Spinal and vertebral dimension charts: precise and accurate characterization for decision-support.

Normal spinal growth results from a delicate balance between muscular tone, gravitational forces and the normal activity of vertebral growth plates. Although this growth process is highly regulated, spinal pathologies and asymmetries often result in significant deformities. Remaining growth and spinal deformity severity at presentation are both important risk factors associated with deformity progression. Early Onset Scoliosis (EOS) is particularly significant as the spinal deformities associated with this entity are at significant risk of severe deformities.

Understanding normal spinal growth is mandatory to better comprehend the abnormal process affecting patients with spinal deformities. “Only comprehensive knowledge of normal growth parameters allows a better understanding of both normal and abnormal spine growth and of the pathologic changes induced in a growing spine by an early onset spinal deformity” (10, 15). With new growth-friendly strategies emerging for the treatment of spinal deformities, it is essential to develop knowledge to better represent normal and abnormal spinal growth. The research effort presented in this research proposal is the result of a collaborative effort between the Growing Spine Study Group and the Children’s Spine Study Group.

A- Objectives
The general objective of this study is to improve knowledge about expected spinal and vertebral growth in healthy young children by providing reference growth charts. The primary objective is to define clinically relevant and mathematically valid measures of the spine and vertebrae. The second objective is to provide precise and accurate estimates of reference values of spinal and vertebral dimensions and growth in healthy children from a large database.

B- Significance
This study represents a first effort to provide reference spinal and vertebral growth charts of healthy children under the age of 11 years, using 3D reconstruction of the spine from accessible low dose imaging methods. In absence of an adequate available growth assessment tool, the results of this study will provide important knowledge on normal spinal evolution and growth of the different age categories in the young population. Developed methods allow to further examine this data in 3D for the determination of the “true” 3D spine height as well as individual vertebra and functional unit dimensions. The elaboration of a spinal reference for height and growth will help healthcare providers better assess their patients’ remaining spinal growth; a key parameter for treatment planning, especially in the context of growth friendly interventions for early-onset scoliosis. This data could be used by health professionals to predict spinal height at maturity or spinal height changes in pathologic conditions. Eventually, the developed methods could be adapted to define reference values of growth of patients with spine pathologies. As we are improving our knowledge of normal growth, it will become possible to evaluate the efficacy of different growth-friendly treatment modalities as compared to the expected normal growth.

C- Background
Deformities in the growing child
Symmetric and harmonious growth characterizes normal spines although spinal growth itself is the product of more than 130 growth plates working at different paces (2,14,15). Disturbance of growth may be due to dietary conditions, skeletal dysplasia, spinal deformity, spinal fusion at an
early age and localized factors- skeletal infections, trauma- etc. In severe scoliosis, growth becomes asymmetrical as a result of growth plate disorganization. Complex spinal deformities alter growth spine cartilage and vertebral bodies become progressively distorted and can perpetuate the disorder.

Spinal fusion has been abandoned as the standard treatment for arresting progression of EOS unresponsive to non-surgical treatment. Reports have demonstrated that it does not address the impact of the deformity on lung parenchyma development or preservation of pulmonary function, does not completely prevent progression, and can adversely affect the development of spine and thorax by changing their shape and reducing mobility (2).

Growth friendly techniques for treatment of progressive EOS have evolved significantly during the past few decades. They globally aim at preserving growth and may even have a potential for growth stimulation. Originally, Harrington (19) recommended distraction instrumentation without fusion for children less than 10 years of age to allow continuous spinal growth. Moe et al. (26) popularized instrumentation without fusion and included periodic construct lengthening to achieve both deformity correction and spinal growth using hooks and single distraction rod. However, the technique requires frequent surgical procedures for lengthening which leads to an increased complication rate and more unplanned surgical procedures. In recent years, other techniques have also been introduced as growth-friendly procedures (25). Skaggs et al. (30) have proposed a classification of the major growth-friendly techniques into 3 main categories: "distraction-based" (e.g., GR, vertical expandable prosthetic titanium rib, and remote control (magnetic growing rods), (3)), "tension-based" (e.g., staple and tether), and "guided-growth" (e.g., Luque-Trolley and Shilla (21)).

