



Voice of the Patient Report
Release date: July 23, 2019

Report written and funded entirely by The XLH Network, Inc., resulting from an Externally-Led Patient Focused Drug Development Meeting Corresponding to the FDA's Patient Focused Drug Development Initiative:

**The Symposium on Hypophosphatemia:
Past, Present, and Future**

October 5, 2018
Baltimore, Maryland

Hosted and underwritten by The XLH Network, Inc.
With some financial assistance from the following organizations:

EveryLife Foundation
Inozyme Pharmaceutical
Ionis Pharmaceuticals
Ultragenyx Pharmaceuticals

This report reflects the perspectives of patients and caregivers who participated in the public meeting and has not been revised or modified in any way after the release date listed on this page. The submitters of this report have obtained the necessary permissions to link this report to the FDA website and this will not violate the proprietary rights of others.

Contributors to this report include The XLH Network board members: Susan Faitos, LMFT, Joyce Inman, PhD, Gin Jones, J.D, Elizabeth Olear, M.S., Carolyn Macica, Ph.D. Additional contributor: James Valentine, J.D.

Carolyn Macica reports research grants and consulting fees from Ultragenyx. Elizabeth Olear reports grant funding and consulting fees from Ultragenyx. Susan Faitos, Joyce Inman and Gin Jones have nothing to disclose.

Point of Contact/Corresponding Author:

Susan Faitos, LMFT
Executive Director, The XLH Network, Inc.
Susan.Faitos@xlhnetwork.org

TABLE OF CONTENTS

I. Introduction

- A. The Event and its Goals
- B. Overview of Chronic Hypophosphatemias
- C. Overview of Available Treatments
- D. Information Gathering

II. Perspectives on Disease Symptoms

- A. Mobility
- B. Chronic pain
- C. Calcifications, and nerve and spinal challenges
- D. Progression of Symptoms
- E. Emotional impact
- F. Dental Issues
- G. Hearing Loss
- H. Family Planning
- I. Transition from Pediatric to Adult Care

III. Perspectives on Treatment Options

- A. Treatment Options
- B. Impacts of Treatments
- C. Factors that Affect Choice of Treatment
- D. Ideal Treatment
- E. Participation in Clinical Trials

IV. Conclusion

V. Appendices

Appendix 1: Benefit-Risk Framework

Appendix 2: Meeting Agenda

Appendix 3: Meeting Speakers

Appendix 4: Online Survey Questions and Answers

Appendix 5: Live-polling Questions and Answers

Appendix 6: Fall 2017 survey

Appendix 7: Glossary

Appendix 8: Additional Resources and Works Cited

I. INTRODUCTION

A. The Event and Its Goals

On October 5, 2018, adult members of the chronic hypophosphatemia community (which includes X-Linked Hypophosphatemia, Autosomal Hypophosphatemia and Tumor-Induced Osteomalacia) met in Baltimore, Maryland, to share their perspectives on living with these disorders, including the wide range of adult symptoms and their effects on daily living, as well as patients' and care-takers' experiences with various treatment options. The event was also open to the public.

Although not organized by the U.S. Food and Drug Administration (FDA) or officially endorsed as a Patient-Focused Drug Development meeting, the event was attended by FDA officials, and the transcripts and this report will be provided to the FDA for their use and public access. As noted by a journalist covering the Symposium, most such Patient-Focused Drug Development meetings have "occurred in advance of regulatory filings, when FDA had questions about a pipeline of maturing development projects or as a catalyst to jump-start new efforts in an overlooked category" (Werber, 2018). The Symposium on Hypophosphatemia, however, occurred after the approval of burosumab in the spring of 2018, and the journalist noted that it "helps confirm the value of the post-approval session to sustain momentum around a new therapy and to support efforts for further projects."

The event was hosted by The XLH Network, Inc., a 501(c)(3) patient advocacy group whose mission is to promote XLH awareness and education for affected families, medical professionals, and the community at-large; to support physicians and other providers of medical care for better diagnosis and treatment; to create resources and a community for affected individuals and their families so they can understand and cope with the complications of the disease; and to foster the search for a cure. <http://xlhnetwork.org/>

The Symposium on Hypophosphatemia was grown out of the realization that the chronic hypophosphatemia community is at a turning point, with new treatment options and better understanding of the wide range of issues faced particularly by adults, since more is known about pediatric symptoms than adult symptoms or treatment.

The goal of the Symposium was to assist in identifying 1) the progression of hypophosphatemia-related symptoms in adults over time, 2) the treatment endpoints that matter most to adult patients, and 3) how those desired endpoints may change with each decade that passes after the growth plates close. This information is intended to be of use to both researchers working on a cure and to clinicians and adult patients who are making decisions about treatment with currently available options. We also refer the reader to a recently published, comprehensive overview of the lifelong impact of XLH (Skrinar, Dvorak-Ewell et al. 2019).

The Symposium confirmed basic facts about living with hypophosphatemia as an adult that are well-known to patients but under-recognized in the medical literature:

1. Chronic hypophosphatemia is not just a childhood disorder;

2. Chronic hypophosphatemia, whether or not treated during childhood, has long-term, adverse health consequences during adulthood;
3. Chronic hypophosphatemia manifests in a variety of potentially disabling ways during adulthood, most notably in spontaneous dental abscesses, hearing loss, chronic pain and fatigue, poor muscle function, osteoarthritis from misaligned joints, and widespread calcifications and enthesopathy that reduce mobility and range of motion; and
4. Chronic hypophosphatemia is a multi-system disorder, affecting not just bones and teeth, but also muscle function and energy levels.

This report summarizes the perspectives of adults living with chronic hypophosphatemia, either as patients themselves or as caretakers for a patient. The information came in the form of live testimony during the Symposium, as well as data collected during a pre-meeting survey and live polling during the event.

B. Overview of Chronic Hypophosphatemia

Hypophosphatemia refers to low levels of phosphorus in the blood. While there are some short-term causes, the subjects of the Symposium were the chronic forms caused either by a genetic mutation or a tumor.

The majority of patients with a genetic (or familial) hypophosphatemia have a mutation of a gene on their X chromosome (Phosphate Regulating Endopeptidase Homolog X-Linked or PHEX), leading to the name, X-linked hypophosphatemia or XLH (Francis, Hennig et al. 1995). There are also autosomal versions, meaning the mutation occurs on non-sex-determining chromosomes. They're known as autosomal dominant hypophosphatemia, or autosomal recessive hypophosphatemia, types 1 and 2. In addition, there is a form of chronic hypophosphatemia caused by a tumor, and not surprisingly referred to as Tumor-Induced Osteomalacia or TIO (Macica 2017).

Regardless of the cause, patients with chronic hypophosphatemia (as opposed to temporary low phosphorus levels due to dietary or other interventional causes) all experience an excess of a particular hormone, produced either in the bone or by a tumor, known as fibroblast growth factor-23 or FGF23 (Bowe, Finnegan et al. 2001, Yu and White 2005). This hormone interferes with the kidneys' processing of phosphorus and also with the transformation of vitamin D into an active hormone known as calcitriol, which is needed for the absorption of phosphorus and calcium from the intestine.

As a result of the phosphate-wasting and reduced calcitriol production, patients' bones and teeth are not properly mineralized and muscles may be prone to fatigue (Carpenter, Imel et al. 2011, Cremonesi, Nucci et al. 2014, Pesta, Tsirigotis et al. 2016). Patients experience a wide range of symptoms across virtually every system of the body, as the event demonstrated. They include bowed (or knock-kneed) legs, short stature, osteoarthritis, spontaneous dental abscesses, hearing loss or tinnitus, mineralizing enthesopathy (bone spurs), chronic pain, chronic fatigue, poor muscle function, and an increased risk of Chiari malformation and craniosynostosis. While the symptoms and their severity are variable from patient to patient, and may also vary from

generation to generation within a single family, all adults with chronic hypophosphatemia have some of these symptoms to some degree (Ruppe 1993).

For more information on chronic hypophosphatemia, please refer to the Symposium video or the transcript of Karl Insogna, M.D., who presented an overview of the condition from a clinician's and researcher's point of view. (Appendix 8).

C. Overview of Available Treatments

For the Phosphate-wasting:

Chronic hypophosphatemia is characterized by phosphate-wasting. Historically, there was no available treatment to stem the phosphate-wasting, so treatments were focused on addressing the symptoms (*i.e.*, poor bone and dental mineralization), rather than the underlying cause.

Pharmaceutical intervention for poor mineralization began in the 1950s with massive doses of inactive vitamin D. Since chronic hypophosphatemia is generally accompanied by the reduced ability to transform inactive vitamin D to active vitamin D, as well as phosphate-wasting, this treatment was largely ineffective.

More recently, beginning commercially around 1980 and continuing to the present, treatment consisted of an attempt to use supplements of phosphorus and active vitamin D (calcitriol) (Linglart, Biosse-Duplan et al. 2014). Calcitriol is an active hormone that can only be obtained by prescription and should not be confused with the vitamin D supplement that can be obtained over-the-counter from the pharmacy. As described by Dr. Karl Insogna, an expert on chronic phosphate-wasting disorders in adults, it's like trying to fill a leaky bucket. The phosphorus leaks faster than it can be replaced and this treatment regimen requires frequent doses to maximize effectiveness, since phosphorus stays in the blood system for only a few hours. They also need to be taken at a time when dairy products are not also ingested (*i.e.*, not too close to meals), since dairy products can prevent the absorption of the phosphorus. Because calcitriol (active vitamin D) is also negatively regulated by FGF23, phosphate supplementation is given along with calcitriol to ensure that phosphate is also reabsorbed in the intestine. The dosage (and response to treatment) is highly variable from patient to patient, and therefore requires a period of trial and error for each patient to achieve an optimal dosing. Even then, the dosage may require adjustment every few years. In addition, calcitriol can cause organs like the kidneys to mineralize resulting in irreversible calcification of the kidney, or nephrocalcinosis. This is a key reason that patients need to be carefully, and frequently, monitored while they are being treated. This treatment with supplements also requires careful monitoring in order to limit other complications, including hyperparathyroidism (excessive production of parathyroid hormone), which may occur even with good monitoring (Alon, Lovell et al. 1992). In addition, treatment with phosphate and calcitriol has been shown to stimulate production of the offending hormone, FGF23, working against the goal of preserving phosphate. Unfortunately, clinicians who are qualified to monitor patients effectively are exceedingly rare, and as a result, many patients have developed one or both of these adverse effects to an unnecessary degree. Not all patients respond to treatment, even when properly prescribed and monitored, and not all patients are able to tolerate treatment, since it can cause serious gastrointestinal distress and organ damage.

Historically (and to a large extent continuing today), even if patients were able to maintain the complicated dosing regimen and responded well to the treatment during childhood, they were often advised to stop treatment in their late teens (when the growth plates closed or shortly thereafter). The reasoning was that during childhood, the risk of nephrocalcinosis and hyperparathyroidism was worth taking in return for improved bone mineralization, straighter weight-bearing bones and increased height. Once bones were fully formed, the old reasoning went, those risks weren't worth taking to address adult symptoms. Until recently, there was little awareness or scientific confirmation of adult symptoms, and it was assumed that they were mild, if they existed at all.

Over time, clinicians who treated adults came to realize that there were indeed a number of ongoing symptoms, ranging from mild to severe, and in at least some cases, it was worth continuing treatment with phosphate/calcitriol therapy during adulthood, despite the associated risks, but with careful monitoring for nephrocalcinosis and hyperparathyroidism. The major comorbidities in adulthood, as previously mentioned, are painful mineralizing enthesophytes and degenerative osteoarthritis, hearing loss/tinnitus and dental abscesses (Liang, Katz et al. 2009, Chesher, Oddy et al. 2018). Generally, the rule of thumb was that phosphate/calcitriol therapy was advisable before bone surgery, while recovering from that surgery, and in a more subjective group of cases, when the patient reported burdensome symptoms (usually bone pain) and found relief from the therapy. It was hoped that this treatment might also have some other general benefits, but recent research has concluded that the therapy had a positive effect on dental health but did not slow the progression of enthesopathy (Connor, Olear et al. 2015).

In 2018, the FDA approved burosumab, marketed as Crysvita, for treatment of XLH in both children and adults, and it has recently been approved in Canada for the same purposes. (It is in clinical trials for tumor-induced osteomalacia; trials for autosomal conditions are currently unknown. Burosumab is the first treatment to focus on the underlying cause of phosphate-wasting: excessive production of FGF23, due to either a genetic mutation or a tumor. Instead of replacing the wasted phosphorus and normalizing levels of phosphorus and vitamin D, burosumab binds to FGF23 and prevents it from causing the wasting of phosphorus (Carpenter, Whyte et al. 2018, Insogna, Briot et al. 2018).

Burosumab is a monoclonal antibody, given by subcutaneous injection, every four weeks for adults (every two weeks for children). While it is still early, the data so far suggests that it does not cause or worsen either nephrocalcinosis or hyperparathyroidism. In fact, there have been no reported significant adverse effects, just some relatively minor adverse effects like injection site irritation, headaches and nausea. Burosumab is able to raise blood phosphorus levels for two to four weeks with a single dose, compared to oral phosphorus/calcitriol. There is some speculation that the bone mineralization process benefits exponentially from having normal phosphorus levels over extended periods, rather than constantly fluctuating, although it is still early to know for sure.

The challenges for patients using burosumab primarily relate to the high cost and the lack of access to clinicians who have the expertise to prescribe, administer and monitor the treatment. The cost has been estimated by Ultragenyx Pharmaceutical to be approximately \$160,000 for children and in excess of \$200,000 for adults (Beck-Nielsen, Brock-Jacobsen et al. 2009, Endo,

Fukumoto et al. 2015). The dosage is dependent on weight, and accordingly increases as the child progresses to adulthood. The cost is obviously out of reach for most patients to pay out of pocket. It is still too early to know whether most insurance companies will provide coverage. There are generous patient assistance programs, through Ultragenyx Pharmaceutical's Ultracare program and The Assistance Fund, but they ultimately depend on health insurance coverage-

Once the hurdle of cost has been cleared, it's still challenging to find a clinician who a) has ever before treated an adult with chronic hypophosphatemia, b) is aware of burosumab, and c) has the time to learn about a condition and/or treatment sufficiently to be able to take on the patient's care. Just as an example, consider the situation in Florida for treating adults with XLH. The state of Florida has a population of approximately twenty-one million residents, of which eighty percent are adults, so statistically, given the XLH incidence of one in 20,000 births, it would be expected that approximately one thousand residents, or eight hundred adults, would have XLH. The XLH Network, Inc., maintains a database of clinicians known to have experience treating XLH. There are currently no identified clinicians in the database in the state of Florida with expertise to treat adult XLH, although there are several pediatric practitioners. This highlights the universal problem of limited or no access to qualified clinicians to treat rare diseases.

However, there is some good news with newer therapies. Treatment with burosumab is much simpler for the clinician than the current standard of care. Based on current data, there are no known serious side-effects, dosing is straightforward (based on weight, with a few exceptions, seldom requiring trial and error, with frequent adjustments). Monitoring with lab tests and kidney scans will be less frequent.

Still, there are aspects of treatment with burosumab that may not be obvious to a clinician who has never treated anyone with chronic hypophosphatemia before. A great deal of medical education will have to be undertaken, and the issues that need to be addressed, beyond basic education about adult symptoms, are just being uncovered now. For example, inexperienced clinicians may not be aware of how variable serum phosphorus levels are, or that some patients with chronic hypophosphatemia can fleetingly reach normal levels while still needing treatment. Accordingly, The test, after eating, could result in a false normal result and preclude a burosumab dose (since it is contraindicated for patients with normal blood phosphorus levels).

Looking to the future, researchers are considering how to go deeper into the cause of chronic hypophosphatemia, searching for the reason why the mutation that causes XLH results in the overproduction of FGF23. And, of course, even further out, is the hope of gene editing, given that over 300 mutations have been identified that cause the genetic forms of chronic X-linked hypophosphatemia.

Pain management:

Separate from treatment for phosphate-wasting per se, adult patients with chronic hypophosphatemia frequently require pain management. Patients experience some or all of the following: bone pain (unrelated to trauma or arthritis), joint pain (the effect of poor joint alignment, joint degeneration of osteoarthritis, and joint osteophytes), and nerve pain from spinal

calcifications (enthesophytes or bone spurs and spinal stenosis), and enthesophytes (bone spurs) formed at tendon or ligament insertions.

A variety of currently available options for pain management have been used by patients with chronic hypophosphatemia, with varying degrees of relief.

Surgical intervention:

While some patients respond well to phosphorus and calcitriol supplements during childhood, many still require surgical intervention (osteotomies and guided growth procedures to straighten deformed lower limbs that occur with weight-bearing. With age, surgical interventions frequently have to be repaired or redone. Because many adults suffer from fractures and osteoarthritis, they too will continue to have surgical interventions including fixation to stabilize bones or joint-replacement surgery (Mills, Iorio et al. 2019). It is too soon to know whether treatment with burosumab during childhood (especially if begun early) will completely eradicate the need for surgical intervention, but for now, some adults will continue to undergo surgery, since it will be many years before all adults will have completed a full course of burosumab treatment during childhood and conceivably, into adulthood.

Physical and occupational therapy and social workers:

While it is believed that physical and occupational therapy, as well as support by social workers to navigate the healthcare system and challenges of a chronic disorder, can be of benefit to patients with chronic hypophosphatemia, there is no published research on this topic. Additionally, as is true with clinicians generally, qualified therapists who have experience with the extensive musculoskeletal challenges of chronic hypophosphatemia are extremely rare. Just as uninformed treatment with supplements can lead to adverse side-effects, so too can uninformed physical or occupational therapeutic interventions.

Alternative treatments

Some patients find relief from low-impact exercise (swimming, tai chi, yoga), heat/ice, or acupuncture. There is no published research on the topic, however.

D. Information gathering

The Symposium consisted of two phases: 1) an online survey to gather basic insights and to help focus the live discussions, and 2) the live event with patient testimony and discussion, along with live polling.

Survey questions and answers:

Survey answers began to be collected 4 months prior to the event. To maximize responses from a community already experiencing survey fatigue, the questions were extremely brief, and the entire set could be completed in just two or three minutes. See Appendix 4 for the full set of questions and answers.

There were 186 survey respondents, representing patients ranging in age from 19-898. (Note that since the subject matter was adult symptoms/treatment, minors were not invited to participate.) Approximately 83 percent (155) were female and 17 percent (31) were male. While it is common for women in any patient group to be more engaged with this sort of event, the disproportion of female responses is also consistent with the fact that there are simply more female patients with XLH, due to the x-linked transmission pattern (statistically, half of the children of an affected mother will inherit the condition, regardless of gender, while all of the daughters of an affected father will inherit the condition and none of the sons will), and the fact that XLH accounts for the vast majority of the chronic hypophosphatemia community.

