

NEW FRAMEWORK AND METRICS FOR ECONOMIC EVALUATION
OF MEDICAL TECHNOLOGY IN THE PRESENCE OF HETEROGENEITY
AND ITS APPLICATION TO THE EVALUATION OF BARIATRIC SURGERY

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ABSTRACT

New Framework and Metrics for Economic Evaluation of Medical Technology in the Presence of Heterogeneity and its Application to the Evaluation of Bariatric Surgery

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Most economic evaluations to date, highlighted by cost-effectiveness analysis (CEA), have primarily focused on informing binary coverage decisions about whether to provide full coverage or no coverage on medical technology. For example, CEAs have followed the notion that if a technology is deemed to be cost-effective, often under the assumption of full uptake, then the technology should be allowed to diffuse in the population. Consequently, most metrics (e.g., cost-effectiveness ratios) used for decision-making have not usually incorporated the extent to which medical technology is used in practice (i.e., technology uptake) and how this extent of use is likely to change over time. (i.e., technology diffusion) From an evaluation perspective, such practice is misleading for two reasons. First, it does not allow for evaluating different policy alternatives on access or implementation that may influence the uptake of the technology. Second, which is the focus of this paper, is that economic evaluations have failed to acknowledge evidence-driven differential uptake across subgroups of patients that can inherently change the overall value of medical technology.

The overall goal of this research is to develop a new framework and appropriate metrics for evaluating the realized value of health care technologies through the lens of different policies that are designed to provide access and to implement the use of these technologies in practice. These metrics can be seamlessly used to inform the entire range of policy decisions that are relevant in the context of evaluating the economic value of medical technology. Also, it provides a way to integrate heterogeneity in incremental cost-effectiveness ratios across different subgroups with selective diffusion patterns in the population to express a ratio or an index. This paper highlighted how these metrics vary from a traditional incremental cost-effectiveness ratio.

In addition, we expand this framework to the evaluation of bariatric surgery focusing on patient subgroups with a higher body mass index with type 2 diabetes in two folds: 1) how does the publication of major clinical evidence link to the use of bariatric surgery and 2) economic returns of providing greater access to bariatric surgery. Bariatric surgery represents a particular example of an advancing medical technology where understanding these relations is important. Despite strong evidence on clinical effectiveness and cost-effectiveness of bariatric surgery, bariatric surgery has been significantly underutilized, and its trend has been stagnated. To improve utilization of bariatric surgery, understanding the role of clinical evidence and coverage policy on the uptake of bariatric surgery has become an important issue.

We believe that this novel framework will be useful not only to evaluate the realized economic value of medical technology but also to estimate the economic value of various decision options. Therefore, we propose that this new framework could substantially improve the decision-making process by producing metrics that are better aligned with the specific policy decisions.

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CHAPTER 1: INTRODUCTION

BACKGROUND

Economic evaluations in health care are meant to inform decision-makers about the likely consequences of their choices. These analyses should provide a formal appraisal of medical interventions regarding their impacts on costs and benefits so that the policy maker can make decisions about allocating scarce resources to achieve maximum social welfare.^{1,2} Such policy decisions in health care include not only binary (full or no) coverage decisions, but also decisions on optimal cost-sharing, program implementation, education, investing in further research, and individualization techniques.

However, most economic evaluations have failed to account for the fact that the realized value of technology is driven by the extent of uptake of the technology in the population. Instead, these evaluations, especially cost-effectiveness analysis (CEA), have followed the notion that if a technology is deemed to be cost-effective, often under the assumption of full uptake, then the technology should be allowed to diffuse in the population.³ Consequently, most metrics (e.g., cost-effectiveness ratios) used for decision-making have not usually incorporated the extent to which medical technology is used in practice (i.e., technology uptake) and how this extent of use is likely to change over time. (i.e., technology diffusion)

From an evaluation perspective, such practice is misleading for two reasons. First, economic evaluations have failed to acknowledge evidence-driven differential uptake across subgroups of patients that can inherently change the realized value of medical technology. In the presence of the heterogeneity in treatment effects, subgroups with higher expected benefits are more likely to adopt the technology. (i.e., selective uptake happens). Therefore, to assess the overall value of medical technology in the face of the evidence on heterogeneity, one must

incorporate such behavior through additional parameters that reflect the anticipated behaviors in response to current evidence. Second, it does not allow for evaluating different policy alternatives on access and/or implementation that may influence uptake patterns of same technologies under evaluation. (e.g., coverage decisions would certainly influence how uptake occurs)

In this dissertation, we propose a new framework and appropriate metrics for evaluating the realized value of health care technologies through the lens of different policies that are designed to provide access and to implement the use of these technologies in practice. In essence, we argue that the incremental value of technology should not be reflected by a single estimate of an incremental cost-effectiveness ratio (ICER), but rather tied to the particular policy that would change the uptake of medical technology in consideration.

CONCEPTUAL FRAMEWORK

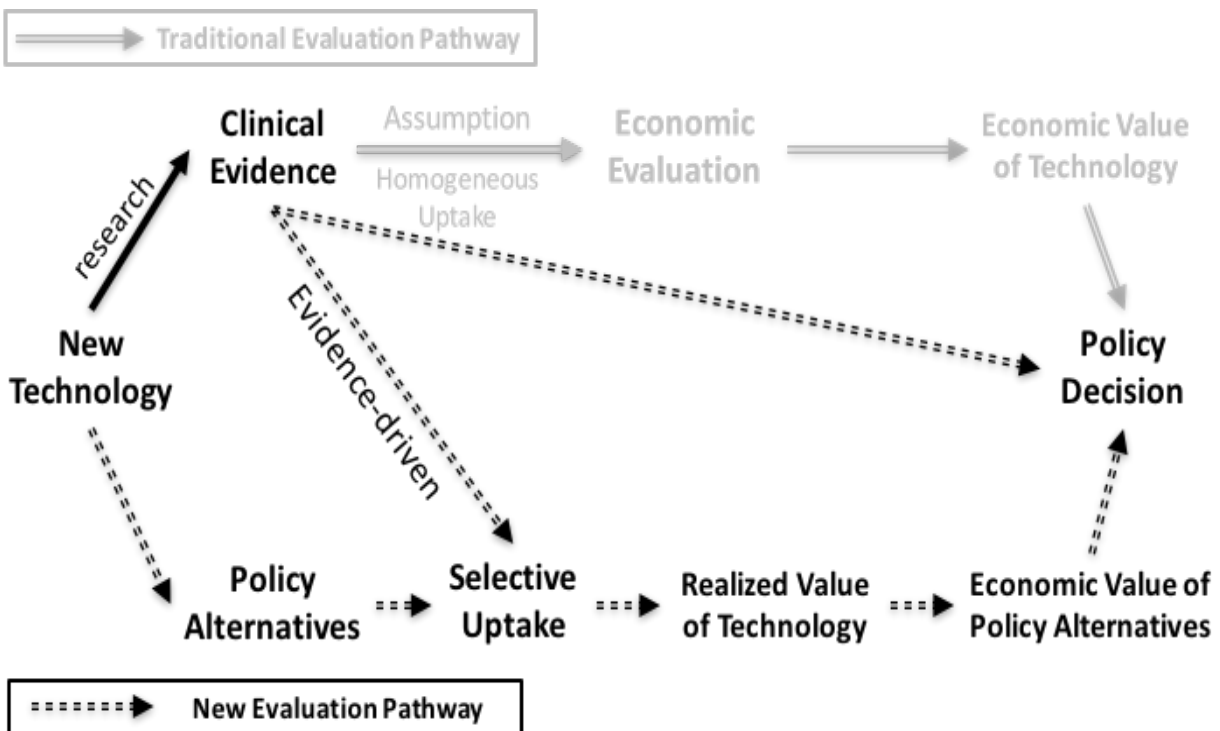


Figure 1. Conceptual model for new evaluation framework

The above figure explains two economic evaluation pathways: a traditional and a new framework. The traditional economic evaluation framework focuses on the research side, rather than the policy side. So, when new technology comes in, researchers conducted clinical trials to generate clinical evidence. Then, analysts estimate the economic value of the new technology based on clinical evidence. Decision makers determine whether or not to provide full coverage or no coverage based on the hypothetical economic value, compared to a decision maker's willingness to pay threshold. The economic value under this traditional framework represents a hypothetical value of medical technology because it assumes the full uptake of the technology at the population level, such as what happened in the clinical trial. This hypothetical value could represent a potential value that could be achieved when the entire population is fully adopting the technology. However, this metric does not provide a realized value of the technology based on the actual level of utilization.

In practice, because of some of the barriers (e.g., insurance coverage, supply-side constraints, and implementation), the potential value of medical intervention could not be fully realized. Also, from a decision maker's perspective, they have to think about the realized value of medical technology under specific policy alternatives. Thus, the new economic evaluation framework that we propose is designed to evaluate the realized value of medical technology based on the actual or predicted rates of uptake. The rates of uptake of a specific technology could depend on both clinical evidence (i.e., when evidence shows heterogeneity in treatment effect) and policy alternatives (i.e., differential level of cost-sharing). Because this new framework estimates the realized value of technology specific to policy alternatives, we could have multiple economic values when evaluating a same set of technologies. Therefore, this new

framework could substantially improve the decision-making process by producing metrics that are better aligned with the specific policy decisions.

SPECIFIC AIMS

The primary objective of this dissertation is to conceptualize new framework and metrics, which forecast the economic returns from policy alternatives, to better align economic evaluations with the decision-making perspective. We expand this framework to the evaluation of bariatric surgery focusing on patient subgroups with a higher body mass index with type 2 diabetes in two folds: 1) how does the publication of major clinical evidence link to the use of bariatric surgery and 2) economic returns of providing greater access to bariatric surgery.

Aim 1: To develop new framework and metrics to evaluate economic returns of medical technology from policy alternatives

Specific Aim 1a incorporated the differential rates of uptake across subgroups driven by heterogeneity in clinical and economic evidence into the existing economic evaluation metrics. We proposed that the modified metric provides a realized value of medical technology based on the actual utilization of technology at the population level, rather than a hypothetical value of medical technology under the assumption of perfect uptake.

Specific Aim 1b examined economic returns of medical technology under various policy alternatives that are designed to provide access and to implement the use of medical technologies in practice. We then tie in other metrics on the value of information literature with this framework.

Aim 2: To understand the effect of major clinical evidence on selective diffusion of bariatric surgery across subgroups

Specific Aim 2a tested whether the publication of major clinical evidence for obese

patients with type 2 diabetes leads to faster uptake of bariatric surgery. We hypothesized that after major evidence came out, this subgroup – that has been shown to benefit more from bariatric surgery, compared to other subgroups – is more likely to a faster rate of uptake of bariatric surgery over time.

Specific Aim 2b extended the scope of this analysis by examining the relationship between rates of bariatric surgery and the following: 1) the incremental effect of an additional major article, 2) the type of evidence, and 3) the tier effect among major articles on the uptake of bariatric surgery.

Aim 3: To understand the realized value of bariatric surgery under the current policy and other policy options

Specific Aim 3a estimated prevalence, the rates of uptake of bariatric surgery, and incremental costs and effectiveness of bariatric surgery in relative to non-surgical interventions among specific-subgroups defined by the level of the body mass index (BMI) and the presence of type 2 diabetes

Specific Aim 3b predicted the rates of the uptake under various coverage options (i.e., changes the level of cost-sharing) and evaluated potential realized value of bariatric surgery among those subgroups under those scenarios.

CONCLUSION

In this work, we proposed a new evaluation framework that can be readily used for evaluating the realized value of medical technology under various policy options. This framework is highlighted by 1) incorporating subgroup-specific differential rates of the uptake driven by heterogeneity in clinical and economic evidence and 2) evaluating economic returns of policy alternatives that potentially affect the uptake of new technology (e.g., the level of cost-

sharing) It is important to acknowledge that these factors can inherently change the overall value of a medical technology, and therefore, from an evaluation perspective, new metrics would better represent the marginal value of a policy decision in the context of evaluating medical technology. Also, this metric can be widely used to inform policy decision from the optimal coverage decisions to other decision-making in health care, such as investments in research and development.

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CHAPTER 2: NEW FRAMEWORK AND METRICS FOR ECONOMIC EVALUATION IN THE PRESENCE OF HETEROGENEITY

ABSTRACT

Background: The incremental cost-effectiveness ratio (ICER) between two treatments can vary substantially based on the policy under which patients can access these treatments and how practice guidelines are implemented. Thus, if economic evaluations are intended to guide policy decision-making, decision-makers should start comparing policies and not treatments, which is typically done in cost-effectiveness analysis. Moreover, behavioral response to heterogeneity in evidence would be necessary to incorporate in such policy evaluations.

Methods: We conceptualize new metrics, which forecast the economic returns from policy alternatives, to better align economic evaluations with the decision-making perspective. We then tie in other metrics on the value of information literature with this framework. We illustrate this framework and metrics using a stylized example of policies on treatment with lipid combination therapy versus monotherapy in patients with type 2 diabetes and mixed dyslipidemia.

Results: The new framework for policy evaluation can directly inform decision-makers about the optimal level of insurance coverage and investment in implementation by choosing a policy that would produce the largest economic returns in the context of a new treatment. In our illustration, we find that traditional ICER can be misleading if differential uptake across subgroups is not accounted for. Also, choosing a policy option that improves implementation of combination therapy into practice, instead of a policy that changes insurance coverage, would improve economic efficiency due to the significant underutilization under the current policy.

Conclusion: We believe that this framework and metrics can be more decision-friendly for decision-makers. More research is needed to study how evidence levels impact adoption in clinical practice to better inform this framework.

1. INTRODUCTION

Economic evaluations in health care are meant to inform decision-makers about the likely consequences of their choices. These analyses should provide a formal appraisal of different policy alternatives regarding their impacts on costs and benefits so that decision-makers can make informed decisions about how to best allocate scarce resources to achieve maximum social welfare. Such policy decisions in health care include not only binary (full or no) coverage decisions, but also decisions about optimal cost-sharing, program implementation, education, investing in further research, and individualization techniques.

Most economic evaluations to date, highlighted by cost-effectiveness analysis (CEA), have primarily focused on informing binary coverage decisions about whether to provide full coverage or no coverage on medical technology.^{1,2} Also, they have not usually incorporated the extent to which medical technology is used in practice and how this extent of use is likely to change over time (i.e., technology diffusion).^{3,4} The latter is perhaps one of the fundamental limitations of the current state of economic evaluations, although it is now well established that realizing how medical technology is used in practice is central to understanding whether medical care generates economic value.^{5,6} Economic evaluations have avoided considering how technology will be used in practice when determining its value. Instead, these evaluations, especially CEA, have followed the notion that if a technology is deemed to be cost-effective, often under the assumption of hypothetical adoption ratesⁱ typically observed in clinical trials, then the technology should be allowed to diffuse in the population.⁸

ⁱ Herein, adoption refers to a time-period-specific rate of technology use by an individual or an organization, whereas diffusion indicates how adoption evolves over time.⁷

From an evaluation perspective, such practice is misleading for two reasons. First, economic evaluations have failed to acknowledge evidence-driven differential adoption across subgroups that can inherently change the overall value of medical technology. Second, it does not allow for evaluating the impact of policy alternatives that potentially change the adoption of those technologies. (e.g., coverage decisions would certainly influence how adoption occurs). Although budget impact analyses, as distinct from CEA, have sometimes incorporated hypothetical adoption rates over time to inform affordability, the corresponding impacts on the effectiveness side have largely been ignored.

In this manuscript, we develop a framework and propose novel metrics for evaluating the value of medical technologies through the lens of different policies that are designed to change the level of insurance coverage and improve the use of these technologies in practice through education and implementing better guidelines. In essence, we argue that the incremental value of technology should not be reflected by a single estimate of an incremental cost-effectiveness ratio (ICER), but rather tied to the particular policy that would change the adoption of this technology.

Consequently, the same technology can have multiple ICERs depending on policy alternatives, and the decision-making for the optimal policy would be driven by choosing the policy producing the best economic return for this technology. We show that these metrics can be seamlessly used to inform the entire range of policy options that are relevant in the context of the medical technology. Specifically, it provides a way to integrate heterogeneity in costs and effectiveness across different subgroups with potential adoption patterns. The metrics can be expressed in a ratio or an index that would better represent the marginal value of a policy decision, and therefore, better suited to inform a decision-maker. We also tie these metrics to the vast literature on the value of information analysis for research prioritization.

2. CONCEPTUAL FRAMEWORK FOR POLICY EVALUATION

Let us suppose that a social insurer (e.g., Medicare) aims to maximize a health outcome (e.g., quality-adjusted life years) given a fixed budget. The social insurer faces a policy decision about whether to provide coverage for a new treatment A for treating a chronic illness versus the standard of care, as denoted by B. Traditionally, one would conduct a CEA comparing treatment A versus B and estimate an incremental cost-effectiveness ratio (ICER),

$$ICER = \frac{E(C_A) - E(C_B)}{E(Q_A) - E(Q_B)} \quad (1),$$

where C denotes costs, Q denotes quality-adjusted life years (QALYs) and E() denotes an expectation. This ICER is then compared to a cost-effectiveness threshold, λ , which represents a social insurer's willingness to pay (WTP) for additional gain in QALYs.ⁱⁱ If the ICER is less than the threshold, it indicates that paying for treatment A will provide good value and vice versa. Without any loss of generality, let's assume that this ICER is greater than λ and treatment A is not deemed to provide good value. (i.e., $ICER > \lambda$)

While these ideas pervade the cost-effectiveness literature, there exists the implicit assumption behind the interpretation of ICER that assumes, if covered, treatment A would be immediately used/adopted by all patientsⁱⁱⁱ. If not covered, treatment A, even though it is an approved treatment available in the market, will not be used by any, and all patients will take option B. However, it is possible that in the latter case, some patients, who may benefit from treatment A, choose to pay out of their own pocket to get treatment A. In this case, with the

ⁱⁱ Theoretically, from the constrained optimization framework, λ actually represents the rate at which QALYs would be forgone elsewhere in the health care sector if the new treatment were paid for, given the fixed budget. Thus, the cost-effectiveness threshold, the marginal costs per addition gain in benefits, should be represented by $1/\lambda$. However, throughout this paper, we denoted λ for the cost-effectiveness threshold, following the general convention in CEA.

ⁱⁱⁱ or a proportion of patient population that reflect the same rate observed in the clinical trial informing this estimate.

availability of new treatment A, the policy under the status quo (i.e., only cover treatment B) may have changed the population level outcomes.³

This brings us to the role of heterogeneity in CEA. There is increasing recognition that individual patients respond to alternative treatments differentially and that heterogeneity in costs, effectiveness and cost-effectiveness should be considered.^{3,9,10} The role of evidence on the heterogeneity of treatment effects in influencing individual-level decision-making is relatively straightforward because decision-making is not centralized, and, in this setting, the expected value of individualized care (EVIC) may be calculated to establish the value of generating evidence to improve individual decision-making.¹¹ However, the role of evidence on heterogeneous effects in population-level (centralized) policy decision-making is less clear. Some have argued that subgroup analyses should be carried out in CEA when the goal is to provide differential coverage across these subgroups.^{12,13} However, such differential coverages are seldom implemented in practice. While new research has delved into the methodological issues of estimating and presenting heterogeneity in cost-effectiveness¹⁴, how such information can be best used to inform population-level decision making is yet to be explored.

To illustrate the heterogeneity in effects more clearly in our stylized example, we can assume that there are three subgroups ($j = 1,2,3$) within the patient population with the chronic disease, indexed by an easily observable characteristic, such as age, over which current evidence documents variability in the ICERs. Let these ICERs be:

$$ICER_{j,AB} = \frac{E(C_{A,j}) - E(C_{B,j})}{E(Q_{A,j}) - E(C_{B,j})} \quad j = 1,2,3 \quad (2)$$

Let $ICER_{1,AB}$ and $ICER_{2,AB}$ be both greater than λ and $ICER_{3,AB}$ be less than λ . (i.e., $ICER_{1 \& 2,AB} > \lambda$ and $ICER_{3,AB} < \lambda$) That is, compared to the threshold λ , using treatment A among patients in the third subgroup would generate value within the health care sector, but not in other subgroups. Despite this evidence of heterogeneity, the traditional ICER in (1), which is used to inform a uniform coverage decision for treatment A, can also be written as:

$$ICER = \frac{E(C_A) - E(C_B)}{E(Q_A) - E(Q_B)} = \frac{\sum_j \{P_j \cdot [E(C_{A,j}) - E(C_{B,j})]\}}{\sum_j \{P_j \cdot [E(Q_{A,j}) - E(C_{B,j})]\}} > \lambda \quad (3)$$

In the above formula, the size of these subgroups with respect to the target population is given as $P_j \leq 1, j = 1, 2, 3$. Like the original interpretation of the ICER, it is assumed that when treatment A is covered, it would be adopted by all patients in all three subgroups, despite evidence suggesting variability in outcomes across these subgroups.

Thus, one could conceivably implement subgroup-specific coverage decisions to overcome the limitations of decision-making using a single overall ICER. However, in many cases, the number of subgroups could be large, and there may not be easy ways to implement such heterogeneous policies due to ethical reasons and feasibility issues. Also, if the goal is to evaluate the realized value of treatment A in practice, one must also understand the role of heterogeneous evidence in the selective adoption of treatment A across subgroups. Therefore, a modified ICER that could incorporate such behavior could be written as:

$$ICER = \frac{\sum_j \{P_j \cdot D_j \cdot [E(C_{A,j}) - E(C_{B,j})]\}}{\sum_j \{P_j \cdot D_j \cdot [E(Q_{A,j}) - E(C_{B,j})]\}} = \frac{\sum_j \{P_j \cdot D_j \cdot E(\Delta C_j)\}}{\sum_j \{P_j \cdot D_j \cdot E(\Delta Q_j)\}} \quad (4)$$

In the above formula, D_j represent the rate of adoption of treatment A in the population subgroup j, and can be estimated as following:

$$D_j = \frac{\sum_{i=1}^{N_j} I(D_i)}{N_j} \quad (5),$$

where N_j is the size of population subgroup j who are receiving or are expected to receive one of the comparators, and $I(D_i)$ indicates whether an individual patient in the specific subgroup would choose to adopt treatment A or not when given full coverage to the treatment.^{iv} This formulation can be easily adapted to capture adoption over time, but we keep that implicit for simplicity of illustration. If the rate of adoption of the technology is same in all three subgroups, we get back the original ICER as shown in (3). However, if the adoption rates are different, as would be expected based on differences in evidence across these subgroups, the modified ICER would be a better reflection of the realized value from this technology in practice.

One can further develop this concept to allow for evaluation of different policies. As noted above, the typical use of ICER is interpreted as the incremental cost-effectiveness of treatment A over B under a hypothetical policy of full adoption of A or B that presumably arises from full coverage of both treatments, although this policy dependence is usually kept implicit. In fact, the ICER from A over B would be very different if the underlying policy being examined were to cover A at 50% cost-sharing versus no coverage, holding coverage for treatment B constant. This implies that ICER as expressed in (2) cannot readily be used to inform more nuanced forms of coverage policies that many public and private payers contemplate, whereas the revised form of ICER in (4) can readily address this issue. Furthermore, if the social insurer

^{iv} In the absence of any other evidence on the heterogeneity of effects, it is assumed that the average incremental outcomes among those who adopt (i.e., $I(D_i) = 1$) and those who do not (i.e., $I(D_i) = 0$) within a subgroup is the same, as there is no other evidence for individuals to select upon.

takes a narrower perspective as a payer, the ICER under a policy k that only accounts for a fraction, f_k , of the incremental costs (i.e., the rest being borne by the patient as cost-sharing) is given as:

$$ICER_{policy_k} = \frac{\sum_j \{P_j \cdot D_{jk}(f_k) \cdot E(\Delta C_j) \cdot f_k\}}{\sum_j \{P_j \cdot D_{jk}(f_k) \cdot E(\Delta Q_j)\}} \quad (6)$$

where $D_{jk}(f_k)$ is the expected adoption of treatment A in subgroup j under Policy k . Note that the numerator includes not only a fraction of the incremental costs borne by the payer^v but also the adoption probability is tempered with cost-sharing in line with price elasticities of demand.

