Incorporating evidence on effect-heterogeneity in CEA

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Background

> **Cost-effectiveness analysis is beginning to play a major role in decision-making for private and some public plans in the US**

CVS Caremark is initiating a program that allows clients to exclude any drug launched at a price of greater than $100,000 per QALY from their plan. The QALY ratio is determined based on publicly available analyses from the

Criticisms

September 12, 2018

Mr. Larry J. Merlo
President and Chief Executive Officer
CVS Health
One CVS Drive
Woonsocket, Rhode Island 02895

Dear Mr. Merlo:

ACCSES
Aimed Alliance
Alliance for Aging Research
Alliance for Patient Access
American Academy of Nursing
American Academy of Ophthalmology
American Association of People with Disabilities
Association of University Centers on Disabilities
Autism Society of America
Autistic Self Advocacy Network
Bazelon Center for Mental Health Law
Beyond Type 1
Black Women's Health Imperative
Bladder Cancer Advocacy Network
Brain Injury Association of America
California Consortium of Addiction Programs and Professionals
Cancer Support Community
Cancer*Care*
CARE About Fibroids
Center for Autism and Related Disorders
Center for Public Representation
Cutaneous Lymphoma Foundation
Davis Phinney Foundation
Depression and Bipolar Support Alliance
Diabetes Patient Advocacy Coalition
Disability Rights Education and Defense Fund
Epilepsy Association of North Carolina
Epilepsy Foundation
Epilepsy Foundation – Alabama
Epilepsy Foundation Maryland
Epilepsy Foundation Metropolitan Washington
Epilepsy Foundation Nebraska
Epilepsy Foundation New England
Epilepsy Foundation Northwest
Epilepsy Foundation of Arizona
Epilepsy Foundation of Colorado
Epilepsy Foundation of Connecticut

Epilepsy Foundation of Georgia
Epilepsy Foundation of Greater Los Angeles
Epilepsy Foundation of Greater Southern Illinois
Epilepsy Foundation of Indiana
Epilepsy Foundation of Iowa
Epilepsy Foundation of Kentuckiana
Epilepsy Foundation of Michigan
Epilepsy Foundation of Middle and West Tennessee
Epilepsy Foundation of Minnesota
Epilepsy Foundation of Missouri and Kansas
Epilepsy Foundation of Nevada
Epilepsy Foundation of Northeastern New York, Inc.
Epilepsy Foundation of Oklahoma
Epilepsy Foundation of Vermont
Epilepsy Foundation Ohio
Epilepsy Foundation Utah
Genetic Alliance
Global Liver Institute
Global Healthy Living Foundation
Health Hats
Illinois Association of Behavioral Health
International Foundation for Autoimmune & Autoinflammatory Arthritis
Judy Olsen
Kidney Cancer Association
Lung Cancer Alliance
LUNGevity Foundation
Lupus and Allied Diseases Association, Inc.
LymeDisease.org
Men's Health Network
Mended Hearts
Mental Health America
National Alliance on Mental Illness
National Infusion Center Association
National MPS Society
National Multiple Sclerosis Society
National Patient Advocate Foundation
No Health without Mental Health
Not Dead Yet
Partnership to Improve Patient Care
Patrick Gee
Pediatric Congenital Heart Association
PXE International
RetireSafe

Rosie Bartel
Roxanne Davenport
TASH
The AIDS Institute
The Arc of the United States
The Asthma and Allergy Foundation of America
The diaTribe Foundation
The National Council on Independent Living
The Veterans Health Council
Tuberous Sclerosis Alliance
U.S. Pain Foundation
United Cerebral Palsy
United Spinal Association
Vietnam Veterans of America

Therefore, we request that you reconsider this decision. CVS Health's stated purpose is "helping people on their path to better health." Reliance on cost-effectiveness thresholds like ICER's falls short of this purpose, replacing deeply personal, individual health care decisions with an opaque algorithm based on average study results that do not address the needs of different patients and special populations.

