10th China Health Technology Assessment Forum

Health Technology Assessment in the United States: Current Developments

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Main Factors Increasing Demand for HTA in US

- Increased prevalence of chronic disease
- Very high prices of certain new health technologies, especially drugs and biologics for cancer and other diseases
- Increased attention to “value” of health technology
- Demand for “personalized medicine,” including molecular diagnostics for selecting expensive therapies
- Stronger voice of patients and interest in shared decision-making (i.e., by patients and their physicians)

United States: Overlap and Blending of These Related Fields

- Health technology assessment (HTA)
- Comparative effectiveness research (CER)
- Patient-centered outcomes research (PCOR)
- Pharmacoeconomics (PE)
- Evidence-based medicine (EBM)

Various organizations conduct activities that are related to HTA but that may not be identified as “HTA”

HTA-Related Organizations in US: Government

Federal (national) government

- Agency for Healthcare Research and Quality (AHRQ)
  - Evidence-based Practice Centers (EPCs)
  - Technology Assessment Program
  - US Preventive Services Task Force (USPSTF)
- Centers for Medicare and Medicaid Services (CMS) Coverage and Analysis Group
- Centers for Disease Control and Prevention (CDC; certain programs)

State governments

- Drug Effectiveness Review Project (DERP, collaborative of 13 state Medicaid and public pharmacy programs)
- Medicaid Evidence-Based Decisions Project (MED, collaborative of 17 state Medicaid agencies)
- Oregon Health Evidence Review Commission (HERC)
- Washington State Health Care Authority

HTA-Related Organizations in US: Private Sector

Payers, health plans/networks

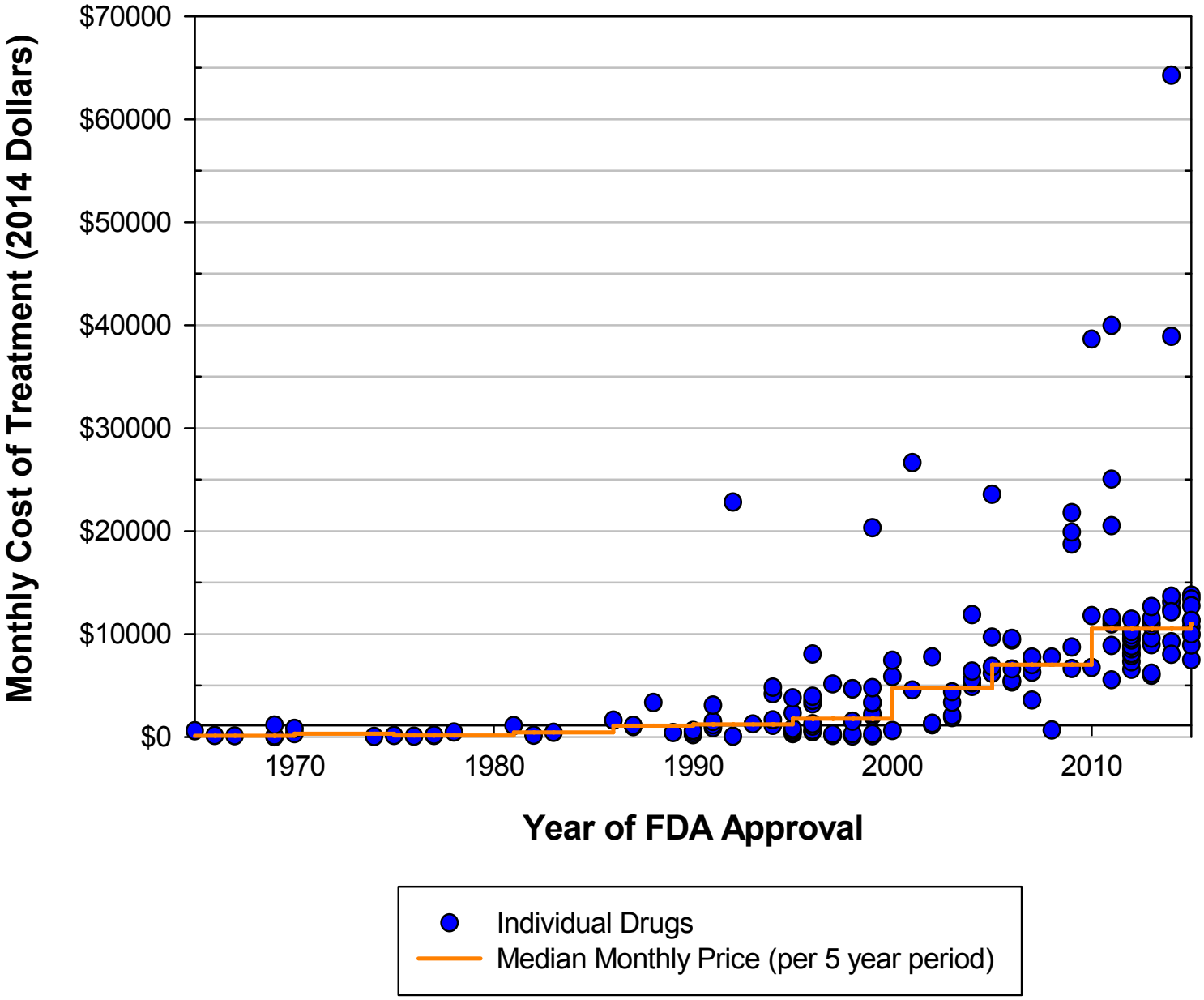
- BlueCross BlueShield Technology Evaluation Center (TEC)
- Kaiser Permanente (an integrated health care network)
  - Interregional New Technologies Committee
  - Drug Information Services
- Commercial insurance companies (e.g., UnitedHealthcare, Anthem, Aetna, Cigna, Humana)
- Pharmacy benefit managers (PBMs, e.g., Express Scripts, CVS Health, OptumRx)