From a health care sector perspective, which accounts for all cost of care irrespective of who bears them, the full incremental costs will be accounted for but the adoption rate would still be driven by cost-sharing. That is, from the health care sector perspective:

$$ICER_{policy_k} = \frac{\sum_j \{P_j \cdot D_{jk}(f_k) \cdot E(\Delta C_j)\}}{\sum_j \{P_j \cdot D_{jk}(f_k) \cdot E(\Delta Q_j)\}} \quad (7)$$

This new ICER formulation, as expressed in (6) or (7), is better suited to inform choices across different policy options in the presence of evidence of heterogeneity in treatment effects and evidence of subsequent selective diffusion across subgroups. Standard decision-making criteria where the ICER is compared to the threshold to assess the cost-effectiveness of a policy decision could be applied here. Note that the biggest difference between this and the traditional ICER is that the traditional formulation provides only one ICER for comparing treatment A to treatment B. Whereas, under the new formulation, ICER comparing treatment A to B varies across policy decisions since these policy decisions could have differential effects on the

^v One can also separate out the costs of the treatment from the other pecuniary consequences of treatment and apply the cost sharing only to the former but not the later.

adoption of treatment A. By doing so, one can allow the adoption rates to be endogenous to the policy decision itself, and consequently, generate a more policy-decision-relevant estimate of value. In what follows, we will continue to adopt the health care sector perspective.

The ICER expressed in a ratio, has been a primary metric in CEA because it eliminates the need to monetize health outcomes and to report an explicit WTP threshold. However, in most cases, decision-makers need to specify their WTP thresholds to make a relevant decision, and there is well-established literature to explain the potential problems of ratio statistics (e.g., interpretation of negative ratios and ignoring the magnitude of the impact).^{15,16} Thus, a net monetary benefits (or a net health benefit) framework may be better suited to make these comparisons, especially in the presence of multiple policies ($k = 1, 2, \dots, K$) for coverage and/or implementation of $t=1, 2, \dots, T$ treatment/interventions, whose effects vary over $j = 1, 2, \dots, J$, subgroups in the population. In this setting, the net monetary benefits (NMB) under a policy k , which could have implications for cost-sharing and/or adoption of any treatment t within subgroup j , would be given as:

$$NMB_{policy_k} = \sum_j \sum_t [P_j \cdot D_{jkt}(f_k) \cdot (E(Q_{jt}) \cdot \lambda - E(C_{jt}))] \quad (8)$$

To ensure whether any different policy action is warranted, it is important to understand the NMB under the status-quo policy. For example, let's take that case of the two treatment alternatives (e.g., new treatment A and standard of care B) again. First, we assume that treatment A is yet to be introduced, and the status-quo policy provides full coverage of treatment B and full adoption of B in all subgroups in the target population. Therefore, $NMB_{Policy_{SQ}}$ is given as:

$$NMB_{Policy_{SQ}} = \sum_j P_j \cdot (E(Q_{jB}) \cdot \lambda - E(C_{jB})) \quad (9)$$

Now consider a new policy, $Policy_{NEW}$, with the introduction of treatment A, where A is also fully covered in addition to B. Under this policy, let $D_{j,Policy_{NEW,A}}$ represent the proportion of the population who would choose A over B in subgroup j. Consequently, the proportion of the population who continue to receive B in subgroup j would be $1 - D_{j,Policy_{NEW,A}}$. Thus, following (7), the NMB for policy $Policy_{NEW}$ is given as^{vi}

$$\begin{aligned}
& NMB_{Policy_{NEW}} \\
&= \sum_j P_j \cdot [D_{j,Policy_{NEW,A}} \cdot (E(Q_{j,A}) \cdot \lambda - E(C_{j,A})) + (1 - D_{j,Policy_{NEW,A}}) \cdot (E(Q_{j,B}) \cdot \lambda - E(C_{j,B}))] \\
&= \sum_j P_j \cdot [D_{j,Policy_{NEW,A}} \cdot (E(\Delta Q_{j,AB}) \cdot \lambda - E(\Delta C_{j,AB})) + (E(Q_{j,B}) \cdot \lambda - E(C_{j,B}))] \quad (10)
\end{aligned}$$

Consequently, the incremental NMB between policy $Policy_{NEW}$ and $Policy_{SQ}$ is given by subtracting (8) from (9)

$$INMB_{Policy_{NEW}-Policy_{SQ}} = \sum_j P_j \cdot [D_{j,Policy_{NEW,A}} \cdot (E(\Delta Q_{j,A}) \cdot \lambda - E(\Delta C_{j,A}))] \quad (11)$$

That is, compared to the status-quo policy, the new policy $Policy_{NEW}$ is cost-effective if

$$\begin{aligned}
INMB_{Policy_{SQ}} &= \sum_j P_j \cdot [D_{j,Policy_{NEW,A}} \cdot (E(\Delta Q_{j,AB}) \cdot \lambda - E(\Delta C_{j,AB}))] > 0 \\
&= \frac{\sum_j \{P_j \cdot D_{j,Policy_{NEW,A}} \cdot E(\Delta C_{j,AB})\}}{\sum_j \{P_j \cdot D_{j,Policy_{NEW,A}} \cdot E(\Delta Q_{j,AB})\}} < \lambda
\end{aligned}$$

^{vi} Here we assume the individual patients or their physicians do not have any other evidence to be able to differentially select treatment within a subgroup. Therefore, the expected benefits of those choosing treatment within a subgroup is equal to the expected benefits of choosing treatment for the whole subgroup.

With the last equality reflecting this specific interpretation of the incremental cost-effectiveness ratio of A versus B as reflected in (4).

Naturally, with multiple policy options, (8) would be better suited to compare these policy options. In fact, one can also account for differential costs of policy implementation (M_K) in this framework and express (8) as:

$$NMB_{policy_k} = \sum_j \sum_t [P_j \cdot D_{jkt}(f_k) \cdot (E(Q_{jt}) \cdot \lambda - E(C_{jt}))] - M_K \quad (12)$$

The policy that maximizes NMB would be deemed as the optimal policy given λ . Therefore, the policy-specific ICERs or NMBs could be used to make policy decisions across a broad range of the decision space. Evaluating medical technology through the lens of specific policies changes the calculus for expected realized value from that technology. Consequently, it should also affect the expected value of future research on this technology. In order to tie together the large literature on value of information analysis that have accompanied the cost-effectiveness literature, we develop two novel concepts termed *efficient diffusion* and *loss with respect to efficient diffusion* in the following section.

3. EFFICIENT DIFFUSION UNDER UNCERTAINTY VERSUS CERTAINTY

3.1. EFFICIENT DIFFUSION

Efficient diffusion represents the phenomenon where only those in the cost-effective subgroups – i.e., where new treatment A is cost-effective for the specific subgroup j, compared to the standard of care B – fully adopt the new treatment, and those in the other subgroups do not elect to adopt the new treatment. If efficient diffusion can be achieved, then there is no need to restrict coverage of treatment A for everyone, as only those who would gain more than the

opportunity cost of consuming treatment A, would use treatment A. This result is Pareto optimal. It produces the maximal value from treatment A, given current evidence. Thus, efficient diffusion implies that all technologies should be covered by insurance as long those technologies are used in an efficient manner, a staple concept in the first-best solution of health insurance markets.^{17,18} In the presence of multiple treatments ($t = 1, 2, \dots, T$), let efficient diffusion for any treatment t within a subgroup j be characterized using binary indicator D_{jt}^* , depending on whether that treatment is cost-effective in that subgroup.

There could be two types of efficient diffusion – one under current information, which includes the inherent uncertainty present in this evidence and the other under perfect information where all uncertainties are resolved. We now describe these two scenarios

3.2. EFFICIENT DIFFUSION UNDER CURRENT INFORMATION (EDCI)

Under current information, efficient diffusion represents perfect implementation (i.e., subgroup-level perfect adoption of technologies) based on what we currently know about the cost-effectiveness of new medical technology. It also implies, that given current evidence, if $NMB_j < 0, \forall j$, then it is sufficient to forgo coverage decisions for new treatment A because treatment A is not cost-effective for any of the subgroups.

Under our stylized example of two treatment and three subgroups, efficient diffusion would imply that even with full coverage of treatment A for all subgroups, only those in the third subgroup fully adopt treatment A (i.e., $D_{3,A}^* = 1$ and $D_{3,B}^* = 0$), whereas those in the first and second subgroup entirely reject treatment A (i.e., $D_{1 \& 2,A}^* = 0$ and $D_{1 \& 2,B}^* = 1$). Under this scenario, the NMB arising out of EDCI is given as:

$$NMB_{EDCI} = P_1 \cdot E[(Q_{1B} \cdot \lambda - C_{1B})] + P_2 \cdot E[(Q_{2B} \cdot \lambda - C_{2B})] + P_3 \cdot E[(Q_{3A} \cdot \lambda - C_{3A})] \quad (13)$$

In a more generalized formula, the NMB under EDCI can be expressed as:

$$\begin{aligned}
 NMB_{EDCI} &= \sum_j \sum_t [P_j \cdot D_{jt}^* \cdot (E(Q_{jt}) \cdot \lambda - E(C_{jt}))] \\
 &= \sum_j P_j \cdot \max_t E(\{Q_{jt} \cdot \lambda - C_{jt}\})
 \end{aligned} \tag{14}$$

Many would recognize that equation (14) is analogous to the second term of the traditional Expected Value of Perfect Information (EVPI) expression ¹⁹. It is also not policy specific as it represents the best one could do under current information through the perfect implementation of current evidence.

3.3. EFFICIENT DIFFUSION UNDER PERFECT INFORMATION (EDPI)

Given the existing uncertainty in NMBs under current information, there is a possibility that even perfect implementation of current evidence would incur some losses. This is tied to that fact that whatever decision is deemed optimal under current information may be suboptimal when uncertainty is resolved. That is, research generating more precise estimates of existing evidence could induce more appropriate adoption of the new treatment across subgroups.

With the stylized example, current evidence suggests that new treatment A is cost-effective in subgroup 3 but not in subgroup 1 or 2. However, there is uncertainty associated with INMB between new treatment A and standard of care B for each subgroup. For example, let us state that the uncertainty is least for subgroup 3, and the results favor treatment A, but there is uncertainty nevertheless. To account for the existing uncertainty, we generate the cumulative distribution function for the INMB between A and B for each subgroup as $F_{INMB_{j,AB}}(x) =$

$\Pr(INMB_{j,AB} \leq x)$, given λ . Under this scenario, the probability that future research could change the current decision on efficient use of new treatment A is given as:

$$\text{For Subgroup 1, Current Decision: Use B; } \Pr(\text{A is optimal}) = 1 - F_{INMB_{1,AB}}(0)$$

$$\text{For Subgroup 2, Current Decision: Use B; } \Pr(\text{A is optimal}) = 1 - F_{INMB_{2,AB}}(0)$$

$$\text{For Subgroup 3, Current Decision: Use A; } \Pr(\text{B is optimal}) = F_{INMB_{3,AB}}(0)$$

Therefore, efficient diffusion that accounts for both today's evidence and the expected value of future research is given as:

$$\begin{aligned} NMB_{EDPI} &= P_1 \cdot [(Q_{1B} \cdot \lambda - C_{1B}) + \{1 - F_{INMB_{1,AB}}(0)\} \cdot E\{INMB_{1,AB} | INMB_{1,AB} > 0\}] \\ &\quad + P_2 \cdot [(Q_{2B} \cdot \lambda - C_{2B}) + \{1 - F_{INMB_{2,AB}}(0)\} \cdot E\{INMB_{2,AB} | INMB_{2,AB} > 0\}] \\ &\quad + P_3 \cdot [(Q_{3A} \cdot \lambda - C_{3A}) - \{F_{INMB_{3,AB}}(0)\} \cdot E\{INMB_{3,AB} | INMB_{3,AB} \leq 0\}] \\ &= \sum_j P_j \cdot \left[\begin{aligned} &\{1 - F_{INMB_{j,AB}}(0)\} \cdot E(NMB_{j,A} | INMB_{j,AB} > 0) \\ &+ \{F_{INMB_{j,AB}}(0)\} \cdot E(NMB_{j,B} | INMB_{j,AB} \leq 0) \end{aligned} \right] \quad (15) \end{aligned}$$

Equation (15) indicates that for each subgroup, there is some probability that our current decision to promote full adoption of A versus B as part of efficient diffusion, may be wrong. And if we completely resolve this uncertainty then we truly know which treatment to adopt for each subgroup. Thus, the expected NMB from efficient diffusion under perfect information (EDPI) would be an expectation over treatment specific maximum NMBs when uncertainty is completely resolved. Note that this represents the first term of the traditional EVPI expression, albeit at the subgroup-specific level, expressed in general as:

$$NMB_{EDPI} = \sum_j P_j \cdot \max_t \{E(Q_{jt} \cdot \lambda - C_{jt})\} \quad (16)$$

4. LOSS WITH RESPECT TO EFFICIENT DIFFUSION (LED) METRICS

To tie the existing value of information framework with the new metrics that we are proposing that incorporate policy-driven rates of selective adoption, we consider three different “*Loss with respect to efficient diffusion (LED)*” metrics. LED metrics estimate how much the realized value of policy alternatives deviates from the ideal scenario, called efficient diffusion. Figure 1 provides graphic representation of new metrics along with the summary of these metrics.

$$LED_{EVPI} = NMB_{EDPI} - NMB_{EDCI} \quad (17)$$

$$LED_{Policy_K} = NMB_{EDCI} - NMB_{Policy_K} \quad (18)$$

$$LED_{Policy_K}^* = NMB_{EDPI} - NMB_{Policy_K} \quad (19)$$

LED_{EVPI} expresses the loss in expected value from efficient diffusion with perfect information (i.e., decision certainty) versus efficient diffusion with current information (i.e., decision uncertainty) Following (11) and (13), LED_{EVPI} is identical to traditional EVPI metric:¹⁹

$$LED_{EVPI} = \sum_j P_j \cdot \max_t \{E(Q_{jt} \cdot \lambda - C_{jt})\} - \sum_j P_j \cdot \max_t E(\{Q_{jt} \cdot \lambda - C_{jt}\}) \quad (20)$$

Here, it is interpreted as the maximum value of future research that would resolve uncertainty in each of the subgroups. However, it should be noted that this value is a comparison of two hypothetical scenarios involving efficient diffusions. The true value of future research could be different from what typically is expressed in EVPI calculations, and could depend on the current policy in place. To understand this point more clearly, we will now examine our second LED metric.

LED_{Policy_K} expresses the expected incremental loss under a specific policy k with respect to NMB_{EDCI} (i.e., expressed in positive terms, such that higher the value, higher is the loss, and less attractive is the policy), which is given as:

$$LED_{Policy_K} = \sum_j \sum_t \{P_j \cdot [D_{jt}^* - D_{jkt}(f_{kt})] \cdot (E(Q_{jt}) \cdot \lambda - E(C_{jt}))\} \quad (21)$$

In this formulation, irrespective of the value of f_{kt} , $[D_{jt}^* - D_{jkt}(f_{kt})] \leq 0$ in subgroups where $D_{jt}^* = 0$ (indicating over-adoption in these subgroups) while $[D_{jt}^* - D_{jkt}(f_{kt})] \geq 0$ in subgroup where $D_{jt}^* = 1$ (indicating under-adoption in these subgroups). The optimal policy decision, therefore, is based on choosing the one that minimizes this loss given threshold λ and current evidence, as long as the ‘status quo’ (do-nothing) policy is included in these comparisons.

$$Policy_{k^*} = \underset{k}{\operatorname{argmin}} LED_{Policy_k} = \underset{k}{\operatorname{argmax}} NMB(Policy_k) \quad (22)$$

The utility of the LED_{Policy_K} metric mirrors the uses of the value of information metrics to prioritize implementation or research investments. For the optimal policy k^* , $LED_{Policy_{k^*}}$ represent the unrealized value due to over and under-adoption of technologies in different subgroups driven by policy k^* , given current evidence. This loss may be caused by either imperfect implementation (i.e., subgroup-level suboptimal adoption due to imperfect translation of current evidence into practice) or imperfect information (i.e., suboptimal adoption due to too much uncertainty in existing information to make an optimal decision) or both. Therefore, depending on understanding the rationale for suboptimal adoption patterns, one could determine future investments on either better implementation of current evidence or generate more precise estimates through research to capture this unrealized value.

If one believes that the underlying rationale of clinical decisions follows an expected value criterion to adopt treatment, then when current evidence shows that new treatment A provides expected benefits over standard of care B in subgroup 3, it should be enough to persuade all clinicians to adopt treatment A for subgroup 3 patients. There should not be any ambiguity in this decision. In such a case, under-adoption or over-adoption observed in clinical practice under policy k^* may be driven by certain system-level factors (e.g., coinsurance rates, supply constraints, physician and patient awareness levels, etc.) not addressed by the policy. Under this rationale, $LED_{Policy_{k^*}}$ can be interpreted in the same way as the expected value of implementation.²⁰ It represents the maximum value that could be attained through investments in relaxing these system level constraints to implementation.

However, one can also question why such implementation strategies are already not considered under alternative policy scenarios. In fact, when a comprehensive set of policy scenarios simultaneously look at both coverage and implementation strategies, and the optimal policy is chosen among all these options, $LED_{Policy_{k^*}}$ is less likely to represent the expected value of implementation. Rather an alternative rationale for individual treatment decision making should be considered to interpret $LED_{Policy_{k^*}}$ appropriately.

For example, individual decision making on adoption may not follow an expected value criterion, even though a social insurer, who is deemed to be risk-neutral, would follow such a criterion. Individual clinicians may care about uncertainty in current evidence. If a clinical decision to use a new treatment A over standard of care B follows how much confidence a physician has on the incremental benefits of the treatment A (i.e., a 95% credible interval of incremental benefits include zero or not), rather than the expected value of the treatment A, the

$LED_{Policy_k^*}$ estimate has a different interpretation. In such a case, it is not only implementation problem but also resolving uncertainty through future research to reach efficient diffusion. Hence, the assumption of individual decision-making criteria would typically drive the interpretation of LED estimates.^{vii}

Finally, $LED_{Policy_K}^*$ would represent the expected loss relative to the expected value of perfection (i.e., perfect implementation with perfect information) under the policy k.²⁰ That is,

$$LED_{Policy_K}^* = LED_{EVPI} - LED_{Policy_K}.$$

In the following section, we present evidence to support our novel metrics on the selective adoption of a new technology under heterogeneous information. We then illustrate how our NMB_{Policy_K} and LED metrics would produce different suggestions for an optimal policy where such subgroup-specific adoption rates are accounted for.

5. EMPIRICAL EXAMPLE

5.1. BACKGROUND

The primary goal of this empirical example is to illustrate how this new framework could be applied in a real-world example. As an illustration, we chose the adoption of combination lipid therapy versus monotherapy among men and women with type 2 diabetes mellitus (T2DM) and mixed dyslipidemia based on three major criteria: 1) evidence of heterogeneous treatment effects by subgroups, 2) subgroup-specific results from economic evaluation of the intervention, and 3) availability of datasets to estimate the rates of adoption of the intervention.

^{vii} Note that implications of decision making criteria apply similarly to the interpretation of traditional value of information metrics (Basu and Meltzer 2016)

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study evaluated the effects of combination therapy with a statin plus a fibrate compared with statin monotherapy on reducing the risk of cardiovascular disease (CVD) among high-risk^{viii} T2DM patients.²¹ Although the ACCORD study, published in 2010, found no significant differences in the annual rate of primary outcomes in all patients (i.e., the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes), the pre-specified subgroup analyses suggested that combination therapy would benefit men while potentially harm women. (i.e., $P=0.01$ for interaction). This finding was in line with a previous cost-effectiveness study, which found that following practice guidelines for controlling lipid levels appeared to be much more cost-effective for men than women, given that men have a higher likelihood of experiencing cardiovascular events.²² The study reported ICERs of \$33,134 per QALY for 60-year-old men vs. \$82,562 per QALY for 60-year-old women from a US healthcare perspective over 20 years.^{ix} Interestingly, the practice guidelines, which was published before the ACCORD study, suggested reducing cholesterol levels in all patients with T2DM to reduce CVD risk. The guidelines recommended statin plus fibrate combination treatment^x for most of the patients with T2DM and dyslipidemia (i.e., uncontrolled level of low-density lipoprotein cholesterol (LDL-C) and/or triglyceride (TG)) – not just men.²³

Our goal was to evaluate the economic returns from policy alternatives for combination therapy with a statin plus a fibrate compared with statin monotherapy in this population among

^{viii} The high risk T2DM patients were characterized by high levels of both plasma triglyceride (TG) and low-density lipoprotein (LDL), and low levels of high-density lipoprotein (HDL).

^{ix} We took the overall ICER in this population and applied their reported proportion of men and women to obtain the subgroup specific estimates.

^x Statin is good for lowering LDL-C, whereas Fibrate is proven to lower TG and improve HDL-C level. Therefore, reducing both TG and LDL-C along with simultaneously increased HDL-C has potential to further reduce CVD risks beyond those demonstrated by lowering LDL-C alone.

privately insured patients. We incorporated the evidence presented by the ACCORD study and the subsequent adoption behavior observed in patients in a large health care database. We rely on estimates of cost-effectiveness ratio for these two subgroups from a previous study.²²

5.2. METHODS

We took the reported subgroup-specific ICER estimates of combination therapy with a statin plus a fibrate (denoted as treatment A) compared with statin monotherapy (denoted as standard of care B) among men and women ($j=2$).²² Then, we applied observed subgroup-specific adoption behavior to study a host of policy questions around coverage for the combination therapy.

In order to address the adoption question, we analyzed the Truven Health Marketscan research claims databases that collect healthcare data from large employers, health plans, and government and public organizations, including person-specific clinical utilization, expenditures, enrollment, and prescription drug fills.²⁴ We estimated two inputs, the size of specific subgroup relative to the target population, P_j and the subgroup-specific rate of adoption, D_j , at the monthly level from the 2010-2013 Marketscan databases, which represents the period immediately after the publication of the ACCORD study. First, we defined the eligible population, which were those who were diagnosed with both T2DM and mixed dyslipidemia; and we then identified those that had a prescription of either statin monotherapy or statin plus fibrate combination. We analyzed the annual enrollment datasets to create the enrollment variable and used the inpatient services, inpatient admission, and outpatient services datasets to identify patients with T2DM and mixed dyslipidemia using the international classification of disease, ninth revision, clinical modification (ICD-9-CM) codes and service dates provided in the datasets. Once we identified the eligible population, we identified the proportions (P_j) of males and females.

In addition, we estimated the subgroup-specific rates of adoption, D_j , through dividing the number of individuals who were prescribed with both statin and fibrate and statin only by the number of eligible population in a given month. Fibrate and statins were identified using the National Drug Code (NDC) corresponding and service dates of the prescription. More details on data analysis are provided in the Appendix A1. We used the average rate of adoption over this period for our illustration exercise. However, adoption rates were fairly stable across this time.

We start by comparing the traditional overall ICER and INMB estimate in this population to that under the current status-quo policy, defined below, based on observed adoption rates from a health care sector perspective. Also, we compare this ICER or INMB to other potential ICERs and INMBs for the combination versus statin monotherapy under alternative coverage policies. INMBs are established using a \$45,000/QALY criterion for illustration purposes. Specifically, we do the following:

1. Report the traditional ICER and INMB following Eq(3), which is just the weighted average of subgroup-specific ICERs or INMBs respectively. We use the estimated subgroup sizes from the Marketscan population to provide weighted estimates.
2. Report the modified ICER and INMB following Eq(4) where the differential adoption rate of the combination therapy was also incorporated. However, this modified ICER or INMB was assumed to reflect a “*status-quo policy*” (#1) where both the combination therapy and statin monotherapy were offered at 20% coinsurance rate (i.e. $f_k = 0.80$), as reflective of the average health plan coverage rate in the Marketscan database.
3. Report the modified ICER and INMB following Eq(7), dubbed as “*Policy #2*”, where full coverage of the combination therapy would have been provided (i.e. $f_k = 1.00$),

while coverage of the statin monotherapy remains unchanged at 20% coinsurance rate. For simplicity, we assume the same price elasticity of demand for a prescription fill for both subgroups. Average estimates of price-elasticity of the probability of fill were obtained from a recent study on value-based insurance design and was estimated to be -0.26.²⁵

4. A “*hypothetical policy (#3)*” scenario where full coverage of the combination therapy would have been provided (i.e. $f_k = 1.00$) while holding coverage of the monotherapy constant, and implementation action (through an education outreach program) increased adoption of the combination therapy by 200% among the males and decreased adoption of combination therapy by 100% among the females. Although not included here, in real application of such an approach, cost of such a program should also be accounted for.

