ASU COMPLEX ADAPTIVE SYSTEMS
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Navigating the Multi-Dimensional Complexity of Drug Pricing

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Fifth Annual Reimbursement and Access Conference
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(Bio)Pharmaceuticals

- one of the most efficient and cost-effective solutions to illness?

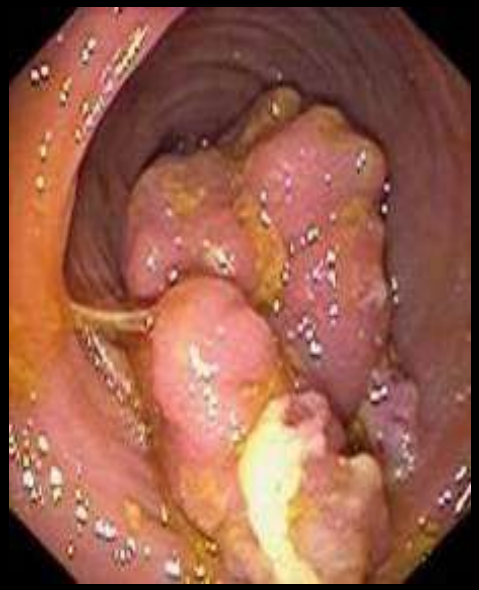
or

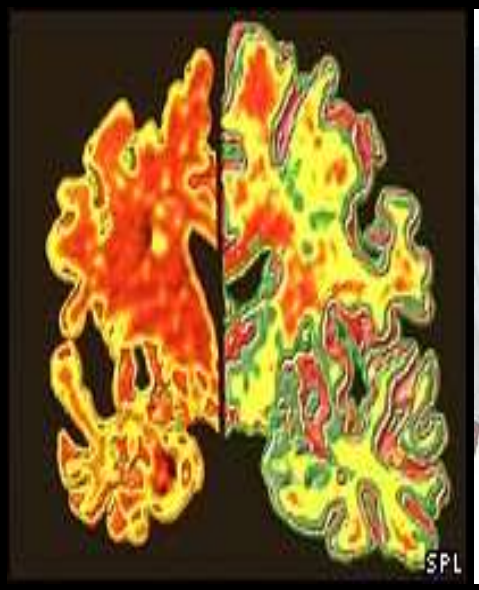
- overpriced and a major contributor to rising healthcare costs (society) and the affordability crisis (society and individuals)?

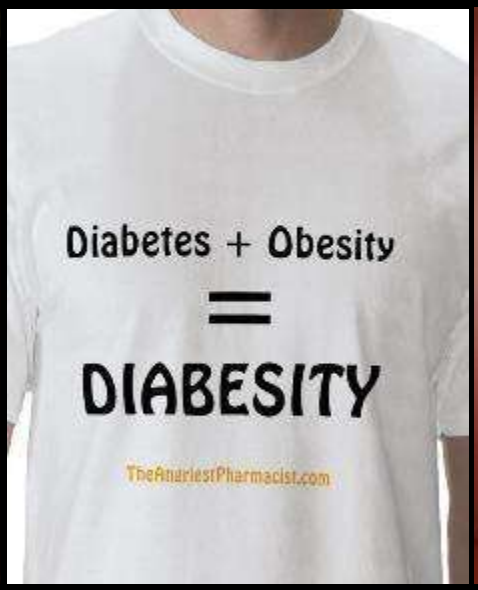
- how are Rx price(s) determined?
- what is a fair price to reward risk and sustain innovation?
- who profits and how much?
- how are value and access determined, by whom and for whom?
- how can affordability be balanced with incentives to sustain R&D investment in new Rx innovation?
- is the pace and cost of overall innovation outstripping our ability to afford certain categories of care?

- are financial returns on biopharmaceutical products excessive?
- why do US patients pay higher Rx prices than other G20 countries?
- is the biopharmaceutical industry receiving a ‘free ride’ by exploiting taxpayer-funded biomedical research?
- should medicines be viewed as an essential public social good and subject to provisions to ensure their availability and affordability?
- do individuals have a ‘right’ to unlimited healthcare services?

Disease Burden:
Confronting the Largest Economic Disruptions and Threats to Sustainable Healthcare

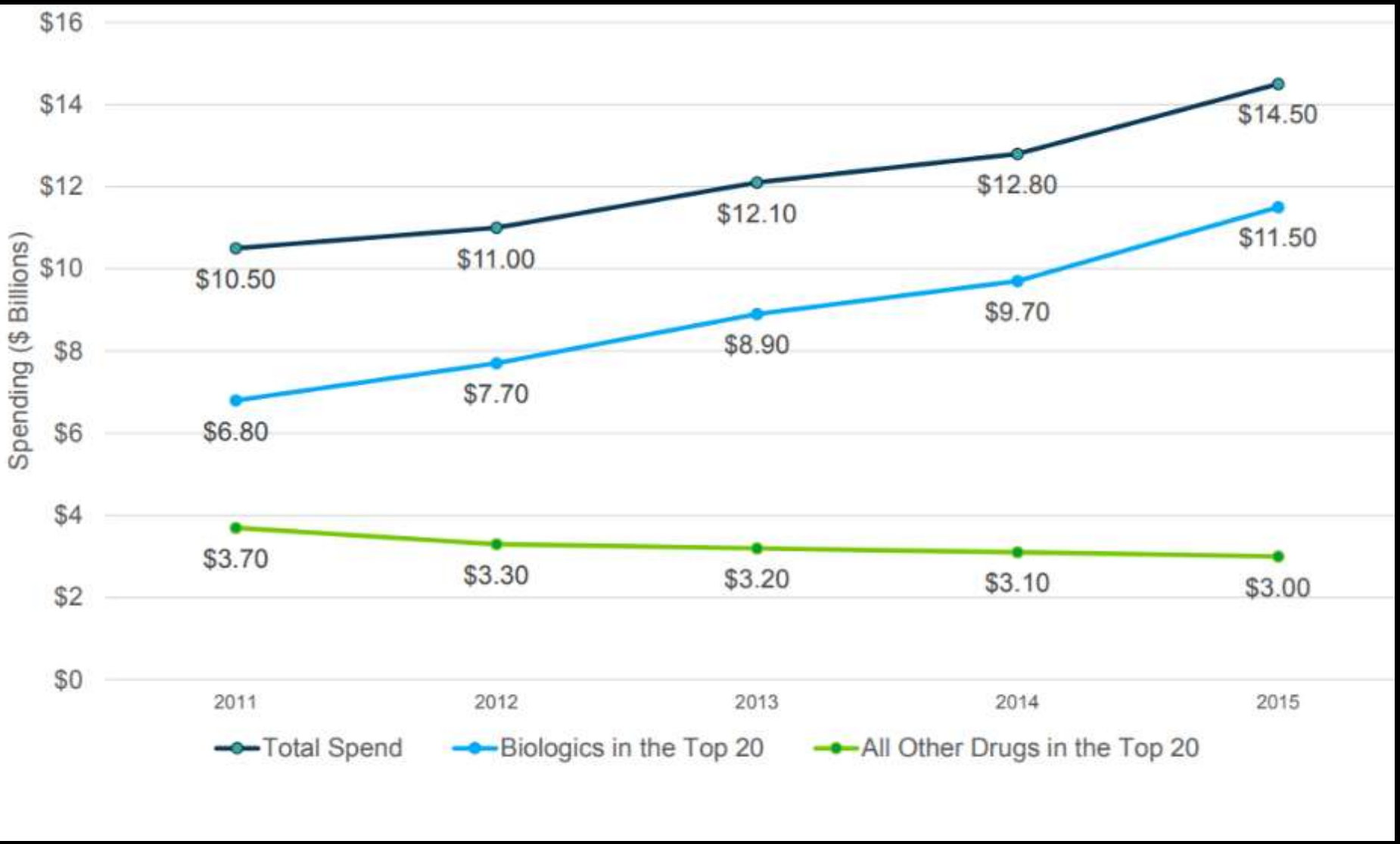






cancer	neurodegeneration	cardio-vascular/ metabolic disease	mental illness

Medicare Top 20 Part B Spending Trends: The Economic Impact of Speciality Pharmaceuticals