In response to questions about the most significant negative impact on their daily lives, not surprisingly, survey respondents chose "mobility or range of motion issues (including arthritis and spinal conditions)" and "chronic pain" as the symptoms with the two most significant impacts. This response is consistent with an earlier survey done by The XLH Network, Inc. in preparation for a meeting with the FDA during its review of the safety and effectiveness of burosumab. Then, the adult respondents stated that chronic pain was the symptom with the most significant impact on their daily lives, with mobility or range of motion problems coming in a fairly close second, while short stature (frequently considered a defining feature for XLH) and time spent on treatment trailed behind all other options.

The online survey answers also reflected a fairly consistent progression of the symptoms. All patients experienced a worsening of their condition between childhood and adulthood. In addition, the increasing severity could be seen by comparing the age of respondents, with younger patients generally reporting mild to moderate symptoms, while the older patients generally fell in the moderate to severe range.

In terms of treatment endpoints, most adult patients desired either an improved ability to go about daily life (60.2 percent) or improved long-term health (27.4 percent), while ease of health management and cost were significantly lesser concerns.

The live-polling results were consistent with those in the online survey. There were approximately one hundred responses (although note that the total includes caretakers responding on behalf of patients, whereas the online survey was patients only). They ranged in age from young adult (18 to 25) to over 55. Almost three-quarters of respondents rated the impact of their disorder as moderate (38 percent) to severe (35 percent). The main challenges were joint stiffness (30 percent), fatigue (23 percent) and bone pain (22 percent). The vast majority (84 percent) felt the adverse impact of their chronic hypophosphatemia had, over time, "gotten greater or affect[ed] additional areas of life (home, work, friendships, etc.)."

Live event:

The Symposium was held in Maryland to encourage participation and attendance by nearby FDA representatives. James Valentine, JD, MHS, an attorney with Hyman, Phelps & McNamara, PC, served as the meeting moderator and Symposium consultant. He previously worked at the FDA where he helped to launch the PFDD program.

Approximately 180 people attended the Symposium in person, including patients, family members, clinicians, and representatives of the FDA and the pharmaceutical industry.

The Symposium consisted of 1) an introductory overview by an well-known expert in treatment of adults with chronic hypophosphatemia, Karl Insogna, M.D; 2) a five-person panel on the topic of adults symptoms; 3) a five-person panel on the topic of treatment options, 4) audience-participation discussions of the two panel topics; and 5) live-polling. Videos and transcripts of Dr. Insogna's presentation, the panel sessions and the discussion sessions are available online. Links are in Appendix 8. The results of the live polling are in Appendix 5.

II. PERSPECTIVES ON DISEASE SYMPTOMS

The first sessions of the day addressed the topic of disease symptoms and the daily impacts that matter most to adult patients. There were five panelists representing a range of experiences: Ramon (familial XLH, age 51), Kelly (familial XLH, age 36), Jim (TIO), Gale (spontaneous XLH, age 76), Athina (spontaneous XLH, age 46). Following their presentations, audience members shared their experiences.

Mobility: This is, according to both the online survey the live-polling results, the most challenging aspect of chronic hypophosphatemia for the majority of patients. It has a number of causes, including misaligned bones, arthritis, and calcifications or enthesopathy. While only a few patients have severely restricted mobility in childhood (not counting time spent in recovery from surgery), most eventually experience it in adulthood.

Kelly explains how it affects her in her thirties:

Mobility is the number one impact that XLH has on my life. From the time I wake up in the morning until the time I lay my head down at night, I find that mobility is a constant issue. Mobility affects every facet of my life. It uses an extreme amount of energy to move, which causes pain, and then causes me to fatigue. All things require mobility. Household chores, shopping, social activities, just to name a few. There are social functions that I found myself making an excuse to cancel, because of the amount of energy and projected pain from the walking and/or standing expected at these events. I do engage with my peers as much as possible. I find great joy in being with others, and it lifts my spirits. But it can drain my energy and cause pain. Oftentimes it will take me several days to recover from this.

Further, mobility challenges can limit the choice of careers or hobbies. Kelly explained:

I really had an interest in cosmetology, teaching, and possibly a healthcare profession. When observing these professions in action, and noticing the amount of time spent

standing, walking, and just the overall amount of energy required, I knew that the degree of my disability would just not allow me to be successful in those occupations. In one particular instance, when I was still capable of employment, I had to decline a promotion because my body could not physically hold up to what would have been required of that position, therefore not only limiting my earning potential, but hindering my chances of future promotions.

Gale (now in her seventies) reported limitations throughout her life on her ability to do housework and child-rearing, beyond what would be typical for other people her age:

As an adult, I've always been physically challenged for stamina to keep house and raise our children. Back pain has caused bending over to become increasingly more difficult as years passed, which has made all of my duties more difficult. So my husband, Roy, does all of the heavy housework now, as well as the laundry, which is in the basement. I mostly take care of household clutter, cooking, folding of clothes, and dusting.

It's not just physical activities that are limited. Even those with sedentary or low-impact careers struggle to get through their days. As Ramon explained:

On my worst days, getting into and out of bed is a painful chore; the car too. The pain in my back even affects my sleeping. It's very hard to get into a comfortable position, when every time that you move, your back hurts. And forget stairs. I have to take them one at a time going down, and very slowly going up. Sitting, too, is difficult. My back stiffens and is painful throughout the day. And my job is a sedentary one, so it ain't a picnic. My stamina is also decreased

Gin (in her sixties) described the limitations on her career:

Between the mobility restrictions and related pain and fatigue, I was unable to continue working as a lawyer, which is generally not a physically demanding career, but I had to stop by the age of fifty-three, and had only been able to work part-time for ten years before that.

Audience member Carol described how her mobility (and pain) affected her ability to work a sedentary job:

I'm blessed to have a sit-down job and to work at home, but even when it's time for my fifteen-minute break, I've only been sitting, only, two hours, and when I try to stand up the muscles in my back, my lower back in particular, just tighten up like they're spasming, and I have to stand still for a few minutes just to get my back to straighten up so that my legs can engage so that I can walk to the bathroom for example. And then, as I'm walking, the pain in my ankles or my knees or my hips or all of the above causes me to stumble. It's like they're catching on something and not flexing, so I stumble.

While Carol was the only person during the Symposium to describe this inability to walk after sitting even for relatively short periods, it is a common experience among chronic hypophosphatemia patients, often discussed within the patient community. It has not been studied specifically, and the exact cause is not known.

Mobility affects patients with TIO as well. Jim described how his mobility changed from the point where he could play basketball and soccer to needing to use a walker and canes. His

situation was exacerbated by not knowing why he had these symptoms, since they weren't connected to his TIO diagnosis for many years.

Chronic Pain: All of the patients reported, to one degree or another, experiencing pain, although they also tended to minimize its effect on them, often making a joke to cover the emotional discomfort. This tendency to downplay the pain, if it carries over to the clinician's office, can adversely affect how well the pain is managed.

Karen, an audience member, described the onset of debilitating pain in young adulthood, after a reasonably comfortable childhood, and how the pain turned her life upside down:

It wasn't until I turned twenty-eight, ... it was a switch flipped one day. And then it never got better, it's only ever [worsened], and I was always told like you could do whatever you want, go to grad school, blah blah, so I decided that I wanted to do a physical job which in retrospect was stupid, but I'm a stage manager for music festivals and I was for fifteen years. I can't do that anymore. I set myself up to do big physical things because I was told that there were no limitations, you'll be over this when you're done growing, don't worry about it. So I was like, okay. So busted my butt, took all these crappy internships, eventually got recognized by the Grammys, got to do Lollapalooza, like really worked hard and now it's gone.

Robin, also an audience member, spoke on behalf of her twenty-six-year-old son (spontaneous XLH) who's a medical student and couldn't attend the Symposium because of his classes:

But one of the things he asked that I please communicate is the bone pain. He's got the joint pain, the stiffness, the muscle pain, and ... short stature, ... He has changed his type of medicine that he's decided to get into. He thought he was going to be anesthesia or surgical, but when he was rotating he realized there's no way that he can stand as many hours. So he's decided to go to emergency medicine where they let them sit to talk to the patients.

A compelling pattern of adult symptoms, noted by Dr. Erik Imel in his summary remarks, emerged during this session. Patients frequently mentioned feeling "good" at various times in adulthood, but that was a relative situation, and never indicated a total absence of symptoms. For example, Ramon reported,

On my best days, things are good. My back is only minimally stiff and painful, and I can get out of bed and into my car without much difficulty. I can walk with relative ease on flat surfaces, and up and down stairs, without much limitation at all as to time and distance. My energy level is good, and I'm not too fatigued when I get home from work. Still, even on my good days, my range of motion is limited, and I have pain.

Note that he describes a "good" day as one that still includes pain and limited mobility and range of motion. Patients simply learn to live with those symptoms, because there hasn't been anything that could be done about them.

Several patients reported a belief that chronic hypophosphatemia patients generally have a higher than average pain-tolerance threshold. They shared their own experiences with pain that others

would consider debilitating but that they considered simply background noise. For instance, Sunindiya, still in her thirties, says

One thing I've learned as I've met more and more people with this disease is that we have a high tolerance for pain. *That does not make it okay for us to have to tolerate so much constant pain.* I will randomly wake up with excruciating joint pain when osteophytes dig into my muscles in my hips or knees. I know I need knee and hip replacements, but I'm told I'm too young, so I work through this pain as best I can.

This impression of high pain tolerance is consistent with the results of the screening of adult patients in the clinical trials for burosumab, where virtually all of the volunteers had healed or healing fractures and pseudofractures, and many of them were unaware of them (Insogna, et al, 2018). Gin was one of those patients, who found out during the screening that she had a still-healing upper-arm fracture from three months earlier that she hadn't known was broken, because the pain wasn't significantly different from the everyday pain she'd long since learned to ignore.

Another example of discounting the pain of a broken bone comes from Billy, who said, There was a time when I stepped in a hole and fractured my femur. I had no idea I'd fractured my bone. I just knew it hurt. As with many of my fellow XLHers, the tolerance for pain is very high, and we grow to expect it daily.

Sometimes it's not the patient, but the clinician who discounts the pain. Athina experienced severe pain after her spinal surgery, and her complaints were ignored by staff. Finally, she was given access to a pain management specialist who informed her that for patients already dealing with chronic pain, it was "not abnormal to need something stronger than morphine" after surgery.

The patient community is familiar with many stories of patients trying to ignore the pain for days or weeks or even months. When they finally sought treatment, they were viewed as drug-seeking. It's an understandable but still frustrating and problematic situation, since the patient presents with a history consistent with drug-seeking (*i.e.*, the pain is widespread or occurs in different spots at different times), and there is little clinical understanding of bone pain that's not associated with trauma that is visible on x-rays or other scans.

Calcifications, and nerve and spinal challenges: Calcifications on and around the spinal cord can lead to mobility restrictions, as well as surgery and ongoing nerve pain. Gale explains, The details of life changed dramatically for me in 2011 [in her mid-sixties], when I woke up one morning with numb toes. The numb, tingling, hypersensitive feeling in the skin crept upward almost to my waist over the next couple of months. It has caused me to become unsteady on my feet and my legs are weak. In 2017, surgery on my mid-back improved the hypersensitivity of the skin. However, my feet are still painful, my legs are still weak, and I'm going to need lower back surgery.

Ramon was temporarily partially paralyzed due to spinal calcifications that came to light after a swimming accident and had to have extensive spinal surgery.

Athina had a slip and fall that for the average person would have resolved quickly, but turned into a multi-year ordeal for her, due to her calcifications.

My neurosurgeon informed me that he has never seen anything like he saw when he opened me up. He informed my husband and I that I have calcifications in my spine, and my spinal cord lining is hardened. He also informed me that there are floaties of calcifications in my spinal cord that he could not remove, and they are like little islands floating in my spinal cord. I did not need a back brace, due to the fact that my back has naturally fused.

Billy experienced calcifications of his Achilles' tendons, requiring surgery before the tendon could snap, and like other patients have experienced, the situation was not straightforward, requiring the orthopedic surgeon to do a bit of experimenting to find a solution:

A plan was formulated to repair my Achilles by removing it, grinding the calcium away, and reattaching the Achilles. This process did not work, as the calcium started returning quickly. One more attempt was made to clean the calcium out and again it did not work. The third time, a surgeon decided to do an FHL transfer, which did work. ... I had five surgeries in two years. This included three stints of eight weeks at a time in a cast, multiple walking boots, and along with months of physical therapy.

Gin has not had surgery but describes her calcifications as bony stalactites sticking into her spinal cord. When irritated with sudden movement, they can cause intense pain and even a few seconds of thoracic paralysis when she is unable to breathe. She also has calcifications throughout her body:

My soft tissues, ligaments, and tendons were calcifying. This is, and continues to be, the most debilitating symptom for me, with much of my spine so calcified ... that I can barely move my torso or my neck. I also have calcifications in my feet, knees, hips, and they all affect mobility and range of motion.

Others have experienced calcifications in the spine, requiring surgery, and then the calcifications returned, necessitating additional surgery.

I had the spinal stenosis surgery maybe five or six years ago after needing it three or four years before that but didn't want to do it until I couldn't drive. And now all that pain has come back. Is that happening to people? You have spinal stenosis surgery, then it gets better, then it gets worse again, and you're repeating the surgeries? Has anyone been through that?

Quite a few heads were nodding in recognition of the shared experience.

Progression of symptoms: The progressive nature of the adult symptoms was apparent in all of the patients' experiences. Many described fairly active childhoods (when not sidelined by surgery). Ramon and Gin were both competitive swimmers as teens and young adults. Gale was an avid gardener. Robin Courtney's son played Lacrosse. Theresa played softball and basketball until surgery interfered with the sports.

In some cases, that physically active period continued into young adulthood. For example, Billy took on a physical career, enlisting in the Navy:

Despite the pain of physical limitations, I was able to get through six years of physical training, the demands of being in confined quarters, and working as a mechanic in the

engine room. I now remember this time when I was working below the deck plates of the ship. I had to spend extra time lying on the deck because I was in such a tight space, and I became so stiff, I could barely move. Somehow, I managed to get myself out of those tight spots and to continue to move forward in the service.

Many also reported being told, on reaching their late teens, that they were done with both treatment and the side-effects, and they expected to have no further effects, other than short stature and whatever bowing or other skeletal abnormalities hadn't been fixed. Time quickly proved those predictions wrong. Patients' health declined, generally to the point they could no longer ignore it and began to seek a return to treatment, in their late twenties or early thirties. It's a pattern well-known among the patient community, but not so well-known among clinicians other than the few who have treated hundreds of adults with chronic hypophosphatemia.

Ramon, in his fifties, described "a decrease in my energy, stamina, and range of motion, and an increase in my bone pain" starting in his early thirties. His surgeon told him that his x-rays looked like the bones of a seventy-year-old. By his early forties, he had ossification of the posterior longitudinal ligament and needed extensive spinal surgery.

Elaine, in her seventies, is more severely affected than many patients, but her experience clearly shows the progression of adult symptoms throughout the decades. The first few years of her young adulthood were good: "No more braces, I could dance, I could wear non-orthopedic shoes, even clogs, I went to graduate school, becoming a professor of mathematics, and could climb the four flights of stairs to my office."

But by Elaine's late twenties, she was unable to walk and had to use a wheelchair. In her thirties, she replaced her regular wheelchair with a powered one, and developed vertigo and hearing loss. In her forties, symptoms worsened, and she had to stop driving. In her fifties, the "progression goes into overdrive and then off a cliff." She explains:

I cannot pick up a piece of paper, write, steer my scooter or do much of anything. ... The muscle weakness is affecting my whole body. ... And I'm developing more and more joint pain, muscle pain, not bone pain, and weakness, fatigue, hearing loss, vertigo attacks or dizziness with brain fog and loss of functional mobility.

By Elaine's early 60s, she had to retire on disability. She has "trouble with almost all the basic activities of daily living and I can't do independent things such as shopping, meal preparation, etc." She can't use a computer and finds that various accessibility features for things like smartphones can't accommodate all of her disabilities simultaneously. One might account for her hearing loss, or her vision limitations, or her difficulty holding the phone, but not all three together.

Emotional impact: There's an emotional impact too, from a combination of restricted mobility and pain, along with fear of what the future will bring. As Gale put it, "My world away from home has grown much smaller, and I do have psychologically down times of missing the freedom to come and go as easily as I used to."

Natascha (audience member) talked about the stress of having a chronic medical condition generally, and especially a progressive one:

I think the financial burden of it causes a lot of stress and losing everything because of the disease. And that's my biggest fear, is that I'll lose my ability to have kids and that the surgeries won't go well because you hear so many times that you've got the rebuilding and things like that. So just the stress of everything I think has affected me a lot more than, I mean that's affected me a lot mentally.

Several patients reported a completely understandable fear of becoming totally incapacitated after having seen family members who went through this decline. Ramon explained:

From the mid 1980s until her death in 2016, I watched my mother deteriorate because of her XLH symptoms. From a working mother raising her own four children and three grandchildren through her late 50s, into a home-bound, largely bed-ridden woman at the age of 65. Unable to bear weight, even with assistance, let alone walk with a cane or walker, even while undergoing traditional XLH treatments. I witnessed first-hand how XLH is a whole-body condition, wreaking havoc on almost every bodily system there is. Skeletal, muscular, hearing, vision, you name it. Having witnessed what she went through, I fear a similar fate awaits me.

Kelly had a similar concern:

I had a first-hand experience in watching the deterioration that XLH can have on a body, when my late grandfather slowly worsened and became home bound in his later years of life. The calcification deposits on his joints and bones had become so disabling and limited his range of motion so much, he could not manage his own daily self-care. Just transferring from his chair to his bed would give him debilitating pain. Many days, he would not move from his bed, because of the degree of pain progressive XLH had caused him. ... The heart-wrenching experience of watching my beloved grandfather, with a similar severity of XLH, is a stark realization that this same future could be mine.

Natascha (audience member) considered herself lucky, with a "very, very mild case of XLH," until she turned thirty (about a year before the Symposium). Then she "started getting really bad pains in my knees, and I went to the doctors and I've had an osteotomy that went bad and I haven't had it fixed yet but it's rebowed, my leg's rebowed. And I need double tibial osteotomies now, and I can't keep a job."

One audience member spoke for many when she expressed concern about the effect, not on herself, but on her family from the progression of her symptoms. She worries about "the burden of care for me or my husband and the impact it makes on our relationship. The more my physical demands are on him, or the more things that I can't do, the more stress it makes on our relationship ..."

Younger adults aren't immune from the emotional impact, even before the symptoms have progressed. As Sunindiya (age 36) explained:

Stress is a constant downside of this and any treatment for XLH. It is really stressful navigating things like building my career, while needing high quality and comprehensive health insurance coverage to be a strong factor in any decision I make. I struggle with

how and when to discuss my disease with my employers, often waiting until I have no choice and need surgery again, not wanting my XLH to define me. All of this is in addition to the increased complexities of someone living with XLH and navigating relationships, wanting children, and everything else that comes with living my life.

