

Cerebral Palsy Research

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Interventions and Management

1. Feasibility Trial of Thumb Taping by Parents in Infants with Cerebral Palsy: Brief Report.

Pearse JE, Cadwgan JE, Wisher V, Jesmont C, Mason-Burton P, Barry M, Jona James J, Kelly S, Basu AP.

Dev Neurorehabil. 2019 Jan 22:1-9. doi: 10.1080/17518423.2019.1566280. [Epub ahead of print]

AIM: To determine the feasibility and acceptability of parent-delivered elastic taping to the thumb and wrist in infants with cerebral palsy (CP). DESIGN: Randomized cross-over feasibility trial. PARTICIPANTS: 20 infants (11 male; mean age 22 months) with CP. INTERVENTION: Groups A and B received taping for 4 and 2 weeks, respectively. OUTCOMES: Primary: Recruitment and retention rates; adherence to protocol; Parent Satisfaction Questionnaire. Secondary: House Thumb score; Zancolli classification; Assisting Hand Assessment (AHA)/mini AHA. Exploratory: Duration of hand regard, thumb in palm, and open hand contact with toys during AHA/mini AHA. RESULTS: recruitment was feasible (95.2% uptake). Completion rates were 80% and 60% in Groups A and B. Questionnaire feedback was generally positive. Some parents reported increased awareness of the taped hand. Objective improvements were rare though one participant showed consistent improvement in thumb position. CONCLUSION: Taping proved feasible and acceptable; individual case benefit suggests further research is required. TRIAL REGISTRATION: ISRCTN41918400.

PMID: 30668211

2. Surgical outcomes of single level bilateral selective dorsal rhizotomy for spastic diplegia in 150 consecutive patients. Jeffery SM, Markia B, Pople IK, Aquilina K, Smith J, Mohamed AZ, Burchell A, Jenkins L, Walsh P, Clark N, Sacree J, Cramp M, Babiker MOE, Atherton WG, Clarke A, Edwards RJ.

World Neurosurg. 2019 Jan 16. pii: \$1878-8750(19)30059-2. doi: 10.1016/j.wneu.2018.12.187. [Epub ahead of print]

OBJECTIVES: Selective dorsal rhizotomy (SDR) is used to improve spasticity, gait and pain in children with spastic diplegia. There is growing evidence supporting its long-term benefits in terms of functional outcomes, independence and quality of life. There is, however, little contemporary work describing the surgical morbidity of this irreversible procedure. The purpose of this study is to evaluate the surgical outcomes and complications of SDR at a single UK centre. METHODS: Demographics, surgical, postoperative and follow-up data for all patients undergoing SDR between 2011 and 2016 were collected from medical records. RESULTS: Preoperative Gross Motor Function Classification System (GMFCS) levels in 150 consecutive patients were II (35%), III (65%) and IV (1%). Median age was 6 years and 58% were male. There were no deaths, CSF leaks, returns to theatre or readmissions within 30 days. There were no new motor or sphincter deficits. Postoperative neuropathic pain was reported by 5.3% and sensory symptoms by 8.7%. Other complications included: postoperative nausea and vomiting (19.3%), superficial wound infection (3.3%), urinary retention (1.3%), headache (6.7%) and urine/chest infection (4.7%). Follow-up data were available for all patients (93% to 12 months, 72% to 24 months). Persistent neuropathic symptoms were reported in 6.5% at 24 months. CONCLUSION: SDR using a single level approach is a safe procedure with low surgical

morbidity. This study complements the growing evidence base in support of SDR for spastic diplegia and should help inform decisions when considering treatment options.

PMID: 30659965

3. Anatomic Trajectory for Iliac Screw Placement in Pediatric Scoliosis and Spondylolisthesis: An Alternative to S2-Alar Iliac Portal.

Ramchandran S, George S, Asghar J, Shufflebarger H.

Spine Deform. 2019 Mar;7(2):286-292. doi: 10.1016/j.jspd.2018.08.003.