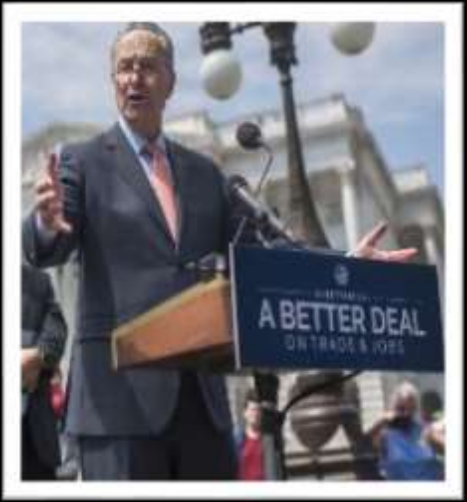


From: D. Mendelson, President, Avalere Health. Statement to Senate HELP committee. 13 June 2017

The Next Wave of High-Priced Biopharmaceuticals

- immuno-oncology combination Rx
  - CTL4 + PD1-PDL1 inhibitors
  - >$200,000 per treatment (before cost of clinical care services)
- immuno-oncology cell therapies
  - individualized TIL, TCR, CAR therapies
  - estimated $0.5 to 2 million/patient
- new orphan drugs and gene therapy

“Unconscionable Price Increases and Price Gouging”: The Biopharmaceutical Sector and Reputational Damage



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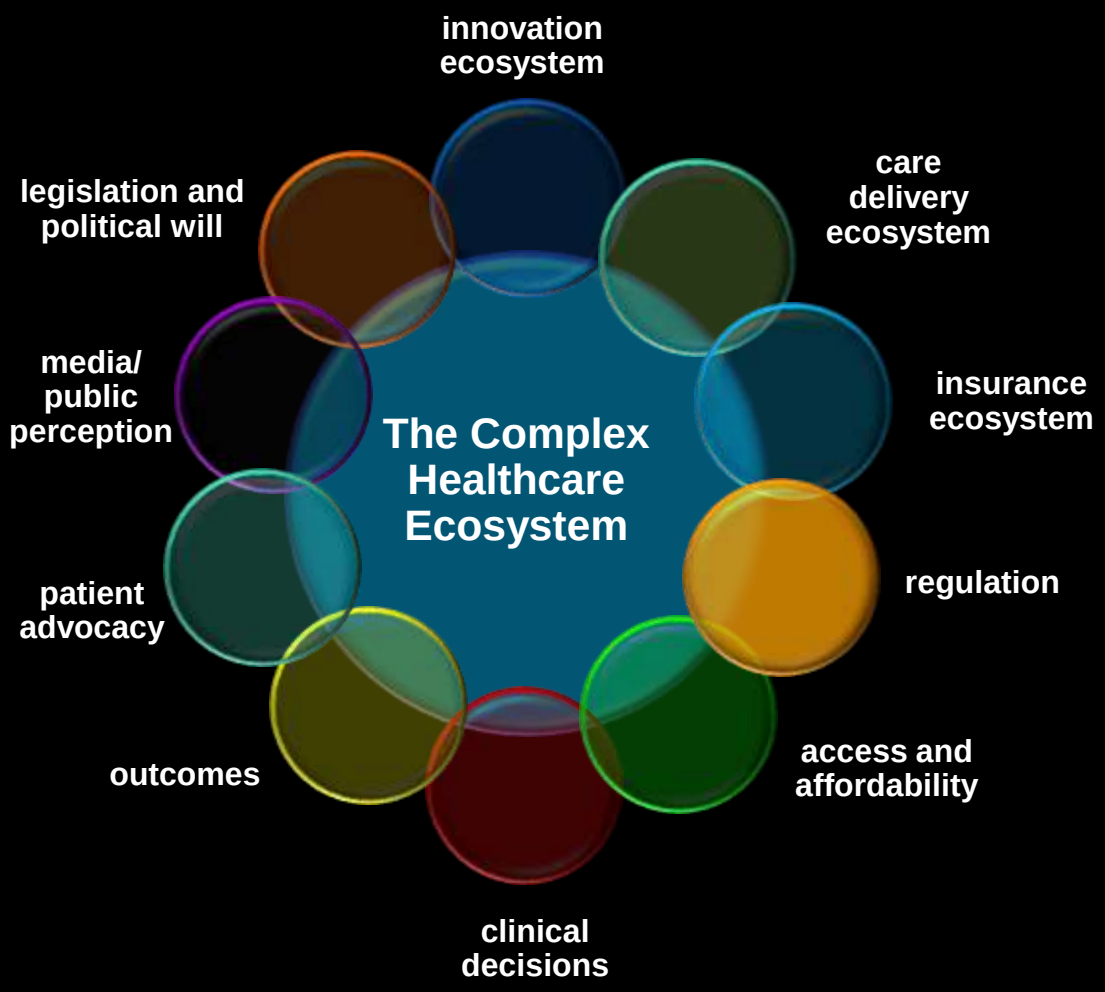
Bio
Biotechnology
Industry
Organization

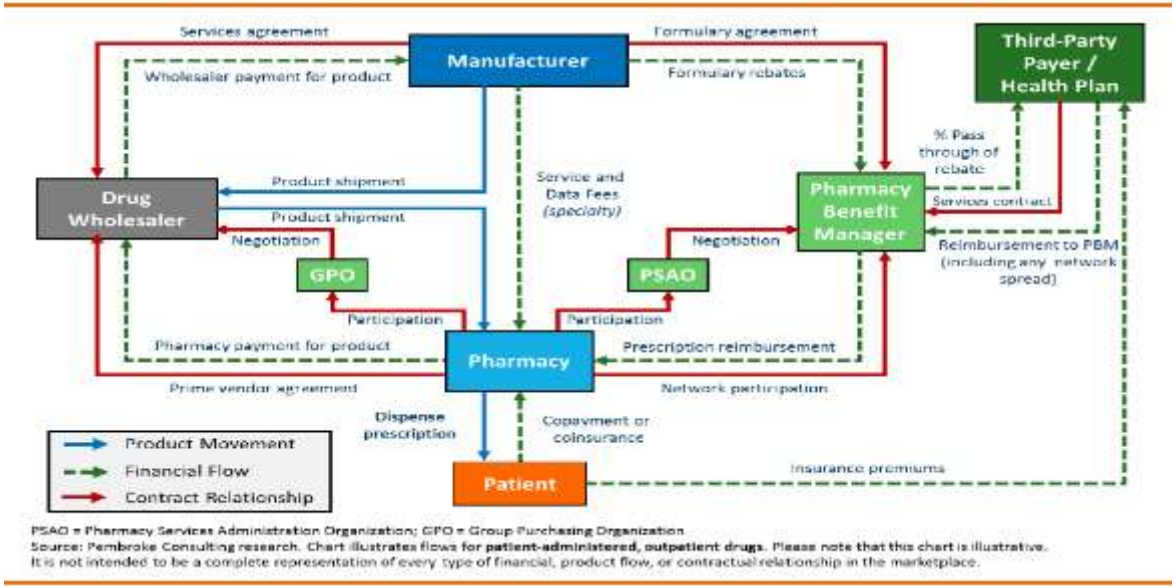
Unidimensional Approaches to Complex, Multidimensional Problems: A Prescription for Flawed Conclusions, Ineffective Policies and Unintended Consequences

unidimensional

multi-dimensional



Transactional Relationships in the US Pharmaceutical Distribution System:



A Byzantine Matrix of Complexity and Opaqueness

June 2017

Drug Pricing and Negative Public Opinion of Biopharmaceutical Companies

- increased OOP spend and increased deductibles make Rx the most visible component of the cost of care to many patients particularly in chronic disease/co-morbidities
- many patients ‘shielded’ from billing for other categories of care that may be highly cost-ineffective and/or subject to high price escalation
- general lack of public awareness of role of PBMs, pharmacies and providers in final price to patient

http://phrma-docs.phrma.org/files/dmfile/Prescription-Medicines---Costs-in-Context---June-2017.pdf