Premise

- Relying on average cost-effectiveness of a new technology have been criticized in the presence of heterogeneity

- Consider three issues in this talk:
  - Stochastic (first-order) uncertainty vs variability
  - Implication for learning by doing
  - Demand-weighted cost-effectiveness analysis
    - Its relationship to indication-based pricing

Stochastic (first-order) uncertainty vs variability

- Stochastic (first-order) uncertainty
  - Represents uncertainty in subject-level outcomes that is entirely due to chance.
  - E.g. even if you specify that subjects have a 5% chance of death, for any single individual at any point in time, either he dies and stay alive.
- This uncertainty is due to pure randomness (e.g. flipping a coin) – UNPREDICTABLE
- Cannot be used as a basis to allocate resources

Stochastic (first-order) uncertainty vs variability

- Variability
  - PREDICTABLE differences in outcomes and costs for subgroups determined by subject characteristics
- Important for resource allocation
  - Heterogeneity may also arise due to system characteristics and also individual preferences
- Efficient allocation of resources should try to directly incorporate variability in decision-making

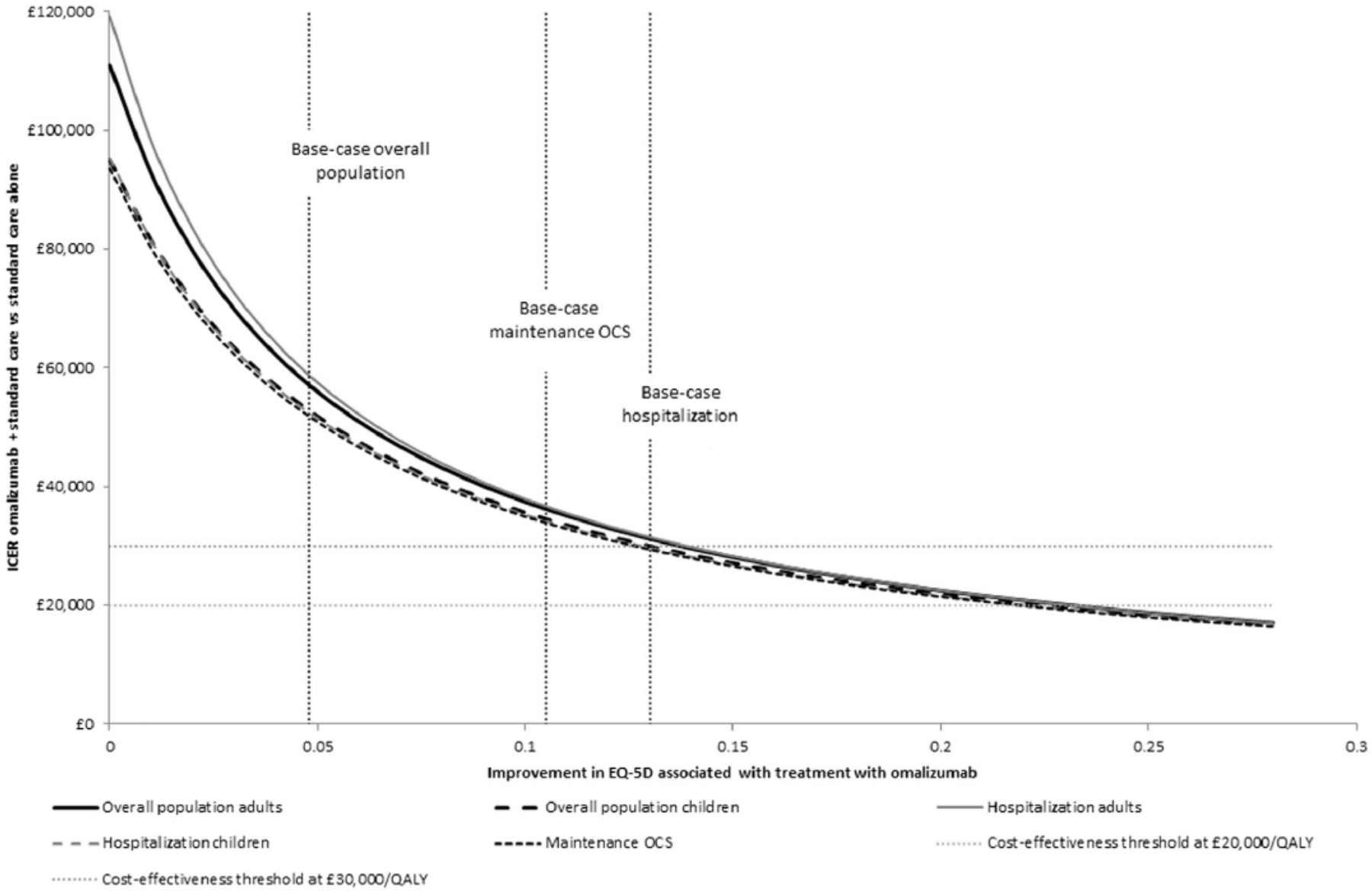

Fig. 2 – Effect of improvements in health-related quality of life on the cost-effectiveness of omalizumab. The subgroups with three or more exacerbations are not shown because the curves overlap the other subgroups and the overall population. EQ-5D, EuroQol five-dimensional questionnaire; ICER, incremental cost-effectiveness ratio; OCS, oral corticosteroid; QALY, quality-adjusted life-year.

Faria et al VIH 2014

