

Navigating the Multi-Dimensional Complexity of Drug Pricing Policies

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NASEM Affordable Drugs Stakeholder Meeting 23 January 2017 Stanford Law School

US Prescription Drug Market Trends

- CAGR of 1.8% 2005-2013
- dramatic 11.5% expansion in 2014
 - HCV, MS, diabetes Rx innovations
- increased tension between innovators and buyers
 - strengthening of innovation pipeline (immuno-oncology)
 - buyer consolidations: PBMs, wholesalers, insurers
- lower rate of patent expirations and fewer generic market entries (except biosimilars/follow-on biologics?)

Speciality Drugs



Specialty Drugs: Background and Policy Concerns

Suzanne M. Kirchhoff Analyst in Health Care Financing

August 3, 2015

Congressional Research Service

\$87.1 billion in 2012

- est. \$192 billion in 2016
- projected \$401 billion in 2020
- **20% CAGR**
- higher impact on patient OOP spend/deductibles than traditional lower cost small molecular weight drugs

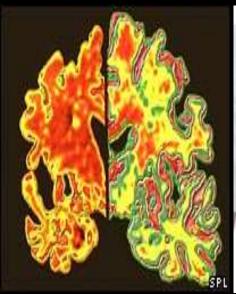
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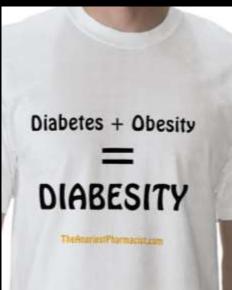
Waiting In The Wings

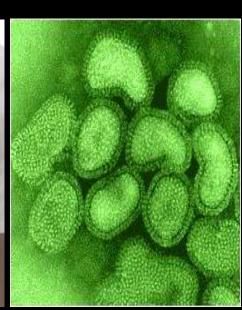
- new orphan drugs and gene therapy
- immuno-oncology combination Rx
 - CTL4 + PD1-PDL1 inhibitors
 - \$300,000 per treatment (before cost of clinical services)
- immuno-oncology cell therapies
 - individualized TIL, TCR, CAR therapies
 - estimated \$0.5 to 2 million/patient

Unmet Medical Needs and Disease Burden: Confronting the Largest Economic Disruptions to Achieve Sustainable Healthcare









cancer

neurodegeneration

cardio-vascular/ metabolic disease infectious disease wildcard



Enough Is Enough

The Time Has Come to Address Sky-High Drug Prices

Unleashing value

The changing payment landscape for the US pharmaceutical industry





Tackling

with Tim Horn

CALITION

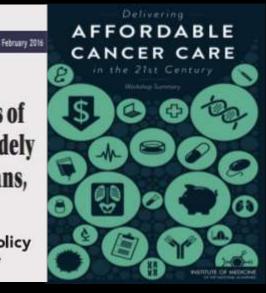
Drug Costs

RxPrice Watch Report
Trends in
Prescripti

Trends in Retail Prices of Prescription Drugs Widely Used by Older Americans, 2006 to 201 AARP

Real Possibilitie

Public Policy Institute



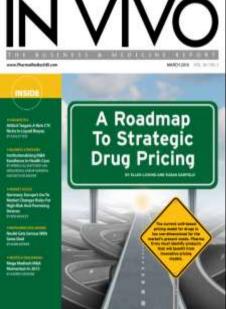
FINAL REPORT

Trends in Hospital Inpatient Drug Costs. Issues and Challenges

OCTOBER 11, 2016

PRESENTED TO Assertan Supral Assertan MO 10th Stone NV See CayComes Wadingson, DC 20001

Pulleration of American Response 750 NA Tarest NW, Suite 600 Washington, UK (2001) PRESENTED BY NORC at the University of Change III East Momen Tones 300 Floor Change, K. 40003





"I'm glad to call the pharmaceutical industry one of my biggest enemies."

Campaign speech August 2016



"The (biopharmaceutical) companies are getting away with murder."

