

Anirban Basu
Departments of Health Services & Pharmacy
University of Washington, Seattle

Intensive vs extensive margins in comparative effectiveness research

"A little learning is a dangerous thing" - Alexander Pope (1709)

Background

- Comparative effectiveness research (CER) conducts head-to-head comparisons to determine which drugs, devices, and procedures are most effective and carry the lowest risk.
- Methods applied to CER have existed since 1920's.
- The 2009 American Recovery and Reinvestment Act & Patient Protection and Affordable Care Act of 2009 called for added investments in CER

Background

- There is a recognition (or assumption?) that CER can lead to improved quality of care, quality of health care delivery and ultimately patient welfare.
- Lessons learned from around the world are being used to tout the need for more CER in US.
- Rigorous discussions about how CER results would lead to payment and coverage decisions.

Background

- Despite the current emphasis on CER in the United States, economic principles guiding the role of CER information in patent welfare is not clearly laid out
- Tendency to fall back on the theory of cost-effectiveness analysis
 - Devised for a homogenous population
 - Heterogeneity is a second-order thought
 - Role of behavior in response to information is largely ignored
 - Conflation of the use of cost-effectiveness results with that of the use of comparative effectiveness results

Tragedy of Averages in CER

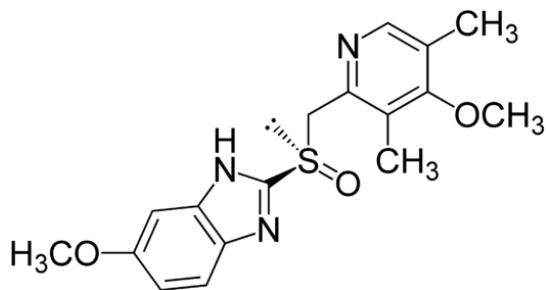
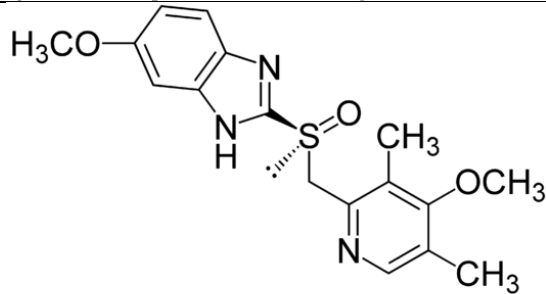
- CER infrastructure has always been and continues to be geared towards finding effectiveness results on averages
 - Sometimes look at heterogeneity based on broad sub groups – often a after-thought. e.g.
 - PCI versus CABG in patients with severe CAD
 - 1st versus 2nd generation antipsychotics in schizophrenia
 - Erlotinib versus Gemcitabine in advanced pancreatic cancer
- Focus on intensive margins, neglect extensive margins

Outline

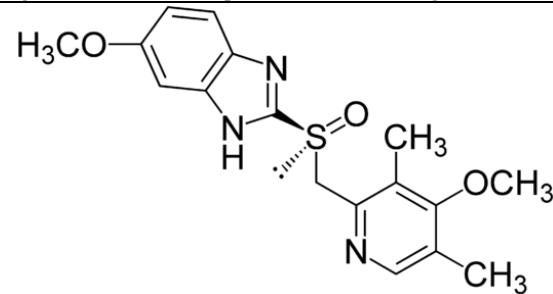
- Clinical example to define intensive vs extensive margins
- Individualized CER (i-CER)
- Economics of i-CER
- Incentives to invest in i-CER
- Methodological challenges for i-CER
- Conclusions

Treatment of GERD - a clinical example

Prilosec
(omeprazole)



Nexium
(esomeprazole)