Caroline (age 26) had the same concerns as Sunindiya:

I would love to see more emphasis on educating the teenagers, coming out of surgeries and out of pediatric care, and then going into young adult care and learning to take over your own care, and really emphasizing that it's important to keep taking care of your body because we do change.

Dental issues: Spontaneous abscesses are extremely painful and are a common experience for adults (and children) with chronic hypophosphatemia due to structural defects related to inadequate phosphorus. Brent's experience is typical: "The majority of my adult teeth have abscessed and have either been root-canaled or pulled and replaced with implants." Ramon, who has experienced spinal surgery, bone pain, and reductions in his mobility, still ranks his dental issues up with those other challenges as one of the biggest adverse effects of XLH on his daily life.

In the online survey, almost six percent of respondents chose spontaneous abscesses as having the greatest impact on their daily life. Similarly, fourteen percent of the live-polling respondents and almost eleven percent of the adults responding to an earlier survey done by The XLH Network, Inc., in the fall of 2017, to prepare for a meeting with the FDA (Appendix 6), chose dental abscesses as having the biggest negative impact on their daily lives.

Hearing loss: The Symposium was organized by an XLH patient with severe hearing loss, and real-time captions were provided for attendees, since progressive, adult-onset hearing loss at a much earlier age than the general population is a common symptom in this community. Tinnitus is also common. The exact cause of the hearing issues is not known, but there is speculation that it has to do with structural problems of the bones necessary for hearing.

Hearing issues may not seem like a huge problem, but one audience member mentioned hearing loss (along with dental issues) as having the largest impact on her daily life. She isn't alone in feeling that way. While it was not a top response during either the online survey or the live-polling, hearing loss was also specifically mentioned as an "other" cause for the most adverse effect by some adult patients responding to an earlier survey done by The XLH Network, Inc., in the fall of 2017, to prepare for a meeting with the FDA (Appendix 6).

Family planning: Family planning is a significant concern for patients, both because of the high likelihood of passing on the disorder (a dominant condition in the vast majority of the genetic cases), as well as the physical demands of pregnancy and child-rearing.

Kelly wanted to have children, but ultimately decided she could never be a mother:

After years of deliberation, my husband and I considered that the physical demands of pregnancy, delivery, and raising children, would just be too hard on my body. For me, also, running the risk of passing XLH on to my children was just too great. Even adoption

was something that I felt was off the table, due to the same physical demands. This choice has been very emotionally painful, and it's one of the most grief-filled parts of my XLH life.

Transition from pediatric to adult care: Sunindiya, age thirty-six, commented on the difficulties for young adults, who are caught in a bit of limbo between pediatric issues (surgery and intense treatment), often feeling reasonably healthy, before the later progression of the disorders. They may or may not have been referred to an endocrinologist who treats adults, and they may or may not have been warned about future symptoms. They're almost certainly left with little information available to them as they're making critical family and career decisions:

There's so much for the children, and when you're an older adult you don't get told you can't have a hip replacement or a knee replacement because you're too young. But then there's this group of us who ... no one tells us if we should have children, what we can expect, how to take care of our bodies.

Additional issues: While The XLH Network, Inc., did its best to solicit a diverse panel and encourage participation by a wide cross-section of audience members, the stories presented here cannot cover every possible issue. Chronic hypophosphatemia, even within a subgroup (e.g., genetic v. tumor-induced, or X-linked v. autosomal), expresses itself with a wide degree of variability from patient to patient.

There are certainly a number of symptoms that were not of primary concern to the representatives of the community who were able to attend the event, and therefore were not addressed. Kidney stones are a symptom that no one mentioned, but they have been experienced by some patients (especially while on supplement treatment). Restless leg syndrome is another one.

And there are many unknowns, which could not be addressed. For instance, there have long been questions about possible increased (or decreased!) risk of heart disease related to elevated FGF23 levels, but that has not been studied to date. There has also been some speculation about elevated blood pressure being linked to chronic hypophosphatemia (possibly aggravated by the salt-loaded phosphorus supplements).

Another area of interest is whether autosomal patients might have slightly different symptoms from X-linked patients. More generally, very little is known about the autosomal variants, other than that one form of autosomal recessive hypophosphatemia tends to cause not just tendon calcification, but life-threatening cardiac calcification.

The bottom line, with respect to these additional issues, as well as the ones that were discussed during the Symposium, is that much more needs to be learned about adult symptoms, translating what the patients know and experience on a daily basis into medical research that can be used by patients and clinicians to improve future outcomes.

III. PERSPECTIVES ON TREATMENT

The afternoon sessions addressed the topic of treatment. There were five panelists: Sunindiya (spontaneous XLH, age 36), Billy (familial XLH, age 55), Gin (spontaneous XLH, age 63), Brent (familial XLH, age 40), and Theresa (spontaneous XLH, age 46).

A. Treatment Options

Some patients had experience with the whole range of options, starting with the massive doses of inactive vitamin D that Gin was given in the 1950s, through the development of phosphorus/calcitriol supplements (which Gin couldn't tolerate at all and others found burdensome), and most recently with burosumab in the clinical trials. Others had only experienced supplement treatment, and some had experienced first the supplement treatment and later the burosumab treatment. Hands-down, all those who had experienced burosumab considered it a vast improvement over prior treatment.

In addition to pharmacological treatments, some had experienced surgery, with less than ideal results. Gale experienced one of the down sides to surgical intervention during childhood: "Twice, I had both legs broken to straighten the bowing. The first one at age eighteen months, and the second, again, at age twelve. I grew more after each surgery, of course, so my legs bowed again."

Surgical intervention for hyperparathyroidism also is less than ideal. Because the underlying problem that was triggering the parathyroid glands wasn't fixed, the remaining sections of the glands tend to enlarge yet again, requiring additional surgery.

Some older adults wore braces during childhood (although it's less commonly recommended for current pediatric patients and has never generally been used for adults). Theresa stated, "I hated those braces because they made me look different than all the other kids, and it was always a fight to make me wear them."

B. Impacts of Treatments

There was a clear consensus on several topics relating to the impact of treatment.

1. Phosphorus/calcitriol supplements are burdensome in both childhood and adulthood.

Sunindiya vividly recalled how it affected her in childhood (and her attempts to avoid doses bring to mind conversations the patient community has had over the years, with parents desperate to find ways to make the doses palatable to their affected children): "For many years, I had to take this [phosphorus supplement] four times daily, being called out of class, and therefore singled out in school, skipping doses whenever I could get away with it." She, like many patients, was taken off treatment when she reached adulthood, but she says, "the pain was even worse as I started to get calcifications and enthesopathies, develop arthritis, and I quickly resumed my treatment."

Brent experienced gastrointestinal distress from the supplements.

I always dreaded the first day of school and explaining to teachers that if I had a stomach attack, I wouldn't have time to ask permission before heading to the restroom. Most of my teachers were understanding, but it was still upsetting every time I'd feel that rumbling, cramping feeling in my stomach and having to jump up mid-lesson, head for the restroom, grab my backpack on the way out the door, just in case I need the spare set of clothes I kept with me.

This gastrointestinal distress can extend into adulthood. Gin, for example, was first introduced to this treatment later in life and was unable to reach a clinically significant dosing of phosphorus, due to such extreme gastrointestinal pain that she thought she had appendicitis.

The sheer number of doses in a given day can be overwhelming. As Jim (adult-onset TIO, so he hadn't needed treatment during childhood) said:

I started taking phosphorus pills and powders, calcium pills, and Vitamin D in different forms and combinations, and calcitriol, also, multivitamin and Tylenol and ibuprofen for pain. I took medicines four times a day and at bedtimes, and I had to time my meds with my eating schedule to make sure they were being absorbed. This got to be very inconvenient and time consuming. I was a walking pharmacy.

2. Phosphorus/calcitriol supplements did not prevent or noticeably improve the most serious adult challenges, such as dental abscesses or the calcification formation/progression that leads to mobility restrictions (Carpenter, et al, 2011)

Some patients did find relief from the worst of bone pain, but others did not, or still needed other forms of pain management.

3. Burosumab provided much better relief for a wide variety of symptoms. As Billy put it, "I didn't know how bad I felt until I felt better on burosumab."

The clinical trial data indicates a significant lessening of pain and fatigue in adults (Insogna, et al, 2018). Brent reported discontinuing his fentanyl patches after going on burosumab. He also regained mobility (and retire his cane), which led to losing excess weight. Sunindiya noted, "For the first time in as long as I can remember, I have moments of being pain-free." It will take more long-term data on calcifications to know for sure if burosumab can prevent or slow their formation and progression, but Gin reported an apparent stabilizing of her widespread calcifications without any additional progression in the two-plus years she was on burosumab. Theresa says that since starting burosumab, "Most of my symptoms are gone. The biggest improvement has been in my muscle tone. I no longer waddle or have back pain or get fatigued easily. I'm able to work a full day and walk several miles without distress."

Unfortunately, however, burosumab cannot reverse structural problems that occurred before the treatment begins, like malformed teeth and bones, or the pre-existing enthesopathy and calcifications.

4. Alternative treatments can provide some relief. Audience members suggested a variety of alternative treatments that, while not a cure, did provide some relief. They included physical

therapy (with a caveat from other audience members that the person providing that therapy needs to understand the unique needs of chronic hypophosphatemia patients), heat and ice, and massage. Acupressure, meditation and talk therapy have also been discussed within the patient community.

5. Pain treatment is inadequate for patients with chronic pain generally and among the members of the chronic hypophosphatemia community. Bone pain, along with dental pain, is acknowledged to be among the most severe forms of pain that exists, and yet little is known about how to treat it. Further, patients with chronic hypophosphatemia experience pain from several different sources: bone pain, arthritic pain, dental pain and neurological pain.

Brent, who has considerable experience with pain management care, stated,

Pain medications, for one reason or another, don't work well for us. You know, things like morphine, hydrocodone, fentanyl, that would treat pain for a normal person, it seems like, I don't know if we burn through the pain medication faster or, you know, some of us have had so many surgeries and been on so many different treatments that maybe we've just adapted but there needs to be some investigation, number one, into why the pain medication doesn't work for us and how to find something that does work. ... Some days you have just a general pain, ... I don't know if it's bone pain, I don't know if it's muscle pain. I don't know where the pain is coming from, but this hurts or that hurts. And nothing would stop it. Even when I was on the .75mg power Fentanyl patches, those are supposed to last you three days. I would get about a day and a half of marginal relief and then I'd have to go through another day and a half of withdrawal symptoms before I could change the patch because I could only change them out every three days. And you'd go to the doctor and you'd try to explain this, and they treat you like a criminal because that level of pain medication should put a horse to sleep. And it doesn't do anything.

6. Treatment of Calcifications and Enthesopathy is critical to adult quality of life. These symptoms lead to mobility restrictions, which are reported to have the most negative impact on the majority of adults, and yet there is little known about how to treat them for either chronic hypophosphatemia patients or the population at large. There is little understanding of how or why these calcifications occur, and the situation is exacerbated by how long it takes for the calcifications to occur. It takes time for the patient to notice them, and by that time, the calcification is, with current treatment options, irreversible. And, worse, there is no recognized treatment to prevent them from worsening and becoming more widespread. Gin reported that her widespread calcifications seem to have stabilized since starting on burosumab, but there is no data on the issue yet.

Complicating the matter even further is that patients who have become accustomed to pain and restricted range of motion, since they've experienced it all their lives, frequently delay seeking treatment well after the first signs of the calcification, until such time as the pain or restriction of the calcification becomes unbearable. Thus, even if burosumab will prevent the formation of calcifications, by the time a patient seeks treatment for them, it will be too late to undo the existing damage. Assuming burosumab can prevent the calcifications, patients would need to be treated *before* the symptoms occur as a preventative measure. And it is not known for sure whether burosumab will indeed prevent the calcifications.

One further complication for treatment of calcifications is that it is not widely known (yet) within the medical community that patients with chronic hypophosphatemia are likely to develop these calcifications. Gin's osteoarthritis and calcifications were noted years before she or her treating physicians were aware that they were related to her XLH. Dr. Erik Imel pointed out that clinicians unaware of the link between calcifications and chronic hypophosphatemia will look for a different cause, because they've been taught that adults don't have symptoms. As a result, patients get "unnecessary evaluation for things that aren't really the problem [when] what needs to be done is address the XLH."

C. Factors That Affect Treatment Choices

No treatment is entirely benign, and treatments before burosumab was approved came with significant risks (and the long-term risks of burosumab remain unknown). Patients need to make decisions in collaboration with their clinicians. Unfortunately, one point that several speakers made was that the decision-making is made more difficult by the lack of clinicians with experience treating chronic hypophosphatemia.

Most endocrinologists for adults have a great deal of experience treating diabetes and osteoporosis, but not with chronic hypophosphatemia. Because these rare disorders are so variable in individual patients' response to treatment, the regimen is not a simple one with a standard set of doses that can be found in a reference book or journal, but is a trial-and-error method that needs constant adjustment until an optimal regimen is developed for each patient. As a result, the patient needs to be monitored closely to see the dose response.

Endocrinologists may not always have the inclination to learn more about a rare condition. Theresa reports, "I've had doctor's offices tell me that their doctors do not talk to specialists outside their practice, even if those specialists could give them vital information about me and my disease." Others may be willing to learn, but simply do not have the time in today's fast-paced professional world, a fact acknowledged by Dr. Erik Imel in his summary of the day's events.

Since patients frequently must deal with clinicians who don't understand their chronic hypophosphatemia, patients often learn to ignore medical advice when it comes to things that are normal for the patient but abnormal for the general population. Sunindiya mentioned going against medical advice recently, because the doctors giving the advice had never seen an XLH skeleton before. She received panicked phone calls from clinicians "after an x-ray or MRI from a radiologist [unfamiliar with XLH] who looks at my spine and thinks I should go to the emergency room ASAP because my spinal cord is about to be crushed." She knows, however, that what they are looking at is normal for her.

While it's too often necessary to ignore the inexperienced clinicians, it sets patients up for possibly dangerous situations. When to ignore a symptom and when to get it looked into is a frequent topic of discussion in the patient community, since patients have too often experienced either the letdown of being told repeatedly that there's nothing that can be done for them, or, worse, are given bad advice due to clinicians' inexperience with chronic hypophosphatemia.

Poor treatment is worse, in some cases, than no treatment at all. The patient community has seen and heard too many examples of clinicians giving too much phosphorus (unaware that the goal is not simply to normalize the blood phosphorus level, but to get it as close to normal as possible without triggering side-effects and not enough calcitriol (or, worse, no calcitriol at all), leading to hyperparathyroidism (Carpenter, et al, 2011).

Even with good treatment, patients can experience hyperparathyroidism from the supplement regimen. Brent reported that at one point in his childhood, "My parathyroid levels began to rise to the point that calcium was being removed from my bones." Adjustments to the treatment regimen didn't help enough, and he had to undergo surgical removal of the majority of the parathyroids. That surgery had to be repeated, a common situation for chronic hypophosphatemia patients, since the underlying cause of the enlargement (the treatment with supplements) hadn't been removed:

First, they removed parathyroid glands, left a small portion in my neck and did the implant into the arm. The second time I had to have parathyroid surgery, they were thinking it was going to be the one in the arm, but it was actually the remainder that they had left in the neck that had enlarged again, so they went in and took that out.

Another side-effect of treatment with supplements is nephrocalcinosis, although none of the patients at the Symposium had experienced serious consequences from that. It's been reported that most patients undergoing treatment during childhood will experience a certain degree of nephrocalcinosis, but if monitored carefully, and assuming treatment is fine-tuned thereafter, the kidney calcification will plateau and not present major problems for patients (Carpenter, et al, 2011). Still, any degree of nephrocalcinosis leaves a patient with compromised kidney health.

While supplements were burdensome and presented several serious health risks, the opposite was true of burosumab. The main concern with respect to burosumab treatment was simply that it hadn't been studied long enough to know for sure what the long-term effects would be, both positive and negative.

Billy reported experiencing temporary back pain after his first several doses with burosumab (and Gin had the same experience, but only after the one first dose) So far, most of the reported side-effects have been minimal (such as injection-site irritation, plus headaches and nausea and other things that may or may not have been related to the treatment), but no one knows for sure if long-term use will lead to other issues or whether burosumab will, in fact, prevent calcifications from forming or stabilize the ones that have already formed. Sunindiya says, "I am willing to take this risk since this disease is all about not knowing what the future will bring."

Another concern about burosumab is cost, which is still a largely unknown factor for most patients. As Theresa said, "This disease requires ongoing medication and ongoing monitoring through doctor visits and lab work. Co-pays, deductibles, travel to a specialist, and other out-of-pocket expenses add up quickly."

Part of the cost issue that is still unknown is whether insurance companies will cover burosumab, and it's still too soon to know if all or even most insurers will cover it, which patients will be covered, and what percentage patients will have to assume as a copay. Even assuming the bulk of the cost of burosumab is covered by most insurers, that still means patients must have access to that coverage. One audience member noted that she "had to change jobs to get better health

insurance for my family. With the flux in the health care system that has led to three jobs in a twenty-six-month period. So just trying to get basic treatment has been a stressor on my family."

D. Ideal treatment

While everyone at the Symposium who had been on burosumab agreed that it was a considerably better treatment than anything they'd been on previously, there was also agreement that it was not the final answer. As noted above, the lack of knowledge about long-term treatment is a concern.

Another issue is the current requirement for the dose to be administered by a professional instead of by the patient at home. Brent stated that it would be much more convenient if it were self-administered, and he received spontaneous, vocal agreement from the audience.

Short of a cure, the keys to an ideal treatment, as laid out by Gin, are 1) it enables strong, straight, properly mineralized bones that are less prone to osteoarthritis, 2) it prevents calcifications, 3) it enables proper dental structure to form, 4) it provides adequate phosphorus for muscle function, and, 5) it doesn't trigger hyperparathyroidism or nephrocalcinosis.

Brent expanded on these issues, saying:

An ideal adult treatment for XLH would be able to reverse the spinal stenosis, bone spurs, and other physical deformities that go along with XLH. There's also still data to be collected to determine whether burosumab will lessen the impact of XLH on adults who were treated with burosumab as children.

An audience member mentioned the need for a treatment that would undo existing damage:

If we could just see some regression of our symptoms. That would be something that all of us could appreciate. If we could gain some height, if we could have our teeth just want to stay in our mouth, if our hearing could come back.

E. Participation in clinical trials

According to the live-polling results, most patients with chronic hypophosphatemia are ready and willing to participate in clinical trials. The biggest limiting factors are 1) not knowing about the trials, and b) not being eligible.

The organizers of the Symposium sought to represent a diversity of experiences on the panels, so not all panelists had experience with clinical trials. Nevertheless, most of the panelists did have this experience, having enrolled in trials for burosumab, some who started even before the first data were available to suggest that it would work. At least one panelist also participated in an unrelated clinical trial that was of scientific value, but unlikely to lead to a useful treatment. One audience member has been in and out of clinical trials for forty years!

