Partnerships in Drug Discovery & Development

NIH Scientific Management Review Board

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Stephen L. Eck, MD, PhD
Vice President
Translational Medicine & Pharmacogenomics
Eli Lilly & Company

Long History of Productive Academic & Government Collaborations with the Pharmaceutical Industry

- Industry-Academia relationships flourished between WWI & WWII.

- Increasing independent research capability by industry required academic expertise
  - Basic research began to replace “botanicals” a source of new medicines
  - Lilly and U of Toronto (1922) collaboration to produce insulin
  - Lilly & Indianapolis City Hospital (1926) open Research Clinic to study pellagra and other disorders
  - Lilly & U of Rochester (1931) collaboration to Rx pernicious anemia

- Nat’l Res. Council Survey (1940)
  - 50 companies supporting 370 projects at 70 universities

D. Blumenthal, NEJM, 2003, 349:2452-8

Historical Perspective

(continued)

Later decline in collaborations post WWII

- Greater independence of industry
- Increasing federal support of academic research through mid ~1970's

Fully integrated pharmaceutical firms owned & controlled most of the drug development process.

- Attempted to mimic AT&T's Bell laboratories, IBM's Watson Research Center and Xerox's Palo Alto Research Center which produced Nobel Prize winning research.

Bayh-Dole Act 1980

- Foster translation of scientific discovery to commercial products.
- Collaboration seen by Congress as a means to advance product development
- Allowed universities to patent & license IP derived from federally funded research
- $MM flowed to universities with shift from chemistry & engineering to life sciences
- Late 1990's: 90% of firms, 25-50% of faculty
- Most universities had equity in their sponsoring companies

D. Blumenthal, NEJM, 1996, 335:1734-9; K. Lim, Research Policy 2004, 33,287-321

Widely Acknowledged Conflicts in Industry-University Collaborations

- "Industry-sponsored clinical research: a double edged sword", (J .Montaner Lancet 2001)

- "Collaborating with Industry-Choices for the Academic Medical Center,"
(H. Moses et al NEJM 2002)

- "Regulating Academic-Industrial Research Relationships",
(T. Stossel, NEJM 2005)

- "Uneasy Alliance: Clinical Investigation and the Pharmaceutical Industry",
(T. Bodenheimer, NEJM 2000)

"In simple terms industry has a primary responsibility to generate profits for shareholders while academics are preoccupied with issues pertaining to scientific inquiry and career advancement."

(J. Montaner Lancet 2001)

- There needs to be a clear separation between research and marketing activities.

- The financial arrangements need to be transparent and well justified.