NICE National Institute for Health and Care Excellence

NICE guidance

Omalizumab for treating severe persistent allergic asthma

Technology appraisal guidance
Published: 24 April 2013
nice.org.uk/guidance/ta278

1 Guidance

1.1 Omalizumab is recommended as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimised standard therapy in people aged 6 years and older:

- who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year), **and**
- only if the manufacturer makes omalizumab available with the discount agreed in the patient access scheme.

https://www.nice.org.uk/guidance/ta278/

Learning-by-Doing

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Learning-by-Doing: Transition of Stochastic Uncertainty to Variability

- Physician and patients learn from the random variation in outcomes
- Develop algorithms to identify subgroups with higher/lowed than average outcome
- Should resource allocation be generous up-front to allow for learning?
  - Fundamentally a trade-off between current health & costs and future health
  - Depends on expected quality-of-learning and the rate of learning
  - Empirical evidence suggest that learning exists but far from perfect.

HEALTH ECONOMICS
Health Econ. **23**: 359–373 (2014)
Published online 9 October 2013 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/hec.2996

HETEROGENEITY IN ACTION: THE ROLE OF *PASSIVE* PERSONALIZATION IN COMPARATIVE EFFECTIVENESS RESEARCH

ANIRBAN BASU[a,*], ANUPAM B. JENA[b], DANA P. GOLDMAN[c], TOMAS J. PHILIPSON[d] and ROBERT DUBOIS[e]

[a]*Department of Health Services, University of Washington, Seattle and the National Bureau of Economic Research, Cambridge MA, Seattle, WA, USA*