IV. CONCLUSION

The Symposium on Hypophosphatemia: Past, Present, and Future, accomplished its goal of identifying, from the adult patients' perspective, 1) the progression of hypophosphatemia-related symptoms in adults over time, 2) the treatment endpoints that matter most to adult patients, and 3) how those desired endpoints may change with each decade that passes after the growth plates close.

Evidence was presented with respect to the following facts, well-known to patients but under-recognized in the medical literature:

1. Chronic hypophosphatemia is not just a childhood disorder
Patients from their twenties to their seventies all reported symptoms that ranged from moderate to severe.
2. Chronic hypophosphatemia, whether or not treated during childhood, has long-term, adverse health consequences during adulthood;
Patients reporting debilitating symptoms included both patients who had received standard of care treatment (phosphorus and calcitriol supplements) during childhood and those who had not.
3. Chronic hypophosphatemia manifests in a variety of potentially disabling ways during adulthood, most notably in spontaneous dental abscesses, hearing loss, chronic pain and fatigue, poor muscle function, osteoarthritis from misaligned joints, and widespread calcifications and enthesopathy that reduce mobility and range of motion;
Mobility issues and chronic pain were considered the most troublesome symptoms, but other issues had significant impacts on patients' lives.
4. Chronic hypophosphatemia is a multi-system disorder, affecting not just bones and teeth, but also muscle function and energy levels.

Treatment with phosphorus and calcitriol supplements is burdensome, comes with the risk of serious side-effects, and does not prevent the most serious adult symptoms, including spontaneous dental abscesses, hearing loss, chronic pain and fatigue, poor muscle function, osteoarthritis from misaligned joints, and widespread calcifications and enthesopathy that reduce mobility and range of motion.

The most recent treatment, burosumab, is able to stabilize blood phosphorus levels and reduce chronic pain and fatigue but is not a cure. The long-term effects are not yet known, in terms of both the possible adverse side-effects from long-term usage, and the full extent of its positive effects, such as whether it will prevent or stabilize the calcifications of tendons and other soft tissues. Cost, insurance coverage issues, and the inconvenience of in-clinic injections are also concerns.

Based on the patient testimony and discussions, and the survey/live-polling responses, there are several key take-aways for future treatment:

1. Both the patient community and the medical community need to be more fully aware that chronic hypophosphatemia is not a pediatric disorder, or one that is limited to challenges with skeletal growth, but is a whole-body, whole-life disorder.

2. The medical community needs to rethink the formula for when adult treatment is appropriate. In the past, treatment of adults carried significant risks (hyperparathyroidism and nephrocalcinosis), and the extent of the benefits wasn't known, so the risk-benefit equation fell heavily on the side of not treating patients, absent certain limited circumstances. Now that there's a treatment with apparently fewer, less dangerous side-effects, and there is far better understanding of just how serious the adult symptoms are, the risk-benefit equation changes significantly. Related to this change in the risk-benefit equation, there's an increased need for educating pediatric patients (and their parents) of the need to transition patients to an endocrinologist who treats adults, since pediatric patients won't automatically be told they no longer need treatment when they're discharged by the pediatric endocrinologist.

3. Patients may minimize their symptoms to both themselves, their families and their clinicians. As Dr. Imel noted, the patients speaking during the Symposium who reported doing well at some point in early adulthood "didn't describe having *no* symptoms, they described having *mild* symptoms, and somewhat manageable symptoms, for a period of time and then gradually getting worse. I think that's important to note, that even doing relatively well-off therapy, may not mean being symptom free."

4. The patient community needs access to more clinicians who are familiar with chronic hypophosphatemia and the treatment options. This is likely to be an ongoing challenge, due to the rarity of the conditions, and the time pressures on health care providers today. It's not possible to expect all endocrinologists to become experts in every rare disorder. The more feasible option is to have more educational materials for endocrinologists who are open to learning about a patient's rare condition. Unfortunately, that's a challenge due to the time pressures of modern-day medical practices.

5. Much more needs to be learned about calcifications and enthesopathy, their causes and best treatment. Even if burosumab can't reverse them, it may be able to prevent these symptoms from forming or worsening, but the answer won't be known for many years due to slow nature of this symptom.

6. And yet, there is hope for the future. Not just because of the reported benefits of the newest available treatment, burosumab, but also because patients and medical care providers are getting together and sharing information, as happened during the Symposium. The transcripts of the patient testimony, along with this report that includes the highlights of that testimony and the survey data, will be distributed widely to continue that sharing of information.

The work of collecting data on chronic hypophosphatemia is not even close to complete. The next step will be the official launch (scheduled for 2019) of *BeyondXLH*, an online disease-monitoring program for patients in the U.S. and Canada with X-linked Hypophosphatemia and other chronic hypophosphatemic disorders. It is intended to characterize XLH and other chronic hypophosphatemic disorders from the patient perspective via a user-friendly mobile application. *BeyondXLH* is a collaborative research effort among industry (Ultragenyx Pharmaceutical, Inc.), academia (Yale University), and a patient advocacy group (The XLH Network, Inc.). If you or your child is a patient with chronic hypophosphatemia (including XLH, autosomal hypophosphatemia or Tumor-Induced Osteomalacia), you can get the details on the program and register for it here: BeyondXLH.com

APPENDIX 1 Benefit-Risk Framework

The FDA has developed a Benefit-Risk Framework for use in its reviews. It's described as "a structured, qualitative approach focused on identifying and clearly communicating key issues, evidence, and uncertainties in FDA's benefit-risk assessment." The framework may be found in the FDA's "Benefit-Risk Assessment in Drug Regulatory Decision-Making, Draft PDUFA VI Implementation Plan (FY 2018-2022)" available at its website:

<https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM602885.pdf>

The key information from the Symposium has been organized below in the analytical portions of that framework in order to bring the adult patients' perspective to future discussions of the risks and benefits of various treatment options, both those existing today and those under consideration in the future.

Dimension	Evidence or Uncertainties	Conclusions and Reasons
<p>Analysis of Condition:</p> <p>Facts:</p>	<ol style="list-style-type: none"> 1. Adult patients experience mobility and range of motion challenges, chronic pain, calcifications and nerve/spinal challenges, and chronic fatigue. 2. The symptoms progress over time, generally from mildly disabling to severely disabling. While some patients have "mild" symptoms or "good" periods at various times, generally during or at the end of pediatric treatment, patients are virtually never completely free of symptoms, especially pain and mobility restrictions. 3. There are significant emotional impacts from the symptoms and the stress of dealing with them. 	<ol style="list-style-type: none"> 1. Chronic hypophosphatemia is not just a childhood disorder. 2. Chronic hypophosphatemia, whether or not treated during childhood, has long-term, adverse health consequences during adulthood. 3. Chronic hypophosphatemia manifests in a variety of potentially disabling ways during adulthood, most notably in spontaneous dental abscesses, hearing loss, chronic pain and fatigue, poor muscle function, osteoarthritis from misaligned joints, and widespread calcifications and enthesopathy that reduce mobility and range of motion.

	<p>4. The mobility restrictions, pain, and fatigue have an adverse effect on choice of career and success or duration of careers.</p> <p>5. Family planning is a challenge, due to both the risk of transmission in genetic cases, and the physical demands of childbirth and child-rearing.</p> <p>6. Too few clinicians have the necessary expertise to treat adults with chronic hypophosphatemia. In addition, insurance restrictions limit some patients' access to clinicians with the necessary expertise.</p>	<p>4. Chronic hypophosphatemia is a multi-system disorder, affecting not just bones and teeth, but also muscle function and energy levels.</p> <p>5. New treatment guidelines for adults need to be developed to take into consideration both the serious nature of adult symptoms and the apparently lowered risk of adverse side-effects from treatment with burosumab.</p>
<p>Uncertainties:</p>	<p>1. A new treatment option, burosumab, appears to be a significant step forward in treatment of adults with X-linked Hypophosphatemia (and Tumor-Induced Osteomalacia), but has only been in use by a limited number of patients over a limited timeframe. Accordingly, the effects, both positive and negative, of long-term use is unknown.</p> <p>2. More specifically, it is not known whether long-term use of burosumab by adults will stop the progression of calcifications and enthesopathy, dental issues, or hearing loss. There is some evidence that it will help with chronic pain, chronic fatigue, and poor muscle function over the long term, but it is still too soon to know for sure.</p> <p>3. Adults today had either no pediatric treatment or the marginally/variably effective treatment with phosphorus and calcitriol supplements. It is not yet known whether treatment with</p>	<p>1. Long-term data needs to be gathered from adults on treatment.</p> <p>2. Treatment guidelines for adults need to consider the uncertainties surrounding long-term use.</p> <p>3. Testing of burosumab on TIO patients needs to be completed.</p>

	<p>burosumab during childhood will lead to better results in adulthood, either with or without ongoing burosumab treatment.</p> <p>4. It is still not known whether there is any correlation between severity of symptoms or response to treatment (both of which are highly variable within the chronic hypophosphatemia populations), and some other factor, such as specific gene mutation, other genetic elements, environment, activity, nutrition, etc.</p> <p>5. Burosumab has not been tested on patients with autosomal hypophosphatemia (an ultra-rare condition), so it is not known whether it will benefit these patients, or which segments of this population might benefit.</p>	<p>4. Additional testing needs to be done on the benefits and risks of burosumab treatment for autosomal hypophosphatemia patients.</p>
Assumptions:	No assumptions have been identified other than the belief, which will take decades to confirm, that better pediatric treatment, along with ongoing adult treatment, will lead to significantly better adult outcomes.	

<p>Current Treatment Options:</p> <p>Facts:</p>	<p>1. There is no cure for any of the chronic hypophosphatemias (except to the extent Tumor-Induced Osteomalacia is cured by removal of the tumor).</p> <p>2. One pharmacological treatment consists of phosphorus and calcitriol supplements. Advantages: the supplements are relatively inexpensive and if prescribed and taken correctly, may improve some patients' symptoms in the short term. Disadvantages: treatment requires frequent, expensive monitoring (blood, urine tests, kidney scans); few clinicians have the expertise to prescribe/monitor correctly; each dose normalizes blood phosphorus for only a few hours, so levels don't stay in the normal range consistently; the</p>	<p>1. A cure is still needed.</p> <p>2. Treatment with phosphorus and calcitriol supplements is burdensome to the patient, has variable effectiveness, and has serious side-effects, including hyperparathyroidism and nephrocalcinosis.</p>
---	---	--

	<p>complicated treatment routine (many doses per day, timed to avoid certain foods) leads to patients not taking the medications; treatment may lead to nephrocalcinosis or hyperparathyroidism; not all patients tolerate the treatment (serious gastrointestinal side effects); not all patients respond to the treatment; has some benefit for bone pain and dental issues, but no known benefit on enthesopathy or calcifications.</p> <p>3. Effective April 2018, there is a new pharmaceutical treatment, burosumab. Advantages: simple routine leads to patients better adhering to treatment plan; no known side effects significant enough for patients to stop use during clinical trials; no known risk of nephrocalcinosis or hyperparathyroidism; less need for frequent, expensive monitoring (blood, urine tests; kidney scans); maintains the blood phosphorus levels over long periods of time (2 to 4 weeks).</p> <p>Disadvantages: burosumab is expensive, and not all clinicians are aware of it or how to prescribe it, and it may not be covered by all health insurance plans.</p> <p>4. Other treatments, including surgery and braces, are secondary ones, more a matter of repairing the failures of pharmaceutical treatment than a first line of treatment. Until the underlying hypophosphatemia is addressed, the bone cannot be truly healed.</p> <p>5. There are additional treatments, such as those for osteoarthritis and pain, which are better addressed in other settings, such as the FDA's PFDD on chronic pain. Effects, both positive and negative, of long-term treatment are unknown.</p>	<p>3. Treatment with burosumab is less burdensome, and appears to be more consistently effective, and without serious side-effects. There remain uncertainties, however, with respect to long-term use.</p>
Uncertainties:	<p>1. Generally, since the treatment is so new (FDA approved on April 17, 2018),</p>	<p>1. Long-term data needs to be gathered from adults on treatment.</p>

	<p>the long-term effects, both positive and negative, are not fully known.</p> <p>2. One issue that will be of particular interest to the patient community is whether burosumab will prevent or at least slow the progress of enthesopathies and calcifications.</p> <p>3. It's also not clear whether early treatment with burosumab, while teeth are still forming, will result in better mineralization and fewer abscesses during adulthood.</p> <p>4. Burosumab is still undergoing clinical trials for use in treating Tumor-Induced Osteomalacia, and while the preliminary results and anecdotal evidence shared among patients are encouraging, the data is incomplete.</p> <p>5. Burosumab has not been tested on patients with autosomal forms of hypophosphatemia. Some forms may respond to this treatment, while others may not, depending on the exact cause of the phosphate-wasting.</p>	<p>2. Treatment guidelines for adults need to take into account the uncertainties of long-term use.</p> <p>3. Testing of burosumab on TIO patients needs to be completed.</p> <p>4. Additional testing needs to be done on the benefits of burosumab treatment for autosomal hypophosphatemia patients.</p>
<p>Assumptions:</p>	<p>No assumptions have been identified other than the belief, which will take decades to confirm, that better pediatric treatment, along with ongoing adult treatment, will lead to significantly better adult outcomes.</p>	

APPENDIX 2 Meeting Agenda

- 9:00 - 10:00 Sign-In, Coffee, etc.
- 10:00 - 10:10 Opening Remarks
Susan Faitos, MA, LMFT, Chair, Symposium Committee, The XLH Network, Inc
- 10:10 - 10:20 FDA Welcome Remarks
Lucas Kempf, MD, Acting Associate Director, Rare Diseases Program, FDA
- 10:20 - 10:40 Clinical Overview of Hypophosphatemia
Karl Insogna, MD, Professor, Yale University School of Medicine
- 10:40 - 10:55 Meeting Overview & Demographic Polling Questions
James Valentine, JD, MHS, Moderator
- 10:55 - 11:20 Topic 1 Panel Comments: What are the disease symptoms and daily impacts that matter most to adult patients?
- 11:20 - 12:10 Topic 1 Polling Questions & Facilitated Discussion
- 12:10 – 1:15 Lunch break
- 1:15 - 1:25 Afternoon Welcome/Video: *Weak Bones, Strong Wills: The Images*
Rachael Jones, Executive Director, The XLH Network, Inc.
- 1:25 - 1:50 Topic 2 Panel Comments: Patients' perspectives on current approaches to treating hypophosphatemia during adulthood.
- 1:50 - 2:40 Topic 2 Polling Questions & Facilitated Discussion
- 2:40 - 2:50 Summary Remarks: Erik Imel, M.D.
- 2:50 - 3:00 Closing Statement/What's Next?
Elizabeth Olear, M.A., M.S., Co-Chair, Symposium Committee

APPENDIX 3

Speakers

General speakers

Susan Faitos, M.A., L.M.F.T serves as a board member for The XLH Network, Inc. She is Chair of the Symposium Committee and co-chair of the XLH Day Committee. After a 30-year career in social work and mental health services in Sacramento, she is now semi-retired, working part-time as Clinical Director of Behavioral Health Services at Community Bridges in Santa Cruz, CA and volunteering for Hospice of Santa Cruz County. In her spare time, she enjoys traveling, swimming, and reading. She was diagnosed with XLH at 18 months of age at Stanford Medical Center.

Karl Insogna, M.D has been funded to do both clinical and translational research throughout his career at Yale. He began his clinical work as a fellow, studying hypophosphatemic disorders, specifically X-Linked Hypophosphatemia, and renal stone disease. He was the first individual to show evidence for renal phosphate conservation in patients with XLH, despite the defect in renal tubular phosphate reabsorption. He was also the first individual to clarify the relationship between serum phosphate and absorptive hypercalciuria in patients with calcium oxalate stone disease. His work in hypophosphatemic disorders has continued uninterrupted over the last 30 years. He has worked closely with Dr. Thomas Carpenter of Pediatrics to explore the natural history of XLH and has undertaken a variety of studies aimed at developing new therapies for this skeletal dysplasia. He is currently lead investigator for a multi-center international study evaluating the role of a neutralizing antibody to FGF23 in the treatment of this disease. He has also had experience with Hereditary Hypophosphatemic Rickets with Hypercalciuria and has published on this disease.

James Valentine, JD, MHS, is an Associate at Hyman, Phelps & McNamara, where he assists medical product industry clients in a wide range of regulatory matters, including new drug and biologic development and approval issues. Before joining the firm, James worked in the US Food and Drug Administration in the Office of Health and Constituent Affairs, where he facilitated patient input in benefit-risk decision-making and served as a liaison to stakeholders on a wide range of regulatory policy issues.

Lucas Kempf, M.D. is the Acting Associate Director for the Rare Disease program in the OND immediate office. Prior to joining FDA in 2012, Lucas spent eight years at the National Institutes of Health with a focus on neuroscience research, working to understand the genetics of neuropsychiatric disease and developing translational approaches and therapeutics to study these disorders. He did post-graduate training in psychiatry at Georgetown and Johns Hopkins before moving to the NIH for fellowship.

Elizabeth Olear, M.S., M.A. is the Senior Clinical Research Associate at the Yale Center for XLH (Pediatric Endocrinology/Yale School of Medicine). She serves as a member of the Board of Directors of The XLH Network, Inc. and is Chair of XLH Day 2018 and co-chair of the Symposium Committee. Her interests include yoga, travel, and culinary adventures. Some of her favorite people have XLH.

Panelists for Topic 1

James DiBlasi was diagnosed with tumor-induced Osteomalacia in his early twenties, after experiencing unexplained orthopedic problems and pain and not being able to carry on his normal activities. He enjoys going to Ohio State football games and spending time with family and friends.

Athina Kinsley was diagnosed with a spontaneous case of XLH when she was seven years old. Now 45, she has had a career in healthcare revenue management, currently working as a Bill Review Supervisor. Married for 27 years, she has one son who also has XLH. She enjoys spending time with her family, traveling, continuing her education and relaxing while watching movies.

Ramon Reyes, 51, was diagnosed with familial XLH in 1968, when he was 1 year old. He was treated with traditional XLH therapies and has had multiple XLH-related surgeries. He continues to suffer from XLH symptoms, although recently he has received much relief since being treated with burosumab. Ramon is a native of Brooklyn NY, where he lives with his wife and two teenage sons. After practicing law for thirteen years, Ramon became a United States Magistrate Judge for the Eastern District of New York in 2006.

Kelly Rushing is 36 and comes from a family with a long history of XLH. She lives in a small town in Texas of only 74 people. She worked in accounting/business administration until 2009 when her body could no longer hold up to the demands of the job. Kelly loves to be outdoors and spends time fishing and camping with her husband, Ricky, and their adopted dogs.

Gale Smith was born in 1942 during WWII when there was no prescribed treatment and very little knowledge of the causes of hypophosphatemia. She had her first bi-lateral tibial osteotomy at 18 months of age. She started treatment with phosphorous and Vitamin D in 1965 when her daughter was born. She lives in Colorado and is married with three grandchildren and two great-grandchildren.

