

**ORIGINAL RESEARCH**

# Cardiac Comorbidity Risk Score: Zero-Burden Machine Learning to Improve Prediction of Postoperative Major Adverse Cardiac Events in Hip and Knee Arthroplasty

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**BACKGROUND:** In this retrospective, observational study we introduce the Cardiac Comorbidity Risk Score, predicting perioperative major adverse cardiac events (MACE) after elective hip and knee arthroplasty. MACE is a rare but important driver of mortality, and existing tools, eg, the Revised Cardiac Risk Index demonstrate only modest accuracy. We demonstrate an artificial intelligence-based approach to identify patients at high risk of MACE within 4 weeks (primary outcome) of arthroplasty, that imposes zero additional burden of cost/resources.

**METHODS AND RESULTS:** Cardiac Comorbidity Risk Score calculation uses novel machine learning to estimate MACE risk from patient electronic health records, without requiring blood work or access to any demographic data beyond that of sex and age, and accounts for variable/missing/incomplete information across patient records. Validated on a deidentified cohort (age >45 years, n=445391), performance was evaluated using the area under the receiver operator characteristics curve (AUROC), sensitivity/specificity, positive predictive value, and positive/negative likelihood ratios. In our cohort (age  $63.5 \pm 10.5$  years, 58.2% women, 34.2%/65.8% hip/knee procedures), 0.19% (882) experienced the primary outcome. Cardiac Comorbidity Risk Score achieved area under the receiver operator characteristics curve =  $80.0 \pm 0.4\%$  (95% CI) for women and  $80.1 \pm 0.5\%$  (95% CI) for males, with 36.4% and 35.1% sensitivities, respectively, at 95% specificity, significantly outperforming Revised Cardiac Risk Index across all studied age-, sex-, risk-, and comorbidity-based subgroups.

**CONCLUSIONS:** Cardiac Comorbidity Risk Score, a novel artificial intelligence-based screening tool using known and unknown comorbidity patterns, outperforms state-of-the-art in predicting MACE within 4 weeks postarthroplasty, and can identify patients at high risk that do not demonstrate traditional risk factors.

**Key Words:** hip and knee arthroplasty ■ machine learning ■ Revised Cardiac Risk Index ■ risk of MACE

**M**ajor adverse cardiac events (MACE), consisting of myocardial infarction and cardiac arrest, are rare early complications in patients undergoing total hip or total knee arthroplasty.<sup>1–11</sup> Total hip and knee arthroplasty are frequently performed surgeries in older adults with multiple cardiac comorbidities, and yet the overall frequency of MACE is low, complicating identification of high-risk patients. Risk calculators

used to predict postoperative MACE following lower extremity arthroplasty have shown modest accuracy.<sup>10,12</sup> The Revised Cardiac Risk Index (RCRI)<sup>13</sup> is a widely used preoperative risk calculator that uses existing cardiovascular (CVD) comorbidities and surgical procedural risk to determine perioperative risk for MACE. RCRI does not include many other known CVD risk factors or identify patients without a formal diagnosis

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## CLINICAL PERSPECTIVE

### What Is New?

- The Cardiac Comorbidity Risk Score (CCoR) is introduced to predict perioperative major adverse cardiac events 2–4 weeks after elective hip and knee arthroplasty.
- CCoR is based on known and yet unknown comorbidity signatures extracted via sophisticated processing of individual patient history of medical encounters without any new laboratory tests or blood work, making it applicable at the point of care, and easily integrable with existing electronic healthcare management systems.

### What Are the Clinical Implications?

- CCoR outperformed the Revised Cardiac Risk Index to identify patients at high-risk of perioperative major adverse cardiac events in patients undergoing hip and knee arthroplasty.
- The CCoR performed well for patients with no Revised Cardiac Risk Index conditions as it effectively identified patients at high-risk of major adverse cardiac events with no previously diagnosed Revised Cardiac Risk Index conditions.
- Integration of the CCoR into electronic healthcare management systems can improve preoperative risk stratification and reduce healthcare costs as compared with the Revised Cardiac Risk Index over the next 2 decades.

### Nonstandard Abbreviations and Acronyms

<b>CCoR</b>	Cardiac Comorbidity Risk Score
<b>MACE</b>	major adverse cardiac events
<b>PFSA</b>	Probabilistic Finite State Automata
<b>RCRI</b>	Revised Cardiac Risk Index

of CVD comorbidities, which may limit its ability to predict perioperative MACE. In this study we sought to develop and validate a more accurate screening tool by systematically incorporating a vastly wider array of comorbidity patterns, including ones that are not already known risk factors for perioperative MACE.

To put in context, machine learning algorithms have been recently applied to assess risk of serious post-operative complications in procedures ranging from liver, pancreatic, colorectal surgeries, gastrectomies, and general in-patient procedures.<sup>14–18</sup> However, use of such tools for lower extremity arthroplasty has not been reported. Additionally, most reported approaches use manually curated fixed set of input features involving results of specific laboratory tests, patient demographic information to populate the inputs to the

machine learning tools. This requirement imposes additional burden on patients, and caregivers, and can exacerbate healthcare use. We aimed to develop a “zero-burden” tool, that may be applied without any such specific data demands, and be operable with the existing patient history on file.

To accomplish this goal, we built upon our previous work<sup>19–22</sup> on algorithmic pattern discovery in electronic health records databases. As a part of a broader trend of applying machine learning in medicine,<sup>23,24</sup> these algorithms identify complex characteristics of comorbidity incidence, timing, sequence, and synchronism, that presage various diagnoses and outcomes,<sup>19</sup> in this case, MACE in the 4 weeks after total hip arthroplasty and total knee arthroplasty. Combining these discovered features with standard machine learning leads to an automated screening tool based only on diagnostic codes already existing in the patient’s medical record. Risk screening using such algorithms therefore entails no additional diagnostic testing or other interventions for the patient, and no completion of risk calculators or other inputs by health professionals. In this study we develop and validate our screening tool for MACE after total hip arthroplasty/total knee arthroplasty, referred to as the Cardiac Comorbidity Risk Score (CCoR). We hypothesized that CCoR would show strong predictive ability on a standalone basis and outperform the RCRI in identifying patients at high risk of myocardial infarction and cardiac arrest following lower extremity arthroplasty.

## METHODS

### Data and Software Availability

Restrictions apply to some or all the availability of data analyzed during this study because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided. A working version of the software tool developed in this study, free for non-commercial evaluation, will be made available by the corresponding author on request. To enable fast execution, some compute intensive features are disabled in this version. Results from this software are for demonstration purposes only, and must not be interpreted as medical advice, or serve as replacement for such.

### Data Source, Patient Selection, and Ethics

Our patient data derive from the Truven Health Analytics MarketScan Commercial Claims and Encounters Database<sup>25</sup> for the years 2003–2018 (the “Truven data set”). The Truven data set combined deidentified patient records from >150 insurance carriers and large self-insurance companies including Medicare Advantage

and provides comprehensive inpatient and outpatient healthcare data obtained for >87 million patients. The Truven data set contains *International Classification of Diseases, Ninth and Tenth Revisions (ICD-9 and ICD-10)* diagnosis codes, current procedural terminology codes, as well as patients' age at arthroplasty and sex. Our study sample from the Truven data set based on the inclusion and exclusion criteria noted in Table S1 and Figure S1 (CONSORT-artificial intelligence extension diagram). In particular, we included patients with a current procedural terminology code that indicated either a total hip arthroplasty or total knee arthroplasty (Table S2). After the initial cohort selection, we applied the following exclusion criteria to patients: (1) <45 years of age, (2) active enrollment in the insurance plan for <12 months before surgery, and (3) continued enrollment in the insurance plan for <26 weeks following surgery. The University of Chicago Institutional Review Board granted an exemption for informed consent since this is an observational study using deidentified data (ID: IRB21-1272).

We use the RCRI version published in 1999,<sup>13</sup> which is calculated on a scale from 0 to 6 points, with 1 point assigned for each of the following conditions: history of (1) ischemic heart disease, (2) heart failure, and (3) cerebrovascular disease, (4) insulin therapy for diabetes, and (5) serum creatinine >2.0 mg/dL; 1 to 3

are identified by the presence of any of the diagnosis codes listed in Table S3 in inpatient or outpatient claims data, and insulin therapy was identified based on at least 1 outpatient prescription for insulin in the year before arthroplasty. Since the Truven database contained insufficient laboratory data on preoperative serum creatinine, we used an *ICD* diagnosis code for chronic kidney disease stage III or higher as a surrogate for creatinine >2.0 mg/dL.<sup>11,26</sup>

The sixth condition contributing to the RCRI is high-risk surgery which includes intraperitoneal surgery, suprainguinal vascular surgery and thoracic surgery. Since our cohort is limited to total hip and knee arthroplasty patients, the maximum number of conditions possible in the context of this study is 5 as enumerated in Table 1 (the contribution from the sixth category is always 0). We map the RCRI score to risk of MACE using published values,<sup>27</sup> and use this estimated risk value for evaluating RCRI performance when comparing with CCoR.

## Outcome

The primary outcome was a MACE diagnosis, defined as myocardial infarction or cardiac arrest, within the 4 weeks of the date of the elective primary total arthroplasty of the hip or knee. MACE events were included if any of the *ICD* codes shown in Table S4 were

**Table 1. Patient Characteristics**

Characteristic, n (%)	All surgeries (N=445391)	MACE within 2 wk (n=722)	MACE within 4 wk (n=882)	No MACE* (n=444509)
Mean age at surgery (SD)	63.5 (10.5)	70.8 (10.3)	70.8 (10.3)	63.4 (10.5)
Men	185992 (41.8%)	385 (53.4%)	464 (52.7%)	185528 (41.8%)
Women	259399 (58.2%)	337 (46.6%)	418 (47.3%)	258981 (58.2%)
Knee surgery	293153 (65.8%)	451 (62.4%)	559 (63.4%)	292594 (65.8%)
Hip surgery	152238 (34.2%)	271 (37.6%)	323 (36.6%)	151915 (34.2%)
RCRI score				
0	295960 (66.6%)	213 (29.5%)	265 (30.0%)	295695 (66.6%)
1	101505 (22.7%)	238 (32.9%)	300 (34.0%)	101205 (22.7%)
2	37145 (8.3%)	186 (25.9%)	212 (24.1%)	36933 (8.3%)
3	9336 (2.1%)	70 (9.6%)	88 (9.9%)	9247 (2.1%)
4	1438 (0.3%)	15 (2.1%)	16 (1.8%)	1422 (0.3%)
5	7 (0.002%)	0 (0%)	0 (0%)	7 (0.002%)
Chronic kidney disease: stage III or higher <sup>t</sup>	18774 (4.2%)	97 (13.4%)	111 (12.5%)	18663 (4.1%)
Ischemic heart disease	98840 (22.1%)	413 (57.2%)	497 (56.3%)	98343 (22.1%)
Congestive heart failure	26309 (5.9%)	139 (19.2%)	167 (18.9%)	26142 (5.8%)
Cerebrovascular disease	64642 (14.5%)	230 (31.8%)	279 (31.6%)	64363 (14.4%)
Preoperative treatment with insulin	783 (0.17%)	1 (0.13%)	1 (0.11%)	782 (0.17%)

MACE indicates major adverse cardiac events; and RCRI, Revised Cardiac Risk Index.

\*The "NO MACE" cohort comprised patients with no recorded MACE in their records during the 26 weeks after arthroplasty.

<sup>t</sup>Because of insufficient availability of relevant laboratory data in the Truven data set, presence of at least 1 diagnostic code for chronic kidney disease stage III or higher in the medical record in the year before the date of arthroplasty was used as a surrogate for the Revised Cardiac Risk Index condition, serum creatinine concentration >2.0 mg/dL.

documented in the medical record during the 4 weeks after arthroplasty. If a patient experienced multiple events during the 4 weeks postarthroplasty, we considered the first one. The 4-week time frame was chosen to be consistent with previous analyses evaluating the timing, incidence, and prediction of MACE after major noncardiac surgery.<sup>4</sup> As a secondary outcome, we evaluated MACE prediction within 2 weeks of surgery.

## Modeling and Prediction

To predict postsurgical MACE we aimed to classify time-stamped sequences of diagnostic codes into positive and control categories, where the positive category refers to patients experiencing the primary outcome. The control cohort comprised patients without any MACE in their records within the 26 weeks after the surgery. For both groups, we based our predictions on the 52 weeks of medical history before the total joint arthroplasty. We considered altogether >126 million diagnostic codes (>36 000 unique codes) (Table S5) in a sex-stratified analysis. We did not preselect any diagnostic code based on its association with MACE risk, using pattern discovery to find predictive precursors instead.

We proceeded by partitioning the set of all diagnostic codes into 26 broad categories (Tables S6 and S7; Figure 1), referred to as “CCoR phenotypes”. Some of the phenotypes encompass a relatively large number of codes aligning roughly with *ICD* categories.<sup>17,18,25,28</sup> Other phenotypes include  $\geq 1$  codes that might have some known or suspected association with MACE. One such phenotype is “frailty” (Table S7), recognized to increase risk of such adverse cardiac outcomes.<sup>29,30</sup> Applied to the individual timestamped history of diagnoses, each phenotype yields a single time series over weeks. Here each week is assigned a value “0” if no code recorded in that week corresponds to the phenotype, “1” if some code in that phenotype is present, or “2” if a diagnostic code from any other phenotype is present. Ultimately each patient is represented by 26 sparse stochastic event streams, which are compressed into specialized Hidden Markov Models known as Probabilistic Finite State Automata (PFSA).<sup>20,21</sup> These models are inferred separately for each phenotype, for each sex, and for the control and the positive cohorts, ie,  $26 \times 2 \times 2 = 104$  PFSA models are inferred altogether, to identify the distinctive average comorbidity patterns emerging at the population level. Variation in the structure and parameters of these inferred models between the positive and control groups delineated the estimated population-level risk of postoperative MACE. Given these models, and a specific patient’s history, we can quantify the log-likelihood (Table S8) of that history being generated by the control PFSA models as opposed to the positive models. We refer to this difference in likelihood as the sequence likelihood

defect<sup>22</sup> (see Data S1) which is one of the key informative features in our approach. Besides the phenotype-specific Markov models, we used a wide range of engineered features that reflect various aspects of the patient-specific diagnostic histories (Table S8). Overall, we computed a total of 380 features for each patient, which were then used to train a standard gradient boosting classifier<sup>31,32</sup> aiming to map individual patients to a raw risk score. Importantly, these features are derived solely from the information available in the patient electronic health records file, with no additional blood work or tests. It is important to note that the trinary encoding described above leads to  $\approx 87\%$  to 89% 0’s, 1% 1’s, and  $\approx 9\%$  to 11% 2’s (Table S9). Since the 1’s code for a specific category of disorders, while 2’s for all remaining categories, it is expected that 2’s will be more frequent.

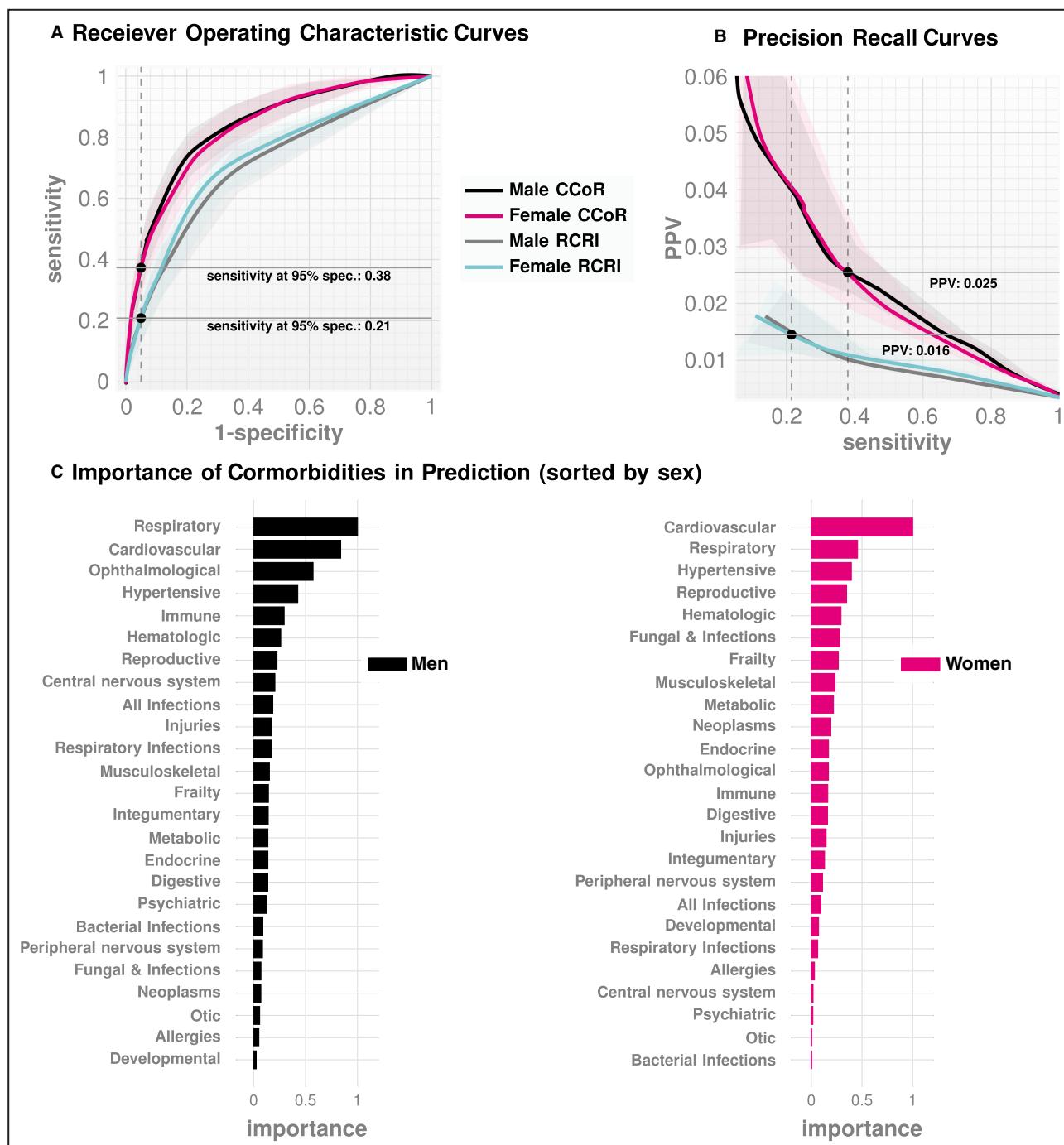
All performance metrics are evaluated on held-back out-of-sample data, ie, on the validation set. We randomly chose 50% of our patients for training the algorithm, with the rest makes up the validation set. Half of the training data set was used for PFSA inference, and the rest for training the gradient boosting classifier. In addition to gradient boosting classifier, we experimented with other prominent classification models including random forests and extremely randomized trees.<sup>33</sup> The gradient boosting classifier emerged as the optimal choice with the highest out-of-sample performance given the initial feature engineering steps discussed above.

## Chart Completeness

Records of medical encounters for patients cannot be guaranteed to be over identical time periods, especially when using a large claims database. Thus, we designed our approach to be applicable to patients with varying lengths of medical histories. The underlying models do not need equal-length inputs for computation. Importantly, we use only data within the inference period. If the set of recorded encounters for a patient do not span at least the past 12 months (52 weeks), then that patient is excluded, as described in our inclusion/exclusion criteria. Prospective studies in the future will evaluate applicability in such short-history situations.

## Imbalance Between Positive and Control Cohorts

The incidence of MACE in patients undergoing total hip/knee replacement is low (0.3%–0.9%),<sup>1</sup> and  $\approx 0.2\%$  in our data set. Such severe imbalances can skew predictors. However, this is not an important issue in our analysis since all reported performance are obtained on out-of-sample data. Nevertheless, we investigated if using a more balanced data set for training would boost



**Figure 1.** Out-of-sample performance of Cardiac Comorbidity Risk Score (CCoR) and Revised Cardiac Risk Index (N=445391) to predict major adverse cardiac events in the 4 weeks after elective primary lower extremity arthroplasty.

The validation cohort comprised the 50% of the study sample not used to develop CCoR. **A** and **B**, The receiver operating characteristics and precision-recall curves, respectively, of the two risk scores by sex. The AUROC of the receiver operating characteristics curve and the precision-recall curve reflect the risk scores' performance in predicting major adverse cardiac events 4 weeks after elective primary total hip or knee joint replacement. CCoR shows a strong prognostic performance that substantially exceeds that of Revised Cardiac Risk Index in both men and women. **C**, The relative importance of phenotypes (comorbidity phenotypes) in CCoR estimation. The 20 top phenotypes by sex are shown in descending order of relative importance in estimating the CCoR. Notably, these importances do not merely sum the predictive contribution from the presence or absence of individual diagnostic codes, a contribution reflected in the comorbidity spectra illustrated in Figure 2. Rather, the relative importance of the phenotypes sums the predictive contribution from all patterns (sequence likelihood defect as well as sequence features, see Methods) emerging from all disorders comprising each phenotype. Note that the sex of the patient matters, eg, respiratory disorders are somewhat overrepresented in women and circulatory disorders in men, and only 3 of the top 5 and 5 of the top 10 phenotypes are shared between women and men. CCoR indicates Cardiac Comorbidity Risk Score; RCRI, Revised Cardiac Risk Index; ROC, receiver operating characteristics; and SLD, Sequence Likelihood Defect.