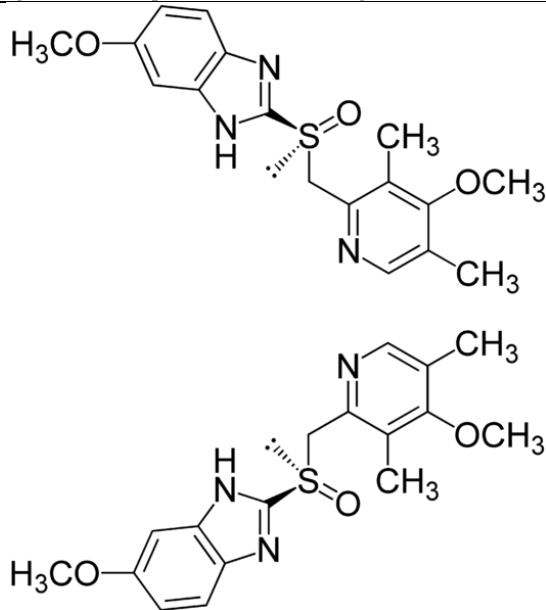


Introduced in 1989
Patent expiration April, 2001
OTC in 2003

Introduced in March 2001
Patent expiration April, 2005
Extended to 2014

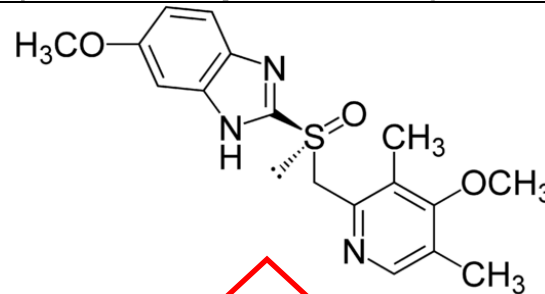
Treatment of GERD - a clinical example

Prilosec
(omeprazole)



Introduced in 1989
Patent expiration April, 2001
OTC in 2003

Nexium
(esomeprazole)



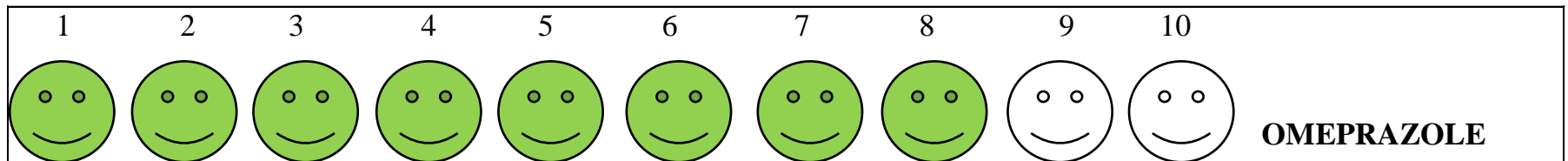
A \$5-billion
blockbuster

Introduced in March 2001
Patent expiration April, 2005
Extended to 2014

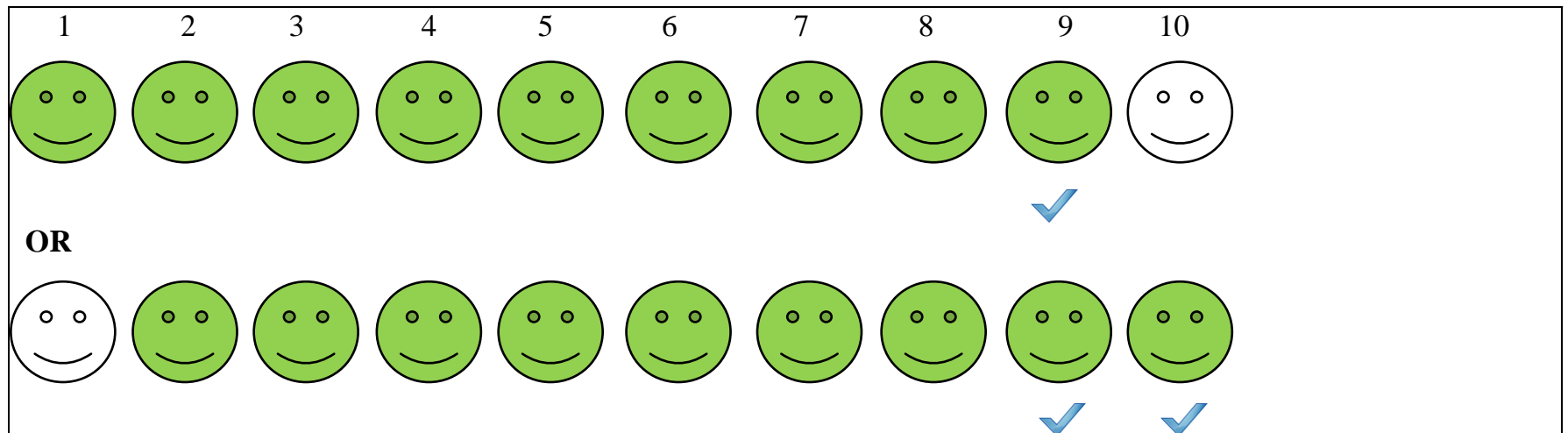
What does CER say?