Industry Perspectives:
The Challenge of 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 payer requirements to demonstrate post-approval 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
- average peak product sales declined from $816 MM (2010) to $416 MM (2015)
  - reimbursement levels, competition and smaller patient volumes
- continued escalation of OOP and capitalized R&D cost per approved new NME/NBE
  - $2.5 billion
  - DiMasi et al. (2016) J. Health Econ. 47, 20

Global Differences in List Prices for 8 Branded Cancer Drugs

D. A. Goldstein et al. (2017) ASCO Abstract 124280

The ‘Price Premium’ for Rx in the USA Versus Lower Costs in Other G-20 Nations

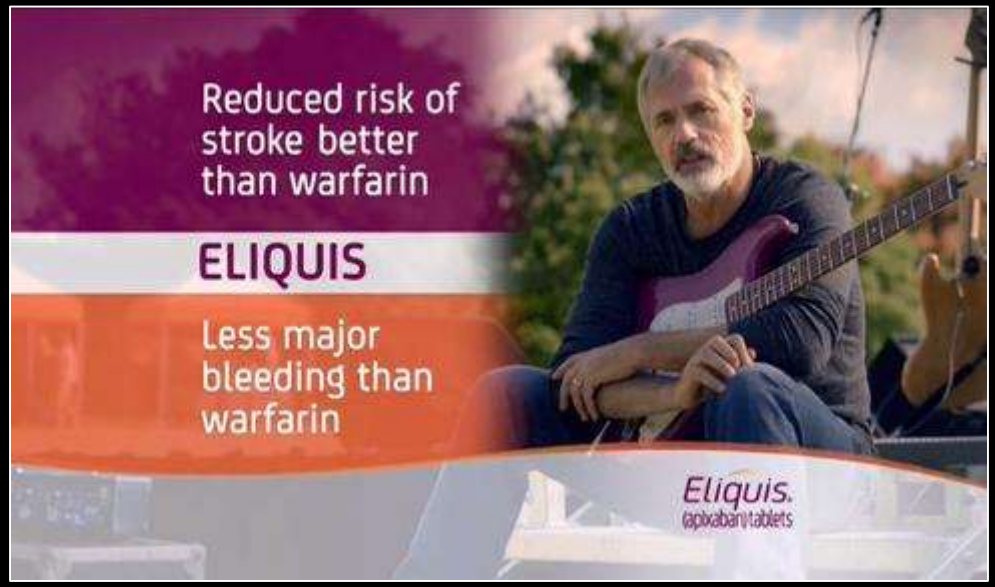
- a.k.a. ‘the free rider’ problem
- industry position that price premium is necessary to sustain investment in high risk: high cost R&D
- role of regulators and other HTAs in pricing negotiations in foreign countries
- monopsony buyers
  - price controls and expenditure caps
  - reference pricing

Excess Revenues Earned Through Premium Pricing Of Products In The US As A Percentage Of The Company's Global Research And Development Expenditures, 2015

	International Price vs USA	Revenues from US Premium as % Global R&D
Abbvie	48%	166%
Amgen	43%	239%
AstraZeneca	36%	101%
Biogen	25%	245%
BMS	45%	76%
Roche	45%	119%
GSK	48%	114%
JNJ	39%	163%

N. Yu et al (2017) Health Affairs Blog 7 March 2017

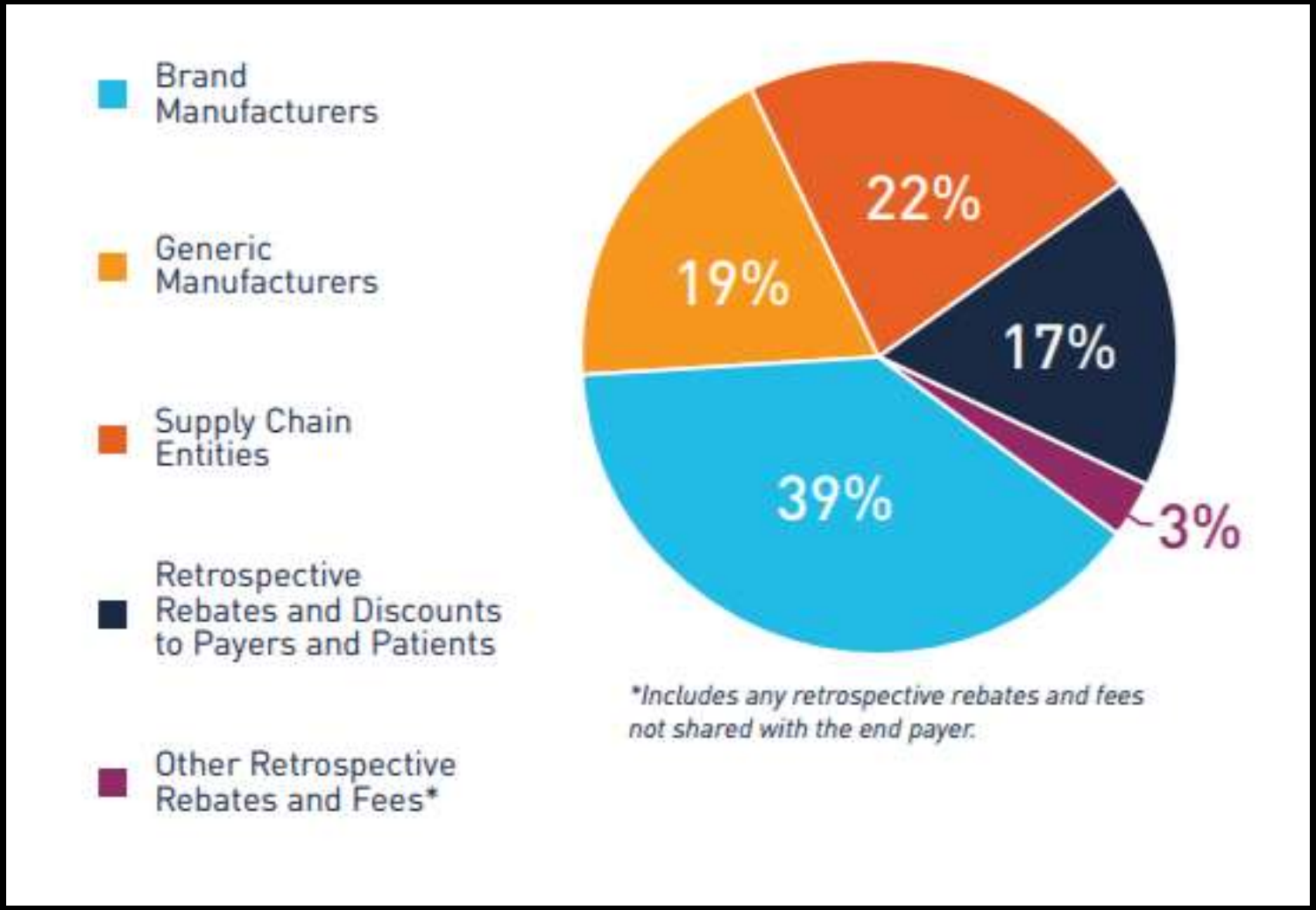
Expensive DTC Campaigns



Industry Critics

- sales and marketing 1.2 to 2.3X higher than R&D
- direct-to-consumer (DTC) advertising
  - drive up Rx use
  - high cost ‘glam-mercials’
  - wow: everyone is healthy, active, affluent and live in nice neighborhood’s
- promotion shift from print to TV to social media
  - identification of high prescriber MDs
  - identification of patients and click tools to ensure ‘brand stickiness’
  - first amendment rights upheld

Distribution of 2015 Gross U.S. Drug Expenditures ($349 Billion) by Manufacturers & Non-Manufacturer Stakeholders



From: A. Vandervelde and E. Blalock (2017)Berkeley Research Group

Biopharmaceutical Pricing

- innovator net margins have remained largely constant despite escalating invoiced prices
- lack of transparency about how the expanded margin is divided
  - relative distribution to PBMs, payers, pharmacies, providers, patients?
- consolidation in PBM and pharmacy sectors
  - scale and ‘negotiation clout’ for discounts and rebates

The Role of Intermediaries in the Final Price Paid by Plans and Consumers

- lack of transparency about pass through of negotiated discounts to plans and consumers
- potential for consumers to pay higher cost than intermediary Rx acquisition cost
  - common experience in high deductible plans with Rx charged at list price
  - for generic drugs consumer co-pay may exceed the cost of the drug
  - uninsured patients typically pay more than insured patients

