Familial Clustering Identified in Periprosthetic Joint Infection Following Primary Total Joint Arthroplasty

A Population-Based Cohort Study

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Background: It is estimated that the cost to treat periprosthetic joint infection in the United States will approach \$1.62 billion by 2020. Thus, the need to better understand the pathogenesis of periprosthetic joint infection is evident. We performed a population-based, retrospective cohort study to determine if familial clustering of periprosthetic joint infection was observed.

Methods: Analyses were conducted using software developed at the Utah Population Database (UPDB) in conjunction with the software package R. The cohort was obtained by querying the UPDB for all patients undergoing total joint arthroplasty and for those patients who had subsequent periprosthetic joint infection. The magnitude of familial risk was estimated by hazard ratios (HRs) from Cox regression models to assess the relative risk of periprosthetic joint infection in relatives and spouses. Using percentiles for age strata, we adjusted for sex, body mass index (BMI) of ≥ 30 kg/m², and a history of smoking, diabetes, and/or end-stage renal disease. Additionally, we identified families with excess clustering of periprosthetic joint infection above that expected in the population using the familial standardized incidence ratio.

Results: A total of 66,985 patients underwent total joint arthroplasty and 1,530 patients (2.3%) had a periprosthetic joint infection. The risk of periprosthetic joint infection following total joint arthroplasty was elevated in first-degree relatives (HR, 2.16 [95% confidence interval (CI), 1.29 to 3.59]) and combined first and second-degree relatives (HR, 1.79 [95% CI, 1.22 to 2.62]). Further, 116 high-risk pedigrees with a familial standardized incidence ratio of >2 and a p value of <0.05 were identified and 9 were selected for genotyping studies based on the observed periprosthetic joint infection/total joint arthroplasty ratio and visual inspection of the pedigrees for lack of excessive comorbidities.

Conclusions: Although preliminary, these data may help to guide further genetic research associated with periprosthetic joint infections. An understanding of familial risks could lead to new discoveries in creating patient-centered pathways for infection prevention in patients at risk.

Level of Evidence: Prognostic Level III. See Instructions for Authors for a complete description of levels of evidence.

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The first total joint arthroplasty in Utah was performed in January 1970. At present, total joint arthroplasties of the hip and knee are two of the most common surgical pro-

cedures performed and recent reports support improved quality of life, measured by patient-reported outcomes^{1,2}. Because of the success of primary total joint arthroplasties of the hip and knee,

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utilization is increasing. Notwithstanding this success, periprosthetic joint infections continue to affect this population, and the rate of reoperation due to periprosthetic joint infection is increasing³. Periprosthetic joint infection affects 0.6% to 2.5% of the primary total joint arthroplasty population and is responsible for 14% to 25% of early reoperations⁴⁻⁹. Periprosthetic joint infection results in additional medical expenses for the patient and also increases the burden on the health-care system and society as a whole¹⁰⁻¹⁴. A recent report by Kapadia et al.¹⁵ demonstrated a 3.5 times greater cost for episodes of primary total hip arthroplasty in patients who developed deep infections. It is estimated that the cost to treat periprosthetic joint infection will approach \$1.62 billion by 2020 in the United States alone¹³.

A myriad of risk factors for periprosthetic joint infection have previously been reported, including young age, male sex, obesity, diabetes, smoking, end-stage renal disease, and malnutrition, to name a few¹⁶⁻²¹. Some of these factors may be optimized before a surgical procedure, and this has been recommended to help to decrease the risk of periprosthetic joint infection in individual patients²¹. It is becoming more evident that, to better understand the pathogenesis of periprosthetic joint infection, we need to better understand the associated host risk factors, including possible familial risks. In 2013, through a large, population-based study, Lee et al.²² reported familial susceptibility to surgical-site infections, including but not isolated to periprosthetic joint infection. An understanding of familial risks could lead to new discoveries in creating patient-centered pathways for infection prevention in patients at risk.

Using a unique research resource, the Utah Population Database (UPDB), which links a Utah genealogy to statewide medical records, we performed a population-based retrospective cohort study to determine if familial clustering of periprosthetic joint infection was observed among relatives of patients who developed periprosthetic joint infection after undergoing total joint arthroplasty compared with relatives of patients who did not develop periprosthetic joint infection after this procedure. Further, we sought to examine both host characteristics and the most common medical comorbidities that contribute to periprosthetic joint infection that may also cluster in families, to determine the confounding effect of their impact on infection. These factors and comorbidities included age, sex, obesity, history of smoking, diabetes, and end-stage renal disease. Finally, should familial clustering be suggested, the UPDB affords us the ability to identify multiple, large, high-risk pedigrees in Utah for genotyping investigations.

