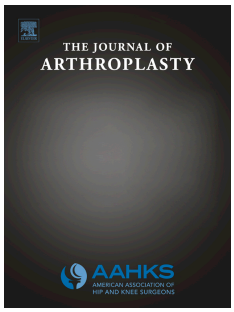


# Preoperative vitamin D repletion in total knee arthroplasty: a cost-effectiveness model

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# Preoperative vitamin D repletion in total knee arthroplasty: a cost-effectiveness model

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Conflicts of interest: none

# Preoperative vitamin D repletion in total knee arthroplasty: a cost-effectiveness model

## ABSTRACT

**BACKGROUND:** Recent studies have identified vitamin D deficiency (serum 25-hydroxyvitamin D {25(OH)D} <20 ng/l) as a potentially modifiable risk factor for prosthetic joint infection (PJI) in arthroplasty. The purpose of this study was to determine whether implementation of preoperative 25(OH)D repletion is cost effective for reducing PJI following total knee arthroplasty (TKA).

**METHODS:** A cost estimation predictive model was generated to determine the utility of both selective and non-selective 25(OH)D repletion in primary TKA to prevent PJI. Input data on the incidence of 25(OH)D deficiency, relative complication rates, and costs of serum 25(OH)D repletion and two-stage revision for PJI were derived from previously published literature identified using systematic review and publicly available data from Medicare reimbursement schedules. Mean, lower, and upper bounds of one-year cost savings were computed for non-selective and selective repletion relative to no repletion.

**RESULTS:** Selective preoperative 25(OH)D screening and repletion was projected to result in $1,504,857 (range: $215,084-$4,256,388) in cost savings per 10,000 cases. Non-selective 25(OH)D repletion was projected to result in $1,906,077 (range: $616,304-$4,657,608) in cost savings per 10,000 cases. With univariate adjustment, non-selective repletion is projected to be cost-effective in scenarios where revision for PJI costs ≥$10,636, incidence of deficiency is ≥1.1%, and when repletion has a relative risk reduction ≥4.2%.

**CONCLUSIONS:** This predictive model supports the potential role of 25(OH)D repletion as a cost-effective mechanism of reducing PJI risk in TKA. Given the low cost of 25(OH)D repletion relative to serum laboratory testing, non-selective repletion appears to be more cost-effective than selective repletion. Further prospective investigation to assess this modifiable risk factor is warranted.

**KEYWORDS:** vitamin D; periprosthetic joint infection; arthroplasty; metabolism; cost-effectiveness

## INTRODUCTION

Total knee arthroplasty (TKA) volume in the United States has increased substantially in recent years and this trend is expected to continue over the coming decades.[1] In concordance with this volume growth, there is an expected rise in the number of devastating and costly complications such as prosthetic joint infection (PJI). While certain risk factors are relatively immutable, there is considerable interest in identifying modifiable, patient-specific risk factors related to general health, nutritional, and endocrine status that may be addressed to decrease complication rates in TKA.[2]

One such proposed modifiable risk factor that has gained recent attention is vitamin D deficiency (serum 25(OH)D < 20ng/ml).[3–5] In the larger scientific literature, vitamin D and its metabolites have known key roles in musculoskeletal health and metabolic processes.[6] More recent mechanistic and animal models have clearly elucidated the role of vitamin D receptor (VDR) signaling pathways in both innate and adaptive immunity.[6–9] In arthroplasty, the appeal of vitamin D as a modifiable perioperative risk factor is attributable to the fact that inadequacy or deficiency is relatively common and that repletion is quick, reliable, and inexpensive.[10–12] Indeed, the incidence of 25(OH)D deficiency ranges from anywhere to 10-80% among patients undergoing primary hip and knee arthroplasty, suggesting a large potential target population.[3,13–15] Furthermore, oral repletion of 25(OH)D to normal can be performed in standardized protocols ranging from one to eight weeks with few risks and high reliability.[16] In practice, evidence demonstrating worse clinical outcomes in arthroplasty patients with vitamin D deficiency has begun to emerge, including documented increases in hospital length of

stay[17], higher perioperative complication rates[3,18], and worse functional and pain outcome scores[19–21]. Importantly, Hegde et al. recently demonstrated a two-fold increase in PJI risk within one year among 25(OH)D-deficient patients (<20 ng/mL).[22] Thus, perioperative 25(OH)D repletion could potentially have tremendous impact on curtailing a costly and devastating consequence after TKA.

