# **Specific Aims**

Total Knee Arthroplasty (TKA) is the most commonly performed inpatient elective surgery in the United States, at approximately 700,000 procedures per year.[1](#_ENREF_1) Although TKA is regarded as effective, the clinical course is highly variable. Depending on the patient, recovery of function can occur rapidly (within weeks), or it can be an arduous, months-long process.[2](#_ENREF_2),[3](#_ENREF_3) Moreover, the surgical population is remarkably heterogeneous—some patients engage in sporting activities (e.g., tennis, skiing),[4](#_ENREF_4) while others struggle to ambulate at walking speeds sufficient for independence in the community. Our team has developed a personalized reference charts (PRCs) that offers a novel approach to precision monitoring and decision making at an individual level (AHRQ R01 XXXXX). The central idea of this “patients-like-me” approach is to identify historical patients who are similar to a new patient and to use the recovery data of these historical patients to generate an estimate of postoperative recovery for the new patient. The analytical approach is based on “curve matching,” which has been used to estimate childhood growth.[10](#_ENREF_10) Our work suggests that PRCs are precise and accurate. However, this approach has not been compared to other statistical methods that are simpler and could provide similar prediction curves. We propose to address this gap by comparing the PRCs to linear mixed models (LMM) that predict the trajectory of recovery for patients after TKA.

Even though we have shown that the PRC approach works well in our dataset there might be other scenarios where similar approaches, perhaps simpler to implement, work just as well or there could be scenarios where the PRC might work substantially better than simpler approaches. The PRC approach needs to define a fixed time at which matches are chosen, which could be for example 90 days after surgery. We propose a dynamic predicted trajectory based on LMM that will use data up to the fixed time (e.g. 90 days) and would provide an individual-specific trajectory which would be useful after 90 days. A key challenge in prediction for new individuals in the context of LMM is prediction of the individual level of heterogeneity (*random effects* in statistical terms) for a new individual; this is often handled, as proposed here, by using some partial, e.g. first time point of the trajectory, information of the new individual.

To compare the performance of the PRCPRC approach to other statistical methods, we propose the following aims:

**Specific Aim 1***:* Apply both the PRC methodology and dynamic prediction based on LMM to two datasets tracking rehabilitation outcomes: TKA with TUG as outcome and Jeremy’s dataset. We will compare the results in terms of calibration, precision bias, and coverage. We will use adapted Markov chain Monte Carlo (MCMC) and bootstrap methods to estimate the predicted outcomes as well as their uncertainty (e.g. confidence intervals).

**Specific Aim 2***:* Assess by statistical/computer simulation the performance of the two methodologies and compare them in terms of calibration, precision bias, and coverage. A wide range of flexible data scenarios will be considered, motivated by Aim 1, as simulating models. Data will be simulated under flexible nonparametric forms, using flexible polynomials for instance, within the framework of LMM.

There is substantial interest from our clinical partners (see LOS) to use this PRC approach in practice at the time of care delivery. Thus, it is quite important to assess its performance in comparison to other simpler methods that are also prediction tools for monitoring. Results of these novel analyses are expected to provide insight on how the PRC approach compares to other traditional methods and the specific circumstances under which one method might work better than the other. Understanding the performance of the methods under different situations will help research teams make decisions about which features of LMM might be feasibly incorporated into improvement of the PRC methodology so that it predicts patient recovery with less bias and more accuracy. Future work will implement PRC monitoring through a clinical trial to test its effectiveness.

Other thoughts

* Should we try to compare to machine learning (ML) algorithms? It seems that some deep learning algorithm might work
* Should we try to improve the package and choose matches based on more than a single point? Perhaps a few equally spaced?
* Jeremy was asking about prediction for high/low performers… should we try to do a group-based trajectory analysis?

The PRC is a nonparametric approach that requires tunning of parameters to be selected, including for example the number of matching curves as well as the degree of smoothness that will be used