Independent assessment organizations

- ECRI Institute
- Hayes, Inc.
- Center for Medical Technology Policy (CMTP)
- Institute for Clinical and Economic Review (ICER), also includes:
  - California Technology Assessment Forum
  - Midwest Comparative Effectiveness Public Advisory Council
  - New England Comparative Effectiveness Public Advisory Council
- US Cochrane Center
- Consulting firms, market research firms, academic centers

Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval

1965-2015



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

The New York Times

Harvoni, a Hepatitis C Drug From Gilead, Wins F.D.A. Approval

$1,125 a pill, or $94,500 for 12-week treatment

The first complete treatment for hepatitis C that requires taking only a once-a-day pill won approval Friday from the Food and Drug Administration.

The drug, called Harvoni from Gilead Sciences, could shorten the duration of treatment and provide the first all-oral regimen for many patients.

The new drug also appears to be a bit less expensive for some patients than Gilead's existing blockbuster hepatitis C drug, Sovaldi, which has become the poster child for those complaining that the cost of medicines is out of control.

Sovaldi costs $1,000 a pill, or $84,000 for a typical 12-week course of treatment, but it must be used with other drugs. Harvoni is even more expensive at $1,125 a pill, or $94,500 for a 12-week course of treatment. But that is roughly in line with the total cost for Sovaldi and the drugs used with it. Many patients will be able to take Harvoni for only eight weeks, at a cost of about $63,000.

Some HTA Trends in the US

1. Greater importance of “real-world evidence” (RWE)
2. Recognition of the importance of heterogeneity of treatment effects (HTEs) across patient populations
3. Greater emphasis on assessing “value” of health care technology and important distinction between cost effectiveness and budget impact
4. Adjusting to advances in molecular diagnostics used to guide pharmaceutical or biologic therapies (“companion diagnostics”)
5. Assessing new models/approaches for organizing, delivering, and financing health care (e.g., episode-based payment, accountable care organizations)
6. Expanding role of patients and consumers in HTA processes
7. Impact of HTA on reorganizing of technological innovation and validation in pharmaceutical and device industries

Greater Importance of Real-World Evidence (RWE)

- Derived from data sources other than traditional RCTs
- Complements -- does not substitute for -- evidence from traditional RCTs
- Uses study designs and methods adapted for routine or community settings
- Informs determinations about effectiveness (vs. efficacy) and external validity (vs. internal validity)
- Re-balances relative importance: RWE vs. traditional pre-marketing clinical trials for regulatory approval
- In US, Patient-Centered Outcomes Research Institute (PCORI) has major role in generating new RWE using “practical clinical trials” and large observational data sources

Greater Importance of Real-World Evidence (RWE)

- Uses advanced, powerful computing to link and analyze very large databases, including one or more of:
  - Payment claims
  - Electronic health records
  - Registries (e.g., of health care utilization or outcomes of patients who received a particular health technology)
  - Laboratory test results
  - Molecular/genomic data
  - Vital statistics (births, deaths, marriages, etc.)
  - Patient-generated data (directly from patients, e.g., from personal phone and computer “apps”)