Distinct Cultures and Resources

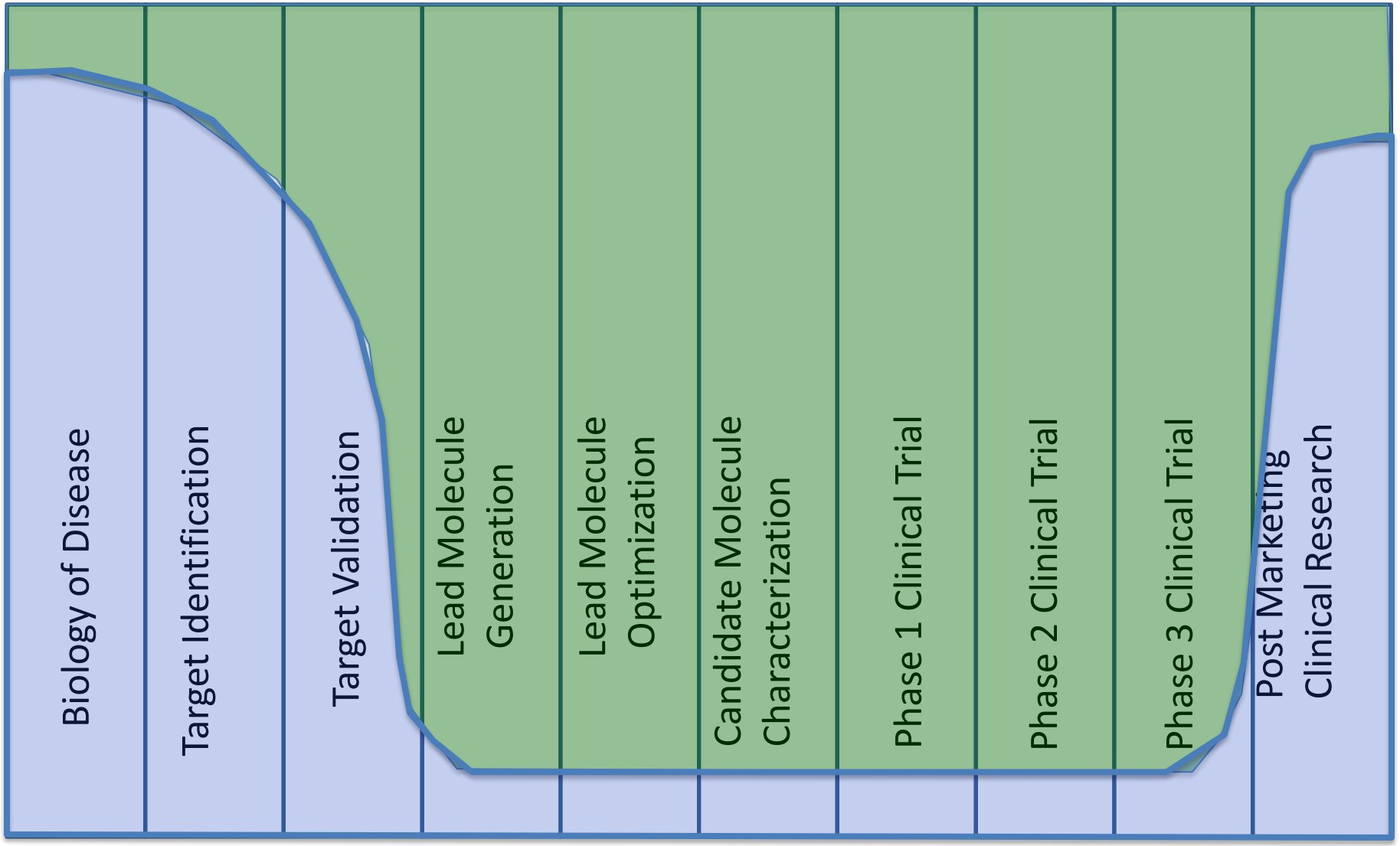
Academia

- Resource limited
- Institutional support limited
- Diverse talent pool
- Project is premier
- Any interesting outcome is valued
- Continuous focus of activity (decades)
- Several missions

Industry

- Limited Intellectual & legal freedom to operate.
- Strong Institutional support
- Narrowly talent pool
- Portfolio is premier
- Only specific outcomes valued
- Areas of interest changes with business climate
- Single mission

Balance of Drug Discovery and Development



Collaboration must address concerns & likely benefits

areas for concerns

Integrity of the university's teaching and research mission

Willingness to disseminate new discoveries

Exchange of scientific reagents, tools and technologies

Patient protection

Conflict of interests at several levels

Ownership

expected benefits

Expedites the public's access to new and important medicines

Returns public value from government investment in research

Fosters business development

Increases support for educational institutions

Enhances the performance of both institutions

Where does the industry need help in advancing innovative medicines?

1. **Target identification and validation**
2. **Understanding patient heterogeneity**
3. **Biomarker development**
4. **Identifying unique subsets of patients responsive to a new drug with a novel mechanism of action**
5. **Providing tools to help physicians manage complex information and derive therapeutic decisions**

1. Target Identification and Validation

Older drugs were based on chance pharmacology

- The observation of clinical activity of a compound leads to clinical development. The mechanism of action is later uncovered.

- Physiologic observations
  - Alkylating agents
  - Natural Products (ACE inhibitors, Digitoxin)
  - Aspirin

Newer drugs are derived from basic academic research

The genetics of rare diseases with extreme phenotypes gives insight into biochemical pathway that lead to new drug targets.

- CETP (cholesterol metabolism)
- PCSK9 (cholesterol metabolism)
- CTLA4 (autoimmunity)*
- NAV1.7 (pain) †
- SOST (bone mineralization)
- Retinoblastoma (cancer)
- Amyloid Precursor Protein/Aβ peptide (Alzheimer's Disease)
- Myostatin (muscle growth)

*P Lindsey, BMS, † D. McHale, Pfizer

2. Understanding Patient Heterogeneity

- *"The suppression of participant heterogeneity in rigorous clinical trials helps to explain why the published clinical literature is overwhelmingly explanatory rather than pragmatic; that is, focused on what works rather than on informing real-world decisions among alternative clinical interventions"*
- **Davidoff, F. Heterogeneity is not always noise: lessons from improvement.** JAMA. 2009 Dec 16;302(23):2580-6.

