Center for
Health Policy
at BROOKINGS

Facilitating Biomarker Development: Strategies for Scientific Communication, Pathway Prioritization, Data-Sharing, and Stakeholder Collaboration

The Brookings Institution • Washington, DC
Tuesday, October 27th, 2015

Facilitating Biomarker Development: Strategies for Scientific Communication, Pathway Prioritization, Data-Sharing, and Stakeholder Collaboration

Biomarker Development and Qualification: Framing the Major Issues

Presented by Robert Califf on behalf of the NIH-FDA Biomarker Working Group

Center for Health Policy at Brookings
October 27, 2015

Context for this Project

- FDA-NIH Joint Leadership Council
  - Help ensure that regulatory considerations form an integral component of biomedical research planning and that the latest science is integrated into the regulatory review process
  - Advance the development of new products for the treatment, diagnosis and prevention of common and rare diseases
  - Enhance the safety, quality, and efficiency of the clinical research and medical product approval enterprise
  - Commitment on the part of both agencies to forge a new partnership and to leverage the strengths of each agency

JLC Projects

- Biomarker Taxonomy
- Communications on NIH grants involving regulatory issues
- Protocol Template
- Strategic Use of Information from ClinicalTrials.gov
- Currently under consideration: larger joint effort to improve national clinical trials enterprise

Biomarkers in Context

- Part of a spectrum of outcome measures for studies
  - Biomarkers
  - Surrogates
  - Clinical outcomes
- Critical to drug development
- But also used in discovery science, translation, device and behavioral therapy development and clinical practice

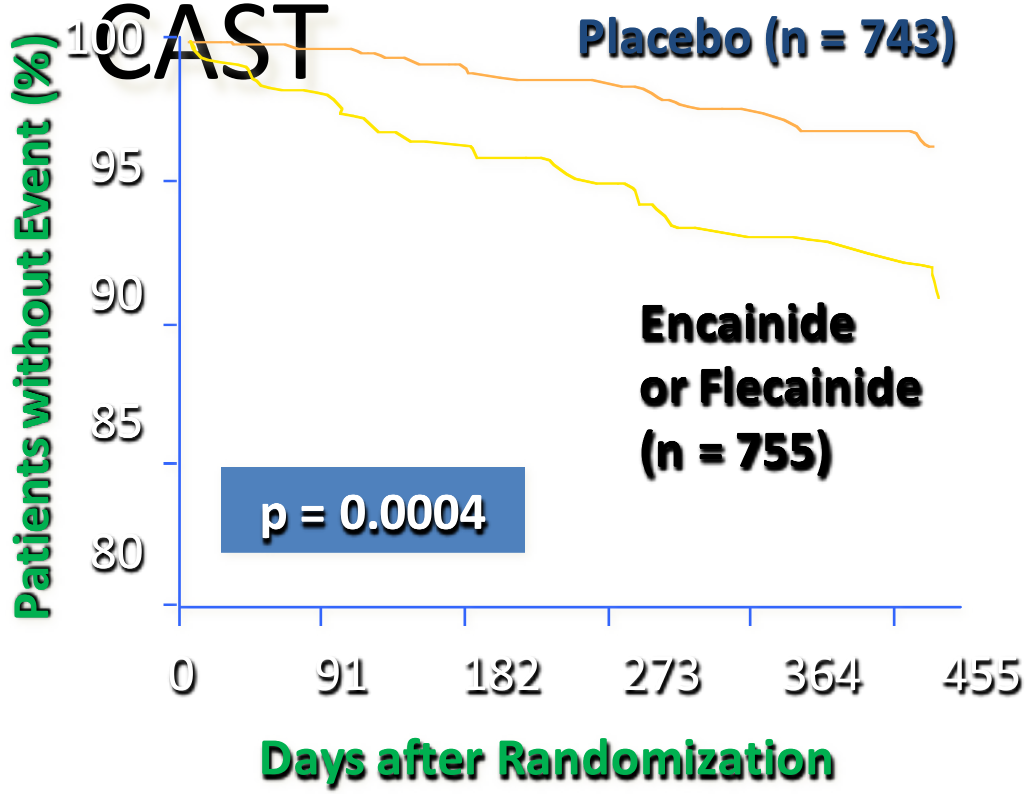
Barriers to Biomarker Development

- Cognitive shortcuts reinforced by sloppy terminology
- Complexity of biology is revealed by systems measurement, large scale informatics and data science
- Validation requires significant investment in clinical trials and observational studies

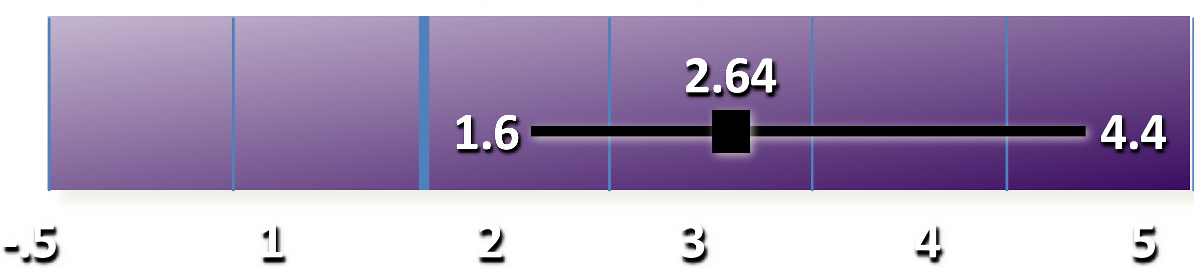
Surrogates

- Major cause of confusion
- Tantalizing to believe that a change in a single measure can accurately predict benefit
- While biomarkers have multiple uses, candidate surrogates have mostly failed to predict clinical benefit
- But validated surrogates are extremely valuable
  - And failing as a surrogate says little about value as a biomarker

CAST



Odds of Death

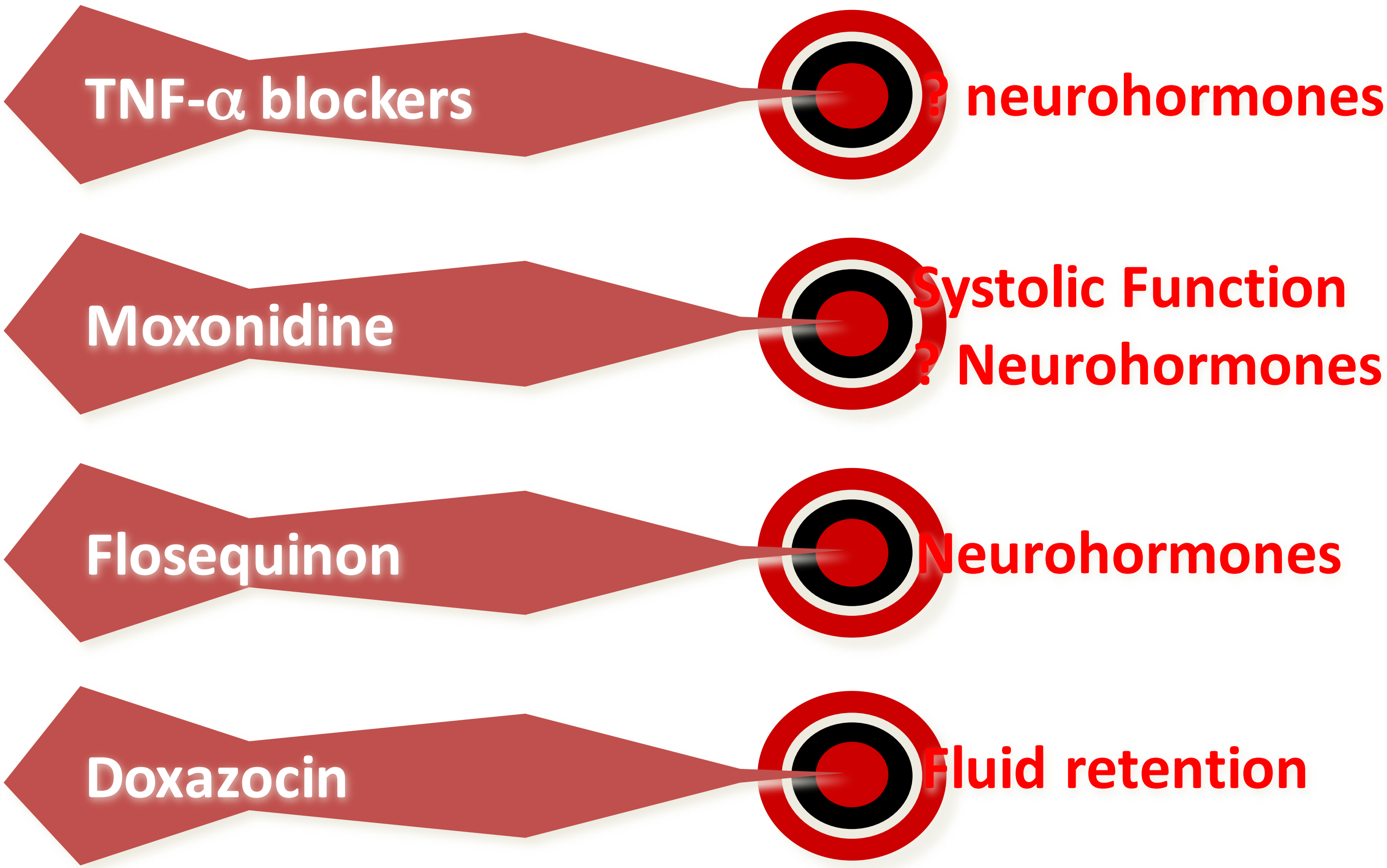


Echt, N Engl J Med, 1991

Unintended Targets

Vesnerinone	? neurohormones
Calcium Blockers	Systolic Function ? Neurohormones
PD Inhibitors	Arrhythmia
Epoprostenol	Neurohormones

Unintended Targets



Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease

Authored by the Committee on Qualification of Biomarkers and Surrogate Endpoints in Chronic Disease

Edited by Christine M. Micheel and John R. Ball

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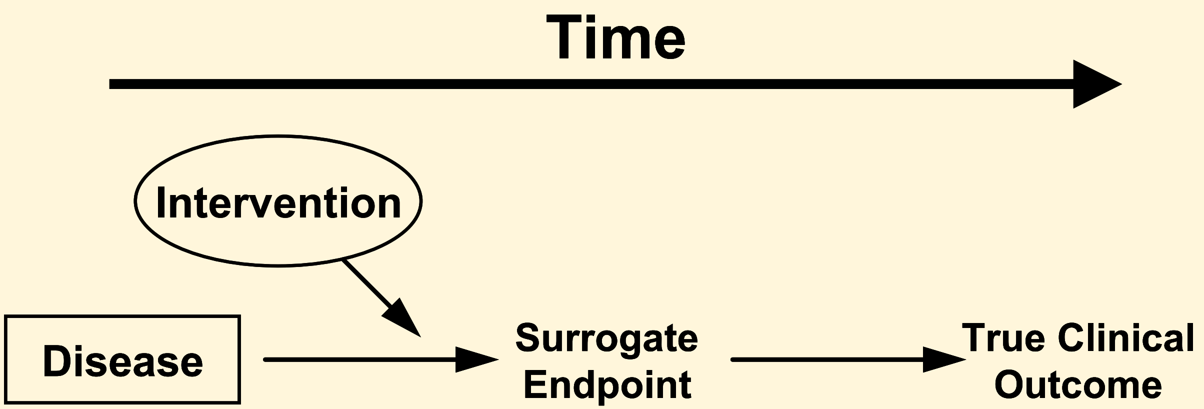
“Even in the best of circumstances, it is possible for surrogate endpoints to be misleading by either overestimating or underestimating an intervention’s effect on clinical outcomes.”



Fleming, T. R., and D. L. DeMets. 1996. Surrogate end points in clinical trials: Are we being misled? *Annals of Internal Medicine* 125(7):605–613.

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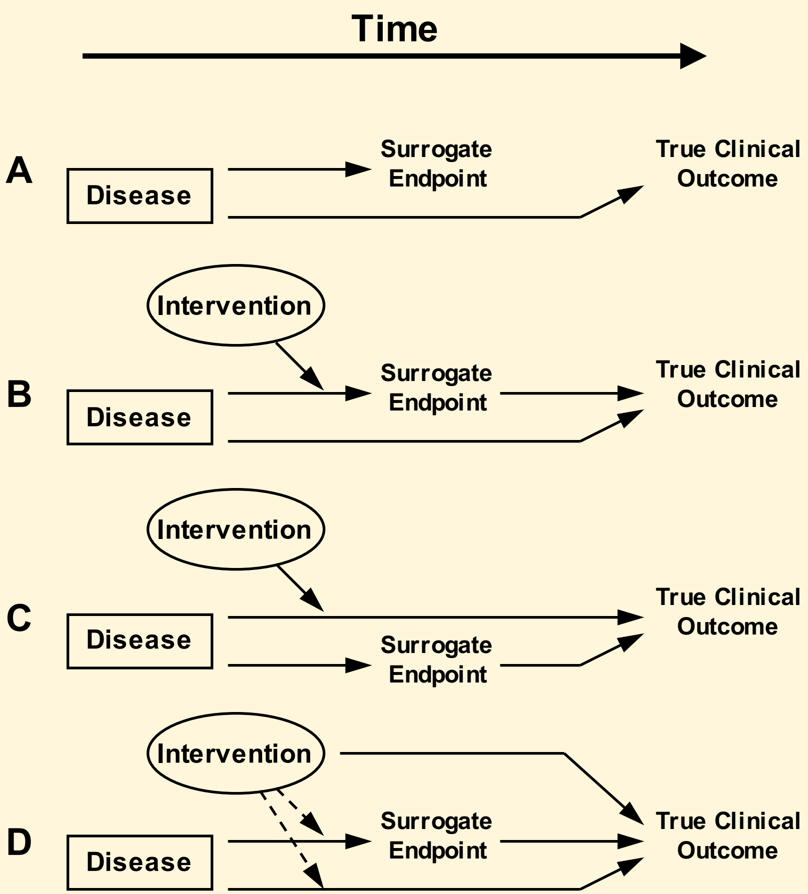
Failures of Surrogate Endpoints



Fleming, T. R., and D. L. DeMets. 1996. Surrogate end points in clinical trials: Are we being misled? *Annals of Internal Medicine* 125(7):605–613.

