Auxiliary Endpoints

- Defined as response variables, or covariates, that can strengthen true endpoint analyses[1]
- May be primary or secondary endpoints within a trial, and are not meant to supplant conventional endpoints
- Auxiliary endpoints first validated in development of AIDS drugs in late 1980s: validation of CD4 count and viral load.
- Examples in oncology: progression-free survival (time to progression), response rate, patient-reported outcomes (quality of life), and biomarkers (e.g., tumor size, circulating tumor cells, and tumor-specific markers)

[1] Fleming TR, et al. *Stat Med.* 1994 May 15;13(9):955-68

Evaluation and Use of Auxiliary Endpoints

- Three proposed principles to consider when selecting auxiliary endpoints for a given trial:

  1) A strong biological rationale should support the potential auxiliary endpoint as a marker of treatment effectiveness

  2) The potential auxiliary endpoint should be shown to explain variability in treatment outcomes in terms of survival for treated patients[2]

  3) Ideal auxiliary endpoints accurately assess the efficacy of the drug being evaluated with minimal risk of subjectivity or bias

- Panel 2 Focus: Progression Free Survival (PFS)

[2] Ellenberg SS. [Editorial]. *BMJ*. 1991; 302:63-4

Progression Free Survival

- PFS is the length of time during and after treatment in which a patient is living with a disease that does not worsen. It employs the RECIST criteria to determine the progression of cancer based on imaging[3]
- Non-trivial improvements in PFS represents clinical benefit. It is a desired endpoint in many settings, but not a surrogate for OS
- Two types of bias that are of primary concern for PFS:
  - Assessment bias
  - Evaluation bias
- The potential for investigator bias has led to the introduction of Blinded Independent Centralized Reviews (BICR) of radiographic scans

[3] RECIST Guidelines, 2000

Blinded Independent Centralized Reviews

- Development of a methodology for an audit to asses the presence of bias is needed
- The use of BICR does not always provide an unbiased estimate of a treatment's effectiveness due to potential differences in the time at which progression may be determined
- However, in a review of phase III oncology trials published in the last 5 years that had BICRs as a component of assessment, no cases were shown to have substantial differences between analyses between the BICR and investigator assessments (Table 1 & 2 preconference report)

Establishing an Audit for PFS

- While overall BICR appears similar to local review, individual investigator can vary
  - In a recent trial, the discrepancy rate between two expert radiologists blinded to treatment assignment was 34%
- Circumstances in which the BICR conclusions differ from those based on the investigators' assessments result in an ambiguous situation
- The discrepancy may be caused by measurement variability, informative censoring, or true evaluation bias.
- Methods that would reduce evaluation bias are needed.

*** *During this session, panelists will present four approaches that are worthy of consideration*

Proposals for audit of PFS

James Doroshow, MD

Case 1: Matter for clarification

No BICR when trials are double-blinded

No BICR when trials are double-blinded

- Blinding of treatment assignment ensures that systematic bias in PFS evaluation related to knowledge of treatment assignment is not possible.
- Exception: if there is an extreme imbalance in side effects across treatment arms that could lead to a considerable level of unblinding.
- Level of imbalance would be characterized by the majority of patients in the control arm experiencing a particular side effect with a virtual absence of this same side effect in the control arm.

Case 2:

An open-label superiority trial with a BICR-based audit of progression

Case 2:
Goal of audit

- Provide assurance that there is not meaningful evaluation bias
- Meaningful evaluation bias is defined by a substantive difference in the estimated treatment effect between local review and BICR

Case 2:
PFS audit

- Evaluation bias assessed with audit of progression determinations in subset
- Systematic discrepancies by treatment arm, not random discrepancies, are source of potential bias
- Meaningful differences in estimates of treatment effect between local review and BICR will be basis of audit
  - Small effect sizes more sensitive to small discrepancies between treatment arms
  - Large effect sizes likely robust to small discrepancies

Case 2:
PFS audit

- Sample size for audit specified in advance
  - Start by auditing a subset
    - For example, 10% or minimum of 100
  - Suspicion of meaningful bias may expand audit
- Goal is to detect actual bias
  - Random discrepancies should be minimized when possible
    - For example, BICR should follow same target lesions

Key steps to development of audit

- Data-driven analyses necessary to develop scientific justification
  - Can meaningful bias be detected with audit? What size audit is necessary?
- Database of trials with BICR (and local review) needed
- NCI and PhRMA have initiated separate (but coordinated) efforts

Case 3:

No audit in open-label superiority trial with large effect size

Debasish Roychowdhury, MD

Case 3:
No audit

- No audit necessary when treatment effects are large enough
  - Evaluation bias is not expected to be of a magnitude that would meaningfully impact the observed effect size
- Increased monitoring of the protocol-specified imaging procedures at the local site could be undertaken.

Case 3:
Increased monitoring without audit

- The investigator is the greatest potential source for bias in a PFS assessment.
- Local radiologist is frequently unaware that patients are a clinical trial.
- Recording radiologist's *and* the investigator's tumor measurements (and progression assessments) recommended
  - Documentation of reasons for investigator's rationale for overriding radiologist's measurements
  - When this occurs more frequently in one treatment arm and reasons are not easy to verify objectively, concern about bias will arise

Case 4

PFS evaluation at two time-points with audit

Two time-point evaluation with audit

- Evaluation of treatment effectiveness by proportion of patients whose cancer has progressed at two time points, rather than using an analysis based on a survival model
- Two time points for imaging assessments would be determined prospectively, corresponding to the approximate median PFS and approximately twice median PFS of the control arm or conventional therapies

Two time-point evaluation with audit

- Summary statistics would include the proportion alive and progression-free at each time point.
- Progressions that have been documented prior to the designated imaging assessment time would be counted as an event for the rate of progression or death.
- Images would be audited at the two time points.

Two-time point evaluation with audit

- While one might have concerns about a loss in power of the trial design, as compared to a log-rank analysis, the loss in power with two time points is less than that from a single time point
- Freidlin et al. (2007) demonstrate that there is little risk in major power loss from this approach.
- The trade-off for some loss in power, however, is decreased susceptibility to bias

Acknowledgements

- William Bushnell, GSK
- Lori E. Dodd, NCI
- Edward L. Korn, NCI
- Boris Freidlin, NCI

Conference on Clinical Cancer Research

Panel 3: Co-Development of Diagnostics and Therapeutics

September 26, 2008
The Hotel Palomar
Washington, DC

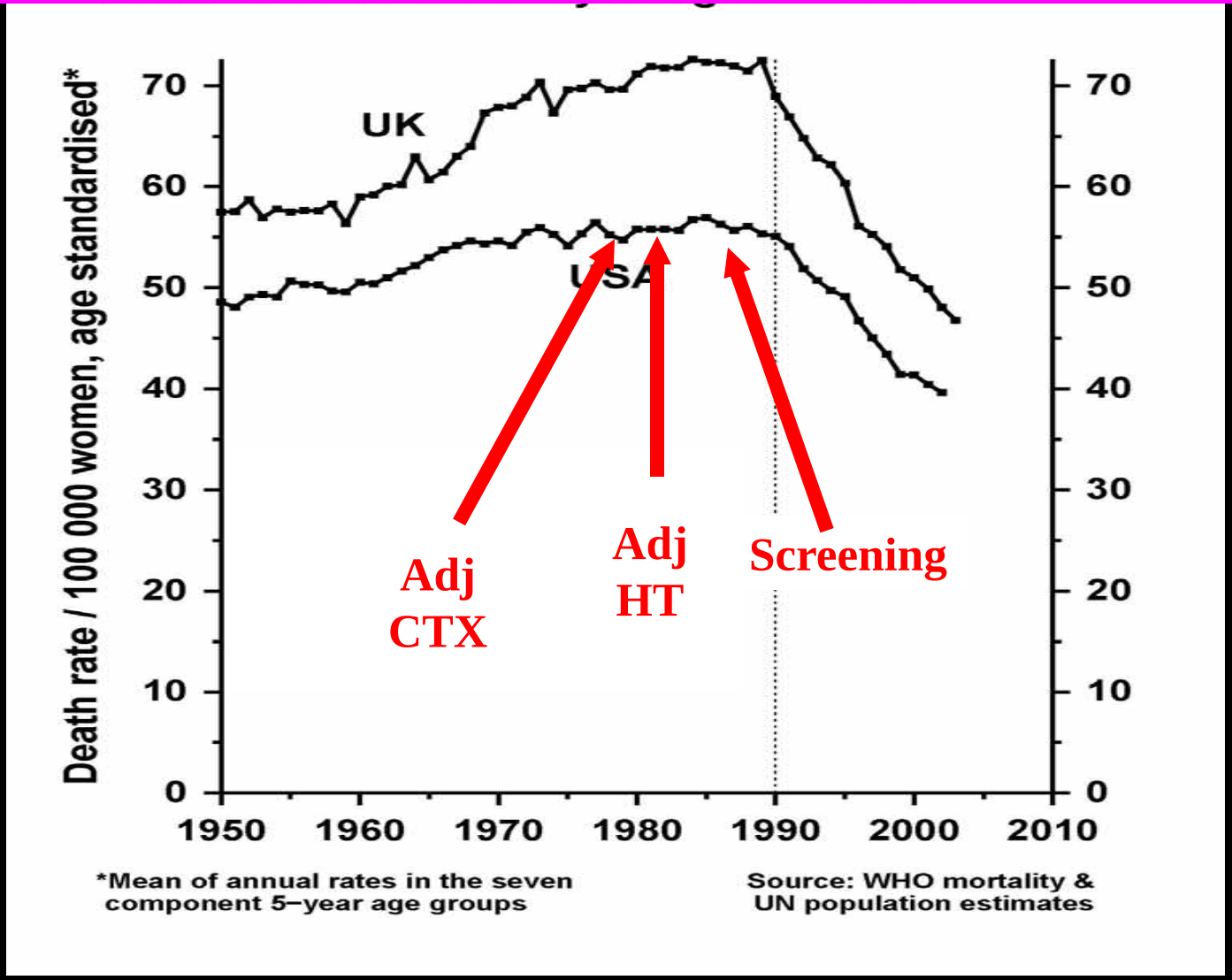
Brookings FDA Panel

Panel #3
Tumor (bio) Markers

Daniel F. Hayes, M.D.