We also compare how the LED metrics vary under each of these scenarios. First, we need to understand uncertainty around costs and effectiveness measures for each subgroup (male and female) and each technology (A – combination therapy and B – statin monotherapy). Unfortunately, the original cost-effectiveness study²² did not report uncertainty estimates and only reported the mean value. Thus, for the illustration purpose, we simulated the standard errors to be 10% of the QALY mean estimates and 75% of the cost mean estimates. We then generated a distribution of the expected INMB of the combination therapy in relative to the statin monotherapy, based on 100,000 simulated values; and we obtained estimates of LED metrics using equations (14), (15) and (20).

5.3. RESULTS

5.3.1 Traditional ICER and NMBs versus modified ICER and NMBs under alternative policy scenarios

Table 1 presents the results comparing traditional ICER and NMBs versus modified ICER and NMBs under alternative policy scenarios. Under the traditional approach, the incremental cost-effectiveness ratio (following Eq (3)) of combination therapy over statin only therapy was estimated to be \$46,000/QALY. For the sake of illustration, we assume that the cost-effective threshold (CET) is \$45,000/QALY, which is corresponding to the revealed £20,000-30,000/QALY threshold used by National Institute for Health and Clinical Excellence (NICE) in the United Kingdom. Under this CET, combination therapy would not be deemed cost-effective. Consequently, statin monotherapy should be adopted, and it produces a per-patient NMB of \$315,869. Note that, had combination therapy been cost-effective, the total NMB, under the traditional approach, would have been calculated assuming that the entire population would adopt the combination therapy.

Policy 1: Status-quo policy

Under the status-quo policy of providing coverage for the combination therapy with a coinsurance rate of 20%, the use of this combination therapy was estimated to be 7.2% among the males and 4.3% among the females in the Marketscan database. Hence, in line with evidence, we empirically observe that males adopt the combination therapy at a higher rate than females given that the benefits to males are higher than the females. Then following Eq(7), when these differential adoption rates were incorporated into the modified ICER formula, the ICER of combination therapy over statin only under the status quo policy was estimated to be \$41,733/QALY. Under our assumed threshold at the \$45,000/QALY, the combination therapy

would be deemed cost-effective, even though traditional analysis would have suggested that covering combination therapy would not be cost-effective. The per-patient NMB in the population under the status quo policy was \$315,910, a slight increase over giving everyone statin monotherapy.

Policy 2: Full coverage of the combination therapy

Under Policy 2, if the coverage of the combination therapy would have been increased to 100% (i.e., coinsurance rate=0%), the share of use of the combination therapy was estimated to be 7.5% among the males and 4.5% among the females, not much different than the status-quo policy. This is primarily because, as it is widely discussed since the RAND health insurance experiment, pharmaceuticals are very price inelastic^{26,27} as well as the relatively low adoption rates under the status-quo policy. Consequently, the ICER for combination therapy under Policy 2 is similar to that in status-quo, but slightly higher at \$41,766/QALY. This is because the relative increase in the use of the combination therapy among males compared to females. The per-patient NMB in the population under the Policy #2 was \$315,911, which is virtually unchanged from the per-patient NMB under the status quo policy.

Policy 3: Full coverage of the combination therapy & Outreach Program

Finally, under the hypothetical policy, where not only combination therapy is fully covered, an educational outreach program is expected to increase adoption of combination therapy among males to 23% and to decrease in females to 2.3%, the ICER would be \$34,848/QALY, and the NMB per patient would be \$316,214. Obviously, one should account for the costs of delivering such an outreach program. For example, if the program costs about \$200

per patient, the NMB decreases to \$316,014, but still is the best policy among all the alternatives considered.

5.3.2. Efficient Diffusion under Current Information vs. Perfect Information and LED metrics

Table 2 reports the NMBs under efficient diffusion under current and perfect information along with the policy-specific LED metrics. Under the current information, efficient diffusion would entail full adoption of the combination therapy among males (i.e. $D_M = 1$ and $D_F = 0$) and no use among females. If this was achieved, the NMB per patient in the population was estimated to be \$317,559 (NMB_{EDCI} , Table 2, Eq (14)).

On the contrary, under the uncertainty structure assumed for this stylized example, if all uncertainty were to be resolved through future research, the probability that statin only therapy would turn out to be the cost-effective one among males was 32% while that among females was 73%. Following Eq (15), NMB_{EDPI} was estimated to be \$366,770.

The difference between NMB_{EDPI} and NMB_{EDCI} , which represents LED_{EVPI} , was estimated to be \$49,211 per patient and reflects the expected value of perfect information with each of the subgroups. The large value of information is driven by the substantial uncertainty in costs that we assume. Comparing the NMB_{EDCI} to each of the NMB_{Policy} provides a policy-specific estimate of LED, which could be interpreted as the expected value of implementation. Naturally, the policy with the highest NMB_{Policy} also has the lowest LED_{Policy} . To what extent this value represents the value of future implementation versus research would depend on understanding the decision-making rationale. The total value of perfection, under the hypothetical policy, was estimated to be \$50,556.

6. DISCUSSION

In this work, we propose a new economic evaluation framework, which is a policy lens for ICERs of new technologies that can be readily applied to compare the economic value of various policy options in health care. This framework is highlighted by 1) incorporating subgroup-specific estimates of selective adoption driven by heterogeneity in clinical and economic evidence and 2) evaluating policy options that potentially affect the adoption of new technology. It is important to acknowledge that these factors can inherently change the overall value of medical technology, and therefore, from an evaluation perspective, these metric would better represent the marginal value of a policy decision in the context of evaluating the medical technology. In fact, our NMB_{Policy} and LED framework can also be used to assess policy options that may often encompass not only coverage decisions but also investments in research.²⁸ Combining such investments under the same policy umbrella has the potential to change the nature of heterogeneous information, thereby directly affecting the efficient diffusion outcomes. In addition, NMB_{policy} metrics produce incentives for manufacturers to provide reliable evidence around heterogeneity so that a single overall ICER metric does not kill the market for a product that works well for some subgroups of the target population and where differential adoption is anticipated or can be demonstrated.

Although this framework is superior to the traditional CEA, which informs coverage decisions based on the average economic value of new technology when full coverage is given to every individual with perfect adoption, there are some limitations to this new framework. First, this framework requires rich information of heterogeneous effects and subgroup-specific results to predict behavioral changes in those groups. Although these types of information are often not readily available, CEA studies are often encouraged to report subgroup-level results that would

help more precisely to estimate the realized value of policy decisions based on diffusion and these new metrics could drive investments in subgroup analyses by funders of research. Also, we ignore costs of implementing a new policy. However, as done in the value-of-information research, one could understand that implementing a new policy would be worth considering if the potential gain in the LED metric is greater than the costs of implementation.

Another important limitation is the inability to predict future rates of adoption of new technology. We analyzed existing claim databases retrospectively to examine adoption patterns of the combination lipid therapy, and having some understanding of potential changes in adoption over time and the responsiveness of these adoption patterns to evidence (i.e., evidence elasticity of demand) would be important to implement this framework for prospective evaluation. Moreover, we used a static perspective throughout this paper and an empirical example. However, realistically, one should view the rate of adoption to be time-varying as well as consider dynamic policy decisions, such as investing in other implementation programs and future research. This perspective would be especially important for the technology that is promising, but lacking sufficient evidence to endorse coverage decisions (e.g., “only in research” recommendation in UK NICE). Also, using this framework, one could evaluate the impact of changes in current evidence on the diffusion of technology and the economic value of the change.

The above limitations notwithstanding, we believe that this novel framework will be useful not only to evaluate the realized economic value of medical technology but also to estimate the economic value of various decision options. Therefore, we propose that this new framework could substantially improve the decision-making process and by producing metrics

that are better aligned with the specific policy decisions that are under considerations for a specific technology.

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TABLES AND FIGURES

Table 1: Illustration of Traditional and Modified ICERs and INMBs under a Health-care Sector Perspective.

Parameter	Males	Females	Overall	Source / Notes
Total Costs per patient under Statin + Fibrate, \$	\$107,021	\$107,023	-	Based on Sorenson 2009
Total Costs per patient under Statin Only, \$	\$98,131	\$98,131	-	Based on Sorenson 2009
Total Incremental Costs per patient, \$	\$8,890	\$8,892	-	Based on Sorenson 2009
Total QALYs per patient under Statin + Fibrate, \$	9.468	9.308	-	Based on Sorenson 2009
Total QALYs per patient under Statin Only, \$	9.200	9.200	-	Based on Sorenson 2009
Total Incremental QALYs per patient, \$	0.268	0.108	-	Based on Sorenson 2009
Subgroup-specific ICER	\$33,130/QALY	\$82,562/QALY	-	
Subgroup-specific INMB*	\$3,170	-\$4,032		
Subgroup size (P_j)	0.533	0.467		2010-2013 Marketscan
Traditional population ICER (Eq 3)			\$46,000/QALY	
Population NMB per patient from statin monotherapy**			\$315,869	
Adoption of Statin + Fibrate under status quo ($f_k = 0.80$), D_j	0.072	0.043		2010-2013 Marketscan
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^\dagger	0.075	0.045		Estimated [†]
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_j^{**}	0.23	0.023		Assumed
Population ICER under Hypothetical Policy ^{††} (Eq, 7)			\$34,848/QALY	
Hypothetical Policy ^{††} NMB per patient (Eq, 8)			\$316,214	

*NMB evaluated at \$45,000/QALY for purpose of illustration.

** Since at a threshold of \$45000/QALY, traditional ICER implies statin + fibrate is not cost-effective and so this is not adopted.

[†] Assuming price-elasticity of demand to be -0.26.

^{††} Hypothetical policy assumes $f_k = 1.00$ and implementation action will increase adoption of the combination therapy by 200% among the males and decrease adoption of combination therapy by 50% among the females from the adoption rate under the status quo policy.

Table 2. Economic Returns from Policy Alternatives based Predicted Diffusion

Parameters	Policy 1: Status-quo Policy ($f_k = 0.80$)	Policy 2: Full Coverage ($f_k = 1.00$)	Policy 3: Full Coverage + Education Program ^{††}	EDCI Eq(14)	EDPI Eq(15)
Male					
P_M	0.533	0.533	0.533	0.533	0.533
D_M	0.072	0.075	0.23	1	-
$F(INMB_{AB})^*$	-	-	-	-	0.32
Female					
P_F	0.467	0.467	0.467	0.467	0.467
D_F	0.043	0.045	0.023	0	-
$F(INMB_{AB})^*$	-	-	-	-	0.73
NMB_{POLICY K}	\$315,910	\$315,911	\$316,214	\$317,559	\$366,770
LED_{EPVI} (Eq. 20)[‡]	-	-	-	\$49,211	-
LED_{POLICY K}	\$1,649	\$1,648	\$1,345	-	-
LED_{POLICY K}[*]	\$50,860	\$50,859	\$50,556	-	-

Abbreviation: EDCl, efficient diffusion under current information; EDPI, efficient diffusion under perfect information; NMB, net monetary benefit; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LED, loss in relative to efficient diffusion

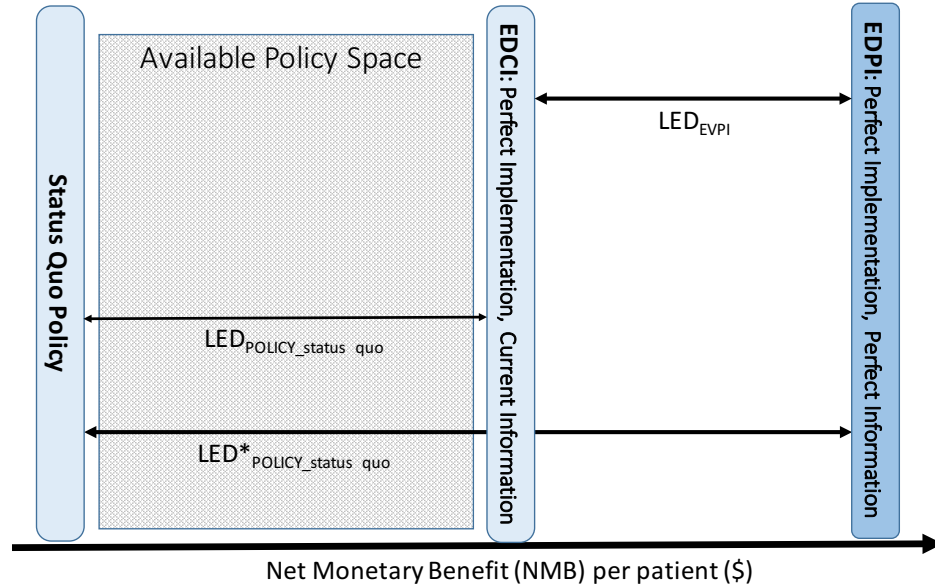
* AB represent comparison between treatment alternatives, here the combination therapy of statin + fibrate vs the statin monotherapy.

†† Hypothetical policy assumes $f_k = 1.00$ and implementation action will increase adoption of the combination therapy by 200% among the males and decrease adoption of combination therapy by 50% among the females.

†: ICER and INMB of the combination therapy in relative to the statin monotherapy

‡: LED_{EDPI} is equivalent to the traditional expected value of perfect information (EVPI), representing the opportunity costs of the suboptimal decision caused by existing uncertainty. Also, this can be understood as a maximal value of investing in further research to reduce uncertainty.

Figure 1. Graphic Representation of New Metrics with Summary



New Metrics	Equivalent Metric / Interpretation
NMB_{EDPI}	Expected of Value of Perfection (EVP) (i.e., perfect implementation with no decision uncertainty)
NMB_{EDCI}	Expected Value of Perfect Implementation (EVPIM) (i.e., perfect implementation based on current evidence; suboptimal decision is possible)
LED_{EVPI}	Expected Value of Perfect Information (EVPI) (i.e., maximum value of future research that would resolve all uncertainty)
LED_{POLICY}	Expected incremental loss under a specific policy k in relative to EVPIM (i.e., maximum value of improved implementation – need to understand the rationale of suboptimal adoption patterns)
LED^*_{POLICY}	Expected incremental loss under a specific policy k in relative to the EVP (i.e., maximum value of future research and improved implementation)

APPENDICES

Appendix A1: Details on Empirical Illustration

Rationale

- Pre-specified subgroup analyses suggested heterogeneity in treatment effect by sex
 - o Beneficial for men and possible harm for women
- Reducing TG in conjunction with LDL-C, and possibly simultaneously increasing HDL-C, has the potential to further reduce cardiovascular risks beyond those demonstrated by lowering LDL-C alone
 - o Statin is good for lowering LDL-C
 - o Fibrates is proven to lower TG and improve HDL-C level
- A previous CE study (Sorensen et al, Clinical Therapeutics, 2009; 31(4): 862-879) found that guideline treatment appeared to be much more cost-effective for men than women, given that generally men have a higher likelihood of experiencing cardiovascular events. (\$33,134 vs. \$82,562)
 - o Also, CE of the guideline treatment also improved with increasing age, given that older adults are at greater risk for events occurring sooner. (\$58,588 aged 55 years vs. \$44,183 aged 65 years)

Group	Current Treatment	Recommended Treatment	ICER (\$/QALY)
LDL-C uncontrolled	Fibrate	Combination	14,405
LDL-C uncontrolled	None	Statin	29,140
TG uncontrolled	Statin	Combination	47,942
TG uncontrolled	None	Fibrate	376,772
LDL-C and TG uncontrolled	Statin	Combination	46,791
LDL-C and TG uncontrolled	Fibrate	Combination	12,690
LDL-C and TG uncontrolled	None	Combination	42,075
Overall			52,107

Background

- ACCORD (Action to Control Cardiovascular Risk in Diabetes) Study
 - o Evaluating effects of combination therapy with statin and fibrate compared to statin monotherapy
 - o Target populations: Patients with T2DM and high risk for CVD
 - o Main outcomes:
 - First occurrence of nonfatal MI, nonfatal stroke, or death from cardiovascular causes
 - o Results
 - No significant differences in the annual rate of the primary outcome
 - 2.2% in the fenofibrate group vs. 2.4% in placebo group
 - HR in the experiment group: 0.92 (0.79 to 1.08, p = 0.33)

Data Analysis Plan

Part I: Define Eligible population / Preliminary Information

- Patients with T2DM and a glycated hemoglobin level of 7.5% or more
 - o LDL cholesterol level of 60 to 180 mg per deciliter
 - o HDL cholesterol level below 55 mg per deciliter for women or below 50mg per deciliter for all other groups
 - o Triglyceride level below 750 mg per deciliter if they were not receiving lipid therapy or below 400 mg per deciliter if they were receiving lipid therapy
- Variables
 - o T2DM
 - 250.00: DM w/o mention of complication, type II or unspecified type, not stated as uncontrolled
 - 250.02: DM w/o mention of complication, type II or unspecified type, uncontrolled
 - 250.10 / 250.12: Diabetes with ketoacidosis
 - 250.20 / 250.22: Diabetes with hyperosmolarity
 - 250.30 / 250.32: Diabetes with other coma
 - 250.40 / 250.42: Diabetes with renal manifestations
 - 250.50 / 250.52: Diabetes with ophthalmic manifestations
 - 250.60 / 250.62: Diabetes with neurological manifestations
 - 250.70 / 250.72: Diabetes with peripheral circulatory disorders
 - 250.80 / 250.82: Diabetes with other specified manifestations
 - 250.90 / 250.93: Diabetes with unspecified complication
 - o High levels of cholesterol / TG
 - 272.0: Pure hypercholesterolemia
 - 272.1: Pure hyperglyceridemia
 - 272.2: Mixed Hyperlipidemia (elevated cholesterol with high triglycerides)
 - 272.4: Other and unspecified hyperlipidemia
 - o The presence of CVD
 - 429.2: Cardiovascular disease, unspecified

Part II: Create Eligibility & Enrollment Table

- Create an enrollment table to identify patients enrolled in each month from 2010-2013
 - o Datasets: Annual enrollment data 2010-2013
 - o Output: *Enroll (0 or 1)*: whether individuals are enrolled in a specific month
- Create an eligibility table to identify patients diagnosed with T2DM and hyperlipidemia
 - o Datasets: Inpatient Services, inpatient admission, and outpatient services
 - o Information:
 - ICD-9 diagnostic codes
 - Service dates is used to create an initial index date
 - o Output:
 - *Eligibility (0 or 1)*: whether individuals are eligible to receive the combination lipid therapy
 - *Index date*: the first date of being diagnosed with both T2DM and hyperlipidemia

Part III: Extract Rx Datasets

- Identify NDC number for fibrate and statin
 - o Datasets: Redbook
 - o Information:
 - thercls = 53 (antihyperlipidemic drugs, NEC): to narrow the drug list
 - Identify statin and fibrate using “thrdtds = XXX” (i.e., detailed description of the drug)
 - For statin: atorvastatin; cerivastatin; fluvastatin; lorazepam; lovastatin; pravastatin; simvastatin; mevastatin; pitavastatin; rosuvastatin
 - For fibrate: Fenofibrate; gemfibrozil; bezafibrate; ciprofibrate; clofibrate; clinofibrate
 - o Output: NDC number for all classes of Statin and Fibrate
- Identify patients who were prescribed with fibrate and/or statin
 - o Datasets:
 - Pharmaceutical claims 2009-2013
 - NDC number for fibrate and statin
 - o Information:
 - NDC number: used to create indicator variable for each drug
 - svcdte: identify the prescription month and year
 - daysupp: assume that patients take prescribed medications for months corresponding to svcdte + daysupp (e.g., if daysupp = 90, then we assume 3 months of utilization)
 - o Output:
 - statin: indicator variable whether a patient is on statin in a specific month and year
 - fibrate: indicator variable whether a patient is on fibrate in a specific month and year
 - cmbn_rx: indicator variable if a patient is on both statin & fibrate

Part IV: Merge Rx datasets with Eligibility/Enrollment Table

- If enr1_elgb = 0 (i.e., patients are not enrolled or not eligible to receive the combination therapy), we treat indicator variables for statin and/or fibrate as missing.
- Variables include:
 - o enrolid; year; month; time; enrollment_eligible
 - o age; sex; employment status; region
 - o statin; fibrate; cmbn_rx
 - o coins; copay; deduct
- Other exclusion criteria
 - o If enrolid is missing, then excluded.
 - o Patients must be enrolled and diagnosed with both T2DM and hyperlipidemia, although we assume that once a patient is diagnosed with both diseases, it passes the eligibility criteria since then.

CHAPTER 3: ASSOCIATION OF THE PUBLICATION OF MAJOR CLINICAL EVIDENCE WITH THE USE OF BARIATRIC SURGERY

ABSTRACT

Importance: Clinical evidence shows bariatric surgery is an effective treatment option for persons with severe obesity and type 2 diabetes. However, with significant underutilization of bariatric surgery, a potential role of clinical evidence in increasing utilization of bariatric surgery remains unclear.

Objective: To assess whether major clinical evidence is associated with increasing utilization of bariatric surgery

Design, Setting, and Participants: The online citation index service, the Web of Science, was systematically searched to identify top 100 cited articles in bariatric surgery between 1977 and 2008. Then, an interrupted time-series analysis (1994-2008) was conducted as a primary analysis using retrospective data for a bariatric cohort of 1,434 patients and a non-bariatric cohort of 45,000 patients enrolled in the Group Health Cooperative (GHC) located in Seattle, WA.

Exposures: A single period of the 4th quarter in 2004 – when two of the top-ranked articles were concurrently published – was used for the primary analysis. Additional characteristics of major clinical evidence, such as an accumulation effect, a type of evidence, and a tier effect were examined in the secondary analysis.

Main outcomes and measures: A receipt of bariatric surgery, measured in the rates of uptake – the number of cases per 100,000 patients per quarter.

Results: The top two-ranked articles were a systematic review and meta-analysis and a prospective matched-controlled study that reported the long-term improvement in clinical outcomes. Both studies provided clinical evidence on not only weight-loss, but also on

significant improvement and/remission of diabetes. Compared to the counterfactual trend, the publication of those major articles was associated with 50 additional cases of bariatric surgery performed per 100,000 individuals with severe obesity and diabetes. Also, one additional publication of randomized-controlled trials (RCTs) is linked to a stronger association with increasing the uptake of bariatric surgery (30 cases per 100,000), compared to other characteristics of clinical evidence.

Conclusions and Relevance: For the GHC enrollees, the publication of major clinical evidence is associated with increasing utilization of bariatric surgery. This finding suggests that positive clinical evidence can be tied to increase in utilization, but further research is necessary to assess whether this association is causal and generalizable.

1. INTRODUCTION

Since David Eddy's seminal contribution to setting national guidelines explicitly based on clinical evidence rather than subjective clinical judgment and consensus¹, the field of evidence-based medicine (EBM) has burgeoned. Initially, EBM was narrowly focused on evidence-based individual decision making, defined as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients"², but later broadened its concept into evidence-based guidelines and other policies to help patients indirectly³ One of the most persistent questions in EBM is how clinical evidence translates into changes in practice.

Several studies have attempted to understand the impact of clinical evidence on changes in practice. For example, Lamas et al. found a significant increase in the use of aspirin for patients who experienced myocardial infarction after the publication of three clinical trials.⁴ Also, clinical alerts disseminated from a carotid endarterectomy trial were found to be associated

with prompt and substantial changes in practice.⁵ Publication of a clinical trial on a new drug (ramipril) in patients at high risk of cardiovascular events led to changes in prescribing patterns.⁶ These findings highlight that clinical evidence can significantly influence practice patterns. These studies, however, were limited to a particular source of clinical evidence – the randomized controlled trial and focused on a single pre-post analysis that measured changes in practice between only two time periods. Therefore, in this study, we examined how clinical evidence is associated with changes in clinical practice over multiple periods with an example of bariatric surgery.