Control of Drug Expenditures by Use of Multi-tier Formularies and Speciality Drug 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 requirement
- ‘step therapy’: treatment with lower cost drug(s) before approval of more expensive Rx
- ‘clinical pathways’: physician (dis)incentives to prescribe particular Rx regimen(s)

Policy Options to Examine the Role of PBMs and Pharmacies in Drug Pricing

- require greater transparency in ranking criteria and weightings used by PBMs in development of multi-tier formularies
- require annual reports from PBMs on percentage of patients failing on lower tier(s) before migration to next tier(s)
  - expand use to quantify RWD or comparative effectiveness
  - economic and clinical impact of futile therapy imposed by step therapy

Patient Co-Pay Assistance Programs (PAPs) from Branded Manufacturers

- estimated $7 billion (2015) versus $1 billion (2010) (IMS data)
- reduce patients' OOP costs
- criticized as tactic to circumvent formularies switching to lower cost generics
- PBM actions to exclude Rx with PAPs from formularies

Granting CMS Authority to Negotiate Drug Prices With Rx Manufacturers

- expand CMS price negotiation authority comparable to other healthcare purchasers
- estimated $15 billion/year cost savings
- uncertain impact in reducing drug prices for 170 million with private health insurance
- concern that companies would seek to recoup ‘diverted profitability’ from private insurers

Potential Regulatory Actions to Reduce Drug Prices

- no formal authority regarding pricing
- expedited review of branded (and generic) products to increase market competition
- FDA / CMS action to allow earlier post-submission/ pre-approval provision of data to PBMs / payers on Rx performance
  - accelerate formulary placement and/or SOC guidelines

Policy Options for Coverage of High Cost Drugs with Accelerated Regulatory Approval

- large fraction of high cost oncology drugs
- approval based on trials with ever smaller patient cohorts
- need to validate real world efficacy / safety
- sponsor provides pricing concessions until confirmatory trials completed
- portion of payment held in escrow account and reimbursed when clinical efficacy confirmed
- FDA enforcement of due diligence in conduct of confirmation trials
  - start date (within 3 months) and completion date (by indication)

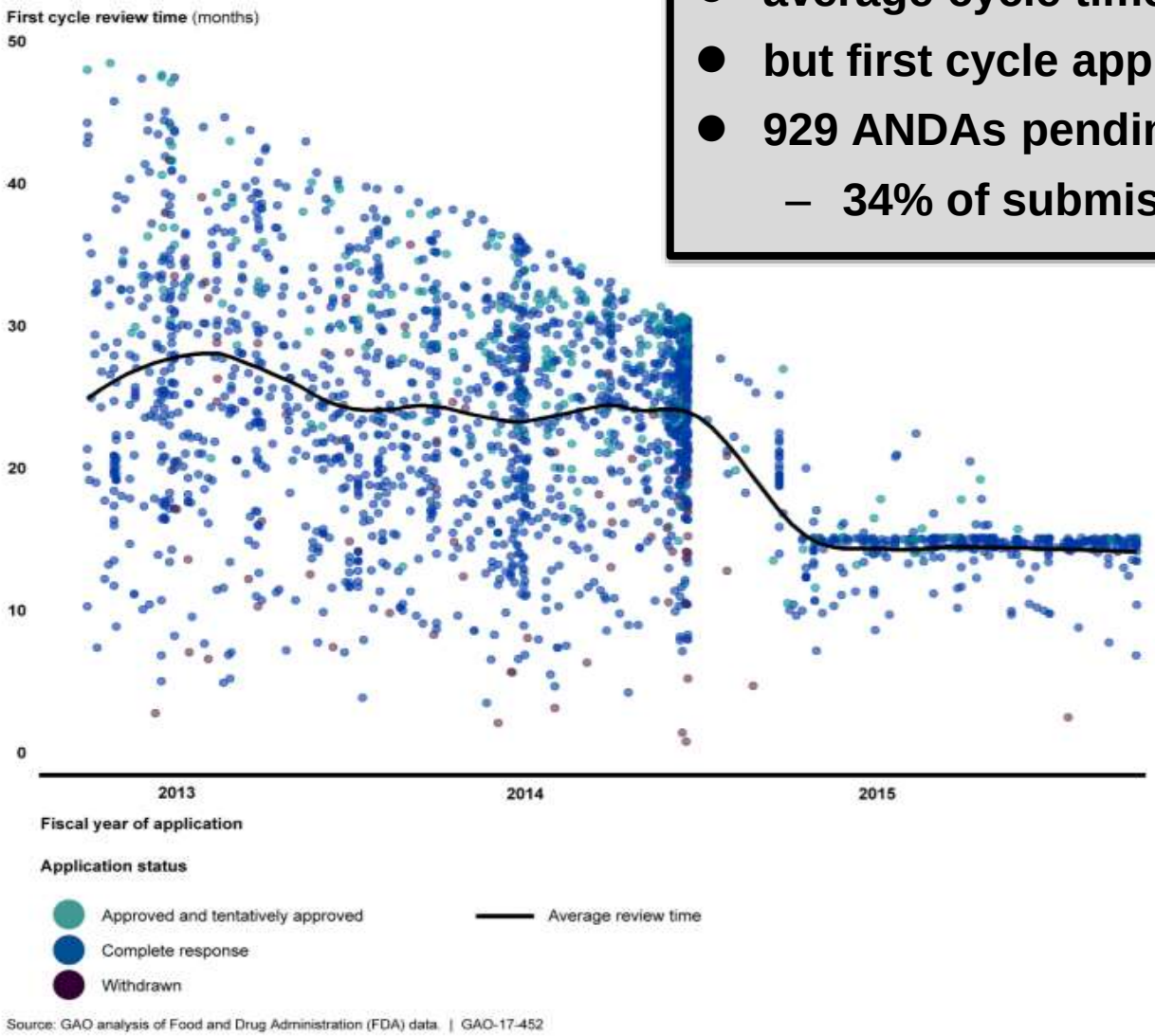
Ratio of Gross Profits on Generic Versus Branded Products

Entity	Ratio
PBMs	x4
wholesalers	x11
pharmacies	x12

From: N. Sood et al (2017) USC Schaeffer 207

http://healthpolicy.usc.edu/flowofmoneythroughthepharmaceuticaldistributionsystem.aspx

FDA Review of ANDAs (2013-2015)



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-17-452

- average cycle time reduced to 14 months
- but first cycle approval rate still <10%
- 929 ANDAs pending review since GDUFA1
  - 34% of submissions in period 2013-15

GDUFA II

Commissioner
S. Gottlieb

- launch 1 Oct. 2018
- eight month priority review pathway for generics with less than three ANDAs approved for the reference brand drug(s)
- list of 267 off-patent drugs that lack generic versions published 27 June 2017
- reduce multi-cycle reviews

Potential Policy Reforms to Enhance Use of Generic Drugs and Biosimilars

- prohibit anti-competitive pay-for-delay transactions with generic manufacturers
- prohibit use of PAPs/co-pay coupons for branded drugs with generic competition
- ensure generic/biosimilar manufacturers gain access to samples of branded products for bioequivalence testing/clinical validation

Potential Policy Reforms to Enhance Use of Generic Drugs and Biosimilars

- convert permissive generic substitution policies to mandatory
- eliminate patient consent requirements for generic substitution
- limit ’carve outs’ for substitution in particular disease categories

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%
  - L.N. Newcomer (2016) The Oncologist 21, 779
- ‘seduction by margin’ exacerbated by 340B programs
  - heavily discounted (30-50%) drugs prescribed to fully insured patients
  - makes use of high cost drugs irresistible
  - M. Kolodziej (2016) The Oncologist 21, 782

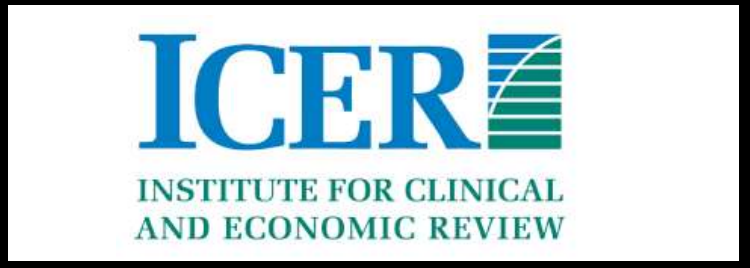
When 340B Hospitals Buy Oncology Practices Prices Go Up

- price for oncology drugs administered in hospital versus typically double price paid for community clinic
- Herceptin
  - hospital/hospital outpatient $5,350
  - independent clinic $2,740
- Avastin
  - clinic ($6,620), hospital ($14,100)
- incentive for purchase of community clinics by hospital systems and reclassification as ‘hospital outpatient clinics’ and eligible for 340B discounts

“Price is what you pay.
Value is what you want.”