The purpose of this study was to determine whether implementation of preoperative 25(OH)D repletion, either selectively, in deficient patients, or non-selectively, in all patients, is cost effective for reducing PJI following TKA. Toward this end, we developed a cost-effectiveness model using published literature values for perioperative cost and incidence data obtained from systematic review and public use sources. Using this model, we also sought to determine critical values for the incidence of serum 25(OH)D deficiency and the cost of two-stage revision for PJI above which supplementation would result in population-level cost savings. Given that 25(OH)D deficiency is relatively common and that repletion is inexpensive, our initial hypothesis was that preoperative repletion would be cost-effective for PJI prevention using currently available epidemiologic and cost data.

## METHODS

To determine cost-effectiveness of serum 25(OH)D repletion in preventing PJI, a stochastic two-state decision tree analysis model was performed with three approaches to preoperative treatment of patients prior to TKA with respect to serum 25(OH)D status: (1) no 25(OH)D repletion, (2) selective 25(OH)D repletion, and (3) non-selective 25(OH)D repletion (Figure 1).[23] Vitamin D deficiency was defined in this study as a serum 25(OH)D <20 ng/mL according to both the Institute of Medicine and Endocrine Society guidelines.[24] Selective repletion was defined as a treatment algorithm wherein preoperative laboratory screening is used to determine serum 25(OH)D levels to identify deficient patients. Here, repletion of 25(OH)D levels to normal (>30 ng/ml) with oral vitamin $D_3$ is performed only for those patients who were deficient; post-repletion confirmatory serum 25(OH)D testing is not performed in this algorithm. Non-selective repletion was defined as treatment of all patients, deficient or sufficient, with vitamin $D_3$ preoperatively without pre- or post-repletion screening for serum 25(OH)D levels.

Using input cost and epidemiological values, simulated cost differences were computed relative to a scenario where no preoperative serum 25(OH)D screening or repletion is performed. Statistical event was defined as PJI requiring two-stage revision arthroplasty within one year. Given that PJI is an uncommon complication following primary TKA, the stochastic model was simulated over 10,000 cases for estimation of population-level cost savings for repletion scenarios. Mean, lower, and upper bounds of one-year cost savings were computed for non-selective and selective repletion relative to the comparison no repletion scenario. Holding other variables constant, the model was also used to compute inflection point for (1) the cost of two-

92 stage revision TKA, (2) the population incidence of 25(OH)D deficiency, and (3) the relative risk
93 reduction above which either selective or non-selective 25(OH)D repletion would result in
94 population cost savings,. All statistical analysis was performed with R version 3.5.0 (2018, R
95 Foundation for Statistical Computing).
96
97 *Model input data*
98 Using PRISMA guidelines, a systematic review of the literature was performed September 2018
99 to determine the published incidence of vitamin D deficiency among TKA patients, as well as the
100 incidence of PJI following TKA in vitamin D deficient (25D <20 ng/mL) and non-deficient (25D
101 ≥20 ng/mL) patients. The following key words were used for the search: “vitamin D”,
102 “cholecalciferol”, “arthroplasty”, “knee”. After manual review, four studies were identified that
103 reported the incidence of serum 25(OH)D deficiency in patients undergoing TKA. Only one of
104 these studies reported the incidence of PJI in serum 25(OH)D deficient and non-deficient
105 patients[22]; probability data was collected from this study for inclusion in the model. Using
106 PRISMA guidelines, a second systematic review of the literature was performed September 2018
107 to determine the costs of primary and two-stage revision TKA for PJI using the key words:
108 “costs”, “arthroplasty”, “knee”, “revision”, “prosthetic joint infection”, “periprosthetic joint
109 infection”. After manual review, only one study reported the one-year hospital costs of both
110 primary and revision TKA for PJI[25]; mean and range cost data was collected from this study
111 for inclusion in the model. The cost of single serum 25(OH)D assay ($55.72) was determined
112 from published reimbursement schedules provided by the Centers for Medicare and Medicaid
113 Services.[26] The repletion method used in this model was 50,000 IU vitamin D/week for a total
114 of 8 weeks as recommended by the Endocrine Society to achieve repletion (>30 ng/mL).[24]