- An 8 week multicenter, randomized, double-blinded parallel group study
 - More patients were healed with one daily 40 mg esomeprazole versus 20 mg omeprazole at week 8 (93.7% vs. 84.2%, p-value < 0.05)
- Other studies showed similar results
- What're missed in these results are the effects on the extensive margin...

Extensive Margin

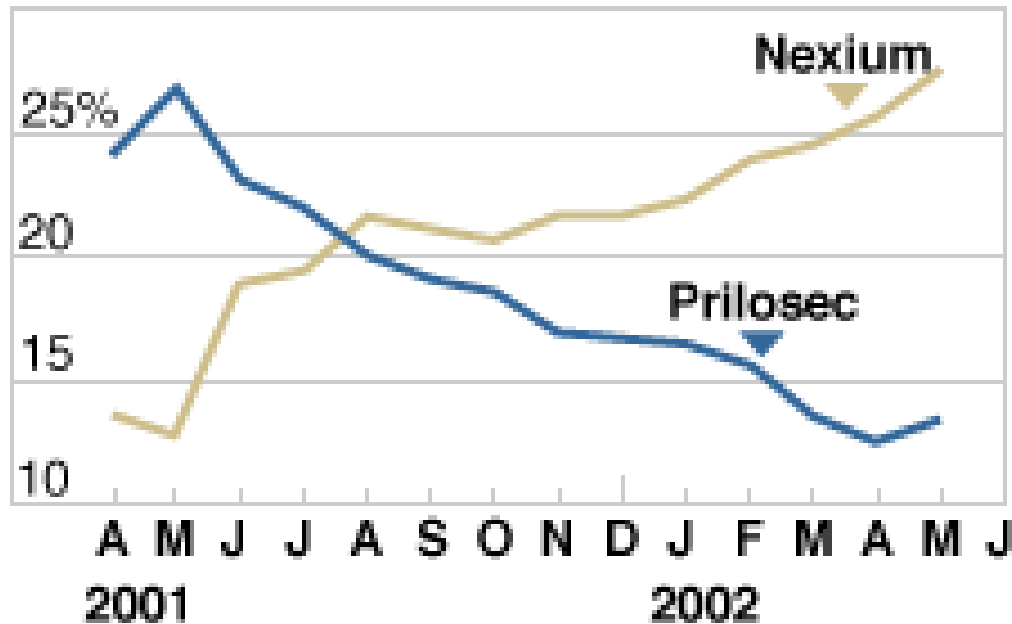


COUNTERFACTUAL POSSIBILITIES WITH ESOMEPRAZOLE



At the extensive margin, the incremental value of esomeprazole over omeprazole exists only for 10 to 20% of the patient population

Ignoring extensive margine



Source: ImpactRx

Nexium costs 10 times more than prilosec

Even after generic omeprazole entry, prilosec shares are higher in 2009

From *Wall Street Journal*, June 2002

Economics of information

- Central to health care reform
- CER is viewed as a cog in health care reform – could be the most important cog
- Prilosec versus Nexium
 - Did the pharmaceutical company did anything wrong?
 - Are the physicians totally agnostic about costs?
 - Was the insurance company wrong in providing coverage?
 - Do we have incomplete information?