Panelists for Topic 2

Sunindiya Bhalla is 36 years old and was diagnosed as a spontaneous case of XLH at 16 months. She is Senior Director of Community Impact at United Way of Massachusetts Bay in Boston, MA. Sunindiya lives just outside of Boston with her mom, Bindiya, and her dog, Midori and is an active member of The XLH Network, Inc, a member of the international XLH coalition of advocates, and a patient ambassador for Ultragenyx Pharmaceutical.

Billy Branch is 55 years old and the Assistant Director of Homestead Energy Services in Homestead Florida. He was diagnosed with familial hypophosphatemia in his teenage years. He has had several surgeries linked to hypophosphatemia with the worst being 5 surgeries within 2 years to correct issues with the Achilles tendon.

Brent Davidson, 40 years old, was adopted at birth and was diagnosed with Vitamin D Resistant Rickets at 15 months old. He discovered later in life that, due to anonymity concerns, the adoption agency had withheld a family history of XLH from his adoptive parents. Brent's biological mother and maternal grandfather both have XLH as do two of his half siblings. Brent is currently an IT Administrator for a title insurance company.

Gin Jones is 63 years old and was diagnosed with spontaneous XLH when she was 3 years old. After retiring early from the practice of law due to disability, she became a bestselling author with a dozen mysteries in print and more on the way.

Theresa Harnar is 46 and started her own home business doing administrative and creative writing after working as a teacher for several years. She also works as the office manager of her church. She has been married for 12 years to a wonderful man and has a great stepson. Theresa was diagnosed with a spontaneous case of XLH at 9 years old.

APPENDIX 4
Online Survey Questions

Question	Answer	Response %
Date of Birth	Ranged from 1936-1996	n/a
Were you treated with phosphorus and/or calcitriol during childhood? (Choose just one.)	A. Yes for the majority of the years from age 1-18 B. Yes, but for only about half the years from age 1 to 18 C. Yes, but for less than half the years from age 1 to 18 D. No	A. 50.5 B. 14.5 C. 11.3 D. 23.7
Which symptom of familial hypophosphatemia has the biggest negative impact on your life? (Choose just one.) (Top choice is in bold.)	A. Lower limb deformities (bowing or knock-knees) B. Mobility or range of motion issues (including arthritis and spinal conditions) C. Short stature D. Spontaneous dental abscesses E. Chronic pain F. Muscle weakness or muscle fatigue G. Chronic fatigue H. Time spent on treatment (doctor/hospital/lab visits) I. Hearing loss J. Other (please specify)	A. 21.0 B. 30.1 C. 3.2 D. 5.9 E. 29 F. 2.7 G. 2.7 H. 1.1 I. 3.2 J. 0
Which symptom of familial hypophosphatemia has the second biggest negative impact on your life? (Choose just one.)	A. Lower limb deformities (bowing or knock-knees) B. Mobility or range of motion issues (including arthritis and spinal conditions) C. Short stature D. Spontaneous dental abscesses E. Chronic pain F. Muscle weakness or muscle fatigue G. Chronic fatigue H. Time spent on treatment (doctor/hospital/lab visits) I. Hearing loss J. Other (please specify)	A. 9.7 B. 24.7 C. 9.1 D. 10.2 E. 21.0 F. 8.6 G. 9.1 H. 2.2 I. 5.4 J. 0

APPENDIX 4

Online Survey Questions

Excerpts from comments:

"As a young adult, I didn't have many problems except some mobility problems. As I got older, arthritis set in along with osteoporosis. I had my knee replaced in 2016 and my other knee and hips are soon to follow. I am 5' 0" tall and I am the tallest member of my family."

"When I transitioned to adult care, treatment for my XLH stopped altogether. I was told I didn't need it anymore. Over the years I revisited this with various endocrinologists who said the same thing. Even now it's hard to convince doctors that my symptoms and pain are real, and that I would gratefully accept any treatment."

"My biggest obstacle is not being able to find doctors in my insurance network who are knowledgeable and can and will treat me. So even though new treatments exist I must go without because I can't travel out of network."

APPENDIX 5
Live-Polling Questions and Responses

Question	Response Options	Response Percentage
I am a (choose all that apply)	A. Person living with hypophosphatemia B. Caregiver of someone living with hypophosphatemia C. Both A and B D. Not sure	A. 53 B. 23 C. 21 D. 2
What is the impact living with hypophosphatemia has on you or your loved one's life on a daily basis:	A. None B. Mild C. Moderate D. Severe E. Extreme	A. 2 B. 12 C. 38 D. 35 E. 13
If you or your loved one are currently being treated to normalize the phosphorus levels in your blood, which treatment(s) are you using?	A. Taking burosumab (brand name Crysvita) B. Taking phosphorus and calcitriol C. No treatment D. Other	A. 46 B. 36 C. 15 D. 1
Your age, or if you are a caregiver, the age of your affected family member:	A. 18-25 B. 26-35 C. 36-55 D. older than 55	A. 4 B. 20 C. 44 D. 31
What are the top two issues that most significantly affects you or your loved one's quality of life?	A. Fatigue B. Bone pain C. Muscle pain D. Joint stiffness E. Hearing loss F. Dental abscesses	A. 23 B. 22 C. 11 D. 30 E. 0 F. 14
If you or your loved one are currently being treated for chronic pain due to your hypophosphatemia, which treatment(s) do you use most frequently?	A. Opiate pain relievers (Norco, Fentanyl, etc.) B. Non-opiate pain relievers (Celebrex, Lyrica, etc.) C. Over the counter pain medications (Tylenol, Aleve, etc.) D. Physical therapy E. No treatment	A. 17.3 B. 18.7 C. 44.0 D. 6.7 E. 13.3
Where do you currently reside?	A. Eastern Time Zone B. Central Time Zone C. Mountain Time Zone D. Pacific Time Zone E. Canada F. Mexico G. Outside of North America	A. 52 B. 17 C. 11 D. 9 E. 0 F. 2 G. 9

<p>Select the most important thing you or your affected love one used to do that you or your family member now can't do as well because of the progression of hypophosphatemia as an adult?</p>	<p>A. Participate in sports or recreational activities B. Communicate with friends or participate in social activities C. Perform well at job or work D. Perform well in school E. Take care of family member F. Other</p>	<p>A. 59 B. 9 C. 17 D. 4 E. 4 F. 7</p>
<p>What is your experience in, and perception of, clinical trials for chronic hypophosphatemia?</p>	<p>A. I am currently participating in a trial B. I have participated in a trial, and I would do so again. C. I have participated in a trial, and I would not do so again D. I have not participated in a trial, because I was not eligible E. I have not participated in a trial because I did not know about the opportunity F. I have not participated in a trial, although I was aware of the opportunity and was eligible G. I would never enroll in a clinical trial. H. Not sure.</p>	<p>A. 10 B. 21 C. 8 D. 23 E. 26 F. 13 G. 0 H. 0</p>
<p>How has the impact of you/your loved one's chronic hypophosphatemia changed over time?</p>	<p>A. Impact has gotten greater or affects additional areas of life (home, work, friendships, etc.) B. Impact has stayed the same C. Impact has lessened D. Not sure</p>	<p>A. 84 B. 11 C. 0 D. 5</p>

APPENDIX 6
Fall 2017 Survey
Preparation for meeting with FDA

Question	Response Options	Percent adults	Percent minors
Which symptom of XLH has the biggest negative impact on your (or your minor child's) life?	A. Lower limb deformities B. Mobility or range of motion problems due to joint damage or calcifications C. Short stature D. Spontaneous dental abscesses E. Chronic pain F. Muscle weakness or muscle fatigue G. Chronic fatigue H. Time spent on treatment (drug regimen, doctor/hospital/dentist visits) I. Other (please specify)	A. 15.8 B. 26.69 C. 1.79 D. 4.46 E. 37.50 F. 2.68 G. 6.25 H. 1.79 I. 3.57	A. 32.14 B. 7.14 C. 10.71 D. 10.71 E. 17.86 F. 6.14 G. 0 H. 14.29 I. 0
What is your age (or if answering for a minor child, the age of the child)?	A. Under 18 B. Over 18 to 30 C. 31 to 40 D. 42 to 50 E. 51 to 60 F. 61 to 70 G. 70+	A. 0 B. 9.82 C. 23.21 D. 32.14 E. 19.64 F. 10.71 G. 4.46	A. 100%
Were your (or your minor child's) symptoms mild, moderate or severe during childhood (to age 18)?	A. Mild B. Moderate C. Severe D. Unsure	A. 24.11 B. 47.32 C. 28.57 D. 0	A. 17.86 B. 53.57 C. 25.00 D. 3.57
Are your adult symptoms mild, moderate, or severe now. (Answer Not Applicable if you're answering for your minor child.)	A. Mild B. Moderate C. Severe D. Unsure	A. 7.14 B. 45.54 C. 46.43 D. 0 E. .89	N/A

APPENDIX 7

Glossary

Autosomal refers to a genetic trait that is determined by a mutation on a chromosome other than the sex-determining X and Y chromosomes.

Burosumab: a newly FDA-approved antibody that binds to FGF23 thereby blocking the ability of Fibroblast Growth Factor 23 to cause phosphate-wasting.

Calcitriol: an active form of vitamin D that increases phosphate absorption. Some patients with hypophosphatemia have a decreased ability to produce this hormone, so it may be used to treat hypophosphatemia.

Chiari Malformation: malformation of the base of the skull that may be associated with genetic forms of hypophosphatemia.

Eight plate surgery: orthopedic surgical procedure that involves the insertion of a plate on one side of a growth plate to guide the bone into a straighter, more anatomically correct orientation.

Endocrine system: the collection of hormones (and the sources of the hormones) that regulate metabolism and other bodily functions. The types of hypophosphatemia discussed in the symposium are disorders of the endocrine system.

Enthesopathy: calcification of tendons or ligaments.

Fibroblast Growth Factor 23 (FGF23): a hormone that may be secreted by bone cells or a tumor; excessive secretion leads to hypophosphatemia.

Hyperparathyroidism: overproduction of parathyroid hormone, may be caused by phosphorus supplements, especially if not sufficiently balanced with calcitriol.

Hypophosphatemia: disorder characterized by low levels of phosphorus in the blood. It may be caused by a genetic mutation or a tumor.

Nephrocalcinosis: calcification of the kidney, a potential adverse effect of treatment with calcitriol or other active vitamin D analogues.

Osteomalacia: soft, poorly mineralized bones in adults.

Osteotomy: orthopedic surgical procedure that cuts a bone to realign it with the joint.

Patient-Focused Drug Development meetings (PFDD): part of an initiative by the U.S. Food and Drug Administration to more systematically obtain the patient perspective on specific diseases and their treatments.

Phosphorus supplements: sometimes referred to as K-phos or Neutra-phos, may be used to treat hypophosphatemia.

Spinal stenosis: narrowing of the spinal canal due to calcifications.

Tumor-Induced Osteomalacia (TIO): disorder characterized by a tumor that produces excessive levels of Fibroblast Growth Factor 23.

X-Linked: when a genetic trait is determined by a mutation on the sex-determining X chromosome.

APPENDIX 8 ADDITIONAL RESOURCES AND WORKS CITED

Videos from the Symposium are available at the Network's Youtube channel:

<https://www.youtube.com/c/XLHNetworkIncVideo>

<https://www.youtube.com/channel/UCOCxS6CV6NeNxoFFivOyNpg>. Or just go to youtube.com and put "XLH Network" in the search box.

The transcripts from the Symposium are available here: www.xlhnetwork.org

For additional resources about chronic hypophosphatemia:

Patients, family members, friends, researchers, and clinicians are encouraged to join our forum to continue the conversation at forum.xlhnetwork.org, or our private Facebook members group page at: <https://www.facebook.com/groups/xlhnetworkmembers/>

To read more about the patient experience, check out the Network's book, *Weak Bones, Strong Wills, the Stories of XLH*, available in both digital and paper formats from major online retailers.

The database of PHEX mutations (the ones that cause X-Linked Hypophosphatemia is here: <https://databases.lovd.nl/shared/genes/PHEX>

For the latest on chronic hypophosphatemia, follow the Network's social media at Facebook ([Facebook.com/xlhnetwork](https://www.facebook.com/xlhnetwork)), Twitter (@XLH_Network) and Instagram (xlhnetwork) or visit our website at xlhnetwork.org.

-
- Alon, U., H. B. Lovell and D. L. Donaldson (1992). "Nephrocalcinosis, hyperparathyroidism, and renal failure in familial hypophosphatemic rickets." *Clin Pediatr (Phila)* **31**(3): 180-183.
- Beck-Nielsen, S. S., B. Brock-Jacobsen, J. Gram, K. Brixen and T. K. Jensen (2009). "Incidence and prevalence of nutritional and hereditary rickets in southern Denmark." *Eur J Endocrinol* **160**(3): 491-497.
- Bowe, A. E., R. Finnegan, S. M. Jan de Beur, J. Cho, M. A. Levine, R. Kumar and S. C. Schiavi (2001). "FGF-23 inhibits renal tubular phosphate transport and is a PHEX substrate." *Biochem Biophys Res Commun* **284**(4): 977-981.
- Carpenter, T. O., E. A. Imel, I. A. Holm, S. M. Jan de Beur and K. L. Insogna (2011). "A clinician's guide to X-linked hypophosphatemia." *J Bone Miner Res* **26**(7): 1381-1388.
- Carpenter, T. O., M. P. Whyte, E. A. Imel, A. M. Boot, W. Hogler, A. Linglart, R. Padidela, W. Van't Hoff, M. Mao, C. Y. Chen, A. Skrinar, E. Kakkis, J. San Martin and A. A. Portale (2018). "Burosumab Therapy in Children with X-Linked Hypophosphatemia." *N Engl J Med* **378**(21): 1987-1998.
- Chesher, D., M. Oddy, U. Darbar, P. Sayal, A. Casey, A. Ryan, A. Sechi, C. Simister, A. Waters, Y. Wedatilake, R. H. Lachmann and E. Murphy (2018). "Outcome of adult patients with X-linked hypophosphatemia caused by PHEX gene mutations." *J Inherit Metab Dis* **41**(5): 865-876.
- Connor, J., E. A. Olear, K. L. Insogna, L. Katz, S. Baker, R. Kaur, C. A. Simpson, J. Sterpka, R. Dubrow, J. H. Zhang and T. O. Carpenter (2015). "Conventional Therapy in Adults With X-Linked Hypophosphatemia: Effects on Enthesopathy and Dental Disease." *J Clin Endocrinol Metab* **100**(10): 3625-3632.
- Cremonesi, I., C. Nucci, G. D'Alessandro, N. Alkhamis, S. Marchionni and G. Piana (2014). "X-linked hypophosphatemic rickets: enamel abnormalities and oral clinical findings." *Scanning* **36**(4): 456-461.
- Endo, I., S. Fukumoto, K. Ozono, N. Namba, D. Inoue, R. Okazaki, M. Yamauchi, T. Sugimoto, M. Minagawa, T. Michigami, M. Nagai and T. Matsumoto (2015). "Nationwide survey of fibroblast growth factor 23

- (FGF23)-related hypophosphatemic diseases in Japan: prevalence, biochemical data and treatment." Endocr J **62**(9): 811-816.
- Francis, F., S. Hennig, B. Korn, R. Reinhardt, P. de Jong, A. Poustka, H. Lehrach, P. S. N. Rowe, J. N. Goulding, T. Summerfield, R. Mountford, A. P. Read, E. Popowska, E. Pronicka, K. E. Davies, J. L. H. O'Riordan, M. J. Econs, T. Nesbitt, M. K. Drezner, C. Oudet, S. Pannetier, A. Hanauer, T. M. Strom, A. Meindl, B. Lorenz, B. Cagnoli, K. L. Mohnike, J. Murken and T. Meitinger (1995). "A gene (PEX) with homologies to endopeptidases is mutated in patients with X-linked hypophosphatemic rickets." Nature Genetics **11**(2): 130-136.
- Imel, E. A., L. A. DiMeglio, S. L. Hui, T. O. Carpenter and M. J. Econs (2010). "Treatment of X-linked hypophosphatemia with calcitriol and phosphate increases circulating fibroblast growth factor 23 concentrations." J Clin Endocrinol Metab **95**(4): 1846-1850.
- Insogna, K. L., K. Briot, E. A. Imel, P. Kamenicky, M. D. Ruppe, A. A. Portale, T. Weber, P. Pitukcheewanont, H. I. Cheong, S. Jan de Beur, Y. Imanishi, N. Ito, R. H. Lachmann, H. Tanaka, F. Perwad, L. Zhang, C. Y. Chen, C. Theodore-Oklota, M. Mealiffe, J. San Martin, T. O. Carpenter and A. Investigators (2018). "A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial Evaluating the Efficacy of Burosumab, an Anti-FGF23 Antibody, in Adults With X-Linked Hypophosphatemia: Week 24 Primary Analysis." J Bone Miner Res.
- Liang, G., L. D. Katz, K. L. Insogna, T. O. Carpenter and C. M. Macica (2009). "Survey of the enthesopathy of X-linked hypophosphatemia and its characterization in Hyp mice." Calcif Tissue Int **85**(3): 235-246.
- Linglart, A., M. Biosse-Duplan, K. Briot, C. Chaussain, L. Esterle, S. Guillaume-Czitrom, P. Kamenicky, J. Nevoux, D. Prie, A. Rothenbuhler, P. Wicart and P. Harvengt (2014). "Therapeutic management of hypophosphatemic rickets from infancy to adulthood." Endocr Connect **3**(1): R13-30.
- Macica, C. M. (2017). Overview of phosphorus-wasting diseases and need for phosphorus supplements. Dietary Phosphorus: Health, Nutrition, and Regulatory Aspects. J. Uribarri and M. S. Calvo. Boca Raton, CRC Press.
- Mills, E. S., L. Iorio, R. S. Feinn, K. M. Duignan and C. M. Macica (2019). "Joint replacement in X-linked hypophosphatemia." J Orthop **16**(1): 55-60.
- Pesta, D. H., D. N. Tsigotis, D. E. Befroy, D. Caballero, M. J. Jurczak, Y. Rahimi, G. W. Cline, S. Dufour, A. L. Birkenfeld, D. L. Rothman, T. O. Carpenter, K. Insogna, K. F. Petersen, C. Bergwitz and G. I. Shulman (2016). "Hypophosphatemia promotes lower rates of muscle ATP synthesis." FASEB J **30**(10): 3378-3387.
- Ruppe, M. D. (1993). X-Linked Hypophosphatemia. GeneReviews(R). R. A. Pagon, M. P. Adam, H. H. Ardinger et al. Seattle (WA).
- Skrinar, A., M. Dvorak-Ewell, A. Evins, C. Macica, A. Linglart, E. A. Imel, C. Theodore-Oklota and J. San Martin (2019). "The Lifelong Impact of X-Linked Hypophosphatemia: Results From a Burden of Disease Survey." J Endocr Soc **3**(7): 1321-1334.
- Yu, X. and K. E. White (2005). "FGF23 and disorders of phosphate homeostasis." Cytokine Growth Factor Rev **16**(2): 221-232.