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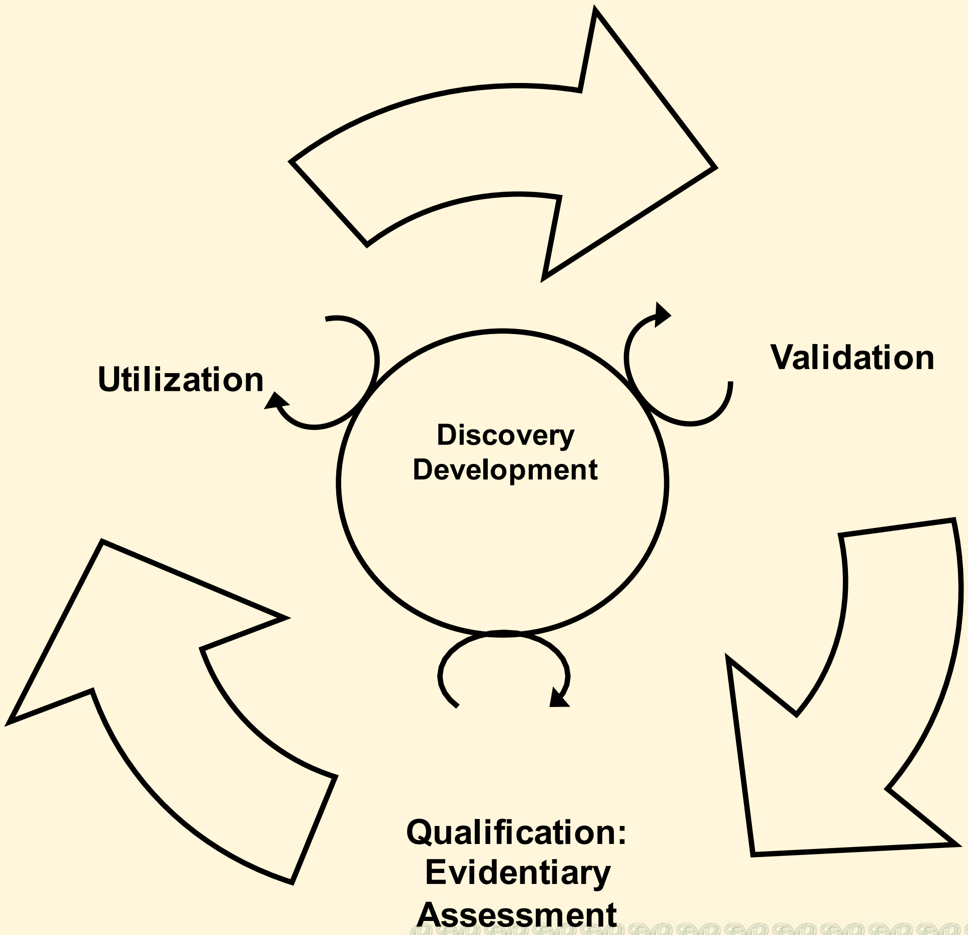
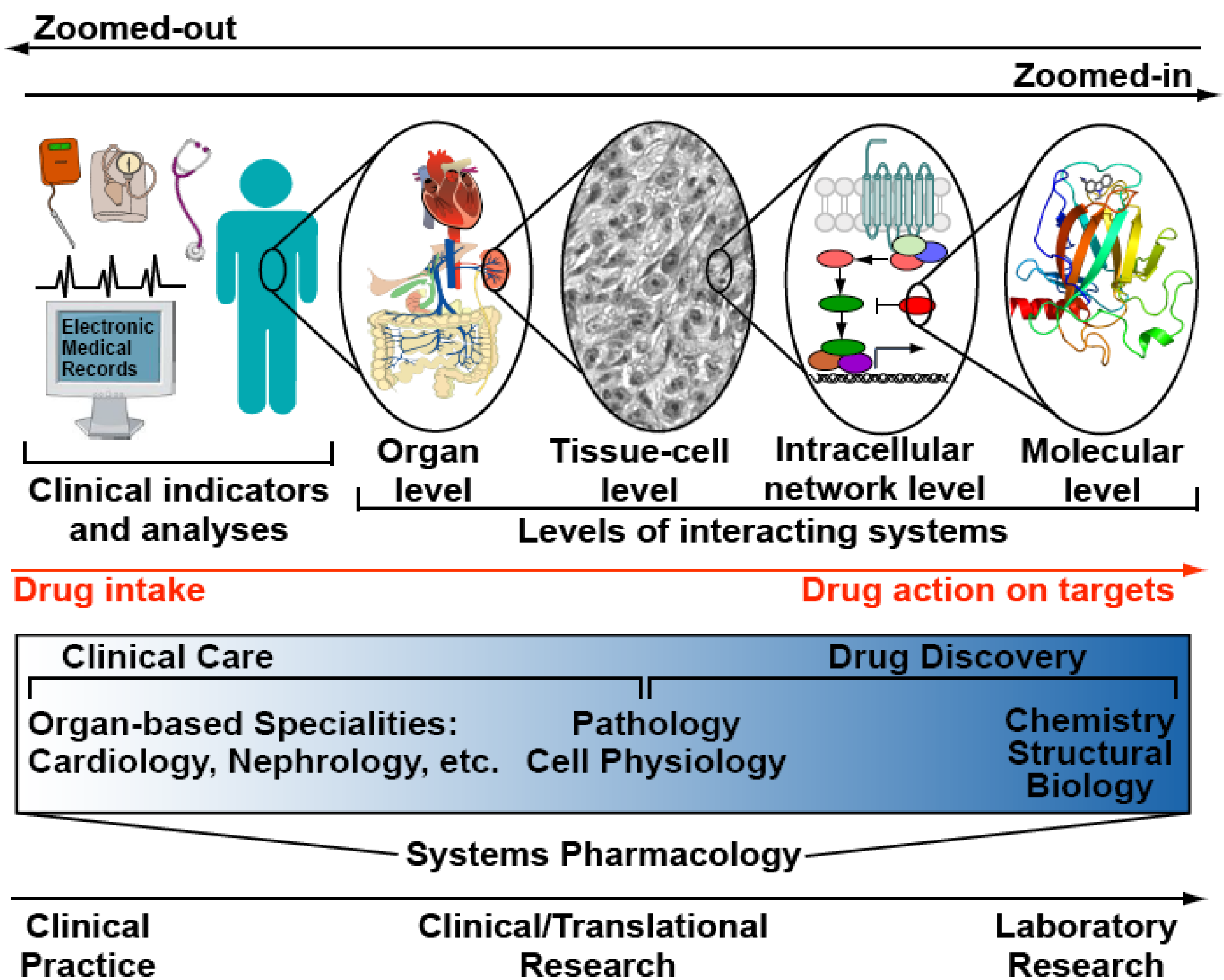
Biomarker Evaluation Framework



Why do we need Systems Biology to identify and predict Biomarker Sets?



Disease and drug action originate at the level of cellular components but physiological effects (e.g. symptoms, drug action) are at the organismal levels.

Unraveling such complexity requires a systems approaches

Iyengar, NYU 2009

Today's Agenda

- Glossary of terms
- Qualification or individual drug development program
- Strategies for improving data standardization and sharing
- Facilitating collaboration and cross-sector communication

Glossary of Terms

- FDA and NIH together recognized that people, including brilliant scientists, were using the same names for different things
- Then we tried to come up with common definitions and found that FDA and NIH had multiple definitions for the same terms
- These definitions have profound meaning for science, regulation, clinical medicine and business
- Sloppiness with terminology can lead to scientific and product development errors
- If FDA and NIH agree, and provide a publicly available, constantly updated source….

Pathways

- Biomarkers are as old as dirt
- And used in almost every successful (and unsuccessful) drug development program
- No qualification is needed for individual development programs or for "grandfathered" old stand-bys (LDL, SBP, CD4, etc)
- But a public Biomarker Qualification Program as currently available at FDA should stimulate both science and medical product development by making the relevant information publicly available

Data Standardization and Sharing

- When biomarkers are developed in individual medical product development programs, the information is often confidential till successful
- Biomarkers in academia are often presented in a limited manner for intellectual property or academic credit motivations
- There is concern about reproducibility
- The disaggregated and splintered science base may be hindering the field; can we change it?

Collaboration and Cross Sector Communication

- Multiple sources have developed a belief that consortia are needed because biomarkers are best developed by academia, industry and government working together
- The best approaches to successful consortia are evolving and there is risk in "group-think" if there is not some element of competition or "coopetition"
- How do we optimize the needed consortium behavior?

"I skate to where the puck is going to be, not to where it has been."

Wayne Gretsky

(the Puck Stops Here!)

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Session I: Developing a Standard Glossary of Terms in Biomarker Development

The Brookings Institution • Washington, DC

Tuesday, October 27th, 2015

Facilitating Biomarker Development: Strategies for Scientific Communication, Pathway Prioritization, Data-Sharing, and Stakeholder Collaboration

Developing a Standard Glossary of Terms in Biomarker Development

Presented by Lisa McShane on behalf of the NIH-FDA Biomarker Working Group

Center for Health Policy at Brookings
October 27, 2015

Why is a glossary needed?

Biomarker
Fit-for-purpose
Surrogate
Risk
Candidate surrogate
Clinical validation
Pharmacodynamic
Clinical validation
Qualification
Reasonably likely surrogate
Monitoring
Diagnostic
Biomarker
Endpoint
Biomarker
Monitoring
Predictive
Context of use
Surrogate
Diagnostic
Predictive
Accelerated approval
Intended use
Analytical validation
Candidate surrogate
Fit-for-purpose
Qualification
Prognostic
Safety
Prognostic
Reasonably likely surrogate
Pharmacodynamic
Context of use
Analytical validation
Intended use
Accelerated approval

Issues with Current Usage of Terms

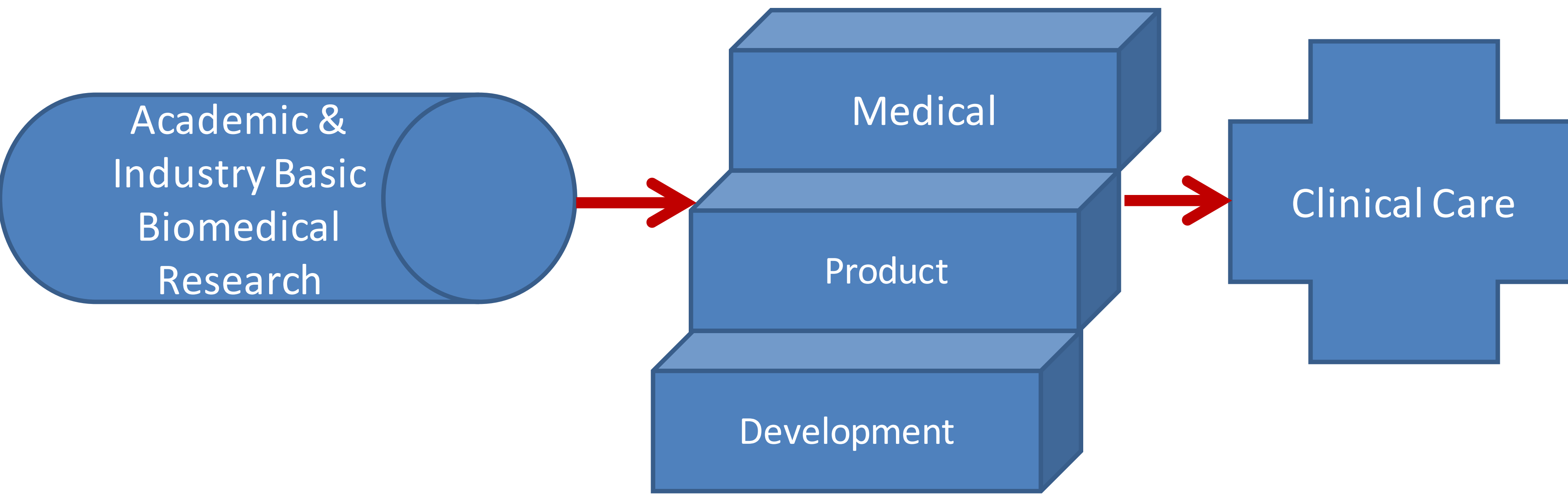
1. Unclear definitions
2. Inconsistent definitions
3. Misunderstanding of concepts
4. Situational nuances

Consequences of Non-harmonized Terminology

1. Interfere with effective communication
2. Misinterpretation of evidence
3. Misunderstanding of evidentiary requirements
4. Hinder efficient translation of promising discoveries to approved medical products

Goal

Create document that will serve as a public resource to clarify the terminology and uses of biomarkers and endpoints as they pertain to the progression from basic biomedical research to medical product development to clinical care



Defining a Term

General Approach

1. Identify existing definitions
2. Identify related terms and definitions
3. Propose a definition
4. Discuss and revise definition
5. Finalize definition

Example Term: Biomarker

Initial Definition

A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

Example Term: Biomarker

Discuss and Revise Definition

- July 17 (new proposed based on comments)
  - A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or ~~pharmacologic~~ therapeutic responses to a therapeutic intervention.
- July 17 (concerns with proposed edits and new proposed edits)
  - A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or ~~pharmacologic~~ therapeutic responses to a therapeutic intervention. A biomarker may be a molecular, histologic, radiographic…[insert others] characteristic.
- August 6 (following face to face meeting)
  - A characteristic that is used as an indicator of normal biological processes, pathogenic processes, or therapeutic responses to a therapeutic intervention. A biomarker may be a molecular, histologic, radiographic…[insert others] characteristic. A biomarker is not a direct assessment of how a patient feels, functions, or survives. Types of biomarkers include:
- August 14 (proposed edits)
  - A ~~characteristic~~ tool that assesses a defined characteristic that is used as an indicator of normal biological processes, pathogenic processes, or ~~therapeutic~~ response~~s~~ to an exposure or ~~therapeutic~~ intervention. A biomarker may be a molecular, histologic, radiographic~~…[insert others]~~ or physiologic characteristic. A biomarker is not an ~~direct~~ assessment of how a patient feels, functions, or survives. Types of biomarkers include:
- August 14 (following workgroup discussion)
  - A characteristic that is used as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. A biomarker may be a molecular, histologic, radiographic, or physiologic characteristic. A biomarker is not an assessment of how a patient feels, functions, or survives. Types of biomarkers include:
- August 26 (comment- I would go back to the earlier version that had more detail)
- October (a few more adjustments)

Example Term: Biomarker

Final Definition

A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are examples of biomarkers. A biomarker is not an assessment of how a patient feels, functions, or survives.