**Figure 2. Comorbidity spectra.**

Disorders that increase the odds of a “true positive” vs a “true negative”; ie, these disorders, ranked here according to the log-odds ratio in ascending order of frequency in “true positive” versus “true negative” patients, are more likely in patients who are in the positive cohort. ICD-10 indicates International Classification of Diseases, Tenth Revision. Panel A and B shows comorbidity spectra for the two sexes, which while similar, have important differences.

our out-of-sample performance. We verify explicitly (Table S10) that such a strategy confers no advantage, and in fact leads to progressive degradation of performance in out-of-sample data as we use more balanced data for training (a matched one-is-to-one balanced data set yields an out-of-sample AUROC of 75.5% for the female cohort, as opposed to >80% when no balancing is attempted). We suspect that any down-sampling to balance the training data causes the predictor to only focus on a subset of patterns, which then makes it less capable of assessing risk in out-of-sample data.

## Feature Importance and Comorbidity Spectra

In addition to estimating risk, our analysis offers insights into the known and unknown comorbid associations of postoperative MACE, via the inferred relative importance of the features used. We computed the relative importance of the features by estimating the mean change in the raw risk via random perturbations of the features (Figure 1C). Additionally, we computed the statistically significant log-odds ratios of specific ICD codes occurring in the true positive versus the true negative patient sets, defining the “comorbidity spectra” (Figure 2). Importantly, the comorbidity spectra are based on individual codes, as opposed to the feature importance shown in Figure 1, which consider the aggregated impact of all features. Every disorder listed in the comorbidity spectra obviously does not appear in a given patient’s records, but codes with high log-odds ratio are significantly more likely in the positive cohort.

## Statistical Analysis

When executed just before surgery, our models predict the raw risk score for a MACE within 4 (or 2) weeks of the procedure. Given the raw estimate, a decision threshold is chosen to make a balanced trade-off between Type 1 and Type 2 errors (or, equivalently, between specificity and sensitivity): if the raw risk is greater than this calibrated threshold, then the patient is predicted to be in the positive category, ie, likely to experience MACE. We compared the out-of-sample predictive performance for CCoR and RCRI using standard metrics, including accuracy, the area under the receiver operating characteristic curve (AUROC), sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios (LR+ and LR-, respectively). The 95% CIs on ROC curves and AUROCs were obtained via bootstrapping, and AUROC *P* values were obtained using the Mann–Whitney *U*-test statistic.<sup>34</sup>

## Cost Analysis

The low prevalence of MACE implies that statistically significant predictive advantage alone might not make

a sufficiently convincing case for the clinical relevance of the performance superiority of CCoR over RCRI. Thus, we evaluated the relative impact of the algorithms in a simple cost model, which also accounts for the impact of relatively high false positive rate arising because of the low prevalence of MACE.

Recent publication of the AJRR (American Joint Replacement Registry) puts the number of total hip/knee replacement procedures at 1.7M (2020),<sup>35</sup> and is projected to be 1.9M in 2025, 2.8M in 2030, and 4.8M in 2040.<sup>36</sup> Mean MACE-related costs incurred for the first event occurring within a few weeks of surgery is high, and was recently estimated to be \$19 642.<sup>37</sup> The reported 30-day incidence (after total hip/knee arthroplasty) of MACE varies from 0.3% to 0.9%.<sup>1</sup> The additional procedures, testing and increased length of hospital stay because of a positive flag from a chosen risk assessment algorithm is estimated to be ≈\$10 624 per patient.<sup>38</sup> These estimates inform our cost model designed to compare the clinical value added by CCoR versus RCRI. In particular, we estimate the cost (*C*) per year to the healthcare system as a result of MACE, with perioperative risk assessment performed by any given algorithm to be:

$$C = (t_p + f_p)C_t + f_nC_M$$

where  $t_p$ ,  $f_p$ ,  $f_n$  are true positives, false positives, and false negatives, and  $C_t$ ,  $C_M$  are the costs per patient for additional testing, and those incurred after experiencing MACE respectively, thus explicitly accounting for the impact of false positives and false negatives. The above equation reduces to:

$$C = \left( s \left( \frac{C_t}{PPV} - C_M \right) + C_M \right) \rho N$$

where  $s$  is the sensitivity of the chosen algorithm,  $\rho$  is the prevalence of MACE among patients undergoing the surgical procedure, and  $N$  is the estimated number of procedures performed per year.

## RESULTS

Our cohort (Table S11) included 445 391 patients undergoing lower extremity arthroplasty, with 0.19% experiencing the primary outcome of MACE within 4 weeks of the procedure (including 0.16% within 2 weeks of surgery). Patient characteristics overall and in the positive and control (negative) cohorts can be seen in Table 1. Rates of MACE within 4 weeks of surgery were 0.21% in patients undergoing total hip arthroplasty and 0.19% in those undergoing total knee arthroplasty, respectively. Table S11 presents the subcohort sizes stratified

by sex and the presence or absence of MACE within 4 weeks of arthroplasty.

## CCoR Performance

The key performance metrics for CCoR to predict the primary outcome are presented in [Table 2](#) and [Figure 1](#), which illustrates the ROC curve, the AUROC, and the precision-recall curves, respectively, shown separately for women and men along with 95% CI. Performance for predicting MACE within 2 weeks of surgery is enumerated in [Table 3](#). For predicting MACE 4 weeks postarthroplasty, out-of-sample AUROC was  $80.1 \pm 1.9\%$  (95% CI) for women and  $80.2 \pm 1.8\%$  (95% CI) for men, with  $36.4 \pm 6\%$  and  $35.1 \pm 1\%$  sensitivities, respectively, at 95% specificity. CCoR accuracy (the fraction of correct predictions) of 95%, and a PPV (the fraction of true positives among all positive flags) of 2.5% was achieved irrespective of sex. It should be noted that because of the low prevalence of MACE in our sample, even 100% sensitivity for a screening tool at 95% specificity would yield a PPV <5%. Given the low prevalence, the likelihood ratios are more relevant metrics here. For the primary outcome of MACE within 4 weeks of surgery, for women, CCoR achieved a LR+ of  $7.28 \pm 0.3$  at 95% specificity ( $13.19 \pm 2.1$  at 99% specificity), implying that the odds of a positive CCoR flag in female patients who do experience MACE is 7.28 times to that in patients who do not, when the tool is operated at 95% specificity. For men, the corresponding LR+ are  $7.19 \pm 2$  and  $12.44 \pm 0.3$  at 95% and 99% specificity, respectively. Similarly, we achieved LR- of  $0.67 \pm 0.05$  for women and  $0.68 \pm 0.01$  for men at 95% specificity, implying that the odds of a negative CCoR result in a patient not experiencing MACE is  $1/0.67 = 1.5$  times more than that in patients who do. For the secondary outcome of MACE within 2 weeks of surgery, CCoR achieves an LR+ of  $7.5 \pm 2.5$  (women) and  $7.65 \pm 0.6$  (males) at 95% specificity, and  $14.48 \pm 0.3$  (women) and  $13.98 \pm 2.1$  (men) at 99% specificity. The corresponding LR- estimates for the 2-week horizon are  $0.87 \pm 0.01$  (99% specificity) and  $0.66 \pm 0.03$  (95% specificity) for both sexes. These results show that CCoR is particularly effective when there is a positive flag (high LR+), and moderately so for negative flags.

CCoR performance in predicting the primary outcome in all studied age-, risk-, and comorbidity-defined subgroups of the validation cohort was comparable with the overall out-of-sample performance ([Table 2](#), [Tables S12](#) and [S13](#)). The score's performance remained high, albeit slightly decreased, when predictions of 4-week MACE with 99% specificities were considered ([Table S14](#)). CCoR performance was slightly stronger (AUROC  $80.9 \pm 2.1\%$  in women,  $81.3 \pm 1.9\%$  in men) for the shorter time horizon of 2 weeks postoperatively ([Table 3](#) and [Table S15](#)).

## Performance Comparison With RCRI

[Tables 2](#) and [3](#) also display performance metrics at 95% specificity for the RCRI to predict the primary and secondary outcomes. In both sexes, ([Figure 3](#)) and across all studied age-, risk-, and comorbidity-defined subgroups ([Tables S12](#) and [S13](#)), the AUROC for CCoR exceeded that of RCRI, often substantially. This pattern held true when specificity was set to 99% or for either the 2-week or the 4-week time frame ([Tables S14](#) and [S15](#)). The differences in positive likelihood ratios are dramatic: CCoR LR+ is  $\approx 62\%$  to 78% larger, and LR- is 24% smaller at 95% specificity for the primary outcome. At 99% specificity, the positive and negative likelihood ratios are 110% to 163% larger and 1% to 6% smaller, respectively. At the shorter horizon of 2 weeks, the ratios are similar to that of the primary outcome.

Importantly the CCoR achieved high performance ( $76.5 \pm 0.7\%$  in women,  $76.6 \pm 1.1\%$  in men, 95% CI) in patients lacking any RCRI condition (RCRI score of 0) for the 4-week prediction horizon, who represented nearly two thirds of the study sample ( $n=296,539$ , 66.5%) and accounted for 29.5% of all patients who suffered a cardiac event (ie, 29.5% of events occurred in RCRI=0 patients). The dramatic positive likelihood ratio in this subcohort ( $9.4 \pm 3.8$  and  $7.25 \pm 1.3$  for at 95% specificity,  $21.8 \pm 1.3$  and  $5.96 \pm 0.9$  at 99% specificity for men and women, respectively, see [Table 2](#) and [Table S14](#)), demonstrates utility to accurately risk-stratify patients completely missed by current screening tools. Also of interest, CCoR performance significantly exceeds that reported by Harris et al<sup>10</sup> to predict 30-day cardiac complications of elective lower extremity total joint arthroplasty. Harris and colleagues achieved an AUROC of  $72\%-73\% \pm 2\%$ , 95% CI, using a limited number of preselected binary comorbidity indicators and patient demographics.

The substantial superiority in achieved out-of-sample AUROC of CCoR over RCRI were found to be statistically significant across different subcohorts that we investigated ([Table S16](#)), for both the primary and secondary outcomes.

## Cost Comparison Between CCoR and RCRI

With the values of the parameters chosen as described in our cost model (and using a prevalence of 0.3% for MACE), we estimate that the overall cost varies with the chosen sensitivity and the PPV as shown in [Figure 3A](#) and [3B](#), respectively. Under current practice, a common operating point to trigger referral for preoperative tests and corrective measures, is an estimated RCRI risk >6%.<sup>27</sup> We estimated that this maps approximately to a sensitivity between 30% and 40% for MACE within 4 weeks of surgery. The

**Table 2. Out-of-Sample\* Prediction of MACE With 4 Weeks of Hip/Knee Arthroplasty (Primary End Point) at 95% Specificity: CCoR Versus RCRI†**

Sex	Cohort	Model	Sensitivity	PPV	Accuracy	LR+	LR-	AUROC
Women	<65	RCRI	0.10±0.01	0.008±0.000	0.947±0.006	0.47±0.0	0.93±0.00	0.639±0.039
Women	<65	CCoR	0.31±0.01	0.025±0.010	0.948±0.006	7.31±3.1	0.72±0.01	0.775±0.035
Men	<65	RCRI	0.18±0.02	0.015±0.007	0.947±0.000	4.23±2.3	0.87±0.02	0.682±0.034
Men	<65	CCoR	0.34±0.00	0.030±0.014	0.948±0.006	8.97±4.7	0.69±0.01	0.783±0.030
Women	65+	RCRI	0.16±0.02	0.012±0.002	0.947±0.000	3.35±0.5	0.88±0.02	0.664±0.028
Women	65+	CCoR	0.32±0.01	0.022±0.010	0.948±0.006	6.48±3.0	0.71±0.01	0.771±0.025
Men	65+	RCRI	0.16±0.03	0.011±0.001	0.947±0.006	3.17±0.4	0.88±0.03	0.661±0.026
Men	65+	CCoR	0.27±0.00	0.019±0.006	0.948±0.006	5.57±1.8	0.77±0.00	0.762±0.023
Women	All patients	RCRI	0.18±0.02	0.014±0.002	0.947±0.000	4.13±0.6	0.86±0.02	0.688±0.023
Women	All patients	CCoR	0.36±0.06	0.025±0.001	0.948±0.006	7.28±0.3	0.67±0.05	0.801±0.019
Men	All patients	RCRI	0.20±0.02	0.017±0.002	0.947±0.000	4.83±0.5	0.84±0.02	0.705±0.020
Men	All patients	CCoR	0.35±0.01	0.025±0.006	0.948±0.006	7.19±2.0	0.68±0.01	0.802±0.018
Women	Frail‡	RCRI	0.12±0.03	0.009±0.002	0.947±0.006	2.50±0.6	0.92±0.02	0.670±0.028
Women	Frail	CCoR	0.31±0.02	0.022±0.007	0.948±0.000	6.40±2.2	0.73±0.02	0.791±0.025
Men	Frail	RCRI	0.23±0.01	0.019±0.003	0.947±0.006	5.46±0.9	0.80±0.00	0.727±0.027
Men	Frail	CCoR	0.38±0.02	0.026±0.008	0.948±0.000	7.56±2.6	0.66±0.03	0.810±0.024
Women	High risk§	RCRI	0.11±0.02	0.008±0.001	0.947±0.006	2.19±0.3	0.94±0.02	0.581±0.029
Women	High risk	CCoR	0.25±0.02	0.017±0.007	0.948±0.000	5.06±2.2	0.79±0.02	0.737±0.026
Men	high risk	RCRI	0.15±0.03	0.010±0.001	0.947±0.006	2.91±0.3	0.90±0.02	0.617±0.026
Men	High risk	CCoR	0.30±0.01	0.021±0.006	0.948±0.000	6.02±2.0	0.74±0.00	0.729±0.024
Women	Low risk	CCoR	0.33±0.04	0.032±0.012	0.948±0.000	9.40±3.8	0.70±0.04	0.765±0.036
Men	Low risk	CCoR	0.33±0.02	0.025±0.004	0.948±0.000	7.25±1.3	0.71±0.02	0.766±0.032

<65 indicates subcohort with patients aged ≤65 years; AUROC, area under the receiver operating characteristic curve; CCoR, Cardiac Comorbidity Risk Score; LR-, negative likelihood ratio; LR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; and RCRI, Revised Cardiac Risk Index.

\*50% of the study sample (n=445391) used for validation.

†Because of insufficient availability of relevant laboratory data in the Truven data set, presence of at least 1 diagnostic code for chronic kidney disease stage III or higher in the medical record in the year before the date of arthroplasty was used as a surrogate for the Revised Cardiac Risk Index condition, serum creatinine concentration >2.0 mg/dL (to convert to micromoles per liter, multiply by 88.4).

‡ICD codes for frailty enumerated in Table S7.

§Low-risk status subcohort comprises patients with Revised Cardiac Risk Index score 0. For RCRI score >0, the patient is deemed to be at high risk.

||No Revised Cardiac Risk Index performance logged for low-risk patients, since their RCRI score is zero.

estimated cost for achieving a 40% sensitivity in the general population with CCoR is ≈667M US dollars per year currently. With RCRI this estimate to 1.48B US dollars, which approximately reflects current practice (see annotation in panel B).

Additionally, at any fixed yearly cost, CCoR is estimated to deliver substantially higher sensitivity and PPV (Figure 3C and 3D), eg, if the total yearly cost to the healthcare system attributable to preoperative testing+post-MACE costs is fixed at 500M, then CCoR can deliver >150% more sensitivity, and >20% more PPV up to around the year 2025. The sensitivity advantage is estimated to be even wider at later years. If the total estimated cost is set at around current practice, then CCoR can deliver an improvement in either sensitivity or PPV >50% (Figure 3C and 3D).

## DISCUSSION

Our study used novel machine learning algorithms to develop and validate a tool to identify comorbidity patterns in past diagnoses to predict postoperative MACE following total hip and knee arthroplasty. We demonstrated 2 key results: (1) our CCoR effectively predicted MACE within 2 to 4 weeks of a total hip or knee arthroplasty, and (2) CCoR is a significantly stronger predictor of perioperative cardiac morbidity after total hip and knee arthroplasty in clinical practice than RCRI. From the inferred relative importance of the features identified we conclude that respiratory and cardiovascular disorders are the most important modulators of risk,<sup>39</sup> followed by hematologic, reproductive, nervous system disorders and infections. While the role of past

**Table 3.** Out-of-Sample\* Prediction of MACE With 2 Weeks of Hip\Knee Arthroplasty (Secondary End Point) at 95% Specificity: CCoR Versus RCRI†

Sex	Cohort	Model	Sensitivity	PPV	Accuracy	LR+	LR-	AUROC
Women	<65	RCRI	0.11±0.01	0.009±0.000	0.947±0.006	0.51±0.0	0.92±0.00	0.647±0.044
Women	<65	CCoR	0.32±0.07	0.025±0.005	0.948±0.006	7.30±1.6	0.71±0.06	0.787±0.039
Men	<65	RCRI	0.20±0.03	0.017±0.003	0.947±0.000	4.95±1.0	0.84±0.04	0.688±0.037
Men	<65	CCoR	0.38±0.03	0.031±0.014	0.948±0.000	9.01±4.4	0.65±0.03	0.797±0.033
Women	65+	RCRI	0.17±0.00	0.012±0.002	0.947±0.006	3.60±0.6	0.87±0.00	0.671±0.030
Women	65+	CCoR	0.31±0.02	0.022±0.012	0.948±0.000	6.37±3.8	0.72±0.02	0.787±0.027
Men	65+	RCRI	0.14±0.02	0.010±0.001	0.947±0.000	2.79±0.4	0.91±0.02	0.667±0.028
Men	65+	CCoR	0.30±0.02	0.021±0.007	0.948±0.006	6.10±2.1	0.74±0.02	0.780±0.025
Women	All patients	RCRI	0.19±0.02	0.016±0.002	0.947±0.000	4.49±0.6	0.85±0.02	0.692±0.025
Women	All patients	CCoR	0.37±0.01	0.026±0.008	0.948±0.006	7.50±2.5	0.66±0.01	0.809±0.021
Men	All patients	RCRI	0.19±0.02	0.016±0.002	0.947±0.000	4.63±0.6	0.85±0.02	0.710±0.022
Men	All patients	CCoR	0.37±0.03	0.026±0.002	0.948±0.006	7.65±0.6	0.66±0.03	0.813±0.019
Women	Fraile‡	RCRI	0.14±0.02	0.011±0.002	0.947±0.000	3.13±0.7	0.90±0.03	0.676±0.032
Women	Frail	CCoR	0.31±0.03	0.023±0.003	0.948±0.000	6.75±0.8	0.73±0.04	0.807±0.027
Men	Frail	RCRI	0.23±0.03	0.019±0.003	0.947±0.000	5.40±0.8	0.80±0.03	0.736±0.029
Men	Frail	CCoR	0.41±0.04	0.028±0.002	0.948±0.000	8.20±0.7	0.62±0.04	0.825±0.025
Women	High risk§	RCRI	0.12±0.00	0.008±0.001	0.947±0.006	2.35±0.4	0.93±0.00	0.584±0.032
Women	High risk	CCoR	0.23±0.05	0.017±0.003	0.947±0.006	4.90±0.8	0.81±0.04	0.742±0.028
Men	High risk	RCRI	0.13±0.01	0.009±0.001	0.947±0.006	2.69±0.4	0.91±0.00	0.628±0.028
Men	High risk	CCoR	0.33±0.03	0.023±0.002	0.948±0.000	6.57±0.6	0.71±0.03	0.737±0.026
Women	Low risk	CCoR	0.43±0.03	0.041±0.017	0.948±0.006	12.20±5.7	0.60±0.03	0.779±0.040
Men	Low risk	CCoR	0.39±0.02	0.029±0.005	0.948±0.000	8.57±1.5	0.64±0.02	0.793±0.035

<65 indicates subcohort with patients aged ≤65 years; AUROC, area under the receiver operating characteristic curve; CCoR, Cardiac Comorbidity Risk Score; LR+, positive likelihood ratio; LR-, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; and RCRI, Revised Cardiac Risk Index.

\*50% of the study sample (n=445391) used for validation.

†Because of insufficient availability of relevant laboratory data in the Truven data set, presence of at least 1 diagnostic code for chronic kidney disease stage III or higher in the medical record in the year before the date of arthroplasty was used as a surrogate for the Revised Cardiac Risk Index condition, serum creatinine concentration >2.0 mg/dL (to convert to micromoles per liter, multiply by 88.4).

‡ICD codes for frailty enumerated in Table S7.