Tragedy of Averages in CER

- Highlights the importance of personalized medicine in CER
- Given the goals of CER, personalization / individualization central to any CER agenda
- Recent legislation calls for exploring even finer levels of heterogeneity, including "genetic and molecular sub-types or quality of life preferences", through CER

Economics of individualized information in CER

No CER information

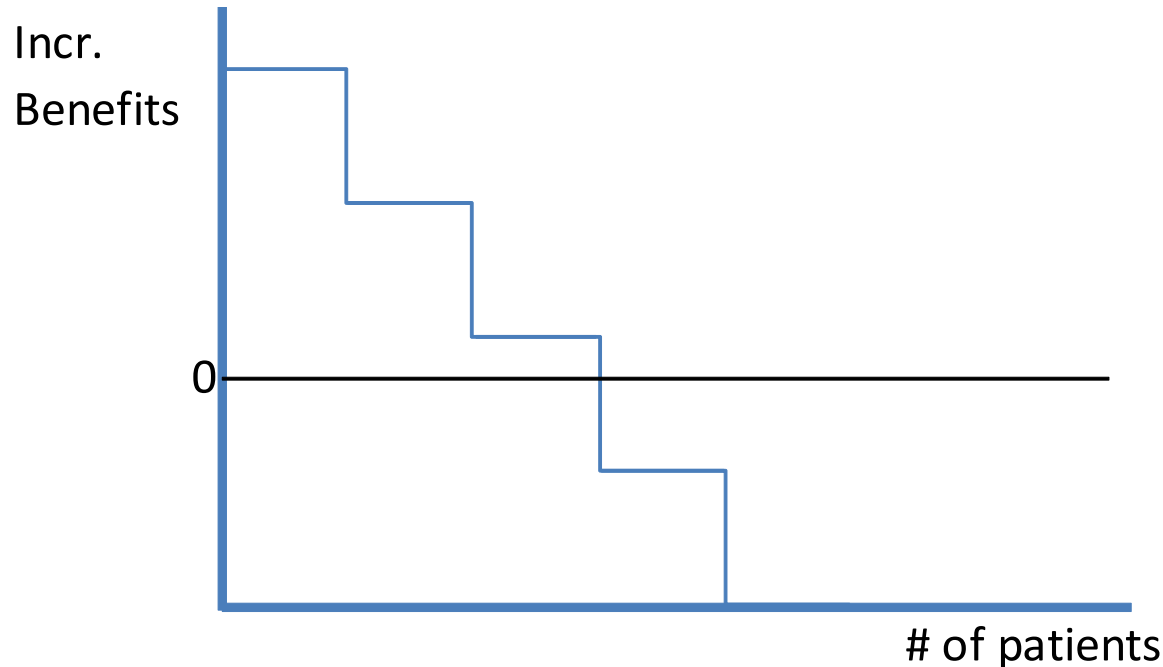
- Individuals' choices of treatment are guided by arbitrary perceptions
 - Do treatments provide incremental value?
 - If so, what are the magnitudes of those benefits?
- Strong incentive for manufacturers to sway public opinion on the benefits of a treatment
 - Raise equilibrium prices, decrease consumer surplus, (or realized patient benefits)
 - Increase dead-weight loss (i.e. inefficient utilization)

No CER information

- Lack of CER information represents a core issue in the US health care system
 - has led to the overuse of technologies, which do not generate any more than average benefits, and often at a price that is inflated due to the inflated demand
- With CER, one hopes to
 - prevent un-validated claims of effectiveness from swaying public opinion about a product, thereby restricting the market and also bringing down prices
 - be able to move patients towards more effective treatment, thereby increasing consumer surplus

How does CER influence welfare?

