

Presentation Abstracts from the  
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*History of Diagnostic & Treatment Challenges and the Necessity of International Collaboration*

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Since the biologic classification of vascular anomalies was introduced in 1982 by John Mulliken, significant improvements have been developed in the management of vascular anomalies. Lymphatic malformations are not anymore considered tumors ("lymphangiomas"), new entities are progressively recognized and, more importantly, vascular anomalies centers now proliferate worldwide in order to manage patients who previously had been medical nomads.

Nevertheless accurate diagnosis of life-threatening lymphatic disorders still remains a challenge for the medical community. Confusing terminology, lack of knowledge regarding lesion behavior, and poorly understood diagnostic criteria are the rule. Despite distinct clinical, radiologic, and histologic findings, aggressive lymphatic anomalies are often confused, and misdiagnosis between entities as Gorham-Stout disease (GSD), different forms of osteolysis, Generalized Lymphatic Anomaly (GLA) with thoracic involvement, pulmonary or intestinal lymphangiectasias, diffuse pulmonary lymphangiomatosis, and thoracic lymphatic malformations is the rule. This complicates both patient care and interpretation of the literature.

Understanding of the variable individual ability to develop alternative pathways for lymph and chyle is necessary for an interpretation of the clinical features in order to decide the opportunity and the timing of active treatments. Delay in their establishment can be as dangerous as overtreatment.

Global collaboration will drive progress toward new treatments, improved public policies and better lives for people with lymphatic disorders.

It is becoming increasingly evident that addressing challenges related to GLA and GSD requires international collaboration.

## *Overview of the Structure & Function of the Lymphatic Vascular System & the Pathophysiology of Lymphangiomas & Gorham-Stout Disease*

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The human body requires the blood vascular system to provide nutrients and oxygen to tissues and the lymphatic vascular system to absorb dietary fats, transport immune cells, and to return fluid to the blood vascular system. The unique structure of lymphatic vessels enables their specialized functions. Lymph flows unidirectionally from lymphatic capillaries to collecting lymphatic vessels that ultimately empty into the venous circulation. Failure of lymphatic function can be due to qualitative (abnormal function) or quantitative (too few or too many) changes, and can lead to lymphedema, lymphatic malformations, lymphangiomas, and other disorders. Genetic mutations have been found in a number of disorders marked by lymphatic dysfunction.

Gorham-Stout disease (GSD) mainly involves the musculoskeletal system and may involve the visceral organs. Patients with Generalized Lymphatic Anomalies (GLA) have multifocal lymphatic malformations. Lymphatic malformations are rare non-malignant masses consisting of fluid-filled channels or spaces thought to be caused by the abnormal development of the lymphatic vascular system. When lymphatic malformations are widespread in bone and soft tissue, the term “lymphangiomas” is used. However, definition of the term “lymphangiomas” is controversial—if it doesn’t involve bone or cortical bone is preserved it will be called GLA. However, if cortical bone is lost it will be called GSD.

## *Similarities and Differences Between Lymphangiomas /Gorham-Stout Disease and Fibrous Dysplasia of Bone: Implications for Treatment*

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Many of you have previously been misdiagnosed with fibrous dysplasia of bone (FD). It is easy to understand how initially this misdiagnosis can be made because there are a number of similarities between FD and GSD. An understanding of the similarities and differences between FD and GSD are important, not only for the correct diagnosis, but because this understanding may begin to guide us in therapies for GSD.

In some ways bone is a very simple structure. It is made up of cells that spin a web of collagen, in which the cells are surrounded and embedded, like a cocoon. A crystal made up of calcium and phosphorus infiltrates

between the threads and hardens creating bone; much like concrete that hardens around the reinforcing bars of a building. In diseases like GSD and FD, the normal bone is eroded and replaced by an abnormal tissue. In the case of FD, the bone is replaced by a dense fibrous, scar-like tissue. In GSD, it is replaced by loose vascular tissue. Also different, is the degree of bone erosion that takes place. Relative to GSD, the erosion that takes place in FD is much less. However, the process of erosion between the two is probably the same. The process includes erosion of the hard mineral component of bone — probably by an acidic environment, and degradation of the collagen component by enzymes called collagenases. These similar processes, and what can be done to control them, will be discussed.

