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Interview

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Global Leadership in Paediatric and Congenital Cardiac Care: "Using data to improve outcomes – an interview with Jennifer S. Li, MD, MHS"

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Abstract

Dr. Jennifer Li is the focus of our second in a planned series of interviews in Cardiology in the Young entitled, "*Global Leadership in Paediatric and Congenital Cardiac Care*". Dr. Li was born in Boston, Massachusetts, United States of America, and moved to Indianapolis, Indiana where she completed her secondary education. She then attended Stanford University, majoring in Chemistry and English and graduating with distinction in 1983. Dr. Li then attended Duke University School of Medicine, graduating in 1987. She then completed her internship at Children's Hospital of Philadelphia in 1987–1989, returning to Duke University Medical Center to complete both her residency in general paediatrics in 1989–1990 followed by her fellowship in paediatric cardiology in 1990–1993. She would later complete her Master's Degree in Health Sciences at Duke University in 2005.

Dr. Li has spent her entire career as a paediatric cardiologist at Duke University Medical Center, where she was appointed a Professor of Pediatrics and Professor of Medicine in 2008 and has held the position as Beverly C. Morgan Endowed Professor of Pediatrics since 2012. She has served as the Chief of Paediatric Cardiology at Duke University Medical Center since 2006. She also was the Director of Paediatric Research at Duke Clinical Research Institute from 2001-2015. Dr. Li has played an instrumental role in evaluating the safety and efficacy of drugs in children, as well as in analysing and linking large multicentric databases to evaluate the outcomes, quality, and cost of paediatric and congenital cardiac care. Dr. Li has received funding from the National Institute of Health of the United States of America, as well as from industry and foundation grants. This article presents our interview with Dr. Li, an interview that covers her experience collaborating with governmental organizations and industry in the pursuit of common interests to design clinical drug trials, link and analyse large, multicentric databases, and improve paediatric health care.

We are very pleased that Dr. Jennifer Li (Fig 1) is the focus of our second in a planned series of interviews in Cardiology in the Young entitled, "*Global Leadership in Paediatric and Congenital Cardiac Care*". Dr. Li was born in Boston, Massachusetts, United States of America, but mostly raised in Indianapolis, Indiana, where she completed her secondary education. She then attended Stanford University, majoring in Chemistry and English and graduating with distinction in 1983. Dr. Li then attended Duke University School of Medicine, graduating in 1987. She then completed her internship at Children's Hospital of Philadelphia in 1987–1989, returning to Duke University Medical Center to complete both her residency in general paediatrics in 1989–1990 followed by her fellowship in paediatric cardiology in 1990–1993. She would later complete her Master's Degree in Health Sciences at Duke University in 2005.

Dr. Li has spent her entire career as a paediatric cardiologist at Duke University Medical Center, where she was appointed a Professor of Pediatrics and Professor of Medicine in 2008 and has held the position as Beverly C. Morgan Endowed Professor of Pediatrics since 2012. She has served as the Chief of Paediatric Cardiology at Duke University Medical Center since 2006. She also was the Director of Paediatric Research at Duke Clinical Research Institute from 2001 to 2015. Dr. Li has played an instrumental role in evaluating the safety and efficacy of drugs in children, as well as in analysing and linking large multicentric databases to evaluate the outcomes, quality, and cost of paediatric and congenital cardiac care. Dr. Li has received funding from the National Institute of Health of the United States of America, as well as from industry and foundation grants. We had the pleasure to interview Dr. Li in order to discuss her experience collaborating with governmental organisations and industry in the pursuit of common interests to design clinical drug trials, link and analyse large, multicentric databases, and improve paediatric health care.

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Figure 1. Jennifer S. Li, MD, MHS.

Dr. Tretter: Tell us about your upbringing, and any role models or events which led both to your pursuit of medicine in general, and specifically to the field of paediatric cardiology.