PatientsLikeMe and the FDA Sign Research Collaboration Agreement

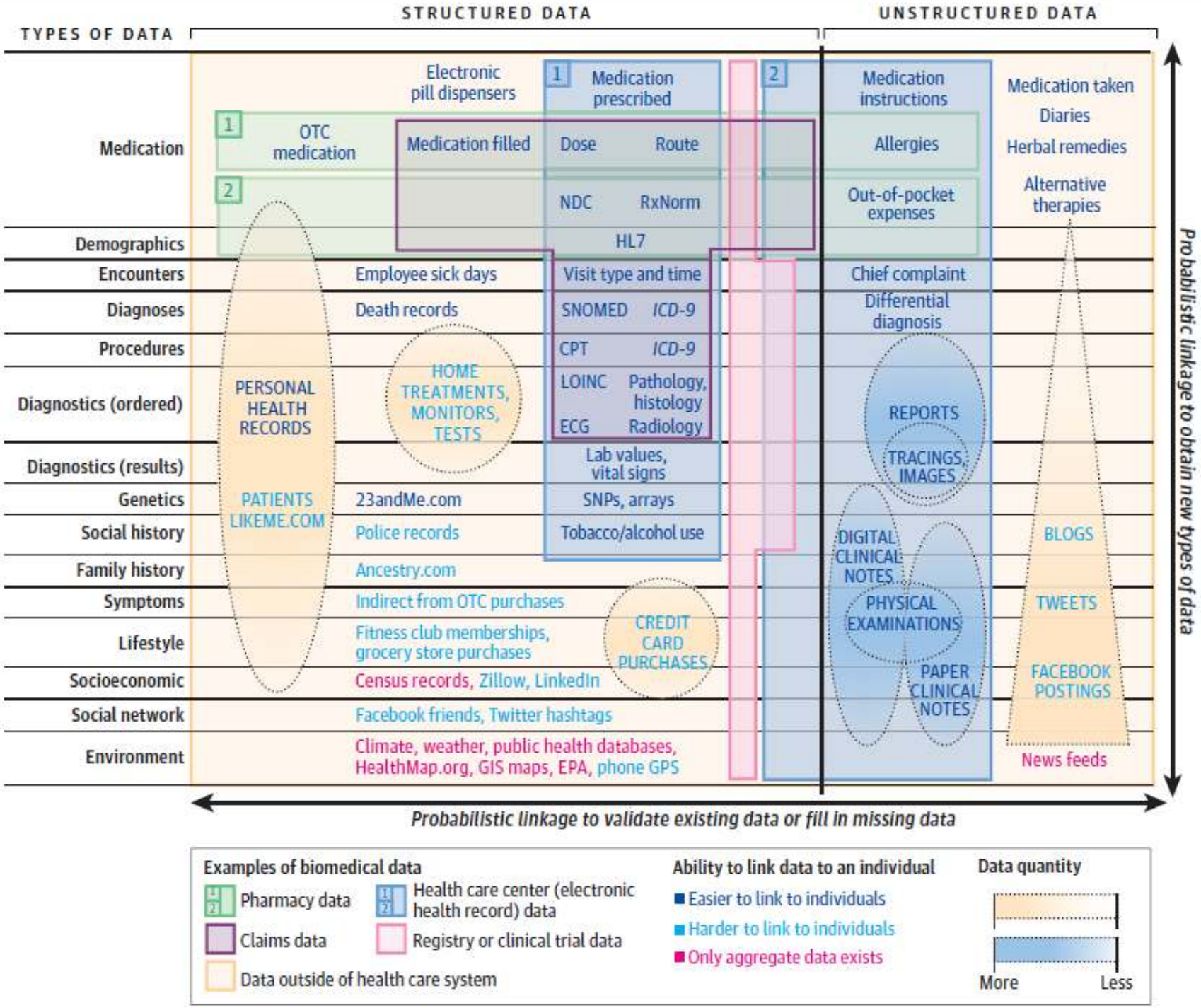
Monday, June 15, 2015 8:00 am EDT

WASHINGTON

WASHINGTON--(BUSINESS WIRE)--PatientsLikeMe and the U.S. Food and Drug Administration (FDA) have signed a research collaboration agreement to determine how patient-reported data can give new insights into drug safety. Under the collaboration, PatientsLikeMe and the FDA will systematically explore the potential of patient-generated data to inform regulatory review activities related to risk assessment and risk management. The announcement was made at the start of the Drug Information Association's (DIA) annual meeting in Washington D.C.

PatientsLikeMe Co-Founder and President Ben Heywood said the agreement is an unprecedented step toward enhancing post-market surveillance and informing regulatory science. "Most clinical trials only represent the experience of several hundred or at most several thousand patients, making it impossible to anticipate all the potential side effects of drugs in the real world. Patient-generated data give a more complete picture about a drug's safety by providing a window into patients' lives and healthcare experiences over time. We're very encouraged by the FDA's action to evaluate newer sources of data to help identify benefits and risks earlier."

Figure. The Tapestry of Potentially High-Value Information Sources That May be Linked to an Individual for Use in Health Care

