FINAL POSNA REGISTRY GRANT REPORT
July 2020

Name of PI: Harry K.W. Kim, MD
Study title: Prospective, International Multi-Center Registry of Legg-Calvé-Perthes Disease
Name of award: POSNA Registry Grant
Year in which the grant/award was funded: 2018

Study Aims: *Aim 1.* Obtain Patient Reported Outcome Information System (PROMIS) data before and after initiating nonoperative and operative treatments. *Aim 2.* Evaluate the role of perfusion MRI (gadolinium-enhanced MRI) in predicting radiographic outcomes in children presenting at the early stage of LCPD. *Aim 3.* Determine the effects of early femoral varus osteotomy on the shape of the femoral head in children with the disease onset between 6 to 8 years of age at 2-year follow up. *Aim 4.* Compare the effects of short (6 weeks) vs. long (6 months) duration of postoperative non-weight bearing following femoral varus osteotomy on the shape of the femoral head in children with the disease onset between 8 to 11 years of age at 2-year follow up.

Research findings: With over 600 hips enrolled from over 15 different countries, this work would not have been possible without the gracious support of the POSNA.

Aim 1. We established PROMIS data collection for 10 key contributing International Perthes Study Group sites during the course of this grant funding. Based on an initial feasibility survey, we built and now offer an alternative data collection tool via REDCap to allow sites to collect PROMIS as a research endeavor, rather than solely standard of care practice. Longitudinal data collection will continue. Domains collected include Mobility, Anxiety, Depressive Symptoms, Fatigue, Anger, Peer Relationships, and Pain Interference, which were validated for our target population in Matsumoto et al. To ensure completion, the domains may be administered using any version currently available. To account for changes in patient age over time, we also collect information about the respondent at each time point to ensure validity of the responses and appropriateness of survey. Among the Pediatric self-report data, 80 surveys were administered to 37 unique hips ages 8.01-14.3. For the proxy report measure, 80 surveys were also collected, representing 40 unique hips, ages 3-7.99. Many are unable to complete data collection prior to surgery; it is more likely that PROMIS was administered at some point during follow-up. This data will be submitted for presentation at the 2022 POSNA meeting.

Aim 2. During the course of funding for this grant, 14 of our study group members have been trained and are reliable measurers of MRI using our HipVasc software program. The program allows us to quantify and evaluate hypoperfusion of each study participant at the time of enrollment. Of the 419 currently eligible early stage participants, the study team currently has completed measurements for 48% (n=201) MRIs either using HIPVASC or in the case of poor image quality, using visual estimation. Our sub-study of visual estimation during this grant period shows the reliability of visually collecting hypoperfusion estimations (Chong et al). Each MRI was assessed by at least 3 previously trained observers. Of the 201 completed measurements, 93 hips were enrolled into the 6-8 surgical arm, 21 were enrolled into the 6-8 non-surgical arm, 23 were enrolled into the 8-11 6-week NWB arm, and 34 were enrolled into the 8-11 6-month NWB arm. The remainder include MRIs for hips enrolled into the <6 registry, >11 registry, 8-11 non-surgical arm, and the MRI observation arms. We have improved processing time substantially by integrating digital means of tracking and sharing images. We continue to assess the role of hypoperfusion in different regions of the femoral head (i.e.- lateral, medial, central third), which may impact prognostication and outcomes.

Aim 3. Data for children enrolled with onset of disease between the ages of 6 and 7 underwent five audit cycles during this award period, resulting in 82% data completion overall. The staging and demographic data were published describing these cohorts (Laine et al & Sankar et al). There are currently 161 hips with 2-year minimum radiographic follow-up in this cohort. Of these, 125 hips have been enrolled in the surgical group (any type of osteotomy) and 36 were enrolled into non-surgical (bracing/casting/soft tissue release) treatment groups. Lateral pillar classification and Waldenstrom is collected routinely at each applicable visit. The Deformity Index

measurements were entered into the database, and the average of these responses serves as the final DI value to be correlated with hypoperfusion, collected in Aim 2. Of the 133 radiographic Deformity Index measurements completed by at least 3 raters (described in previous reports), 6 belong to the 6-8 non-surgical arm, and 59 belong to the 6-8 Surgical arm and had completed a hypoperfusion assessment for correlation analysis. While we anticipate some association, we also know that a two-year outcome measure may not tell the whole story, and that surgical intervention likely confounds this relationship. While this did not reach our expected sample size for adequate power of 73 participants per treatment arm, we will describe our group comparisons for intent-to-treat analysis. We aim to submit this data for presentation at the 2022 POSNA meeting.