University of Michigan
Health System
Comprehensive Cancer Center

Recent decrease in UK and USA breast cancer mortality at ages 35-69 years



Modified from Peto et al. Lancet 355:1822, 2000

Adjuvant Systemic Therapy

- **Should All Patients Receive All Therapy?**
  - **If pt is willing to accept ANY toxicity for ANY benefit: *then treat her with everything***
  - **If pt is willing to forego SOME benefit to avoid SOME toxicity: *then select therapy carefully***
- **Depends on:**
  - **Well -defined subgroups that do or do not benefit from therapy**
  - **Patient's, Doctor's, and Society's Perspectives Regarding Risks, Benefits, and Costs of Therapy**

When is a Marker Clinically Useful?

- **It is either prognostic or predictive**
- **The magnitude of effect is sufficiently large that clinical decisions based on the data result in outcomes that are acceptable**
  - ***Greater chance for benefit***
  - ***Smaller toxicity risk***
- **The estimate of magnitude of effect is reliable**
  - ***Analytical reproducibilty***
  - ***Clinical trial/marker study design is appropriate***
  - ***Results are validated in subsequent well-designed studies (Levels of Evidence I or II)***

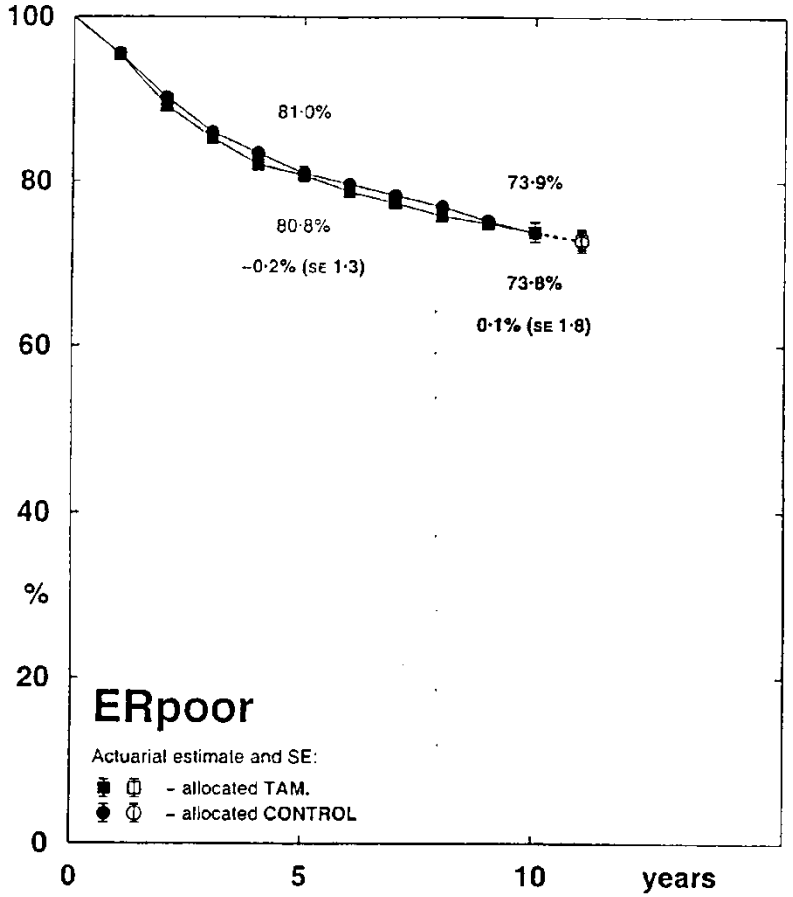
Henry N.L., Hayes DF; Oncologist. 11:541-52, 2006

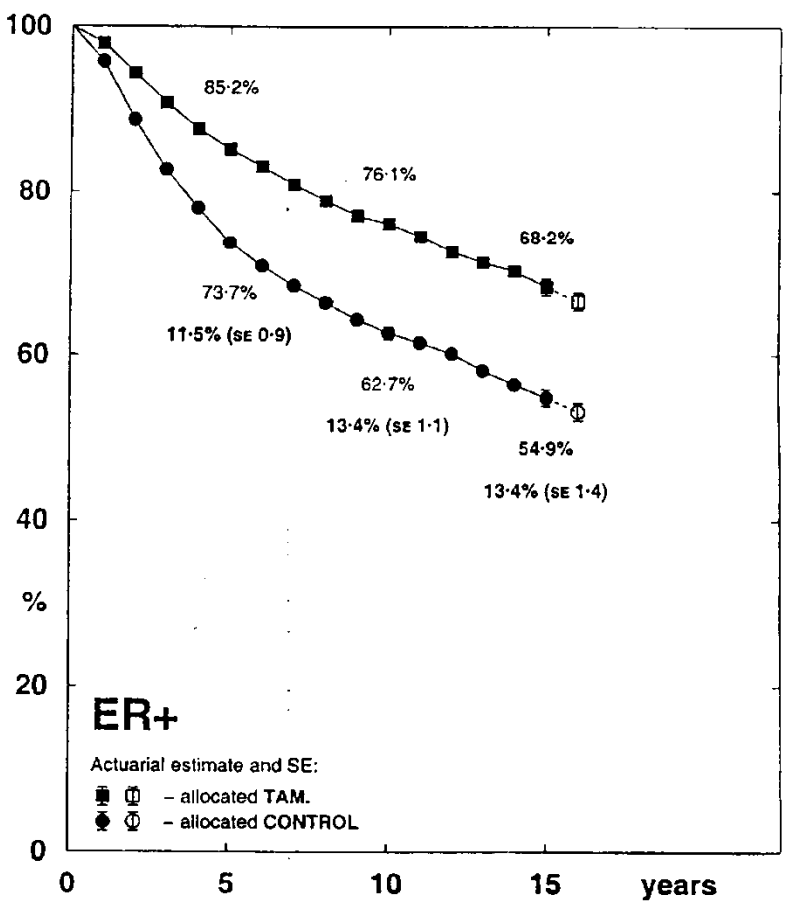
Adjuvant Systemic Therapy

- **The goal of a prognostic or predictive tumor marker is to identify those patients who would FOREGO therapy to AVOID toxicities.**
  - **Some but not all "positive" patients will benefit**
  - **Few if any "negative" patients will benefit, but all are exposed to cost and toxicity**

- **How much absolute benefit will patients forego? Surprisingly small!**
  - ***Coates AS, New York, NY: John Wiley & Sons Ltd; 1992.***
  - ***Ravdin P, J Clin Oncol 1998;16:515-21.***
  - ***Lindley C, J Clin Oncol 1998;16:1380-87.***
- **AdjuvantOnline!**
  - ***Ravdin et al. J Clin Oncol 19:980-91, 2001***

Tamoxifen vs. Not
RECURRENCES
Effect of ER





Early Breast Cancer Trialists' Collaborative Group. Lancet. 365:1687-717, 2005

ASCO Tumor Marker Guidelines Panel

- **ER, PgR** **Select Endocrine Therapy**
- **HER2** **Select Trastuzumab/Lapitinib**
- **UPA/PAI -1** **Avoid Chemo if ER+/Node neg**
- **Oncotype DX** **Avoid Chemo if ER+/Node neg**

Harris L., et al. J Clin Oncol. 2007

ASCO Tumor Marker Guidelines

- **Why Are the Guidelines So Conservative?**
  - **Recommended only those markers for which results would change clinical decisions**
  - **Evidence-based**
  - **Lack of Level of Evidence I or II studies:**
    - ***A Tumor Marker Utility Grading Scale***

Hayes, et al; J Nat Cancer Institute 88:1456, 1996

TMUGS: Levels of Evidence

Level	Definition
I	Prospective, Marker Primary Objective, Well-powered OR Meta-analysis
II	Prospective, Marker Secondary Objective
III	Retrospective, Outcomes, Multivariate Analysis
IV	Retrospective, Outcomes, Univariate
V	Retrospective, Correlation with Other Marker, No Outcomes

Hayes, et al; J Nat Cancer Institute 88:1456, 1996

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MOST TUMOR MARKER STUDIES

Hayes, et al; J Nat Cancer Institute 88:1456, 1996

TMUGS: Levels of Evidence

Level	Definition
I	Prospective, Marker Primary Objective, Well-powered OR Meta-analysis
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IV	Retrospective, Outcomes, Univariate
V	Retrospective, Correlation with Other Marker, No Outcomes