Materials and Methods

The Utah Population Database

The UPDB is a unique research resource that contains 25 million records spanning several decades including a Utah genealogy, Utah birth and death certificates and other vital statistics, statewide hospitalization and ambulatory surgery records, and driver's license data. It is the only database of its kind in the United States and one of only a few in the world²³. The UPDB contains genealogical records dating from the 1800s to the current day and contains family

pedigrees, some of which cover ≥ 12 generations. The UPDB contains records of >8 million individuals and a majority of families living in Utah are represented in this database. Further, it has been reported that the population represented in this database can be extrapolated to represent populations in the Northern European countries²⁴. This population-based cohort study was approved by the institutional review board of the University of Utah and by the Utah Resource for Genetic and Epidemiologic Research (<http://rge.utah.edu>), which oversees use of the UPDB resource. An institutional review board waiver of consent and authorization were obtained to conduct the study.

Study Population

The study population included all patients in Utah who underwent a primary total joint arthroplasty during the time period of January 1, 1996, to December 31, 2013, and who were ≥ 18 years at the time of the surgical procedure. Patients undergoing hip replacement were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedural code 81.51, and those undergoing primary total knee arthroplasty were identified using ICD-9-CM 81.54. The ICD-9-CM diagnosis code 996.66, infection and inflammatory reaction due to internal joint prosthesis, was used to determine an outcome of periprosthetic joint infection in patients undergoing total joint arthroplasty. On the basis of census estimates for July 1, 2015, compared with voter registration and driver's license records, the estimated capture of adults in the database is >90%. Our case cohort consisted of all patients in the database who underwent primary total joint arthroplasty and subsequently developed periprosthetic joint infection. Our control cohort consisted of all patients who underwent primary total joint arthroplasty but who did not develop periprosthetic joint infection. Patients were excluded if they had missing data for covariates or <2 years of follow-up ($n = 10$) based on the most recent event recorded in the UPDB. This resulted in 1,530 patients with periprosthetic joint infection and 65,455 patients without periprosthetic joint infection.

High-Risk Pedigree Selection

We identified families with excess clustering of periprosthetic joint infection above that expected in the population using the familial standardized incidence ratio, which takes into account the number of relatives, degree of relatedness to the patient case or control patient, and person-time at risk²⁵. Exact one-sided Poisson probabilities were calculated under the null hypothesis of no familial aggregation of periprosthetic joint infection. High-risk pedigrees were selected on the basis of a familial standardized incidence ratio of >2 with associated significance of $p < 0.05$, and a nonsignificant familial standardized incidence ratio for total joint arthroplasty. Additionally, from all pedigrees deemed high-risk, we prioritized a set of 9 families who had excess clustering of periprosthetic joint infection and had periprosthetic joint infection occurring in 2 separate generations and/or first cousins affected by periprosthetic joint infection. For each family member in these 9 top-priority pedigrees, we determined obesity (denoted by a body mass index [BMI] of ≥ 30 kg/m²), history of smoking, diabetes, and end-stage renal disease to provide information on potential comorbidities, as well as the time in months to infection.

Statistical Methods and Familial Analysis

All analyses were conducted using a suite of kinship analysis software developed in-house at the UPDB in conjunction with the software package R (Windows version 3.2.2; The R Project for Statistical Computing). The magnitude of familial risk was estimated by hazard ratios (HRs) with 95% confidence intervals (CIs) from Cox regression models to assess the relative risk of periprosthetic joint infection in relatives who also underwent total joint arthroplasty. The relatives were first-degree relatives (parents, siblings, and children), second-degree relatives (grandparents, grandchildren, aunts, uncles, nephews, nieces, cousins, and half-siblings), and spouses. As observations within families are non-independent, a Huber-White sandwich estimator of variance was used to identify clusters of correlated observations,

TABLE I Frequency of Total Joint Arthroplasty and Periprosthetic Joint Infection in Relatives