We need to use patients' clinical and molecular information to make better treatment decisions

About half of all patients fail to respond to medicines they are prescribed

Therapeutic Area	Efficacy Rate (%)
Alzheimer's	30
Analgesics (Cox-2)	80
Asthma	60
Cardiac Arrhythmias	60
Depression (SSRI)	62
Diabetes	57
HCV	47

Therapeutic Area	Efficacy Rate (%)
Incontinence	40
Migraine (acute)	52
Migraine (prophylaxis)	50
Oncology	25
Osteoporosis	48
Rheumatoid arthritis	50
Schizophrenia	60

Source: Spear B., et al. Trends in Molecular Medicine 7(5):201-204, 2001

Using markers to target patients results in smaller possible market, but peak sales are increased

Example: Peak sales increase for marker with 25% frequency

Measure	Base	With marker (3 scenarios)		
Market size (patients)	200k	50k	50k	50k
Response rate	25%	50%	75%	90%
Peak share	20%	80%	80%	95%
Patients prescribed	40k	40k	40k	47.5k
Responders	10k	20k	30k	42.75k
Non-responders	30k	20k	10k	4.75k
Total cycles*	120k	160k	200k	266k
Price per cycle	$1k	$1k	$1k	$1k
Peak sales	$120m	$160m	$200m	$266m
*6 per Responder, 2 per Non-responder		+33%	+66%	+122%

Extent of benefits depends on frequency of and response rate with marker.

3. Biomarker Development

- **Biomarkers serve a variety of needs**
  - Target engagement –does the drug inhibit the target in humans?
  - Pharmacodynamic effect- does the drug modulate the pathway of interest?
  - Efficacy- can the short term biochemical effects be related to overall clinical benefit?
- **Most biomarker have very little "proprietary value".**
  - The value of the biomarker goes up when widely used, understood and accepted.

The Biomarkers Consortium:

Projects Supported by Lilly (through 2009)

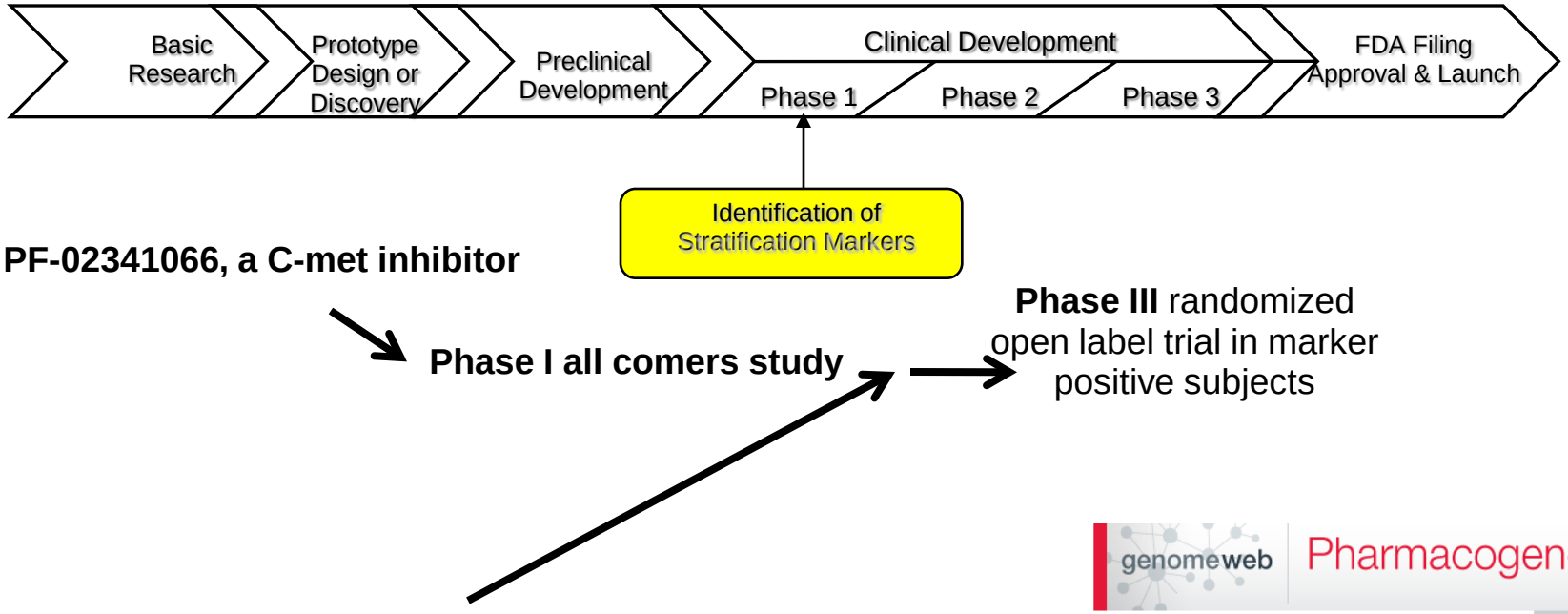
Project Name/ Committee	Description	Total Project Value & Duration	Eli Lilly Investment
Adiponectin Project (Metabolic Disorders SC)	Determine whether adiponectin has utility as a predictive biomarker of glycemic control	$0 (in-kind data sharing project) (18 months) Completed April 2009	1 of 4 companies to provide data and in-kind legal/scientific support
Sarcopenia Consensus Summit (Metabolic Disorders SC)	Generate a consensus definition of sarcopenia to provide guidelines for diagnosis/better regulatory decisions	$463,000 over 24 months 2010-2011	$100,000 (1-time payment; project to conclude in 2011)
Alzheimer's Disease Targeted CSF Proteomics Project (Neuroscience SC)	Qualify a multiplexed panel of known AD CSF-based biomarkers; examine Beta-Site APP Cleaving Enzyme levels in CSF; and qualify a mass spectroscopy panel	$586,100 over 12 months 2Q 2010-1Q 2011	$100,000 (1-time payment; project to launch in 2Q 2010)
PET Radioligand Project (Neuroscience SC)	Develop improved, more sensitive radioligands with higher binding to the peripheral benzodiazepine receptor	$560,500 over 24 months 2009-2010	$93,417 (payable over 2 years in 2009 and 2010)
Placebo Data Analysis in AD and MCI Cognitive Impairment Clinical Trials (Neuroscience SC)	Combine placebo data from large industry trials and analyze them to provide better measures of cognition and disease progression	$556,620 over 36 months 2010-2012	$95,000 (1-time payment)
I-SPY TRIAL 2 (Cancer SC)	A personalized medicine trial that promises to accelerate the pace of identifying effective novel agents for breast cancer; patients will be classified according to biomarker profiles and randomized to control therapy	$26,000,000 over 60 months 2010-2014	$200,000 (to date)
TOTAL (Consortium Programs)			**$588,417**