Bariatric surgery is one example of an advancing medical technology where understanding how clinical evidence influences practice patterns is important. First of all, clinical evidence on bariatric surgery shows overall benefits of bariatric surgery. Systematic reviews, RCTs, and observational studies have concluded that bariatric surgery is associated with a significant and sustained weight-loss⁷⁻¹⁰, decreased long-term mortality¹¹⁻¹³, a significant improvement in the obesity-related comorbidities, especially type 2 diabetes^{9,10,14-17}, and improved quality of life^{18,19} among the recipients. Despite these clinical benefits, only less than 1% of the potentially eligible patients have received bariatric surgery.^{20,21} The potential reasons for the significant underutilization of bariatric surgery have not been well studied. A few studies, however, reported that the biggest challenge is the difficulties in obtaining insurance coverage for bariatric surgery among other reasons, including patient's preference and physician's attitude.

22,23

Clinical evidence is a gateway to change clinical practice mediated through changes in insurance coverage and organizational structures. However, there is a lack of scientific studies to examine this relationship, especially in the context of bariatric surgery that strong evidence

supports clinical benefits of bariatric surgery. Thus, in this study, we examined how clinical evidence on bariatric surgery is associated with changes in clinical practice. First, we approached this scientific question with a trend analysis to examine changes in the uptake of bariatric surgery after the publication of major evidence. Then, we extended the scope of this analysis by examining the relationship between rates of bariatric surgery and the following: 1) the incremental effect of an additional major article, 2) type of evidence, and 3) the tier effect among major articles on the uptake of bariatric surgery.

2. METHODS

Data source

We analyzed an electronic health record (EHR) database provided by Group Health Cooperative (GHC) located in Washington State. The GHC is an integrated health care system that provides the delivery of medical care as well as insurance coverage for approximated 600,000 residents in Washington State. The GHC databases provide a longitudinal electronic record of patient health information, including measured height and weight information, which is critical information for determining obesity that is often missing in large claim datasets. We also extracted all self-reported height and weight information from an annual survey of breast cancer risk factors and screening practices among women in Group Health age 40 years and older. To identify the population of adults who were potentially eligible for bariatric surgery, we limited samples that are clinically eligible to receive bariatric surgery based on the National Institute of Health Bariatric Surgery eligibility guideline²⁴ (i.e., morbidly obese patients with BMI 35-40 and at least one obesity-related disease (ORD)^{xi} or those who are BMI \geq 40).

^{xi} For the purpose of receiving bariatric surgery, we excluded ORDs that potentially contraindicate bariatric surgery, such as mental disorders (schizophrenia, psychoses, eating disorders, bipolar disorder, and post-traumatic stress disorder), gallbladder, cancer, severe cases of heart diseases, congestive heart failure, and stroke, which were

Literature Search

To find out when major clinical evidence came out and categorize those major articles in bariatric surgery, we conducted a literature search on the Web of Science – a citation indexing service provided by Thomson Reuter that provides a comprehensive citation search – using the following keywords: (“bariatric surgery” OR “gastric bypass” OR "gastric banding” OR “sleeve gastrectomy” OR "obesity surgery" OR "gastroplasty" OR "biliopancreatic diversion" OR "jejunoileal bypass"). We initially found 9,913 articles dating back to 1962. We limited our search to articles published up to 2008 to align with the available GHC patient-level data.

Because of our interest in identifying major clinical evidence on the uptake of bariatric surgery, we applied the following inclusion criteria: 1) must be ranked among the top 100 cited articles in terms of total number of citations from year 1977 to 2008 and 2) must describe previously unreported data on the clinical effectiveness (health impact) of bariatric surgery and 3) must involve human subjects only. We provide a flow diagram that summarizes the results of literature search and the number of articles included in FIGURE 1.

Analysis 1: How Does Major Clinical Evidence in Bariatric Surgery Change the Rate of the Uptake

In the fourth quarter of 2004, two of the top-ranked major articles were published: 1) a first systematic review and meta-analysis that examined excess weight-loss (EWL) and changes in diabetes, hyperlipidemia, hypertension, and obstructive sleep apnea⁹ and 2) first prospective matched-controlled study (a.k.a., the SOS Study) that reported the long-term improvement (> 10 years) in EWL, lifestyle changes, and diabetes after undergoing bariatric surgery.²⁵ Among all

diagnosed in inpatient settings.

major articles, the systematic review and meta-analysis was ranked #1 in total citations (2760) and #1 in average citation per quarter (61) and the long-term evaluation of the SOS study was ranked # 2 in total citations (1802) and #3 in citation per quarter (40).

In the first analysis, using this timing of 4Q 2004 as an intervention period, we examined how clinical evidence supported by the top-two of the major articles coming out in the same period is associated with changes in trends of bariatric surgery. (Appendix Figure A1) The primary outcome was whether a patient received bariatric surgery in a given quarter-year period. 1Q 1994 through 3Q 2004 served as the pre-publication period, and we considered the period between 4Q 2004 and 2Q 2005 the publication period that the clinical evidence may diffuse. The post-publication period represented remaining periods from 3Q 2005 to 4Q 2008.

To estimate an association between the major evidence and the uptake of bariatric surgery, we created a comparison cohort (i.e., people with severe obesity who do not have diabetes) and an exposure cohort (i.e., people with diabetes and severe obesity) because both studies focused on not only weight-loss, but also on improvement and/or remission of type 2 diabetes mellitus (T2DM), thereby providing greater clinical evidence supporting the use of bariatric surgery among people with severe obesity and T2DM. The similar trends among both groups in the pre-publication period could confirm that the incremental changes in the post-period in the exposure group can be causally attributed to the major clinical evidence. For modeling trends, we implemented a linear generalized estimating equation regression model^{xii} to account for the within-subject correlation. In addition, we included quadratic time variables in the model to capture non-linear time trends.

^{xii} Link function: identity; Family: Gaussian; Correlation structure: exchangeable

From the estimated coefficients, we produced a counterfactual trend for the diabetic morbidly obese using a recycled prediction method. The detail description of the model is provided in the Online Appendix. Finally, we conducted a falsification test on non-morbidly obese population for bariatric surgery that should not be influenced by those clinical evidence focused on the morbidly obese population.

Analysis 2: Does the accumulation of evidence, the type of evidence, or the influential tier of evidence matter?

To expand from the primary pre-post analysis, we examined the potential impact of an additional influential article, the different types of evidence, and the tier based on the citations per quarter index on the changes in the uptake of bariatric surgery over the time period between 1Q 1994 – 4Q 2008. Because all of the 39 influential articles indicated the overall clinical effectiveness of bariatric surgery in the morbidly obese population, we used all morbidly obese population for all of three analyses. The outcome variable remains the receipt of bariatric surgery in a given quarter-year period. However, based on the expert input, we noticed that a patient-physician dyad generally reaches a clinical decision to receive bariatric surgery 3-6 months before the actual date of receiving bariatric surgery. To account this delay in clinical practice, we modeled the number of major articles available in 2 quarters (e.g., 10 articles available in 1Q 2000) before to predict the receipt of bariatric surgery in the actual date (e.g., the actual receipt of bariatric surgery in 3Q 2000).

In addition, we implemented a fixed-effect multivariate regression model, adjusting for seasonality, age, individual-level fixed effect, and the main predictor for each model. A fixed-effect multivariate regression model accounts for potential unobserved individual characteristics

– race and income level were not available in our database. For example, patient preference, which is not easily observed, can also be associated with whether a patient is more likely to receive bariatric surgery or not. With assuming that this preference is not changing over time for a same individual (may not be entirely true, but reasonable), the fixed-effect model would remove the non-time varying individual-level effect so that the individual-level change can truly contribute to the effect of influential clinical evidence. We validated the use of the fixed effect model through the Hausman test.^{xiii} The details on the model specification are provided in the Online Appendix

The first predictor of interest is a continuous, time-varying variable representing the cumulative number of the influential articles on bariatric surgery in a given time period. This variable indicates the strength of clinical evidence over time, and would measure the impact of an additional influential article on the uptake of bariatric surgery, regardless of types and how influential of the article is. The second predictor of interest is a set of four continuous, time-varying variables representing cumulative number of articles in different types of clinical evidence: 1) randomized-controlled trial (RCT), 2) systematic review and meta-analysis, 3) comparative observational study (e.g., prospective matched case-control study), and 4) observational study without comparators (e.g., case study or cohort study). Two reviewers (DDK and DEA) examined each of 39 influential articles to categorize the type of evidence based on consensus. The third predictor of interest is a set of three continuous, time-varying variables representing cumulative number of articles in the three tier groups, defined by average citations per quarter since its publication to adjust for the period since its publication. The tier 1

^{xiii} The Hausman specification test compares a consistent estimator (e.g., fixed-effect estimators) with an efficient estimator (e.g., random-effect estimators) that is assumed to be consistent. If the null hypothesis is rejected, which is our case, there exists a systematic difference in the estimates, and the efficient estimator is biased.

represents a group of highly influential articles with more than 10 citations per quarter, and the tier 2 and the tier 3 included influential articles with 5-10 citations per quarter and less than 5 citations per quarter, respectively. (Appendix Figure A2) This variable would examine whether more influential articles would be more likely to associate with changes in clinical practice even though all of the articles included were highly cited articles. All of these analyses were conducted in STATA 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

3. RESULTS

Sample Population Characteristics

The GHC database included a bariatric cohort of 1,434 patients who received bariatric surgery at the GHC from 1994 to 2008 and a non-bariatric cohort that contained approximately 45,000 records of patients with severe obesity from 1994 to 2008. Table 1 provides the sample characteristics among patients with severe obesity included in this study. Comparing the bariatric cohort to the non-bariatric cohort at GHC, the bariatric cohort had a significantly higher proportion of females, people with any ORDs, and people who possess insurance coverage for bariatric surgery. Also, a bariatric cohort was associated with higher BMIs and more number of ORDs than the non-bariatric cohort.

Analysis 1: How Does Major Clinical Evidence in Bariatric Surgery Change the Rate of the Uptake

After two of the top-ranked major articles were concurrently published in 4Q 2004, the uptake of bariatric surgery among individuals with T2DM was increased by 27.6% (23.1 cases vs. 18.1 cases per 10,000 individuals per quarter) based on a quarterly average from 2005-2008, compared to the counterfactual trends that those articles would have not appeared. Because there

is no significant difference in pre-trends in both groups (i.e., similar increasing quadratic trends in both groups) and no systematic changes that only affect one of the groups (e.g., changes in insurance coverage only for individuals with severe obesity and diabetes), this finding could be attributed to the impact of the two major articles on the changes in the uptake of bariatric surgery. Figure 2 provides the observed trends in the pre- and post-periods along with the predicted uptake based on the model estimates and the counterfactual trends. Also, we found that there exists a lag effect – the differences between the predicted uptake and the counterfactual are increasing as the time since publication of two major evidence increases as shown in Table 2. By 2008 (i.e., after four years since 4Q 2004), the publication of major evidence was estimated to contribute 64.1% increase (22.0 cases vs. 36.1 cases per 10,000 individuals per quarter) in the uptake of bariatric surgery among the diabetic morbidly obese population. As expected, falsification test on the non-morbidly obese population showed no changes in the uptake of bariatric surgery before and after the introduction of major evidence in 4Q 2004.

Analysis 2: Does the accumulation of evidence, the type of evidence, or the influential tier of evidence matter?

From the extended analysis, we found that not only the accumulation of influential articles matters, but also RCTs and meta-analyses/systematic reviews are associated with stronger influence on the change in clinical practice than other types of clinical evidence are. Given everything else holding constant, one additional RCT, which provides higher quality demonstrations of causal evidence, is associated with increasing the uptake of bariatric surgery by 0.03% (or equivalently 30 cases per 100,000 individuals per quarter) in two subsequent quarters. Also, more influential articles (i.e., articles in higher tiers, which are defined by the

average citation per quarter since article's publication date), are associated with larger changes on the uptake of bariatric surgery, but only articles in tier 1 and tier 2 (i.e., articles with more than 5 citations per quarter on average) are associated with the changes in clinical practice. One additional publication in Tier 1 is associated with increasing the uptake of bariatric surgery by 0.01% (or equivalently 10 cases per 100,000 individuals per quarter). Falsification test found that none of these predictors has a significant impact on the uptake of bariatric surgery among the non-morbidly obese population.

4. DISCUSSION

In this study, we examined how major articles on the clinical effectiveness of bariatric surgery translated into changes in clinical practice. We found that the two of the top-ranked major articles – measured as the number of citations per quarter – on bariatric surgery from 1962 and 2008 were published concurrently in 4Q 2004, and we found that the publication of those articles was associated with the increase in 50 additional cases of bariatric surgery performed per 100,000 eligible individuals per quarter in Group Health Cooperative, compared to the predicted counterfactual trend. We were surprised by the considerably small impact in terms of the magnitude. Because bariatric surgery is still not considered as a necessary medical treatment, we conjecture that patients' stronger autonomy for treatment decision, compared to other medical-related treatment, may downplay the impact of clinical evidence on clinical practice. Also, we observed a lag effect of approximately two years since its publication until the rapid deviation from the counterfactual trend happened. This estimate can be considered as the upper bound of how the most influential clinical evidence would change the clinical practice in the first few years. However, it is possible that extrapolating this finding beyond 2008 may lead to over-prediction because the trend in bariatric surgery is slowing down after 2008, as recent trend

analyses suggested.²⁶⁻²⁸ The recent data of the bariatric surgery trend in Michigan agreed with our findings on faster increases in bariatric surgery among patients with T2DM, compared to non-T2DM patients between 2006-2007 and 2008-2009, but also showed decline in trends after 2008-2009.²⁹

From the extended analysis, one additional influential article marginally increases the uptake of bariatric surgery (1 additional case per 10,000 individuals per quarter), but, in terms of types of clinical evidence, the impact of RCTs on the uptake of bariatric surgery is the greatest (3 additional case per 10,000 individuals per quarter), followed by meta-analyses / systematic review. The findings suggested that the higher quality of clinical evidence based on the existing hierarchy³⁰, the stronger impact on clinical practice. In addition, even among all influential articles, only those articles in the top tiers influence clinical practice. This may be explained by that only a few leading articles (e.g., the first meta-analysis on the effectiveness of bariatric surgery, initial findings of the long-term effectiveness of bariatric surgery, a first study to examine the long-term mortality after bariatric surgery) actually changed the trajectory of clinical practice, whereas other articles, even though still highly cited, only serve as supporting evidence rather than influencing clinical practice.

One of the main limitations of this study is a generalizability issue of these findings to other hospitals and health care systems that may have different supply-side characteristics (e.g., number of surgeons or number of surgical facilities available) as well as population characteristics. However, the GHC serve well for the purpose of this study because there have been only two bariatric surgeons in the GHC throughout the study period to eliminate the possibility of supply-driven uptake of bariatric surgery so that we could focus on how clinical evidence changes clinical practice at the individual level. Also insurance coverage at GHC for

bariatric surgery remained the same during the study period. In terms of population characteristics, a previous study supported that the enrolled population under the GHC is representative regarding age, gender, and ethnicity, but fewer enrollees from high- and low-income population, compared to the general population of the surrounding area.²³

Also, we acknowledge that the approach of using top 100 cited articles based on the total number of citations as a criterion for defining influential articles might underestimate the significant influence on clinical practice for more recently published articles. However, we included top 100 cited articles published before 2008, which provides enough time for those articles to be recognized and get cited. Also, we attempted different approaches to identify influential articles (e.g., period-specific top cited articles or first 5 or 7 years of citations), but the final sample of those articles remains almost identical.

Despite some limitations, this study implemented rigorous statistical models to explain a relationship between clinical evidence on bariatric surgery and changes in clinical practice. We found that positive clinical evidence on people with severe obesity and diabetes are associated with increasing utilization of bariatric surgery in clinical practice, and this evaluation framework can be extended to other types of medical interventions to examine variations across medical interventions.

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TABLES AND FIGURES

Table 1. Sample Characteristics among Patients with Severe Obesity in the Group Health Cooperative

	Bariatric Cohort [†] (N = 1,421, 3.0%)			Eligible, Non-bariatric Cohort (N = 45,665, 97.0%)			BS Cohort vs. Non-BS Cohort
	Mean	SE	Interquartile Range	Mean	SE	Interquartile Range	P-value
Female (%)	82.0%	-	-	72.4%	-	-	0.000
ORDs [§] (%)	96.8%	-	-	91.9%	-	-	0.000
BS Insurance Coverage [#] (%)	71.7%	-	-	51.9%	-	-	0.001
Age	47.6	0.277	40 - 55	47.8	0.058	40 - 56	0.515
BMI	49.9	0.250	43.9 - 54.5	40.4	0.025	36.4 - 42.6	0.000
ORD_index [§]	3.35	0.045	2 - 5	2.49	0.008	1 - 4	0.000

Abbreviation: SE, standard error; BS, bariatric surgery; ORDs, obesity-related diseases

[†]: bariatric surgery cohort represents a group of patients who received bariatric surgery at the GHC from 1994 to 2008

[‡]: Eligible population for bariatric surgery is determined by the National Institute of Health Bariatric Surgery eligibility guideline - morbidly obese patients with BMI 35-40 and at least one obesity-related disease (ORD) or those who are BMI ≥ 40

[§]: *ORDs* is a binary variable representing whether a patient has any ORDs or not, whereas *ORD_index* is a continuous variable expressing the number of ORDs. [#]: A bariatric surgery insurance coverage variable indicates a patient who have ever had the coverage based on the GHC enrollment contract. Individual patients may have additional coverage through other insurance plans, such as Medicare.

Table 2. Predicted Uptake vs. Counterfactual Uptake of Bariatric Surgery after the Publication of Two of the Top-ranked Major Clinical Evidence in 4th Quarter of 2004

	Counterfactual [†] (Case per 100,000 per quarter)	Predicted Uptake (Case per 100,000 per quarter)	Difference (% Change)
Year 1 (2005) [‡]	146	183	+ 17 (+ 25.3%)
Year 2 (2006)	158	154	- 4 (- 2.5%)
Year 3 (2007)	182	203	+ 21 (+ 11.5%)
Year 4 (2008)	220	361	+ 141 (+ 64.1%)
Average[§] (2005 – 2008)	181	231	+ 50 (+ 27.6%)

[†]: represents the counterfactual trends of the uptake of bariatric surgery for people with severe obesity and diabetes if no major evidence – showing the effectiveness of bariatric surgery on remission or improvement in diabetes – came out in 4Q 2004

[‡]: Based on estimates from 3Q and 4Q of 2005

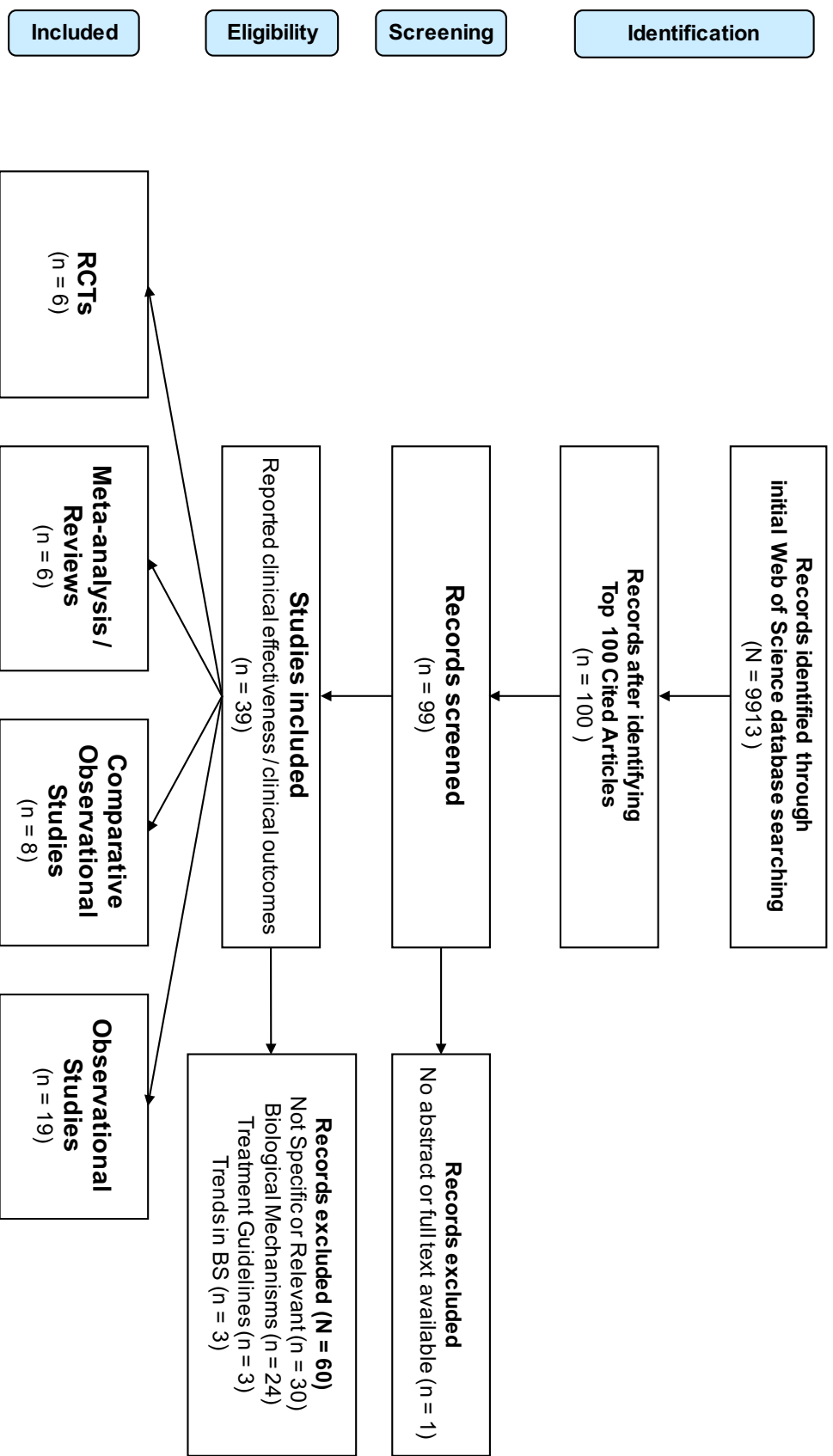
[§]: Based on a quarterly average from 2005-2008

Table 3. The impact of the Accumulation of Influential Articles, the Type of Evidence, or the Influential Tier of Articles on the Uptake of Bariatric Surgery

Dependent Variable	Probability of Receiving Bariatric Surgery		
	MODEL 1 (Total # of Influential Articles)	MODEL 2 (Type of Influential Articles)	MODEL 3 (Tier Effect)
Main Predictor (Evidence)			
Intercept (constant)	0.0034631	-0.0039553	-0.0010668
Time (quarter-year)	0.0000765	0.0001042	0.0001109
Age	-0.0003461	-0.0002705	-0.0003414
Total	0.0001148	-	-
RCT	-	0.0003036	-
Meta-Analysis / Review	-	0.0001186	-
Comp. Obs. Study	-	<i>0.0000707</i>	-
Obs. Study	-	-0.0000349	-
Tier 1	-	-	0.0001070
Tier 2	-	-	0.0000906
Tier 3	-	-	-0.0000428