Relationship	Total*	Total Joint Arthroplasty†‡	With Periprosthetic Joint Infection†§	Without Periprosthetic Joint Infection†#
Cohort	66,985		1,530 (2.3)	65,455 (97.7)
Relatives of patients with periprosthetic joint infection				
First-degree relative	7,338	494 (6.7)	26 (5.3)	468 (94.7)
Second-degree relative	14,591	424 (2.9)	12 (2.8)	412 (97.2)
First and second-degree relative	21,929	918 (4.2)	38 (4.1)	880 (95.9)
Spouse	1,102	120 (10.9)	2 (1.7)	118 (98.3)
Relatives of patients without periprosthetic joint infection				
First-degree relative	389,952	20,020 (5.1)	468 (2.3)	19,552 (97.7)
Second-degree relative	1,097,276	18,408 (1.7)	412 (2.2)	17,996 (97.8)
First and second-degree relative	1,487,228	38,428 (2.6)	880 (2.3)	37,548 (97.7)
Spouses	51,026	5,214 (10.2)	116 (2.2)	5,098 (97.8)

*The values are given as the number of patients. †The values are given as the number of patients, with the percentage in parentheses. ‡The percentages were calculated as the number of patients undergoing total joint arthroplasty divided by the total number of patients in that row. §The percentages were calculated as the number of patients with periprosthetic joint infection divided by the number of patients undergoing total joint arthroplasty in that row. #The percentages were calculated as the number of patients without periprosthetic joint infection divided by the number of patients undergoing total joint arthroplasty in that row.

and it accounts for departures from standard statistical assumptions^{26,27}. Age at the time of the primary surgical procedure and sex were included in the models as covariates. Additionally, we adjusted for confounders on the basis of

reported associations with periprosthetic joint infection risk. These confounders included obesity (BMI of ≥ 30 kg/m²), obtained from height and weight in a driver's license record occurring closest to but before the surgical procedure;

TABLE II Characteristics and Comorbidities of Patients with and without Periprosthetic Joint Infection After Undergoing Total Joint Arthroplasty

Characteristic or Comorbidity	Group with Periprosthetic Joint Infection	Group without Periprosthetic Joint Infection
No. of patients	1,530	65,455
Sex*		
Female	725 (47%)	37,534 (57%)
Male†	805 (53%)	27,921 (43%)
Age‡ (yr)	62 (18 to 93)	65 (18 to 95)
BMI†‡ (kg/m ²)	31 (14 to 64)	29 (13 to 87)
History of smoking*†	416 (27%)	13,412 (20%)
History of diabetes*†	539 (35%)	15,773 (24%)
End-stage renal disease*†	26 (1.7%)	359 (0.5%)
Race*		
White	1,483 (97%)	63,889 (98%)
Non-white	47 (3%)	1,566 (2%)
Ethnicity*		
Hispanic	140 (9%)	3,827 (6%)
Non-Hispanic	1,390 (91%)	61,628 (94%)
Survival‡ (mo)	29 (0 to 207)	88 (0 to 237)

*The values are given as the number of patients, with the percentage in parentheses. †The HRs, with the 95% CIs in parentheses, were significant for male sex at 1.43 (1.30 to 1.59), BMI ≥ 30 kg/m² at 1.38 (1.25 to 1.54), history of smoking at 1.34 (1.20 to 1.50), history of diabetes at 1.53 (1.37 to 1.71), and end-stage renal disease at 2.36 (1.60 to 3.48). ‡The values are given as the mean and the range.

TABLE III Risk of Periprosthetic Joint Infection in Relatives

Relationship	HR*
Proband	Reference
First-degree relative	2.16 (1.29 to 3.59†)
Second-degree relative	1.28 (0.73 to 2.24)
First and second-degree relative	1.79 (1.22 to 2.62†)
Spouse	0.74 (0.20 to 2.78)

*The values are given as the HR, with the 95% CI in parentheses, and were adjusted for sex, BMI ≥ 30 kg/m², history of smoking, history of diabetes, end-stage renal disease, and age strata.
†Significant.

history of smoking identified by ICD-9-CM codes 305.1, tobacco use disorders, and V15.82, history of tobacco use; diabetes identified by ICD-9-CM code 250; and dialysis-dependent end-stage renal disease identified by ICD-9-CM code 585.6. An assumption of proportional hazards was tested, and no covariates were in violation other than age at the time of the surgical procedure. As there was evidence of non-proportionality for age at the time of the surgical procedure, we stratified patients by age at the time of the surgical procedure as 18 to 55 years (≤ 20 th percentile), 56 to 75 years (>20 th to 80th percentile), and >75 years (>80 th percentile). Separate baseline hazard functions were fitted for each stratum. Coefficients of the remaining covariates were assumed to have a constant hazard function. Given an inability to assess for a familial bias involving a surgeon or institutional preference among family members, along with the possibility of low-volume centers having a higher risk of infection, we evaluated the correlation between facility joint replacement volume and rates of periprosthetic joint infection. We obtained blinded facility data for 66,944 patients (99.9% of the study population), which included 51 facilities. Histograms for infection rates at these facilities were reviewed and indicated the data to be skewed; all histograms were positive. A Shapiro-Wilk test was significant at $p < 0.001$, which indicated that the data were not normally distributed. The Shapiro-Wilk test is used when testing for a normal distribution and the underlying distribution cannot be determined by the test result. Given the skewness of the data, we used gamma regression to determine if the facility infection rate was correlated with the mean annual facility volume of total joint arthroplasty. Gamma regression is a widely used method to model these types of skewed and positive data. As a sensitivity analysis, we also performed linear regression of the log transformation of the infection rate.