FOUNDATION FOR THE National Institutes of Health

FNIH Partnerships with Lilly

Project	Description	Federal Investment	Private Investment	Total Investment	Lilly Contribution
Neuroscience Fellowship Program (2004-06)	Allows a young physician researcher apply clinical experience and cellular/molecular research techniques to the field of neurophysiology. *NIH partner: NIMH*	$0	$200,000	$200,000	$200,000
Overcoming Barriers to Early Phase Clinical Trials (2002-2008)	Investigate barriers that prevent patients, especially minority and elderly populations, from participating in early-phase clinical trials of innovative cancer therapies. *NIH partner: NCI*	$2,450,000	$2,550,000	$5,000,000	$600,000
Fogarty International Center 40th Anniversary (2008)	Scientific meetings on global health, other events. *NIH partner: Fogarty*	Not quantified	$200,000	$200,000	$50,000
Promise of Public Private Partnerships: Forging New Alliances in Global Health (2008)	Meeting to explore implementation science and training needs and forge new collaborations to improve global health. *NIH Partner: Fogarty*	$0	$21,000	$21,000	$5,000
The Science of Eliminating Health Disparities Summit (2008)	Summit to establish research agenda. *NIH partner: NCMHD*	Not quantified	$1,375,000	$1,375,000	$25,000
Psychiatric Genome-Wide Association Consortium (2007-2009)	Analyze GWAS data for ADHD, autism, bipolar disorder, major depression disorder, and schizophrenia, to move the entire field of mental health genetic research forward. *NIH partner: NIMH*	$0	$125,000	$125,000	$125,000
Alzheimer's Disease Neuroimaging Initiative (2003-10)	Collects clinical and biomarker data as a public resource to identify promising biomarkers of disease progression for use in AD clinical trials. *NIH partner: NIA*	$40,000,000	$20,000,000	$60,000,000	$2,500,000
Mutational Analysis of the Melanoma Genome (2010-11)	Sequence whole genome of 5 tumor samples and 5 normal samples, analysis, gene sequencing, deep sequencing of mutated genes. *NIH partner: NHGRI*	Not quantified	$250,000	$250,000	$225,000
Best Pharmaceuticals for Children Fund (2001-present)	Clinical trials of drugs approved for adults that are used to treat children. Supports studies of baclofen and hydroxyurea. *NIH partner: NICHD*	Not quantified	$5,000,000	$5,000,000	$500,000
Measures for Clinical Trials of the Treatment of Cognitive Impairment (2006-present)	Identify a widely accepted model for assessing efficacy of cognition enhancing drugs for schizophrenia and translate and adapt an assessment battery for use in international trials of new drug treatments. *NIH partner: NIMH*	Not quantified	$2,233,000	$2,233,000	$203,197
ADNI Cerebral Spinal Fluid (CSF) Extension (2007-present)	Extends collection of cerebral spinal fluid (CSF) in ADNI subjects for a second year. *NIH partner: NIA*	$0	$913,954	$913,954	$100,000
Drug Induced Liver Injury Network *pledged* (2010-2015)	Increase understanding of DILI and effective screening, diagnostic, and treatment options. *NIH partner: NIDDK*	$16,250,000	$1,000,000	$17,250,000	$500,000
Observational Medical Outcomes Partnership (2007-present)	Improve the monitoring of drugs for safety by researching methods that are feasible and useful to analyze existing healthcare databases to identify and evaluate safety and benefit issues of drugs already on the market. *Federal partner: FDA*	$0	$20,000,000	$20,000,000	$1,500,000
Biomarkers Consortium Membership (2007-present)	Core infrastructure to facilitate development of biomarkers projects. *Federal partners: NIH, FDA, CMS* (projects listed on next page)	Not quantified			$350,000
TOTAL, general programs					**$6,883,197**