Tweet 11 January 2016

Prescription Drug Pricing

branded Rx		anaciality By	generic Rx			
		speciality Rx	me-too d	rugs	pharmacies	
essential medicines		wholesalers	access			
***	PE	3Ms discou	nts	drug im	•	
competition	RWE	rebate	es invoi	ice and	private payers	
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pay-for-delay	prefe	rred-tier		alue-Daseu		
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QALYs	. 3	aligned ncentives	health	technolo	financial Ogy toxicity	
patient		YP	ass	sessment		
advocacy		115				

Uni-dimensional Analysis of Complex, Multi-Dimensional, Multi-Component Systems

A Prescription for Flawed Conclusions, Ineffective Reforms and Unintended Consequences

Unidimensional Approaches to Complex, Multidimensional Problems: A Prescription for Flawed Conclusions, Ineffective Reforms and Unintended Consequences

multi-dimensional

unidimensional

unit Rx price



The Innovator Industry Perspective





Industry Perspectives and Concerns High Risk – High Cost R&D

- highest % sales reinvested in R&D in any industrial sector
- 10-15 year R&D cycle: varied estimates of \$1B to 2.6B per drug
- escalation of R&D cost without parallel gains in new product launches
- high attrition rates in clinical trials including advanced Phase III trials
- precision medicine and stratification of major diseases into smaller cohorts
- increased requirements to demonstrate postapproval clinical effectiveness (real world evidence)

Biopharmaceutical Innovation

- declining ROI on R&D investment
 - 10.5% (2010) to 4.2% (2015): Deloitte Sixth Annual Report on Pharmaceutical R&D Performance

Industry Critics

- lack of transparency in claimed \$1 to 2.5 billion
 R&D cost per product
- US subsidizes other countries with prices 1.5 to 3X higher than EU
- "pay-for-delay" and "product hopping" arrangements to slow entry of generic competition for branded Rx
- over-investment in lower risk "me-too" product classes versus high risk, transformative innovation

Ongoing Clinical Trials with New Cancer Immunotherapies



"I have never seen this before, where you have so much development activity in the same class of drugs.

Should these resources,
I'm not only talking about financial resources
but also patient resources, be better off spent
into looking at more novel drugs."

Dr. R. Pazdur,
Acting Director, FDA Oncology Center of Excellence
Cited in Cancer Letter 7 October 2016, p.4

- 803 registered trials with 20 investigational agents (11/16)
 - single agents
 - combinations with other immunotherapies, biologics, chemotherapy and vaccines

A Very Expensive DTC Campaign



Completely Different Animals Or All Part of the Same Rapacious Industry to Critics of Drug Prices?

R&D Intensive Innovator Companies





Zero R&D, Asset Stripping and Extravagant Price Increases in Off Patent Single Source/Limited Competition Markers







Martin Shkreli
Turing
Pharmaceuticals

Michael Pearson Valeant Pharmaceuticals

Heather Bresch Mylan

People in Glasshouses.....

"Many of the same companies that are discovering and developing innovative drugs are also gouging the market, hiking up prices 400 to 500%, year after year, on old drugs, particularly off-patent biologics.

This is the industry's dirty little secret.

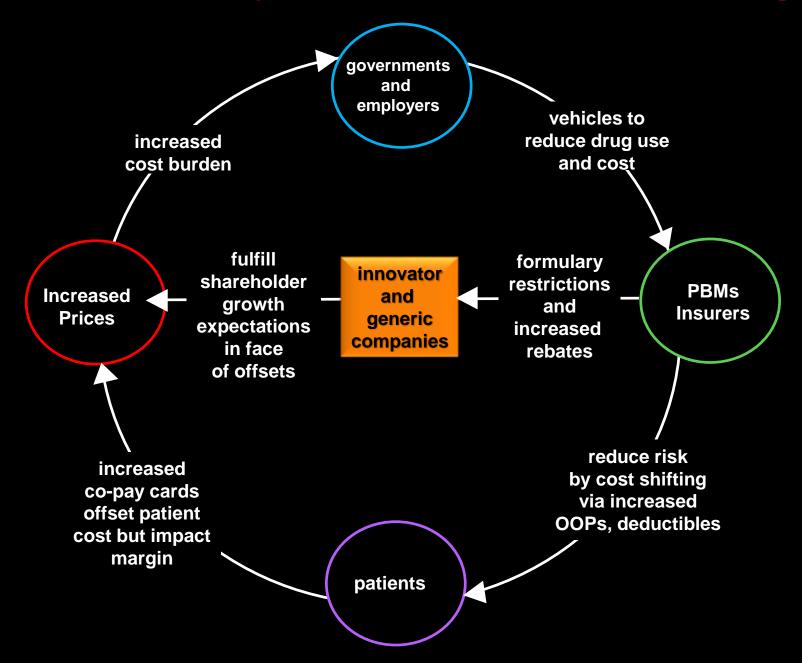
Shkreli's crime was attracting the spotlight to the shadows."