Aim 4. Data for children enrolled with onset of disease between the ages of 8 and 11 also underwent five audit cycles during this award, during which the data was reviewed and queries were initiated for discrepant and missing data. There are 101 hips enrolled into surgical cohorts (osteotomy only) and with 2- year minimum radiographic follow-up. Eleven of these hips also underwent drilling and are not eligible. To date, 47 hips are enrolled into the 6-week non-weight bearing arm, and 54 are enrolled into the 6-month non-weight bearing arm. Lateral pillar classification and waldenstrom are collected on a routine basis at each visit. The study group conducted a series of sub-studies to ensure our chosen radiographic measurements were viable (Tis et al & Laine et al). Of the 133 images measured by three raters for Deformity Index described in Aim 3, 21 belonged to the 6-month non-weight bearing arm, and 9 were enrolled into the 6-week non-weight bearing arm and had completed a hypoperfusion assessment for correlation analysis. While this does not meet our expected power analysis for 73 participants per treatment arm, we aim to continue completing the measurements to increase sample size and submit this data for presentation at the 2022 POSNA meeting.

Expenditures: Please see attached expense report. At this time, we would like to request a 6-month extension of our grant funding to cover additional activities including recruitment, measurement, follow-up, and analysis of these aims.

Presentations:
- Kim HWK. (2021, May 13-15). *Research Registries & Study Groups: International Legg-Calve-Perthes Registry* [Conference presentation]. POSNA 2021 Symposia Session, Dallas, TX, United States.
- McGuire MF, Sansar S, Beckwith T. (2020, September 23-26) *Emerging Concerns and Best-Practices for Multicenter Clinical Research in Orthopedic Settings* [ePoster presentation]. Society of Clinical Research Associates 29th Annual Conference; Virtual.
- McGuire MF, Yap CF, Matthews B, Kim HWK. (2019, June 4-6). *Planning for a multicenter longitudinal pediatric implementation of PROMIS standard of care data collection* [Conference presentation]. PROMIS Health Organization HealthMeasures User Conference; Chicago, IL, United States.

Publications:
- Matsumoto H, Hyman JE, Shah HH, et al. Validation of Pediatric Self-Report Patient-Reported Outcomes Measurement Information System (PROMIS) Measures in Different Stages of Legg-Calvé-Perthes Disease. J Pediatr Orthop. 2020 May/Jun;40(5):235-240. doi: 10.1097/BPO.0000000000001423. PubMed PMID: 31318732.
- Sankar WN, Lavalva SM, McGuire MF, et al. Does Early Proximal Femoral Varus Osteotomy Shorten the Duration of Fragmentation in Perthes Disease? Lessons from a Prospective Multicenter Cohort. J Pediatr Orthop. 2020 May/Jun;40(5):e322-e328. doi: 10.1097/BPO.0000000000001451. PubMed PMID: 31524767.
- Laine, J. C., Novotny, S. A., Tis, J. E., Sankar, W. N., Martin, B. D., Kelly, D. M., Gilbert, S. R., Shah, H., Joseph, B., Kim, H., & International Perthes Study Group (2021). Demographics and Clinical Presentation of Early-Stage Legg-Calvé-Perthes Disease: A Prospective, Multicenter, International Study. The Journal of the American Academy of Orthopaedic Surgeons, 29(2), e85–e91. https://doi.org/10.5435/JAAOS-D-19-00379
- Laine, J. C., Novotny, S. A., Huhnstock, S., Ries, A. J., Tis, J. E., Sankar, W. N., Jo, C. H., Kim, H., & International Perthes Study Group (2020). Reliability of the modified lateral pillar classification for Legg Calvé

Perthes disease performed by a large group of international paediatric orthopaedic surgeons. Journal of Children's Orthopaedics, 14(6), 529–536. https://doi.org/10.1302/1863-2548.14.200055

- Tis, J. E., Laine, J. C., Sankar, W. N., Jo, C. H., McGuire, M.F., Kim, H., & International Perthes Study Group (2021). Reproducibility of Radiographic Measurements Made in the Active Stages of Legg-Calvé-Perthes Disease: Evaluation of a Prognostic Indicator and an Interim Outcome Measure. *Journal of pediatric orthopedics*, *41*(2), 93–98. https://doi.org/10.1097/BPO.0000000000001714
- Chong, D.Y., Schrader, T., Laine, J.C., Yang, S., Gilbert, S.R., Kim, H.K.W., & International Perthes Study Group (2021). Reliability and Validity of Visual Estimation of femoral Head Hypoperfusion on Perfusion MRI in Legg-Calve-Perthes Disease. *Submitted to Journal of Pediatric Orthopaedics on 2/3/2021.*
- Shah, H. et al. (2021). Does the deformity index reliably predict the shape of the femoral head at healing of Legg Calve Perthes Disease? *Submitted to Journal of Pediatric Orthopaedics on 7/1/2021.*

Further grant obtained as result of POSNA funding: None