STUDY DESIGN: Single-center retrospective study. OBJECTIVE: To analyze two-year postoperative outcomes following spinopelvic fixation in pediatric patients using the anatomic trajectory (AT) portal for iliac screws. SUMMARY: Iliac fixation is crucial in situations requiring fusion to sacrum. Challenges include complex anatomy, pelvic deformation, severe deformity, and previous surgery. The PSIS portal requires significant dissection, rod connectors, and complex bends. The SAI portal requires navigating the screw across the SI joint to the ilium. The anatomic trajectory (AT), first reported in 2009, is between the PSIS and SAI portal, without prominence, connectors, or complex bends. METHODS: Fifty-four patients aged <18 years requiring instrumentation to the Ilium with minimum follow-up of two years (mean 44 months) were clinically and radiographically evaluated. Changes in coronal curve magnitude and pelvic obliquity were assessed using paired t test for patients with cerebral palsy. Spondylolisthesis reduction was assessed in patients with moderate- to high-grade spondylolisthesis (Meyerding grade 3 and 4). RESULTS: A total of 108 iliac screws were inserted using AT portal in 54 patients. Twenty-eight neuromuscular and syndromic patients had an initial mean coronal curve of 85° corrected to 23° at two years (p < .001) and a pelvic obliquity of 22° corrected to 4° (p < .001). Twenty patients with moderate- to high-grade spondylolisthesis treated with reduction and interbody fixation improved significantly with respect to their slip angles (7° \pm 14.7° to $-7.9^{\circ} \pm 6.1^{\circ}$, p = .003). In the neuromuscular group, two surgical site infections occurred, two had implant fractures, and 12 had asymptomatic iliac screw loosening, none requiring revision. In the spondylolisthesis group, there were no neurologic complications and one had prominent screw requiring removal. Of 108 iliac screws, 2 rod connectors were employed. CONCLUSION: Iliac screw insertion using the AT portal is a safe and effective method of pelvic fixation in pediatric patients with satisfactory radiographic correction and minimal complications. LEVEL OF EVIDENCE: Level 4.

PMID: 30660223

4. Surgeon and Caregiver Agreement on the Goals and Indications for Scoliosis Surgery in Children With Cerebral Palsy.

Adams AJ, Refakis CA, Flynn JM, Pahys JM, Betz RR, Bastrom TP, Samdani AF, Brusalis CM, Sponseller PD, Cahill PJ.

Spine Deform. 2019 Mar;7(2):304-311. doi: 10.1016/j.jspd.2018.07.004.

STUDY DESIGN: Prospective multicenter comparative study. OBJECTIVES: We aimed 1) to survey surgeons and caregivers to rank the surgical indications for spinal fusion of pediatric patients with neuromuscular scoliosis secondary to cerebral palsy in order of importance and 2) to characterize the agreement of surgeons and caregivers on major (top three) indications. SUMMARY OF BACKGROUND DATA: Surgery for spinal deformity in children with cerebral palsy is a multifaceted and individualized decision that may lead to miscommunication during informed consent. Little data exist on communication effectiveness between surgeon and caregiver during preoperative discussion. METHODS: This is a multicenter, prospective survey of Harms Study Group patient caregivers and their surgeons. Participants ranked their most important of 15 indications in descending level of importance, where the top 3 selections were considered major indications for surgery for the particular patient in question. Demographic and other perioperative factors were recorded. Surgeon-caregiver agreement on major indications was determined, taking into account preoperative factors and intersurgeon differences. RESULTS: 126 surgeoncaregiver pairs responded. The greatest percentage agreement that an indication was major was "to improve sitting" (69.0% major, 0.8% nonmajor), followed by "to prevent pulmonary compromise" (33.3% major, 24.6% nonmajor), "to improve pain" (31.7% major, 20.6% nonmajor), and "to improve head control/position" (20.7% major, 69.0% nonmajor). Preoperative pain showed an association with surgeon-caregiver agreement on pain as a major indication (p=.004), and intersurgeon differences in agreement on gastrointestinal and pain considerations existed (p=.002, p=.007, respectively). CONCLUSIONS: Surgeon-caregiver agreement is greater where literature support for a particular surgical indication is strong (ie, spinal fusion's known improvement of sitting posture in children with neuromuscular scoliosis). Stronger literature support may bolster surgeons' confidence in recommending a particular procedure, fostering greater communication, understanding, and agreement on surgical necessity between caregivers and surgeons. LEVEL OF EVIDENCE: Level II, prospective comparative study.

PMID: 30660226

5. Application of supervised machine learning algorithms in the classification of sagittal gait patterns of cerebral palsy children with spastic diplegia.