Warren Buffet

Measuring the Value of Biopharmaceuticals



Value-Based Frameworks for Drug Pricing

- composite from “scores” to “scales” to traditional QALYs
- no consensus about evaluation criteria and weightings
- QALYs do not assess how to weight AEs or ancillary patient-caregiver 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 potentially overwhelm short term budgets

The Economics of Antiviral Therapies for Hepatitis C

- actuarial analysis
  - B. Pyenson et al (2015) Milliman Inc. (Sept. 2015)
- projected to reduce future healthcare spending by $115 billion
- far less than society will pay for these agents over same period (c. $30 billion)

Is the US Market Primed for Value-Based Contracting?

- performance (outcomes) – based pricing
- indication – based pricing
- reference – based pricing

Performance(Outcomes)-Based Pricing: More Complicated Than It Might Seem

- acute versus chronic diseases
- treatment of chronic diseases by Rx that act on a single target (HCV)
  - “cure”
- chronic diseases with highly variable and extensive underlying disruption in molecular networks
  - cancer, neurodegeneration, mental disorders
  - low efficacy and high inter-patient variation
- monotherapy versus polypharmacy regimens
  - multiple comorbidities

The Need for Holistic, Systems-Based Analysis In Defining the Value of Rx Therapy

- include indirect costs or savings
- cost
  - versus alternatives/SOC
  - need for new procedures/equipment/education and training of HCPs
  - clinical management of toxicities
- savings
  - versus alternatives/SOC
  - reduced (re)hospitalizations and/or duration of stay
  - elimination of costs associated with prior SOC
- greater weighting of patient experience and PROs

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

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 Keytruda™ in NSCLC)

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 if efficacy not maintained
- requires facile mechanism for annuity transfer between health plans
- potential for discriminatory rejection of transfer by new plans or self-funded employer insurance

Monthly and Median Costs of Cancer Drugs at FDA Approval 1965-2016

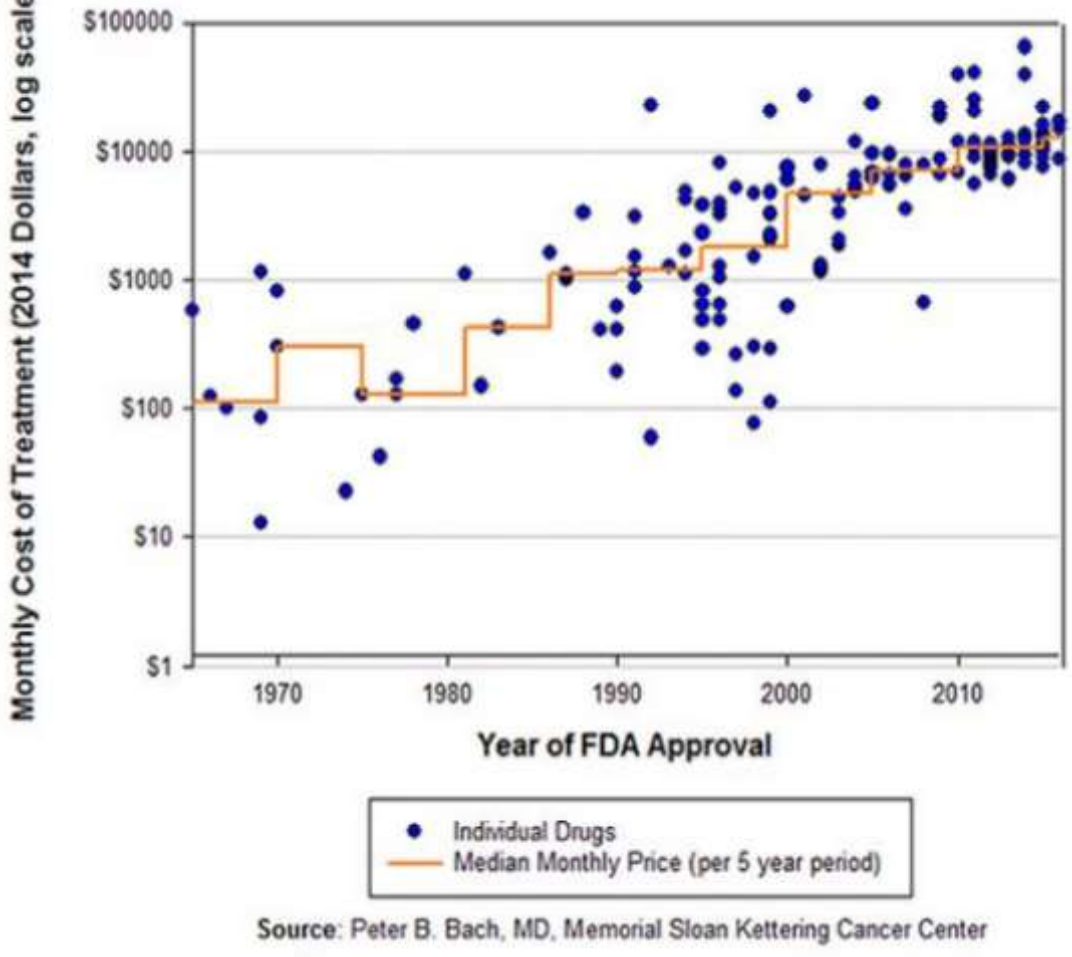
Navigating the Coverage Experience and Financial Challenges for Cancer Patients:

Affordable Care Act Brings Improvements, But Challenges Remain

By JoAnn Volk and Sandy Ahn

Cancer Action Network™ American Cancer Society

CENTER ON HEALTH INSURANCE REFORMS

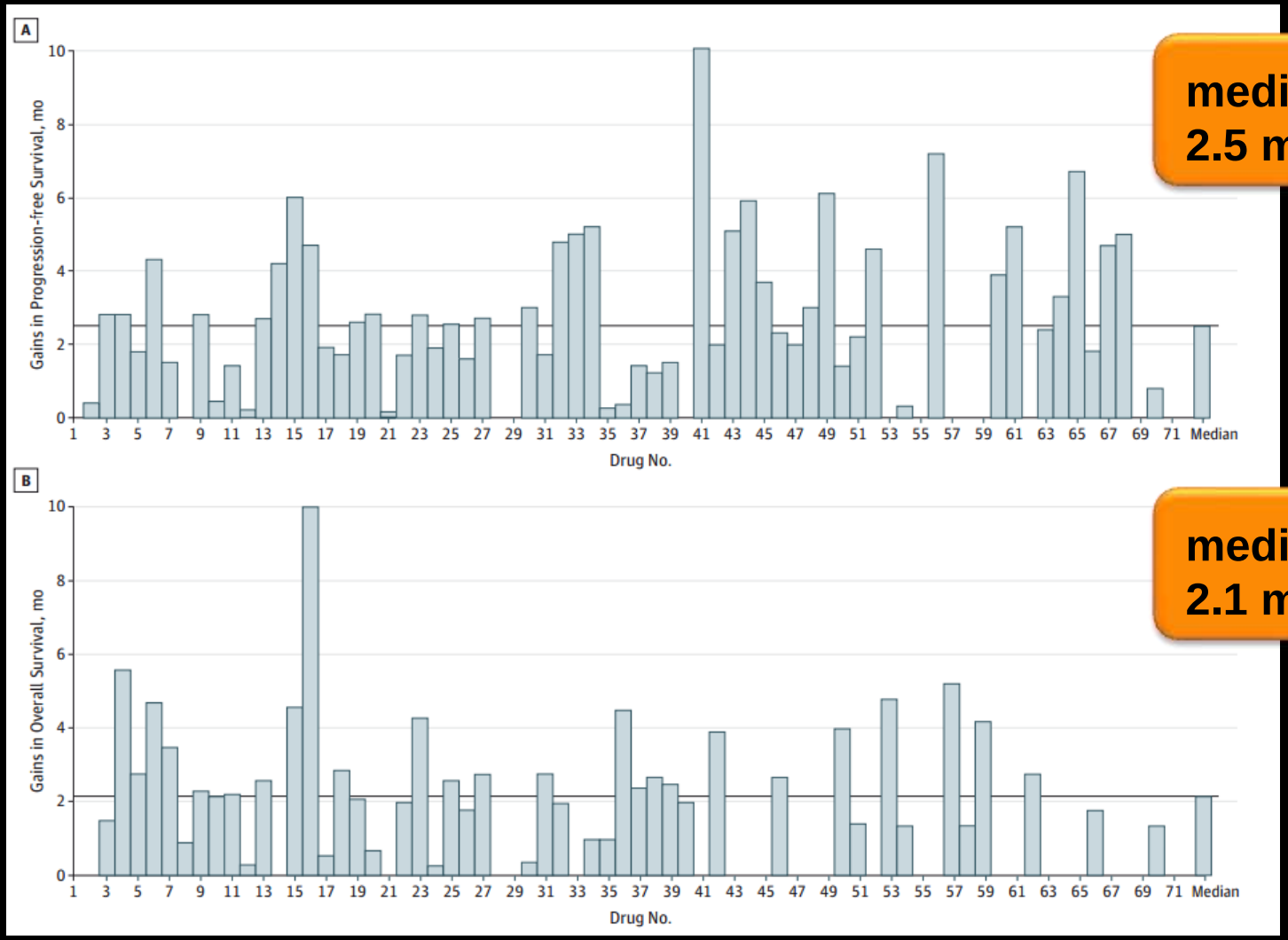


Source: Peter B. Bach, MD, Memorial Sloan Kettering Cancer Center

What Constitutes a Meaningful Clinical Benefit?

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

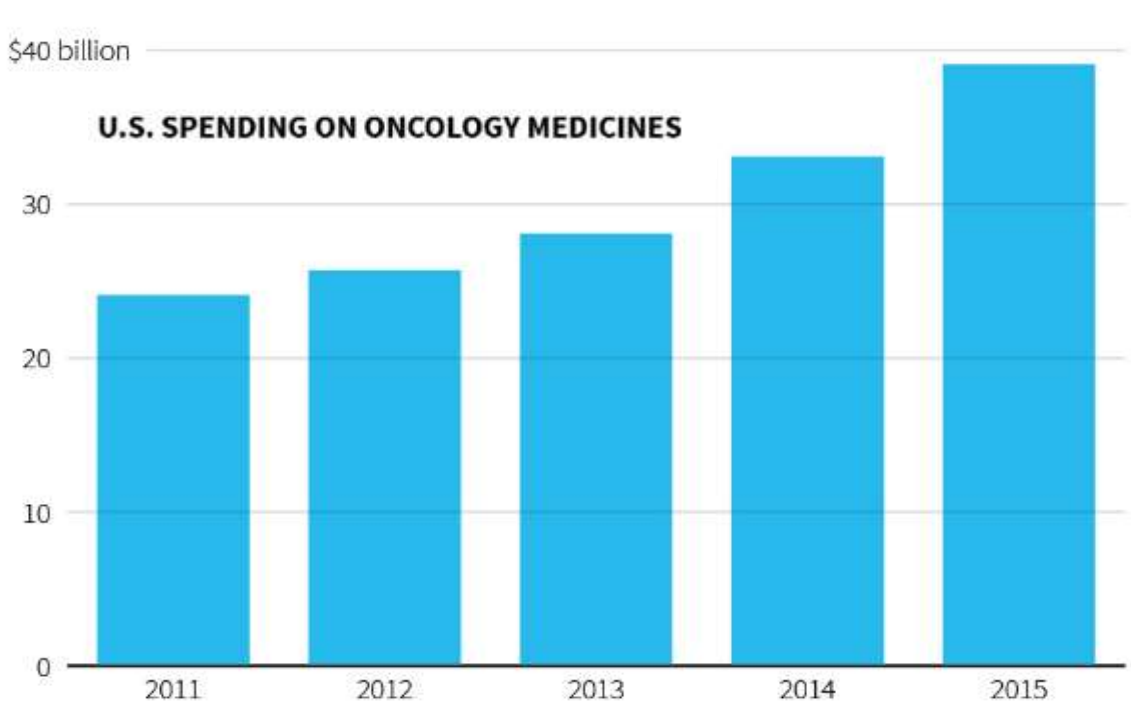


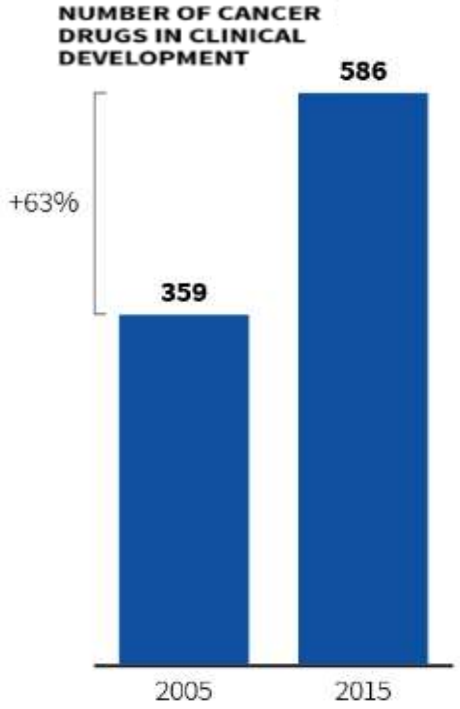
median 2.5 months

median 2.1 months

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

Meeting the Demographic Challenge in Cancer Treatment: All Malignancies Projected to Increase 20% by 2020





PD1/PDL1 CHECKPOINT INHIBITOR PRICES

Estimated average per month*

Opdivo	Keytruda	Bavencio**	Tecentriq
BRISTOL-MYERS SQUIBB	MERCK	PFIZER	ROCHE HOLDING
$13,100	$13,000	$13,000	$12,500

* Drug price is based on the milligrams of medicine used and varies with the weight of the individual patient.
** Bavencio's price is the wholesale acquisition cost for an average patient.

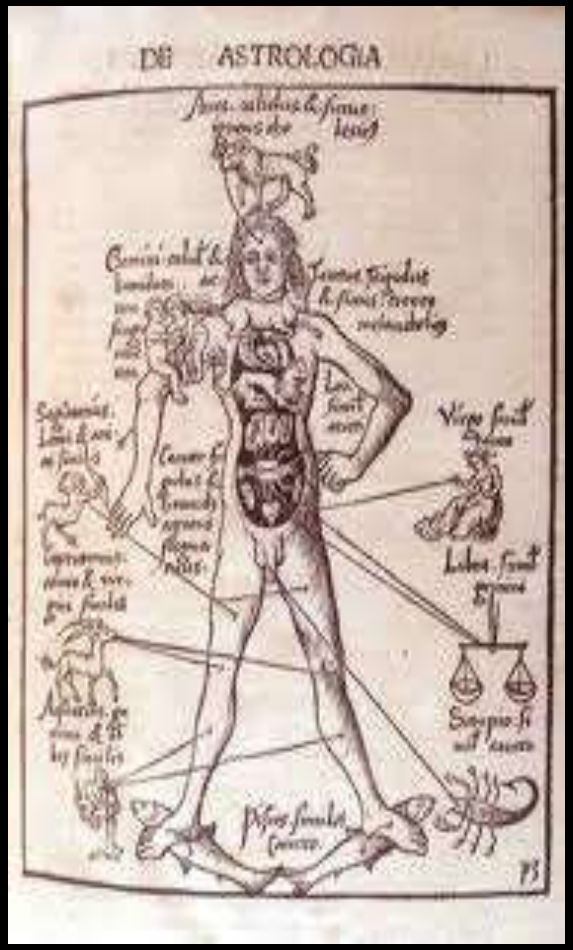
Sources: QuintilesIMS Institute ; Reuters