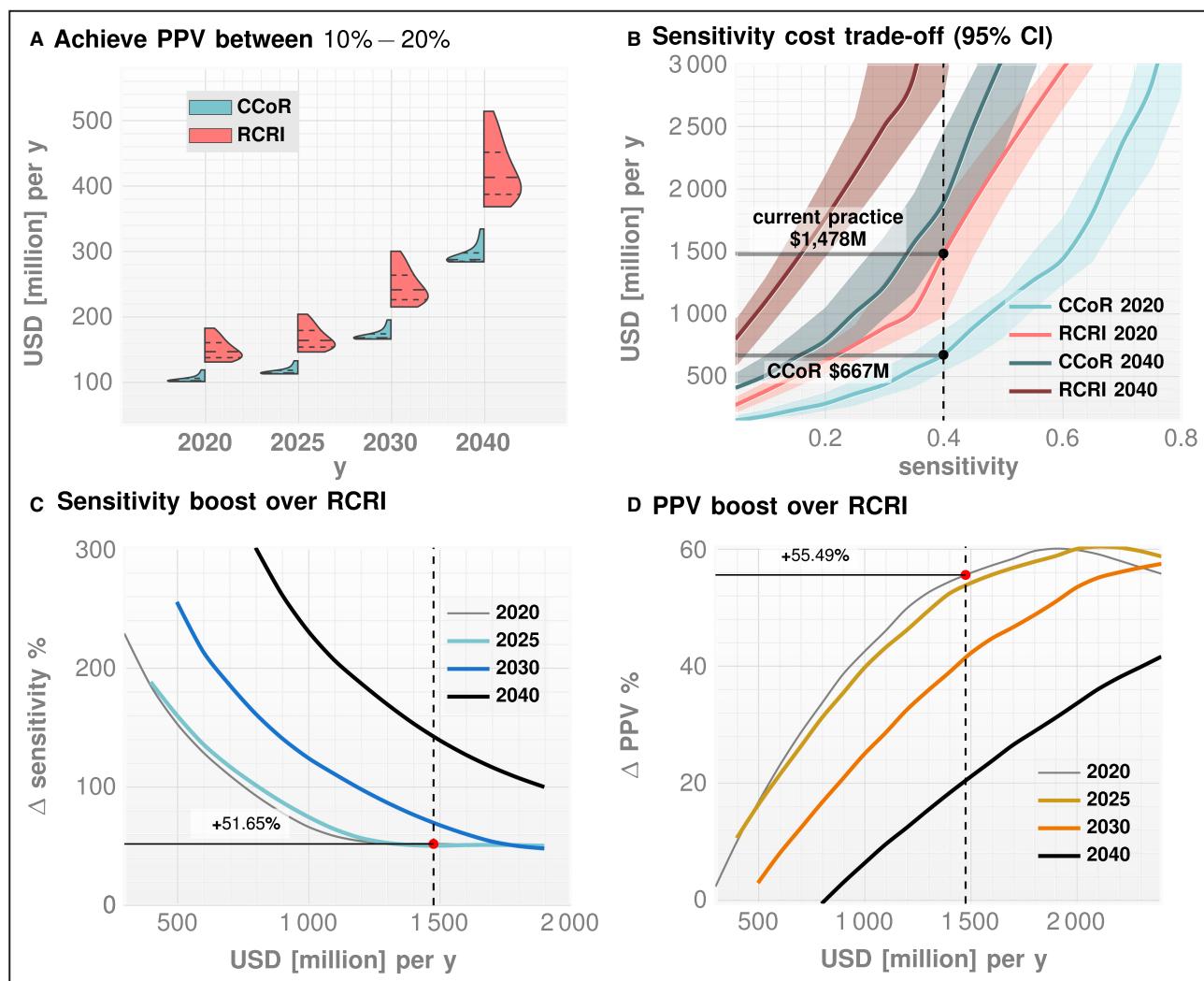
§Low-risk status subcohort comprises patients with Revised Cardiac Risk Index score 0. For Revised Cardiac Risk Index score >0, the patient is deemed to be at high risk.

||No Revised Cardiac Risk Index performance logged for low-risk patients, since their Revised Cardiac Risk Index score is zero.

cardiovascular diagnoses in postoperative MACE has been recognized,<sup>38</sup> prior research<sup>40–45</sup> has examined binary relationships between the presence or absence of a diagnosis (eg, coronary artery disease). This is a major limitation for the RCRI, as a formal diagnosis of coronary artery disease or heart failure is required to identify patients at risk. Our approach can identify patients with patterns and combinations of comorbidities in past medical encounters associated with increased risk for MACE, as opposed to only those with specific CVD disorders. A key conclusion from our study is that CCoR is markedly better at predicting the occurrence of MACE, than predicting its nonoccurrence. Thus, a positive CCoR flag reliably identifies high-risk patients who may experience postoperative MACE. The reliability is lower for concluding that the absence of a CCoR flag implies no MACE in the postsurgical time frames

considered. In either case, CCoR likelihood ratios are superior to RCRI.

Our approach addresses a major limitation of current comorbidity-based risk calculators that require binary diagnoses (eg, heart failure) to deduce an increased risk. Newer cardiac risk calculators, such as the American College of Surgeons National Surgical Quality Improvement Project<sup>46</sup> have improved upon this approach by incorporating symptoms (eg, dyspnea with moderate exertion) and functional status, but are still primarily reliant on a limited set of manually curated diagnoses. Additionally, the calculators can be challenging to incorporate into busy clinic workflows. Our approach integrates directly into standard electronic medical record systems to estimate expected cardiac risk before surgical procedures. This could be readily available to clinicians of all specialties at the



**Figure 3. Cost model.**

**A**, The distribution of estimated cost for Cardiac Comorbidity Risk Score (CCoR) and Revised Cardiac Risk Index (RCRI) over the years for achieving positive predictive value between 10% and 20%. **B**, The cost trade-off with sensitivity for 2020 and 2040 along with 95% CI. Note that the estimated cost of achieving a 40% sensitivity in the general population (which approximately corresponds to >6% risk with RCRI and reflects current practice) with CCoR is ≈750M US dollars per year currently, while with RCRI this increases to 1.5B US dollars per year. **C**, The relative boost in sensitivity achieved by CCoR over RCRI as a percentage for a fixed cost. **D**, The relative boost in positive predictive value achieved by CCoR over RCRI as a percentage for a fixed cost. Thus, if the yearly cost is fixed at 500M, then CCoR can deliver >150% more sensitivity, or almost 20% more positive predictive value up to around 2025. If the costs are set to what is estimated for current practice (\$1478M), then CCoR can deliver a >50% improvement in either sensitivity or positive predictive value. The estimated number of surgeries per year, and values for the costs of additional testing on a positive flag, and for the costs incurred upon experiencing major adverse cardiac events are adopted from published estimates of comparable scenarios. CCoR indicates Cardiac Comorbidity Risk Score; PPV, positive predictive value; RCRI, Revised Cardiac Risk Index; and USD, US dollar.

time of office-based perioperative risk assessment, or even guide who should be scheduled for subspecialty risk assessment. Ultimately, patterns of healthcare use before surgical procedures can be leveraged to identify patients that may require additional testing or interventions to modify risk before a surgical procedure. Given that the Truven data set contains healthcare information from roughly 25% of the nation's population, and that our validation cohort had similar demographic characteristics to those of other published studies undergoing total joint arthroplasties,<sup>47</sup> CCoR

performance in the present study is expected to be widely generalizable in the United States. Furthermore, the significant superiority of CCoR over RCRI across various subcohorts, and in multiple relevant metrics, points to the potential for substantial improvement in clinical outcomes on deployment.

Some observations, discussed next, related to the reported performance estimates might be of clinical interest. For RCRI, the PPV achieved for the age-related subpopulations (<65 and ≥65 years) were both lower than the PPV of the unrestricted population

**Table 4.** Performance Comparison of CCoR When Augmented With History of Prescribed Medications

Sex	Prediction Horizon	AUROC (CCoR)	AUROC (CCoR augmented with prescriptions data)	Sensitivity at 95% specificity (CCoR)	Sensitivity at 95% specificity (CCoR augmented with prescriptions data)
Men	2wk	81.3%	81.5%	34.1%	34.5%
	4wk	80.1%	80.5%	31.8%	32.7%
Women	2wk	80.9%	81.0%	32.5%	31.8%
	4wk	80.0%	80.3%	31.0%	30.2%

AUROC indicates area under the receiver operating characteristic curve; and CCoR, Cardiac Comorbidity Risk Score.

(Tables 2, 3 and Tables S14, S15), which is counterintuitive. However, in this study the PPVs of the different subcohorts are computed separately from that of the unrestricted cohort (indicated as “all patients” in Tables 2, 3 and Tables S14, S15). Since we compute the ROC curves independently in each subcohort, the threshold of binary decision differs from one subcohort to the next, which makes it possible for the estimated PPV to be lower in both younger and older subpopulations compared with the unrestricted cohort.

We also observe that CCoR performance is generally lower in the subcohorts (Tables 2 and 3). We suspect that the unrestricted cohort has a wider range of patient ages, each of which have a different incidence of MACE. This makes them more easily classifiable, on average, using age-at-screening as a feature when considered all together. When we define a subcohort with smaller age-variation, and compute performance within that group, then the predictive advantage of the age-variable disappears, leading to a somewhat lower predictive performance.

In this study, in addition to comorbidity signatures, we investigated how the sex and age of patients modulate MACE risk. This was motivated by the fact that sex and age are both known strong predictors of perioperative MACE.<sup>48,49</sup> Further, cardiovascular disease presentation, diagnosis, and management have been shown to be different between men and women.<sup>50</sup> In addition, patient demographics, clinical variables, specific treatments, and prescribed drugs might also be potentially important predictors, and in general, we expect the performance to improve if we add more informative features. However, it was difficult to assess this hypothesis within the constraints of our current data set which lacked patient demographic information such as race and ethnicity, or extensive data on other clinical variables. We will investigate the impact of demographic characteristics and other relevant clinical variables as part of future research. We did have access to information on the history of prescribed medications for the patients, and we explicitly investigated if adding such information improves our model. Considering the presence/absence and timing of prescriptions such as antibiotics, antidepressants, and beta-blockers did not show any significant improvement in performance

(Table 4). We surmised that in the context of the problem at hand, the diagnostic history of patients already captures most of the predictive information that medication history provides, and hence the latter does not improve results.

We also investigated if the different components of our overall model are all indeed necessary. Our results show that, as expected, on their own the individual components, eg, the PFSA models, do substantially worse (Table S17).

Among the 26 studied CCoR phenotypes (Table S7), those encompassing cardiovascular and respiratory conditions unsurprisingly had high importance for predicting early postoperative MACE in both sexes (Figure 1C). Overall, the sexes differed clearly on the relative importance of phenotypes, with only 3 of the top 5 and 5 of the top 10 phenotypes the same in women and men (Figure 1C). Differences between the sexes were even more marked regarding comorbidity spectra (Figure 2). Of the 57 diagnostic codes with the highest relative prevalence in positive versus control patients, only 3 were present among both women and men, and in all cases, at a different rank: skin carcinoma of the lower limb and hip (*ICD-10* code D04.7), nonspecific malignant neoplasm of the lung in a non-specific part of a bronchus (*ICD-10* code 34.9), and nonspecific diastolic (congestive) heart failure (*ICD-10* code I50.3).

We also estimated that CCoR has the potential to substantially reduce healthcare usage costs. While false positives increase the cost of additional confirmatory tests that must be undertaken for a positive flag, our cost model indicates that even with relatively large number of false positives (lower compared with RCRI), we are more cost-effective.

Finally, we note that a key limitation of this study is the use of administrative codes to ascertain past diagnostic history, which are vulnerable to coding errors, and do not record relevant nuances in diagnostic decisions and uncertainties. Also, while CCoR was derived using a well-validated national database of claims data, local healthcare usage patterns might require some recalibration at the level of an individual local institution. Finally, the CCoR was designed to estimate risk of early MACE following elective lower extremity total joint arthroplasty, and impact on the preoperative workup

(eg, preoperative stress testing<sup>11</sup>) or treatment (eg, new prescriptions) will require further investigation, as will the effect, if any, on clinical and pharmacoeconomic outcomes. Thus, further research and prospective trials are necessary before CcoR can enter everyday clinical practice.

## CONCLUSIONS

We developed and validated CcoR, an automated, potentially widely applicable screening tool to predict myocardial infarction and cardiac arrest in 2 to 4 weeks after primary total hip or knee arthroplasty. CcoR is solely based on patterns of comorbidity incidence, temporality, sequence, and synchronism in data already in the electronic health record, and hence spares patients diagnostic interventions and physicians the need to input and verify data for risk calculators. The impact of CcoR screening on clinical practice and on clinical and pharmacoeconomic outcomes also warrants investigation.

## ARTICLE INFORMATION

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## Supplemental Material

Data S1  
Figure S1  
Tables S1–S17  
References 20, 21, 51–64

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# Supplemental Materials

## DATA S1. SUPPLEMENTAL METHODS

### A. Time-series Modeling of Diagnostic History

Individual diagnostic histories can have long-term memory [52], implying that the order, frequency, and comorbid interactions between diseases are important for assessing the future risk of our target phenotype. We analyze patient-specific diagnostic code sequences by first representing the medical history of each patient as a set of stochastic categorical time-series — one each for a specific group of related disorders — followed by the inference of stochastic models for these individual data streams. These inferred generators are from a special class of Hidden Markov Models (HMMs), referred to as Probabilistic Finite State Automata (PFSA) [53]. The inference algorithm we use is distinct from classical HMM learning, and has important advantages related to its ability to infer structure, and its sample complexity (See Supplementary text, Section VI). We infer a separate class of models for the positive and control cohorts, and then the problem reduces to determining the probability that the short diagnostic history from a new patient arises from the positive as opposed to the control category of the inferred models.

### B. Inference & Event Periods

We train our predictive pipeline with all diagnostic codes that are recorded in the past 26 years from the point at which a prediction is made. This period from which we use data to train our pipeline is called the “inference window”. Our aim is to make predictions on the occurrence of the target diagnostic codes at 2 years from the end of the inference window. For patients in the control cohort, we make sure that no target code appears for 26 years after the end of the inference window. Additionally, when making predictions further into the future (upto 4 years, as described in the main text), we always make sure that the control group has no target codes for 1 year after the predicted time of diagnosis, i.e., if we are making a prediction of a diagnosis 4 years in future, then control group patients are chosen to have no diagnosis in at least next 5 years.

### C. Step 1: Partitioning The Human Disease Spectrum

We begin by partitioning the human disease spectrum into 26 non-overlapping categories. Each category is defined by a set of diagnostic codes from the International Classification of Diseases, Ninth Revision (ICD9) (See Table SI-S7 for description of the categories used in this study). For this study, we ended up using 4879398 and 7753318 diagnostic codes for males and females respectively (17554 and 19209 unique codes) spanning both ICD9 and ICD10 protocols (using ICD10 General Equivalence Mappings (GEMS) [54] equivalents where necessary), from a total 445391 patients. Transforming the diagnostic histories to report only the broad categories reduces the number of distinct codes that the pipeline needs to handle, thus improving statistical power. Our categories largely align with the top-level ICD9 categories, with small adjustments, e.g. bringing all infections under one category irrespective of the pathogen or the target organ. We do not pre-select the phenotypes; we want our algorithm to seek out the important patterns without any manual curation of the input data. For each patient, the past medical history is a sequence  $(t_1, x_1), \dots, (t_m, x_m)$ , where  $t_i$  are timestamps and  $x_i$  are ICD9 codes diagnosed at time  $t_i$ . We map individual patient history to a three-alphabet categorical time series  $z^k$  corresponding to the disease category  $k$ , as follows. For each week  $i$ , we have:

$$z_i^k = \begin{cases} 0 & \text{if no diagnosis codes in week } i \\ 1 & \text{if there exists a diagnosis of category } k \text{ in week } i \\ 2 & \text{otherwise} \end{cases} \quad (1)$$

The time-series  $z^k$  is observed in the inference period. Thus, each patient is represented by 43 mapped trinary series.

### D. Step 2: Model Inference & The Sequence Likelihood Defect $\Delta$

The mapped series, disease-category, and perioperative cardiac event diagnosis-status are considered to be independent sample paths, and we want to explicitly model these systems as specialized HMMs (PFSAs). We model the positive and the control cohorts and each disease category separately, ending up with a total of 104 HMMs at the population level (26 categories, 2 perioperative cardiac event status categories: positive and control, and 2 sexes). Each of these inferred models is a PFSA; a directed graph with probability-weighted edges, and acts as an optimal generator of the stochastic process driving the sequential appearance of the three letters

(as defined by Eq. (1)) corresponding to disease category, and perioperative cardiac event status-type (See Section VI in the Supplementary text for background on PFSA inference).

To reliably infer the perioperative cardiac event status-type of a new patient, i.e, the likelihood of a diagnostic sequence being generated by the corresponding perioperative cardiac event status-type model, we generalize the notion of Kullbeck-Leibler (KL) divergence [55] between probability distributions to a divergence  $\mathcal{D}_{KL}(G||H)$  between ergodic stationary categorical stochastic processes [56]  $G, H$  as:

$$\mathcal{D}_{KL}(G||H) = \lim_{n \rightarrow \infty} \frac{1}{n} \sum_{x:|x|=n} p_G(x) \log \frac{p_G(x)}{p_H(x)} \quad (2)$$

where  $|x|$  is the sequence length, and  $p_G(x), p_H(x)$  are the probabilities of sequence  $x$  being generated by the processes  $G, H$  respectively. Defining the log-likelihood of  $x$  being generated by a process  $G$  as :

$$L(x, G) = -\frac{1}{|x|} \log p_G(x) \quad (3)$$

The cohort-type for an observed sequence  $x$  — which is actually generated by the hidden process  $G$  — can be formally inferred from observations based on the following provable relationships (See Supplementary Text Section VI, Theorem 6 and 7):

$$\lim_{|x| \rightarrow \infty} L(x, G) = \mathcal{H}(G) \quad (4a)$$

$$\lim_{|x| \rightarrow \infty} L(x, H) = \mathcal{H}(G) + \mathcal{D}_{KL}(G||H) \quad (4b)$$

where  $\mathcal{H}(\cdot)$  is the entropy rate of a process [32]. Importantly, Eq. (4) shows that the computed likelihood has an additional non-negative contribution from the divergence term when we choose the incorrect generative process. Thus, if a patient is eventually going to be diagnosed with perioperative cardiac event, then we expect that the disease-specific mapped series corresponding to her diagnostic history be modeled by the PFSA in the positive cohort. Denoting the PFSA corresponding to disease category  $j$  for positive and control cohorts as  $G_+^j, G_0^j$  respectively, we can compute the *sequence likelihood defect* (SLD,  $\Delta^j$ ) as:

$$\Delta^j \triangleq L(G_0^j, x) - L(G_+^j, x) \rightarrow \mathcal{D}_{KL}(G_0^j||G_+^j) \quad (5)$$

With the inferred PFSA models and the individual diagnostic history, we estimate the SLD measure on the right-hand side of Eqn. (5). The higher this likelihood defect, the higher the similarity of diagnosis history to that of women with perioperative cardiac event.

#### E. Step 3: Risk Estimation Pipeline With Semi-supervised & Supervised Learning Modules

The risk estimation pipeline operates on patient specific information limited to the available diagnostic history in the inference period, and produces an estimate of the relative risk of perioperative cardiac event, with an associated confidence value. To learn the parameters and associated model structures of this pipeline, we transform the patient specific data to a set of engineered features, and the feature vectors realized on the positive and control sets are used to train a gradient-boosting classifier [57]. The complete list of 380 features used is provided in Table 6.

We need two training sets: one to infer the models, and one to train the classifier with features derived from the inferred models. Thus, we do a random 3-way split of the set of unique patients into *feature-engineering* (25%), *training* (25%) and *test* (50%) sets. We use the feature-engineering set of ids first to infer our PFSA models (*unsupervised model inference in each category*), which then allows us to train the gradient-boosting classifier using the training set and PFSA models (*classical supervised learning*), and we finally execute out-of-sample validation on the test set. Fig. 1c in the main text shows the top 20 features ranked in order of their relative importance (relative loss in performance when dropped out of the analysis).

## I. THRESHOLD SELECTION ON ROC CURVE

Once the ROC curve has been computed, we must choose a decision threshold to trade-off true positive rate and false positive rate. In situations where the number of negatives vastly outnumber the number of positives (which is the case in our problem), it is better to base this trade-off on a measure that is independent of the number of true negatives. The two popular measures considered in the literature are accuracy and the F1-score:

$$\text{accuracy} = \frac{t_p + t_n}{t_p + f_p + f_n + t_n} \quad (6)$$

$$F1 = \frac{2t_p}{2t_p + f_p + f_n} \quad (7)$$

The F1-score is the same as accuracy where the number of true negatives is the same as the number of true positives, thus partially correcting for the class imbalance.

The selection of the threshold may also be dictated by the current practice of ensuring high specificities in screening tests. Thus, a relevant clinically operating point is the one corresponding to 95% specificity, which is highlighted in Fig. 1a.

## II. NOTE ON RECEIVER OPERATING CHARACTERISTICS (ROC) AND PRECISION-RECALL CURVES

The ROC curve is a plot between the False Positive rate (TPR) and the True Positive Rate (TPR), and the area under the ROC curve (AUC) is often used as a measure of classifier performance. For the sake of completeness, we introduce the relevant definitions:

In the following P denotes the total number of positive samples (number of patients who are eventually diagnosed), and N denotes the total number of negative samples (number of patients in the control group).

**Definition 1.** *True positive rate, true negative rate, false positive rate, positive predictive value (PPV), and prevalence ( $\rho$ ) are defined as:*

$$TPR = \frac{t_p}{P} = \frac{t_p}{t_p + f_n} \quad (8)$$

$$TNR = \frac{t_n}{N} = \frac{t_n}{t_n + f_p} \quad (9)$$

$$FPR = 1 - TNR \quad (10)$$

$$PPV = \frac{t_p}{t_p + f_p} \quad (11)$$

$$\rho = \frac{P}{N + P} \quad (12)$$

where as before  $t_p, t_n, f_p, f_n$  are true positives, true negatives, false positives, and false negatives respectively.

Note that TPR is also referred to as **recall** or **sensitivity**, and PPV is also referred to as **precision**. True negative rate is also known as **specificity**.

A **precision-recall curve**, or a PPV-sensitivity curve is a plot between PPV and TPR.

Denoting sensitivity by  $s$ , and specificity by  $c$ , it follows that:

$$PPV = \frac{t_p/P}{t_p/P + (f_p/N)(N/P)} = \frac{TPR}{TPR + ((N - t_n)/N)(N/P)} \quad (13)$$

$$\Rightarrow PPV = \frac{s}{s + (1 - c)(\frac{1}{\rho} - 1)} \quad (14)$$

Thus, we note that for a fixed specificity and sensitivity, the PPV depends on prevalence. Indeed, it is clear from the above argument that PPV decreases with decreasing prevalence, and vice versa.