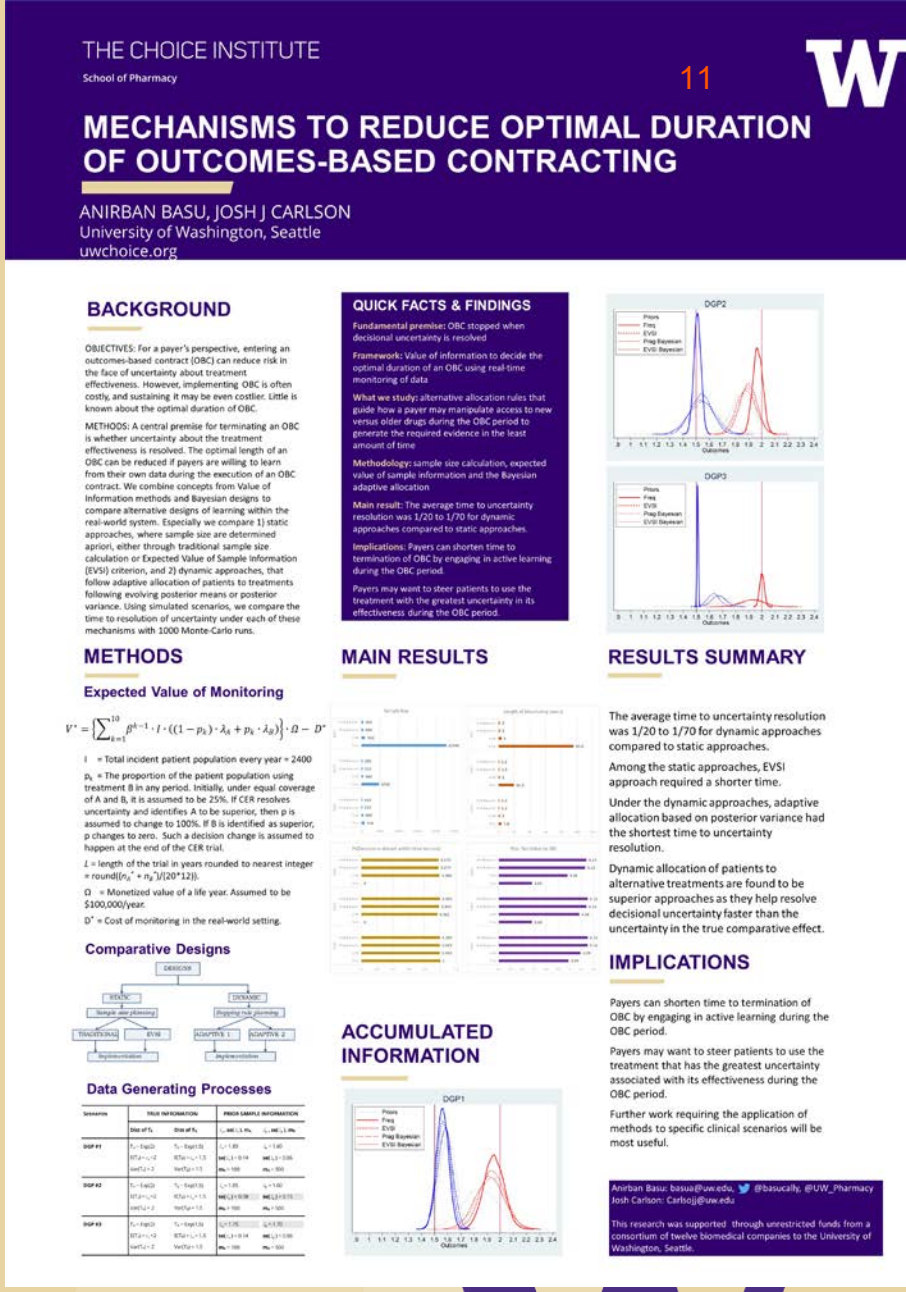
Table II. Predicted impact of generic group atypical antipsychotic drugs (AADs) compared with branded group AADs on average number of hospitalizations in 12 months following initiation of therapy

	All hospitalizations	Schizophrenia-related hospitalizations
Group	Mean (95% CI)	Mean (95% CI)
All patients (ATE)	0.35 (0.02, 0.67)	−0.07 (−0.28, 0.10)
Patients initiating therapy with generic group (TT)	0.17 (−0.17, 0.44)	−0.15 (−0.38, −0.03)
Patients initiating therapy with branded group (TUT)	0.61 (0.29, 1.05)	0.002 (−0.13, 0.22)
TT—ATE	−0.18 (−0.13, −0.28)	−0.08 (−0.04, −0.12)

ATE, average treatment effect; TT, effect on the treated; TUT, effect on the untreated.

Structured learning-by doing

- Centralized learning from doing
  - Learning during the outcomes-based agreement
  - Tuesday Poster 3:00 – 7:00 pm
- Needs structure
  - Determine time for learning
  - Select methods to learn faster
  - Have explicit decision-making tied to the end of learning period



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MECHANISMS TO REDUCE OPTIMAL DURATION OF OUTCOMES-BASED CONTRACTING

ANIRBAN BASU, JOSH J CARLSON
University of Washington, Seattle
uwchoice.org

BACKGROUND

OBJECTIVES: For a payer's perspective, entering an outcomes-based contract (OBC) can reduce risk in the face of uncertainty about treatment effectiveness. However, implementing OBC is often costly, and sustaining it may be even costlier. Little is known about the optimal duration of OBC.

METHODS: A central premise for terminating an OBC is whether uncertainty about the treatment effectiveness is resolved. The optimal length of an OBC can be reduced if payers are willing to learn from their own data during the execution of an OBC contract. We combine concepts from Value of Information methods and Bayesian designs to compare alternative designs of learning within the real-world system. Especially we compare 1) static approaches, where sample size are determined apriori, either through traditional sample size calculation or Expected Value of Sample Information (EVSI) criterion, and 2) dynamic approaches, that follow adaptive allocation of patients to treatments following evolving posterior means or posterior variance. Using simulated scenarios, we compare the time to resolution of uncertainty under each of these mechanisms with 1000 Monte-Carlo runs.