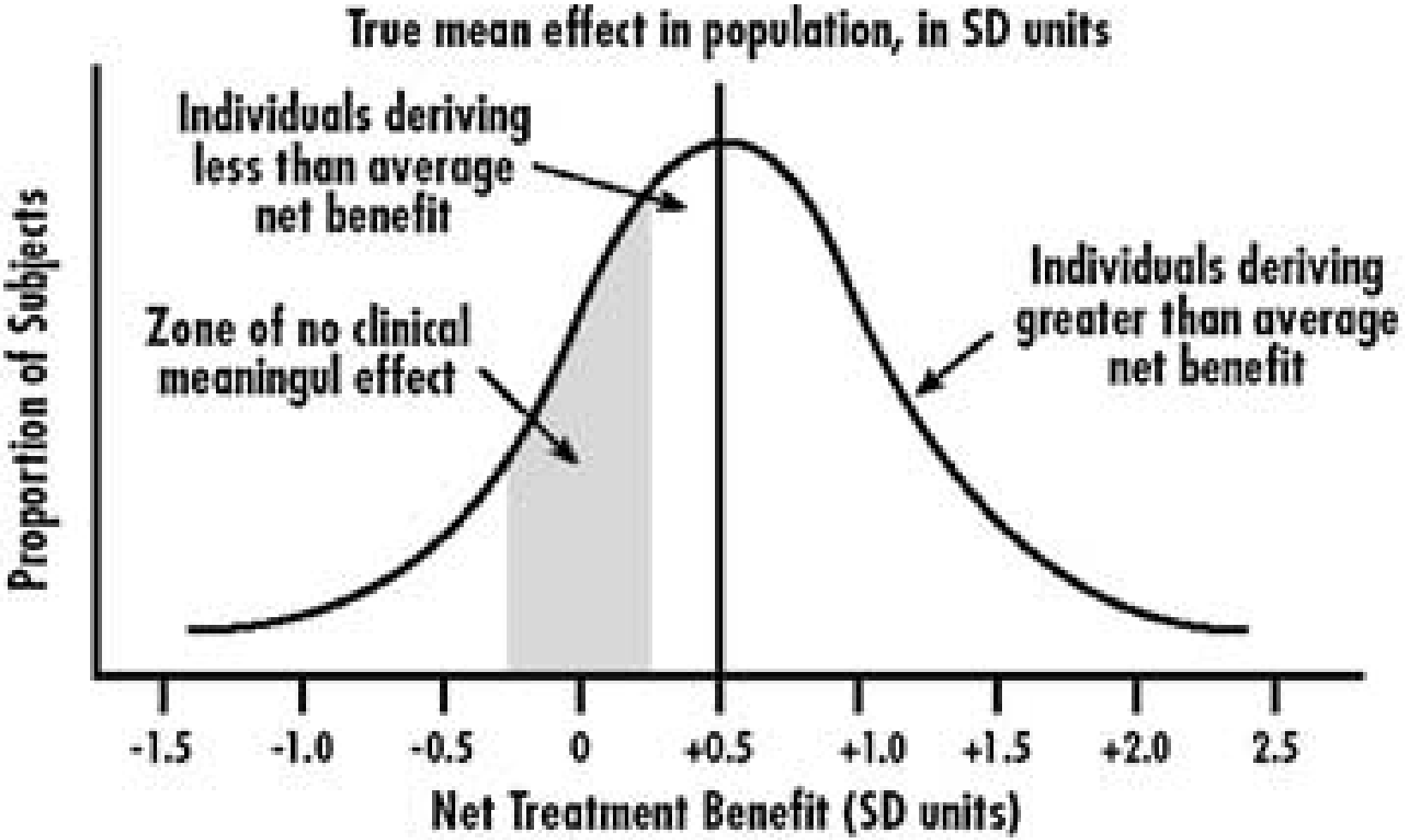


Weber GM, Mandl KD, Kohane IS. Finding the missing link for big biomedical data. JAMA. 2014 Jun 25;311(24):2479-80.

Recognition of Importance of Heterogeneity of Treatment Effects (HTEs)

- HTEs are variations in patient responses observed across types of patient characteristics, e.g., age, sex, comorbidities, genetic traits
- Traditional clinical trials are designed to reduce variations in outcomes and to generate a single summary measure, i.e., an average treatment effect
- “Pragmatic” clinical trials and large observational studies are used to reveal and explore HTEs, in order to generate evidence useful to clinicians, patients, payers, and others

Heterogeneity of Treatment Effects



This curve represents a treatment effect with a normal distribution centered on an effect size of 0.5 standard deviations (SD). The gray zone represents patients with an effect size that is so small (+/−0.25 SD) as to be clinically meaningless. The vertical bar indicates the average treatment effect. Individuals to the right of the bar derive a greater than average benefit; those to the left derive less than an average benefit or even harm.

Source: Kravitz RL, Duan N, Braslow J. Evidence-based medicine, heterogeneity of treatment effects, and the trouble with averages. Milbank Q 2004;82(4):661-87.