## III. EFFECT OF CLASS IMBALANCE

ROC curves are generally assumed to be robust to class imbalance. Note that if we assume that patient outcomes are independent (which is well-justified in the case of a non-communicable condition, particularly in large databases), then  $t_p$  should scale linearly with the total number of positives P, implying:

$$TPR = \frac{t_p}{P} = \frac{t'_p}{P'} \quad (15)$$

implying that with different sizes of the set of positive samples (or negative samples), the ROC curve remains unchanged. In particular, note that even if the prevalence is very small (say 0.01%), we cannot cheat to boost the AUC by labeling all predictions as negative, or stating that risk is always zero: in that case, our P is very small, but our  $t_p = 0$  strictly, implying that our  $TPR = 0$ , thus leading to a zero AUC. We can cheat to boost the accuracy (See the previous section), but not the AUC.

Note that while relative class sizes or imbalance does not affect the ROC (under the assumption that true positives and true negatives scale with the number of positives and negatives), very small absolute sample sizes might still result in poor performance of the model.

The precision-recall curves do get affected by class imbalance, or the prevalence, as shown by Eq (14). However, in diagnostic analysis, they are important since we are generally less interested in the number of true negatives; the ratio of false positives to the total number of positive recommendations by the algorithm is much more relevant, i.e., the PPV or the precision.

## IV. GENERATING PFSA MODELS FROM SET OF INPUT STREAMS WITH VARIABLE INPUT LENGTHS

Our PFSA reconstruction algorithm [53] is distinct from standard HMM learning. We do not need to pre-specify structures, or the number of states in the algorithm, and all model parameters are inferred directly from data. Additionally, we can operate either with 1) a single input stream, or 2) a set of input streams of possibly varying lengths which are assumed to be different and independent sample paths from the unknown stochastic generator we are trying to infer. At an intuitive level, we use the input data to infer the length of histories one must remember to estimate the current state, and predict futures for the process being modeled. Thus, we do not step through the symbol streams with a pre-specified model structure, and avoid the need to have equal-length inputs. More details of the algorithm are provided in the next section.

The ability to model a set of input streams of varying lengths is particularly important, since medical histories of different patients are typically of different lengths.

## V. PROBABILISTIC FINITE STATE AUTOMATA INFERENCE

### A. Probabilistic Finite-State Automaton

Let  $\Sigma$  be a finite alphabet of symbols with size  $|\Sigma|$ . The set of sequences of length  $d$  over  $\Sigma$  is denoted by  $\Sigma^d$ . The set of finite but unbounded sequences over  $\Sigma$  is denoted by  $\Sigma^*$ , the Kleene star operation [58], i.e.  $\Sigma^* = \bigcup_{d=0}^{\infty} \Sigma^d$ . We use lower case Greek, for example  $\sigma$  or  $\tau$ , for symbols in  $\Sigma$ , and lower case Latin, for example  $x$  or  $y$ , for sequences of symbols, i.e.  $x = \sigma_1 \sigma_2 \dots \sigma_n$ . We use  $|x|$  to denote the length of  $x$ . The empty sequence is denoted by  $\lambda$ .

We denote the set of strictly infinite sequences over  $\Sigma$  by  $\Sigma^\omega$ , and the set of strictly infinite sequences having  $x$  as prefix by  $x\Sigma^\omega$ . Let  $\mathcal{S} = \{x\Sigma^\omega : x \in \Sigma^*\} \cup \{\emptyset\}$ , we can verify that  $\mathcal{S}$  is a semiring [59] over  $\Sigma^\omega$ . We use  $\mathcal{F}$  to denote the sigma algebra generated by  $\mathcal{S}$ .

**Definition 2** (Stochastic Process over  $\Sigma$ ). *A stochastic process over a finite alphabet  $\Sigma$  is a collection of  $\Sigma$ -valued random variables  $\{X_t\}_{t \in \mathbb{N}}$  indexed by positive integers [56].*

We are specifically interested in processes in which the  $X_i$ s are not necessarily independently distributed.

**Definition 3** (Sequence-Induced Measure and Derivative). *For a process  $\mathcal{P}$ , let  $\Pr_{\mathcal{P}}(x)$  or simply  $\Pr(x)$  denote the probability  $\mathcal{P}$  producing a sample path prefixed by  $x$ . The measure  $\mu_x$  induced by a sequence  $x \in \Sigma^*$  is the extension [59] to  $\mathcal{F}$  of the premeasure defined on the semiring  $\mathcal{S}$  given by*

$$\forall x, y \in \Sigma^*, \mu_x(y\Sigma^\omega) \triangleq \frac{\Pr(xy)}{\Pr(x)}, \text{ if } \Pr(x) > 0 \quad (16)$$

For any  $d \in \mathbb{N}$ , the  $d$ -th order derivative of a sequence  $x$ , written as  $\phi_x^d$ , is defined to be the marginal distribution of  $\mu_x$  on  $\Sigma^d$ , with the entry indexed by  $y$  denoted by  $\phi_x^d(y)$ . The first-order derivative is called the symbolic derivative and is denoted by  $\phi_x$  for short.

**Definition 4** (Probabilistic Nerode Equivalence and Causal States [60]). *For any pair of sequences  $x, y \in \Sigma^*$ ,  $x$  is equivalent to  $y$ , written as  $x \sim y$ , if and only if either  $\Pr(x) = \Pr(y) = 0$ , or  $\mu_x = \mu_y$ . The equivalence class of a sequence  $x$  is denoted by  $[x]$  and is called a causal state [61]. The cardinality of the set of causal states is called the probabilistic Nerode index, or the Nerode index for simplicity.*

We can see from the definition that causal states captures how the history of a process influences its future. Since the probabilistic Nerode equivalence is right invariant, it gives rise naturally to a automaton structure introduced below.

**Definition 5** (Probabilistic Finite-State Automaton (PFSA)). *A PFSA  $G$  is defined by a quadruple  $(Q, \Sigma, \delta, \tilde{\pi})$ , where  $Q$  is a finite set,  $\Sigma$  is a finite alphabet,  $\delta : Q \times \Sigma \rightarrow \Sigma$  is called the transition map, and  $\tilde{\pi} : Q \rightarrow \mathbf{P}_\Sigma$ , where*

$\mathbf{P}_\Sigma$  is the space of probability distributions over  $\Sigma$ , is called the transition probability. The entry of  $\tilde{\pi}(q)$  indexed by  $\sigma$  is denoted by  $\tilde{\pi}(q, \sigma)$ .

**Definition 6** (Transition and Observation Matrices). The transition matrix  $\Pi$  is the  $|Q| \times |Q|$  matrix with the entry indexed by  $q, q'$ , written as  $\pi_{q,q'}$ , satisfying

$$\pi_{q,q'} \triangleq \sum_{\{\sigma \in \Sigma | \delta(q, \sigma) = q'\}} \tilde{\pi}(q, \sigma) \quad (17)$$

and the observation matrix  $\tilde{\Pi}$  is a  $|Q| \times |\Sigma|$  matrix with the entry indexed by  $q, \sigma$  equaling  $\tilde{\pi}(q, \sigma)$ .

We note that both  $\Pi$  and  $\tilde{\Pi}$  are stochastic, i.e. non-negative with rows summing up to 1.

**Definition 7** (Extension of  $\delta$  and  $\tilde{\pi}$  to  $\Sigma^*$ ). For any  $x = \sigma_1 \dots \sigma_k$ ,  $\delta(q, x)$  is defined recursively by

$$\delta(q, x) \triangleq \delta(\delta(q, \sigma_1 \dots \sigma_{k-1}), \sigma_k) \quad (18)$$

with  $\delta(q, \lambda) = q$ , and  $\tilde{\pi}(q, x)$  is defined recursively by

$$\tilde{\pi}(q, x) \triangleq \prod_{i=1}^k \tilde{\pi}(\delta(q, \sigma_1 \dots \sigma_{i-1}), \sigma_i) \quad (19)$$

with  $\tilde{\pi}(q, \lambda) = 1$ .

**Definition 8** (Strongly Connected PFSA). We say a PFSA is strongly connected if the underlying directed graph is strongly connected [62]. More precisely, a PFSA  $G = (Q, \Sigma, \delta, \tilde{\pi})$  is strongly connected if for any pair of distinct states  $q$  and  $q' \in Q$ , there is an  $x \in \Sigma^*$  such that  $\delta(q, x) = q'$ .

We assume all PFSA in the discussions in the sequel are strongly connected if not specified otherwise. For strongly connected PFSA  $G$ , there is a unique probability distribution over  $Q$  that satisfies  $\mathbf{v}^T \Pi = \mathbf{v}^T$ . This is the **stationary distribution** [63], [64] of  $G$  and is denoted as  $\varphi_G$ , or  $\varphi$  if  $G$  is understood.

**Definition 9** ( $\Gamma$ -Expression). We can encode the information contained in  $\delta$  and  $\tilde{\pi}$  by a set of  $|Q| \times |Q|$  matrices  $\Gamma = \{\Gamma_\sigma | \sigma \in \Sigma\}$ , where

$$\Gamma_\sigma|_{q,q'} \triangleq \begin{cases} \tilde{\pi}(q, \sigma) & \text{if } \delta(q, \sigma) = q', \\ 0 & \text{if otherwise.} \end{cases} \quad (20)$$

$\Gamma_\sigma$  is called **event-specific transition matrix**, with the event being that  $\sigma$  is current the output.  $\Gamma_\sigma$  can also be extended to arbitrary  $x \in \Sigma^*$  by defining  $\Gamma_x = \prod_{i=1}^k \Gamma_{\sigma_i}$  with  $\Gamma_\lambda = I$ .

**Definition 10** (Sequence-Induced Distribution on States). For a PFSA  $G = (Q, \Sigma, \delta, \tilde{\pi})$  and a distribution  $\varphi_0$  on  $Q$ , the **distribution on  $Q$  induced by a sequence  $x$**  is given by  $\varphi_{G, \varphi_0}^T(x) = [\varphi_0^T \Gamma_x]$  with  $\varphi_{G, \varphi_0}(\lambda) = \varphi_0$ . The entry indexed by  $q \in Q$  of the vector  $\varphi_{G, \varphi_0}(x)$  is written as  $\varphi_{G, \varphi_0}(x, q)$ . When  $\varphi_0 = \varphi_G$ , the stationary distribution of  $G$ , we write  $\varphi_{G, \varphi_0}(x)$  as  $\varphi_G(x)$ , or simply as  $\varphi(x)$ , if  $G$  is understood.

**Definition 11** (Stochastic Process Generated by a PFSA). Let  $G = (Q, \Sigma, \delta, \tilde{\pi})$  be a PFSA and let  $\varphi_0$  be a distribution on  $Q$ , the  $\Sigma$ -valued stochastic process  $\{X_t\}_{t \in \Sigma}$  generated by  $G$  and  $\varphi_0$  satisfies that  $X_1$  follows the distribution  $\varphi_0$  and  $X_{t+1}$  follows the distribution  $\varphi_{G, \varphi_0}(X_1 \dots X_t)$  for  $t \in \mathbb{N}$ .

For the rest of this paper, we will assume  $\varphi_0 = \varphi_G$  if not specified otherwise. We can show that, when initialized with  $\varphi_G$ , the process generated by a PFSA  $G$  is stationary and ergodic. We also note the, for the process generate by  $G$ , we have  $\phi_x = \varphi_G(x)^T \tilde{\Pi}$ . Since  $\varphi_G(\lambda) = \varphi_G$ , the symbolic derivative of the empty sequence  $\phi_\lambda$  is the stationary distribution on the symbols.

**Definition 12** (Synchronizable PFSA and Synchronizing Sequence). A **synchronizing sequence** is a finite sequence that sends an arbitrary state of the PFSA to a fixed state [65]. To be more precise, let  $G = (Q, \Sigma, \delta, \tilde{\pi})$  be a PFSA, we say a sequence  $x \in \Sigma^*$  is a synchronizing sequence to a state  $q \in Q$  if  $\delta(q', x) = q$  for all  $q' \in Q$ . A PFSA is **synchronizable** if it has at least one synchronizing sequence. Given a sample path generated by a PFSA, we say the PFSA is **synchronized** if a synchronizing sequence transpires in the sample path.

**Definition 13** (Equivalence and Irreducibility). Two PFSA  $G$  and  $H$  are **equivalent** if they generate the same stochastic process. A PFSA  $G$  is said to be **irreducible**, if there is not another PFSA with smaller state set that is equivalent to  $G$ .

**Definition 14.** Consider a PFSA  $G$  over state set  $Q$ . For a give  $\varepsilon > 0$ , we say a sequence  $x$  is a  $\varepsilon$ -synchronizing sequence to a state  $q \in Q$  if

$$\|\varphi_G(x) - \mathbf{e}_q\|_\infty \leq \varepsilon. \quad (21)$$

---

**Algorithm 1: GenESeSS**


---

**Data:** A sequence  $x$  over alphabet  $\Sigma$ ,  $0 < \varepsilon < 1$

**Result:** State set  $Q$ , transition map  $\delta$ , and transition probability  $\tilde{\pi}$

```

/* Step One: Approximate  $\varepsilon$ -synchronizing sequence */
```

- 1 Let  $L = \lceil \log_{|\Sigma|} 1/\varepsilon \rceil$ ;
- 2 Calculate the **derivative heap**  $D_\varepsilon^x$  equaling  $\{\hat{\phi}_y^x : y \text{ is a sub-sequence of } x \text{ with } |y| \leq L\}$ ;
- 3 Let  $\mathcal{C}$  be the convex hull of  $D_\varepsilon^x$ ;
- 4 Select  $x_0$  with  $\hat{\phi}_{x_0}^x$  being a vertex of  $\mathcal{C}$  and has the highest frequency in  $x$ ;

```

/* Step Two: Identify transition structure */
```

- 5 Initialize  $Q = \{q_0\}$ ;
- 6 Associate to  $q_0$  the **sequence identifier**  $x_{q_0}^{id} = x_0$  and the probability vector  $d_{q_0} = \hat{\phi}_{x_0}^x$ ;
- 7 Let  $\tilde{Q}$  be the set of states that are just added and initialize it to be  $Q$ ;
- 8 **while**  $\tilde{Q} \neq \emptyset$  **do**
- 9     Let  $Q_{new} = \emptyset$  be the set of new states;
- 10    **for**  $(q, \sigma) \in \tilde{Q} \times \Sigma$  **do**
- 11     Let  $x = x_q^{id}$  and  $d = \hat{\phi}_{x\sigma}^x$ ;
- 12     **if**  $\|d - d_{q'}\|_\infty < \varepsilon$  **for some**  $q' \in Q$  **then**
- 13         Let  $\delta(q, \sigma) = q'$ ;
- 14     **else**
- 15         Let  $Q_{new} = Q_{new} \cup \{q_{new}\}$  and  $Q = Q \cup \{q_{new}\}$ ;
- 16         Associate to  $q_{new}$  the sequence identifier  $x_{q_{new}}^{id} = x\sigma$  and the probability vector  $d_{q_{new}} = d$ ;
- 17         Let  $\delta(q, \sigma) = q_{new}$ ;
- 18     Let  $\tilde{Q} = Q_{new}$ ;
- 19     Take a strongly connected subgraph of the labeled directed graph defined by  $Q$  and  $\delta$ , and denote the vertex set of the subgraph again by  $Q$ ;

```

/* Step Three: Identify transition probability */
```

- 20 Initialize counter  $N[q, \sigma]$  for each pair  $(q, \sigma) \in Q \times \Sigma$ ;
- 21 Choose a random starting state  $q \in Q$ ;
- 22 **for**  $\sigma \in x$  **do**
- 23     Let  $N[q, \sigma] = N[q, \sigma] + 1$ ;
- 24     Let  $q = \delta(q, \sigma)$ ;
- 25 Let  $\tilde{\pi}(q) = \llbracket (N[q, \sigma])_{\sigma \in \Sigma} \rrbracket$ ;
- 26 **return**  $Q, \delta, \tilde{\pi}$ ;

---

While there exists PFSA that is not synchronizable, we can show that an irreducible PFSA always has an  $\varepsilon$ -synchronizing sequence for some state  $q$  for arbitrarily small  $\varepsilon > 0$ . Moreover, we can show that as length increases, sequences produced by PFSA become uniformly  $\varepsilon$ -synchronizing. These two are the underpinning properties for the inference algorithm of PFSA (See Alg. 1), because they imply that  $\phi_x$  can be used to approximate  $\tilde{\pi}(q)$  if  $x$  are properly prefixed and long enough.

**Definition 15** (Joint  $\varepsilon$ -Synchronizing Sequence). *Let  $G$  and  $H$  be two PFSA over state sets  $Q_G$  and  $Q_H$ , respectively. For a fixed  $\varepsilon$ , a sequence  $x$  is said to be **jointly  $\varepsilon$ -synchronizing** to  $(q, r) \in Q_G \times Q_H$  if  $x$  is  $\varepsilon$ -synchronizing to  $q$  and to  $r$  simultaneously. We define*

$$\Sigma_{\varepsilon, (q, r)}^d \triangleq \{x \in \Sigma^d : x \text{ jointly } \varepsilon\text{-synchronizing to } (q, r)\} \quad (22)$$

**Definition 16** (Joint Pair of States). *Let  $G$  and  $H$  be two PFSA over state sets  $Q_G$  and  $Q_H$ , respectively. Define*

$$p_G(q, r) \triangleq \lim_{d \rightarrow \infty} p_G(\Sigma_{\varepsilon, (q, r)}^d) \quad (23)$$

*A pair of states  $(q, r) \in Q_G \times Q_H$  is called a  **$G$ -joint pair** of states if  $p_G(q, r) > 0$ . We also define*

$$Q_c \triangleq \{(q, r) \in Q_G \times Q_H : (q, r) \text{ is a } G\text{-joint pair}\} \quad (24)$$

The inference algorithm for PFSA is called **GenESeSS** for Generator Extraction Using Self-similar Semantics. With an input sequence  $x$  and a hyperparameter  $\varepsilon$ , **GenESeSS** outputs a PFSA in the following three steps: 1) approximate an almost synchronizing sequence; 2) identify the transition structure of the PFSA; 3) calculate the transition probabilities of the PFSA. See Alg. 1 [53] for details.

---

**Algorithm 2:** Log-likelihood

---

**Data:** A PFSA  $G = (\Sigma, Q, \delta, \tilde{\pi})$  and a sequence  $x$  over alphabet  $\Sigma$   
**Result:** Log-likelihood  $L(x, G)$  of  $G$  generating  $x$

- 1 Calculate the state transition matrix  $\Pi$  and observation  $\tilde{\Pi}$ ;
- 2 Calculate the stationary distribution over states  $\varphi_G$  of  $G$  from  $\Pi$ ;
- 3 Calculate the stationary distribution of alphabet  $\phi_\lambda^T = \varphi_G^T \tilde{\Pi}$ ;
- 4 Initialize  $p$  by  $\varphi_G$  and  $q$  by  $\phi_\lambda$ ;
- 5 Let  $L = 0$ ;
- 6 **for**  $i$  from 1 to  $|x|$  **do**
- 7   Let  $\sigma$  be the  $i$ -th entry of  $x$ ;
- 8   Let  $L = L - \log q|_\sigma$ ;
- 9   Let  $p^T = [p^T \Gamma_\sigma]$  where  $\Gamma_\sigma$  is defined in 9;
- 10   Let  $q^T = p^T \tilde{\Pi}$ ;
- 11 **return**  $L/|x|$ ;

---

## VI. THEORETICAL DEVELOPMENT OF SEQUENCE LIKELIHOOD DEFECT

**Definition 17** (Entropy Rate and KL Divergence). *By entropy rate of a PFSA, we mean the entropy rate of the stochastic process generated by the PFSA [32]. Similarly, by KL divergence of two PFSA, we mean the KL divergence between the two processes generated by them [66]. More precisely, we have*

$$\mathcal{H}(G) = - \lim_{d \rightarrow \infty} \frac{1}{d} \sum_{x \in \Sigma^d} p(x) \log p(x) \quad (25)$$

and the KL divergence

$$\mathcal{D}_{KL}(G \| H) = \lim_{d \rightarrow \infty} \frac{1}{d} \sum_{x \in \Sigma^d} p_G(x) \log \frac{p_G(x)}{p_H(x)} \quad (26)$$

whenever the limits exist.

**Theorem 1** (Closed-form Formula for Entropy Rate and KL Divergence). *The entropy rate of a PFSA  $G = (\Sigma, Q, \delta, \tilde{\pi})$  is given by*

$$\mathcal{H}(G) = \sum_{q \in Q} \varphi_G(q) \cdot h(\tilde{\pi}(q)) \quad (27)$$

where  $h(v)$  is the based-2 entropy of the probability vector  $v$ .

Consider two PFSA  $G = (Q_G, \Sigma, \delta_G, \tilde{\pi}_G)$  and  $H = (Q_H, \Sigma, \delta_H, \tilde{\pi}_H)$  with  $\mu_G$  being absolutely continuous with respect to  $\mu_H$ . Let  $Q_c$  be the set of  $G$ -joint pairs of states, we have

$$\mathcal{D}_{KL}(G \| H) = \sum_{(q, r) \in Q_c} p_G(q, r) \mathcal{D}_{KL}(\tilde{\pi}_G(q) \| \tilde{\pi}_H(r)) \quad (28)$$

**Definition 18** (Log-likelihood). *Let  $x \in \Sigma^d$ , the log-likelihood [32] of a PFSA  $G$  generating  $x$  is given by*

$$L(x, G) = -\frac{1}{d} \log p_G(x) \quad (29)$$

The calculation of log-likelihood is detailed in Alg. 2.