Dr. Li: My parents both had escaped from China during the Second Sino-Japanese War and subsequent communist takeover of China. My father then grew up in South Africa and my mother in the Philippines. They would eventually come to the United States as foreign students, meeting each other in Boston. I was born in Boston; however, we moved around quite a bit related to my father's medical training. We eventually landed in Indianapolis when I was in fourth grade, where we stayed for the remainder of my primary and secondary schooling. My father was a physician, but very different, being a basic scientist who studied the determinants, biochemistry, and genetics of alcohol-related disorders at various major medical centres. This exposure is what attracted me to the sciences, and, as an undergraduate student at Stanford University, I decided to enter the pre-medicine program. Following undergraduate school, I attended Duke University School of Medicine. Having already fallen in love with paediatrics, I remember during my second year while on my paediatric rotation coming in for a Saturday morning lecture by Dr. Brenda Armstrong. Dr. Armstrong was one of the first African American women to be board certified in paediatric cardiology in the United States. She was physically a very diminutive woman, standing under five feet tall, but she was a powerhouse of a figure. She came into the lecture and stood up on top of two stools - I still remember this vividly. She presented a patient with tetralogy of Fallot, and then drew out the heart and the saturations to discuss the haemodynamics. And that is when I fell in love with paediatric cardiology, listening to her passion as she discussed the anatomy, physiology and clinical course of this patient with tetralogy of Fallot. This lesion remains one of my favourites to deal with as it brings back all the excitement related to managing patients with congenital heart disease, with each patient being different. Dr. Armstrong would become a clinical mentor and major influence for me during my paediatric cardiology fellowship training at Duke University Medical Center, along with prominent research scientists Drs. Page Anderson and Madison Spach. I have remained at Duke University ever since!

Dr. Tretter: Tell us about the history of development of the Paediatric Cardiology Program at Duke University.

Dr. Li: The program really came into prominence during the leadership of Dr. Madison Spach, a basic science electrophysiologist at Duke University in the 1960's. Fortunately, he is still around and active. He trained several paediatric cardiologists at Duke in the basic sciences, including one of my main mentors Dr. Page Anderson, who unfortunately died in 2008. Dr. Anderson was a huge mentor to a lot of us at Duke, being a great scientist and clinician. His research spanned from basic science work in his lab with the myofilament and troponin, to large animal research and clinical research, and he was one of the initial investigators of the Pediatric Heart Network. He also was the program director for the paediatric cardiology fellowship and was heavily involved in training. His main joy was to be at the clinic, and he always saw things from the patient's perspective. Dr. Anderson's teaching and influence has clearly played a positive role in developing the Duke University Paediatric Cardiology Program into what it is today.

Dr. Tretter: You have played a major role in the evaluation of safety and efficacy of drugs for children, with much of this work contributing to the reauthorization of the Best Pharmaceuticals for Children Act in 2012. Can you discuss what sparked your interests in helping to address this issue and what barriers you faced in helping to reinforce this paediatric pharmaceutical focus?

Dr. Li: Anyone who takes care of children realizes that drugs are not primarily developed and brought to market for children, but for adults, because that is how pharmaceutical companies make returns on their investments. Children have historically been an afterthought in the pharmaceutical industry, and for decades paediatric physicians had to make off-label extrapolation for children. There were not many drugs labelled for children, so we did not know the dose, efficacy, or safety for our paediatric patients. This challenge led to a lot of really bad things for children, with unknown side effects, such as chloramphenicol leading to gray baby syndrome[1] and thalidomide leading to limb deformities[2]. So, it became critical to study prescribed drugs in children and have these drugs labelled appropriately. There were several initiatives over time, with the key one being the Pediatric Exclusivity Act authorized by the United States Congress in 1997 to allow the Food and Drug Administration of the United States of America to grant an additional 6-month extension of patent protection to pharmaceutical companies if Food and Drug Administration-requested paediatric trials were conducted.[3,4] The second key measure was the Best Pharmaceuticals for Children Act of 2002, which revitalized the incentives for pharmaceutical companies to study marketed drugs for children.[4,5] These initiatives were critical for establishing safety and efficacy in various prescribed drugs for children in this country.[4,6,7]

Dr. Tretter: What has been some of the benefits and hurdles working with governmental organizations and pharmaceutical companies in pursuing a common interest of drug efficacy and safety for children? What advice would you give to the clinical scientist pursing similar collaborations?

Dr. Li: It is really a challenging area. I did a mini-sabbatical at the Food and Drug Administration, where I worked in the office of the commissioner looking at the written requests for Pediatric Exclusivity, and we looked at the financial incentives and returns on investment. My takeaway from that experience was that everyone wants the same thing. We all want to develop safe and efficacious drugs for children. But, it is challenging. If you want to do drug trials in children, it is astronomically more difficult than it is in adults. This relates to ethical issues as well as the challenges of enrolling vulnerable children who have a lot more heterogenous

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diseases. Figuring out what your endpoint is becomes very difficult. You also want to study drug dosing, and dosing a neonate is a huge difference from dosing a teenager. Studying the entire paediatric spectrum therefore becomes challenging.

Dr. Tretter: What scientific and ethical considerations should the clinical scientist have when designing a drug trial for paediatric patients?

Dr. Li: The critical elements are to know what your patient population is and to design a good clinical endpoint. In our field, we are challenged by sample size and being able to recruit, so we must often use innovative statistical methods. Partnering with an excellent statistician early on is critical. For drug trials, partnering with a pharmacologist is a necessity. Parent groups should be involved to get their perspective on consenting and the entire process.