Zhang Y, Ma Y.

Comput Biol Med. 2019 Jan 16;106:33-39. doi: 10.1016/j.compbiomed.2019.01.009. [Epub ahead of print]

Gait classification has been widely used for children with cerebral palsy (CP) to assist with clinical decision making and to evaluate different treatment outcomes. The aim of this study was to evaluate supervised machine learning algorithms in the classification of sagittal gait patterns for CP children with spastic diplegia. Gait parameters were extracted from gait data obtained from two hundred children with spastic diplegia CP, and were used to represent the key kinematic features of each individual's gait. Seven supervised machine learning algorithms including an artificial neural network (ANN), discriminant analysis, naive Bayes, decision tree, k-nearest neighbors (KNN), support vector machine (SVM), and random forest were compared by constructing a gait classification system based on the same gait data. The performance of these algorithms was then evaluated using a standard 10-fold cross-validation procedure. The results show that the ANN has the best prediction accuracy (93.5%) with a low resubstitution error (5.8%), high specificity (>0.93) and high sensitivity (>0.92). The decision tree algorithm, SVM, and random forest approaches also have high prediction accuracy (>77.9%) with low resubstitution error (<14.3%), moderate specificity (>0.5) and moderate sensitivity (>0.2). The discriminant analysis, naive Bayes and KNN methods have relatively poor classification performance. Given these results for classification performance and prediction accuracy, the ANN is a good candidate for gait classifications for CP children with spastic diplegia. The decision tree is also attractive for clinical applications due to its transparency. Supervised machine learning algorithms can potentially be integrated into an expert gait analysis system that can interpret gait data and automatically generate high-quality analyses.

PMID: 30665140

6. Non-rigid deformation to include subject-specific detail in musculoskeletal models of CP children with proximal femoral deformity and its effect on muscle and contact forces during gait.

Wesseling M, Bosmans L, Van Dijck C, Vander Sloten J, Wirix-Speetjens R, Jonkers I.

Comput Methods Biomech Biomed Engin. 2019 Jan 22:1-10. doi: 10.1080/10255842.2018.1558216. [Epub ahead of print]

To account for proximal femoral deformities in children with cerebral palsy (CP), subject-specific musculoskeletal models are needed. Non-rigid deformation (NRD) deforms generic onto personalized bone geometry and thereby transforms the muscle points. The goal of this study was to determine to what extent the models and simulation outcomes in CP patients differ when including subject-specific detail using NRD or Magnetic Resonance Imaging (MRI)-based models. The NRD models slightly overestimated hip contact forces compared to MRI models and differences in muscle point positions and moment arm lengths (MALs) remained, although differences were smaller than for the generic model.

PMID: 30668171

7. Sensorimotor Robotic Measures of tDCS- and HD-tDCS-Enhanced Motor Learning in Children.

Cole L, Dukelow SP, Giuffre A, Nettel-Aguirre A, Metzler MJ, Kirton A.

Neural Plast. 2018 Dec 18;2018:5317405. doi: 10.1155/2018/5317405. eCollection 2018.

Transcranial direct-current stimulation (tDCS) enhances motor learning in adults. We have demonstrated that anodal tDCS and high-definition (HD) tDCS of the motor cortex can enhance motor skill acquisition in children, but behavioral mechanisms remain unknown. Robotics can objectively quantify complex sensorimotor functions to better understand mechanisms of motor learning. We aimed to characterize changes in sensorimotor function induced by tDCS and HD-tDCS paired motor learning in children within an interventional trial. Healthy, right-handed children (12-18 y) were randomized to anodal tDCS, HD-tDCS, or sham targeting the right primary motor cortex during left-hand Purdue pegboard test (PPT) training over five consecutive days. A KINARM robotic protocol quantifying proprioception, kinesthesia, visually guided reaching, and an object hit task was completed at baseline, posttraining, and six weeks later. Effects of the treatment group and training on changes in sensorimotor parameters were explored. Twenty-four children (median 15.5 years, 52% female) completed all measures. Compared to sham, both tDCS and HD-tDCS demonstrated enhanced motor learning with medium effect sizes. At baseline, multiple KINARM measures correlated with PPT performance. Following training, visually guided reaching in all groups was faster and required less corrective movements in the trained arm (H(2) = 9.250, p = 0.010). Aspects of kinesthesia including initial direction error improved across groups with sustained effects at follow-up (H(2) = 9.000, p = 0.011). No changes with training or stimulation