**Theorem 2** (Convergence of log-likelihood). *Let  $G$  and  $H$  be two reduced PFSA, and let  $x \in \Sigma^d$  be a sequence generated by  $G$ . Then we have*

$$L(x, H) \rightarrow \mathcal{H}(G) + \mathcal{D}_{KL}(G \| H) \quad (30)$$

in probability as  $d \rightarrow \infty$ .

*Proof.* We first notice that

$$\sum_{x \in \Sigma^d} p_G(x) \log \frac{p_G(x)}{p_H(x)} = \sum_{x \in \Sigma^{d-1}} \sum_{\sigma \in \Sigma} p_G(x) \varphi_G(x) \left. \tilde{\Pi}_G \right|_\sigma \log \frac{\varphi_G(x) \varphi_G(x) \left. \tilde{\Pi}_G \right|_\sigma}{p_H(x) \varphi_H(x) \left. \tilde{\Pi}_H \right|_\sigma} \quad (31)$$

$$= \sum_{x \in \Sigma^{d-1}} p_G(x) \log \frac{p_G(x)}{p_H(x)} + \underbrace{\sum_{x \in \Sigma^{d-1}} p_G(x) \sum_{\sigma \in \Sigma} \varphi_G(x) \left. \tilde{\Pi}_G \right|_\sigma \log \frac{\varphi_G(x) \left. \tilde{\Pi}_G \right|_\sigma}{\varphi_H(x) \left. \tilde{\Pi}_H \right|_\sigma}}_{D_d} \quad (32)$$

By induction, we have  $\mathcal{D}_{KL}(G \parallel H) = \lim_{d \rightarrow \infty} \frac{1}{d} \sum_{i=1}^d D_i$ , and hence by Cesàro summation theorem [67], we have  $\mathcal{D}_{KL}(G \parallel H) = \lim_{d \rightarrow \infty} D_d$ . Let  $x = \sigma_1 \sigma_2 \dots \sigma_n$  be a sequence generated by  $G$ . Let  $x^{[i-1]}$  is the truncation of  $x$  at the  $(i-1)$ -th symbols, we have

$$-\frac{1}{n} \sum_{i=1}^n \log \varrho_H(x^{[i-1]}) \tilde{\Pi}_H|_{\sigma_i} = \underbrace{\frac{1}{n} \sum_{i=1}^n \log \frac{\varrho_G(x^{[i-1]}) \tilde{\Pi}_G|_{\sigma_i}}{\varrho_H(x^{[i-1]}) \tilde{\Pi}_H|_{\sigma_i}}}_{A_{x,n}} - \underbrace{\frac{1}{n} \sum_{i=1}^n \log \varrho_G(x^{[i-1]}) \tilde{\Pi}_G|_{\sigma_i}}_{B_{x,n}} \quad (33)$$

Since the stochastic process  $G$  generates is ergodic, we have

$$\lim_{n \rightarrow \infty} A_{x,n} = \lim_{d \rightarrow \infty} D_d = \mathcal{D}_{KL}(G \parallel H) \quad (34)$$

and  $\lim_{n \rightarrow \infty} B_{x,n} = \mathcal{H}(G)$ .  $\square$

## VII. PIPELINE OPTIMIZATION: HYPER-TRAINING, TRAINING, & VALIDATION

Our pipeline comprises a network of individually trained light gradient boosting machine (LGBM) [32] classifiers that focus on complementary aspects of the problem, and operate on different categories of input features as described next. Importantly, some of these features need to be generated non-trivially from the raw data, and these *feature generators* have parameters that need to be trained as well (or comprise models that need to be inferred). We call this inference of the feature-generators as **hyper-training**. Importantly, this is different from the more common notion of hyper-parameters. Hyper-parameters are one or more variables whose scalar values are commonly tuned by grid-search or via some meta-heuristics to optimize classifiers, whereas hyper-training produces generators of features, not simply a set of numbers.

### *Hyper-training & Training*

*Trinary Quantization of Medical Histories:* The medical histories are mapped into trinary disease-phenotype-specific data-streams to enable generation of some of the features described below, as outlined in Section -C (Step 1).

*Feature Categories:* The features used in the pipeline maybe categorized as follows:

*PFSA scores:* The PFSA scores are computed on the basis of the inferred PFSA models as described in the previous sections. The generation of the PFSA models from the trinary data-streams is the first hyper-training step. These scores consist of the negative and positive log-likelihood of a phenotype-specific quantized medical history being generated by the PFSA models for the positive cohort and the control cohort of sex-stratified patients, and the corresponding sequence likelihood defects (See SI-Section -D). Recall that PFSA are specialized HMMs, and these measures encode the dynamics of the underlying processes, and are sensitive to the ordering, and frequency of the codes at the resolution of the disease phenotypes. Also, recall that diseases phenotypes are broad categories of diagnostic codes, and that we generate PFSA models for each category, and separately for the sexes and the positive cohort and the control cohorts).

*Prevalence scores (p-scores):* The p-scores focus on individual diagnostic codes, and we create a dictionary of the ratio of relative prevalence of each code (relative to the set of all codes present) in the positive category (for each sex) to the control category. This is the second hyper-training step. In the later steps of the pipeline, we use dictionary look ups to map codes to their p-scores, and also their aggregate measures such as mean, median, and variance to train a downstream LGBM.

*Rare scores:* These scores consist of a subset of p-scores which correspond to codes with particularly high and low relative prevalences ( $p\text{-score} > 2$  or  $< .5$ ). Thus, this feature category depends on the p-score dictionary generated in the second hyper-training step.

*Sequence scores:* Sequence scores are relatively straight-forward statsitical measures such as mean, median, variance, time since last occurrence etc.. on the trinary phenotype-specific sex-stratified histories. No hyper-training is required for the generation of the sequence features.

Thus we require three splits of the training dataset. The first split is used to carry out hyper-training of the PFSA models and the p-score dictionary. The second split is used to train the score-category specific LGBMs, one for each feature category. And the third split is used to train the final LGBM that takes inputs from the outputs of the four LGBMs in the previous layer.

### *Validation*

In validation, or actual prediction of patient fate, we use the trinary mapping, generate the features using the PFSA models and the p-score dictionary, and calculate the raw-risk via the trained LGBM network. The relative score is then obtained by a choice of the operating point reflecting the specificity/sensitivity trade-off discussed before.

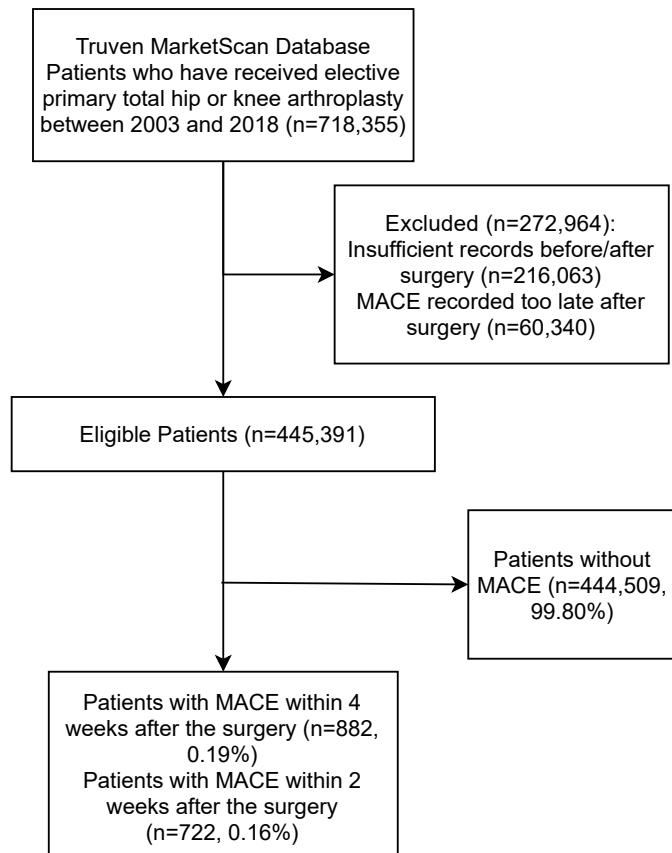


Figure S1: CONSORT diagram conforming to the CONSORT-AI Extension guidelines stated at [https://doi.org/10.1016/S2589-7500\(20\)30218-1](https://doi.org/10.1016/S2589-7500(20)30218-1)

Table S1: Inclusion/Exclusion, Positive/Control Criteria & Cohort Definitions

	<b>Definitions</b>
Inclusion/Exclusion Criteria	<b>Age 45 - 95</b> Has total hip/knee CPT codes (See Table S2) in medical history and length of history available before cardiac event spans $\geq 1$ year Has a myocardial infarction or a cardiac arrest <sup>‡</sup> (See Table S4 for list of target codes used to identify cardiac event in diagnostic history) 4 weeks (2 weeks considered in secondary analysis) after surgery (positive cohort) Has 0.5 yr of medical history available after surgery (control)
Positive & Control Cohorts	<b>Positive Cohort:</b> At least one code for cardiac event (Table S4 ) <b>Control Cohort:</b> No code on cardiac event within 26 weeks of surgery

Table S2: Current Procedural Terminology (CPT) codes for total hip/knee replacement used

CPT code	description
27130	Total Hip Replacement/Resurfacing
27132	Total Hip Replacement/Resurfacing
81.51	Total hip replacement
0SR9	Replacement: Hip Joint, Right
0SRB	Replacement: Hip Joint, Left
27442	Knee Total Replacement - (Arthroplasty)
27443	Knee Total Replacement - (Arthroplasty)
27445	Knee Total Replacement - (Arthroplasty)
27446	Knee Total Replacement - (Arthroplasty)
27447	Knee Total Replacement - (Arthroplasty)
81.54	Total knee replacement
0SRC	Replacement: Knee Joint, Right
0SRD	Replacement: Knee Joint, Left

Table S3: Codes used to determine RCRI

Description	Constituent Codes (*NDC: National Drug Code)
History of Heart Failure	ICD9 codes: 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9, 428.2, 428.3, 428.4; ICD10 codes: I50.1, I50.20, I50.21, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43, I50.810, I50.811, I50.812, I50.813, I50.814, I50.82, I50.83, I50.84, I50.89, I50.9, I50.2, I50.3, I50.4, I50.8, I50.81
History of Cerebrovascular Disease	ICD9 codes: 430, 431, 432.0, 432.1, 432.9, 433.00, 433.01, 433.10, 433.11, 433.20, 433.21, 433.30, 433.31, 433.80, 433.81, 433.90, 433.91, 434.00, 434.01, 434.10, 434.11, 434.90, 434.91, 435.0, 435.1, 435.2, 435.3, 435.8, 435.9, 436, 437.0, 437.1, 437.2, 437.3, 437.4, 437.5, 437.6, 437.7, 437.8, 437.9, 438.0, 438.10, 438.11, 438.12, 438.13, 438.14, 438.19, 438.20, 438.21, 438.22, 438.30, 438.31, 438.32, 438.40, 438.41, 438.42, 438.50, 438.51, 438.52, 438.53, 438.6, 438.7, 438.81, 438.82, 438.83, 438.84, 438.85, 438.89, 438.9, 432, 433, 434, 435, 437, 438, 433.0, 433.1, 433.2, 433.3, 433.8, 433.9, 434.0, 434.1, 434.9, 438.1, 438.2, 438.3, 438.4, 438.5, 438.8; ICD10 codes: I60.00, I60.01, I60.02, I60.10, I60.11, I60.12, I60.2, I60.30, I60.31, I60.32, I60.4, I60.50, I60.51, I60.52, I60.6, I60.7, I60.8, I60.9, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9, I62.00, I62.01, I62.02, I62.03, I62.1, I62.9, I63.00, I63.011, I63.012, I63.013, I63.019, I63.02, I63.031, I63.032, I63.033, I63.039, I63.09, I63.10, I63.111, I63.112, I63.113, I63.119, I63.12, I63.131, I63.132, I63.133, I63.139, I63.19, I63.20, I63.211, I63.212, I63.213, I63.219, I63.22, I63.231, I63.232, I63.232, I63.329, I63.331, I63.332, I63.333, I63.339, I63.341, I63.342, I63.343, I63.349, I63.39, I63.40, I63.411, I63.412, I63.413, I63.419, I63.421, I63.422, I63.423, I63.429, I63.431, I63.432, I63.433, I63.441, I63.442, I63.443, I63.449, I63.449, I63.50, I63.511, I63.512, I63.513, I63.519, I63.521, I63.522, I63.523, I63.529, I63.531, I63.532, I63.533, I63.539, I63.541, I63.542, I63.543, I63.549, I63.59, I63.6, I63.81, I63.89, I63.9, I65.01, I65.02, I65.03, I65.09, I65.1, I65.21, I65.22, I65.23, I65.29, I65.8, I65.9, I66.01, I66.02, I66.03, I66.09, I66.11, I66.12, I66.13, I66.19, I66.21, I66.22, I66.23, I66.29, I66.3, I66.8, I66.9, I67.0, I67.1, I67.2, I67.3, I67.4, I67.5, I67.6, I67.7, I67.81, I67.82, I67.83, I67.841, I67.848, I67.850, I67.858, I67.89, I67.9, I68.0, I68.2, I68.8, I69.00, I69.010, I69.011, I69.012, I69.013, I69.014, I69.015, I69.018, I69.019, I69.020, I69.021, I69.022, I69.023, I69.028, I69.031, I69.032, I69.033, I69.034, I69.039, I69.041, I69.042, I69.043, I69.044, I69.049, I69.051, I69.052, I69.053, I69.054, I69.059, I69.061, I69.062, I69.063, I69.064, I69.065, I69.069, I69.090, I69.091, I69.092, I69.093, I69.098, I69.10, I69.110, I69.111, I69.112, I69.113, I69.114, I69.115, I69.118, I69.119, I69.120, I69.121, I69.122, I69.123, I69.128, I69.131, I69.132, I69.133, I69.134, I69.139, I69.141, I69.142, I69.143, I69.144, I69.149, I69.151, I69.152, I69.153, I69.154, I69.159, I69.161, I69.162, I69.163, I69.164, I69.165, I69.169, I69.190, I69.191, I69.192, I69.193, I69.198, I69.20, I69.210, I69.211, I69.212, I69.213, I69.214, I69.215, I69.218, I69.219, I69.220, I69.221, I69.222, I69.223, I69.228, I69.231, I69.232, I69.233, I69.234, I69.239, I69.241, I69.242, I69.243, I69.244, I69.249, I69.251, I69.252, I69.253, I69.254, I69.259, I69.261, I69.262, I69.263, I69.264, I69.265, I69.269, I69.290, I69.291, I69.292, I69.293, I69.298, I69.30, I69.310, I69.311, I69.312, I69.313, I69.314, I69.315, I69.318, I69.319, I69.320, I69.321, I69.322, I69.323, I69.328, I69.331, I69.332, I69.333, I69.334, I69.339, I69.341, I69.342, I69.343, I69.344, I69.349, I69.351, I69.352, I69.353, I69.354, I69.359, I69.361, I69.362, I69.363, I69.364, I69.365, I69.369, I69.390, I69.391, I69.392, I69.393, I69.398, I69.80, I69.810, I69.811, I69.812, I69.813, I69.814, I69.814, I69.815, I69.818, I69.819, I69.820, I69.821, I69.822, I69.823, I69.828, I69.831, I69.832, I69.833, I69.834, I69.839, I69.841, I69.842, I69.843, I69.844, I69.849, I69.851, I69.852, I69.853, I69.854, I69.859, I69.861, I69.862, I69.863, I69.864, I69.865, I69.869, I69.890, I69.891, I69.892, I69.893, I69.898, I69.90, I69.910, I69.911, I69.912, I69.913, I69.914, I69.915, I69.918, I69.919, I69.920, I69.921, I69.922, I69.923, I69.928, I69.931, I69.932, I69.933, I69.934, I69.935, I69.939, I69.941, I69.942, I69.943, I69.944, I69.949, I69.951, I69.952, I69.953, I69.954, I69.959, I69.961, I69.962, I69.963, I69.964, I69.965, I69.969, I69.990, I69.991, I69.992, I69.993, I69.998, I60, I61, I62, I63, I65, I66, I67, I68, I69, I60.0, I60.1, I60.3, I60.5, I62.0, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.8, I65.0, I65.2, I66.0, I66.1, I66.2, I67.8, I69.0, I69.1, I69.2, I69.3, I69.8, I69.9, I63.01, I63.03, I63.11, I63.13, I63.21, I63.23, I63.31, I63.32, I63.33, I63.34, I63.41, I63.42, I63.43, I63.44, I63.51, I63.52, I63.53, I63.54, I67.84, I67.85, I69.01, I69.02, I69.03, I69.04, I69.05, I69.06, I69.09, I69.11, I69.12, I69.13, I69.14, I69.15, I69.16, I69.19, I69.21, I69.22, I69.23, I69.24, I69.25, I69.26, I69.29, I69.31, I69.32, I69.33, I69.34, I69.35, I69.36, I69.39, I69.81, I69.82, I69.83, I69.84, I69.85, I69.86, I69.88, I69.91, I69.92, I69.93, I69.94, I69.95, I69.96, I69.99
History of Ischemic Heart Disease	ICD9 codes: 410.00, 410.01, 410.02, 410.10, 410.11, 410.12, 410.20, 410.21, 410.22, 410.30, 410.31, 410.32, 410.40, 410.41, 410.42, 410.50, 410.51, 410.52, 410.60, 410.61, 410.62, 410.70, 410.71, 410.72, 410.80, 410.81, 410.82, 410.90, 410.91, 410.92, 411.0, 411.1, 411.81, 411.89, 412, 413.0, 413.1, 413.9, 414.00, 414.01, 414.02, 414.03, 414.04, 414.05, 414.06, 414.07, 414.10, 414.11, 414.12, 414.19, 414.2, 414.3, 414.4, 414.8, 414.9, 410, 411, 413, 414, 410.0, 410.1, 410.2, 410.3, 410.4, 410.5, 410.6, 410.7, 410.8, 410.9, 411.8, 414.0, 414.1; ICD10 codes: I20.0, I20.1, I20.8, I20.9, I21.01, I21.02, I21.09, I21.11, I21.19, I21.21, I21.29, I21.3, I21.4, I21.9, I21.9, I21.A1, I21.A9, I22.0, I22.1, I22.2, I22.8, I22.9, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.7, I23.8, I24.0, I24.1, I24.8, I24.9, I25.10, I25.110, I25.111, I25.118, I25.119, I25.2, I25.2, I25.3, I25.41, I25.42, I25.5, I25.6, I25.700, I25.701, I25.708, I25.709, I25.710, I25.711, I25.718, I25.719, I25.720, I25.721, I25.728, I25.729, I25.730, I25.731, I25.738, I25.739, I25.750, I25.751, I25.758, I25.759, I25.760, I25.761, I25.768, I25.769, I25.790, I25.791, I25.798, I25.799, I25.810, I25.811, I25.812, I25.82, I25.83, I25.84, I25.89, I25.9, I20, I21, I22, I23, I24, I25, I21.0, I21.1, I21.2, I21.A, I25.1, I25.4, I25.7, I25.8, I25.11, I25.70, I25.71, I25.72, I25.73, I25.75, I25.76, I25.79, I25.81
Pre-operative creatinine > 2 mg/dL / 176.8 µmol/L - Approximated by History of Chronic Kidney Disease	ICD9 codes: 585.3, 585.5, 585.6, 585.4; ICD10 codes: N18.30, N18.31, N18.32, N18.4, N18.5, N18.6, N18.3
Pre-operative treatment with Insulin	NDC* codes: 08881242112, 08881250305, 54868582400, 08881750023, 08881242120, 08881250313, 38396043277, 08881250321, 00169369619, 08881520665, 08881242138, 36652040218, 56151171101, 08881520673, 08496275501, 08881250354, 08496275511, 08881250362, 08080810055, 36652040276, 00002831101, 08080040028, 08080040029, 08080040030, 08396800100, 38396043377, 08881750130, 36652040318, 00002831517, 56151171201, 08881750155, 08881512597, 36652400801, 36652400802, 36652400803, 36652400805, 36652400806, 36652400807, 36652400808, 68258889903, 08881103025, 36652040376, 96295010494, 96295010495, 96295010496, 96295010497, 96295010498, 08881512647, 08396800200, 38396043477, 57515008218, 08881750239, 56151171301, 08881750254, 55948009710, 08881250545, 57515008258, 36652400901, 36652400902, 36652400903, 36652400904, 36652400905, 08080032010, 36652400906, 36652400907, 36652400908, 59060183302, 08881512738, 08881512746, 08396800300, 54569165101, 08881701166, 54569165102, 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08287126344