### *Diagnostic & Management Approaches in Pulmonary Lymphangiomas*

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Lymphangiomas and Gorham's disease are rare, severe disorders caused by the inappropriate growth of the lymphatic vessels. The exact cause of this disordered and inappropriate growth remains unknown. Lymphangiomas can affect multiple organ systems with common locations including the bones, GI tract and lungs. The rate of pulmonary involvement in lymphangiomas is unknown; however, when pulmonary involvement is present it often leads to progressive symptoms and increased mortality in patients with lymphangiomas. Dr. Vece will describe for the lay audience the basic function of the lungs and the lymphatic system within the lungs and discuss diagnosis of pulmonary lymphangiomas, including findings in radiology studies and lung biopsy; new imaging techniques have been pioneered at Texas Children's Hospital that may improve diagnosis without need for a lung biopsy. Dr. Vece will briefly discuss pulmonary function testing and how it can be used on a regular basis to follow lung disease in lymphangiomas and will then present data from an ongoing case series of pediatric pulmonary lymphangiomas at Texas Children's Hospital including some of the surgical and medical treatment regimens in use there.

### *Approaches to Clinical Management of Bone Disease in Lymphangiomas and Gorham-Stout Disease*

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Gorham's disease and lymphangiomas are rare disorders characterized by proliferation of benign lymphovascular tissue and bone destruction. Respective definition and limits between these 2 conditions

remain vague, as they largely overlap in the clinical setting and can both associate with pleural effusion, chylothorax and other visceral lesions.

Clinical presentation is variable and depends on the sites and extent of disease involvement. Nature and duration of symptoms are also variable, consisting most often of several months or years of progressive dull aching pain with occasional over-imposed episodes of acute flares, swelling and pathologic fracture. Diagnosis is often made by exclusion and is always based on combined clinical, radiographic and histological features. Disease course and prognosis are quite unpredictable, being initially progressive in majority of cases but showing often the tendency to stabilize over time. Nevertheless, particularly when involving the axial skeleton (spine, scapula, rib, sternum), they may also present with pleural and pericardial chylous effusion, a life-threatening complication associated with significant morbidity and mortality.

Optimal management of bone involvement in Gorham's disease remains undefined. Overall, treatment principles include surgery and non-surgical options. Main indication to surgery is impending or actual pathologic fractures of weight bearing skeletal regions, such as extremities and spine. Surgical options in these circumstances often include the use of tumor-type skeletal reconstructive techniques to address bone loss. Non-surgical options consist of radiation therapy and medical management. Radiation therapy has been associated with appreciable results in skeletal and extra-skeletal areas of disease. Medical treatment currently includes the use of bisphosphonates, interferon and a miscellaneous group of newer agents.

Interdisciplinary collaboration is essential to successful management of lymphangiomatosis and Gorham's disease. Implementation of basic and clinical research is mandatory to improve the understanding of these conditions and optimize management.

### *Nutrition for Lymphangiomatosis and Gorham-Stout Disease*

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The lymphatic system is part of your circulatory system (the system that carries blood). Instead of carrying protein, glucose, vitamins, and minerals from place to place in your body (like blood), your lymphatic system carries fat. It also carries plasma and white blood cells. When we eat, fat that is in our food gets absorbed in our intestines and travels through the lymphatic system to the blood. Lymph (called chyle when it contains fat) also contains protein, sodium, potassium, and enzymes.

When your body has a chyle leak, meaning the lymphatic system has a hole in it, chyle drains into places it isn't supposed to be. When you eat a high fat diet, these fats also drain into places they shouldn't be and can't

be used by your body for energy. Following a low-fat diet that is richer in a special type of fat, called MCT oil, can reduce the amount of fat that is lost, making you healthier while you have a leak. Sometimes TPN is required during a leak in order to allow the body time to heal itself.

### *What's in a Name? The Natural History of Lymphangiomas and Gorham-Stout Disease and the Evolution of Terminology*

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There are several names assigned to lymphatic disorders and the literature uses them inconsistently: generalized lymphatic anomaly, lymphangiomas, Gorham-Stout disease, lymphangiectasia, central conducting lymphatic anomaly, lymphatic malformation, kaposiform lymphangiomas and others. Dr. Trenor will overview these disorders and explain the updated nomenclature approved in April 2014. Possible complications of lymphatic disorders depend on the location of disease and common examples will be reviewed. Given the variety of complications across these disorders, efforts have expanded to gather data from larger numbers of patients to better quantify predictors of complications, responses to therapies and natural history of these conditions. Partnership with research laboratories to understand the genetics alterations in lymphatic diseases, identify and test biomarkers, and accelerate discoveries in lymphatic biology will allow discovery of new treatments. A range of specimens are valuable for study—resected or biopsied tissues, drained lymphatic fluid or effusions, blood, saliva and other fluids. Patient registries are equally critical to this mission and each project serves to answer different questions. Data from registries will serve as a foundation of current disease patterns, treatments and complications while informing the design of clinical trials to formally test important questions in these disorders.