Terms for Today's Discussion

3 Biomarker Subtypes

1. **Susceptibility/Risk biomarker** - A biomarker that indicates the risk for developing a disease or sensitivity to an exposure in an individual without clinically apparent disease
2. **Prognostic biomarker** - A biomarker used to identify likelihood of a clinical event, disease recurrence or progression
3. **Predictive biomarker** - A biomarker used to identify individuals who are likely to experience a favorable or unfavorable effect from a specific intervention or exposure

Delineating Types of Biomarkers

Emergent guiding principles

1. **Flexibility to accommodate** new concepts, methodologies, technologies and regulatory domains
2. **Preserve distinctions** which are useful in achieving alignment with types of evidence and evidentiary standards
3. **Amenable to unification** across stakeholder communities

Delineating Types of Biomarkers

Emergent guiding principles

Flexibility to accommodate new research areas, methodologies, technologies and regulatory domains

Susceptibility/Risk biomarker - A biomarker that indicates the risk for developing a disease or sensitivity to an exposure in an individual without clinically apparent disease

- Disease vs. sensitivity to an exposure
- New methods to measure risk biomarkers and exposures (e.g., new assay methods, wearable monitors)

Delineating Types of Biomarkers

Emergent guiding principles

Preserve distinctions which are useful in achieving alignment with types of evidence and evidentiary standards

Susceptibility/Risk biomarker - A biomarker that indicates the risk for developing a disease or sensitivity to an exposure in an individual without clinically apparent disease

Prognostic biomarker - A biomarker used to identify likelihood of a clinical event, disease recurrence or progression

- No clinically apparent disease vs. greater focus on clinical setting
- Different study designs and expectations for accuracy and reliability of prediction

Delineating Types of Biomarkers

Emergent guiding principles

Amenable to unification across stakeholder communities

Predictive biomarker - A biomarker used to identify individuals who are likely to experience a favorable or unfavorable effect from a specific intervention or exposure

- Intervention vs. exposure
- Favorable vs. unfavorable (e.g., toxicity vs. benefit)
- May need subcategorization
  - Drug response
  - Comparative effectiveness
  - Enrichment criteria (e.g., using companion diagnostics)

Examples

Susceptibility/Risk biomarker

BRCA1/2 mutations used as a susceptibility/risk biomarkers when evaluating healthy women to assess breast cancer risk.

- A biomarker that indicates the risk for developing a disease or sensitivity to an exposure in an individual without clinically apparent disease

Prognostic biomarker

BRCA1/2 mutations used as prognostic biomarkers when evaluating women with breast cancer to assess likelihood of a 2nd breast cancer.

- A biomarker used to identify likelihood of a clinical event, disease recurrence, or progression

Predictive biomarker

BRCA1/2 mutations used as predictive biomarkers when evaluating women with ovarian cancer to assess the likelihood of response to PARP inhibitors.

- A biomarker used to identify individuals who are likely to experience a favorable or unfavorable effect from a specific intervention or exposure

Next Steps

1. Complete definitions
2. Add examples and explanatory text
3. Make accessible on NLM website
4. Continued maintenance and update of “living document”

Discussion Questions

1. What strategies can FDA and NIH pursue to encourage broad adoption of these definitions and ensure that they are
   a. Acceptable to the community
   b. Used widely in medical product development, biomedical research, and clinical care
2. Are there any major gaps in the glossary?
   a. Any important terms that have not been included that should be?
   b. Any medical product settings not adequately covered?
3. Other comments or suggestions?

Biomarker Working Group

Chairs: Robert Califf (FDA), Pamela McInnes (NIH), Michael Pacanowski (FDA)
Project Leads: Nina Hunter (FDA), Melissa Robb (FDA)
Participants:

FDA

- Shashi Amur
- Robert L. Becker
- Aloka Chakravarty
- David Cho
- Ilan Irony
- Chris Leptak
- Katie O'Callaghan
- Elektra Papadopoulos
- Hobart Rogers
- Robert Temple
- Sue Jane Wang

NIH

- Holli Hamilton
- Lisa McShane

Center for Health Policy at BROOKINGS

Session II: Qualification or Individual Drug Development Program? Determining the Appropriate Pathway for Biomarker Development and Regulatory Acceptance

The Brookings Institution • Washington, DC

Tuesday, October 27th, 2015

Defining the Pathways for Biomarker Development and Regulatory Acceptance

Chris Leptak, MD/PhD

OND Biomarker and Companion Diagnostics Lead

Co-Director, Biomarker Qualification Program

Office of New Drugs/CDER/FDA

Brookings Biomarker Meeting

October 27, 2015

Disclaimers

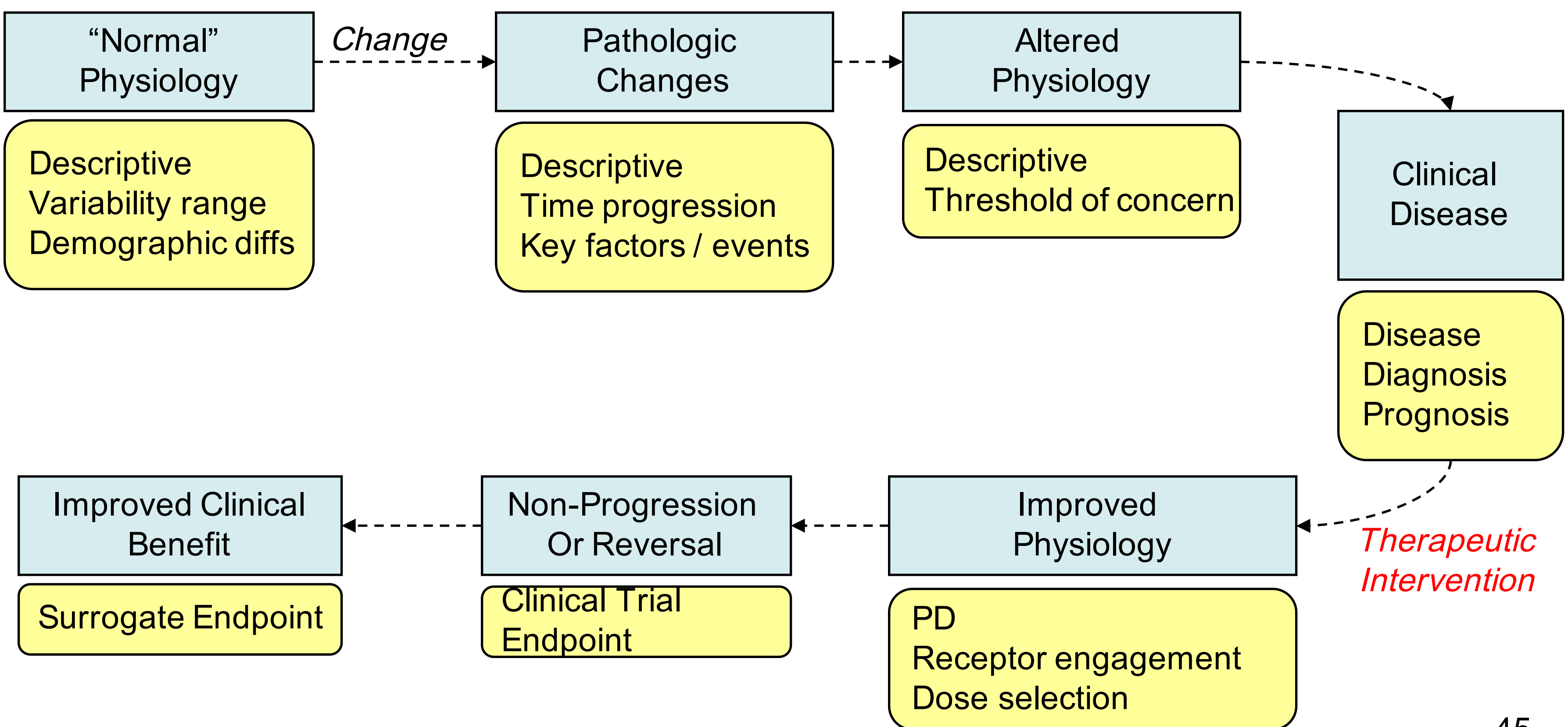
- Views expressed in this presentation are those of the speaker and do not necessarily represent an official FDA position

- I do not have any financial disclosures regarding pharmaceutical drug products

FDA Regulatory Approach to Biomarkers

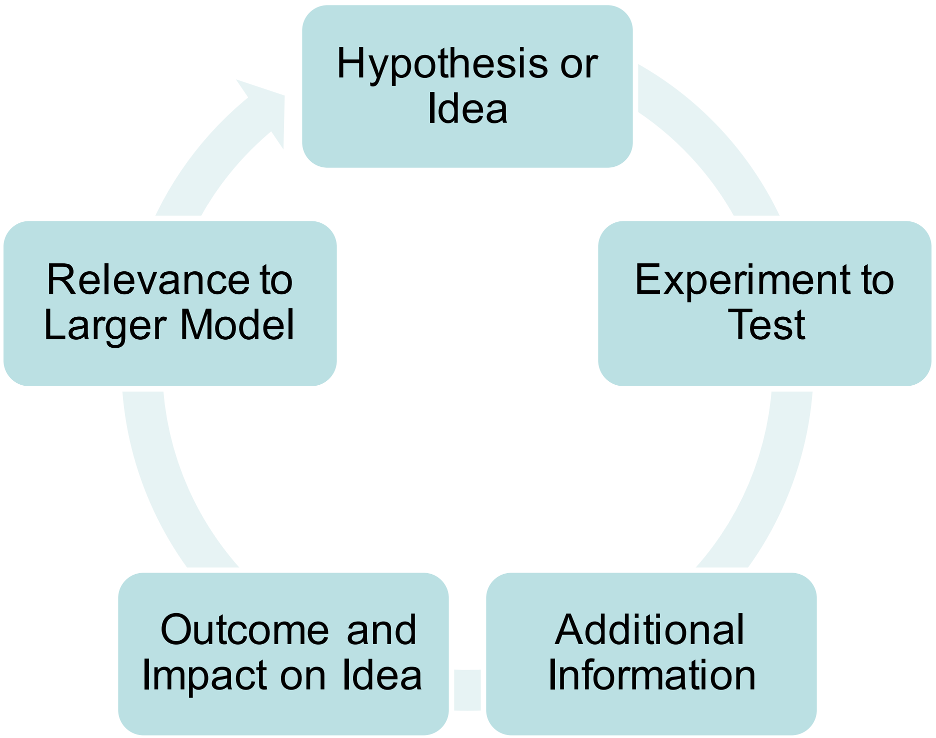
- Definition: a defined characteristic that is measured as an indicator or normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. (Current draft from FDA/NIH 2015 consensus working group)
- Characteristic is not a *clinical* assessment of a patient (contrasted with Clinical Outcome Assessments [COAs])
  - *Not* a measure of how a patient feels or functions or of survival
- Broadly defined (i.e, serum protein, change in tumor size by imaging study, algorithm for QT determination on ECG)
- Consistent with long-standing goals and drug development processes (i.e., data driven)
- Regulatory acceptance focuses on how biomarker is *used in drug development* (contrasted with clinical biomarkers used in doctor/patient treatment decisions or biomarkers as components in biological pathways in scientific research)

"Fit for Purpose": Match Biomarker to Goals, Data, and Likelihood of Causality



"Although it takes a village…

- Scientific understanding is not an isolated nor linear process. It involves integration of information from numerous, complex, and often times disorganized source materials. The process needs to be iterative, elastic, and flexible, requiring frequent reexamination, to be able to adapt and strive towards "truth", which itself is rarely static.



… There are Components of a Successful Biomarker Development Effort”

- Idea: What are the defined hypothesis and goal(s)?
- Data: What is the status of the scientific understanding of the topic? What data or stored samples exist? Do you have access?
- Resources: What resources (financial, staff, IT) are available for additional data collection and analysis? Expertise and resources to develop any necessary analytics? Are there applicable models/*in silico* options to use resources more efficiently?
- Opportunities for mitigating challenges: What are the obstacles hindering progress? Is there a willingness to share information publicly and to collaborate with other interested stakeholders?
- Opportunities for collaboration: Are there existing consortia, patient advocacy groups, or professional societies that can be engaged to assist?

Pathways for Regulatory Acceptance?

- **Community consensus**
- **Drug-specific**
- **Qualification**

Note: The pathways do not exist in isolation and many times parallel efforts are underway within or between pathways. All share common core concepts, are data-driven, and involve regulatory assessment and outcomes based on the available data.