Hayes, et al; J Nat Cancer Institute 88:1456, 1996

Tumor Markers

- **A bad tumor marker is as harmful as a bad drug!**
- **Would you use a drug if:**
  - **You aren't sure how it is mixed?**
  - **You aren't sure what the concentration is?**
  - **You don't have clinical data about how the drug might be useful?**
  - **You don't have reliable clinical research data to determine how much efficacy it might have?**

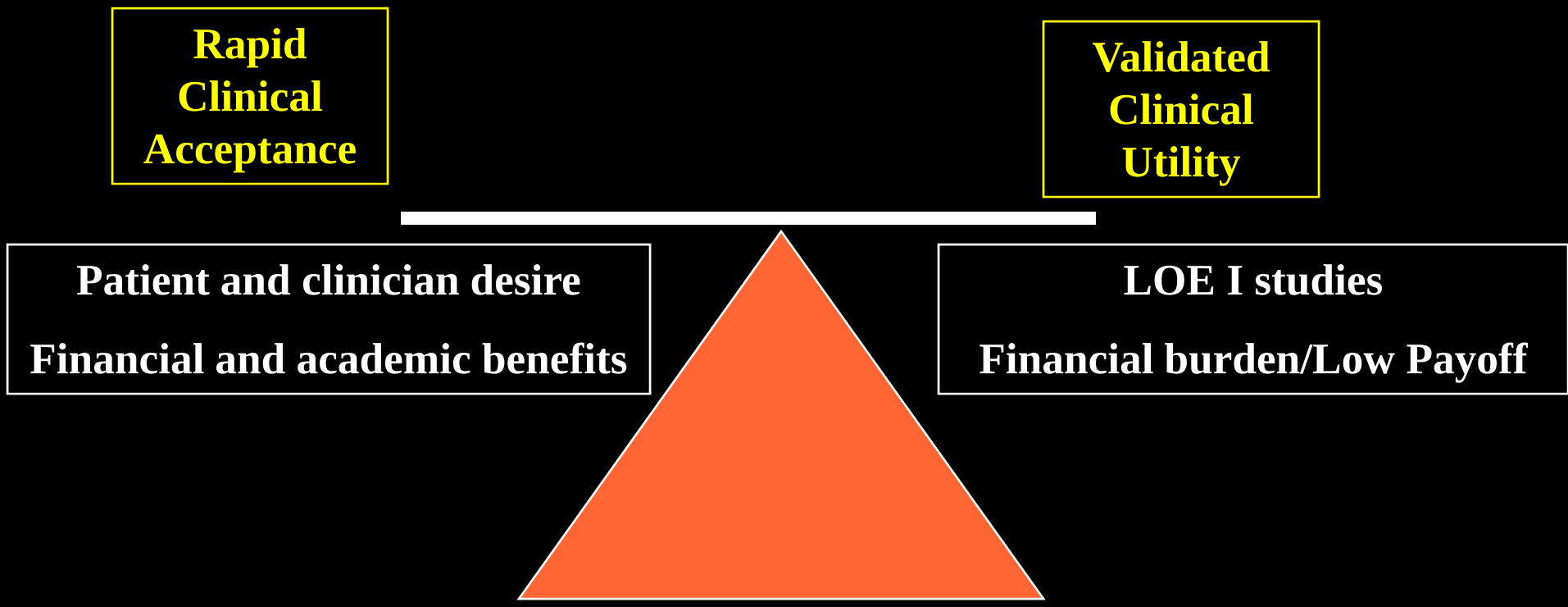
Tumor Marker Evaluation

- **What is the problem?**

  There appears to be an Inconsistent/Unclear path to clinical acceptance:

  - **FDA criteria for clearance/approval may not consider specific clnical utility-**
    - **FDA clearance does not mean an assay should be used clinically**
  - **Home Brew rule-**
    - **An assay can be marketed without FDA clearance**
  - **Disagreement about what outcomes need to be improved, and how to measure them-**
    - **There is a disconnect among Guidelines Panels and between them and FDA**
  - **Low reimbursement-**
    - **Entrepreneurs cannot afford to develop new markers if cost of doing so is substantially increased**

Acceptance of Tumor Markers: Balance of Carrots and Sticks



Tumor Markers: Carrots and Sticks

- **Research**
  - **Funding:** **NCI Cancer Biomarkers Study Section *(CBSS)***

    www.cms.csr.nih.gov
  - **Publication:** **Recommended Guidelines**
    - ***Mcshane et al, REporting Recommendations for Tumor MARker Prognostic Studies (REMARK)***
    - ***Bossuyt et al, Towards complete and accurate reporting of studies of diagnostic accuracy: The STARD Initiative***
  - **Specimen Sources** **Breast Cancer Tissue Resource**

    Breast Cancer Inter-group Correlative Sciences Committee

    www.ctep.nih.gov/resources/tbci/correlative_studies.html

Tumor Markers: Carrots and Sticks

- **Clinical Use**
  - **Guidelines**

Evidence-based Guidelines Panels

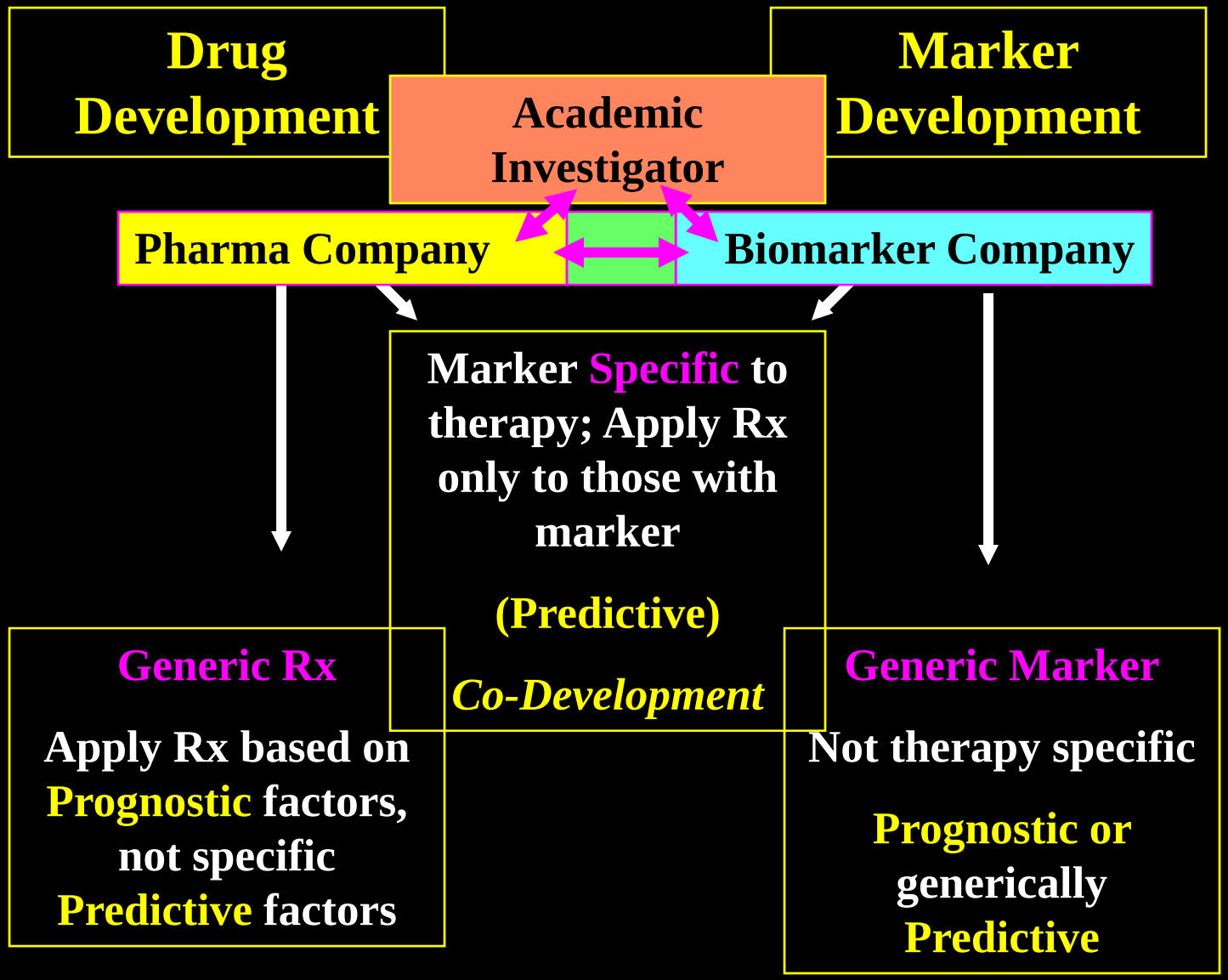
ASCO, NCCN, CAP, NACB

www.asco.org

www.nccn.org

- **Regulatory/Reimbursement**
  - **3rd Party Tech Assessments**
  - **AACR/NCI/FDA**
  - **Center for Medical Technology Policy**
  - **Improved and Clear-cut FDA Rules**
    - **Center for Devices and Radiologic Health**
    - ***www.fda.gov/cdrh/guidance.html***

Tumor Marker Development



Panel 3 Questions ("Strawmen")

- **Develop a clear pathway for Tumor Marker development in consultation with external community**
- **Base Tumor Marker clearance and approval on demonstrated clinical benefit.**
  - **For co-development, pathway must be practical and efficient**
- **Develop an ODAC-like advisory committee for Tumor Marker clearance/approval**

Panel #3 Subquestions

- **Special concerns related to co-development of new therapeutic with target marker assay**
- **Reform reimbursement system to reward entrepreneurs and provide incentive to develop clinically useful marker**

Panel 3

- **Steven Gutman MD, MBA FDA CDER**
  - ***FDA Role and Perspective on Marker Validation***
- **Ray Woosley MD, PhD**
  - ***Proposed model for co-development of marker and targeted drug***
- **Panel Discussion**
  - **Richard Frank MD, PhD GE Healthcare**
  - **Nancy Roach Colorectal Cancer Coalition**
  - **Richard Simon DSc NCI**

Extra Slides

When is a Marker Clinically Useful?