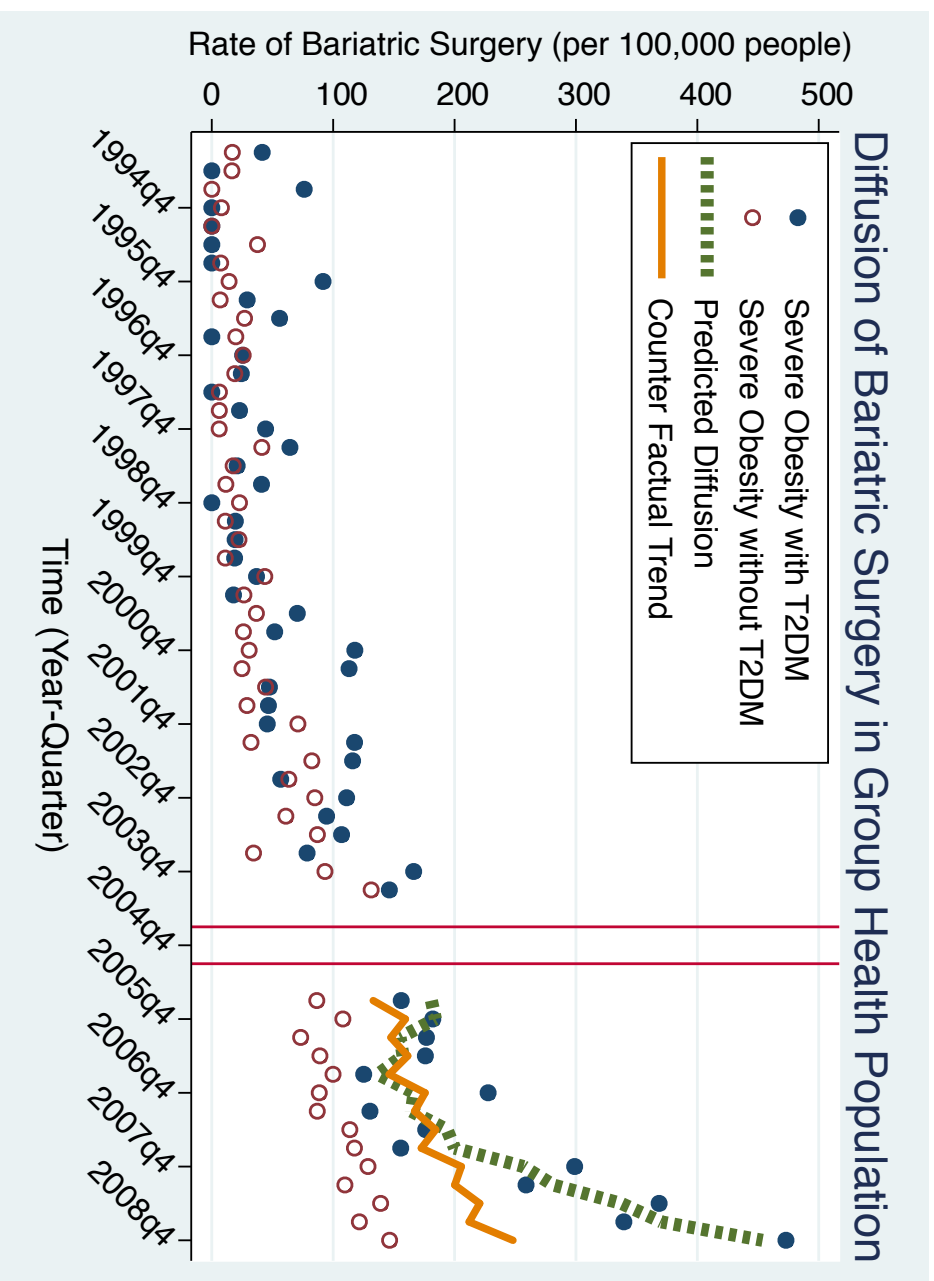
Abbreviation: RCT, randomized-control trial; Comp. Obs. Study, comparative observational study (e.g., matched case-control study); Obs. Study, observational study (e.g., case study)
 Note: Coefficients (**BOLD**: significant at the 0.05 level; *ITALICS*: significant at the 0.1 level)

Figure 1. Flow Diagram of the Literature Search for Major Articles on Clinical Effectiveness of Bariatric Surgery in Humans



Abbreviation: BS, bariatric surgery; RCTs, randomized-controlled trials

Figure 2. Observed, Predicted, and Counterfactual Uptake of Bariatric Surgery Before and After 4th Quarter of 2004



NOTE: The counterfactual trend represents the hypothetical trend in utilization of bariatric surgery among individuals with severe obesity and diabetes if two of the top-ranked articles, which provides clinical evidence on not only the long-term weight loss but also remission or improvement in diabetes, were not published in the 4th quarter of 2004. The counterfactual trend is extrapolating the trend among the exposure group (i.e., people with severe obesity and diabetes) in the pre-publication period based on the trend among the comparison cohort (i.e., people with severe obesity and no diabetes). The difference between the predicted diffusion and the counterfactual trend can be attributable to the change in utilization associated with the publication of the major clinical evidence in 4Q 2004.

APPENDICES

Appendix A: Details on Statistical Analysis

Analysis 1: Changes in the uptake of bariatric surgery after the publication of major evidence

$$\begin{aligned} g(\text{RECEIPT}_{it}) = & \beta_0 + \beta_A \text{AGE}_{it} + \beta_F \text{FEMALE}_{it} + \beta_1 \text{T2DM}_{it} \\ & + \beta_2 \text{TIME}_{it} + \beta_3 \text{TIME}_{it}^2 \\ & + \beta_4 \text{T2DM}_{it} \cdot \text{TIME}_{it} + \beta_5 \text{T2DM}_{it} \cdot \text{TIME}_{it}^2 \\ & + \beta_6 \text{POST}_{it} + \beta_7 \text{TIME}_{it} \cdot \text{POST}_{it} + \beta_8 \text{TIME}_{it}^2 \cdot \text{POST}_{it} \\ & + \beta_9 \text{T2DM}_{it} \cdot \text{POST}_{it} + \beta_{10} \text{T2DM}_{it} \cdot \text{TIME}_{it} \cdot \text{POST}_{it} + \beta_{11} \text{T2DM}_{it} \cdot \text{TIME}_{it}^2 \cdot \text{POST}_{it} \\ & + I[\text{QTR}]_{it} + e_{it} \end{aligned}$$

- RECEIPT_{it} : a binary outcome of the receipt of bariatric surgery
- AGE_{it} : age of the individual
- FEMALE_{it} : sex of the individual
- T2DM_{it} : a dummy variable representing whether individual is diagnosed with T2DM
- TIME_{it} : an index time for the specific quarter-year centered around the 4Q 2004 (a continuous variable)
- TIME_{it}^2 : a quadratic term of the TIME variable to capture the non-linear trends (a continuous variable)
- POST_{it} : a binary indicator for a period after the major evidence came out – 4Q 2004
- $I[\text{QTR}]_{it}$: quarter-specific indicator to capture seasonality

Analysis 2: Does the accumulation of evidence, the type of evidence, or the influential tier of evidence matter?

$$g(BS_RECEIPT_{it}) = \beta_0 + \beta_1 AGE_{it} + \beta_2 TIME_t + \beta_3 EVIDENCE_t + [\theta_i]^* + e_{it}$$

- AGE_{it} : age of the individual
- $TIME_t$: an index time for the specific quarter-year centered around the 4Q 2004 (a continuous variable)
- $[\theta_i]^*$: individual-level fixed effect to represent all of the non-time varying covariates (e.g., gender)
- $EVIDENCE_t$: the cumulative number (#) of influential articles available in 2 quarters before^{xiv} (a continuous variable)
 - Analysis 1: the total # of influential articles, regardless of the type of evidence
 - $EVIDENCE_t = TOTAL_t$
 - Analysis 2: # of influential articles in the specific type of evidence
 - $EVIDENCE_t = RCT_t + MA_SR_t + COS_t + OS_t$
 - RCT_t : # of influential articles categorized as randomized controlled trials
 - MA_SR_t : # of influential articles categorized as meta-analyses or systematic reviews
 - COS_t : # of influential articles categorized as comparative observational studies (case-control study)
 - OS_t : # of influential articles categorized as observational studies (e.g., case study)
 - Analysis 3: # of influential articles in each tier
 - $EVIDENCE_t = TIER\ 1_t + TIER\ 2_t + TIER\ 3_t$
 - $TIER\ 1_t$: # of influential articles that have more than 10 citations per quarter since its publication
 - $TIER\ 2_t$: # of influential articles that have 5-10 citations per quarter since its publication
 - $TIER\ 3_t$: # of influential articles that have less than 5 citations per quarter since its publication

^{xiv} As explained in the main text, this is to account for the lag effect between the clinical decision to receive bariatric surgery and the actual date of bariatric surgery – generally 6 months.

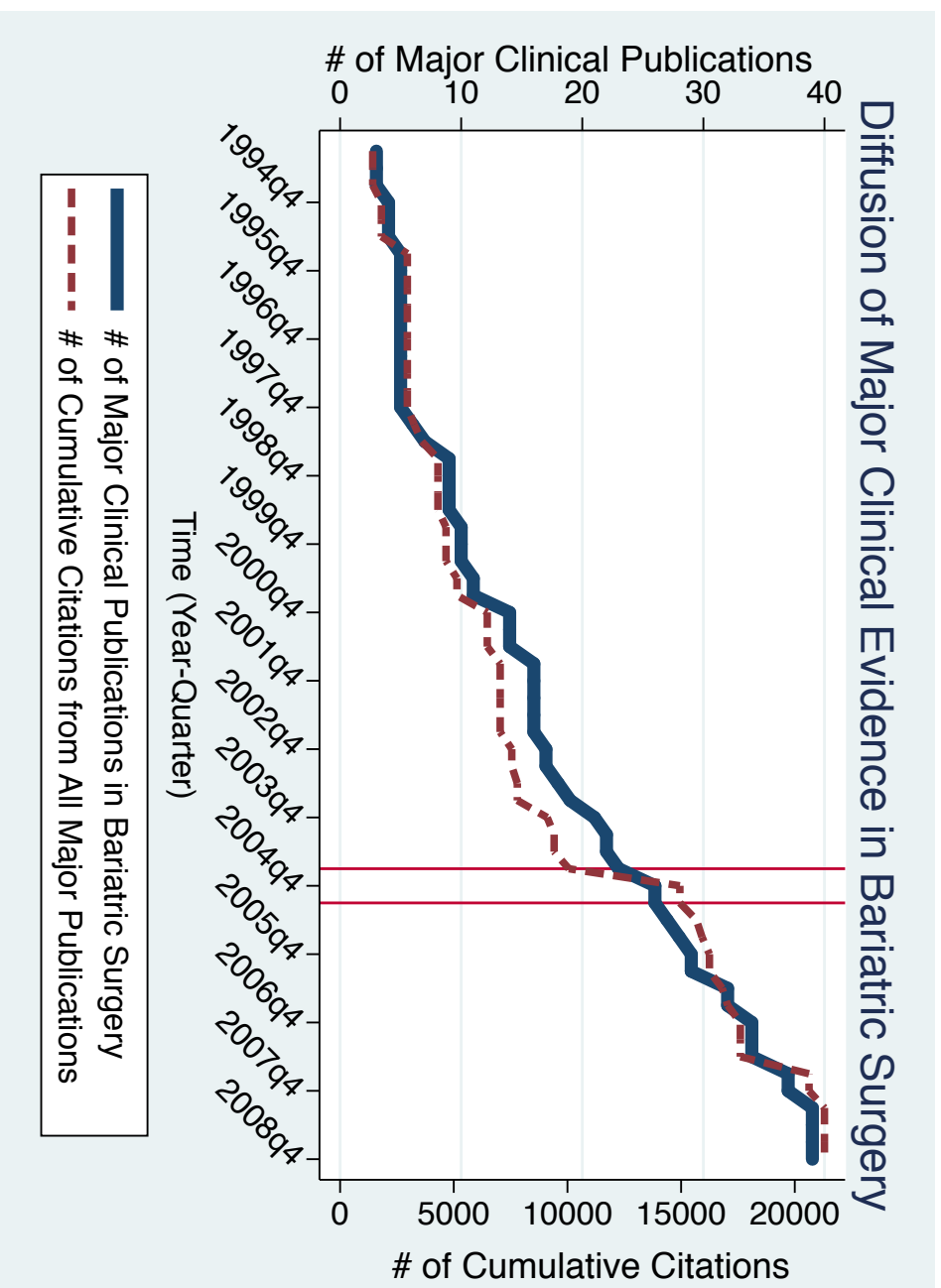
Table A1: Major Clinical Evidence in Bariatric Surgery from 1977-2008 (Among Top 100 Cited Articles in Bariatric Surgery)

First Author	Study Title	PY	QTR	Type	Interventions / Comparators	Primary Outcomes (Time horizon)	TC	RK	TC/CT	CT per QTR	QTR/RK
Buchwald, H	Bariatric surgery: A systematic review and meta-analysis	2004	4	MA	N/A	EWL, ORDs	2780	1	61.78		1
Sjostrom, L	Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery	2004	4	COS	Surgical vs. Non-Surgical	EWL, Lifestyle ORDs (> 10 yrs)	1815	2	40.33		3
Sjostrom, L	Effects of bariatric surgery on mortality in Swedish obese subjects	2007	3	COS	Surgical vs. Non-Surgical	Long-term mortality (> 10 yrs)	1734	3	51.00		2
Pories WJ	Who would have thought it - an operation proves to be the most effective therapy for adult-onset diabetes mellitus	1995	3	OS	Surgical Interventions	EWL & Diabetes control (> 14 yrs)	1142	4	13.95		8
Adams, TD	Long-term mortality after gastric bypass surgery	2007	3	COS	Surgical vs. Non-Surgical	Long-term mortality (> 7 yrs)	1021	5	30.03		4
Schauer, PR	Outcomes after laparoscopic Roux-en-Y gastric bypass for morbid obesity	2000	4	OS	Lap-RYGB	EWL, ORDs, QoL (> 2.5 yrs)	743	6	12.18		9
Maggard, MA	Meta-analysis: Surgical treatment of obesity	2005	2	MA	N/A	BMI > 40	726	7	16.88		6
Dixon, JB	Adjustable gastric banding and conventional therapy for type 2 diabetes - A randomized controlled trial	2008	1	RCT	Surgical vs. Non-Surgical	Diabetes Control (> 2 yrs)	679	8	21.22		5
Christou, NV	Surgery decreases long-term mortality, morbidity, and health care use in morbidly obese patients	2004	3	COS	Surgical vs. Non-Surgical	ng-term mortality; EWL, ORDs (> 5 yrs)	644	9	14.00		7
Schnauer PR	Effect of laparoscopic Roux-en-Y gastric bypass on type 2 diabetes mellitus	2003	4	OS	Lap-RYGB	Diabetes Control (> 5 yrs)	582	10	11.88		10
Nayven, NT	Laparoscopic versus open gastric bypass: A randomized study of outcomes, quality of life, and costs	2001	3	RCT*	Lap RYGB vs. Open RYGB	Outcomes, costs, QoL (1 yr)	566	11	9.76		11
Mason, EB	Vertical Banded gastroplasty for obesity	1982	2	OS	gastroplasty	EWL (1 yr)	511	12	3.79		36
Wirtgove, AC	Laparoscopic gastric bypass, Roux-en-Y - 500 patients: Technique and results, with 3-60 month follow-up	2000	2	OS	LRYGB	outcomes (> 5 years)	480	13	7.62		15
Wirtgove, AC	Laparoscopic gastric bypass, roux-en-y - preliminary report of 5 cases	1994	4	OS	RYGB	EWL	382	14	4.49		33
Sjogman, HJ	A randomized prospective trial of gastric bypass vs. vertical banded gastroplasty for morbid-obesity and their effects on sweets vs. non-sweet eat	1987	2	RCT*	VHGR vs. RYGB	EWL (> 3 yrs)	371	15	3.23		37
Podnos, YD	Complications after Laparoscopic gastric bypass - A review of 3464 cases	2003	3	Review	BS	complications	367	16	7.34		18
Ragan, JP	Early experience with two-stage laparoscopic Roux-en-Y gastric bypass as an alternative in the super-super obese patient	2003	4	OS	2-Stage LSG -> LRYGB	EWL (2 yrs)	364	17	7.43		17
Scopimano, N	Biliopancreatic diversion	1998	3	OS	BPD	Outcomes (> 10 yrs)	360	18	5.14		27
Sjostrom, CD	Reduction in incidence of diabetes, hypertension and lipid disturbances after intentional weight loss induced by bariatric surgery: The SOS Intervention Study	1999	3	COS	BS	EWL, ORDs (2 yrs)	355	19	5.38		26
Heger KD	Complications of the laparoscopic Roux-en-Y gastric bypass: 1,040 patients - What have we learned?	2000	4	OS	RYGB	EWL, complications (1 yr)	347	20	5.69		25
Marean, P	Biliopancreatic diversion with duodenal switch	1998	3	OS	Dual vs. Sleeve Gastrectomy	EWL (4-8 yrs)	346	21	4.94		28
Hess, DS	Biliopancreatic diversion with a duodenal switch	1998	2	OS	BPD-DS	EWL (2 yrs)	340	22	4.79		32
Fium, DR	Early mortality among medicare beneficiaries undergoing bariatric surgical procedures	2005	4	OS	BS	mortality (1-year)	325	23	7.93		13
Himpens, J	A prospective randomized study between laparoscopic gastric banding and laparoscopic isolated sleeve gastrectomy: Results after 1 and 3 years	2006	4	RCT*	AGB vs. LSG	outcomes (3 yrs)	318	24	8.59		12
Chapman, AE	Laparoscopic adjustable gastric banding in the treatment of obesity: A systematic literature review	2004	1	Review	BS	EWL	305	25	6.35		23
Karlsson, J	Swedish obese subjects (SOS) - an intervention study of obesity: Two-year follow-up of health-related quality of life and eating behavior after gastric surgery for severe obesity	1998	1	COS	Surgical vs. Non-Surgical	QoL (2 yr)	299	26	4.15		34
Cotnam, D	Laparoscopic sleeve gastrectomy as an initial weight-loss procedure for high-risk patients with morbid obesity	2006	2	OS	2-Stage LSG -> LRYGB	EWL (1-3yr)	292	27	7.49		16
Fium, DR	Impact of gastric bypass operation on survival: A population-based analysis	2004	4	COS	Surgical vs. Non-Surgical	mortality (10 yrs)	291	28	6.47		20
Griffen, WO	Prospective comparison of gastric and jejunoileal bypass procedures for morbid obesity	1977	4	RCT*	gastric and jejunoileal bypass	complications	282	29	1.84		39
Bolin, RE	Long-limb gastric bypass in the superobese - a prospective randomized study	1992	2	OS	BPD vs. RYGB	EWL (2-3 yrs)	271	30	2.85		38
Ohlsen, PE	Treatment of mild to moderate obesity with laparoscopic adjustable gastric banding or an intensive medical program - A randomized trial	2006	2	RCT	Surgical vs. Non-Surgical	EWL, QoL (2 yrs)	269	31	6.90		19
Karlsson, J	Ten-year trends in health-related quality of life after surgical and conventional treatment for severe obesity: the SOS intervention study	2007	3	COS	Surgical vs. Non-Surgical	HRQoL (10 yrs)	267	32	7.85		14
Ohlsen, PE	The laparoscopic adjustable gastric band (Lap-Band (R)): A prospective study of medium-term effects on weight, health and quality of life	2002	4	OS	AGB	EWL, QoL, ORDs (6 yrs)	256	33	4.83		29
Bolin, RE	Bariatric surgery and long-term control of morbid obesity	2002	4	Review	BS	long-term effectiveness	254	34	4.79		31
Balshar, A	Laparoscopic sleeve gastrectomy: A multi-purpose bariatric operation	2005	3	OS	LSG	EWL (> 2 yrs)	249	35	5.93		24
Ren, CJ	Early results of laparoscopic biliopancreatic diversion with duodenal switch: A case series of 40 consecutive patients	2000	4	OS	BPD-DS	EWL	246	36	4.03		35
Sugerman, HI	Diabetes and hypertension in severe obesity and effects of gastric bypass-induced weight loss	2003	2	OS	RYGB	HTN and T2DM remission (6-7 yrs)	246	37	4.82		30
Ohlsen, PE	Systematic review of medium-term weight loss after bariatric operations	2006	3	Review	BS	EWL	242	38	6.37		22
Christou, NV	Weight gain after short- and long-limb gastric bypass in patients followed for longer than 10 years	2006	4	OS	RYGB	weight gain after BS (> 10 yrs)	239	39	6.46		21

NOTE: the table is sorted based on the ranking determined by the total number of citations

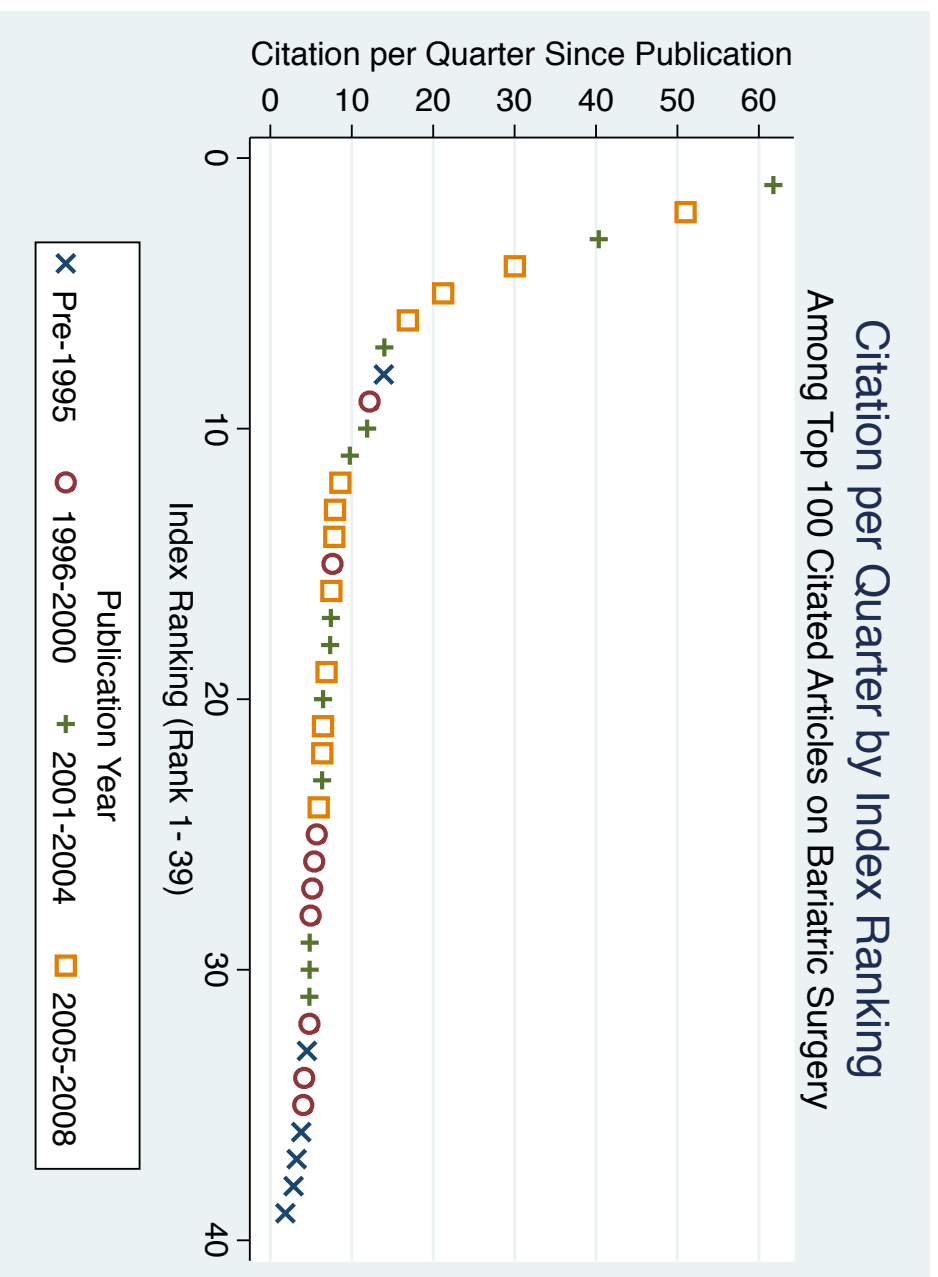
Abbreviation: PY, publication year; QTR, quarter; TC, total number of citations; RC_TC, ranking based on the total number of citations; CT per QTR, the number of citations per quarter since its publication; QTR_RK, ranking based on the number of citations per quarter since its publication

Figure A1: Diffusion of Major Clinical Evidence in Bariatric Surgery from 1994-2008



NOTE: Although there is an increasing trend in the number of major clinical publications (Among top 100 cited articles in bariatric surgery, 39 of them reported clinical evidence) and the number of cumulative citations among these articles, there is a clear jump around the 4th quarter of 2004 when three major articles that showed clinical effectiveness of bariatric surgery were concurrently published. Among the three articles published, two are ranked the top 1 and 2 in terms of the total number of citations. This graph helps us to determine when the major evidence in bariatric surgery came out.