Dr. Tretter: You have been involved with and directed multiple studies of the outcomes, quality, and cost of paediatric cardiac care using the Society of Thoracic Surgeons Congenital Heart Database. Please tell us your thoughts about research involving the Society of Thoracic Surgeons Congenital Heart Database and other multi-institutional databases.

Dr. Li: There are multiple databases available for congenital heart disease, but in terms of children with congenital heart disease who have undergone surgery, the Society of Thoracic Surgeons Congenital Heart Database is the most comprehensive with the greatest number of centres in North America involved. The database started out as a quality improvement initiative, and it is certainly used by the US News survey as one of the quality indicators for outcomes, which is a critical use. But, since it captures so much comprehensive data about the patient and their cardiac lesion, their anaesthesia record, surgical course, and outcomes, it lends itself to data analysis and research. I've worked many years now with Jeffrey Jacobs and Marshall Jacobs, who have both been instrumental in leading the Society of Thoracic Surgeons Congenital Heart Database, on various studies using this database.[8–16] More recently we have a study utilizing the Society of Thoracic Surgeons Congenital Heart Database called the Steroids to Reduce Systemic Inflammation after Infant Heart Surgery (STRESS) trial.[17] In this study, we are randomizing infants to steroids or placebo during cardiac surgery. It is a trial within a registry, which is somewhat novel since we are collecting our clinical trial data through the Society of Thoracic Surgeons Congenital Heart Database. It is an ambitious study; however, as of July 2020, we have enrolled over 750 infants across multiple centres.

Dr. Tretter: One of your research interests has been linking databases together and creating larger databases. By linking two databases, you were able to answer unique questions that neither dataset could answer alone. One of your earlier National Institute of Health (NIH) Grants that involved linking databases was the NIH Challenge Grant. This NIH Challenge Grant was one of the first grants that linked clinical and administrative data to study paediatric and congenital cardiac care, utilizing both the Society of Thoracic Surgeons Congenital Heart Database and Pediatric Health Information System (PHIS) database. By linking these two databases, you were able to answer unique questions that neither dataset could answer alone. This NIH Challenge Grant generated multiple publications.[18–25] Tell us about your overarching opinion about the importance of this NIH Challenge Grant? What do you think its most important accomplishments were?

Dr. Li: Linking databases is very beneficial when you have more than one database collecting different kinds of data with a considerable number of individuals involved, allowing you to enrich the data captured on an individual patient. We have looked at linking databases through probabilistic matching through indirect identifiers, such as age and location of surgery, to avoid issues violating the Health Insurance Portability and Accountability Act of 1996. We used this approach for the aims of the NIH Challenge Grant in order to enrich the patient data gathered from both the Society of Thoracic Surgeons Congenital Heart Database and the PHIS database. For example, the Society of Thoracic Surgeons Congenital Heart Database does not collect medication use while the PHIS database does. Meanwhile, in comparison to the PHIS database, the Society of Thoracic Surgeons Congenital Heart Database collects more detailed clinical data about a given cardiac operation. So, by linking these two databases, we were able to gather the medications administered to a given patient surrounding their surgery as well as detailed clinical information about the operation. The NIH Challenge Grant laid the groundwork for the current STRESS trial.[17] Our NIH Challenge Grant confirmed that we could answer important questions looking at a linked database that could not be answered by a single database in isolation. In fact, one of the aims of the NIH Challenge Grant was to identify important questions for future research. From our work in the NIH Challenge Grant, we noticed that many centres were using steroids during the peri-operative period. We know that steroids have a significant side effect profile, specifically hyperglycaemia and increased infection risk. From this information, we determined that there was likely equipoise to randomize children to receiving or not receiving perioperative steroids. This approach became the impetus to apply for an NIH grant for the STRESS trial. We also recognized it would be pragmatic to do a trial within a registry, using data that is already captured in the Society of Thoracic Surgeons Congenital Heart Database. This "trial within a registry" strategy would lessen the costs and effort necessary for the trial.

Dr. Tretter: What have been the major learning points from being involved in the creation and analysis of large databases that you wish you had understood early on?

Dr. Li: Duke University Medical Center, with its Duke Clinical Research Institute, has provided a very strong infrastructure for databases and clinical trials. It takes a great team to pull off these multicentre trials and manage these large databases, a team that includes data scientists, data managers, project managers, statisticians, clinicians, and people who are very adept at looking at innovative ways to do trials. It is difficult to operationalize multicentre trials using large databases without this extensive underlying infrastructure.