- **It is either prognostic or predictive**
- **The magnitude of effect is sufficiently large that clinical decisions based on the data result in outcomes that are acceptable**
  - *Greater chance for benefit*
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  - ***Analytical Reproducibility***
  - *Clinical trial/marker study design is appropriate*
  - *Results are validated in subsequent well-designed studies (Levels of Evidence I or II)*

Henry N.L., Hayes DF; Oncologist. 11:541-52, 2006

A MARKER ≠ An ASSAY

Example: HER2

Tissue

IHC (at least 3 available)	Protein Expression
FISH	DNA Amplification
CISH	DNA Amplification
rt-PCR	RNA Expression

Blood

ELISA	Soluble protein (extracellular domain)
Immunomagnetic cell assay	Circulating Tumor Cell Expression

Wolff et al;
ASCO/CAP guideline recommendations for human EGFR2 testing in breast cancer.
J Clin Oncol; 2007;25:118-45.
(Published simultaneously in Arch Path Lab Med)

Regulatory Issues in Co-Development – don't forget the diagnostic

Steven Gutman, M.D.

Office of In Vitro Diagnostics

Medical Device Amendments of 1976

- General controls
- Registration and listing
- Good manufacturing practices
- Reporting of adverse events

FDA Device Regulation

- Premarket review
- Risk based (three classic classes)
- Intended use and indications for use
- Different administrative packages
- Same core science

Analytical Performance

- Accuracy
- Precision
- Analytical specificity
- Limits of detection/measurement

Clinical Performance

- Yardstick of truth
- Clinical sensitivity
- Clinical specificity
- Predictive values
- Payment/penalty for weaker surrogates

Transparency

- www.fda.gov/cdrh/oivd
- 510(k) data base
- PMA data base

Epiphany # 1 – Not your father's Oldsmobile

- Diagnostics for sake of diagnostics
- Diagnostics for drug development
- Diagnostics to refine drug use
- Complicates path but potentially enriches the outcome
- If diagnostic drives drug treatment than the drug becomes hostage to the diagnostic

Co-Development –Good News

- Collaborative models in FDA (Her 2 the best)
- Parallel reviews
- Parallel panel meetings
- Cross labeling in real time

Co-Development – Bad News

- FDA underestimated power of pre-analytical, analytical and post-analytical variation in test performance and site variation
- Community ran out of samples – tests fielded on analytical bridges

Epiphany # 2, FDA not the elephant in the room

- Analytical Validity
- Clinical Validity
- Labeling
- Transparency

Epiphany # 2, FDA not the elephant in the room

- Analytical Validity – CLIA alternative; lab developed or home brew tests
- ----------
- Clinical Validity
- Labeling
- Transparency

Epiphany # 2, FDA and CLIA not the elephant in the room

- Analytical Validity
- Clinical Validity
- Labeling
- Transparency
- ----------
- Third party payers
- Users -- education a challenge without information

Epiphany # 3, The health care system is not very healthy

- 2008 > 2 trillions dollars – 16% of GNP
- Current trajectory – 20% (2010) to 25% (2020) of GNP
- Disappointing metrics – uninsured; neonatal outcomes; balance between preventive, mid life and end of life care
- IOM – To Err is Human – 98,000 deaths
- Rand Study (2003) – 52% quality care

Epiphany # 3, The health care system is not very healthy

- Lab tests – 8 billion, $50 billion
- 70% decision making
- Informed use could save money?
- Informed use requires data – no free lunch

Prometheus Unbound -- Shelley

To suffer woes which Hope thinks infinite; To forgive wrongs darker than death or night;
To defy Power, which seems omnipotent;
To love, and bear; to hope till Hope creates
From its own wreck the thing it contemplates;
Neither to change, nor falter, nor repent;
This, like thy glory, Titan, is to be
Good, great and joyous, beautiful and free;
This is alone Life, Joy, Empire, and Victory.

www.C-Path.org

CRITICAL PATH INSTITUTE

Drug-Diagnostic Co-development: A New Paradigm

Raymond L. Woosley, MD, PhD

President and CEO

Critical Path Institute

CRITICAL PATH INSTITUTE

Conflicts on Interest Disclosures

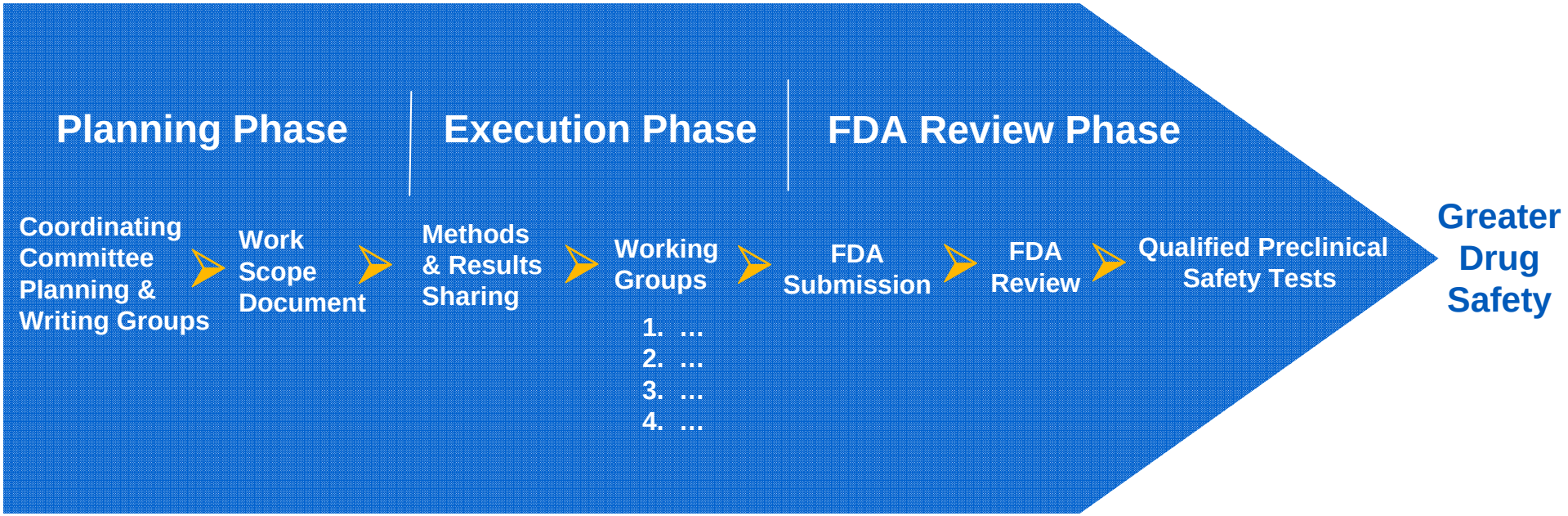
Raymond L. Woosley, MD, PhD

None

Biomarker Qualification

CRITICAL PATH INSTITUTE

Predictive Safety Testing Consortium



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- Pfizer, Inc.
- Roche
- Sanofi-aventis U.S. Inc
- Schering Plough Research Institute
- Wyeth

Advisors: FDA, EMEA

An International Endeavor

CRITICAL PATH INSTITUTE

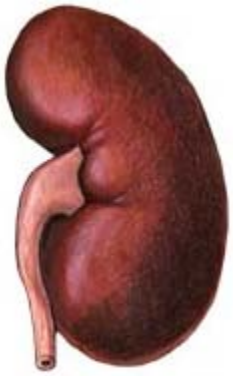
PSTC Convenes 190 Scientists Every 2 Weeks

Kidney Working Group Progress

Creatinine & BUN do not detect subtle drug injury

Twenty three new kidney biomarkers:

- **Extremely Sensitive**
- **Seven had excellent data for submission to FDA and EMEA**



FDA Decision: "Biomarkers Qualified"

CRITICAL PATH INSTITUTE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

April 14, 2008

RE: Review Submission of the Qualification of Seven Biomarkers of Drug-Induced Nephrotoxicity in rats.