Community Consensus Pathway

- Accumulation of scientific knowledge, experience, and understanding over extended period of time. Possible sources of information include the scientific and medical literature as well as professional society consensus statements or practice recommendations. Information may be used by FDA to inform content in guidance or for other regulatory decisions.
- **Pros**
  - Extensive knowledge base for Idea and hypothesis generation
  - Multitude of published studies
  - Cost-sharing and public approach (e.g., NIH grant funding to support research)
  - Opportunity for broad and multiple community inputs
- **Cons**
  - Much of the information is not reproducible, data is difficult to organize/compare/pool, and process is not defined
  - Different study designs, populations, and analytics limits conclusions that can be drawn (data/goal mismatch)
  - Protracted period of time
  - Many times do not have direct applicability to regulatory paradigms

Drug-Specific Pathway

- Development as part of a drug-specific program under IND/NDA/BLA
- **Pros**
  - Biomarker COU usually has well-defined purpose (limited scope)
  - Data (clinical trial information) available to the biomarker developer
  - Opportunities to bring in outside experts (for both FDA and company)
  - Company retains marketing advantage (real or perceived)
  - If the drug is approved, labeling and reviews made public (opportunities for others to use). May also inform recommendations to other companies working in the same area.
  - Can inform content in Indication-specific guidances
- **Cons**
  - Biomarker may not be generalizable to other drug classes or diseases
  - More limited opportunities for additional data sources
  - Company responsible for full development costs
  - May not have expertise for any analytical validation needs
  - More limited opportunities for engagement with other outside stakeholder groups

Qualification Pathway

- Development as part Biomarker Qualification Program (BQP)
- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284076.htm
- **Pros**
  - Biomarker COU usually more generalizable (drug classes, diseases)
  - Opportunities to pool resources and share costs
  - Opportunities to bring in outside experts (for both FDA and company)
  - Leverage outside stakeholder groups (e.g., patient advocacy, foundations)
  - Outcome results in a guidance (public availability for use)
- **Cons**
  - Data (clinical trial information) may not be available to the submitter
  - If part of a group effort (e.g., consortium), member's may have differing goals, level of commitment, and desire to share information
  - May take additional time to set up governance for group

What is Biomarker Qualification (BQ)?

- Qualification is a conclusion that within the stated Context of Use (COU), a medical product development tool (MPDT) can be relied upon to have a specific interpretation and application in medical product development and regulatory review.

- Once qualified, drug developers will be able to use the biomarker in the qualified context in IND and NDA/BLA submissions without requesting that the relevant CDER review group reconsider and reconfirm the suitability of the biomarker.

Context of Use (COU)

- Short-hand term for a statement that fully and clearly describes the way the medical product development tool (MPDT) is to be used and the medical product development-related purpose of the use.
- May include:
  - Range of animal species (nonclinical)
  - Range of clinical disorders
  - Range of drug classes
  - Procedures and criteria for how samples are obtained
  - How the results are interpreted
    - Limitations on the interpretation
- Defines boundaries of known reliability
- Potential of expansion of context of use with additional studies/data supporting future qualifications
- **Note: COU drives what levels of evidence are needed**

Potential BQ Submitters

- Consortium of industry stakeholders
  - Use and share data in a pre-competitive environment (cost-effective, win-win approach)
  - Broad acceptance of biomarker context of use in multiple different drug programs
- Consortium of academic investigators
  - Potential translational application of basic science knowledge to clinical utility

Note: Importance and influence of professional societies and patient advocacy groups

Key Messages

- Biomarkers have been used by FDA for decades to aid in the drug development process
- Ideally, biomarker development, regardless of pathway, uses the same terminology, similar types of contexts of use (COU), analogous evidence to support those uses, and opportunities for engagement of external experts
- “Consultation/Advice” and “Review” are core concepts for all of the pathways
- From an FDA perspective, one pathway is not preferred over another, and since voluntary on the part of the biomarker developer, all of the pathways can be considered
- Part of the decision of which pathway depends upon the developer’s answers to the core questions common to any biomarker development effort
- Characteristics of a biomarker and its COU can affect the choice of pathways for regulatory acceptance
- Because stakeholder communities (regulatory, clinical, and scientific) many times have differing goals/needs, a biomarker’s “acceptance” may not be universal

Case Study Examples: Biomarker Development Pathways

- Total Kidney Volume (TKV) as a prognostic marker for Polycystic Kidney Diease (Qualification)
- EGFR status as a predictive marker for EGFR-targeted therapy in lung cancer (Drug-specific development)

Case Study I: Total Kidney Volume as a Prognostic Biomarker for Polycystic Kidney Disease

Presenters: John Lawrence and Aliza Thompson
Contributors: Steve Broadbent and Ron Perrone

Outline

- Disease Background and Drug Development Perspective
- What the Polycystic Kidney Disease Consortium Did to Support the Qualification of Total Kidney Volume (TKV) as a Prognostic Biomarker
- What FDA Did to Determine the Utility of TKV as a Prognostic Biomarker
- Lessons Learned

Disease Background

- ADPKD, the most common hereditary kidney disease, is characterized by progressive enlargement of the kidneys due to cyst growth and formation.
- Serious manifestations of the disease include the loss or renal function, leading to renal failure in some patients (typically in the late 50’s).
- The loss of renal function occurs over many decades and is preceded by enlargement of the kidneys.
- There are no approved treatments for the disease in the U.S.

Drug Development Perspective

- There is significant interest in developing therapies to treat early stages of ADPKD.
- This has led to interest in the development of biomarkers that can be used in drug development:
  - to identify patients with ADPKD who are more likely to experience progressive disease
  - as a surrogate endpoint for clinical outcomes
- To date, for obvious reasons, Total Kidney Volume has been the lead candidate.

TKV as a prognostic biomarker: Polycystic Kidney Disease Outcomes Consortium Approach

(Joint FDA-EMA submission)

Develop standard common PKD terminology data elements (Clinical data interchange standards consortium (CDISC) data standards for ADPKD to allow for the mapping and pooling of available data into a common database)

↓

Create new database of aggregated data from 3 patient registries and 2 longitudinal cohort studies (N= 2355 with available TKV imaging data)

↓

Develop disease progression model

↓

Submit qualification package to FDA

Slide Courtesy of Shashi Amur

Creation of ADPKD-Specific Data Standard

- 5 sets of case report forms (Emory, University of Colorado, Mayo, CRISP, HALT)
- More than 1200 individual data elements
- 3 face-to-face meetings, multiple conference calls
- Full-time coordinator
- Required approximately one year prior to submission for public (global) comment
- Another 8+ months to complete mapping and data transfer to central database
- Context: Small group of collaborative investigators working in a focused field

Slide Courtesy of Ron Perrone

What the FDA did

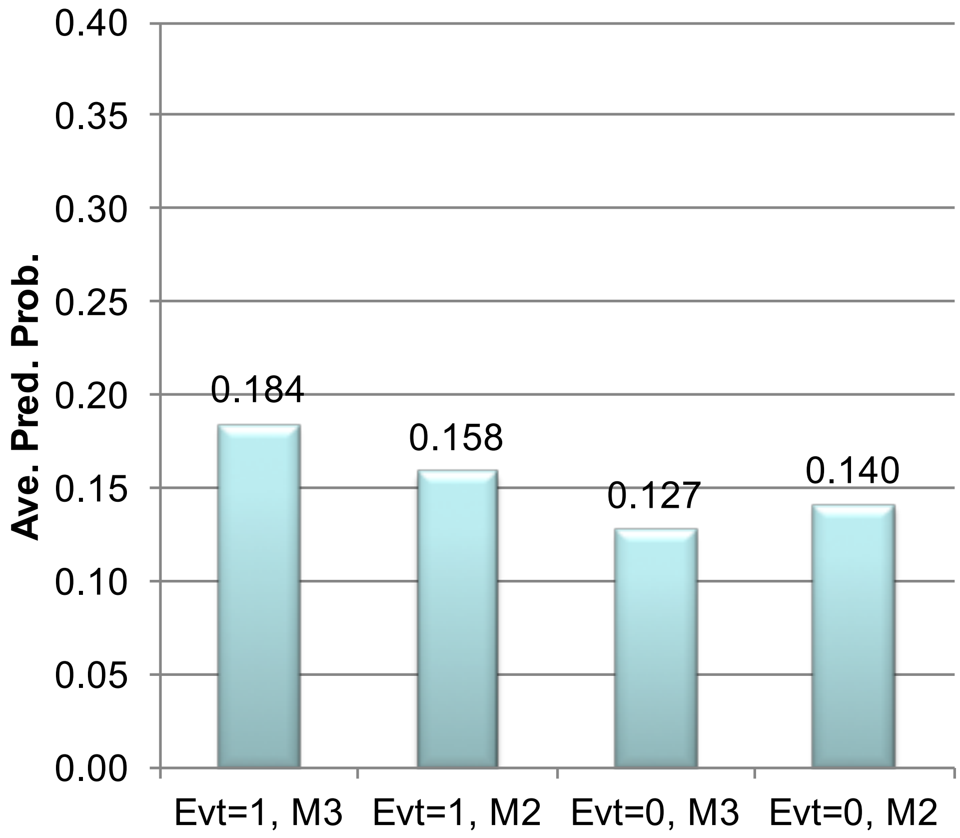
The Biomarker Qualification Review Team conducted additional analyses and performed model development and cross validation.

- Instead of using the entire dataset, FDA limited its analyses to patients at least 12 years of age with an estimated glomerular filtration rate ≥25, which, according to the submitter, represented the population likely to be enrolled in clinical trials.
- The FDA used clinical trial data that were available internally to FDA for independent validation.

What the FDA Did

- Determined best fit models with and without TKV
  - Cross-validation
  - External validation using a separate dataset
- Assessed improvement in model fit and model discrimination
- Evaluated the potential utility of using TKV for trial enrichment

Model Discrimination



Average predicted probability by event status for Model-2 and Model-3 at year-3

- M2: the FDA best fit model without baseline TKV
- M3: the FDA best fit model with baseline TKV
- Evt=1 (ADPKD subjects having a confirmed 30% decline in eGFR)
- Evt=0 (ADPKD subjects not having a confirmed 30% decline in eGFR)

From Executive Summary; Analysis by Sue-Jane Wang

The Value of Enrichment

Predicted event rate in placebo arm over 3 years, number needed to enroll and number needed to treat to get one event using the best fit models with and without TKV.

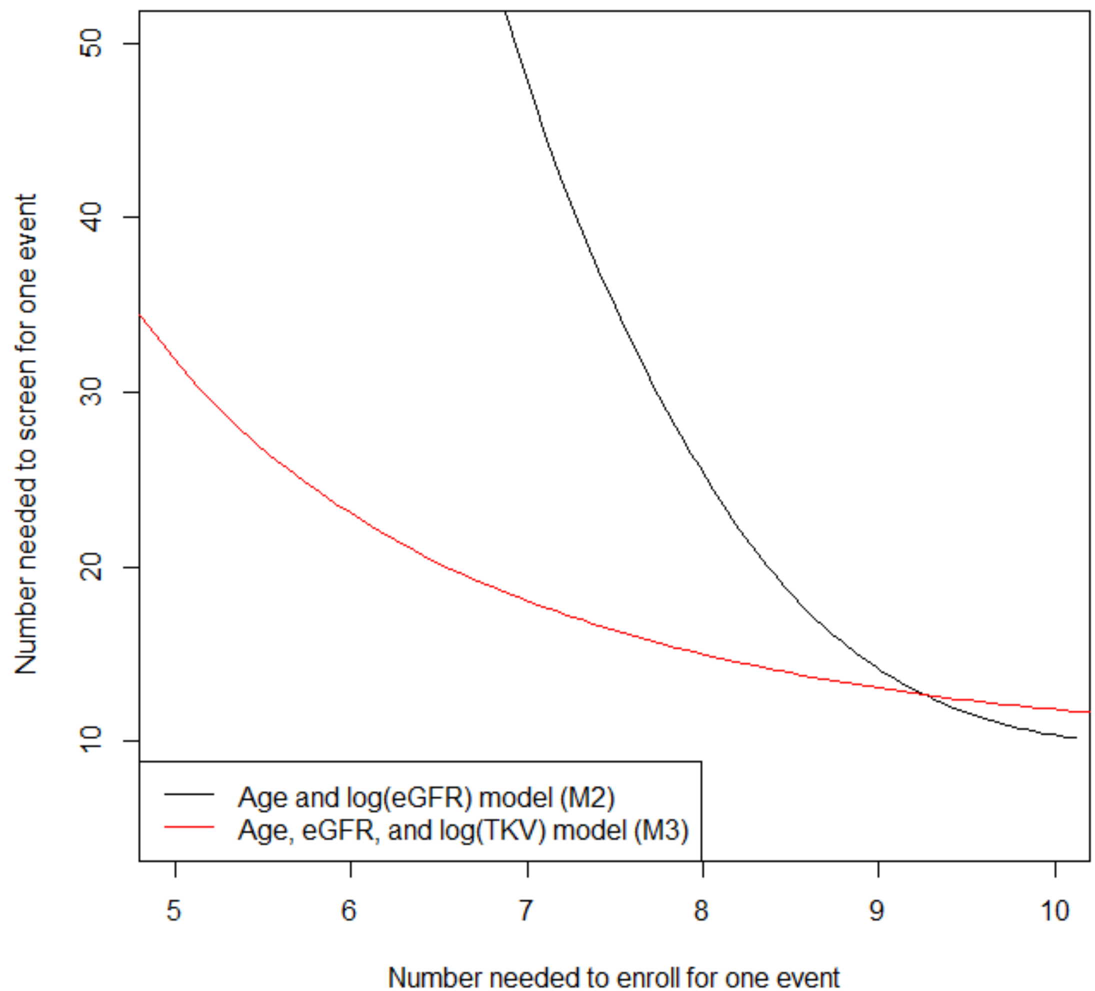
	Model without TKV	Model with TKV, using added criterion of TKV > 1 L
Predicted event rate in placebo arm over 3 years	0.0905	0.110
Number needed to enroll†	11.05	9.09
Number needed to screen	13.01	24.5

Assumes entry criteria of eGFR > 50 mL/min per 1.73 m^2 and age between 20 and 50 years.

From Executive Summary; Analysis by John Lawrence

The Value of Enrichment

The number needed to enroll for one event vs. the number needed to screen using the risk scores from the two models to select patients.



From Executive Summary; Analysis by John Lawrence

Qualification of Biomarker—Total Kidney Volume in Studies for Treatment of Autosomal Dominant Polycystic Kidney Disease

Draft Guidance for Industry

Use Statement:

TKV, measured at baseline, is qualified as a prognostic enrichment biomarker to select patients with ADPKD at high risk for a progressive decline in renal function (defined as a confirmed 30% decline in the patient's eGFR) for inclusion in interventional clinical trials. This biomarker may be used in combination with the patient's age and baseline eGFR as an enrichment factor in these trials.