Based on the average cost from 20 pharmacies in the United States ($17.97), the cost of 8-week repletion was estimated. All costs were adjusted to 2018 U.S. dollars ($) using inflation rates derived from the Consumer Price Index provided by the U.S. Bureau of Labor Statistics.

*Model assumptions*

Stochastic decision tree models have based Markovian and node point assumptions.[27] The present model has three such primary assumptions that are not derived from the constituent input data: (1) that the described pharmacologic serum 25(OH)D repletion protocol brings the infection rate of 25(OH)D-deficient patients to that of those who are replete at baseline, (2) that non-selective 25(OH)D repletion has no effect on PJI risk patients who are replete at baseline, and (3) that cost differences for uncomplicated TKA and two-stage revision for PJI are hospital-based only and are comparable after one year.

## RESULTS

Model input data derived from systematic review and public use data is summarized in Table 1. Using these risk adjustment data, selective preoperative serum 25(OH)D screening and repletion was projected to result in $1,504,857 (range: $215,084-$4,256,388) in cost savings per 10,000 primary TKA cases relative to the no repletion scenario. Similarly, non-selective serum 25(OH)D repletion was projected to result in $1,906,077 (range: $616,304-$4,657,608) in cost savings per 10,000 cases relative to the no repletion scenario.

Using mean values as model input data, inflection point cutoffs for the cost of two-stage revision and the incidence of 25(OH)D deficiency were computed (Table 2). At a population level, selective 25(OH)D repletion is expected to be cost-effective (e.g. cost saving) when the cost of two-stage revision arthroplasty for treatment of PJI is greater than $34,382 (Figure 2). Conversely, non-selective 25(OH)D repletion in primary TKA is expected to be cost-effective when the cost of two-stage revision arthroplasty exceeds $10,636. Holding other variables constant with mean estimates, selective 25(OH)D repletion is expected to be cost-effective when the incidence of 25(OH)D deficiency among TKA patients exceeds 3.7%, while non-selective repletion is expected to be cost-effective when deficiency incidence exceeds 1.1%. Univariate adjustment also demonstrated that non-selective 25(OH)D repletion would be cost effective when the relative risk reduction exceeds 4.2% (absolute risk reduction 0.10%); selective 25(OH)D repletion would be similarly cost effective when risk reduction exceeds 13.1% (absolute risk reduction 0.32%). These differences between repletion algorithms are due to the fact that cost of serum 25(OH)D assay exceeds cost of treatment.

## DISCUSSION

Because of its relatively high incidence in the arthroplasty population and ease of preoperative diagnosis and/or treatment, vitamin D deficiency has great potential as a modifiable risk factor in arthroplasty. Multiple authors have demonstrated that vitamin D deficiency (serum 25(OH)D <20 ng/ml) is associated with worse functional outcomes following TKA.[3,20] Others have demonstrated that persistent 25(OH)D deficiency results in higher rates of postoperative stiffness and longer hospital stays among arthroplasty patients.[19,20,22] However due to its significant morbidity, cost, and impact on quality of life, PJI is one of the most devastating TKA complications and warrants special consideration for risk modification. Studies on the role of vitamin D balance on PJI have been limited. In the systematic review conducted in this study, two clinical studies describing PJI risk in 25(OH)D-deficient patients were identified. Traven et al. found that 90-day PJI rates were significantly higher among patients undergoing revision hip and knee arthroplasty.[18] While risk modification in revision arthroplasty merits recognition and conclusions derived from this study may be indirectly extrapolated and applicable, primary arthroplasty is of greater population-level concern given expected trends. Hegde et al., whose data was used in our cost-effectiveness model, demonstrated significantly increased risk-adjusted rates of PJI within one year among patients undergoing primary TKA.[22] That both selective and non-selective serum 25(OH)D repletion is projected to result in significant population-level cost savings provides additional justification in concrete financial terms for prospective study.