Dear Drs. Dieterle, Mattes, and Sistare:

This letter provides the conclusions from our review of your submission supporting the qualification of seven biomarkers of drug-induced nephrotoxicity in rats. We conclude that:

The urinary kidney biomarkers (KIM-1, Albumin, Total Protein, β2-Microglobulin, Cystatin C, Clusterin and Trefoil factor-3) are acceptable biomarkers for the detection of acute drug-induced nephrotoxicity in rats and can be included along with traditional clinical chemistry markers and histopathology in toxicology studies.

EMEA Decision: "Biomarkers Qualified"

CRITICAL PATH INSTITUTE

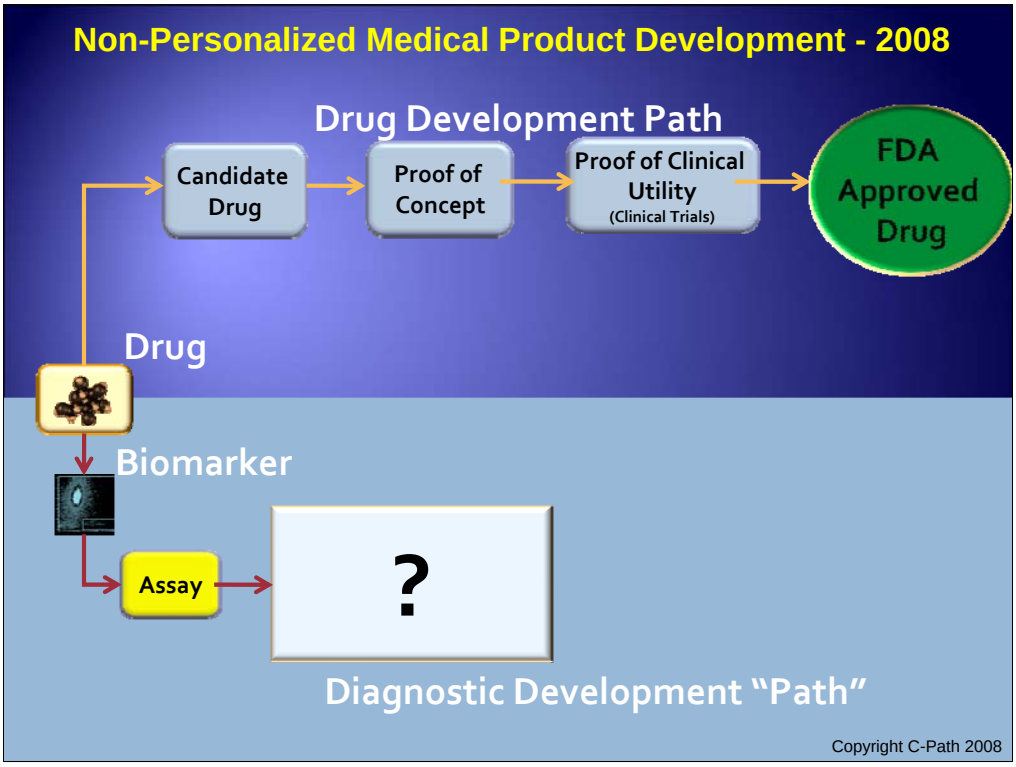
European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 3 July 2008
Doc. Ref. EMEA/250885/2008 Rev. 1

COMMITTEE FOR HUMAN MEDICINAL PRODUCTS

FINAL REPORT ON THE PILOT JOINT EMEA/FDA VXDS EXPERIENCE ON QUALIFICATION OF NEPHROTOXICITY BIOMARKERS.

ADOPTION BY CHMP	April 2008
FOR RELEASE FOR CONSULTATION	May 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	Extended to July 2008

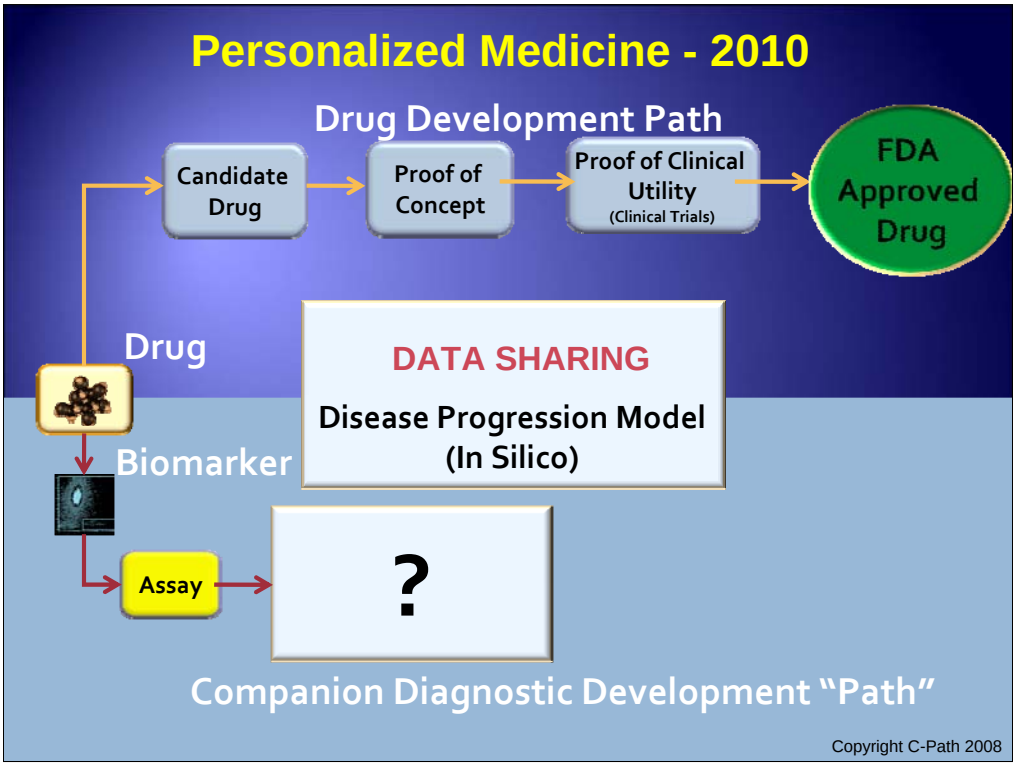


Today there is a well defined but slow and inefficient path for drugs to reach FDA approval.

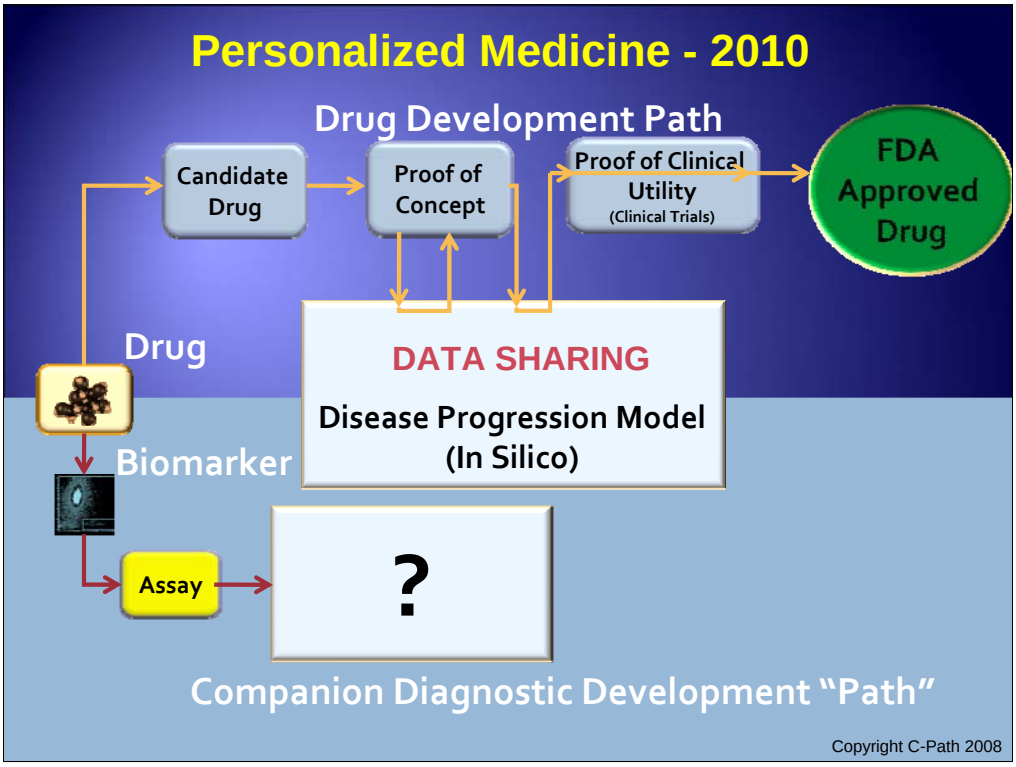
Most drugs are identified because they have demonstrated some laboratory phenomenon that is the basis for their pharmacologic action. That is a lab assay that could be a useful biomarker but there is no proven, reasonable path for it to become an FDA approved diagnostic test. In fact, it is often impossible to know if the drug is truly effective without a test to identify who could respond but ALSO, one can't be sure that the diagnostic predicts response without a drug that is effective. You cannot be sure that one has value without the other, perhaps a Gordian Knot?