Editorial: An Unusual Business Nature Biotechnology (2015) 33, 1113

Biopharmaceutical Pricing: "What the Market Will Bear"

- what "the market will bear" in treatment categories with only one or two branded products
- entry of new competitor products with minimally different properties results in price increases for all
- major price reductions do not occur until LOE and entry of generic Rx
 - rate of generic price decrease influenced by number of competitors
- uncertain impact of biosimilars/follow-on biologics in markets with only one or two entries

The Vicious Cycle in Pharmaceutical Pricing



Biopharmaceutical Pricing

- innovator net margins have remained largely constant despite escalating invoiced prices
- lack of transparency about how the remainder of the expanded margin is divided
 - who receives discounts, rebates, co-pay subsidies?
- opacity in the scale and trajectory of Rx company margin offsets paid to different stakeholders
 - PBMs, payers, insurers, patients?

The Crazy World of Rebates and Subsidies in the Gross to Net Pricing of Branded Pharmaceuticals

- differential (discriminatory) pricing
- payer channels
 - Medicare Part D, Medicaid, DOD, VA, Employer Group Waiver Plans
- therapeutic class
 - HIV, hepatitis C, insulin, ICS/LABA,
 - speciality biologicals, immuno-oncology (I/O)
- disease categories and patient co-pay cards
 - acute, chronic
- disease co-morbidities
 - polypharmacy and bundled care
- Rx life cycle
 - launch, mature, post-LOE (generic)



"The American public and our government need to see what's going on.... it's necessary that the entire (pricing) system come clean."

Ron Cohen
Chairman, Biotechnology Innovation (BIO)
Executive Board
Congressional Testimony
September 2016

The Information Gap



"We don't have enough public information on the effectiveness of new drugs in the real world or about prices and rebate structures

We must increase the transparency of the

We must increase the transparency of the information available about drug pricing and value."

Andy Slavitt
Acting Administrator, CMS
HHS Forum on Drug Prices, 20 November 2015
cited in Scrip 4 Dec. 2015 p.11

Control of Drug Expenditures by Health Plans

- multi-tier formularies
- higher deductibles and co-pays for high-tier drugs
- 'split-fill' for initial Rx regimen to limit waste from stopping due to AEs
- increased prior authorization
- 'step therapy': treatment with lower cost drug(s) before approval of more expensive Rx
- 'clinical pathways': physician (dis)incentives to adopt consistent Rx use

ACA and Growth of Multi-Tier Formularies in Health Exchange Plans

- 'closed' formularies
- only cover a fraction of speciality drugs
- consumers carry full cost for Rx not on formulary
- high deductibles and large co-pays

Pharmaceutical Industry Discount Coupons/Cards 2015*

- estimated \$7 billion in 2015 versus \$1 billion in 2010 (IMS Holdings)
- PBM actions to exclude Rx with coupons from formulary
 - Express Scripts 80 drugs
 - CVS/Caremark 120 drugs
 - UnitedHealth Group 35 speciality drugs
 - 62% coupons are for Rx with low cost alternatives

The Perversity of Site of Service and 340B Abuses on Profit Margins for Administration of Cancer Drugs

UHC

- independent community oncology clinics ASP + 28%
- hospital-owned cancer clinics ASP + 152%
- 'seduction by margin' exacerbated by 340B pricing
 - heavily discounted (30-50%) drugs prescribed to fully insured patients
 - makes use of high cost drugs irresistible
- incentive for hospitals to acquire independent practices and reclassify as 340B eligible hospital outpatient settings

Recommendation

- prohibit sale of 340B highly discounted products at higher prices other than to low income/indigent populations consistent with intent of original 1992 provision
- repeal state provisions that allow mandatory reimbursement for physician selected anti-cancer drugs irrespective of clinical benefit or guideline compliance

Recommendation

- allow Medicare to negotiate improved pricing on brand-name drugs
- require transparency on prices and margins for multiple stakeholder transactions beyond just Rx companies
 - PBMs, pharmacies, providers
- deny tax breaks for DTC prescription drug advertising

Recommendation

- convert permissive generic substitution polices to mandatory
- eliminate patient consent requirements for generic substitution
- limit 'carve outs' for substitution in particular disease categories
- strengthen FDA resources for generic drug review/approval



"Price is what you pay.

Value is what you want."