were observed for position sense. For the object hit task, the HD-tDCS group moved more quickly with the right hand compared to sham at posttraining ($\chi 2(2) = 6.255$, p = 0.044). Robotics can quantify complex sensorimotor function within neuromodulator motor learning trials in children. Correlations with PPT performance suggest that KINARM metrics can assess motor learning effects. Understanding how tDCS and HD-tDCS enhance motor learning may be improved with robotic outcomes though specific mechanisms remain to be defined. Exploring mechanisms of neuromodulation may advance therapeutic approaches in children with cerebral palsy and other disabilities.

PMID: 30662456

8. Statistical Models to Assess Leg Muscle Mass in Ambulatory Children With Spastic Cerebral Palsy Using Dual-Energy X-Ray Absorptiometry.

Zhang C, Whitney DG, Singh H, Slade JM, Shen Y, Miller F, Modlesky CM.

J Clin Densitom. 2018 Dec 15. pii: S1094-6950(18)30181-1. doi: 10.1016/j.jocd.2018.12.004. [Epub ahead of print]

Cerebral palsy (CP) is a movement disorder associated with small and weak muscles. Methods that accurately assess muscle mass in children with CP are scarce. The purpose of this study was to determine whether dual-energy X-ray absorptiometry (DXA) accurately estimates midleg muscle mass in ambulatory children with spastic CP. Ambulatory children with spastic CP and typically developing children 5-11 y were studied (n = 15/group). Fat-free soft tissue mass (FFST) and fat mass at the middle third of the tibia (i.e., midleg) were estimated using DXA. Muscle mass (muscleMRI) and muscle mass corrected for intramuscular fat (muscleMRIfc) in the midleg were estimated using magnetic resonance imaging (MRI). Statistical models were created to predict muscleMRI and muscleMRIfc using DXA. Children with CP compared to typically developing children had lower FFST (38%), muscleMRI (40%) and muscleMRIfc (47%) (all p < 0.05) and a lower ratio of muscleMRIfc to FFST (17%, p < 0.05). DXA-based models developed using data from typically developing children overestimated muscleMRI (13%) and muscleMRIfc (22%) (both p < 0.05) in children with CP. DXA-based models developed using data from children with CP explained 91% of the variance in muscleMRI and 90% of the variance in muscleMRIfc in children with CP (both p < 0.05). Moreover, the estimates were not different from muscleMRI and muscleMRIfc (both p > 0.99). We conclude that DXA-based statistical models accurately estimate midleg muscle mass in children with CP when the models are composed using data from children with CP rather than typically developing children.

PMID: 30661746

9. Vestibular and oculomotor function in children with CP: Descriptive study.

Almutairi A, Cochrane GD, Christy JB.

Int J Pediatr Otorhinolaryngol. 2019 Jan 2;119:15-21. doi: 10.1016/j.ijporl.2018.12.038. [Epub ahead of print]

OBJECTIVE: We aimed to describe vestibular/oculomotor function of 7-12-year-old children with CP, Gross Motor Function Classification System (GMFCS) levels (I-III), in comparison to an age-matched control group to understand the effect of the vestibular system on activities and participation of children with CP. METHODS: Vestibular, oculomotor and balance function were tested in children with CP. Central and peripheral vestibular function was examined using an enclosed rotary chair and infrared video goggles (100 Hz) that measured eye movements. Oculomotor tests included smooth pursuit and optokinetic nystagmus (OKN). Vestibulo-Ocular Reflex (VOR) tests, done in complete darkness, included step rotation (STEP), sinusoidal harmonic acceleration (SHA) test, VOR cancellation and enhancement, and subjective visual vertical and horizontal (SVV/ SVH). The integrity of the saccule was tested with the Cervical Vestibular Evoked Myogenic Potential. If able, the participants' balance abilities were examined using the Sensory Organization Test (SOT) to determine ability to maintain standing balance during six conditions that challenged the visual, somatosensory and vestibular systems. Independent t-tests and Mann-Whitney U tests were used to compare results between groups. RESULTS: Forty-one children with CP (mean age = 9.44 years, SD = 1.66; 23F/18M; Gross Motor Function Classification System levels: I (n = 19), II (n = 7), III (n = 15) and thirty-three typically developing (TD) children (mean age = 10.16 years, SD = 1.6; 13F/20M) were recruited from the Birmingham, AL community. There was no significant difference between children with CP and TD children in saccular function (i.e. C-VEMP test), and peripheral vestibular end organ (i.e. SHA test and STEP test), VOR enhancement, or OKN gain. Velocity gain for horizontal smooth pursuit was significantly worse in children with CP (p = 0.009), compared to TD children. Poor mediation of central vestibular function were that evident with significantly higher VOR cancellation gain in children with CP (p < 0.0001), compared to TD children and significantly higher SVV variance (p = 0.002), SVH mean (p = 0.001), and SVH variance (p < 0.0001) in children with CP compared to TD children. Compromised balance abilities in children with CP was evident with significantly lower composite scores (p < 0.0001), vestibular ratio (p < 0.0001), and visual ratio (p = 0.021). The somatosensory ratio (p = 0.798) of children with CP was similar to children with TD. CONCLUSIONS: Although peripheral vestibular function was intact, children with CP had difficulty coupling eye and head movement (VOR cancellation), using the