4. Identifying unique subsets of patients responsive to a new drug with a novel mechanism of action



Manabu et al, "Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer", *Nature* 448, 561-566 (August 2007)

"Our data demonstrate that a subset of NSCLC patients may express a transforming fusion kinase that is a promising candidate for a therapeutic target as well as for a diagnostic molecular marker in NSCLC."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Pfizer, Abbott Ink Deal to Develop Companion Dx for PGx-based NSCLC Drug

September 02, 2009

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Pfizer has previously touted PF-02341066 as "the first agent in clinical development that selectively targets a unique genetic feature of cancer cells." The drug is currently in Phase III trials, while Abbott is in the process of designing validating trials for a companion test with the capability to detect ALK gene rearrangements.

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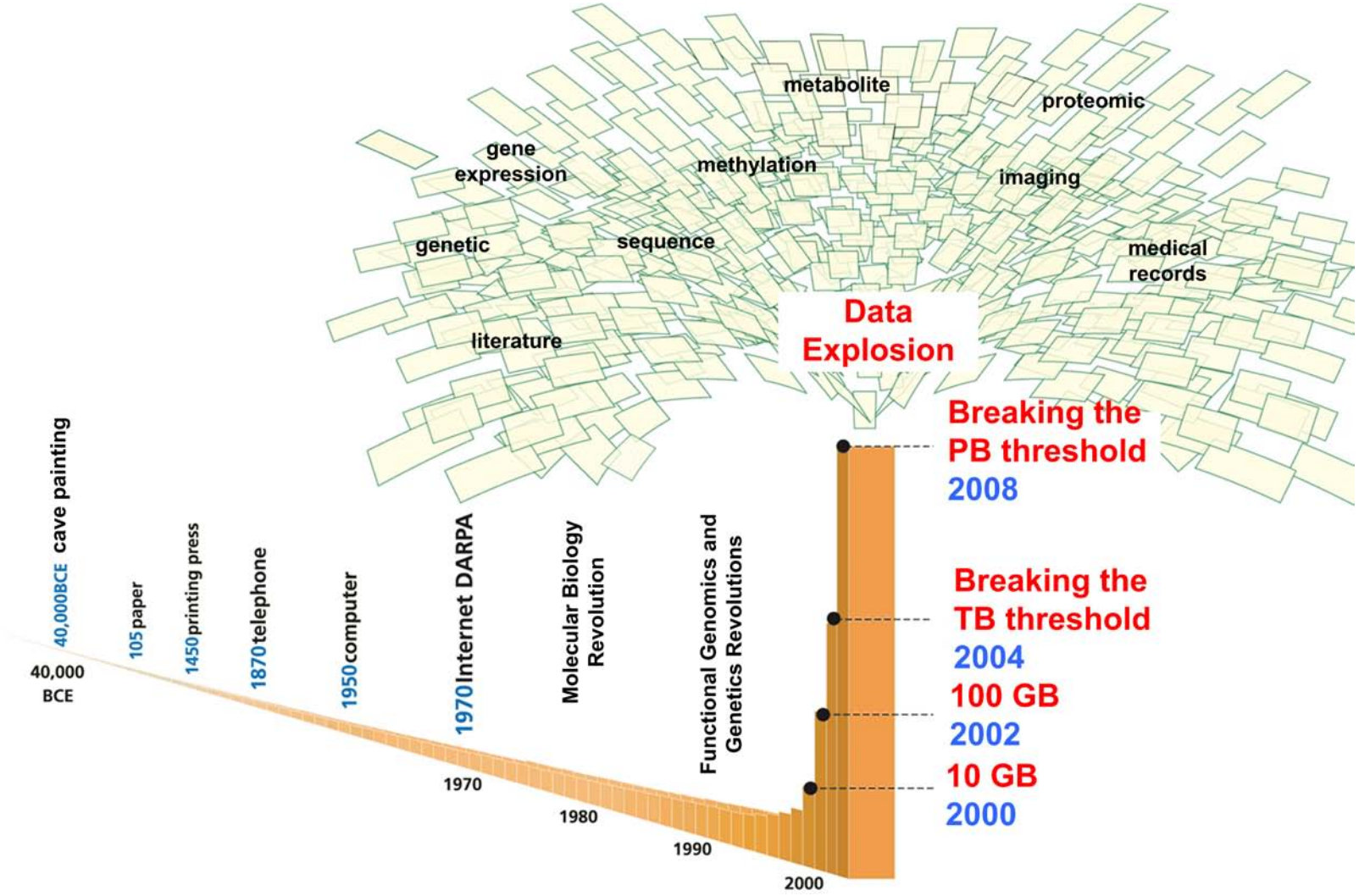