Drugs like Herceptin were initially turned down for approval because only a small percentage responded to the drug. After considerable delay, the FDA was convinced to approve the drug when the tumor had the target.

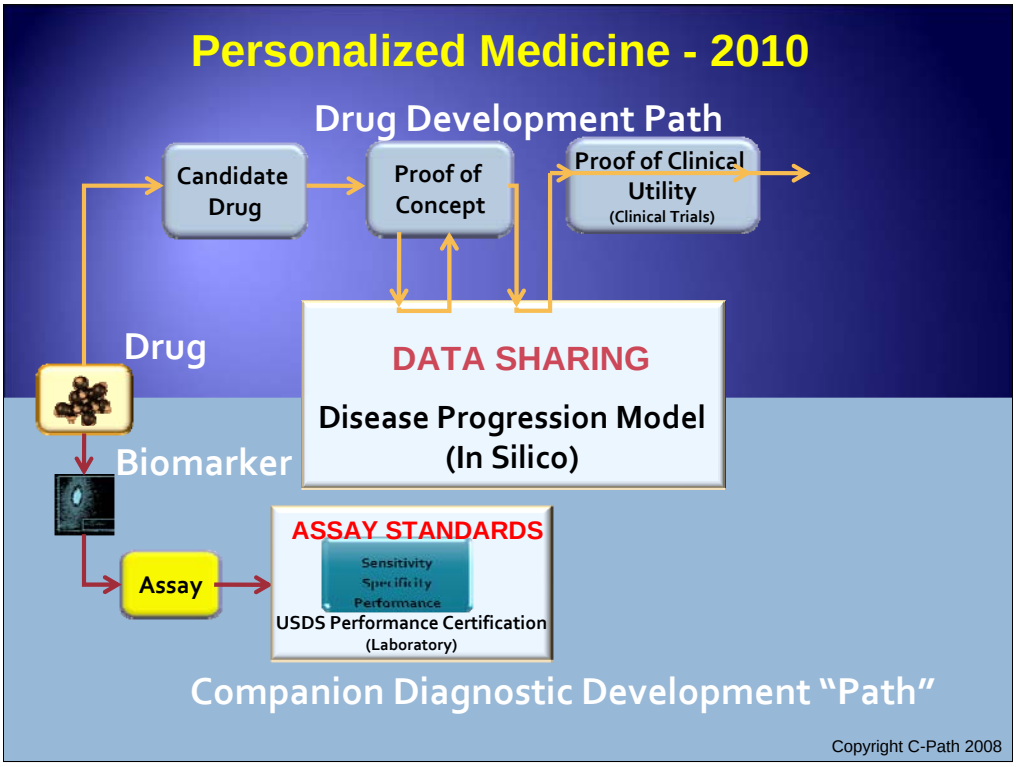
The FDA has published a drug-diagnostic co-development guidance but it is very general and lacks specific information. It is often confused by questions about whether the biomarker is "validated" by a clinical trial(s). There is valid concern about the role of biomarkers as surrogates until they have been "validated." One FDA scientist has been quoted to say that if a biomarker accurately predicts the clinical response to nine drugs, he will consider it valid. But, what would be the value of a biomarker to be used to test the efficacy of a tenth drug in a category. And even then, the results with the recent statin that was found to cause increased cardiac mortality raises questions about cholesterol lowering as a "valid" biomarker.



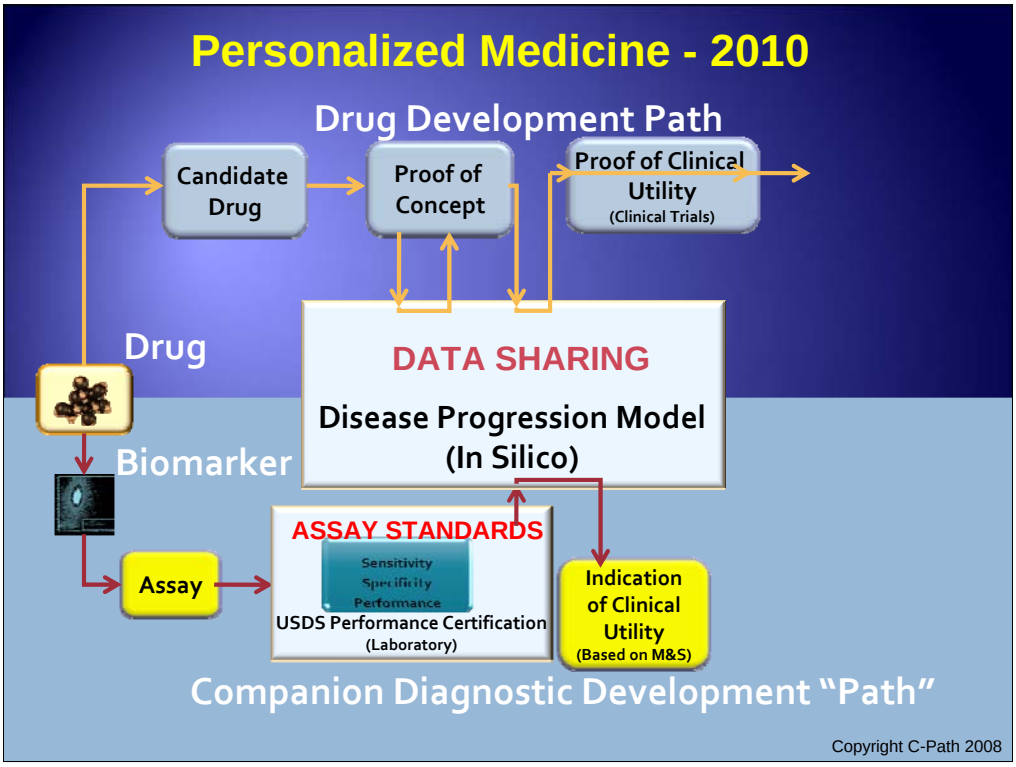
A key contribution to the failure is drug development is a full understanding of the disease. Data integration and sharing are necessary to create a quantitative disease progression model that includes biomarkers that identify subsets of the disease.



Often today, modeling and simulation is used to integrate a "disease model" and a "drug model." The drug model includes information about its pharmacokinetics, pharmacodynamics and the patient specific factors that influence its actions (eg, gender, age,etc)

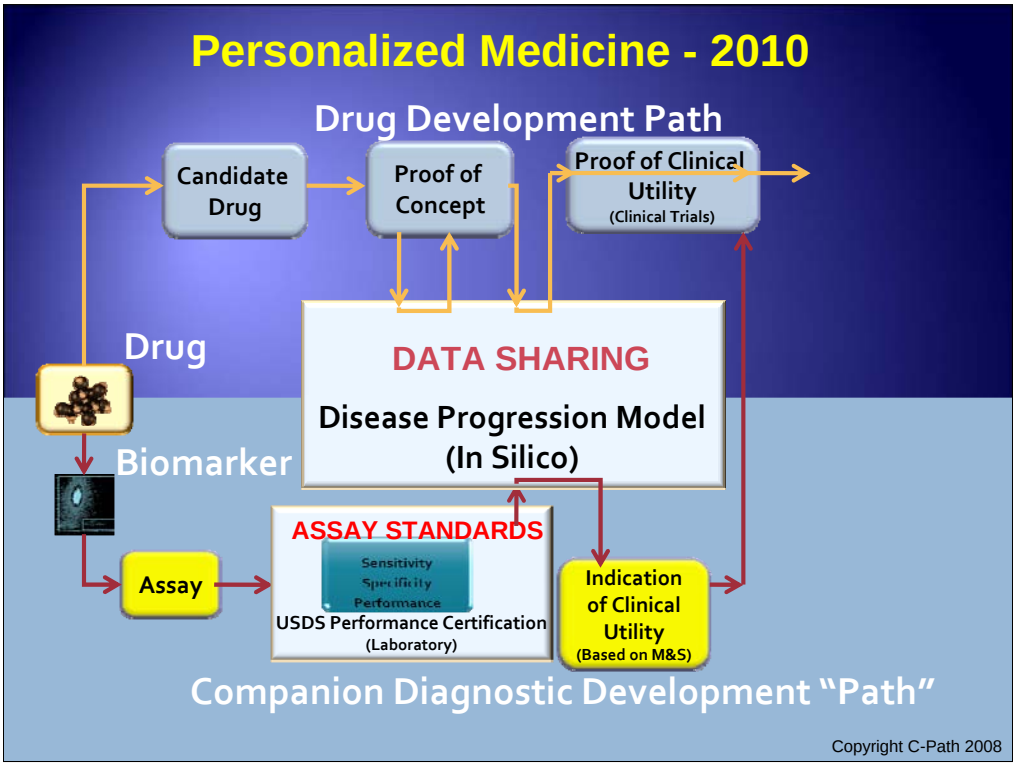


Often missing is an assurance that the assay developed in the research laboratory will perform in the clinical laboratories across the nation. We propose the creation of an independent laboratory to certify the performance of assays, similar to an Underwriters Laboratory or the US Pharmacopeia.



Once the reliability of an assay's performance is established (certified), the question arises, will it have clinical value. It is generally assumed that a clinical trial will assure the value but without a drug with proven efficacy, it is not possible to test the clinical value of a diagnostic test.