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**Pre-operative treatment with Insulin (contd.)**	NDC\* codes: 08881533254, 08881566023, 08881500493, 08881500501, 00002834001, 08881820008, 00069072437, 08881516911, 00169030001, 0808020005, 08881713534, 08271352200, 08881516937, 08080200077, 08881533338, 08290324906, 00002751201, 08290324907, 08290324908, 08290324909, 08290324910, 08290324911, 08290324912, 08290841002, 08290841003, 96295104940, 96295104950, 76300022201, 96295104960, 24385098178, 55948022210, 96295104970, 00002841201, 00002871759, 96295104980, 98302013919, 98302013920, 98302013930, 98302013931, 08271352300, 98302013932, 98302013933, 98302013934, 98302013935, 98302013936, 98302013937, 98302013938, 98302013939, 98302013940, 98302013941, 08881050116, 08881050121, 08290841101, 08290841103, 08080323100, 08881050140, 00003183410, 00069005019, 24385098278, 08080323112, 00003244110, 08080020028, 08080020029, 08080020030, 00002821101, 00002831201, 08881533510, 08470205001, 08881050197, 76300071511, 76300071512, 76300071513, 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Pre-operative treatment with Insulin	<p>NDC* codes: 08290843801, 08881601689, 08290843803, 56151170201, 08881601697, 08881200292, 08881601705, 08881700010, 08881601713, 08881601721, 08881200318, 08881200326, 08496315601, 08881601747, 08881200342, 08881601762, 00536993001, 08881601770, 59060231404, 38396042490, 54569295100, 54569295101, 56151170301, 08881200383, 08881716503, 54868131100, 08881716511, 87701445930, 08881200433, 08881716529, 08881601846, 08881200441, 08881716537, 08881601853, 08881601861, 08881020233, 54868589900, 08881200466, 08881601879, 08290008410, 08290008411, 00182312285, 38396042590, 00182312288, 08290844001, 08290008430, 08290008431, 87701044593, 08881200508, 08222072191, 00904396160, 36652400001, 36652400002, 36652400003, 08881200516, 36652400004, 36652400005, 36652400006, 36652400007, 36652400008, 08290008465, 08290008466, 08881200573, 00839802306, 38396042690, 00069070737, 08881135068, 54868532700, 54868532701, 36652400101, 36652400102, 36652400103, 36652400104, 36652400105, 36652400106, 36652400107, 36652400108, 08881135084, 08214502901, 00002841101, 59060231704, 00839802406, 38396042790, 08080621100, 00002821601, 08881520178, 08080621112, 08881700408, 08881520186, 00002824001, 00002821517, 08881200714, 36652400202, 36652400203, 36652400205, 36652400206, 36652400207, 36652400208, 08222072399, 00169033301, 00002879359, 08214503001, 00169352815, 08881200755, 08881520251, 00839802506, 08290328203, 38396042890, 08080826012, 00003183715, 38396042912, 08881200805, 08290328233, 08496291501, 54868238001, 08881716917, 08496291511, 08881847993, 08290328278, 08290328279, 08290328280, 08290328281, 08290328282, 08290328283, 08290320096, 08290328289, 08290328290, 08290328291, 08881250016, 08881250024, 08881676012, 08290320109, 00839802606, 38396042990, 08881250032, 08290320119, 08881250040, 54868623100, 08080826112, 38396043012, 08214355719, 08881250057, 00002811201, 08881250065, 08222072597, 08881250073, 08881250081, 68258897701, 08881250099, 08881250107, 08881512258, 08881250115, 08881250123, 38396043090, 08881250131, 08290328410, 08290328411, 08290328412, 08290328418, 08881250149, 38396043112, 08290328430, 08290328431, 08881250164, 08290328438, 08290328440, 08881250172, 08881250180, 08881053577, 08290320271, 08290328465, 08290328466, 08290328468, 08881250198, 08290328471, 00002854001, 08881250206, 08881250214, 38396043177, 08881250222, 08881070001, 08080818100, 08080818101, 08881250230, 38396043190, 68115070905, 08080818112, 08080818113, 08881250248, 08881250255, 08080220112, 08881250263, 08881160157, 08881250271, 08881242088, 08881250289, 08881750007 </p>

Table S4: ICD codes for myocardial infarction used to identify positive cohort

<b>ICD code</b>	<b>description</b>
I46.8	Cardiac arrest due to other underlying condition
I21	ST elevation (STEMI) myocardial infarction involving left main coronary artery
410.72	Subendo infarct subseq
I21.01	ST elevation (STEMI) myocardial infarction involving left main coronary artery
410.01	AMI anterolateral init
I21.4	Non-ST elevation (NSTEMI) myocardial infarction
I21.A9	Other myocardial infarction type
I21.A1	Myocardial infarction type 2
410.61	True post infarct init
I21.3	ST elevation (STEMI) myocardial infarction of unspecified site
410.8	AMI NEC unspecified
410.42	AMI inferior wall subseq
427.5	Cardiac arrest
I46	Cardiac arrest due to underlying cardiac condition
I46.2	Cardiac arrest due to underlying cardiac condition
410	AMI anterolateral unspec
410.71	Subendo infarct initial
410.11	AMI anterior wall init
410.12	AMI anterior wall subseq
410.7	Subendo infarct unspec
I21.21	ST elevation (STEMI) myocardial infarction involving left circumflex coronary artery
410.4	AMI inferior wall unspec
410.21	AMI inferolateral init
410.82	AMI NEC subsequent
410.9	AMI NOS unspecified
410.2	AMI inferolateral unspec
I21.9	Acute myocardial infarction unspecified
I46.9	Cardiac arrest cause unspecified
410.1	AMI anterior wall unspec
410.02	AMI anterolateral subseq
410.51	AMI lateral NEC initial
410.52	AMI lateral NEC subseq
410.92	AMI NOS subsequent
I21.02	ST elevation (STEMI) myocardial infarction involving left anterior descending coronary artery
I21.19	ST elevation (STEMI) myocardial infarction involving other coronary artery of inferior wall
410.81	AMI NEC initial
410.41	AMI inferior wall init
410.31	AMI inferopost initial
410.62	True post infarct subseq
I21.09	ST elevation (STEMI) myocardial infarction involving other coronary artery of anterior wall
410.0	AMI anterolateral unspec
410.5	AMI lateral NEC unspec
410.6	True post infarct unspec
410.3	AMI inferopost unspec
410.91	AMI NOS initial
410.32	AMI inferopost subseq
I21.11	ST elevation (STEMI) myocardial infarction involving right coronary artery
410.22	AMI inferolateral subseq
I21.29	ST elevation (STEMI) myocardial infarction involving other sites

Table S5: Number of diagnostic codes encountered in dataset

gender	Number of codes	Number of unique codes
M	4879398	17554
F	7753318	19209
Total	12632716	36763

Table S6: CCoR phenotypes and maximum number of unique ICD codes defining CCoR phenotypes

CCoR phenotype	count of ICD codes in definition (Table S7)
Allergic	191
Cardiovascular	2017
CNS	765
Development	820
Digestive	1317
Endocrine	237
Frailty	557
Health-Services	501
Hematologic	429
Hypertension	80
Immune	1546
Infections-Bacterial	409
Infections-Fungal-and-Other	784
Infections-General	3612
Infections-Respiratory	712
Injuries	53265
Integumentary	1457
Metabolic	373
Musculoskeletal	7533
Neoplastic	3022
Ophthalmological	3401
Otic	856
PNS	394
Psychiatric	1478
Reproductive	2675
Respiratory	724

**Table S7:** Disease Categories With Detailed Set of ICD Codes Used in Definition. Not all infection and injury codes have been listed here.

Constituent ICD9 Codes	
Allergic	Description
	477.2 493.81 T50.995A J67.2 495.6 T78.03x 372.14 J67 J67.0 M13.89 J30.1 995.63 995.65 558.3 T45.0X1A M13.859 716.27 D29.30 D29.1 L27.2 477.9 495.5 493.22 D69.2 T78.00x 287.33 995.60 J45.31 J45.51 D29.20 J67.7 T78.09xA D29.22 M13.80 J30.9 T78.08x 287.8 H10.45 B44.81 716.20 995.61 T78.05xA 493.92 693.1 493.90 T78.40x J45.20 493.82 J45.40 D69.42 495.7 J67.5 493.20 D69.49 J45.32 287.32 708.0 H65.119 995.64 D69.1 J45.21 D69.6 M13.819 716.23 495.4 499.5 495.67 287.1 T78.08xA T78.00xA 477.0 493.02 525.66 T78.02xA J67.1 D69.3 T78.04x T78.2xxA D29.4 716.25 T78.07xA 716.26 T78.07x M13.88 J67.3 495.9 J45.30 493.21 477.495.2 995.62 T78.40xA 995.27 287.2 495.8 495 287.5 995.0 493 T78.05x L50.0 493.11 J45.902 D29.0 J45.990 287.9 J45 D29.21 J30.0 963.0 495.1 D29.32 L25.9 J44.9 J44.0 477.1 M13.879 493.103 J45.209 N99.5 J45.998 692.9 M13.849 995.66 D69.8 995.69 T78.04xA J30 495.3 M13.869 287.30 J45.991 J44.1 995.3 287.4 J45.52 287.0 381.06 716.21 J45.901 J67.4 287.39 493.91 373.32 287.31 T78.06xA J30.89 287 K08.55 K52.2 D29.31 J45.50 495.0 J67.6 D69.9 D29.8 T78.02x 716.24 477.8 381.05 D29.493.12 T78.03xA J67.9 716.22 T78.2xx J30.5 999.4 493.00 M13.829 T78.01x T78.06x 493.10 518.6 716.28 J30.2 H01.119 995.68 M13.839 D69.0 T78.09x 381.04 D29.9 T78.01xA 716.29 J30.81 J45.22 T45.42 T45.0X1 J45.909 D69.41 J67.8
Cardiovascular	I35.0 148.0 I25.728 448.8 P29.38 I94 E63.212 402.00 R10.669 440.30 R18.9 I60.9 I20.1 413.9 I24.1 I80.3 415.1 I77.811 785.9 I69.319 169.339 182.529 R04.1 429.6 G43.619 B12.503 182.611 170.512 175.011 169.834 170.628 K64.9 189.0 I21.0 429.42 447.5 448.2 170.792 170.450.4 170.318 150.83 170.744 405.0 242.6 455.1 170.442 455.3 B12.829 I12 415.433.8 169.320 127.81 444.21 T0.735 182.602 167.89 441.4 425.4 135.9 I70.693 169.234 165.23 427.2 I70.244 149.02 162.91 P29.89 170.719 I69.131 136.8 160.8 160.11 442.82 I69.852 T52.029 438.22 169.120 170.641 160.2 426.51 T0.702 417.3 163.012 R04.2 R02.0 422.7 31 175.718 105.8 170.791 189 426.50 I63.349 149.44 494.89 163.213 I83.12 17.0 182.433 170.608 P29.174.1 428.170 348.182 C29.182 532.69 I63.311 165.0 183.229 170.291 149.8 177.91 169.859 170.644 182.441 163.413 T0.362 405.11 162 I87.012 180.292 411.1 433.70 152.9 176.7 197.638 I87.091 169.998 107.8 111.9 169.390 445.01 169.223 I37.2 187.319 169.932 170.208 182.492 182.891 163.233 I70.319 170.65 I70.341 435.441.9 140.0 163.539 K64.4 195.89 I69.028 182.517 99 Y15.30 172.170 170.768 458.0 G43.601 I21.01 410.71 429.3 169.398 187.399 441.0 170.421 173.7 170.729 E86.0 169.231 182.8 113.0 170.563 142.2 163.431 411.89 T0.709 438.21 438.53 I70.150.84 142.0 170.212 177.74 108.0 P29.2 455.0 410.1 416.1 124.8 43.3 10.170.393 413.1 170.561 187.092 182.183 218.427 60.453.82 I70.153 194.3 173.197 182.197 197.71 169.343 I02.0 405.0 169.364 107.183 169.92 169.928 169.214 170.418 346.63 108.0 410.6 130.12 I70.433 175.013 T0.219 170.431 175.023 182.403 I83.10 155.730 415.13 I13.2 169.814 150.812 I79.179 429.89 169.169.833 I35.2 110.1 170.222 177.6 169.165 160.52 455.81 147.410.10 I83.201 182.419 169.033 115.9.404.0 I69.213 441.7 I82.412 169.261 182.432 417 I24.9 I69.315 438.19 I72.8 136.2 197.648 I70.539 165.5 169.392 I63.521 169.820 177.70 163.00 I70.439 I70.643 433.80 276.50 459.3 I70.522 169.121 433.21 424.6 346.16 I71.150 202.188.8 I55.175 81.1 101.9 I75.229 163.209 454.9 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X49 716.29 714.81 177.6 H01.129 716.85 D86 E08.21 535.51 693.0 H30.129 397 711.21 D80.9 595.1 D72.824 446.3 364.11 242.01 M46.90 M13.149 730.01 M12.379 474.11 373 D81.818 101.9 716.42 478.21 279.11 J34.1 L28.2 370.55 730.28 556.5 E08.40 711.52 373.3 595.3 249.90 582.1 730.07 I80.219 711.63 289.1 D80.5 M12.519 D81.2 288.02 K51.80 556.8 394.9 446 J37.1 288.66 364.00 715.30 D80.7 J44.0 711.76 730.06 M72.2 D89.811 D89.9 696.4 187.009 M36.2 711.09 398.9 E10.65 595.81 446.29 716.91 711.18 O10.9 M12.579 715.04 H15.019 288.01 555.1 I87.099 694.6 M34.1 711.44 519.2 K58.9 477.8 364.1 D86.2 250.71 715.24 086.65 711.24 M05.10 175.16 714.2 714.0 715.17 394 711.50 L20.87 716.84 464.21 M31.30 M86.18 464.4 01.716.49 37.7 711.53 711.47 L27.0 M06.4 461.0 M12.88 J04.10 695.4 M12.19 H01.029 J04.11 372.31 H16.249 363.04 459.19 457.8 478.11 714.31 711.9 E09.65 M02.159 D86.89 493.11 M60.20 711.73 H00.039 J35.1 J45.990 716.60 730.20 711.60 D85 H16.429 457.9 L73.2 459.13 716.12 696.3 K29.0 11.0 M02.179 474 370.557.5 M31.0 711.43 363.14 711.08 H20.9 K29.4 245.4 H05.10 M33.20 363.03 379.01 V11.76 550.25 451.373.34 L92.3 363.20 716.50 464.11 716.63 446.4 173.1 694.60 511.89 715.98 249.31 461.9 L51.1 715.34 106.0 M02.349 J11.33 395.711.88 474.9 716.61 106.1 711.15 715.89 711.30 270.91 J01.20 711.33 H02.3 139.692 D86.84 M02.18 535.50 M00.09 H20.819 708.1 M19.079 M12.319 716.51 556.2 M13.159 L10.9 288.04 289.6 M35.00 279.09 730.0 E08.10 695.12 363.07 459.1 370.63 716.87 692.9 L30.4 364.04 M13.869 451.89 715.21 392.0 M12.119 720.89 249.4 686.09 711.20 H30.93 711.40 715.26 K52.2 L21.9 716.95 D89.2 D82.2 J91.8 379.9 K13.239 J30.3 693.8 715.89 M17.5 D83.1 720.0 249.71 461.2 571.40 711.5 L92.9 D81.7 358.0 H20.13 730.24 249.60 396.8 711.81 M01. 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	<p>041.4 017.10 B02.21 055 098.14 042.9 B09 011.80 569.5 B69 136.4 A19 078.0 057.8 A50.09 017.81 590.3 083.8 016.4 A01.38.3 003.8 B67 341.21 372.05 016.32 380.12      015.62 017.20 466.1 380.2 001.1 001 A52.10 B94.2 H70.009 B35.0 A92.8 017.44 017.82 123.1 115.00 016.71 B74.8 T79.A12S 081 016.60 011.8 B02.24 T50.A15A A05      B60.12 T50.A25D A04.9 B33.23 T50.A11A 682.6 098.41 B35.2 116.2 N37 018.92 040.89 A77.0 117.7 095.8 045.1 A07.4 A63 B08.1 018.01 070.3 B88.2 M90.869 B42.42      A85.1 005.9 041.10 015.3 375.30 A39.83 016.36 013.53 B96.81 011.93 488.11 041.04 A48.51 B26.1 A73 A08.32 B43.1 A18.4 B65.0 A41.02 T80.A19B 018.85 B16.9 006      B87.89 060.1 182.B29 324.9 P36.2 012.85 685 B50.0 027 A66.5 070.70 A66.1 B02.9 T50.A93A P35.1 A48 100 B17.9 590.1 058.1 079.3 130.1 B06.00 B42.89 112 017.9      B60.0 T50.A22D B74.4 B52.9 046.2 077.9 381.1 086.0 0483 056.01 A54.41 016.24 062.4 A83.9 K67 B97.11 449 085.0 007.8 013.62 A92.9 P36.39 T50.A94S 016.1 011.5      J05.10 466.0 A50.07 B00.82 015.61 B81.3 017.76 012.81 B08.01 015.04 771.3 A30.9 063.8 016.93 A52.06 B02.0 A22.2 059.22 041.03 008.69 011.23 381.0 A06.9      380.1 083.1 A28.2 A36.85 B46.0 013.14 070.52 B77.0 082.40 054.1 482.89 112.89 A02.0 T50.B12S 010.02 032.2 A18.5A B27.82 B73.00 008.5 047 036.42 T80.A10D      M79.A21 B45.2 A08.39 681.0 111.0 T50.A25A B40.3 B48.3 375.31 094.1 017.33 014 J31.0 038.4 G00.3 B83.1 045.23 011.43 045.01 T50.B94 041.83 071 015.21 B43.0      016.53 048 094.8 472.1 016.04 010.94 073.7 A96.9 017.4 079.52 015.12 127.8 016.14 T80.A11S A00.1 097.9 A07 011.64 A66.3 038.49 039 100.81 137.3 136.3 382.2      B57.006.0 038.42 A51.45 B87 B95.7 771.1 H70.209 483.8 012.1 A36.9 010.01 063.9 J15.20 B97.89 420.91 B26.85 B45.8 081.2 074.22 A88.0 014.06 042.0 567.3 115.13      B55.1 016.54 016.35 B35.1 573.3 053.13 A37 015.75 079.2 J18.9 N11.8 008.45 056.05 A52.06 A54.83 A23.1 093.8 A53.0 424.9 A54.82 A40.0 H10.239 A48.52 A49.2      112.84 013.23 016.41 099.55 051.0 004.9 093.20 B14 B24 373.4 011.78 B79.098.39 M89.619 T50.B93 A80.9 091.1 A32 A17.82 031.0 M90.879 043.1 488.1 A51.9      J09.X3 A87.2 123.4 G00.9 A21.3 B40.0 B97.4 066.49 A02.24 038.0 B06.01 A48.8 017.06 730.76 421.1 098.5 094.8 020.9 009.1 115.9 015.66 A02.22 A50.03 B37.7      026.0 077.98 482.8 730.75 117.2 055.0 A93.7 A77.8 A04.5 A01.05 B02.32 003.21 A53.9 322.1 B48.0 B56.9 A44.1 098.50 051.70 B17.2 B67.99 H60.399 098.59 T50.A94      T50.B95D G03.9 A01.2 123 039.1 077.4 682.2 P35.2 T50.B15D B31 017.66 B80.39 A81.09 381.3 B78.81 B60.19 B32 038.12 074 321.2 131.9 012.8 A43.8 B57.42 131.8      015.92 482.8 070.7 T50.A13D 025.119.0 072.2 060.9 013.56 027.9 101 B30.9 A06.1 030.2 B97.5 484.8 A41.9 130.0 013.90 078.19 T50.B12 084.8 040.2 102.2 A25.0      B57.2 123.5 I31.2 J15.5 B27.81 099.59 B08.72 B86.9 005.2 094.82 H59.42 112.2 T79.A11 139.1 J85.1 003.9 008.43 003.0 A82.9 480.3 A08.2 083.2 123.9 070.43 078.4      078.1 B38.4 B40.1 B00.89 034.0 A51.5 012.01 B71 006.4 513 J17 074.3 A56.4 A18.12 A77.49 B95.8 132.9 B55.2 011.15 017 008.42 T50.B93D L03.039 B77.81 126.0      A56.09 077.3 B95.4 484.5 233.71 682.074 008.49 B17.11 010.05 A66.8 A85.2 B48.4 B96.5 A51.31 054.2 011.41 A52.8 132.2 A50.45 A04.7 A77.9 B46.5 006.5 115.04      008. A39.82 B37.42 011.0 B08.09 054.73 A44.8 012.84 P36 B85.0 383.21 059.0 040 128.50 T50.B95S 771.0 074.23 323.51 685.0 A26.0 0382.01 B01.2 B88.4 A42.8 B20.7      B67.69 015.97 038.41 B94.1 421.0 021.1 098.86 A68 T50.A15A A49.02 T50.A21D 013.22 A32.7 B58.2 124 099.49 B67.32 079.83 121.0 A54.5 A52.3 J12.0 B87.3 070.1      B08.03 132.1 016.55 111.2 T50.A25 090.7 A36.81 A41.53 018.80 A81.01 B69.1 A21.1 098.82 B30.9 002 102.9 016.9 04 J04.30 A19.8 050.0 017.65 A18.9 060.0 H04.429 P37.0      015.23 078 112.82 041.02 115.92 A41.52 B88.0 B96 022.2 A36.89 A52.9 B35.9 I31.8 A38.8 013.92 B2.23 H66.90 015.94 M35.8 G06.1 391 B46.4 017.86 A02.25      A17.83 122 B90.2 B19.11 T50.A96A T80.A11D A43.0 A74.81 016.51 056.00 A18.39 472.2 102 099.5 A67.0 H70.229 323.4 J09.X9 117.4 015.71 B80.0 B47.1 014.5 126.2      J21.8 484.7 I33.0 016.13 B95 016.95 054.71 043.2 422.93 045.10 128.8 B57.1 059.10 B57.49 091.4 038.2 016.61 021.56.73 B16.58.1 079.81 B37.81 730.91 018.86 B65.3      372.0 B02.23 B39.5 A48.0 B18.8 482.0 381.10 005.3 017.6 464.50 A50.6 P37.8 T50.A96 A52.11 B67.39 H04.339 T50.A14A 039.3 421 T50.A24S B16.1 B51.0 I09.2      053.19 015.56 T79.A22A T80.A19 A52 G05.4 051.2 A44 B33 079 A67.1 380.10 T79.A12D B27 053.22 103.2 771.5 A37.80 B27.19 B2.11 018.8 A22.0 A18.83 A40.0</p>
	<p>017.10 013.95 017.86 A17.83 J12.9 013.42 016.51 011.80 A15.1 017.83 017.42 B18.39 A19 010.91 J09.X9 017.81 015.71 017.03 013.0 013.3 011.37 012.0 016.55 015.62 015.61      011.10 011.9 012.31 017.70 018.01 016.450 011.31 J11.82 042.42 010.06 A14.01 012.0 016.36 J15.8 015.56 T80.A19 013.53 010.14      A19.0 011.93 014.44 A18.4 017.22 T50.J20.9 A17.9 017.22 016.75 J15.20 017.03 017.81 015.44 017.482.41 017.56 015.75 017.81 015.82 017.81 015.83 017.84      017.85 017.86 017.87 017.88 017.89 017.90 017.91 017.92 017.93 017.94 017.95 017.96 017.97 017.98 017.99 017.10 017.11 017.12 017.13 017.14 017.15 017.16 017.17 017.18 017.19 017.20 017.21 017.22 017.23 017.24 017.25 017.26 017.27 017.28 017.29 017.30 017.31 017.32 017.33 017.34 017.35 017.36 017.37 017.38 017.39 017.40 017.41 017.42 017.43 017.44 017.45 017.46 017.47 017.48 017.49 017.50 017.51 017.52 017.53 017.54 017.55 017.56 017.57 017.58 017.59 017.60 017.61 017.62 017.63 017.64 017.65 017.66 017.6</p>