QUICK FACTS & FINDINGS

Fundamental premise: OBC stopped when decisional uncertainty is resolved

Framework: Value of information to decide the optimal duration of an OBC using real-time monitoring of data

What we study: alternative allocation rules that guide how a payer may manipulate access to new versus older drugs during the OBC period to generate the required evidence in the least amount of time

Methodology: sample size calculation, expected value of sample information and the Bayesian adaptive allocation

Main result: The average time to uncertainty resolution was 1/20 to 1/70 for dynamic approaches compared to static approaches.

Implications: Payers can shorten time to termination of OBC by engaging in active learning during the OBC period.

Payers may want to steer patients to use the treatment with the greatest uncertainty in its effectiveness during the OBC period.

METHODS

Expected Value of Monitoring

$$V^* = \left\{\sum_{k=1}^{10} \beta^{k-1} \cdot I \cdot \left((1-p_k)\cdot\lambda_A + p_k\cdot\lambda_B\right)\right\}\cdot\Omega - D^*$$

I = Total incident patient population every year = 2400

p_k = The proportion of the patient population using treatment B in any period. Initially, under equal coverage of A and B, it is assumed to be 25%. If CER resolves uncertainty and identifies A to be superior, then p is assumed to change to 100%. If B is identified as superior, p changes to zero. Such a decision change is assumed to happen at the end of the CER trial.

L = length of the trial in years rounded to nearest integer = round($(n_A + n_B)$/(20*12)).

Ω = Monetized value of a life year. Assumed to be $100,000/year.

D^* = Cost of monitoring in the real-world setting.

Comparative Designs

Data Generating Processes

MAIN RESULTS

ACCUMULATED INFORMATION

RESULTS SUMMARY

The average time to uncertainty resolution was 1/20 to 1/70 for dynamic approaches compared to static approaches.

Among the static approaches, EVSI approach required a shorter time.

Under the dynamic approaches, adaptive allocation based on posterior variance had the shortest time to uncertainty resolution.

Dynamic allocation of patients to alternative treatments are found to be superior approaches as they help resolve decisional uncertainty faster than the uncertainty in the true comparative effect.

IMPLICATIONS

Payers can shorten time to termination of OBC by engaging in active learning during the OBC period.

Payers may want to steer patients to use the treatment that has the greatest uncertainty associated with its effectiveness during the OBC period.

Further work requiring the application of methods to specific clinical scenarios will be most useful.

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Josh Carlson: Carlsojj@uw.edu

This research was supported through unrestricted funds from a consortium of twelve biomedical companies to the University of Washington, Seattle.