Surgeon’s knowledge regarding the various challenges in EOS surgery has also significantly improved during the past several years, and there has been an ongoing research effort to minimize complications associated with most growth friendly procedures (3). Current growth state is tributary of remaining and elapsed growth and any surgical strategy should be adjusted according to remaining growth. All these techniques aim to restore normal spinal growth by controlling the progression of the deformity. However, normal growth is not known at the individual vertebral or vertebral unit level and only sparse data for total expected spinal height are available. There is insufficient support for decision-making for these techniques. Only a critical analysis of all growth parameters over time allows to unmask and understand the magnitude of the deficits induced by an early onset spinal deformity and potential improvement gained by such operating techniques.

Growth reference tables
Growth reference tables describe the growth patterns of a defined population. In simple terms, a reference describes “what is”. The World Health Organization Child Growth Standard and the WHO Growth Reference constitute excellent estimation of standard values of total standing height (and weight) for monitoring the growth of individual children (13).

Standing height is a global marker composed of two components – sitting height and subischial height. As these two regions often grow at different rates and at different times, standing height does not always exactly correlate with trunk height loss in children with severe spinal deformities (2,14,15). Spinal and vertebral dimensions, such as total spinal height, are therefore the measures of choice to characterize normal growth in relation to spinal pathologies.

A rapid review of what is currently available in the orthopaedics textbooks comprises charts like Roaf’s growth charts published in 1960 (28) displaying length of the thoracic and
lumbar spine as a function of age from direct measurements on x-ray films. For research purposes, authors have used radiologic data from spinal specimen or children, over selected spinal segments. For example, Taylor (31) reported vertical radiograph measurements on three spinal levels from fetuses to adults. They reported that growth is greater at L4-L5 level than T8-T9 or C5 globally, that measurements follow fairly the same slope between the age of 2 and 7, and that measurements are similar during childhood between boys and girls. Bradner (8) reported mean and standard deviation at several vertebral levels for vertical/horizontal ratios, in correspondence to total height and skeletal age. Veldhuizen and Webb (35) studied measurements from “normal levels” in 30 scoliosis patients. They provided average growth increments for the 10 to 17 age groups. Gender, age and standing height were measured as stratification factors. Interesting data were published by Ball (7) and Altan (4) from yearly radiologic assessments of boys or girls. However these data focused only on cervical vertebrae. Canavese and Dimeglio (10) published a literature review on how spinal deformities can affect normal spine and thoracic cage growth and were able to provide only sparse data on expected total spine height change during growth and no data at the functional unit level.

In summary, we conclude that surgeons do not have access to detailed measures from healthy children, in normal standing position, nor on all vertebral levels. Available data was not derived from a unique data source, from 3D reconstruction techniques nor on a large sample for precise estimation and generalizability of results. Spinal measurements were previously suffering from radiographic parallax precluding accurate measurements or were made in single plane precluding any consideration of out of plane measurements. In addition, we were unable to report any tool for evaluating remaining growth compared to normal or evaluating current growth in pathologic conditions (disease states growing charts), compared to normal expected growth.

D- Previous work done

Three-dimensional characterization of the trunk geometry has been a major research interest for the Sainte-Justine University Hospital Centre (CHUSJ) research team on spinal deformities for the past 25 years (5,6,11,18,19,23,24). Extensive work in this field has included 3D terminology elaboration, 3D classification of spinal deformities, development and validation of methods in stereoradiography, 3D evaluation of treatment outcomes in spinal deformities, etc.

As pilot testing of the present study, the association between measures of total spinal heights obtained from 3D reconstructions of the spine and age was investigated. Radiographic examinations performed with the EOS system to rule out spinal deformities were retrospectively retrieved and analyzed in 98 asymptomatic patients seen at CHUSJ in the past 8 years.

This preliminary testing showed that a direct relationship is expected between total spinal height and age in the targeted age group. A linear regression model was first fitted to the data presented in the Supplementary material section. As described by Dimeglio and Canavese (15), the T1-S1 segment grows around 10 cm during the first 5 years of life (2 cm/year), about 5 cm between age five and 10 (1 cm/year). These numbers correspond to about 1.25 cm on average in the 3 to 10 period, in concordance with the preliminary regression model we obtained (see Supplementary material). In addition, spinal height is known to be around 30 cm at 5 y.o. and 35 cm at 10 y.o. (15), which corresponds to results that can be extracted from our regression model (respectively 28.3 and 34.4).