In this situation, we recommend utilizing the "disease model" to conduct simulations of the possible outcomes of clinical trials with a hypothetical drug (eg a EGFR antibody) to test the potential reliability of the diagnostic test (also incorporating the performance characteristics into the simulation). If the model predicts that the diagnostic test has a "reasonable" liklihood of accurately identifying a population who would respond to the hypothetical drug, it could then be deemed "qualified" for use in the development of a new drug with the same general characteristics of the hypothetical drug.



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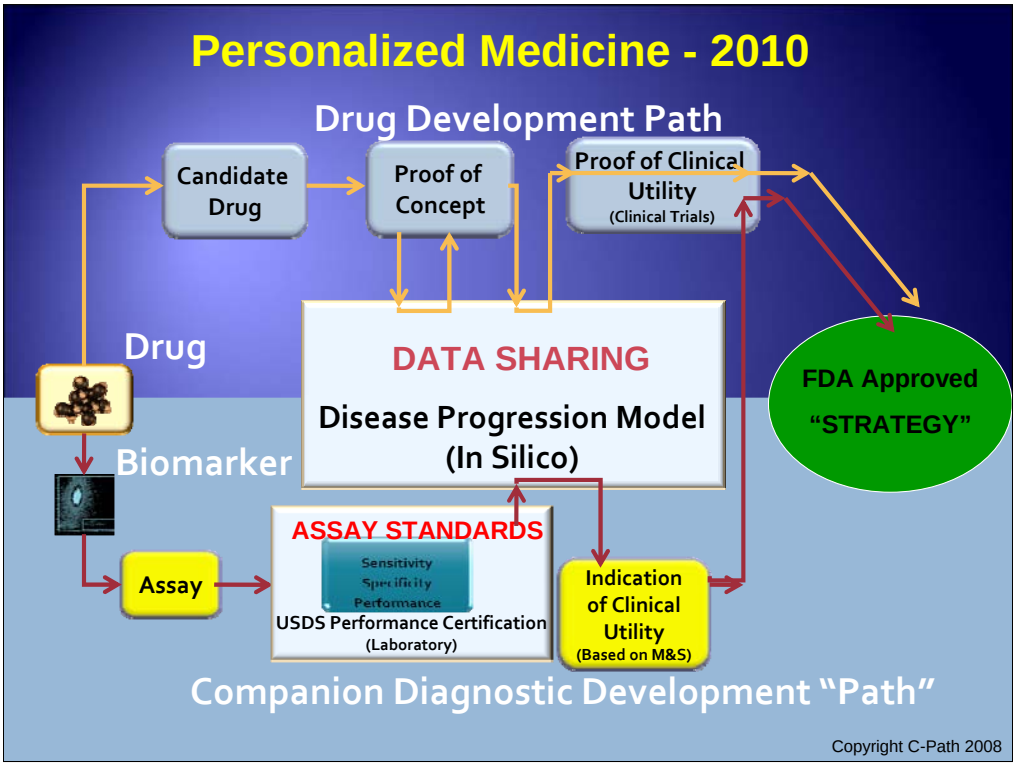


If the clinical trial finds that the population identified by the diagnostic test has the desired clinical outcome when treated with the drug predicted to be effective, the data would be submitted as a "strategy" for approval by the FDA. Instead of a drug approval, or a diagnostic approval, the strategy approved would assume that the drug would only be recommended for use when the diagnostic test predicts a beneficial response…… personalized medicine.

Conference on Clinical Cancer Research

Panel 4: Vision for the future of FDA

September 26, 2008
The Hotel Palomar
Washington, DC

FOSTERING FUTURE INNOVATION

VISION FOR THE FUTURE OF THE FDA

Brookings Conference on
Clinical Cancer Research
September 26, 2008

Robert C. Young MD, Chancellor
Fox Chase Cancer Center

FOX CHASE
CANCER CENTER

VISION FOR THE FUTURE OF THE FDA

WHAT DOES THE PUBLIC WANT?

- **Safe and Effective Drugs and Biologicals**
  - **PUDUFA funds have helped approval but distorted FDA funding and focus**
  - **FDA Ill-equipt to do post-marketing surveillance**
- **New and Innovative Therapies for Unmet Medical Needs**
- **Safe and Effective Medical Devices and Biomarkers**
  - **Products remain available while revised applications await FDA approval**
  - **FDA does not regulate laboratory-developed tests (LDT's)**
    - **LDT's often influence drug selection or dosing**
- **21st Century Scientific Milieu at FDA**
  - **Center Focus vs. Cancer Focus**
  - **Organ-specific science vs. Genomic/Pathway driven science**
  - **Presence of internal and external "silos"**
  - **Ill-defined pathway for chemoprevention drug approval**

FOX CHASE CANCER CENTER

VISION FOR THE FUTURE OF THE FDA

WHAT DOES THE PUBLIC NEED?

- **Safe and Effective Drugs and Biologicals**
  - Balanced for seriousness of illness
  - Timely approval and better post-marketing surveillance
  - Timely integration of lower cost generics and follow-on Biologics
  - Safe pharmaceuticals imported into US - Heparin

- **Safe and Effective Medical Devices and Biomarkers**
  - Cost-effectiveness comparisons
  - Better post-marketing surveillance

- **FDA Structure that Addresses the Cross-disciplinary, Cross-center Nature of Cancer Product Review**
  - Rapid development of new guidance documents
  - Formally establish an FDA Oncology program

- **Broader Transparent Input on Oncology Policy Issues**
  - Board of External Scientific Counselors
  - Enhanced Government-Wide Policy Panel
  - International Program in Cancer Product Development

- **And an FDA with the Manpower, Resources, Expertise To Keep Us Safe**

FOX CHASE CANCER CENTER

VISION FOR THE FUTURE OF THE FDA

WHAT DOES THE FDA FACE?

- **Growing Scrutiny from Congress**
- **Massive Accumulation of Unfunded Statutory Responsibilities**
  - **100 since 1988**
- **Inadequate IT Infrastructure**
  - **CBER ≠ CDER; Road Salt = Table Salt**
- **PUDUFA Funds Mask Shrinking Funds For Core Functions - $250M Lost from 2002-2005**
- **Lack of Personnel - Recent hires only replace those previously lost**
  - **40% of new hires funded by industry user fees**
- **Need Professional Development; Research Collaborations; Better Career Ladders**

VISION FOR THE FUTURE OF THE FDA

WHAT MUST BE DONE?

- **Congress Must Address Funding, Manpower, IT Needs of the FDA**
- **Need FDA Equivalents of Both a Chief Scientific Officer and a Chief Medical Officer**
- **Fully Fund Critical Path Initiative**
- **Create Board of External Scientific Counselors**
- **Create New Science Capability**
  - **Nanotechnology, Systems Biology, Pharmacogenetics, "Personalized Medicine"**
- **Collaborate Better and Eliminate "Center Silos"**
- **More Transparency**

FOX CHASE CANCER CENTER

FDA AND PUBLIC HEALTH

- **Cannot Be Fixed With Existing Resources**
- **Many Excellent Reviews Have Identified Same Deficiencies For Decades**
- **Problem Requires Congressional Action**

Brooks Conference: Clinical Cancer Research

"A Future Vision for Cancer Interventions"

Panel 4

Anna D. Barker, Ph.D.

Deputy Director

National Cancer Institute

Some of the Barriers in Oncology - Science to Inform/Enable the Regulatory Process