### *The Multidisciplinary Team and Developing a Classification System for Diagnosis and Management of Lymphangiomas and Gorham-Stout Disease*

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Gorham–Stout syndrome (GSS) is a rare disease of unknown etiology characterized by lymphatic vessels involving the bones and resulting in progressive bony destruction. Generalized Lymphatic Anomaly (GLA, also known as lymphangiomas) is a related disease that features an increase in the number of lymphatic vessels

in many different tissues including bones. Several names have been used to describe GLA and GSS. We will discuss the emerging, consensus nomenclature and classification for these diseases. In addition we will compare and contrast the signs, symptoms and natural history of patients diagnosed with these two related diseases, highlighting both the similarities and the differences to one another and to patients with other types of lymphatic anomalies. Finally, we will discuss the need for interdisciplinary care teams to maximize quality of life and minimize disease progression in patients with GSS and GLA.

## *Challenges in the Design of Clinical Trials for Rare Diseases with a Discussion of the Efficacy and Safety of Sirolimus in Complicated Vascular Anomalies*

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A clinical trial is the best method for studying a disease. There are many different kinds of trials that can be done whether it is looking back at information on a disease (retrospective) or studying an aspect of the disease in real time (prospective). Clinical trials can assess many aspects of a disease and also assess the effectiveness of new medication or other treatment for a disease process. The Children's Oncology Group is a collaborative organization organized to study all kinds of pediatric cancers. Members from every major and minor medical center across the country and even the world are involved in collaborating to improve the lives of children with cancer. It is not an easy undertaking and took many years to organize but can be used as an excellent example for collaborative research. Clinical trials can be challenging in rare disorders as the diseases are not as well classified, patients have varying presentations and clinical courses and patients are being treated by many different specialists. In this talk, we will discuss the importance of clinical trials in rare diseases. First, we will increase your understanding of clinical trials by discussing all of the aspects involved in running a clinical trial. We will then focus on a clinical trial that was recently completed: Efficacy and Safety of Sirolimus in Complicated Vascular Anomalies. Discussion will include background information on the rationale for this drug, the study design and evaluative endpoints. We will then discuss the results of the study and future trials being developed based on this information.

## *Approaches to Discovering the Genetic Basis of Rare Disease*

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In recent years there have been remarkable technologic and analytic developments in the field of genetics. These advances have the potential to provide essential insights into the cause, consequence, and treatment of sporadically occurring, non-heritable, diseases such as Gorham-Stout disease and lymphangiomatosis. Dr. Warman will explain the difference between somatic (non-heritable) mutations and germline (heritable) mutations and will describe strategies that have been successful in identifying the somatic mutations that are now known to be the genetic causes of a number of disorders having as a component some degree of lymphatic malformation. He also will discuss the use of model organisms to provide insight into how lymphatic malformations occur and behave and how the study of these model organisms may be helpful in developing new strategies for diagnosing and treating individuals affected by lymphatic malformations.

## *The Search for a Blood Test to Diagnose & Assess Effectiveness of Treatment in Vascular Malformations*

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Our project investigates the role of two protein pathways in the bone breakdown that occurs in Gorham-Stout disease and Generalized Lymphatic Anomaly. One pathway (RANKL) is involved in crosstalk between bone cells, and the other (mTOR) is involved in communication between lymphatic channels. We plan to investigate these pathways in blood, pleural fluid, and surgical specimens from patients who choose to participate. It is our hope that by understanding how these pathways contribute to bone breakdown, we can learn to alter the pathways and ultimately develop improved treatments for these diseases.

## *Facilitating Collection of Biospecimens for Investigators*

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The National Disease Research Interchange (NDRI) is a 501(c)(3) not-for-profit, NIH-funded organization that provides project-driven human biospecimen service to academic and corporate scientists. Funded for over 30 years, NDRI empowers research in many areas including lymphangiomatosis & Gorham's disease. Our extensive recovery network has the logistical expertise to provide researchers with samples that may hold the key to new treatments or cures.