These results were presented at the annual meeting of the Quebec Scoliosis Society (32) and will be presented at ICEOS 2014 (33,34). These promising results support the feasibility of the proposed methods and the clinical relevance of expected results. It also encourage
enlargement of the database for precise estimation of growth parameters in the young healthy population and the relevance to extend the characterization to more detailed description including vertebral body and vertebral unit parameters and more complex modeling.

E- Methods
i. Participants
This study examines healthy infants and children aged 3 to 10 y.o. (included) who underwent radiologic examinations of the spine using the EOS system (EOS Imaging, Paris, France). Eligible participants will be identified from radiology databases of spine examinations. These were done in various contexts such as, but not limited to, back pain, ruling out spinal deformity, appendicitis, asthma, trauma. The selection criteria are as follows:

Inclusion criteria:
- Age 3-10 y.o.
- Frontal and lateral full spine x-rays
- Good quality digital spinal images from EOS system

Exclusion criteria:
- Presence of a spinal deformity (Frontal Cobb angle > 10 degrees) or skeletal dysplasia
- Abnormal sagittal profile (Thoracic kyphosis > 50 degrees)
- Previous spinal surgery
- Presence of significant known disease affecting growth and known abnormalities of maturation or height

From the age of 3, measurement of the trunk height is considered appropriate in the standing position, as required in the EOS system (before age 3 – not considered in this study - , the supine position is recommended (15)).

ii. Source data and data management
All EOS Imaging x-rays of asymptomatic patients evaluated in radiology between 2007 and 2014 for a back examination will be identified and reviewed. Retrospective data will be used in the different participating centers: CHU Sainte-Justine (Montreal), IWK Health Centre (Halifax), Rady Children’s Hospital and Health Center (San Diego) and University of Rochester Medical Center (Rochester). Clinical sites involved in the Children’s Spine and Growing spine study group declared their interest in participating in this collaborative effort to build a large database of spinal reconstructions in support of the study’s objectives. Patients with a single examination as well as follow-up patients with repeated evaluations will be considered for inclusion. Single examinations (cross-sectional data) will be included to maximize sample size. Patients with repeated examination (longitudinal data) will be included if they have at least 3 visits so that a minimum of 2 sets of growth data be obtained from all follow-up patients.

Digital Postero-anterior and Lateral calibrated radiographic images will be transferred from all participating centres to the study coordination office. A trained technician considered an expert in the technique will digitize the positions of anatomical landmarks on the images and SterEOS software (EOS Imaging inc.) will be used to compute a 3D reconstruction of the spines’ geometry. The software uses a semi-automated method based on a priori knowledge (22). Pomero et al. showed that there is no difference in terms of mean errors between 3D vertebral models issued from stereoradiography and computed tomographic–scan reconstructions (27). The mean point-to-surface errors were less than 1.5 mm and less than 2° for angular
measurements when compared with conventional computed tomographic-scan reconstructions (22,36).

From this reconstructed geometry, selected parameters (total spinal height, T1-S1 true 3D height, T1-S1 linear height, kyphosis, lordosis, etc.) will be calculated and extracted for further analysis. In addition, vertebral body height at each cervical, thoracic and lumbar levels will be computed as well as vertebral unit height, as defined by the 3D length between the inferior vertebral endplate of the inferior vertebra and the superior vertebral endplate of the superior vertebra, including the intervertebral disk. Total spinal growth, vertebral body growth and functional unit growth will be calculated between visits of same patient from the ratio of the difference in the parameter values to the time between the visits, expressed in mm/year or mm/month. Data retrieved from medical charts of participating children will include: date of birth, gender, weight and height at time of radiologic examination, date of radiologic examination and diagnosis.