Results

Study Population Characteristics

During the 18-year study period, 66,985 patients underwent total joint arthroplasty and 1,530 (2.3%) had a periprosthetic joint infection (Table I). Of patients with periprosthetic joint infection, 53% (805 of 1,530) were male and the mean age was 62 years (range, 18 to 93 years) (Table II). The mean time to periprosthetic joint infection was 29 months (range, 0 to 207 months) after total joint arthroplasty.

Familial Risk

The risk of periprosthetic joint infection following total joint arthroplasty was elevated in first-degree relatives (HR, 2.16 [95% CI, 1.29 to 3.59]) (Table III) and in first and second-

degree relatives combined (HR, 1.79 [95% CI, 1.22 to 2.62]). Thus, infection-free survival was greater in relatives of patients without periprosthetic joint infection; this is further demonstrated in a Kaplan-Meier analysis (Fig. 1). There was not an elevated risk in second-degree relatives in isolation (HR, 1.28 [95% CI, 0.73 to 2.24]). Finally, there was no increased risk of periprosthetic joint infection in spouses of patients with periprosthetic joint infection who also underwent total joint arthroplasty (HR, 0.74 [95% CI, 0.20 to 2.78]). When assessing for a correlation between volume and periprosthetic joint infection, we found no correlation between facility volume and infection rate ($p = 0.439$). This was confirmed in the sensitivity analysis, which also demonstrated no correlation ($p = 0.150$).

Periprosthetic Joint Infection Risk

There was a greater risk of periprosthetic joint infection in male patients and those with a BMI of ≥ 30 kg/m², a history of smoking, diabetes, and end-stage renal disease (Table II). Further, an analysis of patient age demonstrated decreased infection-free survival in younger patients (Fig. 2). Thus, increasing age was protective against the risk of infection, with HRs of 0.74 (95% CI, 0.66 to 0.83) in patients 56 to 75 years of age and 0.63 (95% CI, 0.53 to 0.75) in patients >75 years of age, when compared with the youngest group of patients (those who were 18 to 55 years of age).

High-Risk Pedigrees

In total, we identified 12,707 total joint arthroplasty pedigrees and 218 periprosthetic joint infection pedigrees. In the 218 periprosthetic joint infection pedigrees, 116 were identified as high-risk pedigrees with a familial standardized incidence ratio of >2 and a p value of <0.05 . Finally, we identified 9 high-risk pedigrees with a high ratio of observed periprosthetic joint infection/observed total joint arthroplasty ($>8\%$) that had 2 generations with periprosthetic joint infection and/or at least 1 first cousin affected by periprosthetic joint infection (Table IV). Further, we reviewed these pedigrees by visual inspection to identify pedigrees with a minimal number of family members affected by confounding variables: BMI of ≥ 30 kg/m², history of smoking, diabetes, and end-stage renal disease. An example pedigree can be found in Figure 3; this family has a familial standardized incidence ratio of 7.05 for periprosthetic joint infection ($p = 0.0001$).

Discussion

Consistent with prior reports, the overall proportion of patients with periprosthetic joint infection was 2.3% in our study⁴⁻⁹. Interestingly, the frequency of periprosthetic joint infection in first-degree relatives of patients with periprosthetic joint infection was 5.3% (26 of 494), compared with only 2.3% (468 of 20,020) in the first-degree relatives of patients without periprosthetic joint infection (Table I). Further, the risk of periprosthetic joint infection was greater in the combined first and second-degree relatives of patients with periprosthetic joint infection (4.1%) compared with the relatives of patients