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Metabolic	<p>269 E83.30 270.5 P71.4 276.7 264.1 712.38 M1A.9xx0 274.82 E71.42 278.02 274.19 278.01 276.69 263.8 712.86 E72.8 268.1 275.40 274.03 712.28 M10.30 E66.2      783.1 E74.9 E71.41 270.8 712.19 E83.59 E87.70 M11.80 E50.7 E88.1 275.42 E67.0 260 M10.9 E46 274 E72.20 M11.88 276.3 712.84 E83.50 P19.0 264.3 E50.8 278.2      275.1 E50.1 M11.20 E83.81 R63.4 775.9 277.81 268 712.36 277.88 E83.40 E53.9 271.9 P71.3 E87.1 M11.879 270.7 E52 D84.1 273.9 266.2 264.4 265.1 274.8 712.1      M11.249 712.8 M11.849 277.82 E72.9 M11.269 712.16 E50.4 712.88 M10.40 M11.28 269.9 E88.9 264.9 268.0 E55.9 278.0 712.85 266.9 277.9 E75.21 712.3 712.89      712.27 712.97 277.8 P72.8 M11.859 278.3 264.0 278.03 G93.9 E53.0 E16.1 271.3 251.0 775.89 E70.0 P71.1 E51.11 P70.1 275.5 P70.4 277.7 272.3 712.15 E50.6      277.87 712.39 274.81 712.96 712.10 274.02 E87.8 712.90 E15 273.8 R63.0 271.2 E66.9 277.86 266.0 E53.8 E64.3 263.1 278 E87.0 272.5 E66.3 712.32 E67.1 262      712.92 M11.9 M11.29 712.31 272.1 P19.1 P71.8 M11.279 712.95 277.85 E65 E88.40 775.81 783.22 E61.4 783.2 263.2 261 E83.89 P71 M11.829 P74.0 E74.12      274.89 E70.21 E72.03 712.11 E50.2 M11.869 712.80 P19.9 E50.5 264.3 712.13 275.49 E16.2 E54 E67.8 712.83 276.8 278.4 775.7 712.37 E78.3 270.2 270.4 E53.1      E83.52 M83.9 269.2 269.1 783.21 712.33 M1A.00x E87.4 E87.5 P70.3 268.2 271.8 E87.3 M11.259 7E6.01 E87.2 266.1 P71.2 E88.01 E55.0 251.2 266 273.4 274.00      272.2 275.01 275.8 712.98 E56.8 E56.1 E74.21 E44.1 272.7 712.91 263.9 E88.81 E78.89 E78.9 712.34 269.3 274.01 263.0 P70.9 712.22 277.2 E74.39 263 E67.3 276.6      E88.09 E50.3 E72.10 R63.5 E43 P19 265 275.9 264.5 E66.01 E83.00 E80.0 E88.89 712.18 E83.118 275.4 E63.8 264 274.10 277.5 275.3 712.94 712.12 E44.0 E40      M11.819 276.2 274.0 E51.8 270.6 E78.9 712.23 276.9 272.4 P71.0 G93.89 712.2 712.87 E83.51 P70.2 271.1 276.4 E45 712.93 277.89 P84 P71.9      M11.887 E67.4 E71.17 265.0 E78.8 272.9 277.6 274.9 276.0 E56.9 E70.4 E83.110 M11.229 268.9 712.25 272 270 330.2 271 712.35 M11.839 264.2 275.09 712.30      276.1 R63.6 264.8 277.1 270.9 P70.7 712.21 278.8 272.6 712.9 275.0 M10.0 270.3 270.1 E88.3 E50.0 N20.0 277.8 P70.0 E63.9 E71.50 278.00 712.29 E74.4 274.11      E83.10 712.24 275.2 E78.1 P70.8 712.99 330.3 712.82 712.81 M11.219 M1A.9xx E50.9 251.1 E78.5 E78.6 272.8 P19.2 E71.318 264.7 E71.0 783.0 712.26 712.20 269.8      M1A.00x1 P72.9 265.2 M11.239 712.14 275.1 278.1</p>
Musculoskeletal	<p>553.9 M84.574D Q67.5 M84.442S M70.30 M25.761 M46.87 550.00 M60.231 M71.829 M85.622 M84.675A M84.753D M08.429 733.20 M84.472 M60.239 M84.346K      727.6 M12.332 735.1 M84.550K M62.241 M71.062 M66.219 M05.051 M24.275 552 M67.479 755.67 M89.322 M27.59 M25.842 M80.821S M84.753A M84.573P M54.02      718.80 M53.86 M85.58 Q65.00 733.43 717.41 M24.174 718.9 M85.012 M48.58XG M15.19 M48.52K M41.22 M20.21 M84.522K M16.10 M23.041 M66.211 M19 M13.822      M24.231 717.82 M90.871 M87.035 M48.57XD M96.679 M21.40 M32.12 M93.841 718.82 M46.96 M65.341 M11.10 M25.222 M67.279 M80.019S 719.99 M66.172      M84.462K M84.442K M96.639 M80.011S M08.231 K43.7 M08.849 M23.007 M12.212 M48.02 M84.619G M65.171 M67.229 M66.272 M60.819 719.90 M11.049      M84.553A M85.812 M89.312 719.70 M06.811 M12.449 M44.9 M79.4 260.03 M24.075 M86.151 P13 M24.676 M99.77 M84.651 M10.329 M89.752 M23.91 M05.271      755.30 M80.052 M05.842 M08.826 M96.662 M00.232 M80.069A M85.311 M63.94 727.9 M08.833 T18.47 717.30 M80.012G M05.372 M15.4 M62.511 719.04 M89.542      M84.561S M84.572 M94.9 736.05 551.01 M08.469 M94.9 M79.129 M80.011P M99.7 M07.649 M87.632 M54.519 M25.642 M84.533D M54.15 M05.069 M62.259      M84.662K M24.031 M20.001 M90.551 M03.01 M60.60 M61.14 M24.651 M41.12 M93.811 719.12 M89.619 M10.839 M14.879 M08.3 M05.69 M00.162 M05.722      756.55 M05.431 M18.32 M70.951 M80.859G 730.39 M92.12 M48.43X M65.852 M26.00 M23.052 M24.572 M40.14 M80.079D M86.542 M05.049 M65.261 M65.011      M84.663P M60.172 M05.811 M12.822 M71.21 M85.321 M99.21 M67.971 733.1 M84.364P M02.10 M60.074 M83.1 M35.9 M97.42XK M12.529 M05.879 M87.032      M46.38 754.5 M90.672 M50.22 719.50 M85.859 737.21 M12.9 M84.452S M84.443 M11.869 719.45 M93.879 M36.3 719.25 M89.49 M76.889 M08.929 M71.869 M89.042      M70.21 M87.334 M10.451 M26.23 M85.00 M06.831 727 M80.831 M90.852 M76.42 M89.28 M65.332 M86.661 M23.631 M50.823 M75.00 M05.479 M84.379 M10.321      M86.021 M61.129 M79.0 M84.569K M61.229 Q79.4 260.08 M62.441 M66.811 M06.859 M54.451 M45.1 M84.571G M84.672D M23.005 M47.13 M84.612S M84.542 M67.272      K08.23 M12.379 M24.839 M10.019 M89.439 M48.51X M89.30 M25.149 M23.2X M89.061 719.20 M84.756D M52.3 M60.831 717.10 M89.08 M32.11 M90.861 M42.09      M54.13 M12.519 M92.291 M93.851 719.83 M23.212 M71.21 M87.80 M6.05 M48.462A M99.43 M66.842 M23.322 T22.30 M84.474D M85.331 M7.6021 M24.376      M80.069P M20.031 M72.2 767.5 M61.160 M20.361 M00.811 M26.213 M87.861 M84.673 M75.071 M84.519P M99.18 M71.552 M24.575 M43.04 M12.5179      717.8 M89.78 M12.219 M84.639 M84.563P M89.165 M60.261 M80.00X 730.37 M34.1 K40.10 P11.3 M26.82 M84.322G M84.564 M46.52 M51.05 718.89 M88.88      M05.121 M05.10 M84.674D M84.342D M89.571 M80.872A M84.841 M23.352 M71.051 M93.969 M99.01 M63.869 M48.061 M02.122 M21.379 M65.30 719.92 M21.221      M25.361 M87.29 M84.359P M90.511 M72.0 M11.032 M85.630 M60.262 M80.00XP M84.350A 524.07 M94.261 T18.41 M86.432 M54.81 M84.459 M10.422 M84.446K      M84.572S M23.009 M06.4 M72.6 M87.263 729.39 M14.659 M87.274 M41.41 M84.750A M84.639A M84.672S 719.73 M91.10 M99.00 722.72 M14.621 M61.59 M67.942      M80.869G M89.032 M24.562 359.5 M60.019 M76.61 M24.371 M87.850 M92.219 M84.432G M13.841 M80.822 M84.474D M85.331 719.16 M25.051 M84.353S M94.229      718.73 M19.032 M84.38X 717.83 M80.031 M84.632K M94.232 M90.532 737.41 M84.575 M10.349 M86.621 M21.859 M60.20 M1.612 M93.022 M84.649 M10.159      M71.811 M05.762 718.76 M23 M84.669D M48.8X5 719.91 M87.037 M52 M62.011 M26.31 M74.23 718.4 M31.0 M25.641 M11.219 M65.872 M24.112      M65.141 M21.331 M84.757 M20.092 M80.851D M27.0 M87.151 M99.08 M05.742 M70.971 M97 M84.534S M08.412 M43.8X8 736.02 M84.632A M87.011 M24.021      M61.461 M21.629 718.84 M40.56 M84.369G M87.378 M06.849 M89.157 732.8 M66.89 553.03 M92.299 M42.00 M71.572 M35.8 M02.152 755.65 726.70 M89.8X9      M12.822 M80.042K M84.433G M88.832 M67.411 M23.307 M24.7 M05.759 M67.864 M61.412 M45.08 M10.169 M84.434K M18.50 24.276 M62.89 M84.833 Q65.4      M40.04 M02.022 M85.329 M60.259 733.10 754.81 M80.80XG M90.542 K08.20 M11.019 718.97 M71.121 756.53 M21.029 M62.131 M26.221 M25.129 M34.82 M86.261      M80.040Z M86.462 M47.016 736.75 M46.811 P71.071 M71.21 M20.18 M11.152 M80.829K M12.038 M13.131 M88.841 M85.48 M87.833 M84.361      M60.839 M84.350G M84.422G M19.079 M54.9 718.77 M23.003 M80.852S M60.073 M87.031 M71.479 M61.022 M05.321 719.19 M06.022 M84.352D M34.83 M62.419      M11.051 M84.369K M60.821 M90.551 29.276 M76.891 M66.352 M67.451 M86.061 M24.171 M86.079 M05.429 M97.42XD M44.0 M60.112 M90.552 M06.051 M05.552      M47.28 M08.48 M12.249 M84.439P M00.221 M85.332 M11.021 M85.029 M76.12 M26.52 M86.442 M84.334S M84.632P M90.811 M87.114 M43.20 M24.673 717.81 M14.629      M85.342 M85.879 524.06 M85.821 M10.359 M84.475S M12.532 717.7 M27.62 M26.73 M43.01 M12.861 M60.869 M84.459A M17.55 M85.061 M48.55X M88.839      M76.892 M19.022 M80.861A M84.321S M65.311 M80.852P M96.843 524.41 M80.019G M93.839 737.34 M84.632P M90.811 M87.118 M43.20 M24.673 717.81 M14.629      M61.032 M05.461 M85.652 M24.562 642 M67.89 M89.163 721 M35 M87.20 M99.41 M05.169 M84.575K M08.40 732 M05.349 M42.9 M08.80 M84.434A M86.559 M12.852      M70.11 M51.25 794.221 M96.5 M25.28 M66.351 M84.345S M84.752 S56.69 M70.611 M87.261 M70.969 719.17 738.7 M84.312P M33.93 M66.371 M84.662A      M48.54XS M89.124 Q65.1 M86.039 M65.821 M25.075 718.0 M84.532A M76.841 M75.52 M80.00XD M17.31 M11.142 M66.311 M01.X22 M65.062 M84.652S M80.019A      M89.162 M60.046 M32.9 M84.631D M87.132 M23.8X2 M84.552D 722.6 M43.4 M87.271 M84.542D M62.76 M62.58 M84.751 719.77 M84.671P M96.655      M99.31 M26.06 M62.529 M62.28 M12.121 M60.032 736.22 M71.862 M79.609 M87.00 M05.49 M48.34 M25.039 M24.232 M92.9 M20.42 M80.859P M90.579 M62.459      M20.039 M99.33 733.82 754.44 736.29 M06.321 M84.753P M60.279 M80.861P M84.433D M26.24 M33.02 M80.029G M11.221 M84.443A M65.121 M06.011 M25.531      M21.239 553.2 727.4 M66.852 M86.466 M70.869 M01.X39 M50.221 M84.662S M99.47 M80.052D M84.839 754.42 M10.072 M87.135 M31.31 M87.076 M19.229      M85.842 738.9 M12.361 M79.3 M48 M05.222 M48.56XG 719.56 M84.353A M77.00 M80.851S M80.051D M24.271 735.4 M84.362G M86.569 M80.862K M63.842 526      M80.069D 717.40 M80.88XK 736.0 M87.077 M92.30 M02.211 M25.532 737.29 M74.54 733.94 726.8 M67.371 M85.572 M41.30 M08.229 M05.351 M05.512 M24.25.229      M02.39 754.60 M42.13 M25.871 719.64 717.5 M06.272 Q66.3 M66.132 M61.239 M66.839 M08.042 M21.061 M93.952 M89.462 M96.661 M25.142 M86.8X3 M85.421      M10.131 M91.42 M89.321 M25.419 M71.451 M87.339 M70.911 524.12 M61.00 754.6 M06 M84.451G M86.329 M89.221 M80.052G M89.359 M05.712 M84.758 M86.659      M40.37 718.18 M24.451 M60.061 M47.25 M01.X32 M05.562 M84.476K 726.72 M97.02XD M14.661 M80.052P M87.236 M85.422 M86.172 M89.339 M80.822A M21.539      718.08 M41.43 M84.434 M05.672 754.7 M84.431P M85.839 M05.052 M67.829 M84.663D M75.32 M90.859 M87.363 M12.369 M84.476S M12.062 M80.019 M06.331      M75.35 M12.079 M60.162 M84.532 M84.633D M99.16 M06.09 M24.312 M95.4 M90.662 K45.8 M46.05 M08.012 M11.272 M61.19 M46.24 M84.671 M84.673 M48.8X9      M79.9 M84.755S M12.39 M84.58XA 736.73 M21.511 M00.271 M21.162 M66.329 M47.14 M84.443P 719.01 M05.741 M66.331 M84.659G M67.429 M20.22 M80.831P      M84.431A M60.045 M25.339 M60.242 M20.62 724.01 M19.279 M48.56XG M65.172 M84.41XG K08.26 M71.821 M06.012 M66.322 M12.09 M66.369 M66.279 M47.813      M11.271 550.11 M12.462 M54.14 M05.122 M79.645 M71.039 M89.231 M87.372 M62.449 M11.11 M05.862 M92.01 Q72.10 M47.24 M9</p>

Neoplastic	C21.2 C05.8 D04.20 C81.30 202.64 172.5 C93.Z1 D46.C 277.84 C44.301 229 C60.0 C75.3 C44.691 D28.2 C66.9 D37.030 160.0 C91.00 D07.69 D3A.023 173.01 233.30 C34.01 C85.80 D44.4 C45.0 234.0 217 D41.8 209.3 273.3 C44.292 D30.8 227.9 194.9 D06.0 237.2 171.9 202.53 173.41 D29.22 206.2 151.5 C44.112 D38.5 D27.1 C45.7 600.1 D02.4 D07.2 C45.1 210.5 201.72 174 C16.8 155.2 C85.29 155.1 C57.12 192 D44.12 C50.128 C82.02 140 C81.77 149.8 C91.01 C25.8 201.50 237.3 C81.40 C89.9 C84.42 140.6 C83.19 152 186.0 198.8 D23.12 181 146.1 C44.622 211.1 C66.1 202.55 C78.6 200.50 C91.40 236.7 195.0 C96.1 196.0 196.6 173.92 C49 216.8 205.11 D23.21 198.7 206.82 C93.32 189.2 193 D05.01 173.9 140.1 200 200.21 C44.92 233.9 D30.4 C26.0 236.6 C84.07 C44.199 202.2 238.74 228.03 C10.2 D3A.020 C82.44 229.0 C83.72 150.235 C62.00 C33 202.31 D46 C78.7 144.9 188.6 C85.21 C50.422 218.1 C73 C06.80 C69.62 D31.00 D36.13 C76.41 172.2 201.74 187 172.9 173.82 161 D25.1 C44.82 C50.129 C48.8 200.16 175.0 D35 C25.9 C81.04 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224.3 C84.04 C81.78 C90.00 D31.3 C78.02 209.31 157.8 C50.611 D12.1 236.99 D09.22 D17.4 202.85 C22.0 C77.9 D37.01 D06.1 D37.5 231.2 224 209.61 C84.97 C50.812 C00.0 C50.019 C84.72 173.4 222.0 C7A.022 D10.39 205 C81.32 C83.01 C83.77 227.6 C79.32 D37.2 D23.0 200.27 C85.96 621.30 C90.10 C10 200.31 C79.11 C88.18 N60.49 C89 C91.Z2 C72.9 209.02 200.67 140.5 C13.2 204 D31.40 235.5 D07.39 239 C28.9 C92.12 I82.C23.6 C54.0 217.2 I82.C23.153.7 C81.05 C41.9 C00 183.3 D04.61 202.38 C06 174.4 D17.71 H40.130 C84.500 D16.6 C84.600 D16.7 C84.700 H59.322 H35.313 H33.11 H31.02 C44.022 C83.36 C66.12 C44.422 C83.37 C66.13 H31.02 C44.422 C83.38 C66.14 H31.02 C44.422 C83.39 C66.15 H31.02 C44.422 C83.40 C66.16 H31.02 C44.422 C83.41 C66.17 H31.02 C44.422 C83.42 C66.18 H31.02 C44.422 C83.43 C66.19 H31.02 C44.422 C83.44 C66.20 H31.02 C44.422 C83.45 C66.21 H31.02 C44.422 C83.46 C66.22 H31.02 C44.422 C83.47 C66.23 H31.02 C44.422 C83.48 C66.24 H31.02 C44.422 C83.49 C66.25 H31.02 C44.422 C83.50 C66.26 H31.02 C44.422 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H83.3X9 H93.293 H68.012 H62.8X2 H74.42 H72.12 H70.202 380.0 H74.8X3 H60.60 H61.113 H61.819 H93.243 386.48 H65.31 H73.003 380.00 H82.3 H95.88 389.03 H65.06 H79 H60.03 H81.41 H61.393 388.60 H92.13 388.00 H83.3X1 H60.10 389.0 H62.43 H83.19 H95.133 380.50 H61.019 H81.01 H93.091 H73.384.1 H66.23 H71.10 H74.391 H80.03 H72.02 H60.599 H66.91 380.51 380.52 381.62 H60.592 H71.32 H70.011 385.0 H73.099 H66.12 H71.93 H68.023 H93.232 H93.8X2 H77.388.11 H72.823 H60.00 H70.093 H65.93 H81.93 H67.2 H93.3X9 389.16 386.5 H60.559 389.08 H73.019 H61.013 H60.512 385.01 H95.113 H70.209 H81.49 H65.21 H74.323 H73.813 H70.012 389.14 H69 H62.42 H61.001 H90.A22 386.43 385.23 H61.102 H95.21 H68.129 H83.01 H61.161 H65.196 H72.90 H65.32 H83.2X2 384.8 H73.22 H95.136 H65.90 H74.384 H72.00 H91.20 H81.8X2 H74.81 H72.11 H70.202 380.0 H74.8X3 H60.60 H61.113 H61.819 H93.243 386.48 H65.31 H73.003 380.00 H82.3 H95.88 389.03 H65.06 H79 H60.03 H81.41 H61.393 388.60 H92.13 388.00 H83.3X1 H60.10 389.0 H62.43 H83.19 H95.133 380.50 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386.5 H60.559 389.08 H73.019 H61.013 H60.512 385.01 H95.113 H70.209 H81.49 H65.21 H74.323 H73.813 H70.012 389.14 H69 H62.42 H61.001 H90.A22 386.43 385.23 H61.102 H95.21 H68.129 H83.01 H61.161 H65.196 H72.90 H65.32 H83.2X2 384.8 H73.22 H95.136 H65.90 H74.384 H72.00 H91.20 H81.8X2 H74.81 H72.11 H70.202 380.0 H74.8X3 H60.60 H61.113 H61.819 H93.243 386.48 H65.31 H73.003 380.00 H82.3 H95.88 389.03 H65.06 H79 H60.03 H81.41 H61.393 388.60 H92.13 388.00 H83.3X1 H60.10 389.0 H62.43 H83.19 H95.133 380.50 H61.019 H81.01 H93.091 H73.384.1 H66.23 H71.10 H74.391 H80.03 H72.02 H60.599 H66.91 380.51 380.52 381.62 H60.592 H71.32 H70.011 385.0 H73.099 H66.12 H71.93 H68.023 H93.232 H93.8X2 H77.388.11 H72.823 H60.00 H70.093 H65.93 H81.93 H67.2 H93.3X9 389.16 386.5 H60.559 389.08 H73.019 H61.013 H60.512 385.01 H95.113 H70.209 H81.49 H65.21 H74.323 H73.813 H70.012 389.14 H69 H62.42 H61.001 H90.A22 386.43 385.23 H61.102 H95.21 H68.129 H83.01 H61.161 H65.196 H72.90 H65.32 H83.2X2 384.8 H73.22 H95.136 H65.90 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Reproductive	<p>764.96 O41.91x O70.0 628.0 646.03 O31.30x 634.91 608.22 679.10 662.11 N135.0xx P24.21 O13.9 656.0 'O34.00 P57.0 649.7 662.00 669.82 656.23 663.60 618.0      670.2 O34.529 671.80 O03.32 646.51 771.8 E28.2 668.03 674.80 651.2 653.50 661.11 629.9 N82.5 676.32 661.21 646.93 763.9 O36.0110 659.90 673.34 649.03 660.33      669.0 674.02 656.13 O92.5 675.11 668.50 676.20 617.1 602.2 O00.1 O99.350 N88.0 A48.51 660.31 O22.91 611.72 O01.9 651.50      661.2 648.51 642.53 634.50 O98.03 604.0 679.14 O35.4xx 66</p>
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Table S8: Feature Definitions (Total number of features used: 380)