Data will be processed in parallel to data collection. Monthly transfer of data will be done at the coordination centre for processing and quality control. System calibration within and among sites is a key aspect of such studies. Since retrospective data are here used here, past periodic evaluations of the local systems will be assessed. In addition, data accuracy and precision as a function of time (stability of errors) over the observation period will be monitored. Raw data and all computed parameters will be saved in denominatorized format in a project-specific secured Access database.

iii. Sample
Retrospective data will be retrieved on an 8 year period, according to expected sample size from the participating centres. The target sample size is the maximum possible to achieve sample size requirements. From what is known of global annual spinal growth, the sample size should be sufficient to measure a difference of 1 cm on the total spinal height and of 2 mm on a single vertebral body while minimizing type1 and type2 errors. Precise estimates are required for each age group (3 to 10) and known variability of total spinal height measures is between 14 (<8 y.o.) and 26 (8-10 y.o.) mm from CHUSJ pilot data (section D). According to the standard formula of the estimation of a mean (or one-sample t-test), a sample size of 75 patients in each age group is suggested to achieve 90% power, in mean estimation of total spinal height (main outcome) based on the CHUSJ pilot data, with a significance level of 0.05.

The targeted total sample size is therefore 600 participants (single examination). These numbers should also be sufficient for multivariate modeling since we expect a data/parameters ratio exceeding 10. For longitudinal data a ratio of 1:5 of the cross-sectional sample of participants is considered appropriate (13,37), which means that we are expecting at least 120 patients with a minimum of 3 visits each.

iv. Analysis
Descriptive analyses
The mean values, standard deviations, minimum and maximum values of each parameter will be calculated for all age categories. Scatter plots of the selected measures will be built according to age group. Data distribution will be characterized and outliers data will be tested. Means and standard deviation of corresponding age group will be used to derive Z-scores.
**Modeling studies**

Centiles will be estimated from available data as a function of age. The 100p centile of a random variable \( Y \) is the value \( y \) such that \( p(Y \leq y)=p \), (the inverse cumulative distribution function of \( Y \) applied to \( p \)). The growth centile reference tables as a function of age are the main deliverables and the most clinically relevant information for clinicians. The methodology for creating growth centile references will include the LMS (Lambda-Mu-Sigma) method (12) and its extension the Box-Cox power exponential distribution (29). The GAMLSS software (available from R library) will be used for centile estimation. The goodness-of-fit will be addressed using the deviance and the Akaike Information Criterion. Growth charts will then be built based on these centiles tables using spline smoothing. The chosen modeling approaches follows WHO’s selection of best methods (38).

Different models will be assessed to characterize spinal measures as a function of age according to data distribution (usual postulates for linear regression modeling will first be tested). In particular, the Weight estimation procedure will be evaluated since the variance of spinal height differs according to age. Correlations will be calculated and regression models will be built to relate spinal measures and age. Multivariate models will be considered in order to adjust for:

- Gender
- Height and weight
- Data collection site
- Date of examination

The identification of variability sources and of adjustment variables or possible interactions (e.g. age*gender) will afford multivariate modeling for informative assessment and easy interpretation of height and growth curves. Multilinear and non linear models will also be considered if data distribution requires it (Non linear regression IBM SPSS 20 package).

For follow-up data (growth estimation), multi-level modeling approaches for repeated measures will be investigated. The Mixed model package of IBM SPSS 20 will be used for model building. Quality of adjustment will be evaluated by the intraclass correlation coefficients.

**Data validation**

Published and generally recognized measurement errors acquired by the EOS technique will be identified. Intraobserver (dedicated technician) assessment of reliability will be done on 10% of the sample (37) of patient reconstruction cases (60 reconstructions will be done twice by the technician). Variability in 3D point coordinates will be computed and expected to be inferior to known reconstruction errors. Test-retest reliability coefficients are expected to be very high. In addition, characterization of measurement errors on the reconstructed models will be done to ensure intersite comparison of data prior to the study. The same EOS system was installed in all participating centers. However, to validate data pooling, we are currently documenting accuracy of the parameters as a posteriori validation of retrospective data, using a synthetic bone spine model. The CT-scan reconstructions (gold standard) and the 3D reconstructions from EOS obtained from each site of the Sawbone spine will be compared using point-to-surface registration of the models.