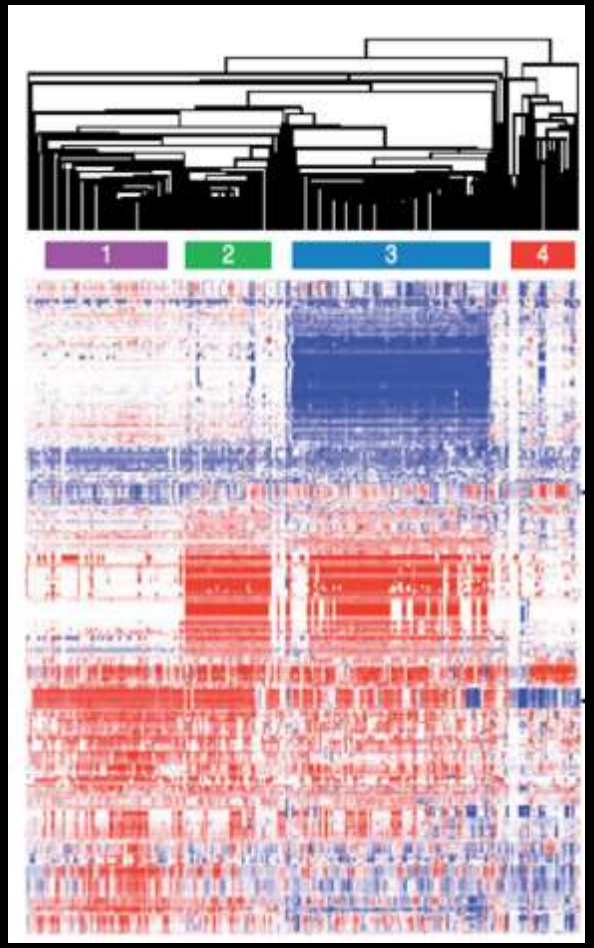
The Promise of Immunotherapy: Is Widespread Adoption Economically Feasible?

- 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

The Path to Precision Medicine:
From Superstitions to Symptoms to (Molecular) Signatures





Precision Medicine:
Multi-Omics Profiling of Alterations in Molecular Signaling Networks in Disease

- (epi)genome
- RNAome
- proteome
- metabolome
- regulome
- exposome

- right disease
- right drug
- right patient
- right time
- right dose
- right outcome

Population-Based Treatment and 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

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

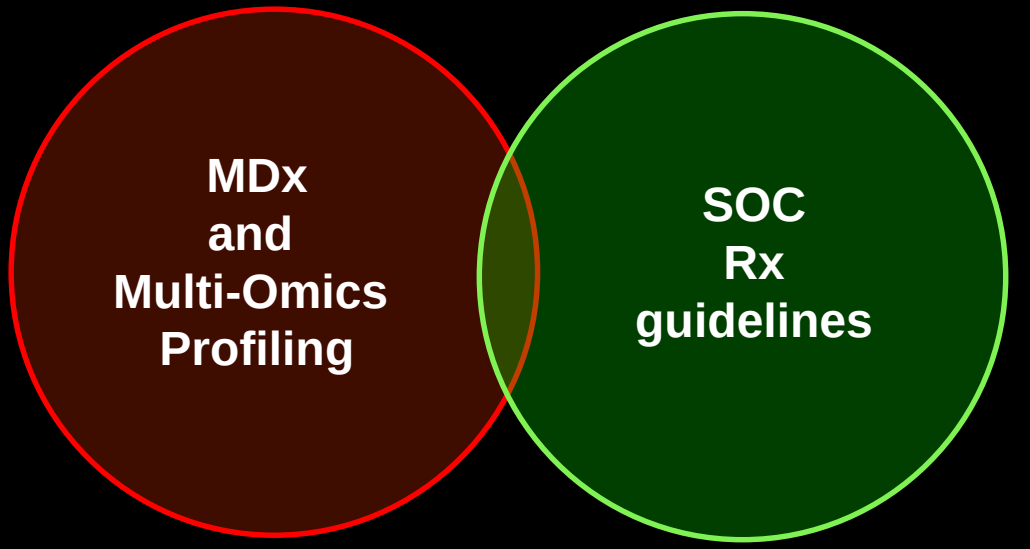
- market segmentation into R and NR subsets as disincentives to Rx companies without guaranteed premium pricing for performance-based outcomes in R subset(s)
- current reimbursement policies for molecular diagnostics as major obstacle to develop R-NR profiling assays

A Pricing and Reimbursement Dichotomy

MDx

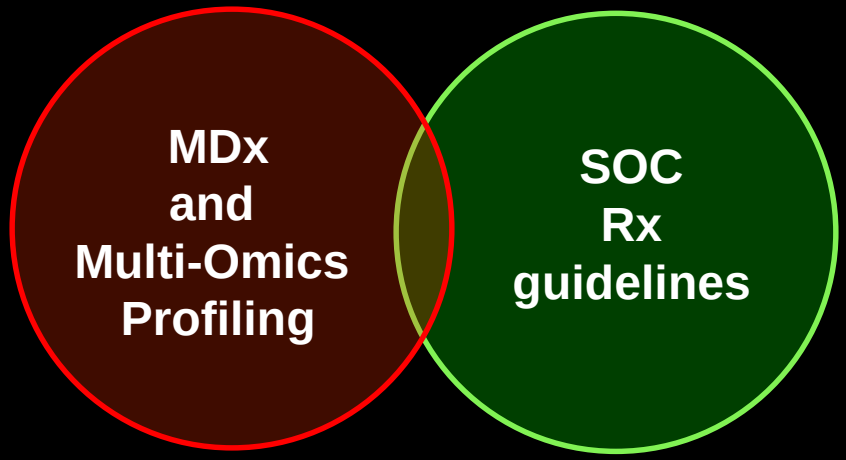
Rx

Conflicts and Contrasts in Reimbursement Policies and Clinical Utilization of Molecular Diagnostics (MDx) and Therapeutics (Rx) in Oncology



Disease Subtyping and ID of Rx-Responsive Cohorts	High Cost Rx Without Subset Profiling
Precision Diagnosis and Rational Treatment Selection	Propagation of Therapeutic Regimens With Variable Response Rates

Conflicts and Contrasts in Reimbursement Policies and Clinical Utilization of Molecular Diagnostics (MDx) and Therapeutics (Rx) in Oncology



- Cost-Based Versus Value-based Pricing of MDx
- Uncritical Acceptance of Rx Pricing
- Barriers to Innovation and Recovery of Increased R&D Cost
- Incentives to Sustain One Size-Fits-All Regimens

Multigene Test Reimbursement Policies for Five Largest US Private Payers (Enrollment 112 Million Lives)

Payer	# Policies	# Tests Included	% Policies Covering All Included Tests	% Policies Covering Some But Not all Included Tests	% Policies Covering None of Included Tests
1	7	48	43	29	29
2	15	116	13	27	60
3	4	40	25	50	25
4	15	54	13	13	73
5	14	55	29	36	36
Total	55	313	22	27	51

Adapted from: K.A. Phillips et al (2017) Nature Biotechnol. 35, 616

Development of Molecular Diagnostic Assays to Identify Rx Responder (R) and Non-Responder (NR) Patients

- guarantee premium pricing for Rx use in R patients only
  - labeling and obligate need for companion MDx
- incentivize industry to invest in MDx by imposition of progressive Rx price reductions over five year post-launch period until R-NR assay introduced
  - price reductions amortized over five years based on cost of futile Rx in documented percentage of NR patients

Biomedical Products As a Public Good

Adoption of ‘Public Utility’ Model for ‘Essential’ Biomedical Assets

Application of the Public Utility Model for Essential Public Goods Products to Pharmaceuticals

water, electricity, gas, critical infrastructure

- regulated pricing plus periodic price increases
- commodity products/services with known performance characteristics and markets

biopharmaceuticals and other technology-intensive biomedical products

- who sets R&D priorities?
- how would R&D risk (failure) be amortized in final pricing of pharmaceuticals?
- what fraction of revenues would be reinvested to sustain next cycle of innovation?
- competitiveness versus private sector in EU/China?