Demand-weighted CEA

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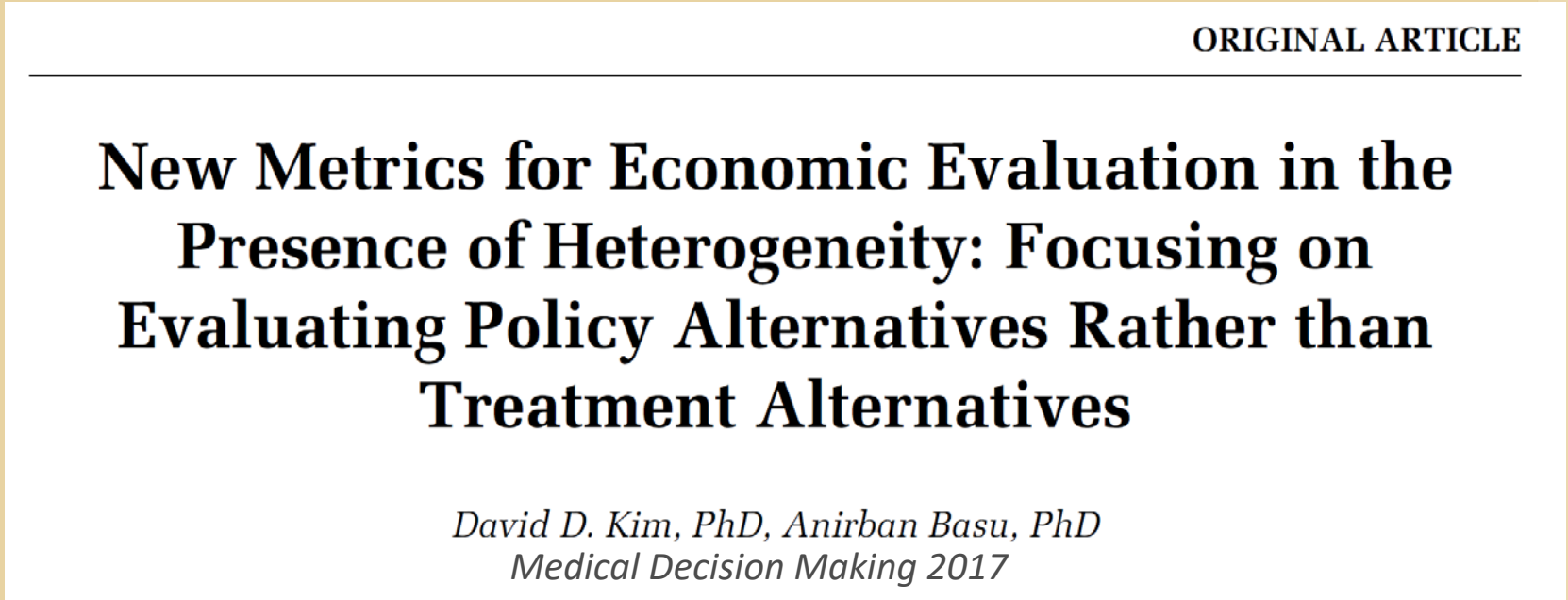
Demand-weighted cost-effectiveness

- **Evidence on variability is important even if**
  - **there is no learning-by-doing**
  - **there is no opportunity to implement sub-group-based coverage**



ORIGINAL ARTICLE

New Metrics for Economic Evaluation in the Presence of Heterogeneity: Focusing on Evaluating Policy Alternatives Rather than Treatment Alternatives

David D. Kim, PhD, Anirban Basu, PhD
Medical Decision Making 2017

ICER for Alternative Treatments

Typical ICER compares Treatment A vs B

$$ICER = \frac{E(C_A) - E(C_B)}{E(Q_A) - E(Q_B)} = \frac{E(\Delta C_{AB})}{E(\Delta Q_{AB})}$$

$$= \frac{\sum_j \{P_j \cdot E(\Delta C_{AB,j})\}}{\sum_j \{P_j \cdot E(\Delta Q_{AB,j})\}} \qquad j = 1,2,3$$

P_j = Size of Subgroup j

- Suppose, clear evidence on variability in ICER across subgroups.

ICER for Alternative Treatments

- ICER comparing potential realized value of Treatment A vs B

$$ICER = \frac{\sum_j \{P_j \cdot \boldsymbol{D_j} \cdot E(\Delta C_{AB,j})\}}{\sum_j \{P_j \cdot \boldsymbol{D_j} \cdot E(\Delta Q_{AB,j})\}} \quad (4)$$

- D_j: the rate of adoption of treatment A in the population subgroup j

- Similar to "Volume weighted price" across indications

ICER for Alternative Policies

- The Rate of the uptake is endogenous to the policy
- So ICER should be comparing two coverage policies – Policy *k* vs Status quo

$$ICER_{policy_k} = \frac{\sum_j \left\{ P_j \cdot D_{jk}(f_k) \cdot E(\Delta C_{AB,j}) \cdot f_k \right\}}{\sum_j \left\{ P_j \cdot D_{jk}(f_k) \cdot E(\Delta Q_{AB,j}) \right\}}$$

- f_k: a fraction of the incremental costs under a policy k borne by a payer

Table 1 Illustration of Traditional and Modified ICERs and INMBs under a Health-Care Sect