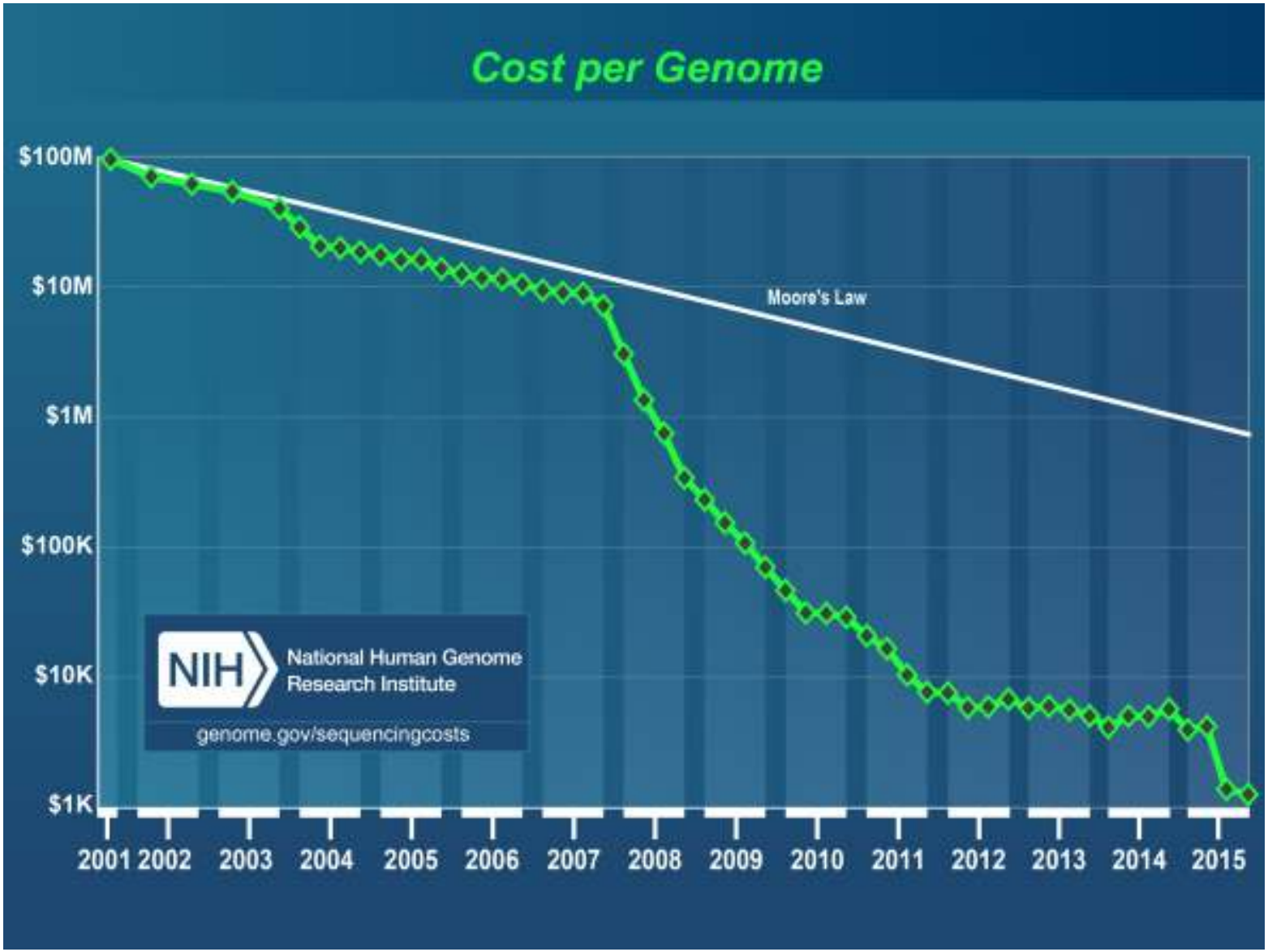
Personalized Medicine

- Personalized medicine (PM) is the tailoring of medical care to the particular traits (or circumstances or other characteristics) of a patient that influence response to a heath care intervention.
- These may include genetic, sociodemographic, clinical, behavioral, environmental, and other personal traits, as well as personal preferences.
- PM does not refer to the creation of interventions that are unique to a patient, but the ability to classify patients into subpopulations that differ in their responses to particular interventions.

Personalized Medicine – Examples

- *CYP2C9* and *VKORC1* genetic testing for warfarin anticoagulation response for patients with atrial fibrillation, mechanical heart valves, deep vein thrombosis, etc.
- *HER-2/neu* receptor testing for trastuzumab for breast cancer
- *BRCA 1,2* testing for pharmaceutical and surgical prevention options for and surveillance for breast cancer
- *KRAS* testing for use of EGFR inhibitors (e.g., cetuximab, panitumumab) for colon cancer
- Oncotype Dx® for adjuvant chemotherapy for certain cancers
- UGT1A1 testing for irinotecan for colon cancer
- Socioculturally-tailored therapy to treat certain ethnic minority patients with diabetes and depression
- Alternative procedure techniques (gastric banding, gastric bypass, etc.) for bariatric (morbid obesity) surgery
- Alternative regimens to treat infertility

Cost of Sequencing a Human-Sized Genome



Data from 2001-2015 represent costs of generating DNA sequence using first generation sequencing technology. Beginning January 2008, data represent costs of generating DNA sequence using 'second-generation' (or 'next-generation') sequencing platforms. The change in instruments represents the rapid evolution of DNA sequencing technologies that has occurred in recent years.

Source: Wetterstrand KA. DNA Sequencing Costs: Data from the NHGRI Genome Sequencing Program (GSP) Available at: www.genome.gov/sequencingcostsdata. Accessed 9.1.16.

ARE PAYERS READY TO ASSESS THE COMBINED VALUE OF DRUGS WITH A COMPANION DIAGNOSTIC?

by Anick Dubois PhD and Marie-Pierre Dubé PhD

Targeted drugs that are tailored to biomarkers are most often developed or co-developed with a companion diagnostic to identify patients who are good responders. Such companion diagnostic (CDx)-drug-(Rx) pairs have gained substantial interest in the recent years. This market is currently worth approximately $42 billion and should be worth over $60 billion by 2019[1]. The oncology area leads the market (e.g. Herceptin, Erbitux, Vectibix, Gleevec, Iressa, Glotrif, Zelboraf, Xalkori, Mekinist, Tafinlar). Currently, 42% of all drugs and 73% of oncology drugs in development are targeted drugs[2]. In 2014, 20% of drug approvals in the United-States (US) were targeted drugs[3].

The high cost (average of $100,000 to $300,000 USD per year)[4] and rapid market expansion of CDx-Rx pairs has put pressure on Health Technology Assessment (HTA) bodies to conduct joint assessment and to provide reimbursement guidelines for CDx-Rx pairs. HTA bodies and payers have much experience in the assessment of drugs, but adding a test to the assessment of a drug is creating additional challenges. In particular, the establishment of a unique and clear approach for the assessment of CDx has been difficult. Consequently, guidance on the appraisal of the combined value of CDx-Rx pairs for decision-making is lacking.