Figure A2: Average Citation per Quarter Since Article's Publication Date and Relative Ranking Based on the Index.



NOTE: We created a citation per quarter index (i.e., the number of citations per quarter since its publication) to determine tiers among all major clinical evidence without discriminating newer publications. A higher tier represented a group of more influential clinical evidence. There was a clear cut among the articles with more than 10 citations per quarter based on the citation per quarter index. (N = 10) Thus, more than 10 citations per quarter served as a threshold for determining the Tier 1. The next threshold for the Tier 2 was between 5 and 10 citations per quarter. (N = 17). The major articles with less than 5 citations per quarter put into the Tier 3. (N = 12)

CHAPTER 4: ECONOMIC RETURNS OF PROVIDING GREATER ACCESS TO BARIATRIC SURGERY

ABSTRACT

Introduction: Despite its clinical effectiveness and cost-effectiveness, bariatric surgery has been significantly underutilized. To improve utilization of bariatric surgery, designing optimal coverage policy to incentivize patient subgroups who are likely to benefit the most from bariatric procedures has become an important issue. Thus, the purpose of this study is to evaluate potential economic returns under various coverage options for bariatric surgery among patient subgroups defined by the body mass index (BMI) levels and the presence of type 2 diabetes mellitus (T2DM).

Methods: We evaluated economic returns of providing greater access to bariatric surgery by varying the level of cost-sharing, especially targeted for the high-value population (patients with $BMI \geq 40$ and T2DM). The 2008-2014 National Health and Nutrition Examination Survey data were used to estimate the size of the subgroups. Then, we estimated the rates of uptake of bariatric surgery using the 2008-2014 Marketscan databases. Combined these estimates with subgroup-specific long-term costs and benefits of bariatric procedures, we predicted utilization under proposed coverage alternatives and evaluated the potential economic returns of these policies.

Results: The rate of uptake for bariatric surgery among the high-value population was 121.3 cases per 100,000 patients at the average cost-sharing level of 6% in 2014. From a private insurer's perspective, the realized value of bariatric surgery in this population was \$66.3 per individual. If the insurer decides to provide full coverage (i.e., 0% patient's cost-sharing) for bariatric surgery in the high-value population, the rate of uptake for bariatric surgery would

increase to 141.9 cases per 100,000 patients. This increased utilization would provide the realized value of \$68.0 per individual. The increase of \$1.7 per individual could translate into the \$7.07M increase in the realized value of bariatric surgery at the population level.

Conclusion: We found that reducing patient's cost-sharing would potentially lead to improving the utilization of the cost-effective intervention and resulting in a greater value to payers. This framework could help decision-makers to understand the realized value of intervention under current coverage policy and design optimal policies to incentivize patient subgroups who are likely to benefit the most.

1. INTRODUCTION

The ever-rising prevalence of obesity and its potential adverse health effects have led to a current epidemic of obesity. In the United States, recent estimates provided that the prevalence of obesity exceeds 40% and 35% among adult women and men, respectively.¹ The increased rates of obesity have contributed to a substantial financial burden on our society. A recent meta-analysis reported that an obese individual incurs additional \$1,901 of annual medical expenditure than individuals with normal weight, accounting for \$149.4 billion at the national level.²

With increasing attention to minimizing adverse effects of obesity, bariatric surgery is found to be associated with better long-term weight loss and significantly higher reduction in obesity-related comorbidities, especially in remission of type 2 diabetes, compared to lifestyle interventions or pharmacotherapy.³⁻¹⁰ Prior economic evaluations demonstrated that bariatric surgery is cost-effective (i.e., benefits of bariatric surgery are worthy of investment), but not cost-saving (i.e., bariatric surgery costs less with more benefits, compared to the usual care) due to the high costs of its procedure (\$20,000-\$30,000).¹¹⁻¹⁴ Despite its clinical effectiveness and cost-effectiveness, bariatric surgery has been significantly underutilized, and its trend has been

stagnated.¹⁵⁻¹⁷ The lack of appropriate insurance coverage for bariatric surgery has been identified as the main driver for underutilization.^{18,19} For example, only less than half of the newly-created 51 state exchanges provided coverage for bariatric surgery even though additional coverage of bariatric surgery was not associated with increasing the average monthly premium.^{20,21}

To improve utilization of bariatric surgery, designing optimal coverage policy to incentivize patient subgroups who are likely to benefit the most from bariatric procedures has become an important issue.^{22,23} Public payers (e.g., Medicare) and private payers only provide coverage for bariatric surgery among individuals with severe obesity, which is broadly defined as an individual with body mass index (BMI) greater than 40 or BMI greater than 35 with at least one obesity-related comorbidity. This coverage decision is based on the outdated guidelines established in 1991 and has not been updated.²⁴ Since then, increasing concerns exist that BMI should not be an eligible criterion for surgical indication because it does not appropriately capture individual benefits and harms.^{25,26} Also, with increasing evidence of heterogeneity in treatment effect of bariatric surgery (e.g., diabetic vs. non-diabetic patients with severe obesity or BMI subgroups), there is a growing interest in evaluating the impact of differential coverage options by subgroups.

Thus, the purpose of this study is to evaluate potential economic returns under various coverage options for bariatric surgery among patient subgroups defined by the BMI levels and the presence of type 2 diabetes mellitus (T2DM).

2. METHODS

Study design

In the previous chapter, we proposed a novel framework and metrics that focus on evaluating economic returns of policy alternatives, which are designed to improve the uptake of specific technology through changing the level of coverage and/or educating patients and physicians. We applied this framework to estimate economic returns of different coverage options that could change the uptake of bariatric surgery. By incorporating subgroup-specific rates of uptake of bariatric surgery into the existing economic evaluation metrics (e.g., cost-effectiveness ratios), we could capture the realized value of bariatric surgery based on its actual or predicted utilization. In contrast, traditional economic evaluation metrics intrinsically assume that everyone in the target population would receive the medical intervention, creating a hypothetical value of the intervention.

To estimate the realized value of bariatric surgery under policy alternatives in consideration, we first defined ten patient subgroups – to whom clinical benefits and economic value of bariatric surgery may be different – based on clinical characteristics of BMI level and the presence of T2DM. Policy alternatives were designed to focus on the high-value groups – BMI \geq 40 with T2DM – to incentivize the utilization of bariatric surgery among those with higher anticipated clinical benefits and greater economic value to payers. First, we empirically estimated the size of each subgroup and the rates of uptake of bariatric surgery among these subgroups. Then, we estimated costs and benefits of bariatric surgery in each of these subgroups. Finally, we predicted anticipated uptake under proposed policy alternatives and evaluated the potential economic returns of these policies for bariatric surgery.

Subgroup-specific prevalence and the uptake

Two subgroup-specific information is required to estimate the realized value of bariatric surgery at the population level: the size of a specific subgroup in relative to the entire population and the subgroup-specific rate of uptake of bariatric surgery. These two parameters were used to estimate the weighted-average utilization of bariatric surgery across subgroups defined by BMI levels and the presence of T2DM. The size of subgroups was empirically estimated from the 2008-2014 National Health and Nutrition Examination Survey (NHANES). The NHANES dataset provided the measured BMI values and personal interview data on diabetes and allowed us to generate the nationally representative estimates using with sample weights and survey design.

To estimate the uptake of bariatric surgery by subgroups, we analyzed the Truven Health claims (Marketscan) databases that collect healthcare data from large employers, health plans, and government and public organizations.²⁷ From the 2008-2014 Marketscan database, we estimated the number of bariatric procedures performed using the international classification of disease, ninth revision, clinical modification (ICD-9-CM) procedure codes. Since the aim of this study is to estimate costs and benefits of the initial bariatric surgery (i.e., revisions are considered as adverse events of the initial procedure), we excluded the procedure code for revisions. Then, we identified individuals belonging to specific subgroups using the ICD-9-CM diagnosis codes for T2DM (250.XX for type 2 diabetes) and obesity (278.00, V85.30-V.85.34) or morbid obesity (278.01, V.85.35-V85.45). Using the estimated size of each subgroup as a denominator, we calculated subgroup-specific rates of uptake of bariatric surgery with the total number of bariatric procedures as a numerator and the size of subgroup as a denominator to estimate the rates of the uptake. The details of the estimation process were reported in Appendix A.

Subgroup-specific economic evaluations

We estimated both short-term (first five years after surgery) and lifetime costs and outcomes associated with three bariatric procedures – open gastric bypass (ORYGB), laparoscopic gastric bypass (LRYGB), and laparoscopic adjustable gastric band (LAGB), compared to non-surgical intervention (e.g., behavioral counseling or no intervention). For base case analysis, we evaluated the lifetime cost-effectiveness of LRYGB for 53-year-old female patients, compared to non-surgical intervention. We utilized the existing cost-effectiveness simulation model (i.e., bariatric outcomes and obesity modeling (BOOM) cost-effectiveness model) to generate subgroup-specific costs and outcomes as baseline estimates. The details of the BOOM cost-effectiveness model were reported in previously published articles^{14,19} as well as in Appendix B.

Policy evaluation

With the estimated subgroup-specific rates of uptake, we evaluated the realized value of bariatric surgery under different coverage options. We utilized net monetary benefits (NMB) framework – subtracting costs associated with an intervention from monetized health benefits – to represent the economic return of bariatric procedures under current policy and policy alternatives. The NMB framework is used to highlight the changes in the magnitude of economic value after adjusting for the uptake of the invention, which cannot be comprehended from the ratio statistics (e.g., incremental cost-effectiveness ratio, ICER). We applied \$100,000/QALY as a willingness-to-pay threshold, which is considered a reasonable estimate in the United States.²⁸

With this framework, we first presented the realized value of bariatric surgery based on the observed rates of uptake and the average level of patient’s cost-sharing in 2014. Then, we evaluated the potential economic returns from a range of cost-sharing level (0% - 25%) for high-

value population (BMI \geq 40 with T2DM). We focused changes in the cost-sharing among the high-value population because bariatric surgery provided higher clinical benefits and greater economic value to them. However, we also simultaneously changed the level of cost-sharing among both high-value population and other obese population to evaluate economic returns in those scenarios. Using the estimates of the price elasticity of demand for health care from the RAND Health Insurance Experiment ²⁹ – how individuals change their demand in response to changes in price, we predicted the uptake of bariatric surgery under each scenario.

We evaluated those scenarios from two perspectives: a health care sector (e.g., public payer, such as Medicare) perspective and a private payer perspective. We assume that a private payer is more likely to care about the short-term consequences of medical intervention (e.g., 5-year-post surgery costs and outcomes) and only responsible for health care costs that only fall on their budget. On the contrary, we showed the result from a health care sector perspective using the lifetime costs and outcomes of bariatric surgery.

3. RESULTS

Population with Obesity and Diabetes

From the 2013-2014 NHANES datasets, we estimated the overall prevalence of diabetes and obesity among the US adult population as 9.75% and 37.9%, respectively. Both estimates are comparable to the previously published estimates.^{1,30} Since 2008, both of the prevalence of diabetes and obesity have increased. Especially, individuals with $40 \leq \text{BMI} < 50$ (with and without diabetes) have been growing at the fastest rate. Table 1 provides the summary of characteristics of the obese population with and without diabetes. The detail estimates of the subgroup-specific prevalence of obesity and diabetes from 2008-2014 were presented in Appendix C.

Trends in bariatric surgery

After reaching its nadir in 2010, the overall trends in bariatric procedures increased, recording 27,469 cases (excluding revisions) in 2014. The uptake of laparoscopic sleeve gastrectomy (LSG) procedure is rising fast since its introduction in 2013, accounting for more than two-thirds of all procedures in 2014. (Appendix D) However, as supported by clinical evidence, gastric bypass procedures (LRYGB and ORYGB) are the most popular choice among patients with severe obesity and T2DM. More than 30% of the surgery recipients for those procedures were diagnosed with T2DM, compared to 22.3% of sleeve gastrectomy (LSG) receipts were. (Figure 1) Also, we examined the distribution of diabetic patients by surgery recipients' BMI groups. The proportion of diabetic patients was the greatest in the BMI 35-39 group with 30.7% whereas all of other BMI subgroups reported a similar proportion of diabetic patients. (Figure 1) This finding highlighted the relative importance of remission or improvement in diabetes among patients with lower BMI.

The overall rate of uptake for bariatric surgery among patients with severe obesity was 64.8 cases per 100,000 individuals. The rate of uptake was consistently much higher in patients with severe obesity and T2DM from 2008-2014 than individuals without T2DM. In 2014, the rate of uptake was 90.4 cases per 100,000 patients with severe obesity and T2DM, compared to 59.1 cases per 100,000 individuals without T2DM. (Figure 2)

Economic evaluations of bariatric surgery by subgroups

Bariatric procedures were most cost-effective for a patient with T2DM and higher baseline BMI (e.g., \$5,804/QALY for lifetime cost-effectiveness of LRYGB, compared to non-surgical intervention, among the age of 53 years old female patient). All of three bariatric procedures (LRYGB, ORYGB, and LAGB) were consistently more cost-effective as a patient's

baseline BMI increases and with T2DM. (Figure 3) As comparing the cost-effectiveness of different bariatric procedures, LRYGB is the most cost-effective procedures. However, we did not include LSG as a comparator. The laparoscopic sleeve gastrectomy procedures reported similar effectiveness as LRYGB³¹, but slightly cheaper (~\$1,500) based on our analysis of the Marketscan database. So, the overall cost-effectiveness of LSG could be slightly more favorable than LRYGB, but the subgroup-level cost-effectiveness is not available, especially by the presence of T2DM.

Considering the long-term weight-loss and improvement in obesity-related comorbidities, the cost-effectiveness of bariatric procedures was greater when evaluating in the lifetime horizon, compared to the short time horizon of the first 5-year-post surgery. Appendix E provides full results of cost-effectiveness analysis by each of subgroups.

Characteristics of Current Coverage for Bariatric Surgery

In 2014, the average cost of bariatric procedures was \$24,914, ranging from \$22,120 for LAGB to \$32,211 for open biliopancreatic diversion with a duodenal switch (OBPD-DS). The average cost-sharing among bariatric surgery recipients (i.e., the sum of co-insurance, co-payment, and deductible) was 6.24%, ranging from 5.5% for LAGB to 6.39% for LSG. After adjusting for the inflation using the medical care consumer price index (CPI) into 2014 US dollars, overall trends in costs of bariatric procedures slightly increased over time. Also, the level of cost-sharing moderately increased since 2008 despite a slight dip between 2011-2012. (Appendix F) The combination of increased costs of bariatric procedures and the level of cost-sharing imposes a greater financial burden on the severely obese patients who desire to access to one of the better treatment options.

Economic Returns of Coverage Policies

Based on the average level of cost-sharing of 6% (equivalent to \$1,577) in 2014, the observed rate of uptake for bariatric surgery among the high-value population (BMI \geq 40 and T2DM) was 121.3 cases per 100,000 patients. From a perspective of private payers who care for the shorter-term return on investment, the net monetary benefit (NMB) of bariatric surgery was \$85,256 under the traditional way of estimating the economic value of bariatric surgery, because it intrinsically assumes everyone in the high-value population would receive bariatric surgery. This value can be considered as the maximum value of bariatric surgery that can be achieved if all of the patients with BMI \geq 40 and T2DM indeed receive bariatric surgery. However, when incorporating the observed rates of uptake into the estimation, the average realized value of bariatric surgery among the high-value population under the current coverage policy was \$66.3 per individual. Table 2 provides contrast between hypothetical value and realized value of bariatric surgery as the level of cost-sharing is varied from 0 to 25 percent for the high-value population. (Table 2)

Figure 4 provides economic returns of coverage options that could simultaneously change the level of cost-sharing for both the high-value group and the non-high-value group. For example, if a private payer decreases the level of cost-sharing for the high-value group to 0 percent while increasing the level of cost-sharing for the non-high-value group to 10 percent, the realized value of bariatric surgery would be \$62.2 per individual. (Time horizon: 5-year-post-surgery) However, regardless of the choice of the time horizon, reducing cost-sharing to 0% provides the largest economic returns for bariatric surgery. The primary reason is that bariatric procedures are so much cost-effective so that it is worthy of providing full coverage to incentivize its utilization, especially for the high-value group.

4. DISCUSSION

Creating optimal coverage policy to incentivize patient's utilization of high-value interventions has been an imperative issue in the U.S. health care system. However, existing economic evaluation metrics (e.g., ICERs) provide a hypothetical value of medical intervention, assuming the full uptake of the intervention at the population level, rather than the realized value based on the actual rates of the uptake. This hypothetical value could represent a potential value that could be achieved when the entire population is fully adopting the intervention. Because of some of the barriers (e.g., insurance coverage, supply-side constraints, and implementation), however, the potential value of medical intervention could not be fully realized. In this paper, we approached one of those issues by examining how to improve the realized value of bariatric surgery by changing the level of insurance coverage. We evaluated economic returns of providing greater access to bariatric surgery by varying the level of cost-sharing, especially targeted for the high-value population (patients with BMI ≥ 40 and the presence of T2DM).

We found that the rate of uptake for bariatric surgery among the high-value population was 121.3 cases per 100,000 patients based on the average patient's cost-sharing level of 6% in 2014. From a perspective of a private payer who is only responsible for costs that could fall on their budget, the realized value of bariatric surgery in this population was \$66.3 per individual. If the payer decides to provide full coverage for bariatric surgery in the high-value population (i.e., 0% cost-sharing for obese patients with BMI ≥ 40 and T2DM, while keeping average 6% cost-sharing for the rest of the obese population), the rate of uptake for bariatric surgery would increase 141.9 cases per 100,000 patients. This increased utilization would provide the realized value of \$68.0 per individual. With the estimated prevalence of 1.75% for this high-value obese population (i.e., 4.16 million individuals among the US adult population), the increase of \$1.7

per individual could translate into the \$7.07M increase in the realized value of bariatric surgery at the population level.

Also, we found that the traditional framework of evaluating the economic value of medical intervention could be misleading when determining the optimal coverage. For example, a private payer could determine the optimal level of cost-sharing based on the maximum economic returns from medical intervention. In this case, the payer would choose for 25% cost-sharing under the traditional framework based on our main results, because they only account for 75% of the total costs with mistakenly assuming to accrue all of the potential benefits through 100% uptake of bariatric surgery. However, this approach ignores the important reality that a patient is less likely to demand health care with the increased level of the cost-sharing. As evaluating the realized value of bariatric surgery after incorporating the rates of the uptake, the optimal coverage would be 0 percent cost-sharing from a private payer's perspective. This finding highlights the importance of estimating realized value of medical intervention by incorporating the actual or predicted uptake of the intervention under investigation.

Despite the importance of this new framework, we acknowledge some of the limitations of this study. The primary limitation is to make predictions on the uptake of bariatric surgery in response to changes in the out-of-pocket costs, assuming everything else constant. Although we estimated the predicted uptake anchoring on the average cost-sharing of 6%, there exists significant variation of the level of cost-sharing among bariatric recipients, and there were many bariatric recipients who reported no cost-sharing (Appendix H). However, without bariatric coverage information among all eligible population, we were unable to examine whether self-selection happens or not (i.e., they choose to receive bariatric surgery because of no/low cost-sharing or non-recipients choose not to receive because of high cost-sharing). Because the

proposed change in the level of cost-sharing would be in effect for all of the high-value obese population, we decided to use the average cost-sharing level as a baseline estimate.

Besides, one could argue that a policy option that improves the uptake of bariatric surgery through educating patients about the potential value of receiving bariatric surgery could provide greater economic returns, compared to changing the level of cost-sharing. However, there is no readily available scientific evidence on how much the rate of the uptake would be changed through these types of education programs. Also, implementation costs would potentially be much greater in employing education programs than changing the level of cost-sharing. Estimating this information remains for the future work, and once this information is readily available, a range of policy alternatives to be evaluated would broaden.

Another limitation pertains to the MarketScan datasets and the BOOM cost-effectiveness model. Although the MarketScan databases cover a fairly large sample of Americans with employer-sponsored health insurance and Medicaid, it is excluded some of the population, especially older population covered by Medicare. So, our estimates could underestimate the total number of bariatric cases and could not be nationally representative. However, the trend estimates in this study were almost identical to estimates from a recent trend study using a different dataset.¹⁵ Also, the BOOM cost-effectiveness model was created based on the sample population in the Group Health Cooperative (GHC) located in Seattle, WA. Depending on the health care setting, the costs and the long-term outcomes of bariatric surgery could be different. For example, in 2008, the average cost of bariatric procedures was \$18,313 (17,347 – 19,279) among the GHC patients, whereas the average cost was slightly higher at \$21,139 (20,088 – 20,503) in the MarketScan patients. If we incorporate the additional price of bariatric surgery (~\$2,000) among the MarketScan population, the CE ratios could be slightly increased. (e.g., the

lifetime ICER of LRYGB for a 53-year-old female patient is increased from \$5,889/QALY to \$6,534/QALY) However, the overall results and implication of this study would not be affected.

In this study, we provided a novel framework to estimate the realized value of bariatric surgery under various levels of cost-sharing. We found that reducing the level of cost-sharing would lead to increase the potential utilization of the cost-effective intervention and result in greater value to payers. We wish that this framework could help decision-makers to understand the realized value of intervention under current policy and design optimal coverage policy to incentivize patient subgroups who are likely to benefit the most.