The present simplified model suggests that non-selective repletion of serum 25(OH)D (25(OH)D ≥ 30 ng/ml in all TKA patients appears to be more cost-effective than selective screening and

treatment of 25(OH)D-deficient patients. Indeed, this is due to the low cost of serum 25(OH)D repletion relative to the cost of serum 25(OH)D assay. We note that this preferability of non-selective repletion is purely reflective of cost and does not consider the potential risks associated with non-selective vitamin D repletion, as was an assumption in our stochastic model. Vitamin D repletion is generally safe, with an 8-week course of 50,000 IU/week having very few reported complications; even higher doses have been reported to be safely used for repletion.[11,24] Indeed, vitamin D toxicity which occurs almost exclusively from long-term excess dietary intake, is rare and presents clinically with dehydration, fatigue, gastrointestinal symptoms, muscle weakness, and metastatic soft tissue calcification.[11] Nevertheless, selective screening and repletion may be more practical clinically and more amenable to research design and institutional board review. As an example, in the Vitamin D and Arthroplasty Surgery Outcomes (VASO) randomized controlled trial underway in the United Kingdom, selective repletion in 25(OH)D-deficient patients is being performed, rather than non-selective treatment of all patients.[28]

The projected cost savings from the present study represent a middling estimate based on presently available and limited incidence and cost data identified by our study design. In our review, the incidence of serum 25(OH)D deficiency among arthroplasty patients and the cost of revision arthroplasty for PJI are the two most elusive data points. Our secondary analysis found that serum 25(OH)D repletion would result in cost savings for arthroplasty populations where deficiency rates exceed 1.1% and 3.7% for non-selective and selective repletion respectively. From our review, the incidence of 25(OH)D deficiency ranges from 9.5%-81% in the arthroplasty population, significantly above these cost inflection points.[3,15,29] While

speculative, we surmise that this wide range likely reflects global epidemiologic differences based on geographic location and demographics leading to differences in sun exposure, dietary supplementation, and genetic predisposition.[30] In the United States, Unnanuntana and colleagues reported a 9.5% prevalence of 25D deficiency in a cohort of 200 patients undergoing total hip arthroplasty[31], while Lavernia et al. reported a 30% prevalence.[14] In the United Kingdom, Jansen and Haddad found a 24% prevalence of vitamin D deficiency among arthroplasty patients.[3] Even higher rates were reported from other European nations such as Finland (36%), Greece (81%), and Germany (64%).[15,29,32] As such, our study suggests that the utility and cost savings of preoperative 25D repletion in reducing PJI would be greater in regions where vitamin D deficiency is endemic.

Similarly, this model estimated that non-selective and selective vitamin $D_3$ supplementation would be cost efficient when the cost of two-stage revision for PJI is greater than $10,636 and $34,382, respectively. While accurate cost data remains elusive and highly variable in the orthopedic literature, these figures strongly favor the widespread implantation of vitamin D supplementation to raise serum 25(OH)D levels into the range of normal. From the case series' data used in this model, the lowest in-hospital cost of two-stage revision for PJI was $44,000.[25] As a surrogate, costs associated with even primary TKA, which is less costly than revision TKA from an in-hospital and implant related standpoint, are significantly above the threshold for non-selective repletion.[25,33] Furthermore, considering the high out-of-hospital costs of care associated with treating PJI (e.g. intravenous antibiotic therapy, laboratory monitoring, outpatient follow-up), the true cost savings are likely greater than the estimates provided here.[34]

Perhaps more importantly, univariate adjustment also found that 25(OH)D repletion would be cost effective with relative risk reductions that exceed 4.2% and 13.1% for non-selective and selective repletion, respectively. Given the low incidence of PJI in general, these correspond to very small reductions in absolute risk (0.1-0.3% as found in this study) that would be necessary to achieve cost savings. Though this is perhaps the most evasive data point in the literature[22], these findings that show significant cost savings from very modest reductions in PJI risk with 25(OH)D repletion are a strong justification for further research on this modifiable risk factor. These baseline values may be helpful in contextualizing the usefulness and implementation of preoperative 25(OH)D repletion as results from prospective trials emerge.