vestibular system for postural control (SOT), demonstrated poor perception of upright (SVV/SVH), and had difficulty following a slow moving target (smooth pursuit eye movement). These results implicate a central vestibular and oculomotor function impairment the severity of which corresponded with severity of the level of CP.

PMID: 30660854

10. The role of the practice order: A systematic review about contextual interference in children. Graser JV, Bastiaenen CHG, van Hedel HJA.

PLoS One. 2019 Jan 22;14(1):e0209979. doi: 10.1371/journal.pone.0209979. eCollection 2019.

AIM: We aimed to identify and evaluate the quality and evidence of the motor learning literature about intervention studies regarding the contextual interference (CI) effect (blocked vs. random practice order) in children with brain lesions and typically developing (TD) children. METHOD: Eight databases (Cinahl, Cochrane, Embase, PubMed, Pedro, PsycINFO, Scopus and Web of Knowledge) were searched systematically with predefined search terms. Controlled studies examining the CI effect in children (with brain lesions or TD) were included. Evidence level, conduct quality, and risk of bias were evaluated by two authors independently. A best evidence synthesis was performed. RESULTS: Twenty-five papers evaluating TD children were included. One of these studies also assessed children with cerebral palsy. Evidence levels were I, II, or III. Conduct quality was low and the risk of bias high, due to methodological issues in the study designs or poor description thereof. Best evidence synthesis showed mainly no or conflicting evidence. Single tasks showed limited to moderate evidence supporting the CI effect in TD children. CONCLUSION: There is a severe limitation of good-quality evidence about the CI effect in children who practice different tasks in one session, especially in children with brain lesions.

PMID: 30668587

11. The Functional Communication Classification System for children with cerebral palsy: the potential of a new measure.

Mccartney E.

Dev Med Child Neurol. 2019 Jan 22. doi: 10.1111/dmcn.14162. [Epub ahead of print]

PMID: 30671944

12. Identifying Factors Associated With Severe Intellectual Disabilities in Teenagers With Cerebral Palsy Using a Predictive Learning Model.

Bertoncelli CM, Altamura P, Vieira ER, Bertoncelli D, Thummler S, Solla F.

J Child Neurol. 2019 Jan 22:883073818822358. doi: 10.1177/0883073818822358. [Epub ahead of print]

BACKGROUND: Intellectual disability and impaired adaptive functioning are common in children with cerebral palsy, but there is a lack of studies assessing these issues in teenagers with cerebral palsy. Therefore, the aim of this study was to develop and test a predictive machine learning model to identify factors associated with intellectual disability in teenagers with cerebral palsy. METHODS: This was a multicenter controlled cohort study of 91 teenagers with cerebral palsy (53 males, 38 females; mean age \pm SD = 17 \pm 1 y; range: 12-18 y). Data on etiology, diagnosis, spasticity, epilepsy, clinical history, communication abilities, behaviors, motor skills, eating, and drinking abilities were collected between 2005 and 2015. Intellectual disability was classified as "mild," "moderate," "severe," or "profound" based on adaptive functioning, and according to the DSM-5 after 2013 and DSM-IV before 2013, the Wechsler Intelligence Scale for Children for patients up to ages 16 years, 11 months, and the Wechsler Adult Intelligence Scale for patients ages 17-18. Statistical analysis included Fisher's exact test and multiple logistic regressions to identify factors associated with intellectual disability. A predictive machine learning model was developed to identify factors associated with having profound intellectual disability. The guidelines of the "Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis Statement" were followed. RESULTS: Poor manual abilities ($P \le .001$), gross motor function ($P \le .001$), and type of epilepsy (intractable: P = .04; well controlled: P = .04= .01) were significantly associated with profound intellectual disability. The average model accuracy, specificity, and sensitivity was 78%. CONCLUSION: Poor motor skills and epilepsy were associated with profound intellectual disability. The machine learning prediction model was able to adequately identify high likelihood of severe intellectual disability in teenagers with cerebral palsy.