Stephen Friend 2009

5. Tools to help physicians manage complex information and derive therapeutic decisions.

- **Significant limitations of current guidelines**
  - Guidelines not patient-specific enough to be useful and rarely allow for individualization of care.
  - Most guidelines have a one-size-fits-all mentality and do not build flexibility or contextualization into the recommendations. (Shaneyfelt & Centor JAMA, 2009)
- **There are limits on our capacity for processing information**.

  The magic number is 7 ± 2. (Miller, Psych. Review,1956;63(2):81-97)

- **Clinicians may already be discarding important information simply due to cognitive limits**.
- **Many new medicines will require the co-launch of a decision-making tool**

Tests to Select Therapies

- Safety

  ⇒ CYP2D6 genotypes' effect on metabolic rate for drugs

  ⇒ HLA allele B*1502 as a marker for carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis

  ⇒ HLA B5701 genotype for risk of hypersensitivity in patients taking abacavir and flucloxacillin

  ⇒ KRAS mutation for inefficacy of cetuximab, panitumumab

- Effectiveness

  ⇒ HER2 positive breast cancer patient selection for trastuzumab

  ⇒Oncotype Dx screen for ER+, node negative patients considering treatment options

- Dosing

  ⇒ VKORC1 and CYP2C9 genotype to predict warfarin dose.