Lessons Learned- A Regulatory Perspective

- TKV has been used for some time as a prognostic biomarker in individual drug development programs; perhaps the greatest benefit of the effort was that it quantified the amount of information that "was added" by using TKV to enrich the trial population.
- Registry data can be critical for establishing the value of a biomarker as a tool in drug development but there are challenges associated with using and interpreting registry data.

Lessons Learned- A Regulatory Perspective

- Biomarker qualification packages are based on the totality of data available to the submitter; however sometimes FDA has access to other large datasets (i.e., data from drug development programs) that speak to the utility of a biomarker.

It is unclear when and how we should use these sources of information to confirm the utility of a biomarker for a proposed context of use.

A Closing Comment

- A quantitative model describing how a biomarker and other factors influence the outcome of interest is, in general, of great value, and can be a key output of the biomarker qualification process.
- The model should incorporate uncertainties in the parameters of the model and in the resulting predictions.
- The model output should have direct applicability to the intended use (e.g., for a biomarker prognostic for clinical events, outputs should inform the numbers needed to screen and to enroll in order to achieve a single outcome event).

We endeavored to do this in the TKV qualification.

Participants

- *CDISC:* B Kisler, C Tolk, S Kopko
- *C-Path:* S Broadbent, J Neville, E Dennis, B Leroy, G Lundstrom, B Stafford, K Romero
- *Pharsight:* JF Marier, S Moukassi
- *PKD Foundation:* L Rome, J Panetta
- *NIH:* R Star, M Flessner
- *Mayo:* V Torres, M Irazabal
- *Emory:* A Chapman
- *U Colorado:* B Gitomer
- *Tufts:* J Castedo, D Miskulin, R Perrone
- *CRISP DCC:* J Bost, T Bae, D Landsittel
- *Pharma:* Amgen, Genzyme, Novartis, Otsuka, Pfizer, Roche
- *FDA:* S Amur, J Lawrence, S-J Wang, J Hung, S Pendse, N Xu, A Thompson, N Stockbridge, D Marathe, J Florian, M Sahre, H Rogers, M Noone, D Krainak, J Delfino

Thanks.

EGFR mutation status as a predictive marker for EGFR-targeted therapy in non-small cell lung cancer (NSCLC)

Sean Khozin, MD, MPH
Senior Medical Officer
Office of Hematology and Oncology Products (OHOP)
Food and Drug Administration (FDA)

Lung cancer is the leading cause of cancer deaths worldwide

- 2015 estimates (US):
  - 221,200 new cases
  - 158,040 deaths
- ~ 85% NSCLC
- Most patients present with advanced stage at the time of diagnosis
- Median overall survival (OS) with supportive care is 3 to 6 months
- Standard chemotherapy has overall response rate (ORR) of ~ 30% and median OS of ~10 months

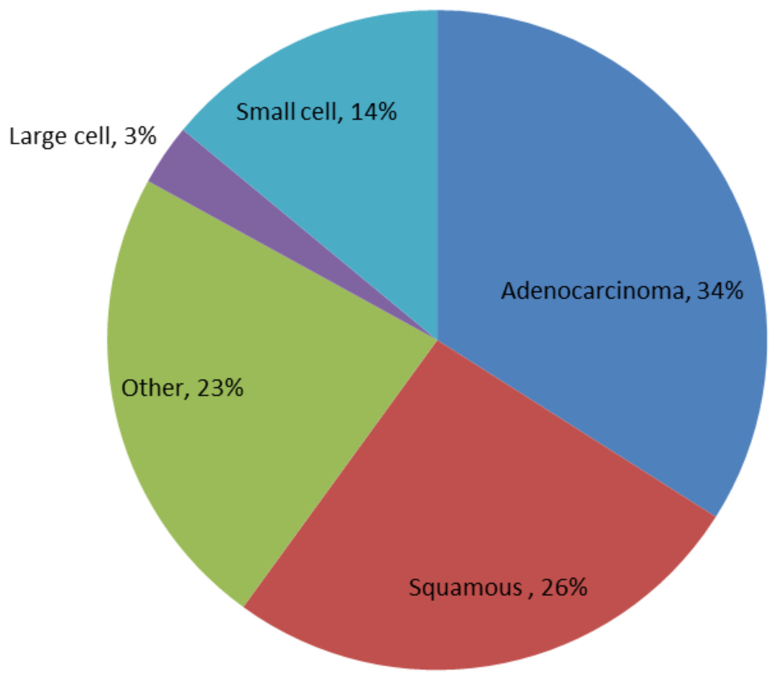
Siegel, et al. CA Cancer J Clin. 2015:65(1):5-29.
Marino P, et al. Chest 106(3):861-865.
Kelly K, et al. JCO 19(13):3210-3218.
Scagliotti GV, et al. JCO 20(21):4285-4291.
Fossella F, et al. JCO: 21(16):3016-3024.

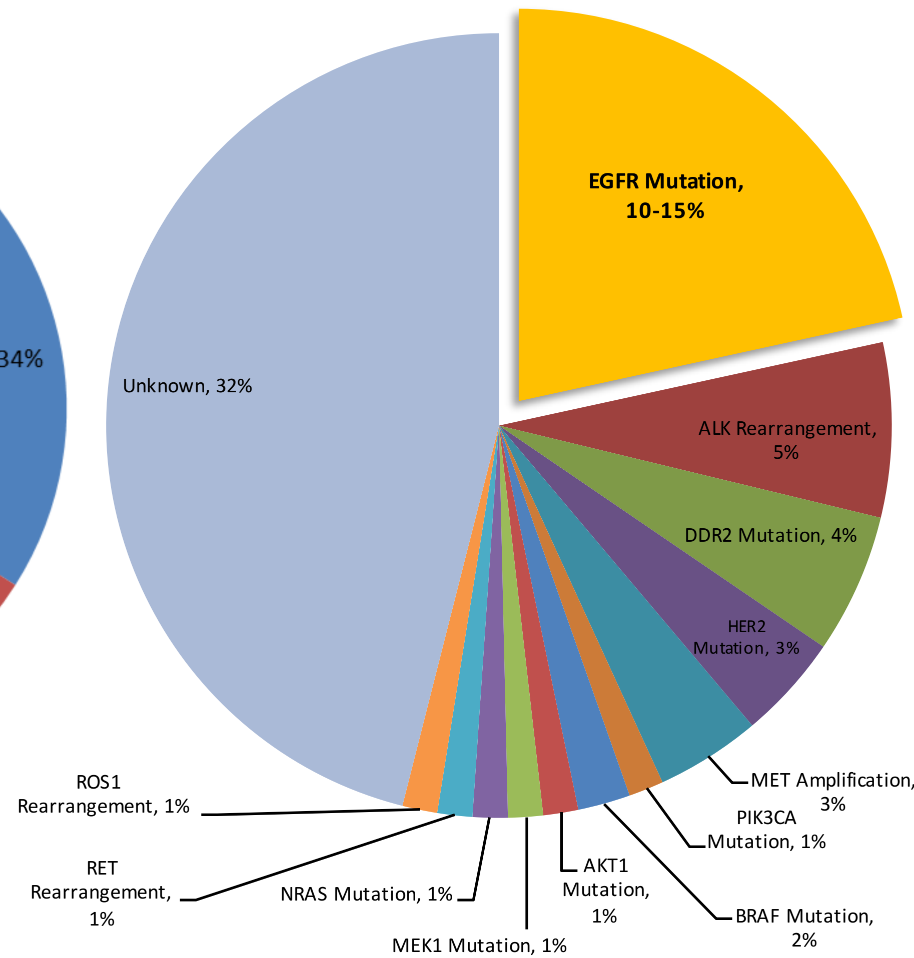
Shifting paradigm in lung cancer treatment

Traditional: Based on histology

Molecular: Based on genomic profile

Chemotherapy





"Targeted" therapy

EGFR as a predictive biomarker in NSCLC: early evidence

- May 5, 2003, gefitinib received accelerated approval based on an ORR of 10.6% with a median DOR of 7 months in the third-line treatment of NSCLC
  - Antiproliferative effects against the growth of the A431 tumor cells with high levels of expression of EGFR
- Failed confirmatory trial: 1,692 NSCLC patients after one or two prior regimens randomized to gefitinib vs placebo
  - No OS benefit in overall population or EGFR expression positive patients
  - Label revised to restrict use to patients under treatment and benefiting

Ciardiello F, et al. Clin. Cancer Res., 6:2053-2063, 2000.
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm163112.htm

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

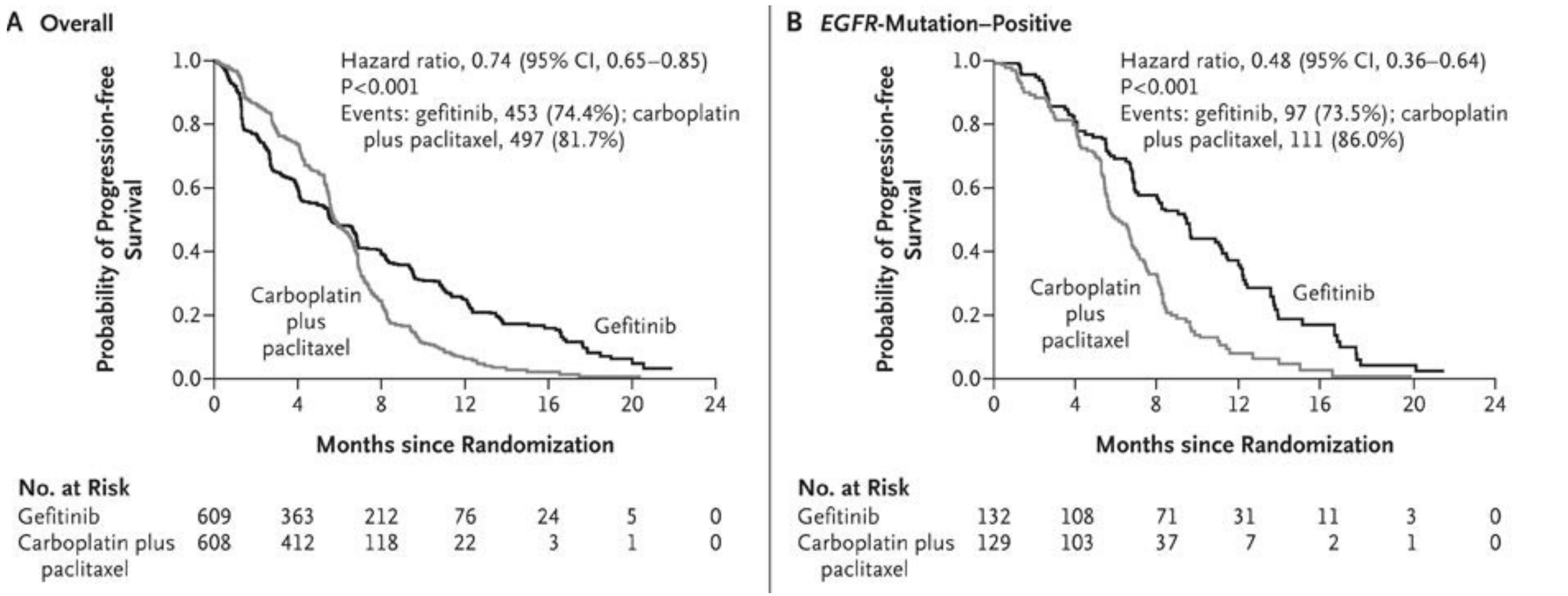
Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

"Somatic mutations were identified in the tyrosine kinase domain of the EGFR gene in eight of nine patients with gefitinib-responsive lung cancer, as compared with none of the seven patients with no response"

Association with adenocarcinoma histology, Asian ethnicity, female sex, and never-smoker status

Iressa Pan-Asia Study (IPASS) trial

1,217 patients in East Asia (never smokers and light ex-smokers) were randomly assigned (1:1) to receive gefitinib or carboplatin plus paclitaxel



- EGFR mutation data for 437 (36%) patients
- 261 (60%) were positive for a mutation

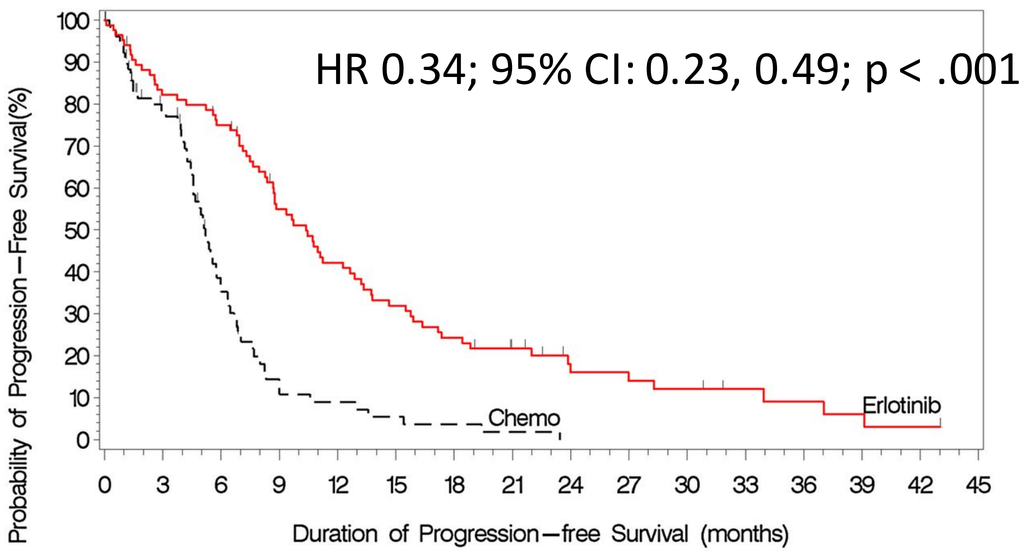
Mok TS, et al. N Engl J Med 2009;361:947-957

- Subsequent trials conducted in Japan and China, prospectively selecting for EGFR mutations, showed results similar to IPASS

- The European Tarceva versus Chemotherapy (EURTAC) built on these experiences to test the hypothesis that the presence of EGFR mutations can predict a superior response, as compared with standard chemotherapy (n=174)

Fukuoka M, et al. J Clin Oncol 2011;29:2866-2874
Mitsudomi T, et al. Lancet Oncol 2010;11:121-128.
Maemondo M, et al. N Engl J Med 2010;362:2380-2388.