Warren Buffet

Value-Based Pricing Models

- bundled payment models
- performance (outcome)-based risk sharing
- indication-specific pricing
- annuity model
- reference pricing
- essential social goods and public utility model

Performance-Based, Risk Sharing Contracts



- Januvia (sitagliptin)/Janumet (plus metformin)
- reduction in HbA1C levels in T2 diabetes



- Rebif (interferon Beta-1a)
- reduction in ER visits/hospitalization in MS patients



- Harvoni (sofosbuvir/ledipasvir)
- elimination of HCV genotype 1 in carriers



- Crestor (rosuvastatin)
- LDL cholesterol reduction

Outcomes-Based Pricing: More Complicated Than It Might Seem

- consensus on clinical and/or molecular biomarker metrics as efficacy/ effectiveness endpoint(s)
- consensus on 'observational/ PCT' protocols to be used
 - duration and data collection parameters
- mechanisms to encourage/ enforce protocol compliance and ID protocol deviations

Outcomes-Based Pricing

- acute diseases versus chronic diseases
- chronic diseases with uni-focal Rx target
 (e.g., HCV) versus chronic diseases with
 complex multi-focal perturbations in complex
 molecular networks (e.g., cancer, neurodegeneration)
- monotherapy versus polypharmacy protocols (multiple comorbidities)

Hypothetical Scenarios for Indication-Based Drug Pricing

Drug and Indication	Median Survival Gain In Years	Current Monthly Price	Price Based On Indication With Most Value					
Abraxane (Celgene)								
Metastatic breast cancer	0.18	\$6,255	\$6,255					
Non-small cell lung cancer	0.08	\$7,217	\$2,622					
Pancreatic cancer	0.15	\$6,766	\$448					
Tarceva (Roche/Astellas)								
First-line treatment metastatic non- small cell lung cancer	0.28	\$6,292	\$6,292					
Pancreatic cancer	0.03	\$5,563	\$1,556					
Erbitux (BMS/Lilly)								
Locally advanced squamous cell carcinoma of head/neck	1.64	\$10,319	\$10,319					
First-line treatment recurrent or metastatic squamous cell carcinoma of head/neck	0.23	\$10,319	\$471					
Herceptin (Roche)								
Adjuvant treatment breast cancer	1.99	\$5,412	\$5,412					
Metastatic breast cancer	0.40	\$5,412	\$905					
Source: JAMA article by Peter Bach, Oct. 3, 2014								

Adapted from: P. B. Bach JAMA (2014) 312, 1629 Pink Sheet 20 Oct. 2014

Measuring the Value of Biopharmaceuticals













Value-Based Frameworks for Drug Pricing

- no consensus about evaluation criteria and weightings
- composite from "scores" to "scales" to traditional QALYs
- QALYs do not assess how to weight AEs or ancillary patient-caregiving Ux benefits
- evaluation of individual therapies does not address overall budget impact
 - sofosbuvir for HCV has acceptable QALY but large patient volume creates aggregate cost that overwhelms budgets

Reference Pricing

- uniform pricing of Rx deemed "clinically comparable"
- how should "clinically comparable" be defined?
- instructive precedents?
 - demise of antibiotic R&D
 - immuno-oncology drugs with apparent common MOA but different efficacy (Opdivo™ vs Keytrada™ in NSCLC)

Drug Pricing in Europe

- one country uses price of Rx in a basket of countries to derive benchmark/reference price
- erratic variation in size/composition of basket for comparison
- formulaic variation
 - branded products only vs brands + generics
 - average of lowest prices or lowest price in the basket
- impact of currency variation and distortion of parallel importing
- Rx shortages in countries with low prices

Interventions With Potential for Curative Outcomes

Criteria	Gene Therapy	Stem Cells	TIL, TCR CAR	Organ Transplant	Implantable Devices
one-time procedure	✓	✓	✓	✓	✓
major upfront cost	✓	✓	\checkmark	✓	✓
high R&D complexity	✓	✓	\checkmark	N/A	✓
clinical complexity	L – M	L – M	н	L – M	L – M
life changing potential	✓	√	✓	✓	✓

Pricing and Reimbursement Models for Ultra-High Price Biotherapeutics With Potential 'Curative' Outcomes

- pricing claims based on 'one time' efficacy and elimination of accrued cost of multi-year care (multi-modalities)
- proposals for capped annuity schemes to spread cost over multiple years and limit risk of efficacy not maintained
- requires facile mechanism for annuity transfer between health plans
- potential for discriminatory transfer rejection by new plans or self-funded employer insurance

The Cost of Cancer (USA)

- average price of new cancer drugs has increased 5-10 fold over past 15 years.
- trends in insurance coverage for OOP co-payments by patients has increased to 20-30% drug cost
- average annual US household gross income is \$52K and \$24.1K for Medicare beneficiaries
- US cancer patients more than twice as likely to declare bankruptcy versus other chronic diseases

Cancer Exceptionalism: No Limits-Clinical or Economic?