c.f. Gene Pennello, DIA Statistics Forum, April 2010

Coumadin Label Information

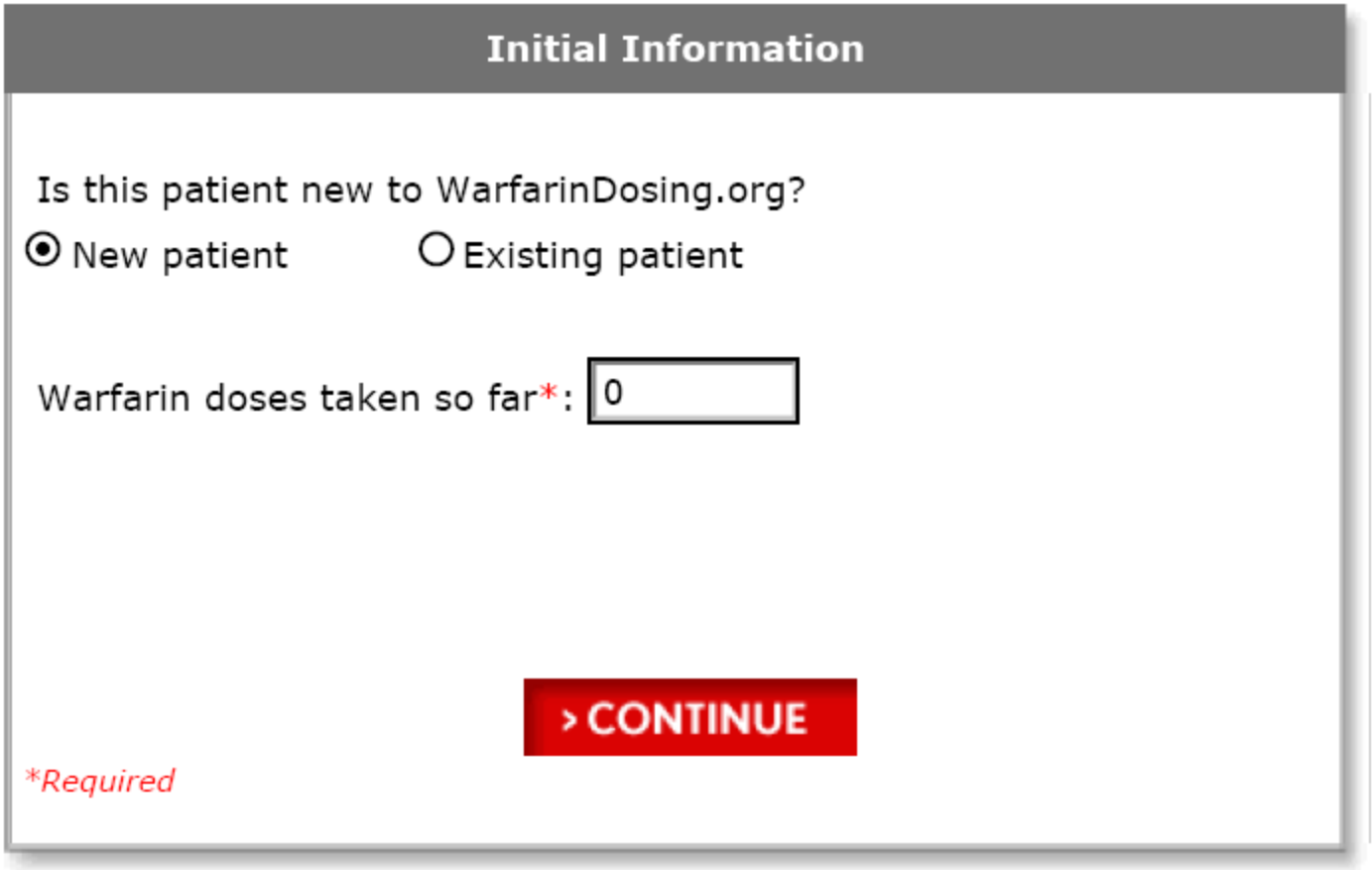
1/22/2010

Table 5: Range of Expected Therapeutic Warfarin Doses Based on CYP2C9 and VKORC1 Genotypes†

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

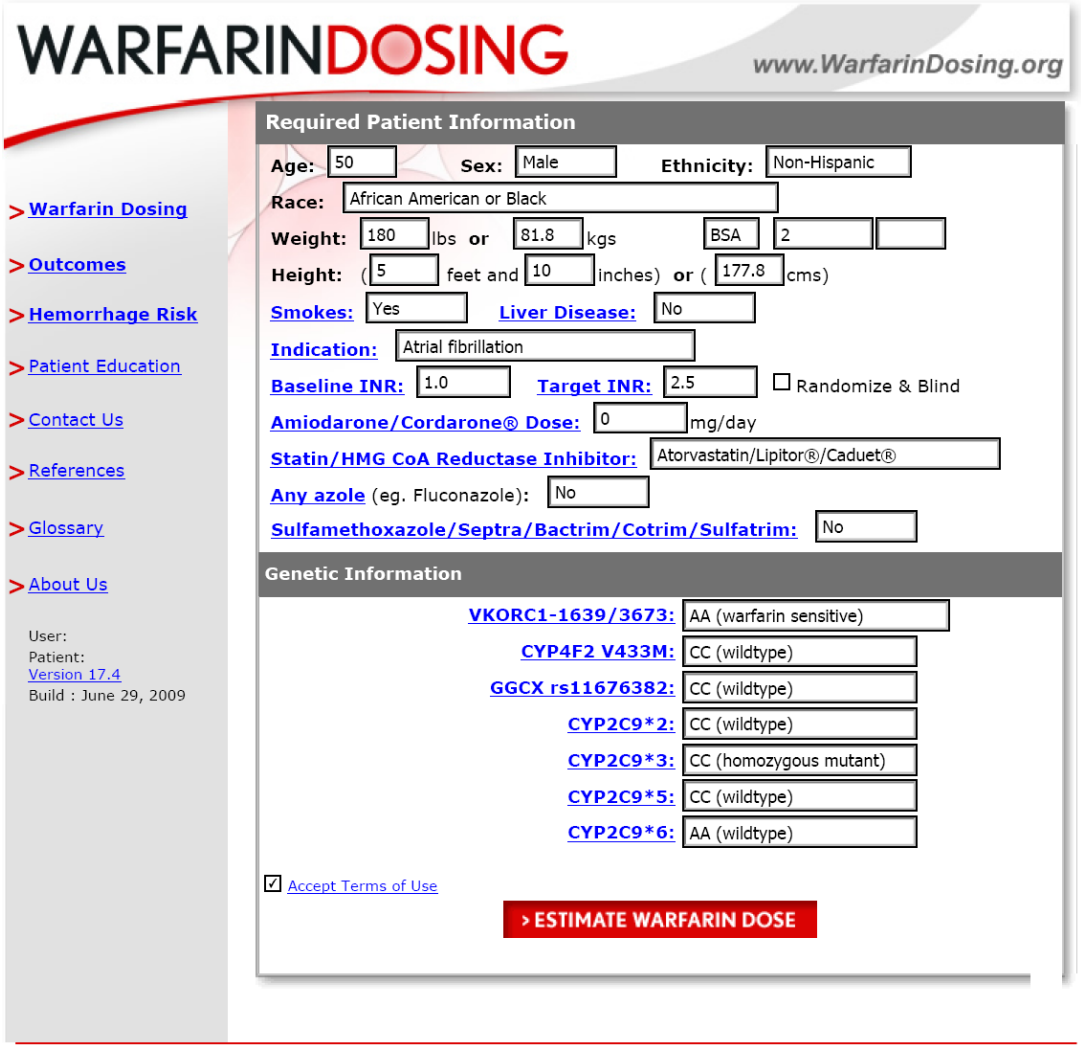
Ranges are derived from multiple published clinical studies. Other clinical factors (e.g., age, race, body weight, sex, concomitant medications, and comorbidities) are generally accounted for along with genotype in the ranges expressed in the Table. VKORC1 –1639 G → A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3 and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen.