EURTAC: results



Chemo	88	53	22	8	5	3	2	1	0	0	0	0	0	0	0	0
Erlotinib	86	69	62	43	33	25	19	14	8	7	6	4	3	2	1	0

- PFS 10.4 months with erlotinib vs 5.2 months with chemo
- ORR 65% vs 16%
- Patients tested for EGFR mutation by laboratory developed test (LDT)
- Approved concurrently with Cobas® EGFR Mutation Test
    - Analytical validation
    - Bridging study

Khozin S, et al. The Oncologist 2014;19:774-779

Cobas analytical validation

1,276 patients screened by LDTs

1,044 patients had tumor specimens available for determination of mutation status

- 225 patients (22%) were EGFR positive by LDT

487 tumor specimens tested in a blinded fashion with both cobas® and Sanger sequencing

444 specimens with valid cobas test results tested with massively parallel sequencing (MPS)

~400 had valid results by both cobas and MPS

Analytical accuracy of cobas® compared with each reference method by estimating:

- Positive percentage agreement (PPA)
- Negative percentage agreement (NPA)
- Overall percentage agreement (OPA)

cobas® EGFR Mutation Test vs. Sanger Sequencing Using Phase 3 Specimens

cobas® EGFR Mutation Result	Sanger Sequencing Result								
	Result in aggregate			Exon 19 deletion			Exon 21 Mutation		
	MD	MND	Total	MD	MND	Total	MD	MND	Total
MD	112	34	146	71	25	96	41	9	50
MND	4	256	260	2	308	310	2	354	356
Total	116	290	406	73	333	406	43	363	406
PPA (95% CI)	112/116 = 96.6% (91.5%, 98.7%)			71/73 = 97.3% (90.5%, 99.2%)			41/43 = 95.3% (84.5%, 98.7%)		
NPA (95% CI)	256/290 = 88.3% (84.1%, 91.5%)			308/333 = 92.5% (89.2%, 94.9%)			354/363 = 97.5% (95.4%, 98.7%)		
OPA (95% CI)	368/406 = 90.6% (87.4%, 93.1%)			379/406 = 93.3% (90.5%, 95.4%)			395/406 = 97.3% (95.2%, 98.5%)		

cobas® EGFR Mutation Test vs. MPS Sequencing Using Phase 3 Specimens

cobas® EGFR Mutation Result	MPS Result								
	Result in aggregate			Exon 19 deletion			Exon 21 Mutation		
	MD	MND	Total	MD	MND	Total	MD	MND	Total
MD	142	6	148	94	1	95	48	5	53
MND	9	251	260	4	309	313	5	350	355
Total	151	257	408	98	310	408	53	355	408
PPA (95% CI)	142/151 = 94.0% (89.1%, 96.8%)			94/98 = 95.9% (90.0%, 98.4%)			48/53 = 90.6% (79.7%, 95.9%)		
NPA (95% CI)	251/257 = 97.7% (95.0%, 98.9%)			309/310 = 99.7% (98.2%, 99.9%)			350/355 = 98.6% (96.7%, 99.4%)		
OPA (95% CI)	393/408 = 96.3% (94.0%, 97.8%)			403/408 = 98.8% (97.2%, 99.5%)			398/408 = 97.5% (95.5%, 98.7%)		

MD denotes Mutation Detected

MND denotes Mutation Not Detected

First-line treatment of patients with metastatic NSCLC with EGFR mutations

[exon 19 deletions or exon 21 (L858R) substitution mutations]

- **May 14, 2013: Erlotinib (n=174, 1:1 randomization in EURTAC)**
  - PFS 10.4 vs 5.2 (chemo) months [HR 0.34 (95% CI: 0.23, 0.49), p <0.001]
  - *Cobas® EGFR Mutation Test*
    - *Bridging study with tumor tissue from 134 patients assessing the concordance of cobas to LDT*
- **July 12, 2013: Afatinib (n=345; 2:1 randomization)**
  - PFS 11.1 vs 6.9 (chemo) months [HR 0.58 (95% CI: 0.43, 0.78), p <0.001]
  - *Therascreen® EGFR PCR Kit*
    - *Bridging study with tumor tissue from 264 patients assessing concordance of Therascreen to LDT*
- **July 13, 2015: Gefitinib**
  - Single arm trial n=106
    - ORR 50% (95% CI: 41, 59); DOR 6.0 months (95% CI 5.6, 11.1)
    - *Therascreen® EGFR PCR Kit*
      - *Bridging study with tumor tissue from 87 patients assessing concordance of Therascreen to LDT*
  - Subset analysis of 186 of 1217 EGFR+ patients (15%) by LDT in IPASS
    - PFS 10.9 months vs 7.4 months (chemo) HR 0.54 (95% CI: 0.38, 0.79)

Afatinib label: uncommon mutations

Table 4 Objective Tumor Responses in GILOTRIF-Treated Patients Based on Investigator Assessment in the "Other" (Uncommon) EGFR Mutation Subgroup

EGFR Mutations	Number of GILOTRIF-Treated Patients	Number of Patients with Partial Responses	Duration of Response
L858R and T790M	5	1	6.9 months
L858R and S768I	2	1	12.4+ months
S768I	1	1	16.5+ months
G719X	3	1	9.6 months

+ Censored observation

Summary

2003 — Gefitinib approved for previously treated NSCLC based on ORR 10% of long duration in single arm trial

2004 — EGFR mutations found to be predictive and associated with unique clinical features

2005 — Gefitinib label revised with restrictions

2009 — Gefitinib showed benefit in clinically enriched patients (Asian light ex/never smokers)

2010 — Role of EGFR mutations further defined. Prospective selection in randomized trials in Japan and China

2014 — Erlotinib and afatinib approved concurrently with CoDx assays for first-line treatment of EGFR+ NSCLC

2015 — Gefitinib approved for EGFR positive NSCLC patients

Thank You

http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm459727.htm

Center for Health Policy at BROOKINGS

Session II: Qualification or Individual Drug Development Program? Determining the Appropriate Pathway for Biomarker Development and Regulatory Acceptance

The Brookings Institution • Washington, DC

Tuesday, October 27th, 2015

TKV Qualification

- Why Qualification?
  - Spur development of new therapies in a therapeutic area without any approved drugs
  - Share costs and risk of developing evidence to support clinical use
  - Access to more data
  - First step on the path to a much needed surrogate endpoint
  - Move the science further for all, including FDA
  - Approved once and for all (within context of use) not just for one drug trial
  - Helpful to smaller companies who can’t go it alone
- Strongly supported by companies with drug in progress to spur better understanding of science, quantify value

TKV Qualification Key Points

- How will this be used, what decisions will be made?
  - Developing appropriate Context of Use is key
  - Surrogate endpoint has a very high bar
- Data standardization and aggregation
- How is the new biomarker better than current standard?
- Assay validation considerations
- Working with EMA – similarities and differences
- What statistical methods will be used?

Take away points- Ron Perrone

- Data Standards key
- Retrospective mapping of data standards is time consuming
- Ideally, data standards should be developed prospectively
- Standards should map to SDTM for regulatory analysis and/or submission
- Work with organizations like C-Path for optimal efficiency
- Data Standards facilitate collaborations and aggregation of data

Facilitating Biomarker Development and Qualification: Strategies for Prioritization, Data-Sharing, and Stakeholder Collaboration

Embassy Suites-Convention Center, Washington, DC
October 27, 2015

Session II: Qualification or Individual Drug Development Program? Determining the Appropriate Pathway for Biomarker Development and Regulatory Acceptance

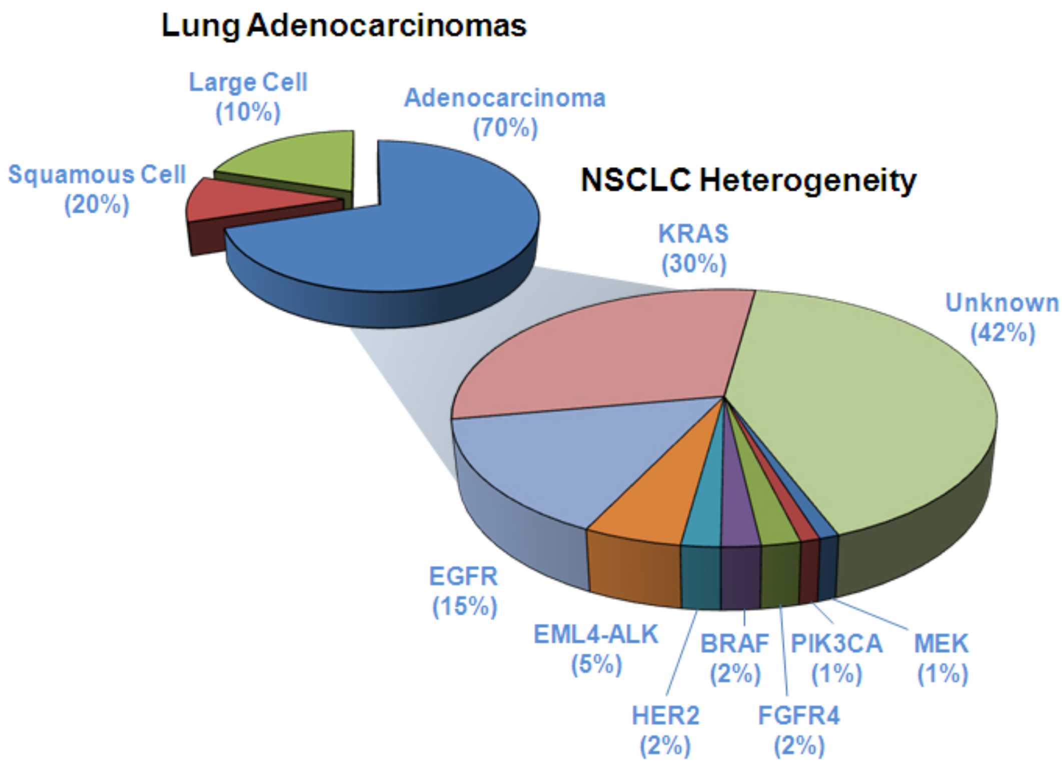
Gary J. Kelloff, MD

National Cancer Institute

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

FNIH	• Nonprofit Convener and Partnership Builder
Diagnostics/ Devices Industry	• Companion Diagnostics • Imaging-based Biomarkers • Improved Business Models
Pharma	• More Efficient Drug Development and Approval Path • Better Early Response Criteria
FDA	• Provides for Evidence-Based Regulatory Policy
Academia, NCI	• Better Clinical Data • More Effective Treatment/Management
Patients	• Opportunity to Drive Path to Personalized Treatment • Potentially More Effective Treatment/Management
Non-Profit Foundations	• Education, Advocacy, Specific Issues, Funding Source
CMS, Payers	• Helps Define Reasonableness and Need

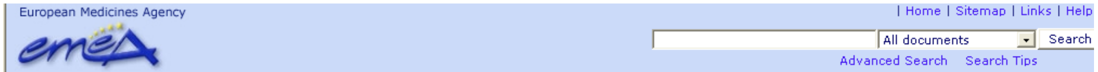
Genomic Heterogeneity in NSCLC



FDG-PET Utility Claims

- FDG-PET/CT scans are sensitive and specific for detection of FDG-avid malignant tumors.
- FDGPET scans reliably reflect glucose metabolic activity of cancer cells and can be measured quantitatively and with high reproducibility over time.
- Quantitative longitudinal or serial changes in tumor FDG activity during therapy predict clinical outcomes [*e.g.*, overall survival (OS), progression-free survival (PFS), *etc*.] earlier than changes in standard anatomic measurements.
- Therefore, tumor response or progression as determined by tumor FDG activity will be able to serve as an endpoint in well-controlled phase 2 and 3 efficacy studies of cytotoxic and targeted therapies in FDG-avid tumors in both primary lesions and metastatic disease.
- In tumor/drug settings where phase 2 trials have shown a statistically significant relationship between FDG-PET response and an independent measure of outcome, changes in tumor FDG activity can then serve as the primary endpoint for regulatory drug approval in registration trials.

EMA & FDA - 2008
Favorable Review Decisions

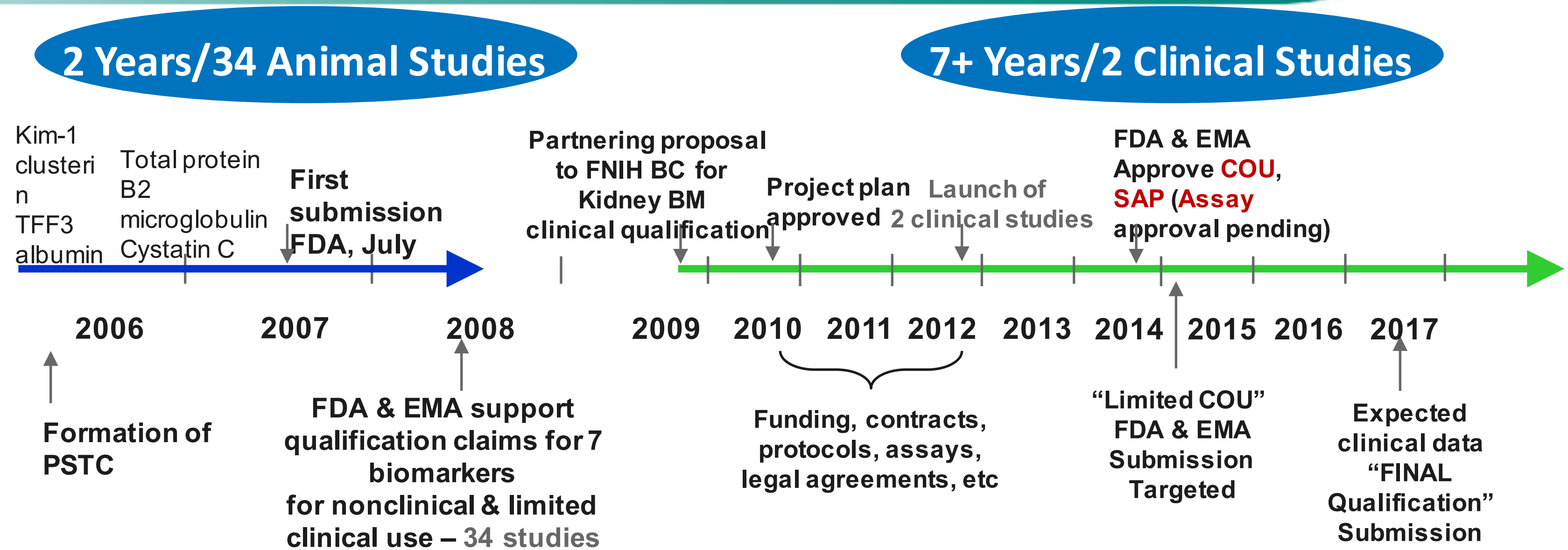


Following assessment, both regulatory agencies came to the conclusions that:

- the renal biomarkers submitted ***were acceptable in the context of non-clinical drug development*** for detection of acute drug-induced renal toxicity;
- the renal biomarkers provide additional and complementary information to the currently available standards;
- ***the use of renal biomarkers in clinical trials is to be considered on a case-by-case basis*** in order to gather further data to qualify their usefulness in monitoring drug-induced renal toxicity in man.