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TABLES AND FIGURES

Table 1. Summary Table of Population with Obesity and Diabetes

BMI Group	T2DM	Eligible for Coverage ¹	Prevalence	Bariatric Surgery Uptake ²	ICER ³ (\$/QALY)
50 ≤ BMI	Yes	Yes	0.004	143.3	5,804
	No	Yes	0.022	84.2	7,080
45 ≤ BMI < 50	Yes	Yes	0.005	122.3	6,333
	No	Yes	0.013	140.8	7,673
40 ≤ BMI < 45	Yes	Yes	0.008	98.3	6,963
	No	Yes	0.035	83.7	8,363
35 ≤ BMI < 40	Yes	Yes	0.015	37.6	7,703
	No	No	0.077	17.1	9,161
30 ≤ BMI < 35	Yes	No	0.028	0.05	8,565
	No	No	0.174	0.03	10,076

Abbreviation: BMI, body mass index; T2DM, type 2 diabetes mellitus; ICER, incremental cost-effectiveness ratios

1: Based on the current Medicare national coverage determination and clinical guidelines

2: Number of cases per 100,000 individuals

3: Based on lifetime costs and benefits of laparoscopy gastric bypass, compared to non-surgical intervention

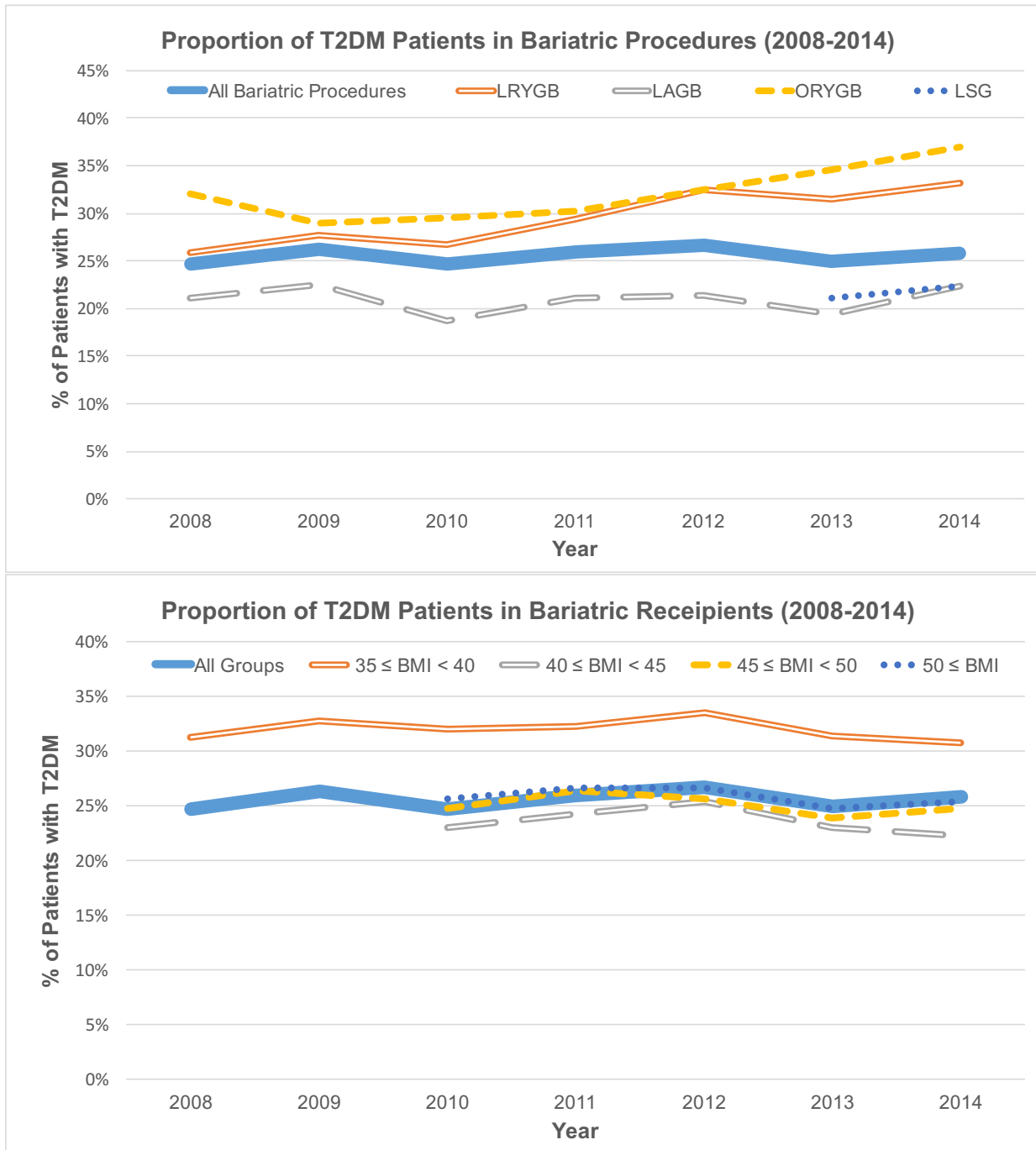
Table 2. Comparisons Between Hypothetical vs. Realized Value of Bariatric Surgery

(From a private payer’s perspective¹ with using the 5-year-post-surgery costs and outcomes, assuming \$100,000/QALY as a willingness to pay threshold)

	The Level of Cost-sharing for Bariatric Surgery among the High-value Patients ^{2,3}						
	0%	3%	6%	10%	15%	20%	25%
Predicted Uptake ⁴ (per 100,000 patients)	141.9	131.6	121.3	107.6	90.4	73.2	56.0
Hypothetical Value ⁵ (NMB)	\$84,020	\$84,638	\$85,256	\$86,080	\$87,110	\$88,141	\$89,171
Realized Value ⁶ (NMB)	\$68.0	\$67.1	\$66.3	\$65.1	\$63.7	\$62.2	\$60.6

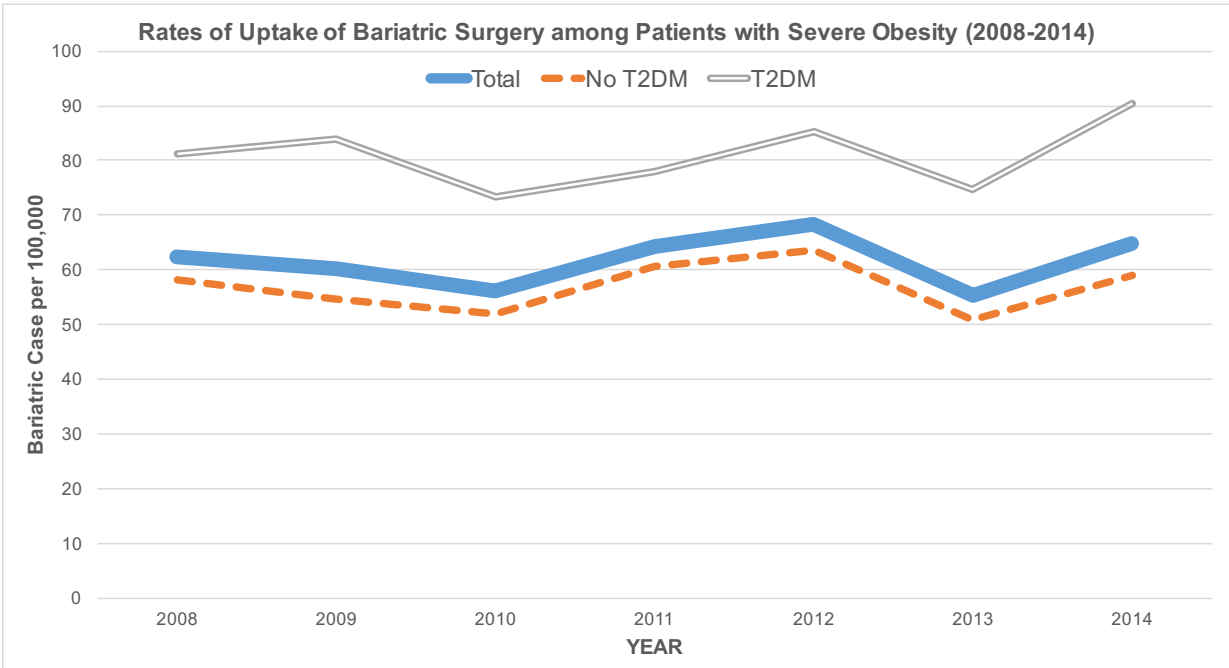
- 1: A private payer is assumed to be responsible for health care costs that only fall on their budget, which is equivalent to (1 – cost-sharing)*total costs.
- 2: High-risk patients represent severely obese patients with T2DM and BMI \geq 40.
- 3: In this table, we assume that the level of cost-sharing for the non-high risk obese patients stays same as the observed level of cost-sharing, 6%.
- 4: This represents the predicted uptake of bariatric surgery among the high-risk patients in response to changes in the level of cost-sharing. The rates of uptake for the non-high-value obese patients remains constant as the observed rates of uptake, 72.6 bariatric cases per 100,000 non-high risk obese patients.
- 5: This is the traditional way of estimating value of bariatric surgery, assuming that every one of the morbidly obese population receives the bariatric surgery.
- 6: This is the realized value of bariatric surgery under the different level of cost-sharing and the predicted uptake of bariatric surgery. Because only a small fraction of the target population would receive bariatric surgery, the realized value of bariatric surgery per patient is quite small.

Figure 1. Trends in Bariatric Procedures by BMI Groups and Diabetes



Abbreviation: BMI, body mass index; LRYGB, laparoscopic gastric bypass; LAGB, laparoscopic adjustable gastric banding; ORYGB, open gastric bypass; LSG, laparoscopic sleeve gastrectomy; T2DM, type 2 diabetes mellitus

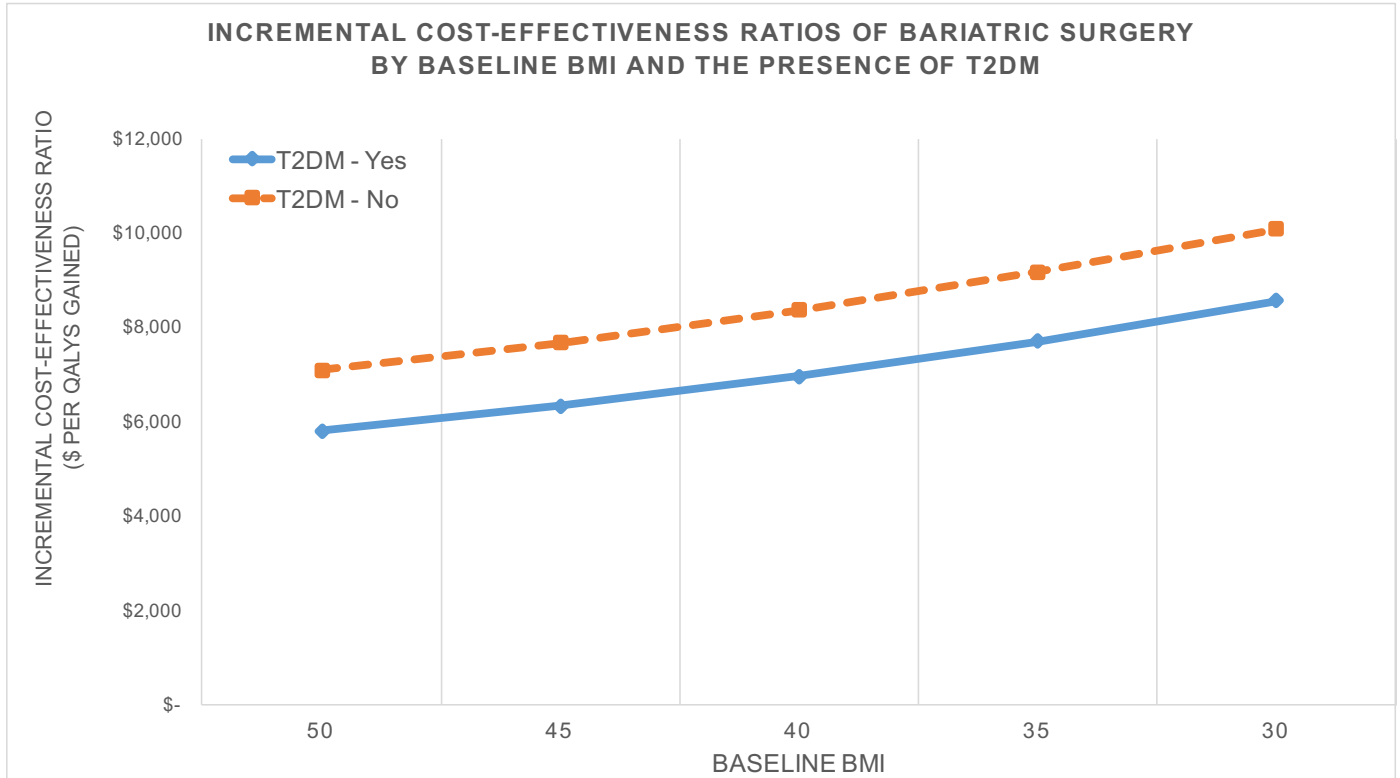
Figure 2. Rates of Uptake of Bariatric Surgery among Patients with Severe Obesity



Abbreviation: T2DM, type 2 diabetes mellitus

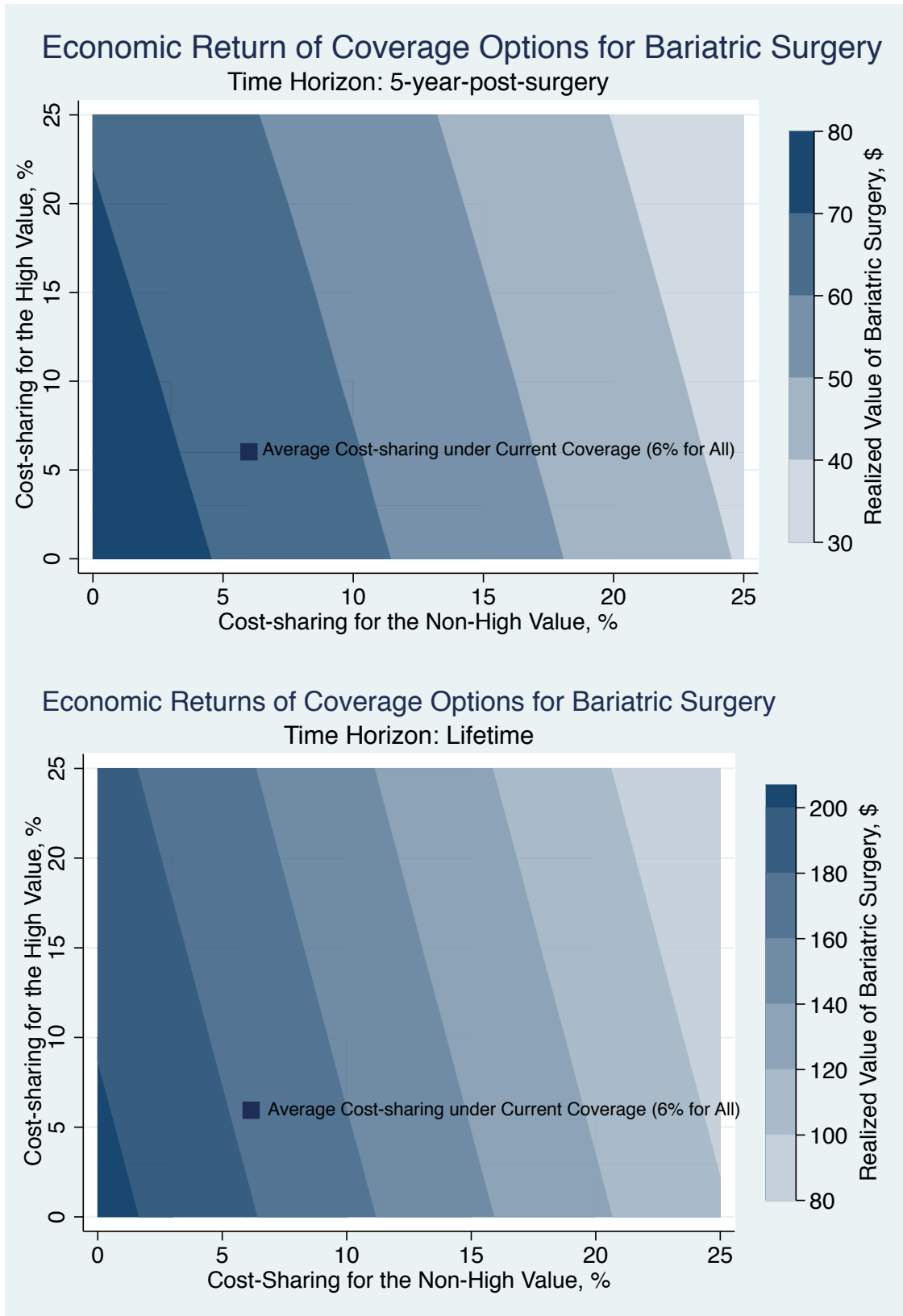
Figure 3. Cost-effectiveness Analysis Results by Clinical Subgroups

(Base case: lifetime cost-effectiveness of LRYGB for an age of 53 years old female patient, compared to non-surgical intervention)



Abbreviation: LRYGB, Laparoscopic Roux-en-Y gastric bypass; BMI, body mass index; T2DM, type 2 diabetes mellitus

Figure 4: Economic Returns of Various Coverage Options for Bariatric Surgery



APPENDICES

APPENDIX A: Estimation of Subgroup-specific Rates of Uptake of Bariatric Surgery

Part 1: Identification of individuals who received bariatric surgery Inclusion criteria:

Primary datasets: the Truven Health claims (Marketscan) inpatient admission databases from 2008 – 2014

Note: (*variable*) represents the variable name in the Marketscan datasets

- a. adult patients (age \geq 18)
 - b. Individual observation with enrollment ID (*enrolid*)
 - c. Primary diagnosis code (*pdx*) should be obesity (278.00) or morbidly obesity (278.01) using the ICD-9-DX diagnosis code.
2. The principal procedure code (*pproc*) contains one of the following bariatric procedures based on the ICD-9-CM procedure code
- (Note: we excluded the procedure codes associated with revisions):
- a. Open vertical banded gastroplasty: 44.68
 - b. Open adjustable gastric banding: 44.69
 - c. Open biliopancreatic diversion with a duodenal switch: 45.91, 43.89, 45.51
 - d. Open biliopancreatic diversion: 43.7
 - e. Open Roux-en-Y gastric bypass: 44.39
 - f. Laparoscopic Roux-en-Y gastric bypass: 44.38
 - g. Laparoscopic adjustable gastric banding: 44.95
 - h. Laparoscopic sleeve gastrectomy: 43.8
3. Using the following ICD-9 diagnosis code (*dx1-dx15*) to label individuals with T2DM
- a. '25000', '25002', '25010', '25012', '25020', '25022', '25030', '25032', '25040', '25042', '25050', '25052', '25060', '25062', '25070', '25072', '25080', '25082', '25090', '25092'

4. Using the following ICD-9 diagnosis code (*'dx1-dx15'*) to label individuals with obesity or morbid obesity or BMI groups.
 - a. Obesity: 278.00, V85.30-V.85.34
 - b. Morbidly obese: 278.01, V.85.35-V85.45
 - c. BMI 35-39: V85.35 – V85.39
 - d. BMI 40-44: V85.41
 - e. BMI 45-49: V85.42
 - f. BMI over 50: V85.43, V85.44, V85.45

5. Estimate the number of bariatric procedures by BMI / T2DM subgroups over time

Part 2: Estimate the number of individuals (i.e., prevalence) in each of those subgroups by BMI levels and the presence of T2DM

Primary datasets: Multiple National Health and Nutrition Examination Survey (NHANES) datasets (2007-2008, 2009-2010, 2011-2012, 2013-2014)

1. Merge demographic, body measurement, diabetes questionnaire datasets by individual ID (*'seqn'*)
2. Using the survey design and sample weights, estimate the number of individuals at the national level.

Part 3: Estimate subgroup-specific rates of uptake of bariatric procedures from 2008-2014

$$D_j = \frac{\sum_{i=1}^{N_j} I(D_i)}{N_j}$$

- D_j : subgroup-specific rates of uptake for bariatric surgery
- $\sum_{i=1}^{N_j} I(D_i)$: the total number of bariatric surgery cases in the specific subgroup
- N_j : the size of subgroup estimated from the NHANES datasets

APPEDIX B: Characteristics of the 2nd Generation BOOM Cost-effectiveness Simulation Model

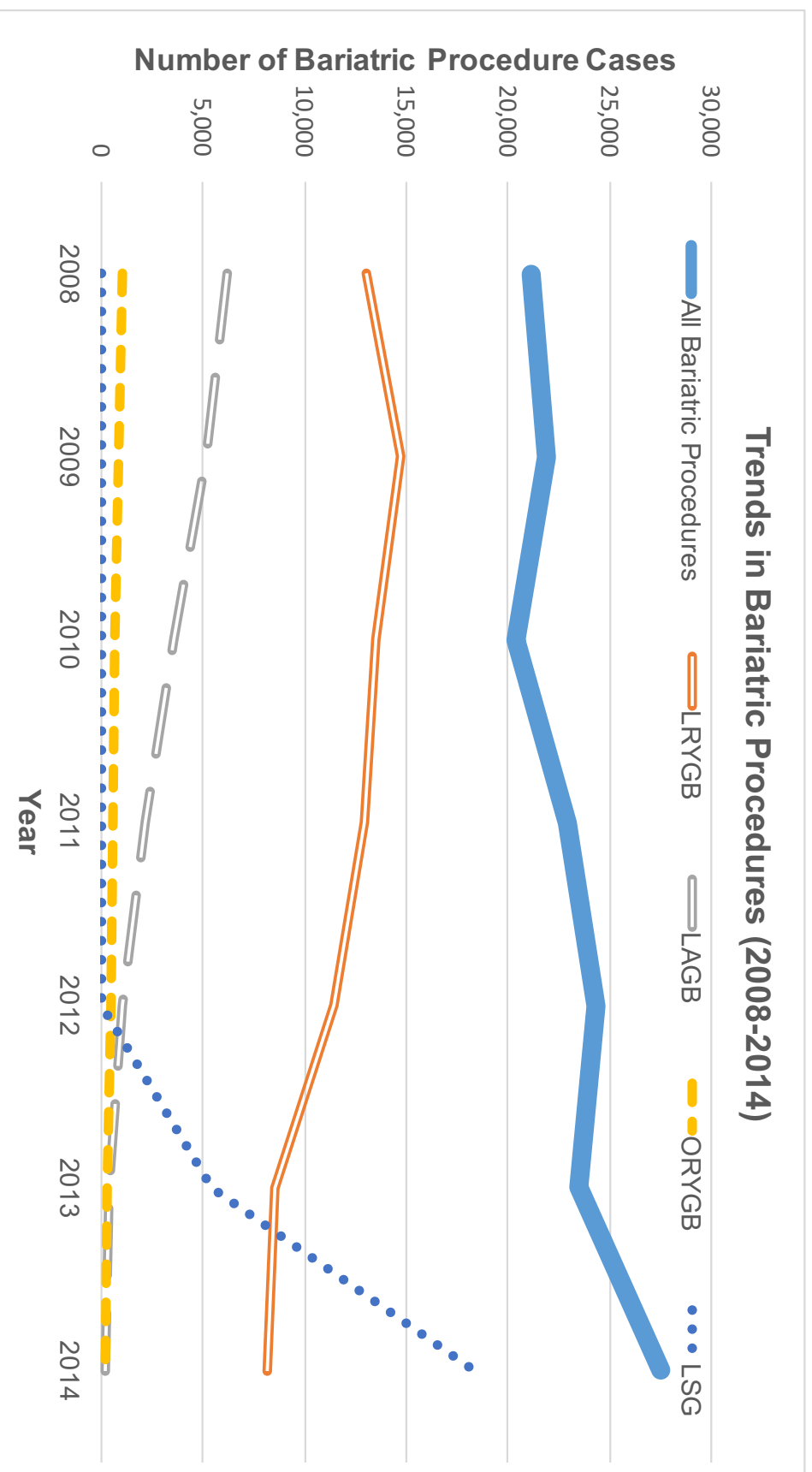
- **Comparators:**
 - Non-surgical care
 - Open Roux-en-Y gastric bypass (ORYGB)
 - Laparoscopic Roux-en-Y gastric bypass (LRYGB)
 - Laparoscopic Adjustable Gastric Banding (LAGB)
- **Target Population:**
 - Propensity-matched cohorts of patients from GHC:
 - a bariatric surgery cohort and a non-surgical cohort of patients eligible for bariatric surgery
 - The propensity score was calculated for every individual based on the following variables, identified in the previous chapter: gender, age and BMI at index, diabetes mellitus, hypertension, dyslipidemia, coronary heart disease, and a comorbid condition index (CCI)
- **Perspective:** Health care sector perspective
- **Discount Rates:** 3% on both costs and health outcomes.
- **Data Source:** Group Health cooperation (GHC) database and Medical Expenditure Panel Surveys (MEPS)
 - Utilities:
 - For the first 5 years within bariatric surgery, utility measures were derived from the systematic review by Picot et al (*Health Technol Assess.* 2009)
 - For the natural history model, utility measures were estimated using MEPS from 2000-2006, which provided self-reported health status of the general adult U.S. population as assessed by the EQ-5D.
 - Costs
 - Estimation of annual direct medical costs in the first 5 yrs post-surgery was conducted by GLM with a log link function and gamma distribution

- Unlike the original BOOM model that used the Medicare claims database to directly estimate rates, the revised BOOM model used the GHC data to be consistent with the rest of inputs and to estimate the direct medical costs
 - Adjusted by specific comorbidities: diabetes, hypertension, dyslipidemia, CHD, and a comorbidity index
 - For the natural history model, medical costs associated with changes in BMI were derived from MEPS datasets.
- **Time horizon:** First 5-year post-surgery and lifetime
 - A decision-analytic model for first 5 years after a bariatric procedure based on estimated direct medical costs and health outcomes associated with specific comorbidity conditions to simulate each surgical procedure and estimate changes in BMI, costs, and QALYs from the time of procedure to 5-year post-surgery, compared the impact of surgical procedures to non-surgical care
 - The annual changes in BMI associated with two of the three procedures from the GHC database were validated with the SR of literature by Picot et al.
 - Lifetime simulation model is based on extrapolation of natural history model to project BMI-dependent costs and health outcomes for the lifetime
 - Using longitudinal data from patients with BMI ≥ 35 enrolled in GHC, this sub-model predicts BMI changes over time given starting age, baseline BMI, and gender
 - Life expectancy was based on BMI, age, gender (no inclusion of comorbidities due to the lack of long-term information)
 - The National Health Interview Survey, linked to the National Death Index, was used to estimate the survival model
- **Study Design:** Probabilistic cohort-state transition model