It is also important to note that 25(OH)D repletion may have other cost and quality of life benefits independent of PJI risk that were not included in this model. 25D deficiency has been associated with postoperative stiffness requiring manipulation under anesthesia, documented range of motion deficits, prolonged hospital stay, and worse postoperative pain reported outcomes.[3,18,20–22,35] Due to limited quality data on incidence and costs associated with these differences, our study could not incorporate these variables into the cost savings model. However, as literature documenting these differences continues to emerge, attention to these other outcome disparities among 25(OH)D-deficient and -sufficient arthroplasty patients is warranted.

This study provides relevant data on the cost utility of vitamin $D_3$ supplementation but has limitations that merit discussion. Firstly, such decision tree models have intrinsic assumptions that were previously delineated. The assumption that pharmacologic 25(OH)D repletion in

25(OH)D-deficient patients brings PJI risk to baseline levels for patients who are serum 25(OH)D-replete is a fundamental basis of the conclusions and estimates presented here. For other musculoskeletal and metabolic conditions, serum 25(OH)D repletion is effective in reversing the health effects associated with 25(OH)D deficiency.[24] However, no clinical study has explicitly proven this among arthroplasty patients and indeed such a prospective study is justified in part by the potential cost savings elucidated here. There is preclinical evidence to support the role of 25(OH)D supplementation in PJI risk reduction.[12] Secondly, the reliability of the computed cost savings data presented here is dependent on the incidence and cost data input into the model. Input data on the incidence of 25(OH)D deficiency, relative PJI risk among 25(OH)D-deficient and non-deficient patients, and costs of primary and revision TKA were elusive from our systematic review and necessarily derived from multiple sources. Thirdly and for these same reasons, the present study provides analysis from a cost perspective only and provides no data on quality of life benefits that may be associated with reduced PJI risks. As such, it is likely that the argument for serum 25(OH)D repletion in arthroplasty would be strengthened when quality of life conditions measures associated with PJI are considered.[36]

In conclusion, this predictive model supports the potential role of preoperative restoration of serum 25(OH)D levels to normal as a cost-effective mechanism of reducing the risk of PJI in TKA. Given the low cost of vitamin $D_3$ repletion treatment relative to serum 25(OH)D laboratory testing, non-selective screening appears to be more cost-effective than selective screening. The cost savings are projected to be greater in populations where the incidence of 25(OH)D deficiency is higher and the cost associated with revision TKA is higher. Further investigation with a prospective clinical trial to assess this modifiable risk factor is warranted.