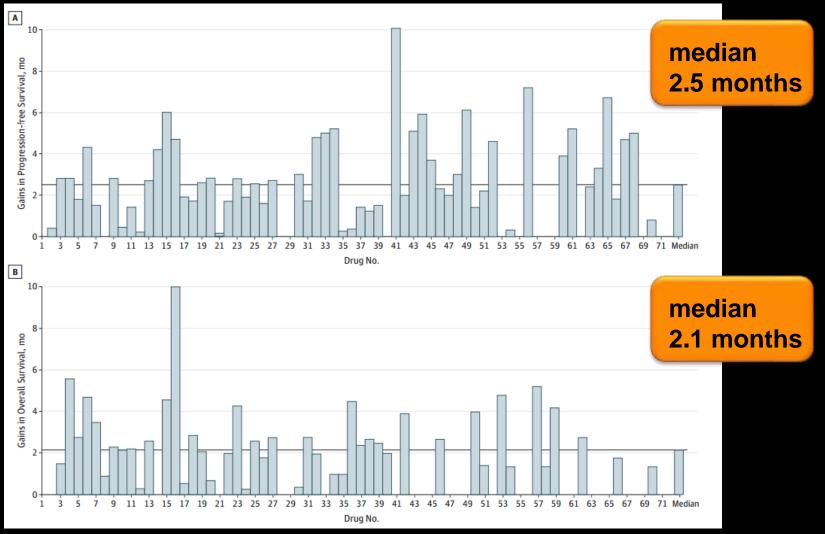
What Represents a Meaningful Advance in Clinical Effectiveness?

Are Regulatory Approval Hurdles Too Low and 'Breakthrough' Status Being Granted Too Frequently?

Is There a Price Point That is Unacceptable Regardless of Long Term Value?

Performance Comparison for New Anti-Cancer Drugs Approved 2002-2014 for Top Ten Pharmaceutical Companies

Gains in Progression-Free Survival (PFS) and Overall Survival (OS) for 71 Drugs Approved by the FDA From 2002 to 2014 for Metastatic and/or Advanced and/or Refractory Solid Tumors



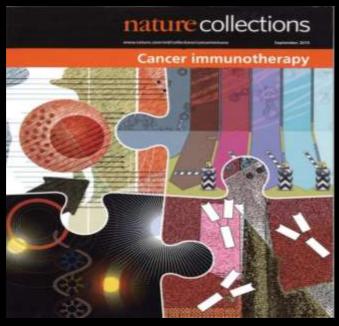
From: T. Fojo et al. (2014) JAMA Otolaryngology-Head & Neck Surgery 140, 1225

Futile Therapy in End-of-Life Care Recommendation

- require providers to absorb cost of administration of futile Rx last two weeks of life in patients with advanced chronic diseases other than for symptom palliation and comfort
 - confronting the 'hang the chemo-bag' or start a new chemo-regimen for cancer patients in ICU or hospice care and deteriorated performance status
 - pharmacy data on prevalence and providers

The Promise of Immunotherapy









The Promise of Immunotherapy: Is Widespread Adoption Economically Feasible?



- unit Rx cost (> \$100K)
- indirect care cost
- escalating cost of combination Rx regimens (> \$200K)
- extravagant cost of cell-based therapies (\$500K - \$1.5 million)
- complex clinical management challenges and compatibility with community oncology services

40-80% patients fail to respond even with I/O – I/O combinations

R&D Costs Continue To Increase In An Increasingly Cost-Sensitive Market

The Imperative to Improve the Efficiency of the R&D Process

Precision Medicine and Implications for Biopharmaceutical R&D and Pricing

Factors Influencing Growth in Clinical Trial Costs

- increased complexity
 - data points per patient
- wide variation in IRB performance
 - delays and overall trial extension
 - institution-specific protocol revisions
- cost of clinical site setup costs and training
- high dropout rate of recruited centers
- patient recruitment and retention
- increased use of comparator trial aims to address payer requirements for RWE

Streamlining Clinical Development

- implement cost reduction process efficiencies
 - use of centralized IRBs versus multiple institutional IRBs
 - new analytics for faster remote data entry and uploading to EHRs
 - increased use of remote health status monitoring, protocol adherence and patient-reported outcomes

Streamlining Clinical Development to Reduce Cost and Accelerated Access for Patients Recommendation

 allow post-registration, pre-approval communication with payers to accelerate formulary placement and reimbursement negotiations

Biopharmaceutical Innovation: The Need to Improve R&D Efficiency

- reluctance to use molecular profiling to segment patient cohorts to differentiate Rx responder and non-responder subsets
 - Companion (CoDx) and complementary (CmpDx) diagnostics
 - market fragmentation versus traditional onesize-fits-all Rx regimen(s)
 - labeling restrictions to limit Rx to CDxidentified responder subpopulation(s)