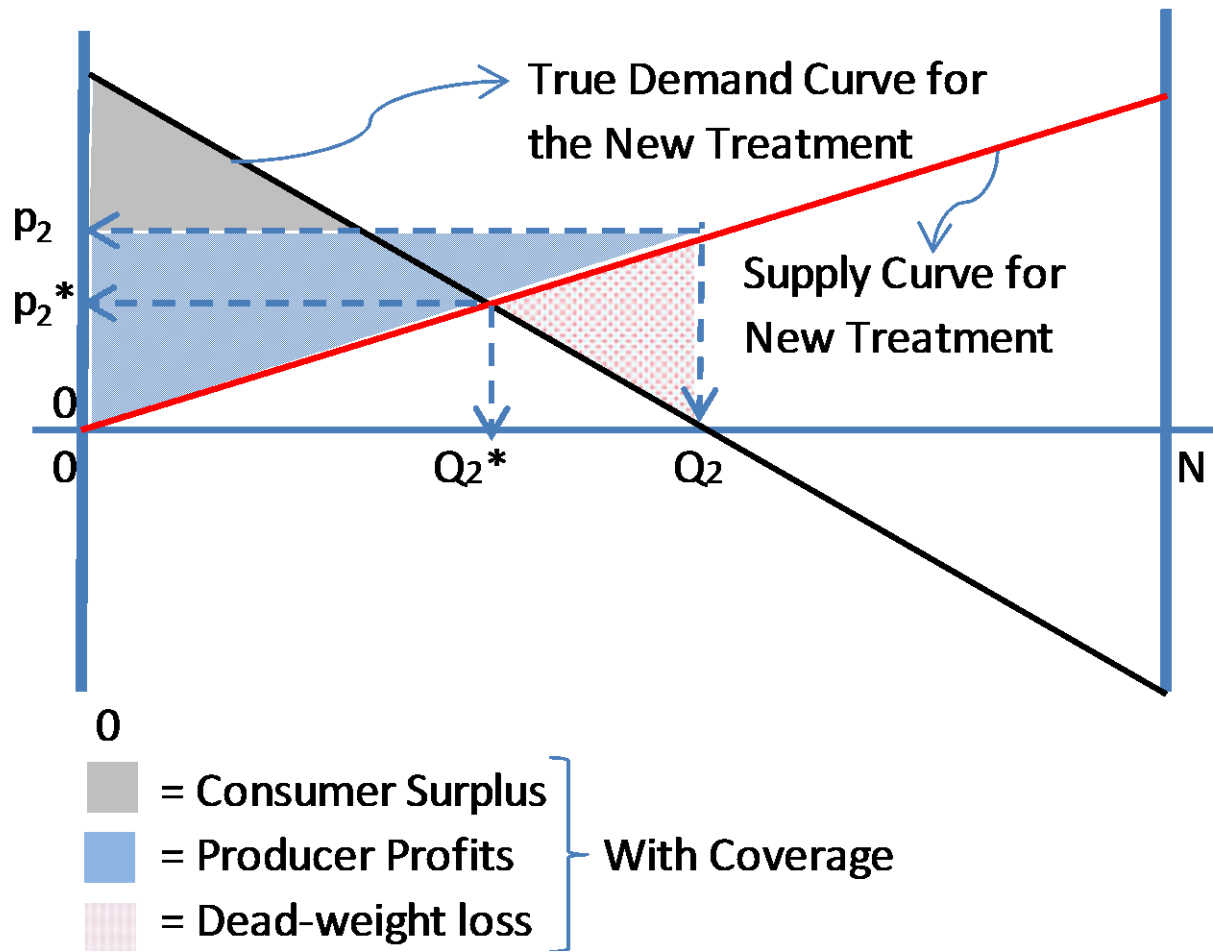
- CER information help shape the marginal benefits (demand) curve in the population



- Such perceived demand curve impact decision-making both at the individual patient and the societal levels.