Be well

Translational Kidney Safety Biomarkers: Regulatory Qualification Timelines & Value Proposition



Summary of hypothetical but reasonable examples of drug development scenarios that support the patient health, scientific and business case for qualifying new translational safety biomarkers. [Sistare, Frank D and DeGeorge Joseph J, Biomarkers Med 2011 5(4) 497-514]

Phase of Development	Example	Summary Description	Estimated Benefit from Deploying New Safety Biomarker
Pre-Candidate Selection Phase Applications	#1 Renal Injury De-Risked at Cmpd Selection	NHP exhibits renal tox with lead that is thought to be human relevant. 3 candidates selected for minimal study using renal biomarker longitudinal measurements.	Safest of 3 candidates selected for development to minimize drug development delay.
Preclinical GLP Animal Toxicology Studies and / or Clinical Trials	#5 Rat-only Kidney Pathology First Seen in Chronic Study	New translational kidney biomarkers demonstrate monitorability of kidney toxicity. Shorter rat studies and chronic monkey studies are negative. Clinical studies show no changes in kidney biomarkers.	Ambiguities about human safety concerns are eliminated. $31M+ in clinical development preserved. Delays in development avoided.
	#6 NHP-only Kidney Pathology Seen in First GLP Study	New translational kidney biomarkers demonstrate monitorability of kidney toxicity seen only in NHP w "medium" margin. Clinical studies conducted show no changes in kidney biomarkers.	Ambiguities about human safety concerns are eliminated. $10M+ in preclinical development preserved. Delays in development avoided.

Recent publication exemplifying value of new translational kidney safety biomarkers…

AJKD
Case Report
Am J Kidney Dis. 2013;62(4):796-800

Acute Kidney Injury During Therapy With an Antisense Oligonucleotide Directed Against PCSK9

Eveline P. van Poelgeest, MD,[1] Reinout M. Swart, MD,[2] Michiel G.H. Betjes, MD,[2] Matthijs Moerland, PhD,[1] Jan J. Weening, MD,[3] Yann Tessier, DVM,[4] Michael R. Hodges, MD,[4] Arthur A. Levin, PhD,[4] and Jacobus Burggraaf, MD, PhD[1]

Antisense oligonucleotides have been explored widely in clinical trials and generally are considered to be nontoxic for the kidney, even at high concentrations. We report a case of toxic acute tubular injury in a healthy 56-year-old female volunteer after a pharmacologically active dose of a locked nucleic acid antisense oligonucleotide was administered. The patient received 3 weekly subcutaneous doses of experimental drug SPC5001, an antisense oligonucleotide directed against PCSK9 (proprotein convertase subtilisin/kexin type 9) that is under investigation as an agent to reduce low-density lipoprotein cholesterol levels. Five days after the last dose, the patient's serum creatinine level increased from 0.81 mg/dL at baseline (corresponding to an estimated glomerular filtration rate [eGFR] of 78 mL/min/1.73 m^2) to 2.67 mg/dL (eGFR, 20 mL/min/1.73 m^2),

A post hoc analysis of biobanked spot urine samples, which had been collected before each dose of study medication was administered, was performed to assess the kidney injury markers β_2-microglobulin, α-glutathione *S*-transferase (α-GST), kidney injury molecule 1 (KIM-1), and *N*-acetyl-β-D-glucosaminidase (NAG). NAG levels were unchanged, but urinary β_2-microglobulin levels increased 4-fold, α-GST levels increased 24-fold, and KIM-1 levels increased 60-fold upon administration of SPC5001 (Fig 2). Importantly, these markers preceded the increase in serum creatinine level, having increased already after the first administration of SPC5001. These observations suggest that SPC5001 adversely affects proximal tubular function.[15,16]

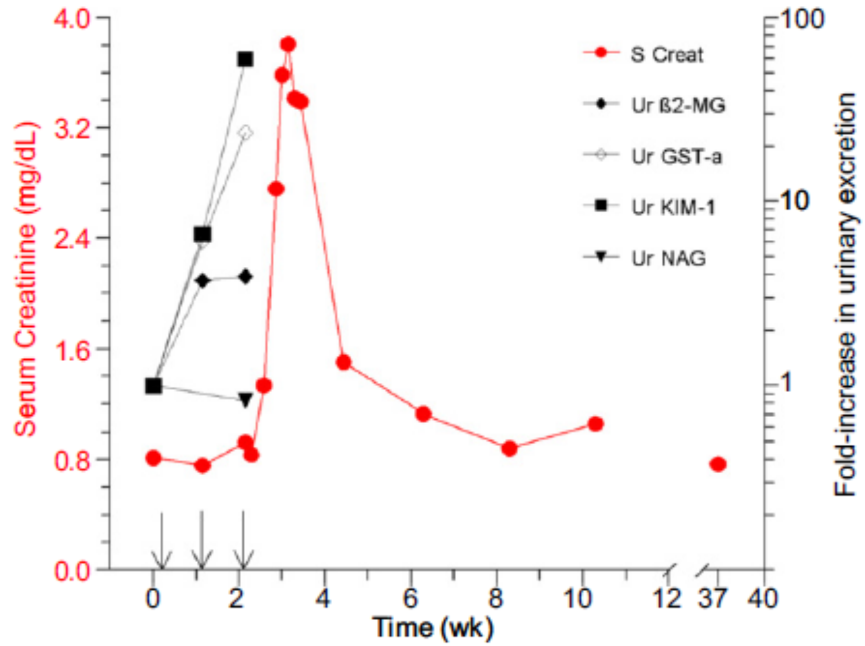


Figure 2. Time course of serum creatinine (S Creat) and urinary kidney damage marker levels. Arrows denote administration of SPC5001 on study days 1, 8, and 15. Conversion factor for S Creat in mg/dL to μmol/L, ×88.4. Abbreviations: Ur β2-MG, urinary β_2-microglobulin; Ur GST-a, urinary α-glutathione *S*-transferase; Ur KIM-1, urinary kidney injury molecule 1; Ur NAG, urinary *N*-acetyl-β-D-glucosaminidase.

BACKGROUND

- COPD is a disease with many different domains of outcome importance
  - Symptoms
  - Lung function
  - Exacerbation frequency
  - Mortality
  - Lung imaging progression
- These markers may move independently and at varying rates in individuals
- COPD is a disease with attributes that often progress so slowly that surrogate biomarkers are necessary for developing drugs that impact long-term decline

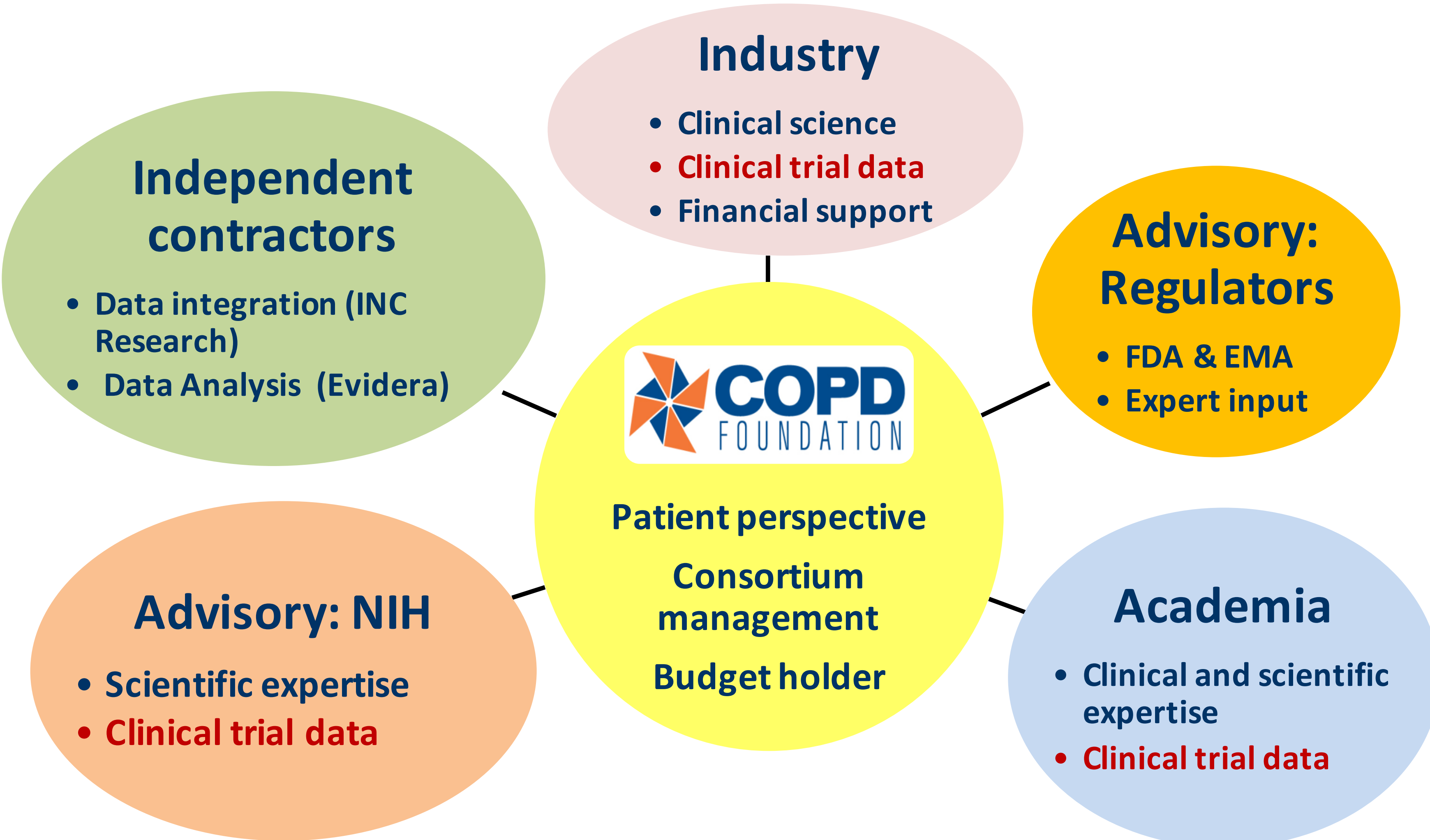
MISSION OF THE COPD BIOMARKERS QUALIFICATION CONSORTIUM

COPD FOUNDATION

ESTABLISHED IN 2010

- **Qualify biomarkers and patient centered outcomes to facilitate development of new treatments for COPD**
  - ❑ FDA and EMA (Europe)
- **Identify drug development tools for which sufficient data exist to warrant consideration for qualification**
  - ❑ Source: Industry, Academic and Government databases
- **Fill required gaps by facilitating collaborations among global consortia or investigators**