Dr. Tretter: You have also been involved with multiple studies in the Pediatric Heart Network?[26–30] Please tell us your thoughts about research involving the Pediatric Heart Network? What are the strengths and limitations of this type of research?

Dr. Li: The Pediatric Heart Network was one of the first major collaborative initiatives within the National Institute of Health to

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study children with heart disease, with a number of landmark studies developing the necessary infrastructure to answer important questions in this population. Examples of studied populations include those with Kawasaki Disease, children with hypoplastic left heart syndrome, and children with functionally univentricular circulation including those with Fontan palliation. Not all centres, however, can be part of the Pediatric Heart Network, as members are selected with a competitive application process, with the core sites mostly represented by larger centres in the United States and Canada. The opportunity for participation is what is different with the Society of Thoracic Surgeons Congenital Heart Database and the STRESS trial because any willing and able centre can participate in the Society of Thoracic Surgeons Congenital Heart Database and the STRESS trial, thus being much more representative and distributive of outcomes across various types of centres covering more of the population.

Dr. Tretter: What has been your experience in implementing machine learning in analyses of paediatric databases? Is the application of machine learning to large multicentre databases the answer towards improved understanding of outcomes in congenital cardiac care?

Dr. Li: I think that is really where our field is going to go: linking databases and applying machine learning towards predictors of outcomes and quality of life. We are starting to apply machine learning in various linked databases to assess large cohorts of children with congenital heart disease. Again, it becomes necessary to involve the proper expertise: researchers and statisticians familiar with the ins and outs of the applications of machine learning. One of the important features we are learning in one of these studies is that there are significant health disparities, specifically in congenital heart disease, but generally across all paediatric and adult health care. These disparities relate to race, rural versus urban residency, distance from health centres, and public versus private health insurance. The COVID-19 pandemic has brought to light many of these disparities, including the issues of systemic racism.

Dr. Tretter: It is clearly impactful that the mining of large databases and the application of machine learning could help shed light on such important health disparities. Thank you for sharing this valuable information. To change gears, I would like to ask you what is the historical context that led towards your focus on infectious endocarditis and questioning the Duke criteria leading towards its modification?

Dr. Li: One of the fascinating and most enriching things about a field like paediatric cardiology is that you can have so many aspects of your interests change with time and develop throughout your career. Early in my career, I primarily focused on echocardiography and was always fascinated with endocarditis. I got involved in a collaborative at Duke University Medical Center looking at the Duke Criteria. We evaluated our database of over 800 cases with definite or possible infective endocarditis since 1984. Through this evaluation, we were able to establish the role of echocardiography in diagnosing infective endocarditis as a major criteria, which was not part of the original Duke Criteria.[31]

Dr. Tretter: With all this excellent clinical and academic work, you have also established an exceptional track record of mentoring future academic leaders in the field of congenital cardiac care: Dr. Sara Pasquali and Dr. Anne Marie Valente, to name a few. You are clearly a great role model, balancing being the Division Chief of your paediatric cardiology program, continuing to be grant funded and academically immersed, and maintaining clinical responsibilities. What are the constituents towards the making of a successful clinical scientist? What advice do you give to someone like me who is early on in their academic career?

Dr. Li: The main thing is to find the opportunities that you love and have passion for. The second thing is to find likeminded people to collaborate with. To do these complicated, multicentre studies, you need a great team working towards a common goal. Children with congenital heart disease are relatively unique and rare, so it takes multicentre collaboration to answer the important questions. One of the fascinating things about paediatric cardiology is that your interests can change along the way. I have gone from imaging to clinical trials to outcomes studies to machine learning. It has been sort of a wandering path, but extremely rewarding along the way.

Dr. Tretter: Before we let you go, tell us something about your interests and hobbies outside of medicine. If you are not busy with administrative responsibilities, taking care of patients, managing clinical trials, or mentoring trainees, where would we find you?

Dr. Li: I love to travel. I enjoy reading detective novels. Now that we are spending more time at home during this pandemic, my youngest of three daughters and I are enjoying doing some challenging jigsaw puzzles.

Dr. Tretter: Dr. Li, the Editorial TEAM of Cardiology in the Young are beyond thankful that you have joined us for our second in a planned series of interviews in Cardiology in the Young entitled, "Global Leadership in Paediatric and Congenital Cardiac Care".

Dr. Li: This process that you have taken me through has been incredible. It is rare that one reflects so deeply on their career. This exercise helps to crystalize what has been important and rewarding, and what has not. So, thank you.

Dr. Tretter: I am glad to hear this was a positive experience. Dr. Li, it was a pleasure to speak with you and learn more about you and your exceptional career.

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