**Symposium on Hypophosphatemia:
Past, Present, and Future**

October 5, 2018
Baltimore, Maryland

Hosted and underwritten by
The XLH Network, Inc.
Connecting, Educating, Advocating

With some financial assistance from:
EveryLife Foundation
Inozyme Pharmaceutical
Ionis Pharmaceuticals
Ultragenyx Pharmaceuticals

Voice of the Patient Report Transcripts

Report written and funded entirely by The XLH Network, Inc.

TRANSCRIPTS:

Introduction

My name is Susan Faitos, and I serve as a board member for The XLH Network, and as Chair of this Symposium committee. I can't tell you how excited I am to be here today. Today's meeting is the result of almost two years of visioning and ten months of hard planning and a lot of work by many people.

As I look around this room, I am just so humbled and grateful by all these people that are here ready to participate and to help support families with hypophosphatemia. On behalf of the entire board of The XLH Network, welcome to this Externally-led, Patient Focused Drug Development Meeting: The Symposium on Hypophosphatemia, Past, Present and Future.

Whether you're here in person, or if you're joining us through our live stream, whether you're an individual affected with hypophosphatemia, or a family member or a caregiver, we are grateful that you are here taking the time to come together as a community to voice your experience and perspectives. You are the experts, and it is through your testimony, your polling answers, your survey results and your comments today, that we teach those that need to know that chronic hypophosphatemia is, in fact, a whole-life, whole body, disorder.

Our hope is that after this meeting patients, clinicians, industry members, academic researchers, and other stakeholders will have improved tools to use when treating adult patients with

hypophosphatemia. We hope that we will be able to reduce the number of times a patient leaves a doctor's appointment in frustration, exhausted by the number of times they've had to argue with their doctor that their pain and their stiffness are real symptoms of their illness. We hope that through this meeting and our data reports and video deliverables, that patients will feel increased empowerment when advocating for themselves in the medical arena.

Our belief is that the impact of hypophosphatemia on adults has been poorly recognized and undertreated, and that the treatment endpoints that matter most need to be identified. That more people need to recognize that while once thought of as a childhood disorder, that magically disappeared when the growth plates closed, hypophosphatemia does have long-term adverse health consequences. It can manifest in a variety of potentially disabling ways later in life, most notably in spontaneous dental abscesses, hearing loss, chronic pain and fatigue, poor muscle function, osteoarthritis and other factors that reduce mobility and range of motion. We want others to understand that chronic hypophosphatemia is a multi-system disorder, affecting not just bones and teeth, but also muscle function and energy levels. And that all of these symptoms can understandably affect emotional and mental health as well.

We think our impetus is best summed up by this quote we received from a patient who responded to our pre-event survey. "When I was a child, I thought that the worst thing about having XLH was that I was different and that I couldn't always do the things my friends did in sports and stuff. And that I was short and people made fun of me. I also thought, or I was told, that it would all go away when I became an adult. Little did I know that this disease would knock me down far worse in adulthood than any mean comment on the playground ever would."

We recognize that our community is at a turning point, with increased treatment options. This past year has been one of change and hope for us, and we're grateful for this. We also know that there is more to be done. The burden of this disease has shifted, and now the focus must be on helping those that aren't eligible for the current treatments find a treatment that works for them, and on finding improved ways to treat the impact of living for years without inadequate phosphorous levels, and on ultimately finding a cure. The work cannot stop now.

There are so many people to thank for this opportunity to make our voice heard today. Meghana Chalasani and Pujita Vaidya from the office of Strategic Programs/Center for Drug Evaluation and Research at the U.S. Food and Drug Administration have been invaluable in helping us navigate this process, and their encouragement and support along the way have been appreciated. We are pleased to have Doctor Theresa Kehoe in the audience with us today. Doctor Kehoe is a Clinical Team Leader in the Division of Bone, Reproductive, and Urologic Products within FDA's Center for Drug Evaluation and Research. We thank you and your colleagues in the room and online for being with us today.

We wouldn't be here today also without the support of our sponsors, including Ultragenx, Inozyme, Ionis, and the Everyday Life Foundation. We thank you for your support as well.

I am here today not only as Chair of the planning committee, but as a person with hypophosphatemia who was told at age nineteen that I no longer needed to be treated for my XLH. Who was told the same thing repeatedly over the years whenever I sought help for what I

knew were XLH-related challenges. Who didn't meet a doctor with any real experience in XLH until I was 54 years old. I am here because while I know we can't change the past, and we can't reverse the joint damage and the hearing loss and the other issues that might already be in existence for adults, we can change the landscape ahead for others.

I am also here because in 1962, after being told by the medical team at a renowned university hospital that they were befuddled by my condition, my mother wrote to famed scientist Linus Pauling to inquire about a theory she had about the cause of my low phosphorous levels. I can only imagine how scared and alone she must have felt to do so, and it is my hope that forums like this one today help to reduce the chances of anyone else having to feel such uncertainty about their loved one's health. Linus Pauling did write back, and her theory was incorrect, but she's my hero for trying.

And speaking of heroes, I want to thank our panelists who were brave enough to volunteer to be here today. We know it's not always easy to open up and share your story, but that's exactly what we needed you to do. Lift the curtain and let others see the truth about the impact of hypophosphatemia in adults. Your courage, your commitment, and your hard work as we prepared for this day has been absolutely inspiring to watch. We encourage all of you here with us today, in the room and online, to follow their example and speak your truth today as well.

FDA remarks by Lucas Kempf, M.D.

[Intro by Susan Faitos] Dr. Lucas Kempf is the Associate Director for the Rare Disease Program in the Office of New Drugs in FDA Center for Drug Evaluation and Research. Prior to joining the FDA in 2012, Dr. Kempf spent eight years at NIH with a focus on neuroscience research, working to understand the genetics of neuropsychiatric disease, and developing translational approaches and therapeutics to study these disorders. He did postgraduate training in Psychiatry at Georgetown and Johns Hopkins, before moving to the NIH for Fellowship. We are very fortunate to have Dr. Kempf with us today as he is a key official in the review of drug products for rare diseases like XLH.

Thank you very much for having me. It's great to see so many people here in Baltimore.

As this audience probably well recognizes, rare diseases are a very important aspect of public health, which is why we actually have a Rare Diseases Program at the FDA. Because 30 million people in the United States are actually affected with rare diseases, that means it's about one out of 10 people are actually affected.

80% of these are genetic disorders, and are clinical, progressive, and have life-limiting aspects of the disorders. And, the third point, I heard several of you talking about just as before the session started, that part of the problem, like with XLH, is that the presentations are heterogenic. That's sort of the fancy, scientific way to say that everybody has slightly different disease. So it's very hard to develop drugs, particularly for these sort of disorders, because some people are affected with the hearing loss, some affected with growth and bone disorders. It doesn't make it nice and easy like, treating blood sugar, and diabetes, or something like that.

When you look at the 7,000 rare disorders we still have quite a bit of work to do. Even though this community does have some products that have been developed about, that's part of the 5% of rare diseases that actually have a treatment. And so you're a little bit on the cutting edge as far as I can tell, of folks who now have to start thinking about second generation drugs, and what do you want next, and then augmenting them and continuing the curve, so that your children don't have the same problems that you had to deal with. A lot of this is being driven by the continued advocacy by patient groups such as yours.

Why do we do patient-focus drug development? The patient's input is probably one of the most important things, and this has been more recognized by legislators, and the regulators in the drug and device industry. You don't necessarily want a drug that isn't right for you, doesn't address the things that are most important for you all. Patients all have different perspectives, right? What affects one person, is not necessarily the thing that's most important to the next person.

Part of having patient-focused drug development is to capture everyone's voice, and in the survey method, get the full spectrum of what's going on with people, and sort of get a maximum saturation of that information, because you don't necessarily want drug development just being driven by a couple people who are the most vocal within your community. We really want to hear from all of you.

This helps the FDA when we have to come and do risk benefit analysis for new drugs. We base our risk/benefit analysis on the information that we know about from your community, and especially in rare communities, sometimes that information isn't really well-known, or documented.

You're going to have a series of questions presumably today, where you're going to be asked what are your most bothersome symptoms, and disease complications? What are the short-term and long-term aspects that affect these disorders affect your lives? What is your experience with existing treatments? How do they affect you? How could they be improved? What is preventing you from actually using some of them? And then also, what is your own personal risk tolerance, what are you willing to do? Obviously, many people have had some pretty serious surgeries, who have this disorder. And that has huge impacts on the way that you've had to grow up, and live your lives. What is currently an unmet medical need within your community? Where do you actually need drugs, or other therapies to be approved? And then also, what is your own personal preferences?

The patient perspective is important throughout the drug development process, so it's very important to get the input early before drugs are actually on the market, before a development program is started, so that the developers design their programs for you, with your own personal priorities built in. So when decisions are being made about what drugs and formulations should be developed, they need to know what you would all perhaps, want. What the endpoints are actually going to be in the drug studies. When you have a heterogenic disorder, everybody comes sometimes with their own endpoint. And how do you balance that in the drug development program? What is the drug actually going to do, and how are we going to measure it is a huge problem within drug development.

Sometimes the information that comes out of these meetings is very helpful to the drug developers, in order to decide what they're going to measure the endpoints with, so it's just not height, or whatever, but is actually things that impact your life.

Also, the patient input is are very important in sort of the post-marketing period, where you can identify gaps and safety risks that came out of the medications. And also, they provide a means in some communities to provide communication about what to expect if you try a different kind of drug, which I'm sure this community has already had with your previous treatments and with the surgeries, and what to expect. I'm sure this community's already well familiar with that, so it's going to be an involving conversation that you all have as new drugs come out for you.

We get asked frequently how do people engage with the FDA in a meaningful fashion, and this became such a focus that one of our authorization legislations for the FDA, what we call PDUFA, actually had a requirement for these meetings. The FDA was committed to this, and then started hosting several of these meetings, and then also provide input to groups, because obviously we can't do all 7,000 [rare diseases]. But we can provide a structure and a framework for folks to be able to do this within their own community, so you can design the drug development for yourselves in the direction that you want it.

More recently, we have developed a guidance. The first one out of a series of four guidances, has come out that helps advise groups who are going to be doing patient-focused drug development, how to do this sort of survey method in the most sort of scientific means in order to capture the full range of symptoms that people have. The full range of needs and demographic issues. So that it's just not like growth, like we heard at the beginning, it's just not growth, or maybe hearing, but people have a lot of issues within this community that should be captured. And their experiences with those that you all want to be addressed in some sort of manner. And there's also been a lot of innovation in the ways that people are collecting this data. It seems like you all are on the forefront of this. You've already had surveys, have gone out electronically to sample what you might want to talk about.

And this goes into clinical designs, and incorporating the patient perspective and preferences, where we can count every patient. So the drug studies aren't just being developed for one small sliver of your community, but they can include everybody, and everybody can benefit as they go into new experimental drugs. I look forward to hearing the rest of this conference. And it looks like it's going to be a good one from what I was looking at the schedule.

Dr. Karl Insogna: Clinical overview

[Introduction by Susan Faitos] It's now my pleasure to introduce Dr. Karl Insogna. Throughout his career at Yale, Dr. Insogna has been funded to do both clinical and translational research. He began his clinical work as a fellow, studying hypophosphatemic disorders, specifically x-linked hypophosphatemia and renal stone disease. He was the first individual to show evidence for renal phosphate conservation in patients with XLH despite the defect in renal tubular phosphate reabsorption. He was also the first individual to clarify the relationship between serum phosphate and absorptive hypocalcemia in patients with calcium oxalate stone disease. His

work in hypophosphatemic disorders has continued uninterrupted over the last 30 years. He has worked closely with Dr. Thomas Carpenter of Pediatrics to explore the natural history of XLH and has undertaken a variety of studies aimed at developing new therapies for this skeletal dysplasia. He's currently lead investigator for a multi-center international study evaluating the role of neutralizing antibody to FGF23 in the treatment of this disease. He has had experience with hereditary hypophosphatemic records with hypercalcaemia and is published in this disease. Welcome, Dr. Insogna.

It's a great pleasure to be here, and I'd like to thank the organizing committee for allowing me to participate in this really important symposium that allows care-givers like myself, members of regulatory agencies like the FDA, and other stakeholders to hear first-hand from patients with this disease. To hear about what it's like having this disease in different parts of the country, at different stages in your life, so that we can collectively come together and think about ways that we can lessen the burden of this disease.

My charge this morning is to provide an overview of FGF23-mediated hypophosphatemias. You remember that the introduction mentioned the fact that I've been doing this for thirty years, so holster your iPhones, put away your iPads, take off your Beats headphones, and just like I did so many years ago in that little red school house way out on the raw, windswept prairie, when Willa Cather taught me the three R's, take out your slate writing tablets, dip your quill in the ink, school is in session.

What we're going to try and talk about is what is FGF23, and how does it regulate blood phosphorus? Why does too much FGF23 cause bone problems? What bone problems does too much FGF23 cause? What diseases are associated with too much FGF23? How is overproduction of FGF23 treated?

Fibroblast Growth Factor 23 is made in cells embedded in bone, called osteocytes. They make FGF23. An important feature of the way they make FGF23 is that it's produced inside the cell, but then the cell decides how much the body needs, and depending on how much it needs, it either makes the active hormone, which has got two pieces, or it cuts it in half, and secretes the two halves which are inactive.

The final regulation of this hormone in the blood, is made after the hormone is made in the cell, when the cell decides how much you really need. If you don't need much, it chops it in half, if you need much, it doesn't chop it in half and lets the whole molecule be secreted.

It acts in the kidney, and in the kidney, it acts to reduce the ability of the kidney to reclaim phosphates. Much of the phosphates we eat, we pee right out. Just as soon as we pee it out, we reclaim most of it. How affectively we reclaim it, dictates what our blood phosphate is.

The way the kidney reclaims that phosphate is by opening little ports on the kidney that allow the phosphate to come back in. What FGF23 does is close those ports so you pee out more phosphate, and in doing so, you lower your blood phosphate.

The other thing it does, is inhibit the synthesis of the active form of vitamin D, which is called

1,25 dihydroxyvitamin D, and that is made in the kidney. FGF23 inhibits the production of that active form of the hormone by inhibiting the step that makes it, and stimulating the step that breaks it down. The net effect of that is lower levels of this active form of vitamin D, 1,25 dihydroxyvitamin D, and that is important for absorbing phosphate from your intestine. FGF23's main job is to defend your blood phosphate, to make sure it doesn't go too high. It does it by having you pee out a lot of phosphate, and absorb less from the intestinal tract.

Now when there's too much FGF23, it adversely affects bone. Bone is actually a pretty complex tissue. It has multiple parts, so there's a hard outer shell of bone called a cortex, there's this trabecular bone, the sort of spiculated bone in the middle that you see when you crack open a chicken bone. That's where the bone forming cells are made, and then there's this thin smooth surface that lines our joints called articular cartilage. Cartilage is also present in growing bone, and it's where bone grows and it's that cartilage that's effected by FGF23 excess, as we'll see. The two tissues in bone that are affected by FGF23 are the mineralized tissue itself, both cortical and trabecular, and the articular cartilage, and the cartilage.

Excess FGF23 leads to renal phosphate wasting and a chronic low blood phosphorous. It does it by the same mechanisms that is usually uses to control your blood phosphate, but it does so in excess. Again, it closes the ports on the kidney so you pee out too much phosphate, and that lowers your blood phosphate. It inhibits production of the active form of vitamin D, which is also made in the kidney, and that impairs phosphate absorption so you don't absorb as much of the phosphate that you eat. You're peeing out too much, you're not absorbing enough, bad condition.

It's also important to point out, that when you suppress this active form of vitamin D, you also impair the ability to absorb calcium, so it's a double whammy: your phosphate's low and you're not absorbing calcium. And that leads to rickets and osteomalacia, which are two conditions that we're going to talk about that affect the two components of bone that I mentioned.

Rickets reflects the problems that are developed in the cartilage at the growth plate, and osteomalacia reflects what happens in the mineralized tissue of bone. Again, what's happening is that in FGF23, you've basically punched a hole in a bucket. So you're trying to fill the bucket that is your blood stream with phosphate, but it keeps leaking out at the kidney because of those pores being closed. Our therapies to date have had the problem of sort of trying to fill the bucket and not being able to fix the hole.

Chronic phosphate wasting and hypophosphatemia causes a defect in normal cartilage growth that results in an abnormal growth plate. The growth plate is the place where the bone grows. It is a very complicated cartilaginous structure. It's sort of like building a skyscraper. It's the place where the bone grows longer, and it grows longer because the cells in the growth plate have very distinct roles. The cells at the top of the growth plate are starting to expand and proliferate. The cells at the bottom of the growth plate are actually dying, they go to the big chondrocyte corral in the sky. They have to do that because the bone has to come in and replace those dying chondrocytes. In fact, the dying chondrocytes help to call in the bone forming cells.

The structure of a growth plate is shown in the lower left [see the video for the diagram]. In the purple, these are the cells that are proliferating, they're called hypertrophic chondrocytes. Those

are the ones that expand and make the bone grow. On the right is shown what happens when you don't have phosphate around. Phosphate is a key signal that changes these proliferating chondrocytes and those chondrocytes that are going to die. But you can see over here, they're just all still happily proliferating, which sounds like a good thing but it's not a good thing, as we'll see. They don't have the signal to stop growing because phosphate is that signal. So what does that lead to? That leads to rickets in childhood.

So the abnormality leads to rickets in growing children, which as all of you know, presents as swollen wrists, bowing deformities of the lower extremities, and bone pain. In the top two panels, we see this is a normal radiograph of a child's wrist, and you can see these nice clear dark lines. You can't see the cartilage, it doesn't show up on an x-ray, but you can see how nice and sharp these lines are because those are normal growth plates. Over here, we see that the growth plate is fuzzy and indistinct. That's because this normal process of mineralization is gone awry. Here's a child whose legs don't look that bad, but when you take x-rays, you see that they have marked bowing deformity, and that's again, because these growth plates are not functioning normally. Here's a child with knock knees, again, for the same reasons. Genu valgum, genu varum, both conditions associated with an abnormal growth plate.

In the mineralized tissue, a different problem arises. In the mineralized tissue, when you don't have enough phosphorous, you can't mineralize bone. What does that mean? We make bone in a two stage process, we lay down a sort of putty-like scaffolding that's called osteoid, and then we pour mineral into that to harden it up. If you don't have enough calcium and phosphorous, you can't harden up that scaffolding.