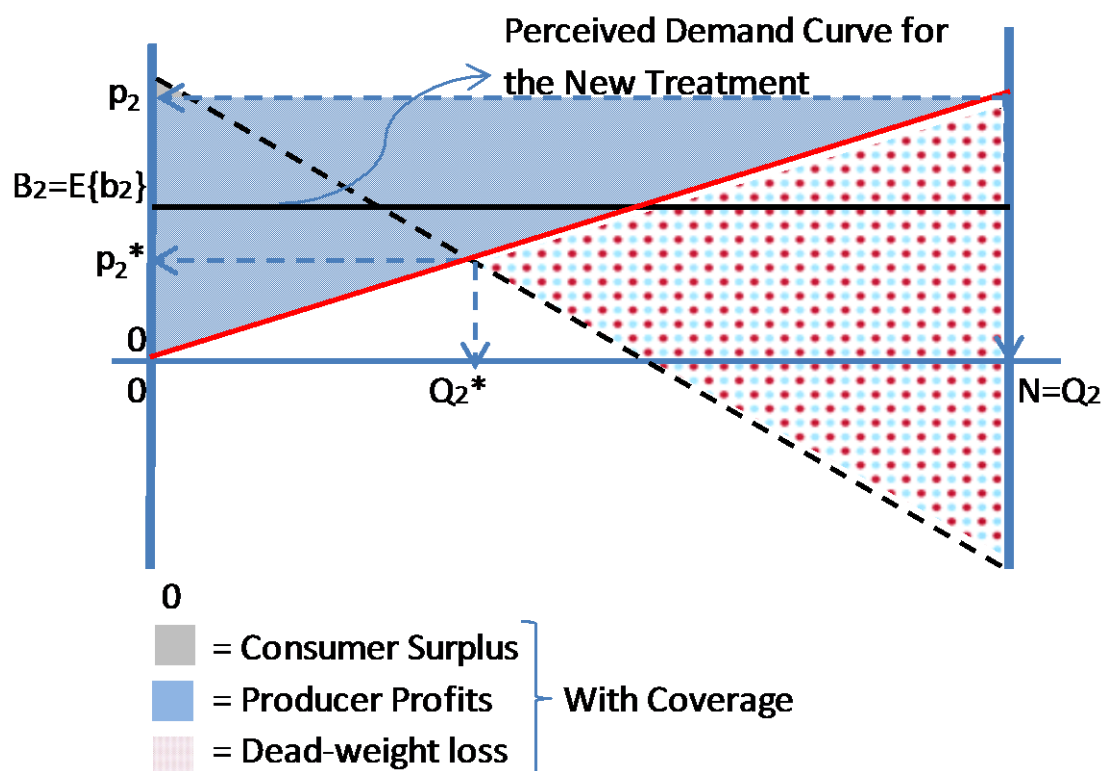
How does CER influence welfare?

- With perfect CER information



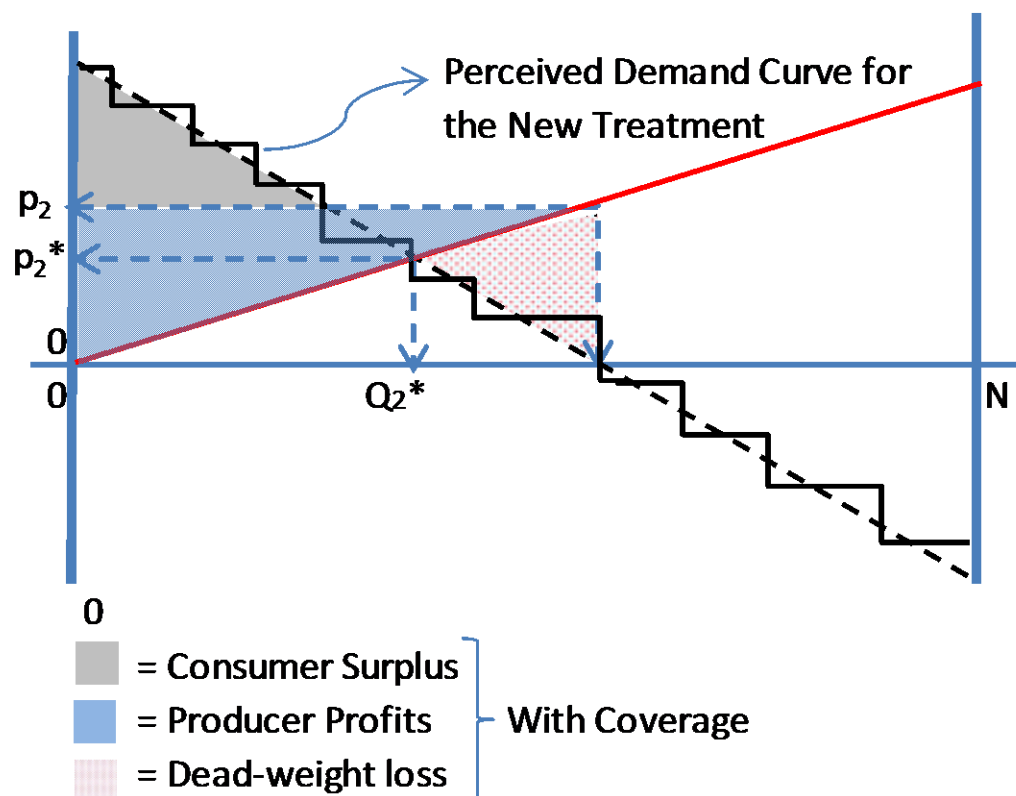
How does CER influence welfare?