ORGANIZATION OF THE CBQC



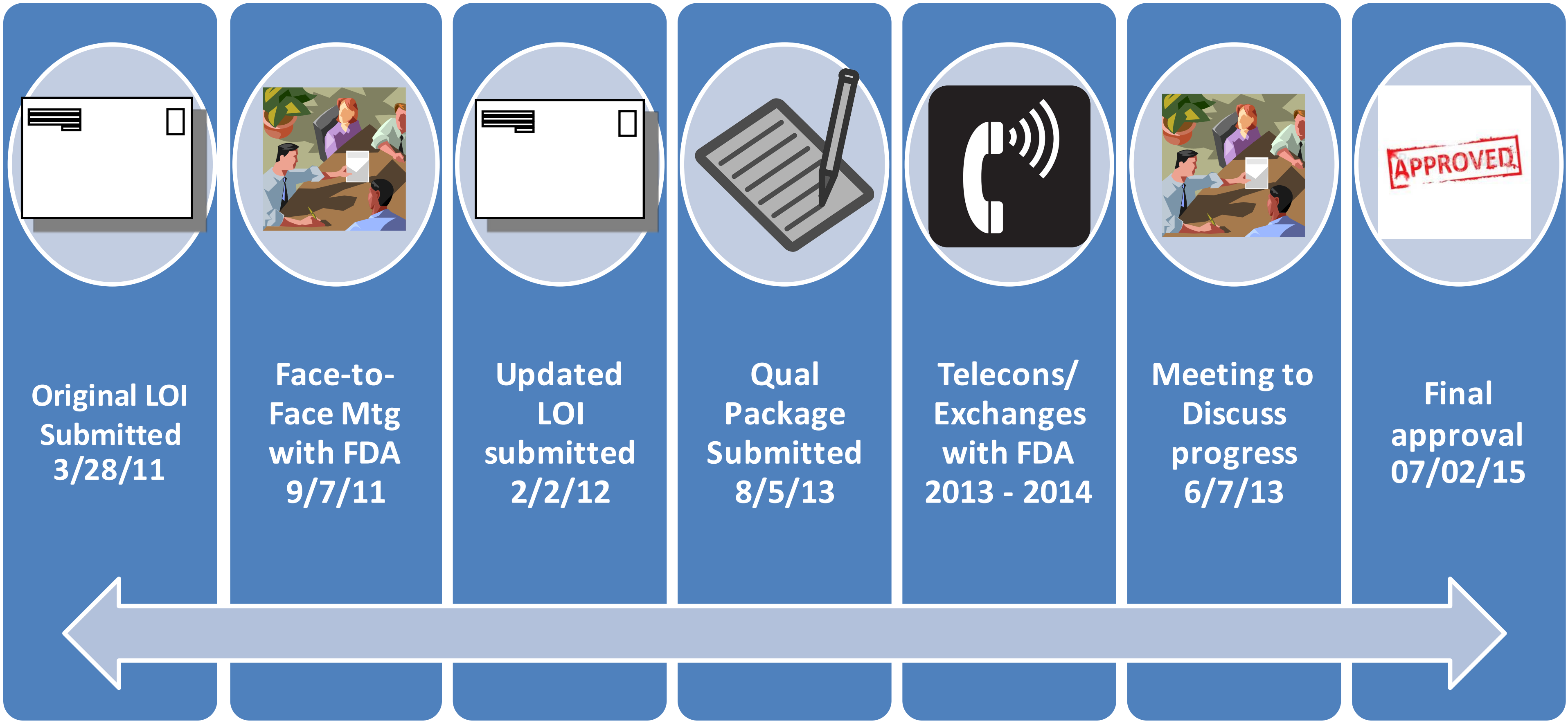
Modified from Casaburi et al. J COPD, 10:367–377, 2013

CBQC STRATEGY & PLANS

We have a multi-faceted biomarker approach including:

- **Stratify for risk of exacerbation and mortality**
  - Fibrinogen, 6 Minute Walk Test (6MWT)
- **Define subgroups of disease, e.g. emphysema, airway, pulmonary vascular**
  - Eosinophils, imaging
- **Provide Indicators of outcome measures that reflect patient-impacted disease progression not always represented by FEV1**
  - SGRQ, Constant Work Rate Exercise, 6MWT (possibly), CAT
- **Provide indicators of outcome related to unique of very slow progression phenotype**
  - sRAGE (and others), desmosine, imaging

FIBRINOGEN TIMELINE



4+ Years

CHALLENGES AND LESSONS LEARNED TO DATE

- Current published FDA guidance documents may lag behind the evidence and even the conventional FDA use of established biomarkers such as 6MWT and SGRQ
- The processes the FDA has developed have provided some structure to help with development, review and approval, but the timing is still too long.
- Harmonization between the U.S. and EU will be helpful
- Assay development and validation remains a challenge, as most of the new biomarkers have limited data. Fibrinogen was the “best case” and was still a big hurdle

CHALLENGES AND LESSONS LEARNED TO DATE

- Continued dialogue with the FDA will be important, and some of the new processes (e.g. Letter of Support) may be useful to us
- Public/private consortia represent a strong mechanism to do this work, but require strong commitment and engagement by the partners, as well as a strong governance and organization "hub" (e.g. the COPD Foundation)

Session III: Strategies for Improving Data Standardization and Sharing

The Brookings Institution • Washington, DC
Tuesday, October 27th, 2015

Session IV: Facilitating Collaboration and Cross-Sector Communication

The Brookings Institution • Washington, DC
Tuesday, October 27th, 2015

Challenges

- The development of an evidentiary framework and the resources needed (i.e., data, financial, expertise) for biomarker development requires active dialogue and collaboration among stakeholders
- Need for high-level collaboration across consortia and groups to prioritize limited resources and minimize duplicative efforts
- What is the optimal path to follow in order to promote collaboration between consortia?

Executive Office of the President

The President's Council of Advisors on Science and Technology

Policy Recommendation: PCAST report (2012) – proposal for a broad-based public-private partnership

- **Mission:** to promote innovation and improvement in the discovery, development, and evaluation of new medicines for important public health needs
- **Functions:**
  - Coordinate existing partnership and consortia
  - Identify key needs and opportunities and prioritize limited resources to high-impact initiatives
  - Facilitate the development of new collaborations and partnerships to address key issues
  - Develop and maintain the infrastructure for biomarker data aggregation and curation

Current Legislation: 21st Century Cures Act – Council for 21st Century Cures

- **Mission:** The "Council on 21st Century Cures" will be a public-private partnership whose purpose is to accelerate the discovery and development of new cures, treatments, and preventative measures for patients in the United States
- **Functions:**
  - Foster collaboration among stakeholders
  - Undertake communication and dissemination activities
  - Establish a strategic agenda for biomedical innovation
  - Identify gaps and opportunities, and develop recommendations based off of these
  - Propose recommendations that will facilitate the development of precompetitive collaborations
  - Identify opportunities to work with other organizations, while minimizing duplication of existing efforts

Precedent: Innovative Medicines Initiative – Europe's Public-Private Partnership for Accelerating Biomedical Innovation

- **Mission:** Accelerate patient access to innovative medicines by facilitating collaboration between key players in biomedical research
- **Budget:** €3.3 billion (half from EU/half from in-kind contributions from industry)
- **Model:** broad-based partnership that establishes research priorities and helps to facilitate and launch collaborative projects around these issues
- **Impact:** Over 50 consortia actively working on a diverse range of topics including biomarkers research

IMI - European's partnership for health

Neutral trusted platform to align public and private interests

EU funding goes to:

Universities

SMEs

Mid-sized companies

Patient groups

etc…

IMI2 Budget

€1.638 bn

€1.425 bn

Other

€213 m

IMI 2 total budget

€3.276 billion

EFPIA companies

receive no funding

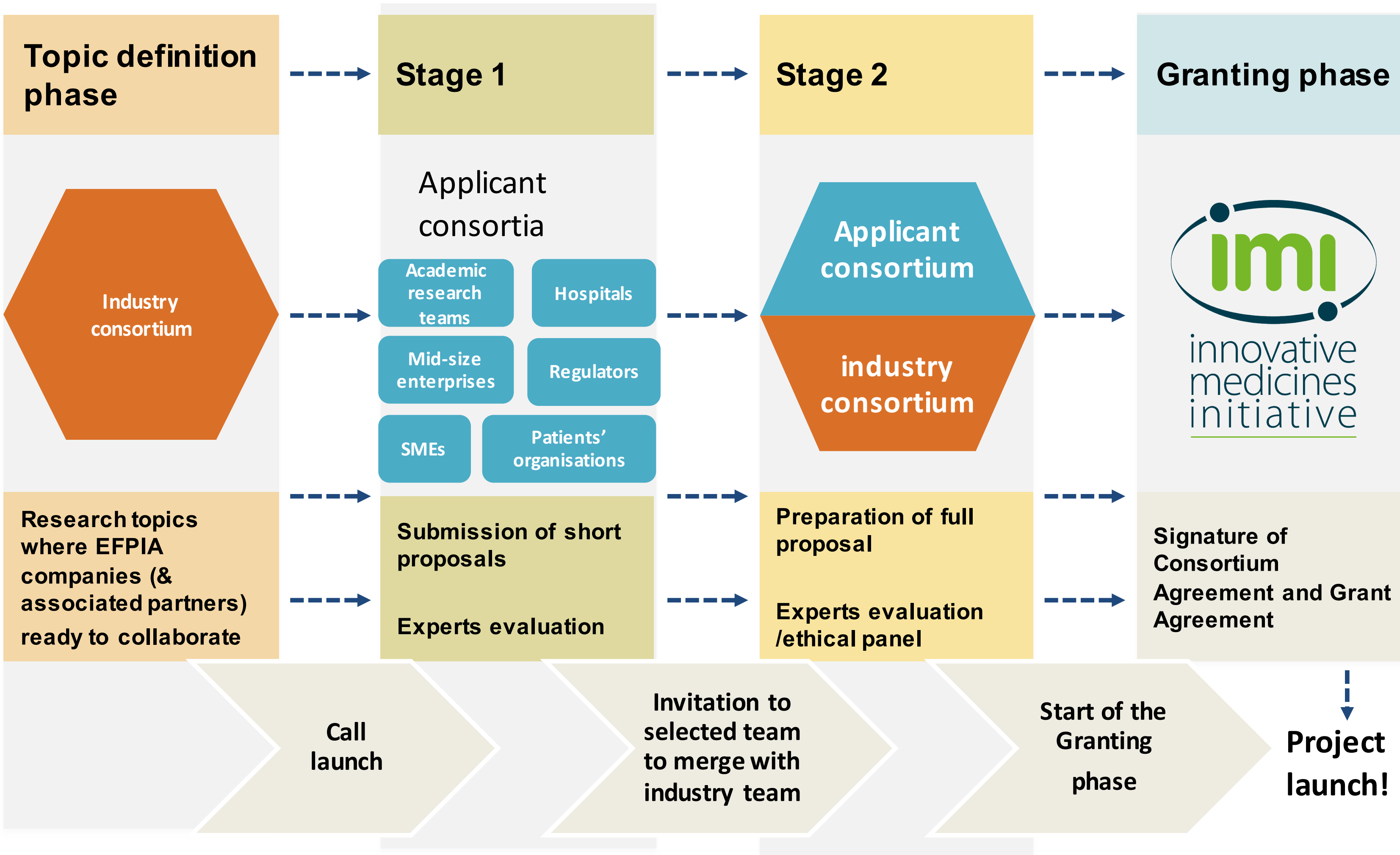
contribute to projects 'in kind'

Associated Partners

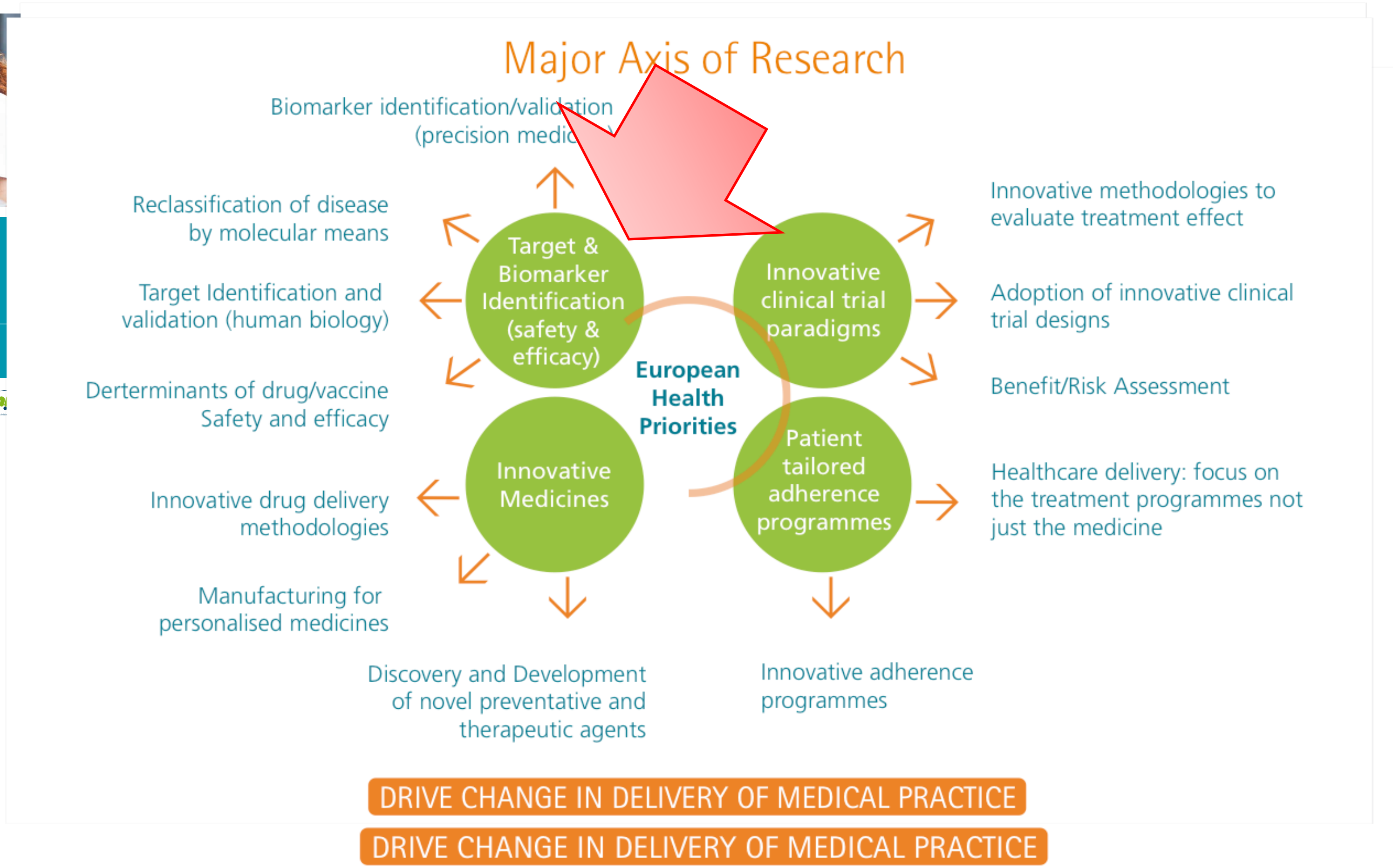
e.g. charities, non-EFPIA companies

- Non-competitive collaborative research
- Competitive Calls for proposals
- Open collaboration in public-private consortia
  - Data sharing, dissemination of results…

IMI 2 calls: Two stage procedure



IMI2 SRA – reduced attrition, faster patient access, improved outcomes



Center for Health Policy at BROOKINGS

Facilitating Biomarker Development: Strategies for Scientific Communication, Pathway Prioritization, Data-Sharing, and Stakeholder Collaboration

The Brookings Institution • Washington, DC
Tuesday, October 27th, 2015