Appendix C: Estimates of Population Size based on the 2008 – 2014 NHANES datasets

	Adult (Age ≥ 18) Population	Overall Prevalence	Subgroup-level Prevalence		
2008	222,807,580	Diabetes		Without Diabetes	With Diabetes
		0.0829	BMI_3034	0.1649	0.0233
			BMI_3539	0.0677	0.0143
		Obesity	BMI_4044	0.0264	0.0070
		0.3406	BMI_4549	0.0091	0.0032
		BMI_over50	0.0198	0.0043	
2009-2010	226,166,183	Diabetes		Without Diabetes	With Diabetes
		0.0824	BMI_3034	0.1751	0.0233
			BMI_3539	0.0748	0.0146
		Obesity	BMI_4044	0.0293	0.0086
		0.3591	BMI_4549	0.0131	0.0027
		BMI_over50	0.0131	0.0044	
2011-2012	231,919,832	Diabetes		Without Diabetes	With Diabetes
		0.0897	BMI_3034	0.1764	0.0230
			BMI_3539	0.0658	0.0140
		Obesity	BMI_4044	0.0258	0.0105
		0.353	BMI_4549	0.0121	0.0035
		BMI_over50	0.0170	0.0048	
2013-2014	237,548,244	Diabetes		Without Diabetes	With Diabetes
		0.0975	BMI_3034	0.1743	0.0275
			BMI_3539	0.0766	0.0154
		Obesity	BMI_4044	0.0345	0.0084
		0.3798	BMI_4549	0.0127	0.0048
		BMI_over50	0.0215	0.0043	

Appendix D: Trends in Bariatric Procedures from 2008 - 2014



Abbreviation: LRYGB, laparoscopic gastric bypass; LAGB, laparoscopic adjustable gastric banding; ORYGB, open gastric bypass; LSG, laparoscopic sleeve gastrectomy

Appendix E: Cost-effectiveness Analysis Results (3% discount rates for both costs and health outcomes)
 Time-horizon: First 5-years post-surgery

Baseline BMI	T2DM	Gender	Costs (\$)				QALYs				ICER (\$/QALY)			
			Non-Surgical	LAP RYGB	LAP BAND	OPEN RYGB	Non-Surgical	LAP RYGB	LAP BAND	OPEN RYGB	Non-Surgical	LAP RYGB	LAP BAND	OPEN RYGB
50	Yes	Male	38,955	57,556	53,736	72,943	3.18	4.35	4.25	4.34	-	15,908	13,778	29,336
		Female	41,790	58,546	54,594	74,246	3.09	4.19	4.09	4.18	-	15,243	12,768	29,809
	No	Male	29,552	51,434	48,103	65,286	3.18	4.35	4.25	4.34	-	18,715	17,293	30,843
		Female	32,317	52,501	49,062	66,672	3.09	4.19	4.09	4.18	-	18,362	16,698	31,553
45	Yes	Male	37,624	56,779	52,909	71,917	3.31	4.44	4.35	4.43	-	17,035	14,708	30,791
		Female	40,396	57,646	53,657	73,067	3.21	4.28	4.19	4.27	-	16,160	13,500	30,907
	No	Male	28,186	50,622	47,272	64,220	3.31	4.44	4.35	4.43	-	19,953	18,365	32,354
		Female	30,903	51,580	48,030	65,471	3.21	4.28	4.19	4.27	-	19,370	17,436	32,702
40	Yes	Male	36,262	56,111	52,183	71,029	3.44	4.53	4.45	4.52	-	18,333	15,784	32,432
		Female	38,984	56,857	52,736	72,029	3.33	4.37	4.29	4.35	-	17,235	14,281	32,188
	No	Male	26,794	49,906	46,450	63,277	3.44	4.53	4.45	4.52	-	21,346	19,486	34,031
		Female	29,473	50,756	47,198	64,395	3.33	4.37	4.29	4.35	-	20,523	18,406	34,015
35	Yes	Male	34,873	55,556	51,472	70,286	3.57	4.61	4.55	4.60	-	19,811	16,919	34,270
		Female	37,557	56,181	52,009	71,135	3.44	4.45	4.39	4.44	-	18,479	15,297	33,664
	No	Male	25,381	49,289	45,735	62,460	3.57	4.61	4.55	4.60	-	22,900	20,746	35,882
		Female	28,031	50,032	46,466	63,445	3.44	4.45	4.39	4.44	-	21,830	19,512	35,504
30	Yes	Male	33,462	55,119	51,056	69,692	3.69	4.70	4.65	4.69	-	21,482	18,401	36,322
		Female	36,117	55,623	51,488	70,390	3.56	4.54	4.49	4.53	-	19,907	16,568	35,352
	No	Male	23,949	48,773	45,213	61,772	3.69	4.70	4.65	4.69	-	24,623	22,239	37,919
		Female	26,578	49,411	45,845	62,626	3.56	4.54	4.49	4.53	-	23,301	20,767	37,182

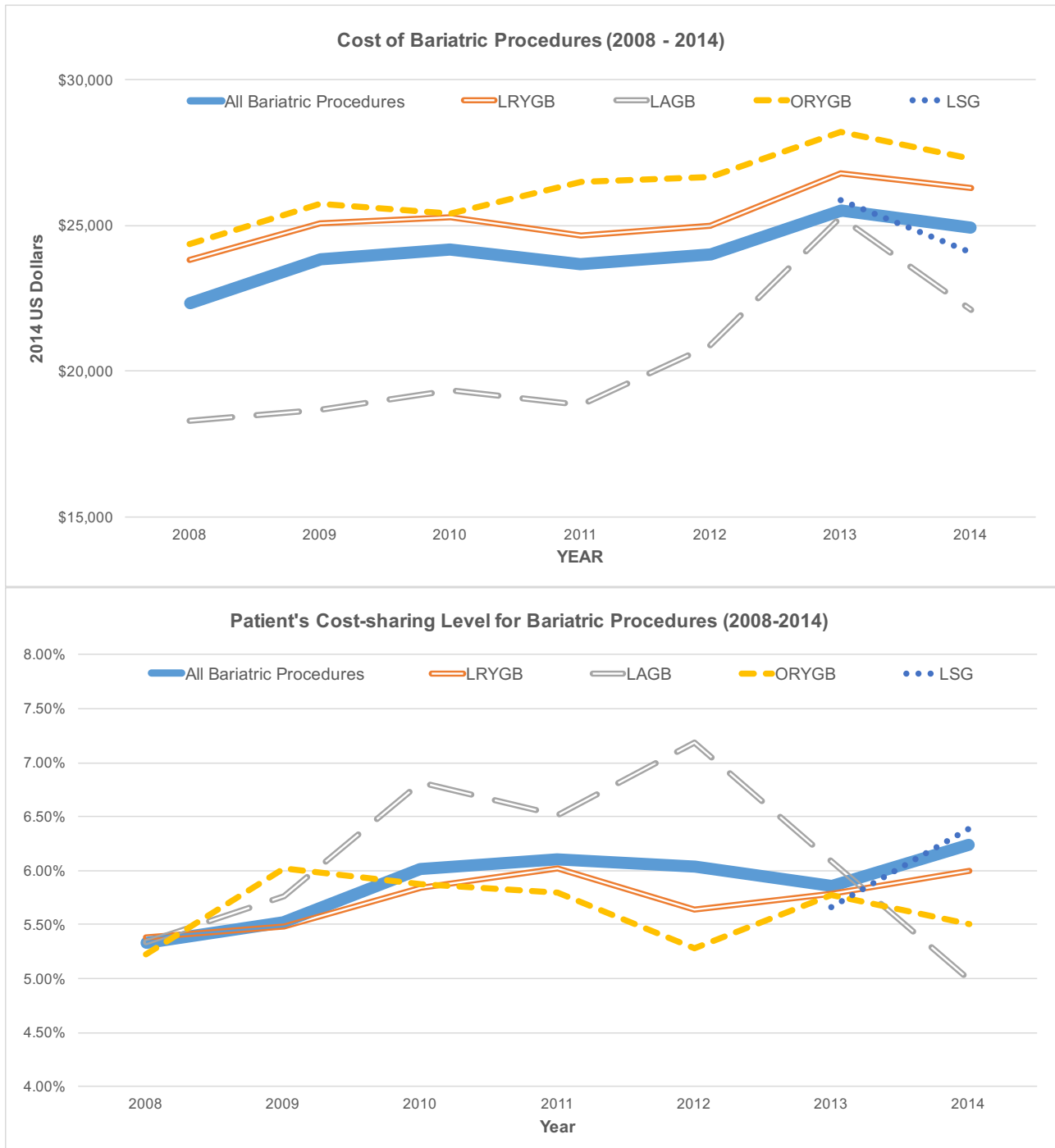
Abbreviation: LAP RYGB, laparoscopic gastric bypass; LAP BAND, laparoscopic adjustable gastric banding; OPEN RYGB, open gastric bypass; QALYs, quality-adjusted life years; ICER, incremental costs-effectiveness ratios (i.e., bariatric procedures vs. non-surgical interventions)

Time Horizon: Lifetime

Baseline BMI	T2DM	Gender	Costs (\$)				QALYs				ICER (\$/QALY)			
			Non-Surgical	LAP RYGB	LAP BAND	OPEN RYGB	Non-Surgical	LAP RYGB	LAP BAND	OPEN RYGB	Non-Surgical	LAP RYGB	LAP BAND	OPEN RYGB
50	Yes	Male	186,404	204,597	202,828	219,985	9.78	12.87	12.38	12.85	-	5,889	6,306	10,908
		Female	206,342	221,933	220,245	237,633	10.78	13.47	13.03	13.46	-	5,804	6,170	11,694
	No	Male	177,000	198,476	197,195	212,327	9.78	12.87	12.38	12.85	-	6,952	7,754	11,475
		Female	196,869	215,888	214,712	230,059	10.78	13.47	13.03	13.46	-	7,080	7,919	12,404
45	Yes	Male	182,836	201,641	199,655	216,779	10.44	13.36	12.92	13.35	-	6,439	6,759	11,664
		Female	202,443	218,647	216,719	234,068	11.34	13.90	13.52	13.89	-	6,333	6,570	12,411
	No	Male	173,398	195,484	194,017	209,082	10.44	13.36	12.92	13.35	-	7,562	8,286	12,263
		Female	192,950	212,581	211,091	226,472	11.34	13.90	13.52	13.89	-	7,673	8,349	13,155
40	Yes	Male	179,184	198,756	196,532	213,674	11.09	13.84	13.46	13.83	-	7,099	7,298	12,560
		Female	198,495	215,449	213,178	230,621	11.90	14.34	14.00	14.33	-	6,963	7,005	13,250
	No	Male	169,717	192,551	190,800	205,922	11.09	13.84	13.46	13.83	-	8,283	8,869	13,184
		Female	188,984	209,348	207,640	222,986	11.90	14.34	14.00	14.33	-	8,363	8,900	14,024
35	Yes	Male	175,457	195,948	193,380	210,678	11.73	14.32	14.00	14.31	-	7,882	7,887	13,604
		Female	194,501	212,341	209,804	227,295	12.45	14.77	14.47	14.76	-	7,703	7,562	14,223
	No	Male	165,965	189,680	187,643	202,851	11.73	14.32	14.00	14.31	-	9,123	9,539	14,248
		Female	184,975	206,192	204,261	219,605	12.45	14.77	14.47	14.76	-	9,161	9,530	15,020
30	Yes	Male	171,663	193,224	190,481	207,797	12.35	14.80	14.53	14.79	-	8,800	8,652	14,812
		Female	190,466	209,330	206,609	224,097	12.99	15.19	14.94	15.18	-	8,565	8,253	15,343
	No	Male	162,151	186,878	184,638	199,877	12.35	14.80	14.53	14.79	-	10,092	10,339	15,465
		Female	180,928	203,118	200,966	216,333	12.99	15.19	14.94	15.18	-	10,076	10,245	16,152

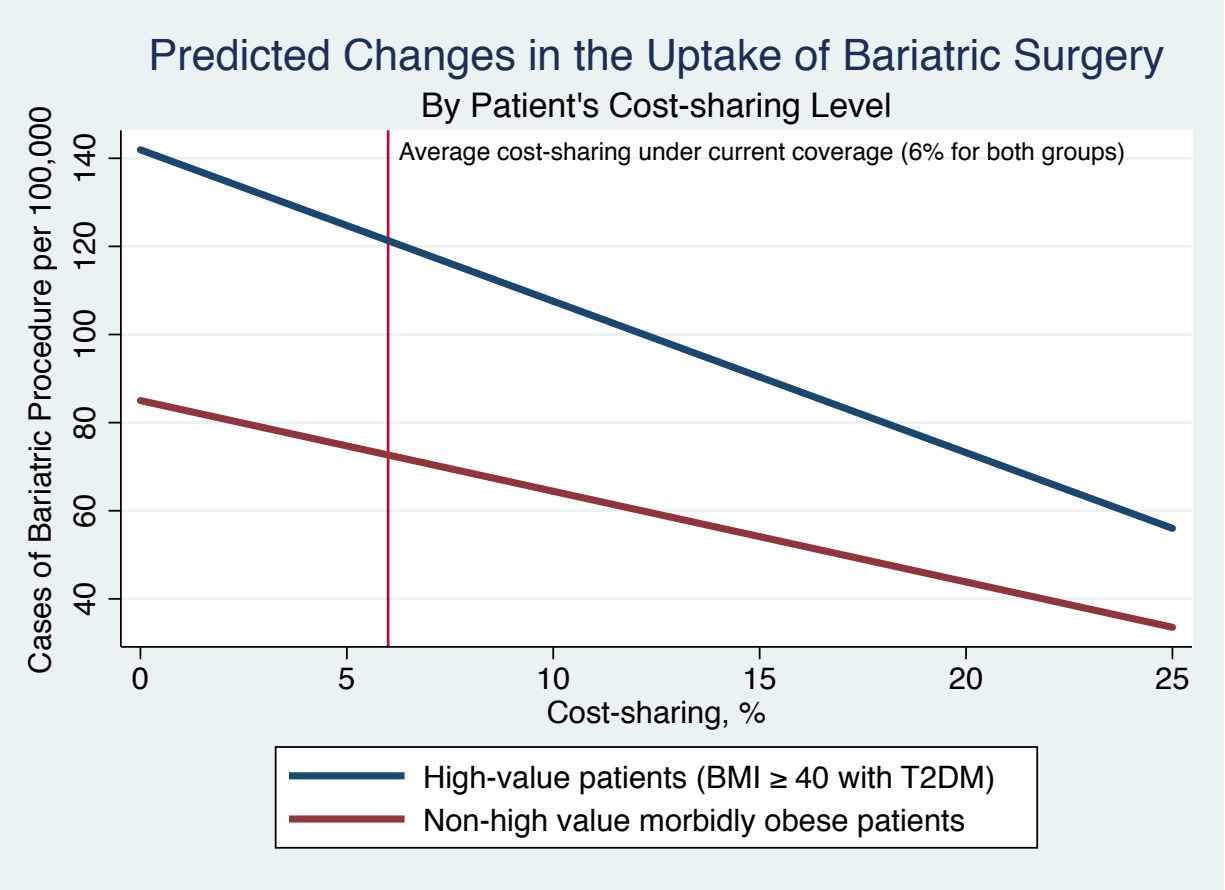
Abbreviation: LAP RYGB, laparoscopic gastric bypass; LAP BAND, laparoscopic adjustable gastric banding; OPEN RYGB, open gastric bypass; QALYs, quality-adjusted life years; ICER, incremental costs-effectiveness ratios (i.e., bariatric procedures vs. non-surgical interventions)

Appendix F: Changes in Total Costs and the Level of Patient's Cost-Sharing for Bariatric Procedures (2008-2014)



Abbreviation: LRYGB, laparoscopic gastric bypass; LAGB, laparoscopic adjustable gastric banding; ORYGB, open gastric bypass; LSG, laparoscopic sleeve gastrectomy

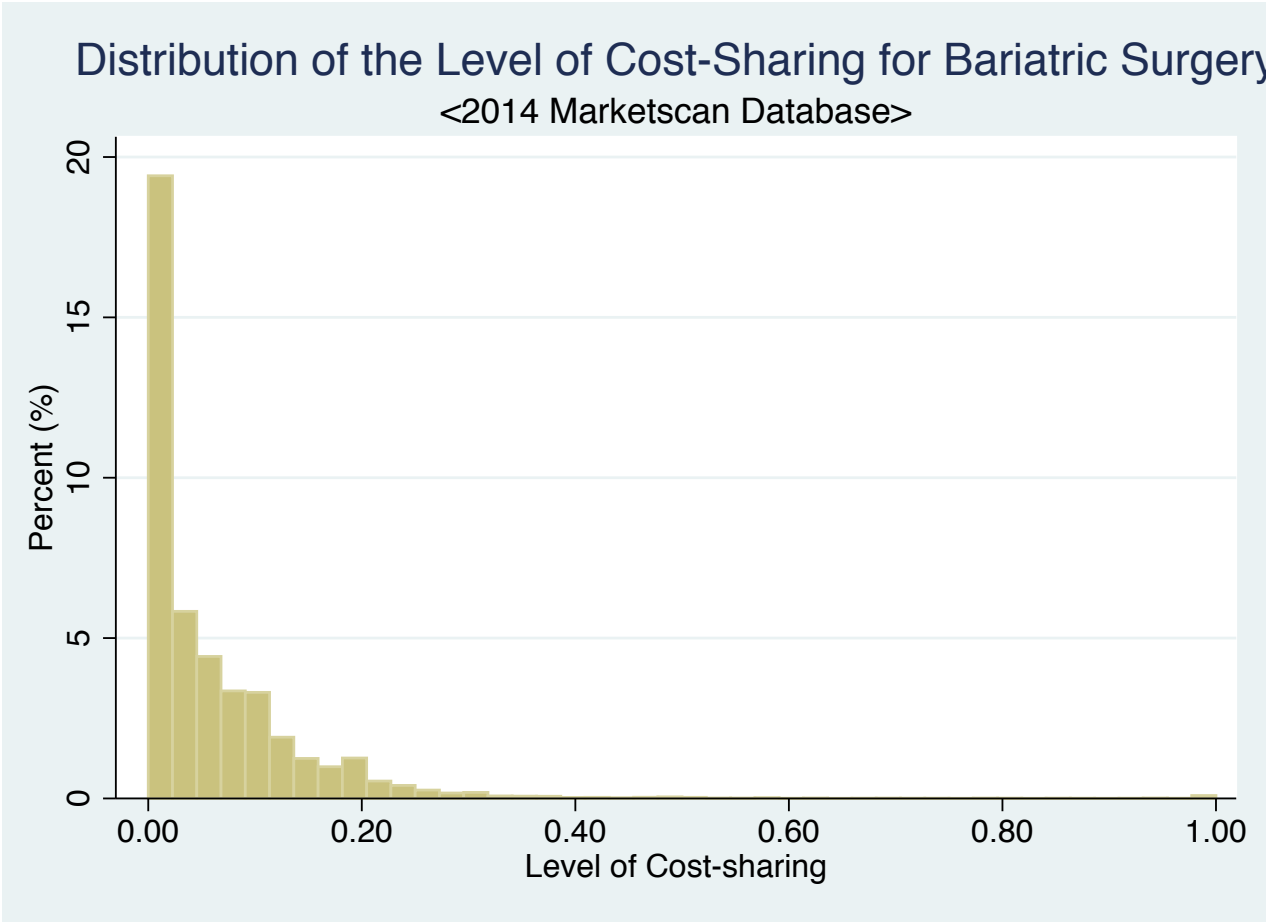
Appendix G: Predicted Changes in the Uptake of Bariatric Surgery in Responses to Changes in Cost-Sharing Level



Abbreviation: BMI, body mass index; T2DM, type 2 diabetes mellitus

Note: We used -0.17 as a price elasticity of demand for health care. This estimates was derived from the RAND Health Insurance Experiment for coinsurance rates between 0 and 25 percent. The baseline uptake was based on the average cost-sharing level in 2014 (6%)

Appendix H: Distribution of Cost-Sharing among the Bariatric Surgery Recipients in 2014



Note: Mean: 0.0624; Standard Deviation: 0.098; 25 percentiles: 0; 50 percentiles: 0.032; 75 percentiles: 0.091

CHAPTER 5: CONCLUSION

Current decision-making in health policy often involves evaluation of alternative technologies in terms of benefits and costs.¹ Appropriate economic evaluation, such as Cost-effectiveness analysis (CEA) seeks to improve efficiency through allocating scarce resources to achieve maximum social welfare.^{2,3} However, most economic evaluation studies are based on “what works” on average, yet fail to capture the scope of translation of a medical technology into practice.^{4,6} In practice, as average treatment effects dictate reimbursement decision, and insurance coverage is one of the main determinants of receiving treatment, the current practice of “one-size-fits-all policy” may lead to inefficient use of medical resources by ignoring evidence on individual heterogeneous treatment effect.⁷ Thus, without incorporating how individuals respond to heterogeneity in treatment effect in practice (i.e., technology uptake), current methods in economic evaluation may not precisely estimate the realized value of medical technology. In this dissertation, we presented a new framework and metrics that can be used to evaluate realized value of medical technology in the presence of heterogeneity in treatment effects with its application to the evaluation of bariatric surgery.

SUMMARY

Chapter 2 provided a new economic evaluation framework and appropriate metrics that focused on evaluating the realized value of medical technology through policy alternatives. This framework is highlighted by 1) incorporating subgroup-specific estimates of selective uptake driven by heterogeneity in clinical and economic evidence and 2) evaluating policy options that potentially affect the uptake of new technology. It is important to acknowledge that these factors can inherently change the realized value of medical technology, and therefore, from an

evaluation perspective, these metric would better represent the marginal value of a policy decision in the context of evaluating the medical technology.

Chapter 3 examined how major clinical evidence is associated with increasing utilization of bariatric surgery, considering significant underutilization of bariatric surgery with strong supportive evidence on clinical effectiveness. We found that the publication of major clinical evidence is associated with increasing utilization of bariatric surgery among patients with severe obesity and diabetes enrolled in the Group Health Cooperative located in Seattle, WA. This finding suggests that positive clinical evidence can be tied to increase in utilization, but further research is necessary to assess whether this association is causal and generalizable.

Chapter 4 estimated economic returns of providing greater access to bariatric surgery, especially targeted for the high-value population, defined as patients with body mass index ≥ 40 and diabetes. We found that reducing patient's cost-sharing would potentially lead to improving the utilization of the cost-effective intervention and resulting in a greater value to payers. Also, because of ignoring the actual utilization of medical technology, we noticed that the traditional framework of evaluating the economic value of medical intervention could be misleading when determining the optimal coverage.

IMPLICATIONS

The new framework for policy evaluation can directly inform decision-makers about the optimal level of insurance coverage and investment in implementation by choosing a policy that would produce the largest economic returns in the context of a new treatment. For example, this framework could help decision-makers to understand the realized value of intervention under current coverage policy and design optimal policies to incentivize patient subgroups who are likely to benefit the most. Also, one could also evaluate a policy option that improves the uptake

of medical technology (e.g., bariatric surgery) through educating patients about the potential value of the technology. By comparing the potential realized value of medical technology under the education program with implementation costs, the framework could be useful to determine whether the investment would be deserving.

However, one of the main limitations of this approach is that the novel framework requires rich information, such as heterogeneous in treatment effects, subgroup-specific costs and benefits of technology under consideration, subgroup-level rates of uptake at the baseline to predict behavioral changes in each group. Although these types of information are often not readily available, patient-centered outcome researches, comparative effectiveness studies, and cost-effectiveness studies are moving toward to report subgroup-level or patient-level results that would help more precisely to estimate the realized value of policy decisions. Also, this new framework could drive investments in subgroup analyses by funders of research.

Despite some limitations, we believe that this framework could help decision-makers to understand the realized value of intervention under policy alternatives and to improve the decision-making process by producing metrics that are better aligned with the specific policy decisions.

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