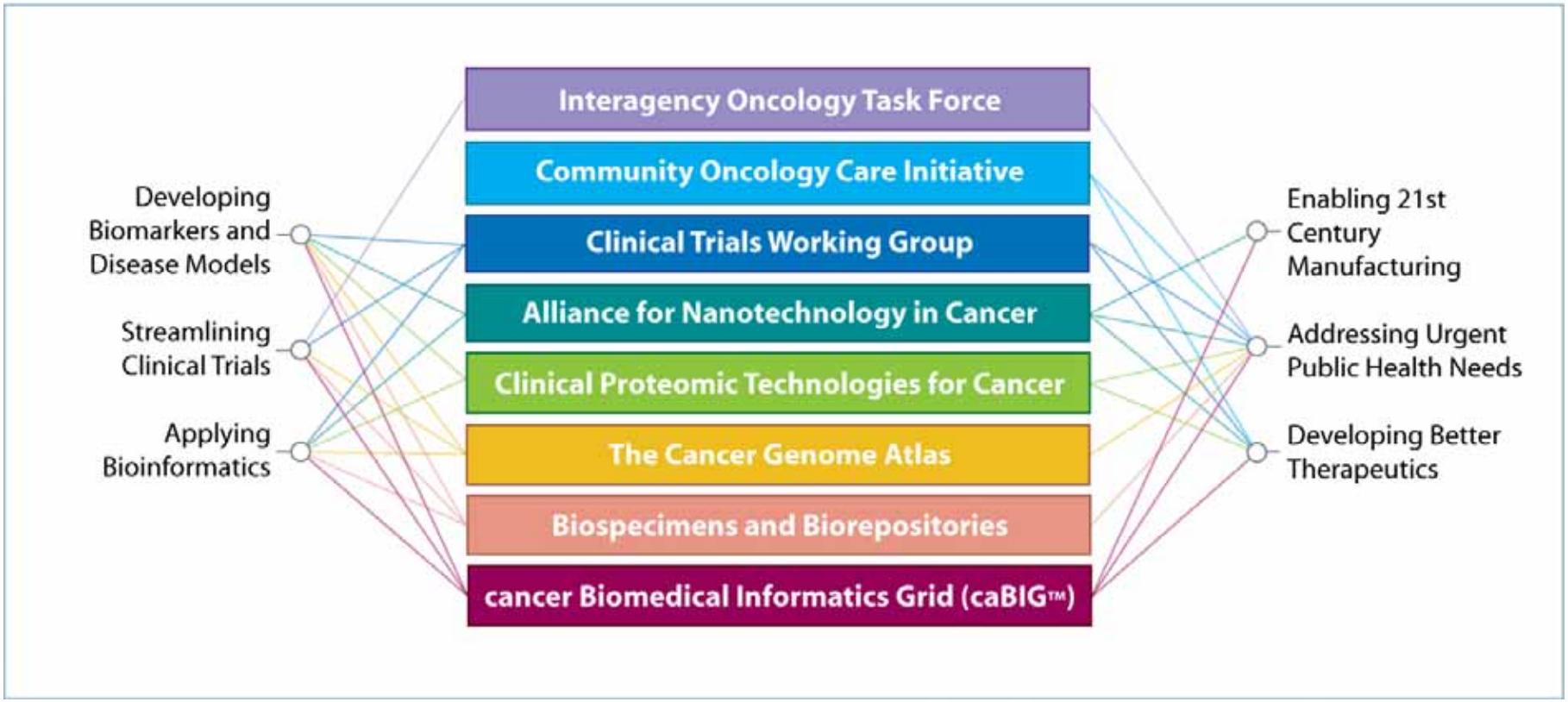
- Overall - lack of a coordinated – integrated system
- Whatever happens – one size fits all doesn't/won't fit all (across – within oncology)
- Among us all - no real scientifically based acceptance of target definition
- Lack of technology standards (genomics, proteomics, emerging technologies)
- Information management reporting and management – disconnected and lacking standards
- Lack of validated biomarkers/surrogate endpoints for target definition – clinical trials
- Need for new clinical trials design models
- Your favorite

Bottom Line: Unprecedented potentially-transformative advances in the molecular sciences – "gaps" in terms of developing the tools/standards/processes needed for assessment of the mechanism's) in drug-device development

Focus Areas for the Critical Path

- Developing biomarkers and new disease models
- Streamlining clinical trial
- Applying bioinformatics
- Enabling 21st century manufacturing
- Addressing urgent public health needs

NCI's Strategic Initiatives and FDA Critical Path Opportunities

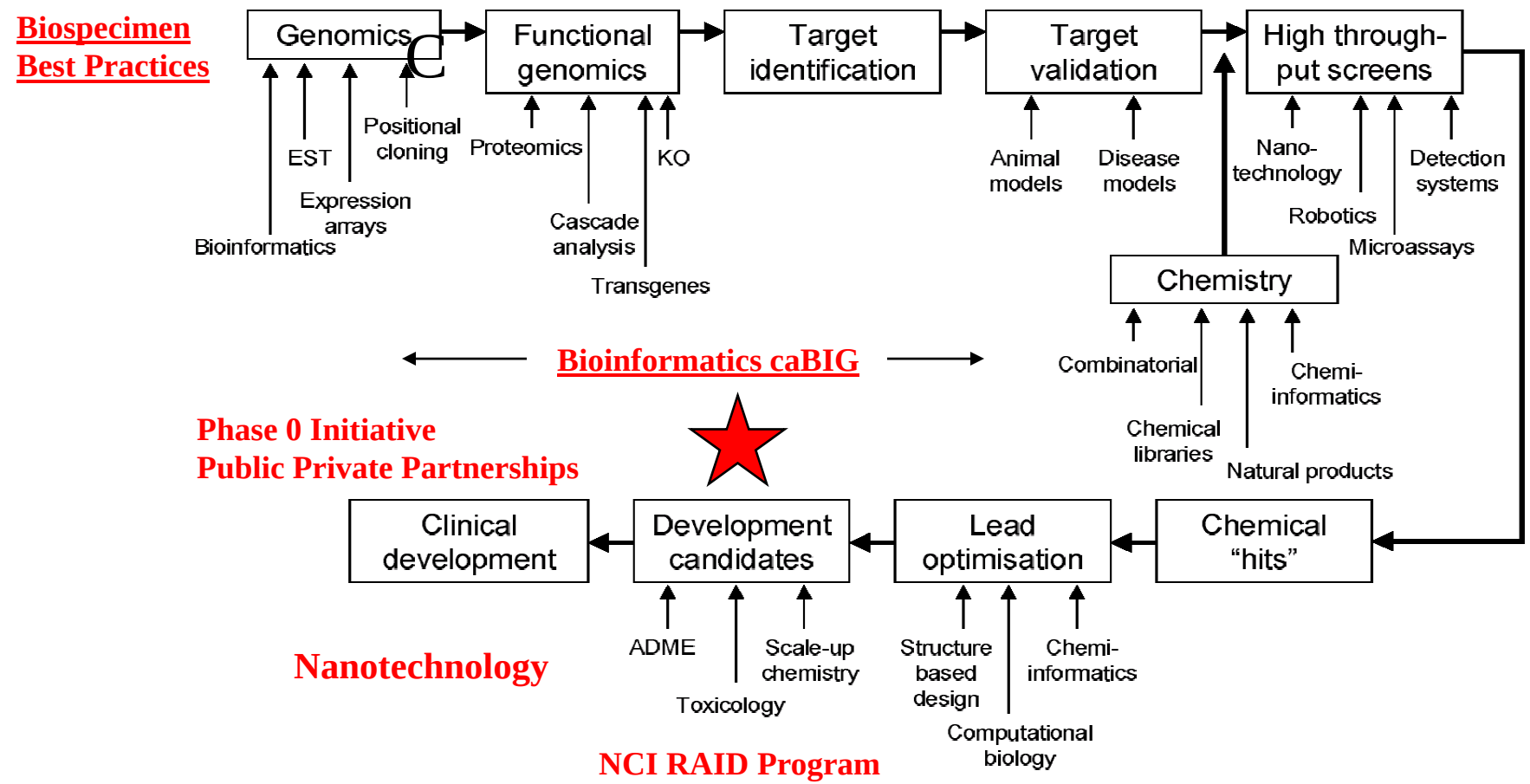


Emerging RX/DX Model for More Directed Cancer Interventions

*Lehman Bros.: The Fruits of Genomics

NCI TCGA, Clinical Proteomics (Biomarkers)

NCI's Chemical Genomics Program
Nanotechnology Alliance for Cancer



The NCI-FDA Interagency Oncology Task Force

- Interagency Agreement – FDA/NCI Partnership – May 2003
- Process Enhancement – Exploratory INDs for Small Molecules; New GMP Regulations for Experimental Agents
- Biomarkers Qualification – Imaging Endpoints; Biomarker-Driven Diagnostics; Biochemical Endpoints – the Oncology Biomarker Qualification Initiative
- New Common Bioinformatics Platforms – Standards for Clinical Trials Submissions; e-INDs; CRIX Project
- Advanced Technologies – Critical Path Initiatives (Nanotechnology and Molecular Diagnostics)
- Biomarker Think Tank
- Training and Joint Appointments – 3 Training Programs for PhDs and MDs

Desired Future State

- Science Driven – knowledge of molecular construct and function of the cancer as a whole
- A continuum –predictive process
- Embraces and employs advanced technologies
- Evidence/Standards based
- Electronic – digital process…real time
- Large data base - real-time learning – centric
- Virtually no re-invention of the wheel

Anticipative….Proactive……Predictive….Requisite Numbers of Safe/Efficient Molecularly-Based Directed Interventions per Disease

Panel 4 – Vision for the Future of FDA

The need for "Change" (*as if we don't hear it enough*)

- **Complex science is at the base of all discussions today, but a clear path forward is needed.**
- Recognize that the process is always evolving- can never have a degree of certainty.
- Diverse stakeholder input is critical.
- Ultimately these decisions are about the patient.

FRIENDS of CANCER RESEARCH

Panel 4 – Vision for the Future of FDA

Establishment of clear FDA Oncology Program

- Concise, consistent guidance is necessary.
- Transparency and consistency to regulatory procedures.
- Improve scientific initiatives – Implement Critical Path projects.
- Develop FDA fellowship programs for training and work with academic centers.

FRIENDS of CANCER RESEARCH

Panel 4 – Vision for the Future of FDA

Better Mechanisms for Community Outreach & Scientific Input for FDA

- Through sister agencies, non conflicted scientific advisers- can integrate the science and get input from the broad community.
- NCI/FDA Interagency Oncology Task Force could be expanded to a task force with external representation.
- Federal Advisory Committee Act (FACA) - Original statutory establishment of govt. advisory committee structure.
- Expansion of FDA advisory capacity could provide additional expert input on scientific priorities and programs – integrate specific expertise that may not be represented on an ODAC.

FRIENDS of CANCER RESEARCH

Panel 4 – Vision for the Future of FDA

Important to keep the momentum of this conference going and others toward action rather than rhetoric

Source: New Yorker, July 3, 2008

FRIENDS of CANCER RESEARCH

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