Feature name	Explanation	n <sub>features</sub>
<b>feature</b> scores relative to phenotype score	Mean p-score of <b>feature</b> codes within sequence divided by general p-score of <b>feature</b>	26
<b>feature</b> scores relative to whole score	Mean p-score of <b>feature</b> codes within sequence divided by mean p-score of all codes in the record	26
aggregation score	aggregation of the p-scores in the record	13
high scores proportion	proportion of codes with very high p-scores among all codes in the record	1
low scores proportion	proportion of codes with very low p-scores among all codes in the record	1
dynamics of mean score	mean p-score of second half of the record divided by mean p-score of first half of the record	1
dynamics of geometric mean score	geometric mean p-score of second half of the record divided by mean p-score of first half of the record	1
dynamics of st.dev score	standard deviation of p-scores of second half of the record divided by standard deviation of p-scores of first half of the record	1
dynamics of score range	range of p-scores of second half of the record divided by range of p-scores of first half of the record	1
dynamics of score skew	skew of p-scores of second half of the record divided by skew of p-scores of first half of the record	1
aggregation relative to phn score	aggregation of all <b>feature</b> 's mean scores divided by corresponding general p-score of <b>feature</b>	9
aggregation relative to whole score	aggregation of all <b>feature</b> 's mean scores divided by mean p-score of all codes in the record	9
predicted risk from pfsa model	predicted risk from pfsa model	1
predicted risk from seq model	predicted risk from seq model	1
predicted risk from pscore model	predicted risk from pscore model	1
predicted risk from rare model	predicted risk from rare model	1
age at screening	Patient age at the moment of the screening	1
<b>feature</b> proportion	Ratio of number of weeks with the codes of a given phenotype to the total number of weeks in sequence	26
<b>feature</b> prevalence	Ratio of number of weeks with the codes of a given phenotype to the number of weeks with any diagnosis code recorded	26
<b>feature</b> first incident	Time interval from observation date to the first phenotype code, normalized by record length	26
<b>feature</b> last incident	Time interval from observation date to the last phenotype code, normalized by record length	26
<b>feature</b> mean position	Mean time position of phenotype codes in the record, normalized by record length	26
<b>feature</b> streak	Length of the longest uninterrupted subsequence of weeks with the codes of a given phenotype recorded	26
Max/Mean/Std/Range intermission	Maximum/Mean/Standard Deviation/Range of the lengths of subsequences of consequent weeks with codes	4
Max/Mean/Std cluster	Maximum/Mean/Standard Deviation of the lengths of subsequences of consequent weeks without codes	3
Max/Std/Range prevalence	Maximum/Standard Deviation/Range of the phenotype prevalences	3
Density of DX Record	Proportion of weeks in a record observed where at least one DX code was recorded	1
<b>feature</b>	Sequence Likelihood Defect for a given phenotype	26
<b>feature</b> neg llk	Negative LogLikelihood score for a given phenotype	26
<b>feature</b> pos llk	Positive LogLikelihood score for a given phenotype	26
<b>feature</b> llk ratio	Ratio of Positive to Negative LogLikelihood score for a given phenotype	26
Mean $\Delta$	Mean Sequence Likelihood Defect	1
Std. deviation $\Delta$	Range of Sequence Likelihood Defects	1
Range $\Delta$	Standard Deviation of Sequence Likelihood Defects	1
Mean neg llk	Mean Negative LogLikelihood score	1
Range neg llk	Range of Negative LogLikelihood score	1
Std. deviation neg llk	Standard Deviation of Negative LogLikelihood score	1
Mean pos llk	Mean Positive LogLikelihood score	1
Range pos llk	Range of Positive LogLikelihood score	1
Std. deviation pos llk	Standard Deviation of Positive LogLikelihood score	1
Mean llk ratio	Mean LogLikelihood score ratio	1
Range llk ratio	Range of LogLikelihood score ratio	1
Std. deviation llk ratio	Standard Deviation of LogLikelihood score ratio	1
high scores proportion	proportion of codes with very high p-scores among all codes in the record	1
low scores proportion	proportion of codes with very low p-scores among all codes in the record	1

<sup>\*</sup> $\Delta$ : Sequence Likelihood Defect (See Methods)<sup>†</sup> neg llk: loglikelihood of observed sequence being generated by the model inferred from control (See Methods)<sup>‡</sup> pos llk: loglikelihood of observed sequence being generated by the model inferred from positive (See Methods)

Table S9: Proportion of 0's, 1's and 2's on average in trinary encodings with 95% CI

<b>cohort</b>	<b>sex</b>	<b>proportion of 0</b>	<b>proportion of 1</b>	<b>proportion of 2</b>
control	Female	0.879 ± 0.002	0.013 ± 0.001	0.106 ± 0.002
control	Male	0.891 ± 0.003	0.012 ± 0.001	0.095 ± 0.003
positive	Female	0.858 ± 0.040	0.015 ± 0.013	0.126 ± 0.038
positive	Male	0.873 ± 0.037	0.014 ± 0.012	0.111 ± 0.035
TOTAL	Female	0.879 ± 0.002	0.013 ± 0.001	0.106 ± 0.002
TOTAL	Male	0.891 ± 0.002	0.012 ± 0.001	0.095 ± 0.002

Table S10: Out-of-sample performance achieved (mean AUC) when training dataset is balanced (Note: performance degrades as we attempt to train with more balanced data, e.g., downsampling ratio of 1 is the case where we sample the control cohort to use only as many patients as in the positive cohort)

<b>sex</b>	<b>downsampling ratio</b>	<b>all patients</b>	<b>age 65+ years</b>	<b>age &lt; 65 years</b>	<b>frail</b>
Female	1	0.755	0.715	0.694	0.732
Female	2	0.756	0.723	0.700	0.736
Female	5	0.768	0.735	0.727	0.752
Female	10	0.781	0.750	0.737	0.769
Female	20	0.772	0.750	0.728	0.759
Female	40	0.790	0.760	0.743	0.772
Male	1	0.724	0.665	0.690	0.721
Male	2	0.743	0.701	0.698	0.746
Male	5	0.754	0.708	0.722	0.761
Male	10	0.751	0.711	0.718	0.757
Male	20	0.759	0.718	0.725	0.759
Male	40	0.759	0.714	0.729	0.759

Table S11: Cohort Sizes

<b>sex</b>	<b>cardiac event within week</b>	$n_{\text{positive}}$	$n_{\text{control}}$	$n_{\text{high risk}}$	$n$
M	2	385	185528	146782	185913
M	4	464	185528	146782	185992
F	2	337	258981	204170	259318
F	4	418	258981	204170	259399
	Total	882	444509	350952	445391

Table S12: Out-of-sample predictive performance to predict MACE 4 weeks after surgery in sub-cohorts with pre-existing conditions

Pre-existing phenotype	Female CCoR	Female RCRI	Male CCoR	Male RCRI
Allergic	0.77	0.71	0.81	0.78
CNS	0.80	0.67	0.89	0.75
Cardiovascular	0.78	0.69	0.80	0.67
Development	0.77	0.83	0.86	0.68
Digestive	0.81	0.73	0.80	0.71
Endocrine	0.80	0.69	0.80	0.67
Frailty	0.78	0.69	0.85	0.73
Health Services	0.81	0.71	0.83	0.71
Hematologic	0.80	0.72	0.85	0.74
Hypertension	0.77	0.68	0.80	0.66
Immune	0.81	0.71	0.82	0.70
Infections Fungal and Other	0.80	0.76	0.84	0.68
Infections General	0.80	0.75	0.84	0.68
Infections Respiratory	0.76	0.64	0.83	0.63
Injuries	0.79	0.73	0.84	0.69
Integumentary	0.78	0.69	0.80	0.72
Metabolic	0.80	0.70	0.82	0.70
Musculoskeletal	0.81	0.71	0.83	0.70
Neoplastic	0.87	0.75	0.78	0.68
Ophthalmological	0.79	0.69	0.76	0.65
Otic	0.79	0.75	0.84	0.62
PNS	0.80	0.70	0.84	0.73
Psychiatric	0.85	0.74	0.89	0.72
Reproductive	0.80	0.70	0.82	0.79
Respiratory	0.81	0.70	0.83	0.67

Table S13: Out-of-sample predictive performance in sub-cohorts stratified by age

age	gender	auc CCoR	auc RCRI	n <sub>positive</sub>	n <sub>control</sub>
45 - 55	F	0.59	0.58	3	9056
45 - 55	M	0.89	0.79	5	7027
55 - 65	F	0.80	0.66	31	27256
55 - 65	M	0.78	0.63	39	20244
65 - 75	F	0.81	0.73	34	14235
65 - 75	M	0.73	0.58	31	9635
75 - 85	F	0.70	0.65	25	8515
75 - 85	M	0.79	0.71	36	5164
85 - 95	F	0.80	0.67	8	1578
85 - 95	M	0.75	0.48	12	847

Table S14: Out-of-sample\* performance for predicting MACE with 4 weeks of Hip or Knee Arthroplasty (Primary Endpoint) at 99% Specificity: CCoR vs. RCRI\*\*

sex	cohort	model	sensitivity	PPV	acc	LR+	LR-	AUC
Female	< 65	RCRI	0.01±0.02	0.008±0.000	0.987±0.006	0.04±0.1	1.00±0.02	0.639 ± 0.039
Female	< 65	CCoR	0.14±0.06	0.047±0.004	0.987±0.006	14.12±1.1	0.87±0.06	0.775 ± 0.035
Male	< 65	RCRI	0.07±0.03	0.025±0.003	0.987±0.000	7.42±0.8	0.94±0.03	0.682 ± 0.034
Male	< 65	CCoR	0.15±0.06	0.065±0.003	0.987±0.006	19.94±0.9	0.85±0.06	0.783 ± 0.030
Female	65+	RCRI	0.03±0.01	0.012±0.002	0.987±0.000	3.39±0.5	0.97±0.01	0.664 ± 0.028
Female	65+	CCoR	0.09±0.06	0.036±0.004	0.987±0.006	10.70±1.1	0.92±0.06	0.771 ± 0.025
Male	65+	RCRI	0.03±0.01	0.011±0.001	0.987±0.006	3.17±0.4	0.98±0.00	0.661 ± 0.026
Male	65+	CCoR	0.09±0.05	0.031±0.002	0.987±0.006	9.09±0.6	0.92±0.05	0.762 ± 0.023
Female	all patients	RCRI	0.05±0.01	0.016±0.003	0.987±0.000	4.67±0.8	0.96±0.01	0.688 ± 0.023
Female	all patients	CCoR	0.13±0.01	0.044±0.007	0.987±0.006	13.19±2.1	0.88±0.01	0.801 ± 0.019
Male	all patients	RCRI	0.05±0.01	0.019±0.002	0.987±0.000	5.44±0.7	0.95±0.01	0.705 ± 0.020
Male	all patients	CCoR	0.12±0.05	0.042±0.001	0.987±0.006	12.44±0.3	0.89±0.05	0.802 ± 0.018
Female	frail***	RCRI	0.03±0.00	0.009±0.002	0.987±0.006	2.59±0.6	0.98±0.00	0.670 ± 0.028
Female	frail	CCoR	0.11±0.03	0.036±0.002	0.987±0.000	10.36±0.7	0.90±0.03	0.791 ± 0.025
Male	frail	RCRI	0.06±0.04	0.020±0.002	0.987±0.006	5.91±0.7	0.95±0.04	0.727 ± 0.027
Male	frail	CCoR	0.15±0.03	0.050±0.002	0.987±0.000	15.02±0.7	0.86±0.03	0.810 ± 0.024
Female	high risk****	RCRI	0.02±0.00	0.008±0.001	0.987±0.006	2.19±0.3	0.99±0.00	0.581 ± 0.029
Female	high risk	CCoR	0.07±0.03	0.026±0.002	0.987±0.000	7.73±0.6	0.94±0.03	0.737 ± 0.026
Male	high risk	RCRI	0.03±0.01	0.010±0.001	0.987±0.006	2.91±0.3	0.98±0.00	0.617 ± 0.026
Male	high risk	CCoR	0.09±0.05	0.033±0.002	0.987±0.006	9.61±0.7	0.92±0.05	0.729 ± 0.024
Female	low risk†	CCoR	0.22±0.04	0.071±0.004	0.987±0.000	21.81±1.3	0.79±0.04	0.765 ± 0.036
Male	low risk	CCoR	0.11±0.04	0.042±0.003	0.987±0.000	5.96±0.9	0.90±0.04	0.766 ± 0.032

Abbreviations. AUC, area under the receiver operating characteristic curve; CCoR, Cardiac Co-Morbidity Risk Score; LR+, positive likelihood ratio; LR-, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; acc, accuracy; RCRI, Revised Cardiac Risk Index

\*50% (n=445391) of cohort used for validation

\*\*Because of insufficient availability of relevant laboratory data in the Truven dataset, presence of at least one diagnostic code for chronic kidney disease stage III or higher in the medical record in the year before the date of arthroplasty was used as a surrogate for the RCRI condition, serum creatinine concentration > 2.0mg/dL (to convert to micromoles per liter, multiply by 88.4).

\*\*\*Frail subcategory was defined by codes specified in Table S7

\*\*\*\*Low risk subcohort comprises patients with RCRI score 0. High risk patients have RCRI score > 0.

†No RCRI performance logged for low-risk patients, since their RCRI score is zero.

Table S15: Out-of-sample\* performance for predicting MACE with 2 weeks of Hip or Knee Arthroplasty (Secondary Endpoint) at 99% Specificity: CCoR vs. RCRI\*\*

sex	cohort	model	sensitivity	PPV	acc	LR+	LR-	AUC
Female	< 65	RCRI	0.01±0.02	0.009±0.000	0.987±0.006	0.04±0.1	1.00±0.02	0.647±0.044
Female	< 65	CCoR	0.11±0.01	0.073±0.023	0.987±0.006	22.87±8.5	0.90±0.01	0.787±0.039
Male	< 65	RCRI	0.09±0.02	0.032±0.009	0.987±0.000	9.33±2.8	0.92±0.02	0.688±0.037
Male	< 65	CCoR	0.14±0.04	0.056±0.004	0.987±0.000	16.83±1.3	0.87±0.04	0.797±0.033
Female	65+	RCRI	0.04±0.04	0.013±0.002	0.987±0.006	3.66±0.6	0.97±0.03	0.671±0.030
Female	65+	CCoR	0.10±0.03	0.041±0.002	0.987±0.000	12.08±0.7	0.91±0.04	0.787±0.027
Male	65+	RCRI	0.03±0.00	0.010±0.001	0.987±0.000	2.79±0.4	0.98±0.00	0.667±0.028
Male	65+	CCoR	0.09±0.03	0.032±0.002	0.987±0.000	9.32±0.6	0.92±0.03	0.780±0.025
Female	all patients	RCRI	0.05±0.01	0.018±0.003	0.987±0.000	5.17±0.9	0.96±0.01	0.692±0.025
Female	all patients	CCoR	0.14±0.06	0.048±0.001	0.987±0.006	14.48±0.3	0.87±0.06	0.809±0.021
Male	all patients	RCRI	0.05±0.01	0.018±0.002	0.987±0.000	5.15±0.7	0.96±0.01	0.710±0.022
Male	all patients	CCoR	0.14±0.02	0.047±0.007	0.987±0.000	13.98±2.1	0.87±0.02	0.813±0.019
Female	frail***	RCRI	0.03±0.01	0.012±0.003	0.987±0.000	3.43±0.9	0.98±0.01	0.676±0.032
Female	frail	CCoR	0.12±0.03	0.041±0.009	0.987±0.000	11.78±2.7	0.89±0.03	0.807±0.027
Male	frail	RCRI	0.06±0.01	0.020±0.003	0.987±0.000	5.82±0.9	0.95±0.01	0.736±0.029
Male	frail	CCoR	0.17±0.03	0.059±0.009	0.987±0.000	17.76±3.0	0.84±0.03	0.825±0.025
Female	high risk****	RCRI	0.02±0.03	0.008±0.001	0.987±0.006	2.35±0.4	0.99±0.02	0.584±0.032
Female	high risk	CCoR	0.08±0.00	0.029±0.006	0.987±0.006	8.45±1.9	0.93±0.01	0.742±0.028
Male	high risk	RCRI	0.03±0.03	0.009±0.001	0.987±0.006	2.69±0.4	0.98±0.02	0.628±0.028
Male	high risk	CCoR	0.09±0.02	0.033±0.007	0.987±0.000	9.66±2.3	0.92±0.02	0.737±0.026
Female	low risk†	CCoR	0.28±0.07	0.092±0.002	0.988±0.006	28.78±0.7	0.72±0.07	0.779±0.040
Male	low risk	CCoR	0.12±0.04	0.047±0.004	0.987±0.000	6.78±1.1	0.89±0.05	0.793±0.035

Abbreviations, AUC, area under the receiver operating characteristic curve; CCoR, Cardiac Co-Morbidity Risk Score; LR+, positive likelihood ratio; LR-, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; acc, accuracy; RCRI, Revised Cardiac Risk Index

\*50% (n=445391) of cohort used for validation

\*\*Because of insufficient availability of relevant laboratory data in the Truven dataset, presence of at least one diagnostic code for chronic kidney disease stage III or higher in the medical record in the year before the date of arthroplasty was used as a surrogate for the RCRI condition, serum creatinine concentration > 2.0mg/dL (to convert to micromoles per liter, multiply by 88.4).

\*\*\*Frail subcategory was defined by codes specified in Table S7

\*\*\*\*Low risk subcohort comprises patients with RCRI score 0. High risk patients have RCRI score > 0.

†No RCRI performance logged for low-risk patients, since their RCRI score is zero.

**Table S16:** Statistical significance of CCoR AUC > RCRI AUC (\* denotes significance at 95% level, \*\* denotes significance at 99% level)

sex	model	weeks after surgery	RCRI auc	CCoR auc	p value	significance
Female	all patients	2	0.692	0.809	0.010	**
		4	0.688	0.801	0.007	**
	frail <sup>†</sup>	2	0.676	0.807	0.017	*
		4	0.670	0.791	0.014	*
	high risk <sup>‡</sup>	2	0.584	0.742	0.005	**
		4	0.581	0.737	0.003	**
	65+	2	0.671	0.787	0.020	*
		4	0.664	0.771	0.020	*
	< 65	2	0.647	0.787	0.036	*
		4	0.639	0.775	0.028	*
Male	all patients	2	0.710	0.813	0.010	*
		4	0.705	0.802	0.009	**
	frail	2	0.736	0.825	0.045	*
		4	0.727	0.810	0.042	*
	high risk	2	0.628	0.737	0.017	*
		4	0.617	0.729	0.011	*
	65+	2	0.667	0.780	0.017	*
		4	0.661	0.762	0.019	*
	< 65	2	0.688	0.797	0.047	*
		4	0.682	0.783	0.042	*

<sup>†</sup>Frail subcategory was defined by codes specified in Table S7

<sup>‡</sup>Low risk subcohort comprises patients with RCRI score 0. High risk patients have RCRI score > 0.

**Table S17:** Out-of-sample performance achieved using only PFSA component of the CCoR model (Note: the performance is significantly degraded, with all p-values < 0.01.)

sex	prediction horizon	AUC
Female	2 weeks	0.696 ± 0.082
Female	4 weeks	0.698 ± 0.074
Male	2 weeks	0.679 ± 0.074
Male	4 weeks	0.656 ± 0.067

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