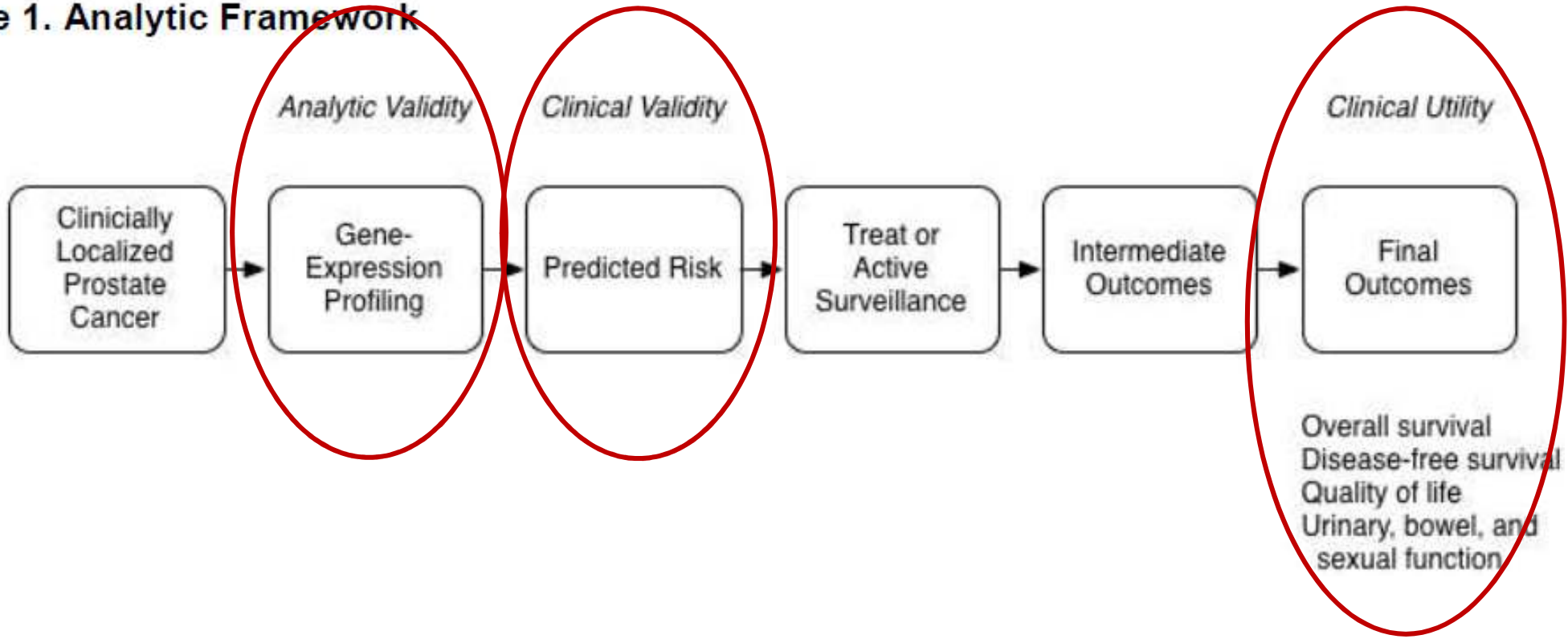
HTA Framework for Tests

- **Analytic validity**: how well a test detects (or measures) a property or trait it is intended to detect (e.g., a genotype)
- **Clinical validity**: how well a test detects or predicts a clinical condition (e.g., a phenotype)
- **Clinical utility**: extent to which a test result affects a decision that affects patient outcomes
- **Ethical, legal, social implications**: impact of the test on individuals, families, society (stigma, discrimination, lack of equity, etc.)
- **Cost effectiveness**: gain in health outcomes per unit cost per patient
- **Budget impact**: impact of the test on the budget (overall costs) of a health system (or hospital) when used for the indicated patient population

Gene Expression Analysis for Prostate Cancer Management – Jan. 2015

What is the incremental value of gene expression testing compared with clinical criteria for discriminating men with aggressive cancer from those with indolent disease to guide treatment decisions that improve overall net health outcomes?

Figure 1. Analytic Framework



Gene Expression Analysis for Prostate Cancer Management – Jan. 2015

Author Conclusions and Comment

Two RTPCR-based gene expressions tests -- Prolaris® and Oncotype Dx® Prostate -- are commercially available in the United States. We evaluated published evidence on their use in combination with current clinical criteria (Gleason score, PSA serum levels, clinical stage) to further stratify biopsy-diagnosed, localized prostate cancer according to expression levels of discrete sets of genes that, when overexpressed, are considered to reflect increased biological aggressiveness of a lesion. Such information would assist in initial clinical disease management, specifically to decide whether a patient should proceed to definitive therapy (i.e., surgery) or could safely proceed to active surveillance. Published evidence is sparse and insufficient to draw conclusions on the analytic validity, clinical validity, or clinical utility of Prolaris ®, and is insufficient to determine the clinical validity or utility of Oncotype Dx ® Prostate in patients under active surveillance program.

Greater Emphasis on Assessing "Value"

- High prices of some health technologies, especially drugs and biologics for cancer, hepatitis C, and PCSK9 inhibitors (for preventing heart disease), have focused attention on value
- Value: Usually defined as health outcomes achieved per dollar (or other monetary unit) spent, or other combination of health and economic factors
- Compared to some other wealthy countries, the US has been slow to use explicit thresholds or criteria for cost effectiveness
  - ➢ Interesting that the private sector, not government, is doing more to emphasize these

Important Distinction …

- Cost-effectiveness:
  - Is this technology worth the price for each patient who could benefit from it?
- Budget impact: Even if the technology is cost-effective for each patient who could benefit from it, …
  - Do we have enough funds to pay for this technology for all of our patients who could benefit from it?

Frameworks for Assessing Value

- American College of Cardiology/American Heart Association (ACC/AHA)
- American Society of Clinical Oncology (ASCO)
- European Society of Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale
- HTA agencies: NICE (UK), PBAC (Australia), etc.
- Institute for Clinical and Economic Review (ICER)
- Memorial Sloan Kettering DrugAbacus
- National Comprehensive Cancer Network (NCCN)
- Porter (outcomes hierarchy)

Important examples in the US …

ACC/AHA Statement on Cost/Value Methodology in Clinical Practice Guidelines and Performance Measures

Journal of the American College of Cardiology Vol. 63, No. 21, 2014

Table 2. Proposed Integration of Level of Value Into Clinical Guideline Recommendations*

Level of Value
High value: better outcomes at lower cost or ICER <$50,000 per QALY gained
Intermediate value: $50,000 to <$150,000 per QALY gained
Low value: ≥$150,000 per QALY gained
Uncertain value: value examined but data are insufficient to draw a conclusion because of no studies, low-quality studies, conflicting studies, or prior studies that are no longer relevant
Not assessed: value not assessed by the writing committee

Proposed abbreviations for each value recommendation:

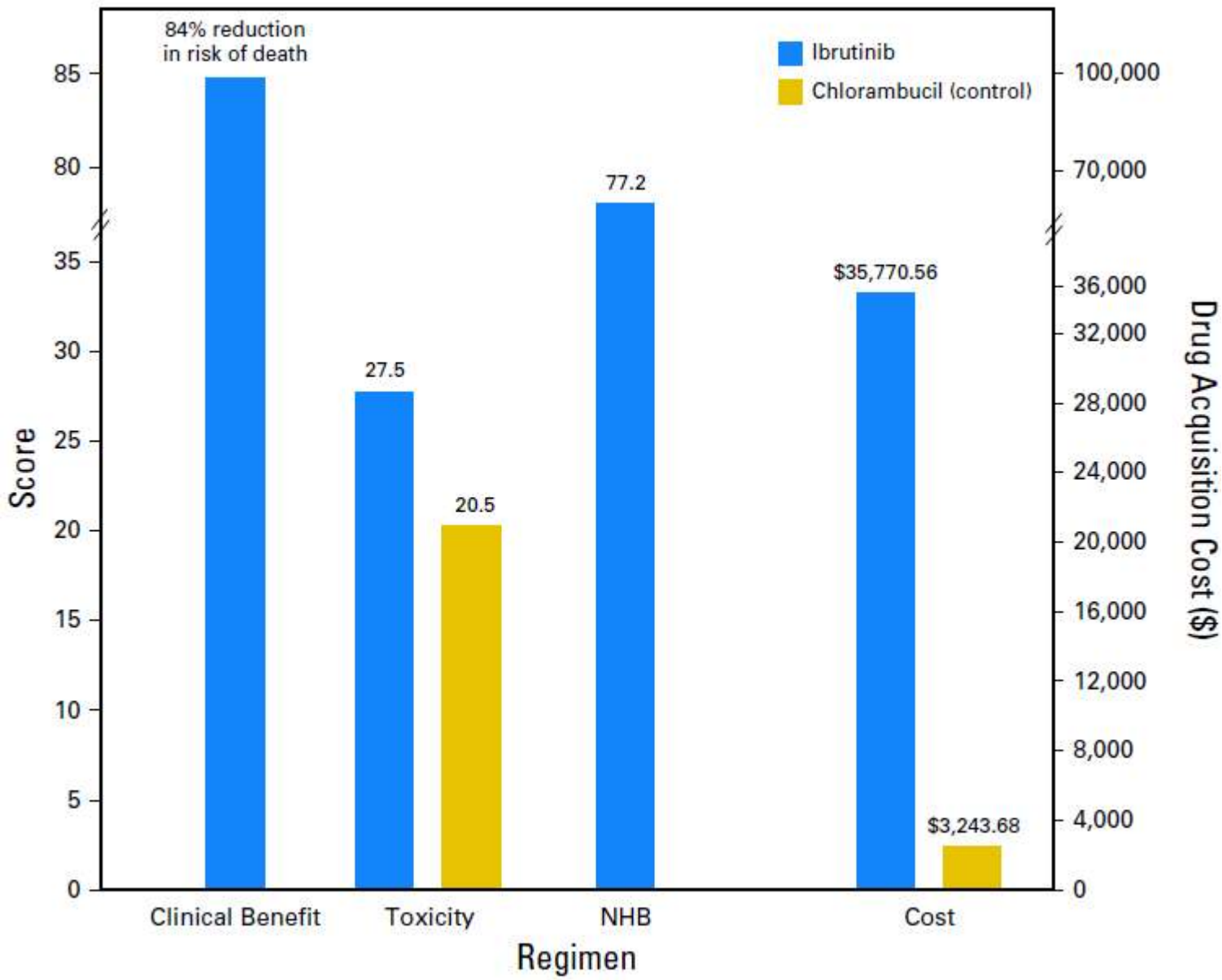
Level of Value: H to indicate high value I, intermediate value; L, low value; U, uncertain value; and NA, value not assessed

*Figures used in this table are based on U.S. GDP data from 2012 and were obtained from WHO-CHOICE Cost-Effectiveness Thresholds (24).

GDP indicates gross domestic product; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; and WHO-CHOICE, World Health Organization Choosing Interventions that are Cost Effective.