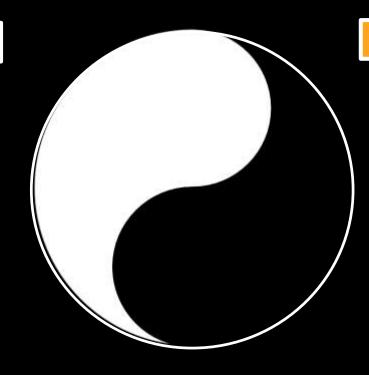
Population-Based Payment Models

- "one-size-fits all" Rx regimens
- treating both responder and non-responder cohorts distorts cost-effectiveness calculus
- additional cost of adverse events from inappropriate exposure of non-responder cohorts to futile Rx

Precision Medicine and Drug Pricing: Confronting the Non-Responder Problem

Industry Risk

- criticism and harsh spotlight on high cost Rx with high nonresponder fraction
- futile therapy
- AE risk and cost



Industry Opportunity

- robust predictive identification of responder (R) and non-responder (NR) patients
- premium pricing and risk sharing
- improved outcomes
- cost savings by elimination of futile Rx/AE risk

oncology drugs as demonstration platform

Confronting the Non-Responder Problem

Industry Risk

- criticism and harsh spotlight on high cost Rx with high nonresponder fraction
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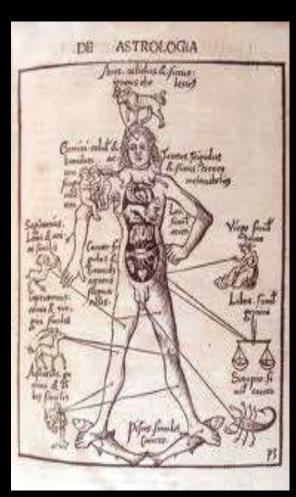
The single Greatest Opportunity For Industry Innovation and ive Cost Effective RX Use? and onder (NR) remium pricing and risk sharing

unity

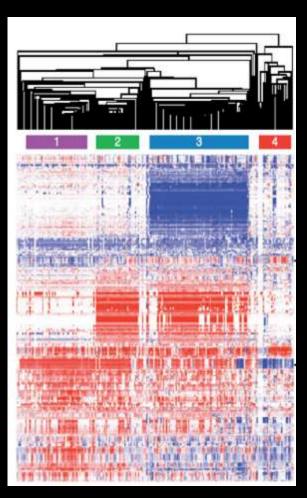
- improved outcomes
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oncology drugs as demonstration platform

The Path to Precision Medicine: From Superstitions to Symptoms to Subtype Signatures







Precision Medicine: Molecular Subtypes, Endophenotypes and the Dynamic Range of Clinical Phenotypes

Symptom and Organ-Based Disease-Based Classification









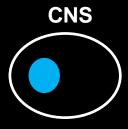
Molecular
Subtypes and
Prevalence







Shared
Network
Perturbations
in Different
Diseases







Challenges in the Use of Molecular panOmics Profiling to Identify Rx Responder (R) and Non-Responder (NR) Patients

- market fragmentation into R and NR subsets as disincentives to Rx companies without guaranteed premium pricing for performancebased outcomes in R subset(s)
- current public and private sector reimbursement policies as major obstacle to develop R-NR profiling assays

A Pricing and Reimbursement Dichotomy





Dx

Rx

Challenges in the Use of Molecular Profiling to Identify Rx Responder (R) and Non-Responder (NR) Patients

- anachronistic reimbursement policies for CoDx/CmpDx assay development
- traditional unianalyte LDTs @ <\$100 and low development cost (<\$5MM)
- new complex multianalyte panOmics platforms for CoDx/CmpDx validation requires larger sunk R&D cost, clinical trials and regulatory validation
 - \$100-300 million
- current reimbursement policies as existential threat to emerging molecular diagnostic industry and delayed trajectory for precision medicine

Development of Diagnostic Assays to ID Rx Responder (R) and Non-Responder (NR)

- incentivize Rx industry to develop diagnostics to differentiate R and NR cohorts
 - premium pricing and labeling constraints for use in R patients only
- overcome current industry reluctance to invest by imposition of progressive price reduction over five year post-launch until R-NR assay introduced
 - reduction amortized over five years based on projected cost of futile Rx in documented percentage of NR patients

Recommendation

- establish reimbursement policies for products and services that improve medication adherence
 - innovator companies, providers
 - telemedicine, wearables
 - use of digital assistants
 - patient coaching and education tools
 - provider alerting systems of non-adherence patterns that pose serious clinical risk

WORLD VIEW Nature (2016) 533, 439 A personal take on events



Society must seize control of the antibiotics crisis

Pressure from the public could force firms to develop new drugs that treat resistant infections, says Carlos Amábile-Cuevas.