Warfarin Dosing



http://www.warfarindosing.org/Source/DoseResults.aspx

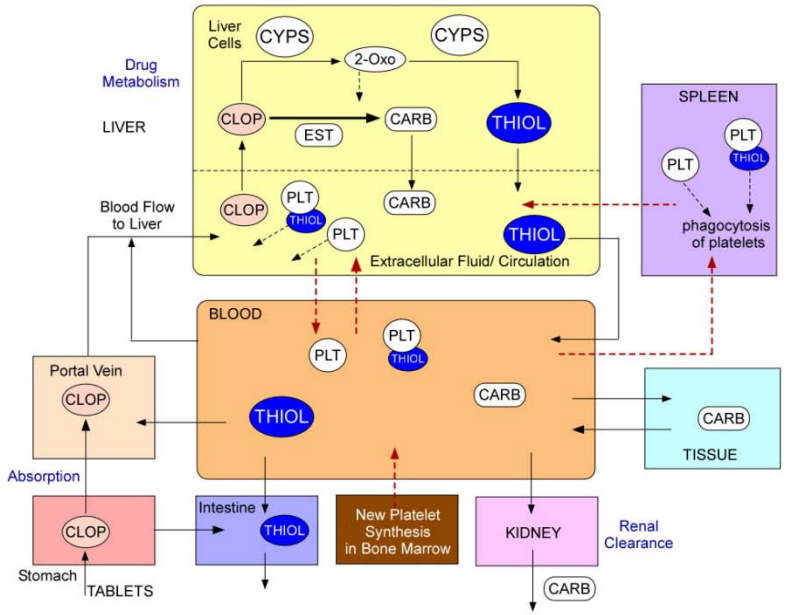
Warfarin Dosing



http://www.warfarindosing.org/Source/DoseResults.aspx

Clopidogrel Mechanistic Model

PK ⇒ PD ⇒ Clinical Outcomes



Data used for this model includes:

- ***in vitro* liver microsomal data**
- ***in vitro* competitive inhibition data**
- **Published data about Ki**
- **Healthy volunteer PK data**
- **Diseased patient PK data**
- **Healthy volunteer PD data**
- **Healthy volunteer PD data with other drugs**
- **Diseased patient PD data**
- **Published data on platelets**
- **ACS patients' genotype, PD and clinical outcomes**

- 31 ordinary differential equations for PK
- 30 ordinary differential equations for PD
- 25 input variables
- 11 baseline patient characteristics
- 6 genetic parameters (including 2C19, 2C9, & ABCB1)
- 8 concomitant medications
- PK/PD to clinical outcomes still being constructed

Summary of Areas of Collaboration

- **Pre-clinical Research**
  - Target Identification and Validation
  - Understanding which patient subgroups would benefit from targeted therapies with specific mechanisms of action.

- **Clinical Research**
  - Biomarker Research
    - Pharmacogenomics
    - Disease specific markers of benefit
  - Comparative Effectiveness Research
    - Who needs what medicine and why?
  - Pharmacoeconomic Research
    - What is valued? What benefit at what cost?
  - Advance Regulatory Science
    - What constitutes the appropriate data?
  - Implementing Personalized Medicine in a Regulated Environment
    - Designing robust decision-making tools for Physicians and Healthcare providers

Key Aspects of Successful Collaborations

- Clear expectations of the objectives, timelines, resources and overall mission
- Frequent interactions
- Interdependence of knowledge and resources.
- Consistent with both the corporate goals and the academic mission.
- Absolute transparency in all aspects of collaboration

Answers That Matter.