Parameter	Males	Females	Overall
Total costs per patient under Statin + Fibrate, $	$107,021	$107,023	-
Total costs per patient under Statin Only, $	$98,131	$98,131	-
Total incremental costs per patient, $	$8,890	$8,892	-
Total QALYs per patient under Statin + Fibrate, $	9.468	9.308	-
Total QALYs per patient under Statin Only, $	9.200	9.200	-
Total incremental QALYs per patient, $	0.268	0.108	-
Subgroup-specific ICER	$33,130/QALY	$82,562/QALY	-
Subgroup-specific INMB[a]	$3,170	-$4,032	
Subgroup size (P_j)	0.533	0.467	
Traditional population ICER (eq. 3)			$46,000/QALY
Population NMB per patient from statin monotherapy[b]			$315,869
Adoption of Statin + Fibrate under status quo ($f_k = 0.80$), D_j	0.072	0.043	
Modified population ICER ($f_k = 0.80$, eq. 7)			$41,733/QALY
Status-quo policy NMB per patient ($f_k = 0.80$, eq. 8)			$315,910
Adoption of Statin + Fibrate under Policy 2 ($f_k = 1.0$), D_j[c]	0.075	0.045	
Modified population ICER under Policy 2 ($f_k = 1.0$, eq. 7)			$41,766/QALY
Policy 2 NMB per patient ($f_k = 1.0$, eq. 8)			$315,911
Adoption of Statin + Fibrate under Hypothetical Policy,[d] D_j	0.23	0.023	
Population ICER under Hypothetical Policy[d] (eq. 7)			$34,848/QALY
Hypothetical Policy[d] NMB per patient (eq. 8)			$316,214

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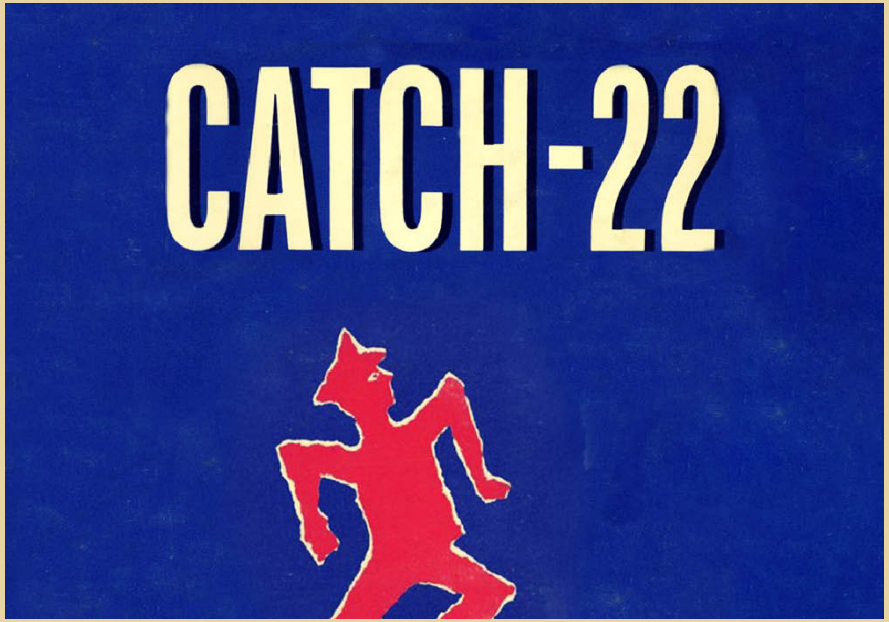
Future Work in CEA

- To use demand weighted CEA at launch
  - Can we develop reliable estimates for *evidence elastic of demand?*
    - *Discrete choice experiments*
    - *Retrospective analysis*
    - Validated prediction model for technology diffusion
- CEA at 5 year assessment
  - Direct estimate from real-world use.

Crossroads

Decision makers focus of population averages because of the lack of reliable evidence on heterogeneity



Manufacturers argue that there is no incentive to generate evidence on heterogeneity

Conclusions

- **Are we are failing to produce the necessary evidence of heterogeneity of effects, which can improve value in the society, by not providing sufficient reward incentive for such information.**

> **Importantly to create an environment that respects and rewards evidence on heterogeneity.**

> **Laying a clear path of incorporating reliable evidence on heterogeneity in third-party assessor's base analysis. This includes**

  - **not reporting population average cost-effectiveness results when there are distinct differences in subgroup-specific results,**
  - **experimenting with demand weighted cost-effectiveness approaches.**