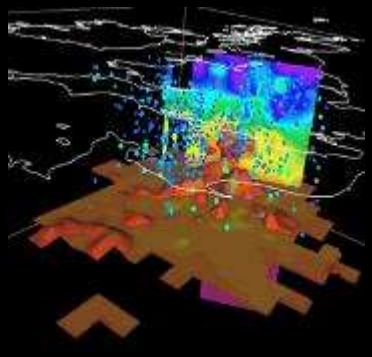
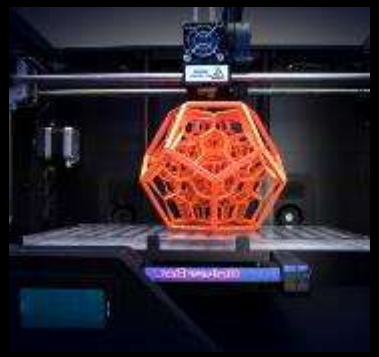
“People have the right to know
how much was paid by the taxpayers
in the form of research to develop that (sic) drug.”

Debra Whitman
Chief Public Policy Officer, AARP
HHS Forum on Drug Prices, 30 Nov. 2015
Cited in Bioworld Today 26, 224

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

- origins of most technological advances are diffuse, diverse and typically spread over several decades
- how to demarcate (and reward?) research done in overseas research laboratories
- academic biomedical research is increasingly dependent on innovations originating in industry
- reciprocal industry entitlement to recoup failed investments based on publically funded research that was not reproducible?

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

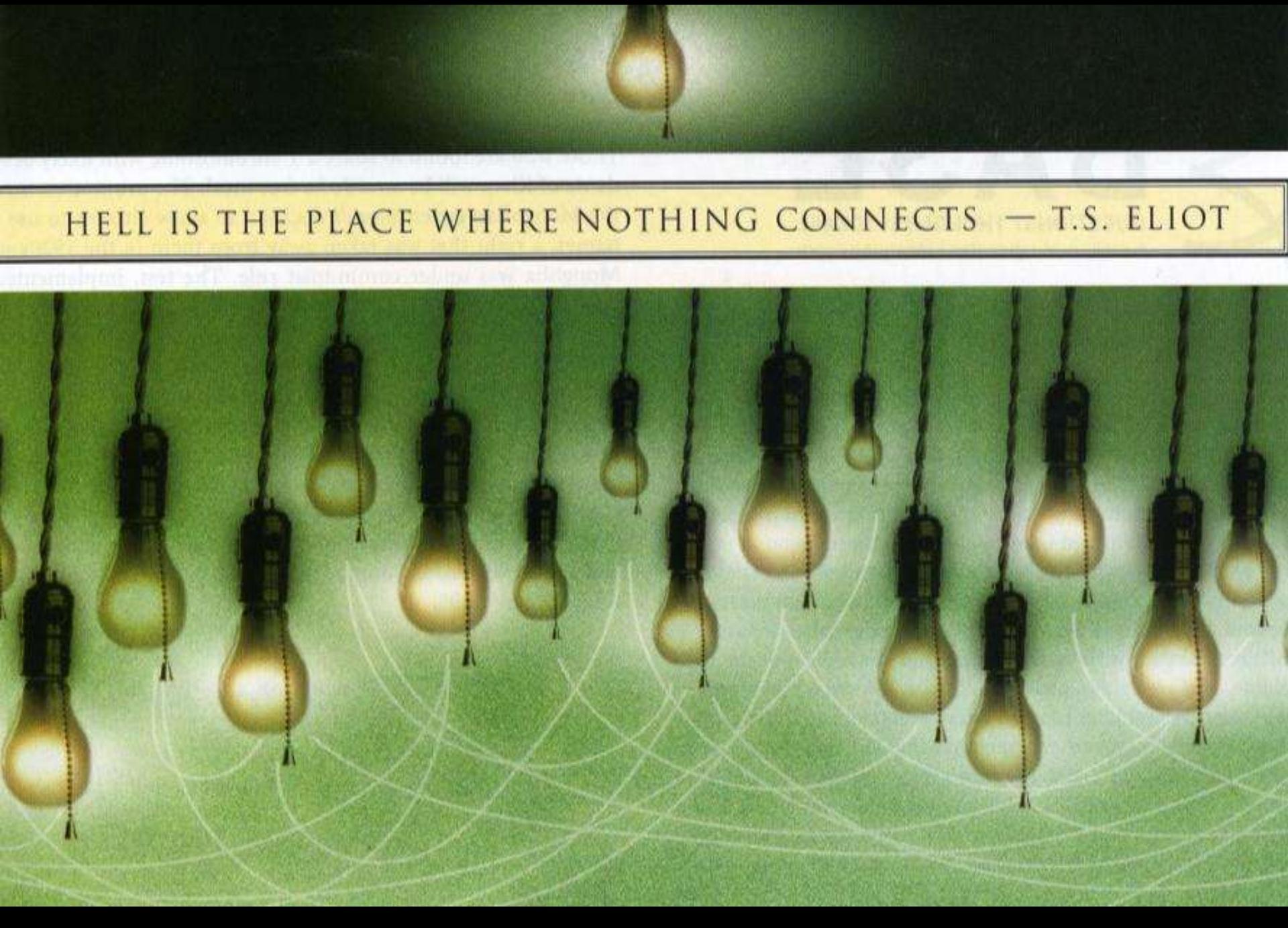
Telcoms	GPS	Computing	Internet	Social Media
				
Novel Materials	**Geophysics**	**Robotics**	**3D printing**	**Biotechnology**
				

Are Returns on Biopharmaceutical Products Excessive?

Returns to Whom?

Who Decides?

How to Balance Access and Affordability With Incentives to Sustain Innovation in High Risk-High Cost Biomedical R&D?


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


HELL IS THE PLACE WHERE NOTHING CONNECTS — T.S. ELIOT
WELCOME TO THE MULTI-DIMENSIONAL OPAQUE MATRIX OF HEALTHCARE PRICING

Elusive Core Components in the Drug Pricing Debate

- addressing drug pricing as a complex multi-dimensional problem versus simplistic, unidimensional focus on list prices
- transparency in multi-party financial transactions re: costs, discounts, rebates
- consensus on what constitutes “value” in Rx use
- parallel need for sophisticated analyses of how Rx selection and use patterns affects the performance and pricing of other components of the healthcare ecosystem

- **the sale and pricing of biopharmaceuticals (and much else in healthcare) do not conform 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 across the supply chain opaque**
  - **Rx companies, wholesalers, PBMs, pharmacies, GPOs, payers, providers**

Under-Researched Topics

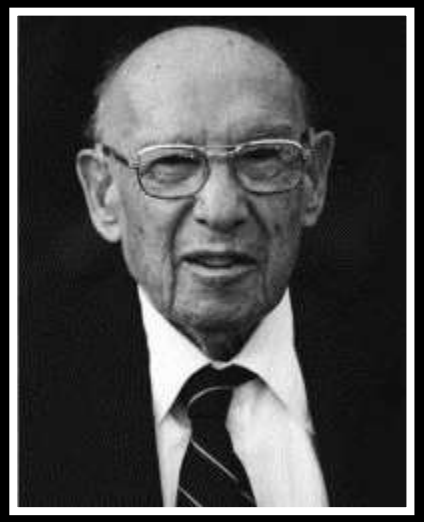
- impact of M&A activity and consolidation on Rx industry R&D productivity and pricing power of PBMs and pharmacies
- factors affecting the low productivity of NIH-funded research in translational biomedicine
- potential impact of large scale data analytics, deep learning and machine intelligence to improve R&D productivity, reduce failure in clinical trials and lower source cost

The Politically Expedient Search for Unidimensional 'Quick Fixes' to Multi-dimensional Problems and the Law of Unintended Consequences

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

- H.L. Mencken

Unidimensional "Quick Fixes"



"The greatest danger in times of turbulence,
is not the turbulence,
it is to act with yesterday's logic."

Peter Drucker

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