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## FIGURE AND TABLE LEGENDS

**TABLE 1:** Incidence and cost data input into the stochastic decision tree model

**TABLE 2:** Stochastic model inflection points with univariate adjustment

**FIGURE 1:** Flow chart of cost estimation predictive model

**FIGURE 2:** Projected cost savings (per 10,000 primary TKA) relative to cost of two-stage revision TKA for PJI

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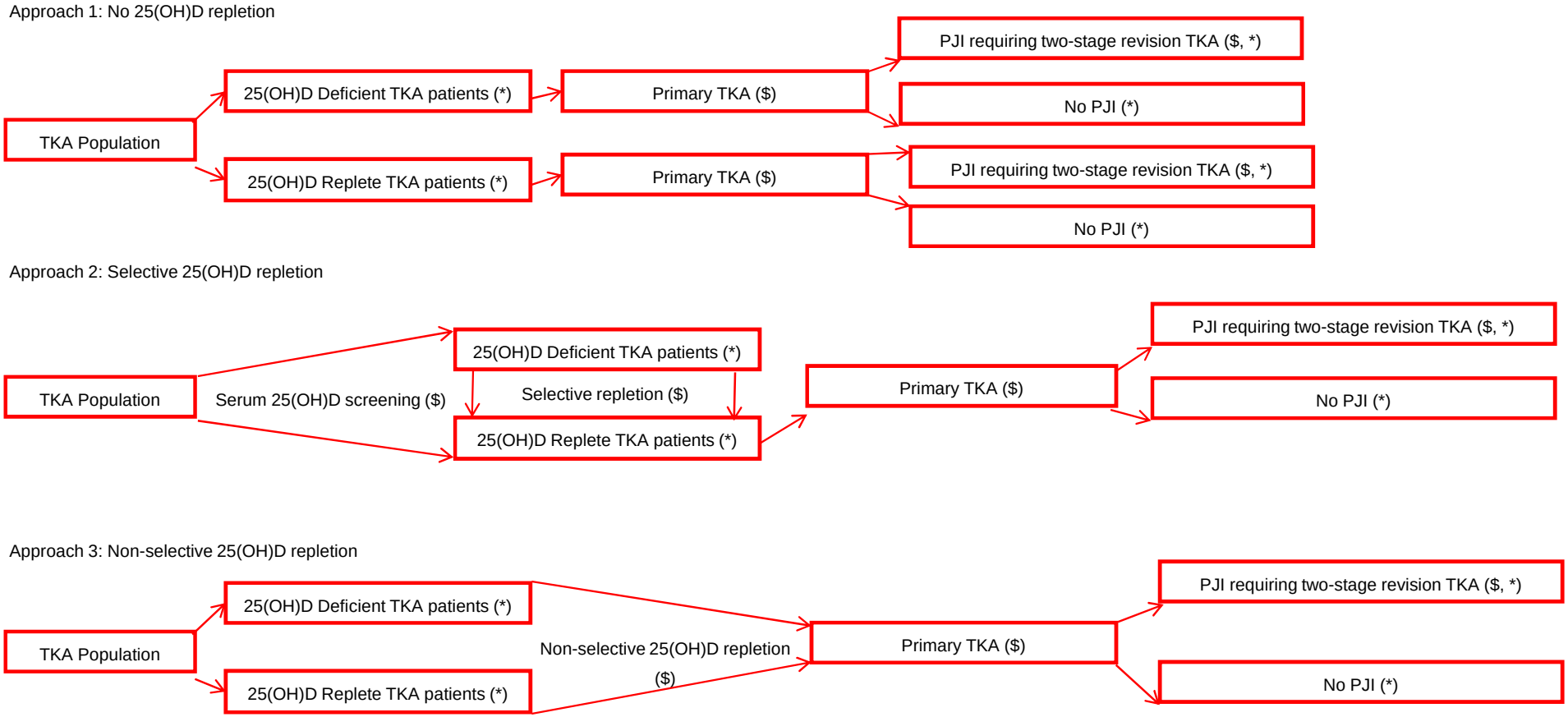
**TABLE 1:** Incidence and cost data input into the stochastic decision tree model

| | | |
|---|---|---|
| Annual cost of primary TKA ($) | $29,964 ($21,696-$50,868) | Kapadia et al., *J Arthroplasty* 2014 |
| Annual cost of infected TKA ($) | $123,448 ($47,112-$286,299) | |
| Cost of screening with 25D assay | $55.72 | CMS Reimbursement Schedules 2018 |
| 25D high-dose repletion | $17.97 | |
| Incidence of 25D deficiency in TKA patients | 13.20% | |
| Incidence of PJI within one year (25D deficient) | 2.42% | Hegde and Arshi et al, *Orthopedics* 2018 |
| Incidence of PJI within one year (25D replete) | 1.14% | |

**TABLE 2:** Stochastic model inflection points with univariate adjustment

| Variable adjusted | Non-selective repletion | Selective repletion |
|---|---|---|
| Cost of two-stage revision TKA for PJI | ≥ $10,636 | ≥ $34,382 |
| Population incidence of 25(OH)D deficiency | ≥ 1.1% | ≥ 3.7% |
| Relative risk reduction of PJI following repletion | ≥ 4.2% | ≥ 13.1% |

# Figure 1




* indicates a model input value for incidence

$ indicates a model input value for cost

# Figure 2