## *International LGDA Registry for Lymphatic Malformations*

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The International LGDA Registry for Lymphatic Malformations was established for the purposes of helping to (1) establish the number of individuals who have lymphangiomatosis and Gorham-Stout disease, (2) tabulate the symptoms, complications, and co-morbidities reported by patients (or parents, in the case of minors) and how these impact the participants, and (3) to establish and maintain a database of known patients who are willing to share their de-identified information in order to accelerate the pace of basic and clinical research.

## *Managing the Adult Patient with a Rare Disease*

David E. Gerber, M.D.  
Melissa Mayer, R.N.  
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Ms. Mayer and Dr. Gerber's talk will focus on the roles of the nurse and physician and nurse as an advocate for patients and managing the adult patient with a rare disease. They will discuss the following: (1) how to translate pediatric treatment recommendations to adult patients; (2) how to work with insurance companies to obtain coverage for the treatment of rare diseases; (3) how to work with the FDA to obtain access to drugs for the treatment of rare diseases.

## *In Partnership: LAM Clinics Providing Specialty Care to Adults with Pulmonary Disease Related to Lymphangiomatosis or Gorham-Stout Disease*

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Dr. McCormack will discuss parallels between lymphangiomyomatosis (LAM) and lymphangiomatosis, and the potential benefits of formally inviting adult pulmonary lymphangiomatosis patients to be evaluated and treated in the International LAM Foundation Clinic Network. There are currently 29 domestic and 16 international LAM Foundation clinics, each comprised of a medical director, and co-director, consultants and support staff. The mission of the LFCN program has been to focus LAM referrals to specialized centers with the expertise and resources to offer multidisciplinary care and conduct coordinated research as part of a network. Chylous and cystic lung diseases that can mimic LAM are often referred to LAM Clinics, and expertise in a wide variety of rare lung diseases has grown over time. Many of these rare disease communities have asked to be formally adopted by the LFCN, including Birt-Hogg-Dube, pulmonary Langerhan's Cell Histiocytosis, Sjogren's syndrome and others, and have posted the LFCN on their websites as their own. The network has been renamed the Rare Lung Disease Clinic Network, and a NIH grant has been submitted to support it. The philosophy of the RLDCN is that expertise should be nurtured, and distributed to key academic centers throughout the world, to provide for expert care and impactful clinical research closer to home. The RLDCN will connect experts in lymphangiomatosis to Clinic Directors around the world, through various means of electronic communication, to provide immediate access to the most up to date concepts regarding diagnosis and management of lymphatic disorders. Patience will be required in the beginning stages since the only way to become an expert is to see many patients with a given condition, and few RLDCN physicians will have seen even a single lymphangiomatosis patient in their lifetime at the beginning of the program.

## *Minimally Invasive Management of Chylous Effusions*

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Chylous leaks are devastating complications of the congenital and acquired lymphatic disorders. Recent development in lymphatic imaging and minimally invasive techniques allowed effective treatment of these conditions. The imaging of the lymphatic system and understanding of its anatomy are unique and crucial for performing successful interventions. The new methods of central lymphatic imaging such as intranodal lymphangiogram and contrast enhanced MR lymphangiogram open new insights in the lymphatic anatomy and physiology in pathological conditions. Based on this imaging, minimally invasive techniques of the central

lymphatic system interventions, including thoracic duct embolization and lymphatic disruption, provide an effective method in treatment of the chylous effusions. These methods became a gold standard therapy of the lymphatic effusions with minimal complications and high success rate.

### *Directions in Research*

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Despite recent advances in basic science and clinical research, much still remains unknown about generalized lymphatic anomaly (GLA, also known as lymphangiomatosis) and Gorham-Stout disease (GSD). This lack of knowledge has hindered the identification of effective therapies to treat these diseases and prompted the creation of the Lymphatic Malformation Institute (LMI). The LMI is a non-profit organization that funds basic science and clinical research on GLA and GSD. The LMI is currently working with leading researchers from around the world to develop research tools to study GLA and GSD, animal models of GLA and GSD, and to identify the genetic underpinnings of GLA and GSD. In this presentation, I will review several of the research projects funded by the LMI and discuss the future of research on GLA and GSD. It is our hope that these intense research efforts will lead to a better understanding of the causes of GLA and GSD and will help identify therapies to treat these diseases.