Fig. 1

Survival curve showing the probability of periprosthetic joint infection-free survival among the combined first and second-degree relatives of patients with and without periprosthetic joint infection, adjusted for sex, BMI ≥ 30 kg/m², history of smoking, diabetes, or end-stage renal disease. PJI+ = patients with periprosthetic joint infection and PJI- = patients without periprosthetic joint infection.

without periprosthetic joint infection (2.3%). Additionally, there were similar frequencies of periprosthetic joint infection for relatives (2.3%) and spouses (2.2%) of patients with without periprosthetic joint infection compared with the overall population (2.3%). This study exhibits a potential for a familial susceptibility toward periprosthetic joint infection in first-degree relatives alone and in combined first and second-degree relatives. However, we were unable to iden-

tify an increased risk of periprosthetic joint infection in second-degree relatives alone. Given the potential for environmental risk factors, we also compared the risk for spouses of patients with periprosthetic joint infection who had also undergone total joint arthroplasty and found no increased risk of periprosthetic joint infection. This would allow for some argument against attributing the results to environmental factors and further supports the potential for a familial

Fig. 2

Survival curve showing a lower probability of periprosthetic joint infection-free survival in younger patients undergoing total joint arthroplasty. In this model, patients undergoing total joint arthroplasty were stratified into 3 surgery age percentiles: ≤ 20 th percentile (age 18 to 55 years), >20 th to ≤ 80 th percentiles (age 56 to 75 years), and >80 th percentile (age >75 years), adjusted for sex, BMI ≥ 30 kg/m², history of smoking, history of diabetes, and end-stage renal disease.

susceptibility to periprosthetic joint infection. Additionally, to determine if a familial bias toward a given low-volume center resulted in increased rates of periprosthetic joint infection, we attempted to correlate joint replacement volume per facility with rates of periprosthetic joint infection per facility. We found no correlation between joint replacement volume and

periprosthetic joint infection, and although we cannot truly assess for a familial bias, the lack of correlation between facility volume and infection rates suggests that, in our dataset, institutional preference due to any familial bias should have had no impact on the frequency of periprosthetic joint infection.

TABLE IV High-Risk Pedigrees Demonstrating Excess Clustering of Periprosthetic Joint Infection

Founder*	Descendants	Periprosthetic Joint Infection			Total Joint Arthroplasty			
		Familial Standardized Incidence Ratio	P Value	Observed	Familial Standardized Incidence Ratio	P Value	Observed	Ratio†
1†	5,876	7.05	0.0001	7	1.22	0.0874	54	0.13
2	2,999	9.82	0.0002	5	1.27	0.1175	29	0.17
3	2,675	10.51	0.0001	5	1.51	0.0179	31	0.16
4	3,672	9.29	0.0002	5	1.58	0.0059	37	0.14
5	3,747	9.08	0.0003	5	1.58	0.0053	38	0.13
6	4,591	7.41	0.0007	5	1.32	0.0535	39	0.13
7	6,468	5.55	0.0009	6	1.31	0.0246	62	0.10
8	7,060	4.26	0.0071	5	1.05	0.3836	54	0.09
9	8,302	4.67	0.0021	6	1.14	0.1686	65	0.09

*A founder is the ancestor from whom all family members are descended. †This founder is shown in Figure 3. ‡This ratio is periprosthetic joint infections per total joint arthroplasty.

In their study, Lee et al.²² were able to identify an increased risk of surgical-site infection in first, second, and third-degree relatives. However, they included the diagnoses of non-healing surgical wounds, periprosthetic infections, and infections related to catheters or infusions in a general

population not undergoing total joint arthroplasty, suggesting an overall familial susceptibility to infection. More recently, patients with a history of treated periprosthetic joint infection were found to be at greater risk of subsequent periprosthetic joint infection after undergoing another total

Fig. 3

An example of a high-risk pedigree with confounding variables included as well as the number of months to infection and the facility for each patient undergoing total joint arthroplasty. PJI = periprosthetic joint infection, TJA = total joint arthroplasty, Mo = months, and ID = identification.

joint arthroplasty²⁸. In that study, the authors suggested that host factors, including an inherent predisposition to subclinical immune deficiencies, may increase the risk of periprosthetic joint infection in these patients. Those studies, in combination with the elevated familial risk associated with periprosthetic joint infection found in this current study, support the potential for a heritable predisposition to periprosthetic joint infection.