Biomedical Products As a Public Good

Proposals for Adoption of a 'Public Utility' Model for 'Essential' Biomedical Assets

The Public Utility Model for Essential Public Goods Products

- water, electricity, gas, critical infrastructure
- regulated pricing plus periodic price increases
 - inflation
 - infrastructure depreciation and new investments
 - R&D investment in new technological alternatives for supply chain improvements and/or consumer benefit

Alternative Models for Increased Public Sector Engagement in Biopharmaceutical Development

- current non-biomedical adoption involves known commodity products
- unclear how R&D risks (failure) would be translated to 'final price'

Alternative Models for Increased Public Sector Investment in Biopharmaceutical Development

- independent public sector network for conduct of clinical trials and product registration
 - more transparent cost?
 - superior process efficiency?
 - poor performance of AMCs, NCATs, NCCN as benchmark precedents?

GoCo model

- which elements of discovery, development and registration?
- manufacturing only?
- poor performance of NIH in CBW countermeasure translation/development (Bioshield) as benchmark?

"Double Dipping"



"Taxpayers who helped fund drug development find themselves unable to afford the cost of treatment."

Rep. Jan Schakowsky (D.IL)



"These (biopharmaceutical) companies grow their businesses with the benefit of taxpayer-sponsored research and then they turn around to gouge the same taxpayers without whom the drug may not even exist."

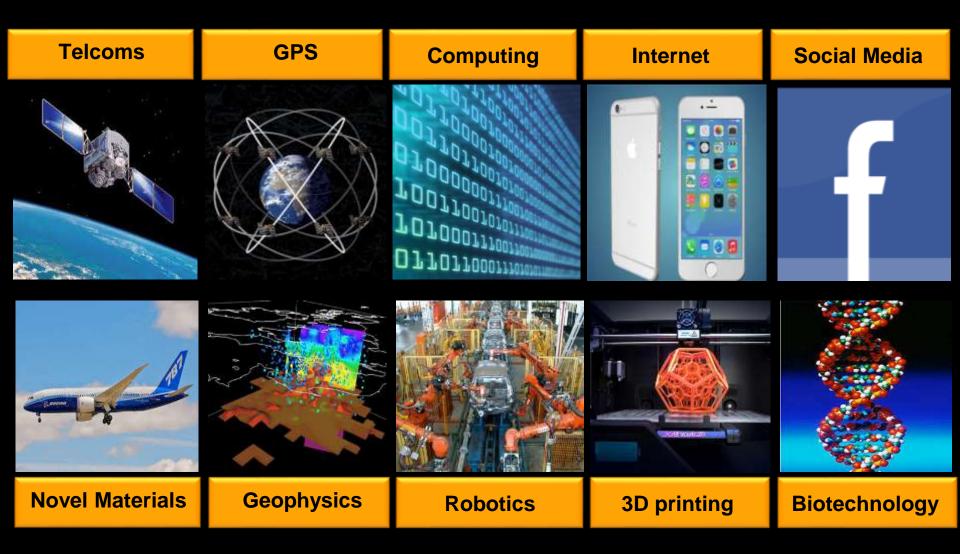
Rep. Rosa DeLauro (D.CT)

The Affordable Drug Pricing Task Force (Democrats Only)

How to Identify and Quantify the Contributions of Taxpayer-Funded Research to Commercial Products

- intellectual lineages of conceptual or technological advances are diffuse and diverse
 - how to demarcate who funded what, when and who?
- contemporary academic biomedical research is increasingly dependent on innovations originating in industry
- reciprocal industry entitlement to recoup investments based on public funded research that cannot be reproduced?

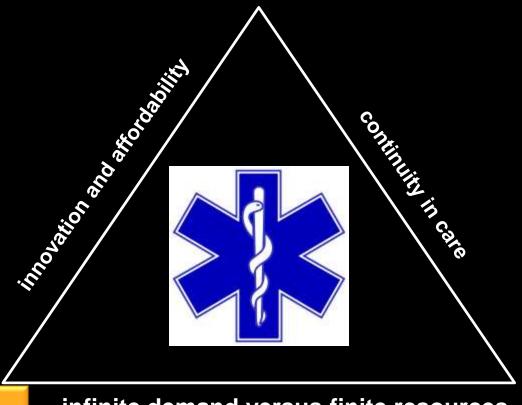
Why Focus on Pharmaceutical R&D as a Beneficiary of Taxpayer-Funded Research and Exclude Other Industrial Sector Beneficiaries?