That scaffolding is called osteoid, and when it builds up in bone, it makes the bone weak. It builds up both in that trabecular compartment that we talked about in the middle of the bone and in the cortex of the bone. There are yellow arrows that point to the osteoid, which is the red stuff. The green stuff is the mineralized bone, the light red stuff is your bone marrow, but all the dark red staining stuff is osteoid that should've been mineralized but was not. This biopsy is riddled with that and it's important to note that it's in the cortex, because the cortex is very important in the bones of your lower extremities to prevent fracture. As you know, people with XLH often fracture in their lower extremities and it's because the cortex is poor quality, in part because of that osteomalacia. In contrast, over here, on the left, we see what looks like normal bone. Now the staining is different, here the light purple is the mineralized bone, and the very light which you really can't see, is the osteoid.

Normally, you shouldn't have very much unmineralized osteoids. When it starts to accumulate like it does in hypophosphatemic disorders, that's not a good thing, it impairs the mineralization ability of this bone. This is what it looks like normally. Normally we just have a very thin layer of osteoid with lots of new bone forming beneath it. With osteomalacia, you have this thick glacier of unmineralized osteoid, and very little new bone formation because the cells that need to form that bone, can't penetrate this thick layer of osteoid to get down here to make new bone. What does osteomalacia lead to? Osteomalacia leads to fractures. This patient obviously has lots of problems besides simply this insufficiency fracture, but that thin, dark line there is an insufficiency fracture that occurs despite the fact, obviously, that this person has a plate in place.

Now let's talk about the disorders that are caused by excess FGF23, and I've divided them into three parts. First, are genetic disorders where the gene is known, the offending gene is known, is present in all cells, and a relationship between the gene and the disease can at least be surmised. By that, I mean, in most of these conditions, we think we have some idea how it relates to the disease, we don't really know, there's one exception that I'll mention, and these would be considered inherited diseases. These are ones that can be passed on from parents to children. The poster child for that, of course, is X-Linked Hypophosphatemia, and the gene involved is PHEX.

Probably the condition where we understand best the pathogenesis, is another inherited disorder called autosomal dominant hypophosphatemia. The disorder is that the gene mutates at FGF23 itself.

Then, there are three incredibly rare disorders, autosomal recessive hypophosphatemia Types one, two, and three, rare as hen's teeth, no pun intended, where the genes are listed, DMP1, ENPP1, and FAM20c. Then there's this even more rare disease, osteoglophonic dysplasia, which I've actually never seen a patient with, due to a mutation in a receptor for FGF23. Then there are genetic disorders where the gene is known, is not present in all cells, and a relationship between the gene and the disease is unclear. That includes fibrous dysplasia, Epidermal Nevus Syndrome, and we won't touch on those. The genes that are associated with them, at least in the affected tissue, are shown there.

Then finally, there are diseases that are not genetic, that are acquired, and the one disease I'll mention is Tumor-Induced Osteomalacia. In that disease, the tumor itself has a peculiar genetic abnormality where two genes are fused together. People think that this may somehow play a role in the pathogenesis of that disorder, but that is, at this point, speculative.

Again, we'll be talking about autosomal dominant hypophosphatemia, Tumor-Induced Osteomalacia, and X-Linked Hypophosphatemia. Autosomal dominant hypophosphatemic rickets is due to a mutation in FGF23 itself, as you may remember. Normally, the production of FGF23 protein, as I mentioned, is regulated by intracellular cleavage of the protein, not by controlling how much is actually made. A mutation in the cleavage site disables this regulatory mechanism. Again, the cell makes the protein, then decides how much you need, and if you don't need much, it chops it in half and secretes the inactive fragments. But in autosomal dominant hypophosphatemic rickets, there's a mutation at this cleavage site so the cell can't cleave it, so that regulatory step, which is a key regulatory step, is lost. The more you make, the more you secrete from the cell. That leads to excess circulating amounts of FGF23. Every time production of FGF23 gene goes up, the cell releases more active FGF23.

What are the manifestations? They're very similar to x-linked hypophosphatemia, rickets and osteomalacia, fractures and pseudofractures, but it's a little more variable in its presentation, sometimes not detected until late childhood, even adolescence and rarely even young adulthood. Dr. Erik Imel [who will be speaking later in the program] had some interesting data presented earlier this week, that suggest that iron deficiency makes the disease worse, and in iron-deficient patients with this disease, iron pills seem to improve the disease.

Now, what about x-linked hypophosphatemia? This disorder is due to a mutation in the gene

PHEX. We still don't understand why it is that when you have too much PHEX or when you lose function in PHEX, you make too much FGF23. We do know they're both in the same cell, PHEX doesn't directly regulate FGF23 but somehow, when you mutate PHEX, you make too much FGF23. Then the same pathophysiology we've talked about a couple of times, comes into play. You don't absorb enough phosphate from the kidney, you don't reabsorb enough phosphate in the kidney, you don't absorb enough phosphate from the intestinal tract, you get chronic low serum phosphate. That leads, again, to rickets and osteomalacia. In childhood, rickets results in bowing deformities of the lower extremities, as we talked about. These are growth curves for children with XLH, showing the different patterns of growth that can occur as a child moves through childhood with XLH. Sometimes they can start low and fall off the growth curve, all different patterns. The bottom line is, the combination of defects in the growth plates of the lower extremities, and probably defects in the growth plates in the spine, lesser extent in the spine, lead to this disproportionate short stature that is a burden in childhood and remains a burden throughout life.

Dental disease is a huge problem in this disorder. Because dental insurance is so terrible and dental care is so expensive, people needlessly lose their teeth and many patients lose most of their teeth by young adulthood. Why is it that dental disease is so prevalent? We don't know; we know that the teeth are abnormal. Here's a normal tooth, here's a patient with XLH, what their tooth looks like. There's an expansion of this pulp cavity, where the nerve and the blood vessel pass through. We know that, not the hard outer shell of bone, which is called enamel, but rather the bone just below it, called dentin, is abnormal in its micro-architecture. We also know that the periodontal ligament that holds the tooth in place, doesn't seem to attach to the tooth as firmly as it should, and as a consequence of that, presumably, bacteria get into that space and cause abscesses. Which I'm sure many of you, unfortunately have experienced. They wax and wane and many times wind up causing tooth loss. In addition to that, lots of patients complain of brittle teeth that fracture and that may be because the dentin is abnormal.

As I mentioned, fractures and enthesopathy (well I mentioned fractures but I didn't mention enthesopathy), are major complications of this disease. Enthesopathy is the calcification of the ligaments and joints that limit the range of motion of joints. Here is the hip of a patient like that who could not abduct her legs when she was trying to birth her child because she just couldn't abduct her legs because of these entheses. We see it very early in adulthood. It occurs as early as 18 years of age, particularly in the heel bone, the calcaneus.

Another complication is spinal ligament calcification. This leads to chronic back pain and limitation in range of motion of the joints. Degenerative joint disease of the spine is common, but also, this peculiar calcification of normally non-calcified ligaments that run in front of the spine and run in back of the spine. The ones that run in the back of the spine are butting the spinal canal, and I've actually had a patient who developed weakness in all four extremities when he was thrown to the ocean floor swimming, and had to have emergency decompression surgery because these calcifications were impinging on his spinal cord.

Finally, hearing loss is a major problem in patients with XLH. It affects the middle ears of the bone but probably also affects the cochlea, which is the place where the sound is transduced to and also the site where balance is regulated. A lot of patients have symptoms that are very

reminiscent of Meniere's disease, dizziness, ringing of the ears, as well as hearing loss.

Tumor-induced osteomalacia is due to overproduction of FGF23 by small, often very difficult to detect, usually benign tumors called Phosphaturic Mesenchymal Tumors. They can be anywhere in the body, in the nasopharynx, in any bone, and soft tissue. Dr. Suzanne Jan deBeur sitting in the front here, is an expert in this disease. Usually goes undiagnosed for years. Patients often present with many pseudofractures, profound weakness, and are very disabled. Surgical resection, when possible, results in immediate cure. One of the interesting things is that patients with tumor-induced osteomalacia will have serum phosphates as low as patients with XLH. Patients with XLH can walk around and function, albeit with difficulty, while the same patients with tumor-induced osteomalacia is incapacitated. Can't walk, is in a wheelchair, and it's interesting that somehow, lifelong hypophosphatemia, the body makes adaptations to allow you to function pretty well with it. But as an adult or a child, when you've been used to a normal phosphate and it suddenly drops because of the appearance of this tumor, you're really incapacitated.

This is a patient that I saw earlier this year that actually was the focus of an article in the *New York Times Magazine* this summer, who came to me. She was a jogger, completely incapacitated when I saw her, developed over four years, no one could figure out what was wrong with her. She had this little golf ball size tumor in the soft tissue of her leg on the left, lit up like a Christmas tree bulb on a special scan called an octreotide scan. We were able to take it out, it's only about three centimeters long. Her phosphate before surgery was 1.4. Two days after surgery, it was 2.9. Two weeks after surgery, it was 3.7, so rapid improvement.

This is a slide that was given to me by Dr. Ward from Canada showing the response of a patient, a young child with excellent hypophosphatemia with TIO, who has resection of the tumor at time zero and you can see that FGF23 falls like a stone. This is the normal range, the serum phosphate rises immediately into the normal range. We often see this overshoot of 1,25 vitamin D that's been suppressed all these many years and shoots up with exuberance before it becomes normal again. Importantly, the osteomalacia shown here with all this red, now normalizes with correction.

For treatment of tumor-induced osteomalacia, treatment is directed at finding the tumor and removing it when you can. For XLH and other causes of FGF23-mediated hypophosphatemia, the treatment has been calcitriol and phosphorous, and that's true for tumor-induced osteomalacia as well. Again, it's an unsatisfactory approach. It's not without efficacy, when done correctly, and when patients are able to take it, it does help substantially, but again, it doesn't address the underlying problem, which is you've got a leaky bucket.

In April of this year, as you all know, burosumab was approved by the FDA for the treatment of XLH, so at least for that disease, there is now an alternative that has been rigorously evaluated for safety and efficacy. Basically, what this blocking antibody burosumab does, is let the body heal itself. It blocks the excess FGF23, allowing 1,25 vitamin D production to increase, improving phosphate reabsorption in the kidney. Most importantly, it blocks the FGF23 effect at the level of the kidney and allows improved phosphate reclamation, reduced phosphate excretion, and serum phosphate normalizes.

It's fundamentally different from what we've been doing before. It allows the body to heal itself by blocking FGF23, and it's important to point out that it doesn't block all FGF23, because that would not be a good thing. The developers of this drug were smart. They didn't choose to develop their most potent antibodies; they chose them with sort of in the middle range, that blocked some of the FGF23, but not all of the FGF23.

What do we know so far about findings with this drug? It improves rickets in children, and preliminary data, presented by Dr. Imel, indicate that it is better than calcitriol and phosphorous in a head-to-head pediatric trial. In a double blind trial in adults, compared to a placebo, it caused healing of fractures and pseudofractures. In fact, patients taking the drug in the double blind placebo portion of the trial, were seventeen times more likely to heal with the drug. After one year of treatment, study participants self-reported stiffness, physical function, and pain improved. Importantly, bone biopsy data indicate marked improvement in the osteomalacia with resumption of normal bone formation.

There's still a lot we don't know and still a lot we need to know. Does every adult with XLH need burosumab? Will it be safe over the life span? We've never had a monoclonal antibody therapeutic that potentially could be used from age two to age 92. Should there be a "hiatus" a break in therapy after epiphyseal closure like so many of you were told years ago? That is, what about the nineteen-year-old with XLH, treated her whole life, who's about to go off to college, who says she feels perfectly fine and looks great, and the last thing she wants to do is get a shot every month?

Does burosumab completely heal osteomalacia? Does it have to heal the osteomalacia completely, or is partial good enough? Does it prevent all the late complications of the disease: dental disease, hearing loss, fractures and pseudofractures, enthesopathy? Does it improve muscle function? How do PHEX, phosphate, and so many other factors, regulate FGF23? Are there other therapeutic approaches that can be developed?

Overview: James Valentine

[Introduction by Susan Faitos] It is my great pleasure to introduce James Valentine who will be moderating the rest of this meeting today. James is an attorney at Hyman, Phelps & McNamara where he assists medical product industry and patient advocacy organization clients in regulatory issues in drug and biologic development. James previously worked at the FDA where he facilitated patient input in benefit/risk decision-making, including helping launch the PFDD Initiative. We are fortunate to have James with us today as our Moderator as he has been central to the transition of the FDA Patient-Focused Drug Development program to externally-led meetings, having helped through the planning and moderating of fourteen of these meetings. For my co-chair Elizabeth Olear and myself, I think we would say that James has been an invaluable source of information for patients and support. I know he's pulled me off the wall more than once over the last six months. He's been a great asset to our team and we thank him for being here today.

We've had already covered a lot of ground helping set the stage now for what is really the core of today's symposium, which is hearing from all of you in the community, the patients, the family members, and caregivers of individuals living with hypophosphatemia. We heard from Dr. Insogna about breaking out the slate and quills to take some notes. Well, now it's our turn to ask all of the doctors in the room, the FDA officials, members of industry to break out their iPads or at least the notepad and a ballpoint pen to now start taking notes, because we're here to really learn from all of you, the experts, with your personal experiences with your disease.

As Moderator, I'm going to start this portion of our agenda by giving you a little bit of an overview of how we're going to be working together over the next several hours to elicit your experiences and your preferences. I'll give that overview a few ground rules, and then we're going to jump right into it and start hearing from each and all of you.

The organizers of this meeting really designed this symposium to systematically gather the perspectives of you, individuals living with hypophosphatemia, including the perspective of caregivers of patients on your condition and available treatment options. As you heard from Dr. Lucas Kempf from FDA, your perspective helps inform the context for the assessment of benefit-risk and decision-making for new drugs, biologics, and medical devices. This not only helps during drug and product development but also during the review of applications for approval. Not only will FDA officials and other stakeholders be here listening to you today, but the XLH Network will be preparing a summary report called "A Voice of the Patient" report that will be submitted to the FDA so they have it for their continued reference.

Now let's talk about how we will be working together through the remainder of the agenda. First off, the meeting is organized into two major topics. First, we're going to be exploring and understanding how your experience with hypophosphatemia and its daily impacts affect your quality of life, and then second, we're going to explore current approaches to treating hypophosphatemia and your perspectives and preferences for future therapy.

For each of these two topics, we're going to first hear from a panel of patients and caregivers. The purpose is to set a good foundation for our discussion, and the panelists were selected to reflect the range of experiences with hypophosphatemia. Following those panels, we will broaden the dialogue to include patients and caregivers that are here in the audience, and what we will first do is give everyone a chance to answer polling questions. And that will be for not only those that are here in the room but those of you that are following along on the livestream. I will provide you with instructions for how to do this either over the web or by text, and we do ask that only patients and their caregivers respond to those questions. And then finally, for each of these topics, we will build not only on the panel discussion and the polling questions, but with the discussion of all of our patients and caregivers that are here today in the audience. During that time, I will be asking discussion questions and inviting you to raise your hand to respond. I'll ask that you just state your name and your, the type of hypophosphatemia that you have before answering.

Also, knowing that we only have so much time today and, of course, that not everyone from the community could be here with us in person, we will also be sending all registrants and posting on the XLH Network website instructions for submitting written comments, which, in addition to

the input provided today, will be incorporated into that summary report.

Finally, for our ground rules, first, we are here today to hear from patients and their caregivers, and as Susan so passionately said, "We encourage all of you to please actively participate." Along those lines, FDA industry clinicians and researchers are here to listen. We won't be asking them questions and we ask that they remain in listening mode throughout this period. We ask that all of you that are participating keep the discussion focused on the discussion questions that I will be asking. We know that there are many other aspects of your and your loved ones' journey with hypophosphatemia, but the questions that we're using were designed to focus on what is most important for our audience today.

We also know that the views that are expressed today are going to be personal, and we expect that there will be differences in experiences and in preferences. So we request that you please be respectful of one another and to that end, given that we do have limited time today, please try to make your remarks concise and to the point.

Before we go to our first set of polling questions, I do want to also say that if you need to get up, move around, go stretch, go to the side of the room, back of the room, or even excuse yourself, please feel free to do so anytime. Also, I understand, of course, that hearing loss is an aspect of these conditions, and so, if at any time, you need me to repeat myself or have someone else repeat themselves, please just raise your hand, wave me down, and ask me. We want everyone to be able to fully and actively participate today, and being able to hear what's going on in the room is key to that.

PANEL ONE

[Introduction by James Valentine] As I mentioned, we have two topics that we're going to be discussing here today. And we're going to go ahead and dive into the first of those two. So if our panel one panelists can come on up. Topic one, is really understanding the symptoms and health effects of your hypophosphatemia, and the impacts of those symptoms and health effects on your daily life. During this topic, both from what you hear from the panel, and then what we'll discuss with each and all of you, we want to understand which of those burdens and impacts have the greatest burden on your daily life, and how that impacts activities in your daily life that are important to you. As part of this discussion, we want to understand how those symptoms and impacts have changed over time, as well as how they vary; whether that be varying day-to-day, week-to-week, or month-to-month. Also, as part of this discussion of the impacts of hypophosphatemia on your daily life, we also want to know what concerns you most about living with your condition. And so, to kick us off in our discussion today, we've put together, what I think is a stellar panel, who will be sharing their experiences with living with hypophosphatemia in daily life. As they get settled, I'll just introduce them as a panel. We have Ramon, Kelly, Jim, Gale, and Athina. Ramon, I'll ask you to go ahead and take it away.

[Ramon Reyes] Good morning everyone. My name is Ramon Reyes, and I was diagnosed with XLH in 1968 when I was a little over a year old. My mother also had XLH, and over the years she suffered greatly from its debilitating symptoms.

I was rather an active kid, and although I had bowed legs, obvious short stature, and numerous dental problems, I was able to maintain an otherwise active life, including being a competitive swimmer through my freshman year in college, when my knees became so painful from the progressive bowing of my legs that I had to have surgery. Following my bilateral osteotomies at the Shriners Hospital in St. Louis in 1985, other than continued dental problems, my health was relatively good. Not much bone pain, my range of motion and stamina were okay. This general positive path of my health continued through college, law school, and into my early working life.

At about 30, however, I started to notice a decrease in my energy, stamina, and range of motion, and an increase in my bone pain, especially in my feet, knees, and back. Throughout this period of time, from my childhood through my early thirties, my teeth were always an issue. I can't tell you how many root canals, apicoectomies, re-root canals, extractions, and failed implants I've had. I remember distinctly, when I was about thirty-one, my right knee became so painful and unstable, that I had to have orthoscopic surgery. When my surgeon met me, he said, "Mr. Reyes, when I viewed your x-rays, I figured you were a seventy-year-old man. You will eventually have to have your knee replaced."

This slow, gradual decrease in my health and ability to conduct activities of daily living continued. Shortly after I turned forty, I had an accident while swimming off the coast of Tybee Island, Georgia, which Dr. Insogna already told you about today, where I had to be pulled from the water, largely paralyzed. The accident revealed pre-existing XLH-related ossification of the posterior longitudinal ligament, and resulted in a cervical laminectomy and fusion from my second cervical vertebrae, to my second thoracic vertebrae.