- Pop. Average CER information (intensive margins) leads to perception of flat marginal benefits curves
 - Demand is more price responsive → more inefficiency



How does CER influence welfare?

- Individualized CER information can help identify the extensive margins
 - Demand is less price responsive → less inefficiency



Incentives for i-CER

Incentives for individualized CER

- Social value is enormous; Private value varies
- Manufacturer's incentives:
 - For a Manufacturer whose product is the "winner"
 - Leads to shrunken market size – reduction may be more under private (competitive) coverage system
 - Recover in price?
 - Less so for competitive product markets
 - Less so in single payer market that has more leverage for price negotiations (not Medicare)
 - May protect against risk (e.g. Vioxx)

Incentives for individualized CER

- Manufacturer's incentives:
 - For a Manufacturer whose product is the "loser"
 - Leads to recapture of a market segment –may be more quickly under private (competitive) coverage system
 - Competitive pressures from "losers" may create incentives for "winners"
 - May protect against risk for both manufacturer

Incentives for individualized CER

- Payer's incentives:
 - Private payers may have incentive if stratification algorithm is proprietary
 - Shrinks demand within their beneficiaries without big jump in prices
 - Legal disjoint between public coverage of treatments (Medicare & Medicaid) and decisions to invest in CER (AHRQ, NIH)

Incentives for individualized CER

- NIH perspective – need to understand incentives for alternate stakeholders. Often public-private partnerships may be useful

	Single (Public) Payer	Multiple (private) payers
Less competitive product market	Manufacturer's: -ve/+ve Payer's: -ve	Manufacturer's: -ve/+ve Payers' : +ve (may be)
More competitive product market	Manufacturer's: -ve Payers' : -ve	Manufacturer's: -ve Payers' : -ve

Methodological Principles for i-CER

Methodological Approaches

- **Strong implications for how comparative effectiveness research is practiced in general**
 - Relying only on “Hypothesis testing”-driven approaches by subgroups are inefficient
 - Need to balance Type I & II errors at the intensive vs extensive margins
 - Need prediction algorithms for individual-level treatment effect heterogeneity
 - Viewed as a hypothesis generation exercise at the individual level
 - Represent necessary inputs to confirmatory trials
- **Key is to align information generation with the needs of decision making**
- **A Bayesian approach seems to be ideal.**

Methodological Approaches

- Two parts to individualization
 - To recognize individual level heterogeneity in treatment effects (observed & unobserved)
 - Observational data may be key to the this part
 - The curse of “selection” may be a boon when properly understood and adjusted for
 - To relate identifiable / measurable characteristics to levels of treatment effects
 - Need a rich collection of biomarkers and other data both at baseline and also longitudinally as part of CER

Unobserved heterogeneity: When individuals have private information

- Individuals may have more information on the extensive margins that are unobserved by a social planner (SP)
 - Individuals can anticipate how benefits vary with some factors unobserved to the SP
 - Individuals have an opportunity to reveal *the potential effects* using trial and error methods on both treatments
- The perceived marginal benefits curve by the SP is usually more elastic than the one shaped by the individuals' information set.

Conclusions

- Individual-level heterogeneity in CER is essential to grasp its full potential
 - CER information influence behavior of individual patients and their providers → produces a market demand curve
 - Average CER results produce flatter or more elastic market demand curve than it truly should be.
- Can help to distribute market shares among competitors, may limit expenditure growth
- Can guide research prioritization in the future

Conclusions

- Incentives to invest in individualization vary
 - Manufacturer may have incentive to invest for the potential for capturing a market segment or from competitive pressures of investments
 - Payers in private markets may have incentives if they can keep stratifying information proprietary
 - Public payer generally do not have incentive to invest unless they can negotiate prices
 - Public R&D should understand these dynamics to prioritize investments, especially when social value of stratification remains high.

Conclusions

- A paradigm shift in the design of CER studies may be needed
- The recognition that heterogeneity in effects is the only relevant information in CER may be hard to digest for traditional trialists & observational data researchers.
- But establishing extensive margins in comparative health outcomes is necessary to truly mimic market-based outcomes
- Bayesian methods and statisticians can lead the way to develop new methods for i-CER