The Healthcare Challenge: Sustaining Innovation, Improving Outcomes and Reducing Cost

Improved Outcomes

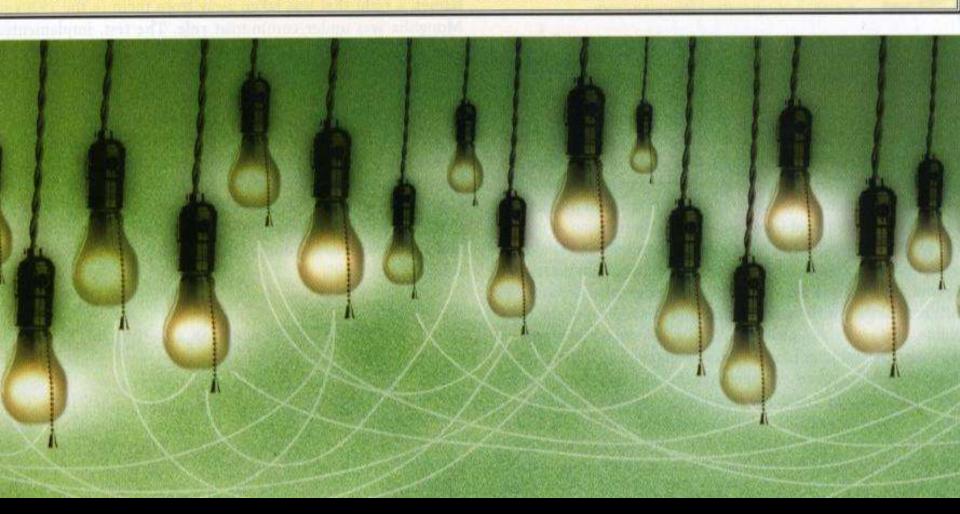
clinical, economic, quality-of-life

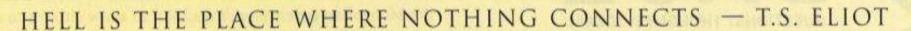


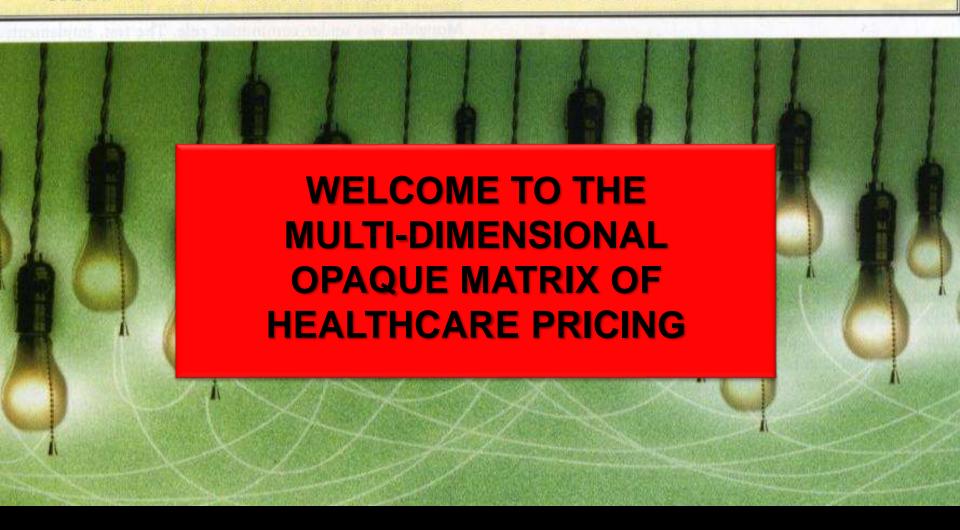
Unmet Medical Needs infinite demand versus finite resources

Access to Affordable Care

HELL IS THE PLACE WHERE NOTHING CONNECTS - T.S. ELIOT







- the sale and pricing of biopharmaceuticals (and much else in healthcare) do not confirm to free market principles
- the pricing of drugs and all aspects of healthcare financing are shaped by myriad sectorial inefficiencies and perverse information asymmetries that render the true costs and profit distribution opaque across the entire supply chain

The Elusive Core Components in the Drug Pricing Debate

- transparency in diverse transactional components in the Rx supply chain
- consensus on what constitutes value in Rx use
- addressing drug pricing as a complex multidimensional problem versus a simplistic, unidimensional focus on list prices
- sophisticated analysis of how Rx selection and use patterns affect the effectiveness and cost of other components of the healthcare ecosystem



"For Every Complex Problem There Is an Answer That is Clear, Simple and Wrong."

- H.I. Mencken

Slides available @ http://casi.asu.edu/