Study results will be generally compared with sparse data reported by Dimeglio (and other authors) for standing heights and spinal growth at specific ages. Finally, as a strategy to assess model generalizability, the whole data set will be separated into training and validation sets of data that will be respectively used for model building and for empirical validation.
F- Timeline

| Study planning, training of personnel and implementation of data collection modalities | Month 1 | Month 2 | Month 3 | Month 4 | Month 5 | Month 6 | Month 7 | Month 8 | Month 9 | Month 10 | Month 11 | Month 12 |
| Validation of the data collection process (pretesting of the methods, determination of accuracy, reliability studies) | x | x | | | | | | | | | | |
| Data collection in the participating centers | | | x | x | x | x | x | x | x | x | x | |
| Data analysis | x | x | x | x | x | x | x | x | x | x | x | |
| Final report and diffusion of study results | | | | | | | | | | | | x |

G- Cited references


H - Supplementary material

This graph presents the results of the pilot study on retrospective CHUSJ data testing the association between the total spinal height measured in 98 asymptomatic children as a function of age. The equation of the linear regression model is also presented on the graph, featuring a good determination coefficient.
I- Animal IRB statement
Non applicable.

J- Human IRB statement
This study will be conducted on retrospective data from 600 patients who had EOS examinations in the participating centres during the defined observation period (see section E i-iii for more details).

This research project involves minimal risks as it does not alter any treatment modalities as to the underlying pathologies. No harm is expected from allowing the data collected to be used for research purposes. No additional radiologic examination is required for the project. No new procedures or devices will be introduced in this study. No adverse events are expected by allowing the data collected to be used for research purposes. There are no direct benefits to the clinical subjects in the study for allowing their data to be collected. However, by improving knowledge on normal growth, better care may be provided to future patients referred in orthopaedics for spine assessment and spine pathology treatment.

Data collection and management will be performed by our research team. Data handling and protection are in accordance with the guidelines of ICH-GCP and applicable NIH regulations to which the researchers agree to comply. Required authorisations to retrospectively access medical records will be obtained in the participating centres (IRB approval is already in place at Ste-Justine hospital who will be coordinating the).

For this study, patient data retrieved from medical records and radiographic images will be de-identified and given a unique numerical identifier. A separate patient study log will be kept by the Principle Investigator linking the unique identifier to the patient data. All CRF data and the patient study log will be stored in a locked filing cabinet in a locked office at the CHU Sainte-Justine located at 3175 Cote Sainte-Catherine, Montreal, QC, H3T 1C5 under the responsibility of Dr Stefan Parent. The results from this study maybe published; however, the participant’s
name will not be used in any publication. Study data will be kept for 5 years after the results have been published in a healthcare journal.

**K- Role of the Orthopaedic Surgeon**
Dr Stefan Parent is a spine orthopaedic surgeon treating high volume of pediatric patients with spine pathologies. He has recently extended his practice to develop expertise into growth friendly devices and interventions. As a researcher, he was involved since his PhD thesis in the thorough characterization of the 3D geometry of healthy and pathological spine. As the PI of this application, Dr Parent has elaborated the main research question and will contribute to the study design, planning of the study and support for cases identification. He will also be extensively involved in height/growth data tabulation, in the choice of spinal and vertebral parameters, in charts elaboration and model interpretation as well as in the clinical relevance of data presentation.

The other orthopaedic surgeons are experts involved in the choices and definition of the spinal and vertebral parameters from the literature and past personal research work. They will also be facilitators for data collection and have an indisputable role into data interpretation and model significance.

**L- Relevance to POSNA mission**
With its mission of improving the care of children with musculoskeletal disorders through education, research, and advocacy, POSNA is well positioned to promote research strategies aiming at providing fundamental data in support to physician’s decision for best patients’ management.

This research is innovative in its methods and in the deliverables. It is fundamental work that has multiple applications in support to decision-making: to decide in which patients the intervention is appropriate, to determine the reservoir of potential growth, to decide the localization and the number of vertebral levels to be included in the intervention, to tailor prediction of growth in function of characterization of functional units involved, to select best intervention parameters, as well as to validate novel treatment approaches and predict outcomes of growth friendly devices interventions.

The project is well oriented to methods of secondary and tertiary prevention of disorders of the musculoskeletal system by better informing decision for surgical management and augmenting the capacity to restore normal growth.

The proposed retrospective study is at the same time providing currently unavailable data that will answer clinicians’ everyday questions and offering the required step for preparing a prospective study (de Onis 2004). Therefore, the financial support from POSNA will represent a structuring effort for the group to build the first geographically diverse, accurate and precise database on spinal and vertebral dimension and growth from 3D reconstructions. This will lead to strong data for the team to be well positioned to solicitate NIH funding for a prospective study in the years to come.