The understanding of host factors and patient optimization prior to total joint arthroplasty is becoming more important as we continue down the path of precision medicine. It has been recommended that the optimization of all known host factors associated with the risk of periprosthetic joint infection be performed prior to total joint arthroplasty^{3,17,21}. With an increasing rate of reoperation for periprosthetic joint infection, there is an increasing need to better understand all potential risk factors for this debilitating complication. Given our findings, gathering a family history of periprosthetic joint infection in clinic seems imperative as the risk of periprosthetic joint infection in first-degree relatives of affected individuals approaches that of patients with dialysis-dependent end-stage renal disease.

We were able to identify 116 high-risk pedigrees potentially available for genotyping, which is a major strength of this study. Nine of these pedigrees have a high ratio of observed periprosthetic joint infection/observed total joint arthroplasty and would allow for targeted genotyping studies. Additionally, this study had the ability to capture data on a large number of patients undergoing total joint arthroplasty ($n = 66,985$), which is necessary when performing studies on periprosthetic joint infection given its low prevalence. Inherently, the familial standardized incidence ratio does not simultaneously account for comorbidities; thus, as a robustness check, we visually assessed the high-risk pedigrees to identify families without excessive confounding by these risks.

Although this study has nearly 20 years of medical records linked to multigenerational family data, the lack of diagnosis data beyond this time frame limited our ability to detect an association of periprosthetic joint infection in second-degree relatives. Further, it is understood that environmental factors may have had an effect on first-degree relatives, making it more difficult to separate a familial susceptibility from the environmental factor. However, when assessing the risk for spouses of our patients with periprosthetic joint infection who also underwent total joint arthroplasty, we found no increased risk of infection in those individuals.

The use of a single ICD-9-CM code for the diagnosis of periprosthetic joint infection (996.66) may be considered a limitation. However, Bozic et al.²⁹ have reported that the ICD-9-CM code 996.66 has a high positive predictive value and moderate correlation when compared with clinical documentation. Further, the use of this ICD-9-CM code requires an infection surrounding a prosthetic implant, which could potentially eliminate irrelevant diagnoses (for example, isolated wound complications). Finally, the percentage of

patients with periprosthetic joint infection (2.3%) in the database is within the expected range.

Although we assessed some of the most common risk factors for infection, we were unable to assess all of them. This is an inherent limitation of secondary data analyses in large database studies, in which incomplete or non-discrete data are unavailable. For example, we were unable to obtain the American Society of Anesthesiologists (ASA) Physical Status Classification, as this variable was not routinely documented as discrete data. Similarly, surgery-specific variables such as operating room time were also not consistently available. Even though prior surgical procedures have been reported as a risk factor, including them would be extremely difficult in a large database study as the laterality of the prior surgical procedures is not available. We considered including alcoholism, but there has been a relatively low apparent rate of alcohol consumption reported in Utah³⁰. That, combined with the underreported diagnosis of alcoholism, makes this a less reliable method for assessing risks associated with alcohol use. Finally, we elected not to control for inflammatory arthropathies given the broad number of diagnoses and the known impact of the associated immunosuppressant medications.

The study was confined to procedures occurring in Utah and may not have represented family members who underwent total joint arthroplasty outside of Utah. However, the net in-migration (gross in-migration – gross out-migration) has been positive since the 1970s, with the exception of the 1980s, with net in-migration rates of 37% in the 1970s, 0% in the 1980s, 42% in the 1990s, and 28% from 2000 to 2010, suggesting a low rate of out-migration in the state³¹.

Given the small number of relatives of patients with periprosthetic joint infection who also experienced periprosthetic joint infection, this study may have inadequately shown the familial risk of periprosthetic joint infection. Despite low numbers, significance was found in the first-degree relatives and the combined first and second-degree relatives. It is likely that our study was underpowered to detect a difference in the second-degree relatives alone because of the lack of diagnosis data in that time frame and the limited use or availability of joint replacement surgical procedures in prior generations. Further, the numbers available to identify high-risk pedigrees were small, which could have resulted in a misinterpretation of the actual periprosthetic joint infection/total joint arthroplasty ratio (Table IV). This may also be the case for spouses, in whom the numbers may be insufficient to detect an increased risk. Thus, these data should be interpreted with caution. However, to our knowledge, this is the largest database study on familial clustering related to periprosthetic joint infection and the first to identify individual families with increased risks of periprosthetic joint infection.

Although preliminary, these data may help to guide further genetic research associated with periprosthetic joint infections. Identifying those at greater risk of infection, including those with familial predispositions, may allow for improved preventative pathways following primary total joint arthroplasty. Future studies should be focused on whole genome sequencing to identify the potential genes responsible

for the risk of periprosthetic joint infection and their association with subclinical immune deficiencies. ■

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