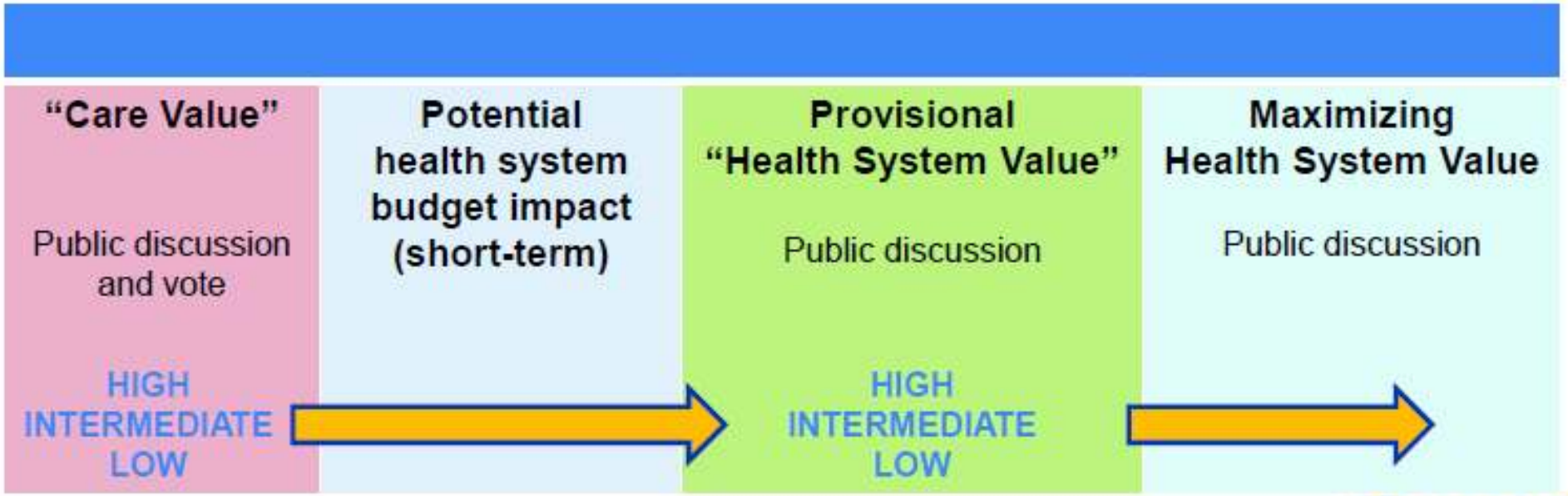
ASCO Value Framework: Example

Ibrutinib vs. Chlorambucil for Treatment of Chronic Lymphocytic Leukemia



Schnipper LE, et al. American Society of Clinical Oncology Statement: Updating the American Society of Clinical Oncology Value Framework: Revisions and Reflections in Response to Comments Received. J Clin Oncol May 31, 2016..

ICER Value Assessment Framework



ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Source: Institute for Clinical and Economic Review, updated April 2016: http://icer-review.org/

PCSK9 Inhibitors for Treatment of High Cholesterol: Value Graph

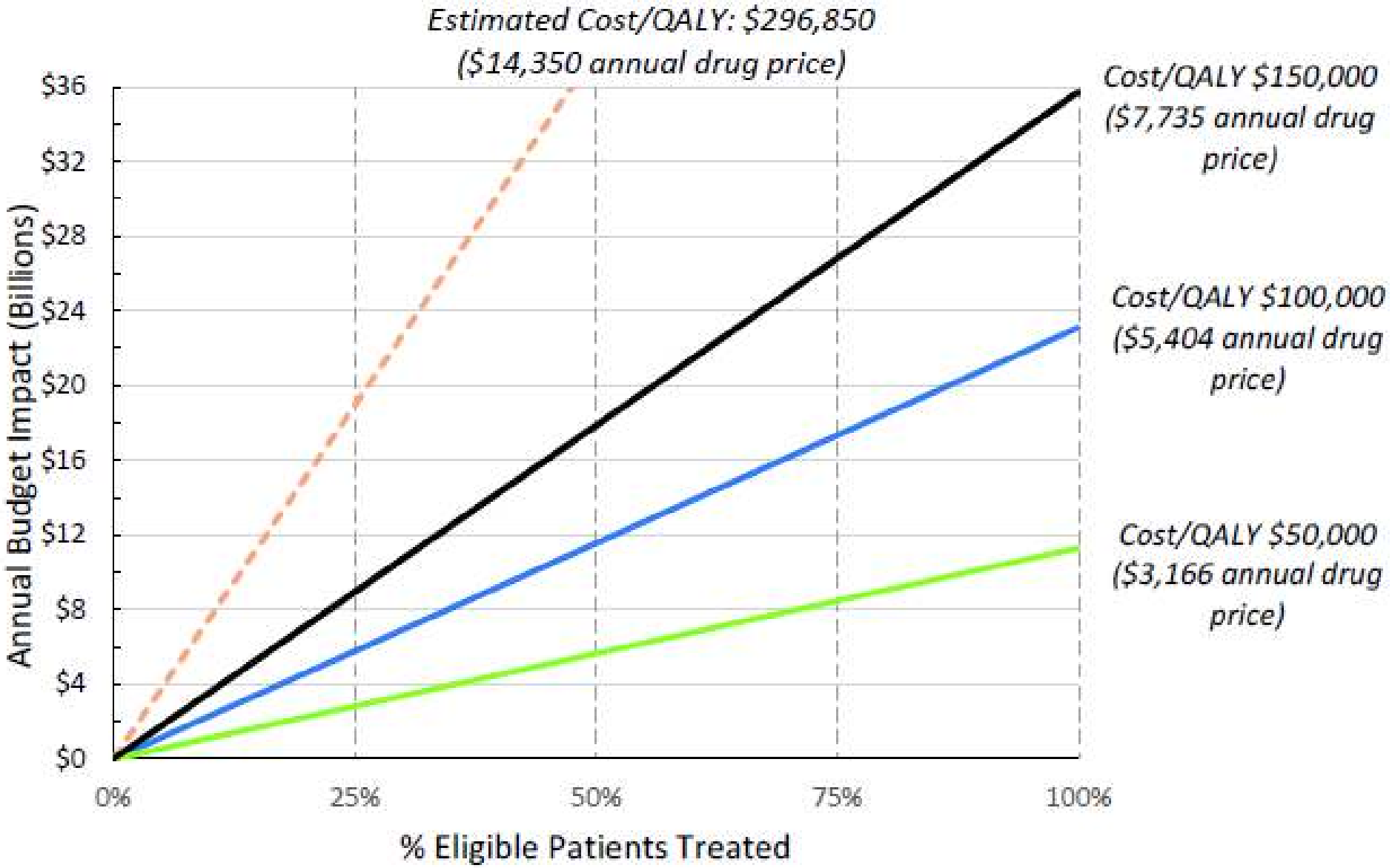


Figure ES1. ICER value graph combining cost-effectiveness and potential budget impact analyses. Colored lines represent the impact on annualized budget impact of different uptake patterns (eligible patients treated) at the actual list price of the drug (dashed line) and at drug prices needed to achieve common incremental cost-effectiveness ratios.

Source: Institute for Clinical and Economic Review. PCSK9 Inhibitors for Treatment of High Cholesterol: Effectiveness, Value, and Value-Based Price Benchmarks. Final Report. Nov. 24, 2015.

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