PMID: 30665307

13. Prevalence of metabolic syndrome and cardiovascular disease risk factors in adults with cerebral palsy. Heyn PC, Tagawa A, Pan Z, Thomas S, Carollo JJ.

Dev Med Child Neurol. 2019 Jan 20. doi: 10.1111/dmcn.14148. [Epub ahead of print]

AIM: To investigate the prevalence of metabolic syndrome and cardiovascular disease (CVD) risk factors and the association between common metabolic markers and Gross Motor Function Classification System (GMFCS) levels in ambulatory adults with cerebral palsy (CP). METHOD: Metabolic markers and GMFCS levels were evaluated in a cross-sectional study of 70 ambulatory adults with CP (34 males, 36 females; mean age 24y 5mo [SD 5y 4mo], range 18y 6mo-48y 8mo) to determine the prevalence of metabolic syndrome and CVD risk factors, and were compared to age-matched, population norms from the National Health and Nutrition Examination Survey (NHANES) registry. The Framingham Heart Study (FHS) CVD risk estimation was also used to evaluate an individual's risk for CVD. RESULTS: Metabolic syndrome was identified in 17.1% of the cohort, higher than the 10% in the NHANES registry. The FHS CVD 30-year lipid and body mass index (BMI)-based risk factor results showed that 20% to 40% of the cohort was at greater risk of developing CVD (BMI-based: 39.7% 'full' CVD risk factor; lipid-based: 26.5% 'full' CVD risk factor) as compared to the FHS normative population data. There was a positive correlation between GMFCS level, waist circumference (r=0.28, p=0.02), and waist-to-hip ratio (r=0.28, p=0.02). INTERPRETATION: Adults with CP are at higher risk of CVD and metabolic syndrome compared to the general population, which is probably because of impaired mobility.

PMID: 30663044

14. Japan Obstetric Compensation System for Cerebral Palsy: Strategic system of data aggregation, investigation, amelioration and no-fault compensation.

Ushiro S, Suzuki H, Ueda S.

J Obstet Gynaecol Res. 2019 Jan 22. doi: 10.1111/jog.13906. [Epub ahead of print]

The Japan Obstetric Compensation System for Cerebral Palsy (JOCS-CP), which investigates, develops preventive mechanisms and awards monetary compensation, to cases of cerebral palsy was urgently introduced in 2009 in response to growing concern about Japan's deteriorating perinatal care and low birthrate. Under the political leadership, the Japan Council for Quality Health Care launched the JOCS-CP with support of various stakeholders. The JOCS-CP features of no-fault-based compensation which was discussed decades ago in the Japan Medical Association aiming at financial aid to patient and family and early settlement of dispute. As of 2017, 2233 petitions had been approved by the Review Committee for compensation. All the approved cases were consecutively put on analysis in the Investigation Committee which has compiled more than 1000 Investigative Reports. The reports were delivered not only to the childbirth facility but to the guardians/families. Survey revealed that most of childbirth facility and the guardians/families responded in favor of the reports. With regard to amelioration of profound cerebral palsy, the Prevention Report has been published on annual basis through analysis of all the Investigative Reports. The Prevention Reports and other educational materials were produced and distributed not only among medical professionals but among pregnant women. It is notable that the number of lawsuit filing related to obstetrics demonstrated rapid decrease compared to that of other medical specialties. The JOCS-CP could be described as a social experiment. It was overhauled in 2015 but deserves further discussion on reform for evolving into better system.

PMID: 30672080