Thereafter, the range in motion in my neck decreased substantially. I started to experience increased mid and lower back pain, and decreased range of motion, due to calcification and spinal stenosis. This decrease has continued. By far, the XLH symptoms that have had the most significant impact on my adult life, are the dental problems, and ever-decreasing range of motion in my joints, especially knees, hips, and feet, and the joint and back pain. I cannot tell you how difficult it has been dealing with the painful dental issues I've had over the years. And that's not to say that the decreased range of motion and bone and joint pain isn't significant, because it is. Overall, my current difficulty in pain, dealing with normal activities of daily living is substantial. As one simple example, the routine task of clipping the toenails of my right foot is exceedingly difficult. Combine the stiffness, pain, and limited range of motion in my right leg and hip, and my back, and it's just a chore to clip my toes.

A more complex example is like engaging in the do-it-yourself projects at home that I've done over the years, and I've engaged in many, including two complete bathroom renovations, laying down hardwood floors in our living room and dining room, and rewiring the entire second floor in our house electrically. It's just getting too difficult to do the remaining projects that I have, and I have many. I can't bend, stretch, reach, kneel, lift, push, pull, or climb a ladder like I used to. It's just too difficult to do so.

On my best days, things are good. My back is only minimally stiff and painful, and I can get out of bed and into my car without much difficulty. I can walk with relative ease on flat surfaces, and

up and down stairs, without much limitation at all as to time and distance. My energy level is good, and I'm not too fatigued when I get home from work. Still, even on my good days, my range of motion is limited and I have pain. There's just no getting around the enthesopathy and arthritis. Putting on socks and bending down is difficult, and forget about kneeling. And the decreased range of motion in my neck and back is a given. These are just constant facts of life.

On my worst days, getting into and out of bed is a painful chore; the car too. The pain in my back even affects my sleeping. It's very hard to get into a comfortable position, when every time that you move, your back hurts. And forget stairs. I have to take them one at a time going down, and very slowly going up. Sitting, too, is difficult. My back stiffens and is painful throughout the day. And my job is a sedentary one, so it ain't a picnic. My stamina is also decreased. I just can't do as much as I can on my best days.

What worries me most about my XLH is quite simple. Because of the increased debility over time, I'll become an overwhelming burden on my family. From the mid 1980s until her death in 2016, I watched my mother deteriorate because of her XLH symptoms. From a working mother raising her own four children and three grandchildren through her late 50s, into a home-bound, largely bed-ridden woman at the age of 65. Unable to bear weight, even with assistance, let alone walk with a cane or walker, even while undergoing traditional XLH treatments. I witnessed first-hand how XLH is a whole-body condition, wreaking havoc on almost every bodily system there is. Skeletal, muscular, hearing, vision, you name it. Having witnessed what she went through, I fear a similar fate awaits me.

[Kelly Rushing] Good morning, my name is Kelly Rushing. I'm thirty-six years old and from Wyatt, Texas. I was diagnosed with XLH when I was approximately twelve months old. There is a multi-generational history of XLH in my family on my mother's side, with an estimated twenty-nine different cases. With this previous knowledge, and my physical symptoms presenting early, my parents knew that XLH was a likely diagnosis.

As an adult, I worry mostly about my long-term ability to stay mobile, dealing with pain, and staying independent. While XLH is defined as a metabolic disorder with physical symptoms, there are several emotional and mental impacts, as well as difficult decisions that I have been faced with in my life.

Mobility is the number one impact that XLH has on my life. From the time I wake up in the morning until the time I lay my head down at night, I find that mobility is a constant issue. Mobility affects every facet of my life. It uses an extreme amount of energy to move, which causes pain, and then causes me to fatigue. All things require mobility. Household chores, shopping, social activities, just to name a few. There are social functions that I found myself making an excuse to cancel, because of the amount of energy and projected pain from the walking and/or standing expected at these events. I do engage with my peers as much as possible. I find great joy in being with others, and it lifts my spirits. But it can drain my energy and cause pain. Oftentimes it will take me several days to recover from this.

I have learned to live my life of limited mobility as a balance. I would love to be able to do more activities with my husband, my family, and my friends, but without worry of how far am I going

to have to walk, and how much is it going to hurt tomorrow. When deciding on a career, I had to first consider what sort of physical requirements would be expected, and needed, to be successful. I really had an interest in cosmetology, teaching, and possibly a healthcare profession. When observing these professions in action, and noticing the amount of time spent standing, walking, and just the overall amount of energy required, I knew that the degree of my disability would just not allow me to be successful in those occupations. In one particular instance, when I was still capable of employment, I had to decline a promotion because my body could not physically hold up to what would have been required of that position, therefore not only limiting my earning potential, but hindering my chances of future promotions.

When choosing a home, there was no way that a second story or a significant number of stairs, was going to work as a manageable living environment. I would use up all of my energy just moving up and down those stairs. I actually had custom stairs built for the outside of my home. They measure four inches tall and twelve inches wide, creating a more gradual rise, with a reinforced handrail to aid in my stability. Yes, there are more stairs total, but they are significantly easier for me to go up and down on a daily basis. In certain circumstances where there is a large step into a building, with no handrail, my wonderful husband, Ricky, will automatically extend his arm and allow me to grasp his arm in an effort to provide, or his elbow, in an effort to provide added stability. When out alone, I will avoid challenging steps and curbs altogether, or find a way to accommodate on the fly. Most of the time, a handicap accessible solution is readily available. However, I have encountered instances where this was not true.

Being a female with a more-severe case of XLH, having my own biological children was a consideration whenever I was first married. After years of deliberation, my husband and I considered that the physical demands of pregnancy, delivery, and raising children, would just be too hard on my body. For me, also, running the risk of passing XLH on to my children was just too great. Even adoption was something that I felt was off the table, due to the same physical demands. This choice has been very emotionally painful, and it's one of the most grief-filled parts of my XLH life.

I had a first-hand experience in watching the deterioration that XLH can have on a body, when my late grandfather slowly worsened and became home-bound in his later years of life. The calcification deposits on his joints and bones had become so disabling and limited his range of motion so much, he could not manage his own daily self care. Just transferring from his chair to his bed would give him debilitating pain. Many days, he would not move from his bed, because of the degree of pain progressive XLH had caused him.

As a person who relies on myself, I have learned to make adjustments and accommodations to suit situations and make them work for my own needs. The heart-wrenching experience of watching my beloved grandfather, with a similar severity of XLH, is a stark realization that this same future could be mine. It is the total loss of freedom that scares me. I am proactive in my attempts to prevent this. But as my body gets older and things wear down, there is only so much I can do to prevent it. Thank you.

[Jim DiBlasi] My name is Jim DiBlasi. I am from Columbus, Ohio. I began to be identified as a TIO patient after many years of not knowing what was happening to me. My TIO is caused by a

tumor in the left side of my skull near my brainstem. It took quite a while to connect that my mobility problems and two hip fractures were connected to my tumor.

In my early twenties, a few years after my first tumor surgery, I began to struggle with balance and unexplained backaches, knee problems, and bone pain. As time went on, I began falling on steps and even flat surfaces for no reason. I began walking with a limp, and we still didn't know what was going on. These problems began to slow me down constantly. I couldn't play basketball or soccer with my friends, or move about easily in large crowds or stadiums with my family.

Over the next five years, I continued to lose my mobility. I had to start using a walker and canes to help getting around. The doctors kept running a lot of tests on me. After they did the testing, they finally figured out my tumor caused my frail bones. The doctor said I had osteomalacia. I began to take a lot of medicine. I started taking phosphorus pills and powders, calcium pills, and Vitamin D in different forms and combinations, and calcitriol, also, multivitamin and Tylenol and ibuprofen for pain. I took medicines four times a day and at bedtimes, and I had to time my meds with my eating schedule to make sure they were being absorbed. This got to be very inconvenient and time consuming. I was a walking pharmacy.

Slowly, some of my problems I had got a little better, but I was still struggling to get around and keep my balance, and my bones still hurt. Three years ago, I became part of a clinical trial for a new medicine to help my TIO. Now, I don't need to take my medicines all day long. I get one shot every four weeks. It's so much easier. I'm feeling a lot better. I can get around a lot faster now. I am more like before I had TIO. I'm feeling more like my normal self before I got sick. Even my friends and family are noticing the difference. They're having trouble keeping up with me now.

[Gale Smith] My name is Gale Smith. I am seventy-five years old. It's a pleasure to be here with my husband Roy. We live in Denver, Colorado. When I was born in 1942, there were no other cases of XLH in our family, and our daughter is the only one of our three children who has inherited it. And I might say, she has a pretty severe case.

I was diagnosed at the age of nine at Shriners Hospital in Portland, Oregon. Twice, I had both legs broken to straighten the bowing. The first one at age eighteen months, and the second, again, at age twelve. I grew more after each surgery, of course, so my legs bowed again. During my school years, I always got very poor grades in gym, because with bowed legs I was unable to run fast, or even very well. I always came in last, far behind the other girls, if I finished at all. When I was fourteen, our family moved from Portland to Los Angeles, and I was out of medical treatment for the next ten years, until our daughter was diagnosed in 1965. We both began taking Vitamin D and phosphorus together, and have been on it ever since. That's fifty-three years with the same medication, many times a day, as Jim said.

It's quite exciting now to realize that there is a new, and so much more effective medication to treat this disease. My first tooth abscess happened in my early teens. I've had many more since, so I'm missing teeth and have numerous root canals with crowns.

As an adult, I've always been physically challenged for stamina to keep house and raise our children. Back pain has caused bending over to become increasingly more difficult as years passed, which has made all of my duties more difficult. So my husband, Roy, does all of the heavy housework now, as well as the laundry, which is in the basement. I mostly take care of household clutter, cooking, folding of clothes, and dusting.

I was a stay-at-home mom while we were raising the children, but later worked as a switchboard operator at a hospital until I retired. It was during that time that I lost hearing in one ear, and now I'm losing it in the other. We have lived in our home in Denver for forty years.

I used to have four large flowerbeds, which I could care for quite well, after Roy did the digging. But as bending became more careful I had to sit on a stool if I wanted to pull weeds. Within a few years that became painful too, so I began sitting on the ground. By about age fifty, I could neither get down to the ground, nor get up again. So I began giving all my plants away, and letting my gardens die out. However, this year, I just had to get my hands into the dirt again, so we created small raised beds, by putting buckets on top of overturned trash cans. That brings my gardens up to my standing height, and involves no bending. I'm able to work on just a few buckets at a time.

The details of life changed dramatically for me, actually, in 2011, when I woke up one morning with numb toes. The numb, tingling, hypersensitive feeling in the skin crept upward almost to my waist over the next couple of months. It has caused me to become unsteady on my feet and my legs are weak. In 2017, surgery on my mid-back improved the hypersensitivity of the skin. However, my feet are still painful, my legs are still weak, and I'm going to need lower back surgery.

Because of these things, my world away from home has grown much smaller, and I do have psychologically down times of missing the freedom to come and go as easily as I used to. Because I am an avid reader, I fill my time with more books than I used to. Because leaving the house is a huge energy drain, I order the books online and Roy picks them up at the library. Almost all of my shopping is now done online, and the only stores I go to are the ones that have mobility scooters available.

My main concern at this time is for how well I will function in the future. Both my knees have been replaced and may need that again; I'm really hoping not to go through that. I am not on burosumab, but hope to be able to start it soon. My hope is that it will keep me from becoming wheelchair-bound.

[Athina Kinsley] My name is Athina Kinsley. I am living with XLH and was diagnosed at the age of seven. I am a spontaneous case. I have a son with XLH.

I would like to share a very difficult time in my life where I realized, as an adult, the medical manifestations of having XLH. I was raised in California and moved to Naperville, Illinois, in 2012, for my husband's job. I was not familiar with snow or ice. I fell backwards on our front porch steps in 2013. I was taken to the ER and told I did not have any fractures, based on x-rays. I was given pain meds and sent home.

My back and buttock area had continued exacerbated pain. I gradually started losing feeling in my right leg, and noticed my foot would twitch uncontrollably as I was putting my shoes. I could not open doors, get into bed without help. During the progression of my issues, I went to several different provider specialties to get help and answers. I had low-back steroid injections with no success.

During this time I was progressing to the worst. I got to the point that I had no balance and had to rely on my husband to hold onto for walking. I eventually went to a walker. After all the types of providers and treatments, nothing worked. I was depressed, scared, and desperate to get my daily functions back. I finally gave it one more chance, to see a neurosurgeon to get a second opinion. When I talked to the neurosurgeon and gave my symptoms, he gave me a foot test and really heard me. It was then he recommended a stat MRI of the cervical spine and thoracic spine. He received the results the next day, and called me to inform me that I need to see a neurosurgeon ASAP for surgery. He explained that I had a spinal cord injury in my thoracic spine region.

During this time I was in the process of moving back to California. I did my research and found a neurosurgeon in LA. In my search, I looked for someone that was highly credentialed with complex spinal conditions. He also was recognized as a humanitarian. I wanted someone that is good, but was also willing to listen. I went to my consultation with my MRIs and radiology readings. He informed me and my husband the importance of needing this surgery as soon as possible. I needed a thoracic laminectomy in my T7 through T10 area of the spine. He also indicated I would need a back brace during the healing process. I would plan on being in the hospital for three days. After my appointment I told my husband, "There was no way it will be only three days. I know I will be there longer."

I had my surgery, and ended up with a punctured spinal cord, lying flat for twenty-four hours in ICU. I was in excruciating pain, and was in agony even with the morphine drip. The rounding physicians would see me for the first day and a half, and I kept complaining to the level of pain I was in. They informed me that this is normal, and to manage it with the morphine drip and Tylenol. I was told that I would need to begin to get up out of bed and start walking. I could not manage to get myself erected out of bed to even go to the bathroom without help.

With persistent fighting and pushing, I was given a consult to a pain management specialist. She did the consult with me and informed me that with chronic pain sufferers, this is not abnormal to need something stronger than morphine. She immediately started me on dilaudid. As I began the medication regimen, I started to get up and go to the bathroom and work on getting physical therapy for treatment.

During the first few days of the inpatient stay, it was then that discovered that I needed to be transferred to inpatient rehab facility. My neurosurgeon informed me that he has never seen anything like he saw when he opened me up. He informed my husband and I that I have calcifications in my spine, and my spinal cord lining is hardened. He also informed me that there are floaties of calcifications in my spinal cord that he could not remove, and they are like little islands floating in my spinal cord. I did not need a back brace, due to the fact that my back has naturally fused.

I ended up being transferred to the hospital's inpatient rehab for four weeks, for occupational therapy, physical therapy, and pain management care. My husband was with me during this time. He understood the body mechanics, and helped me throughout getting out of bed and going through therapy.

This journey has taught us both that this disease, and the manifestations that occur, makes it more complex in the healing process, and a considerable process for therapy, pain management, and guidance with support. I continued physical therapy when I was discharged, and had to do that for months before I could even walk with a cane, or eventually, on my own.

As I continue through my aging adulthood, I will always know that I am my own healthcare advocate, along with my husband, helping me with the awareness of the complexities with XLH.

[James Valentine] Wow. I just want to say that it did really require the courage that Susan spoke about for you to get up today and share those stories. So please join me in another round of applause for our whole first panel.

DISCUSSION 1st topic

[James Valentine] What I have projected up on the slide are some discussion questions. They should seem familiar, they very much are similar to the polling questions that we asked you, and here we really want to dive in and understand which of your symptoms of hypophosphatemia have the most significant impact on your life. When we're understanding which ones do have the greatest impact, we want to understand why, and as part of that one way to think about it might be, is it because they have the greatest impact on those activities that are really most important to you, that you're not able to do or do as well because of your hypophosphatemia.

I'd like to start off this conversation broad, having it open up to whichever symptoms or health effects of hypophosphatemia might be most burdensome to you. And I'd like to ask you to raise your hand, and again when I call on you just provide your name, the type of hypophosphatemia that you have, and please share your experience of a symptom that is most burdensome to you and that follow up question of why.

So who would like to break the ice from our audience here today? We're seeking any range of the issues we've talked about, whether hip fractures, dental abscesses, stiffness, pain, whatever it is that has that impact on you most.

[Mary Anne Hardy on behalf of patient Elaine Jacobson] Hi, I'm actually here for Elaine Jacobson who lives with XLH, and she wanted to be on the panel but is not able to travel.

[Reading from written statement]:

Hello everyone. When I told my physical therapist that I was going to do this writeup, he jokingly suggested that all I had to say was, "hello, my name is Elaine Jacobson, I have XLH and it sucks." That about sums it up but I'm going to give you more details.

I've tried every treatment except the newest one, and the treatments are significant to the patient experience and contribute greatly to the social and psychological challenges presented by the disorder. This applies especially to those that significantly limit, interrupt or prevent one's participation in life. I've come to call these visits to medical land.

The first decade: It's interesting to note here that my mother had no outward symptoms and thus never even knew she had XLH until decades later when she was finally tested. My sister and I developed very severe bowing of the lower limbs. I was unable to stand, walk normally or for normal periods of time. I also had aching pains in my legs, probably bone pain.

Age 11 to 20: the severe bowing and problems with standing and walking continue. I develop a kidney stone from one of the treatments that I started during this period. These include continued need for braces, parathyroidectomy, massive doses of vitamin D, and a long visit to medical land for many osteotomy surgeries.

Age 21 to 30: thanks to the osteotomy surgeries I had some very good years here. No more braces, I could dance, I could wear non-orthopedic shoes, even clogs, I went to graduate school, becoming a professor of mathematics, and could climb the four flights of stairs to my office. But by my late twenties, even though I weighed only 95 pounds, I was unable to walk. It felt like my muscles were yelling no more of this. The progressive decline had begun. I never got back to my best days from this point on.

More symptoms in my thirties include vertigo attacks and hearing loss. I also start to need a wheelchair. At first I could use a manual wheelchair, but by my late thirties I could no longer do this and had to switch to a power scooter. I also had to revamp my career plans from professor to researcher in the commercial world where I could work sitting at a desk.

Age 41 to 50: The vertigo attacks get much worse and my physical functioning is slowly ebbing away. Weakness begins in my neck and arms, it gets harder to go to work, shower, dress, cook, and get in and out of my scooter or the car, be comfortable without pain in various types of furniture or environments, participate in activities outside the home, and in general have enough stamina to get through the day. I can no longer drive. This progression is gradual like watching grass grow. Eventually you know something's happening but going to many doctors, even XLH experts, doesn't help much. So as usual I simply adjust to the changes and keep on going.

Age 51 to 60: now progression goes into overdrive and then off a cliff. By my mid-fifties my arms, shoulders and upper back suddenly become so weak I can barely lift my arms at all. I cannot pick up a piece of paper, write, steer my scooter or do much of anything. Within a year, the muscle weakness is affecting my whole body. I find a good physical therapist whose individualized treatment keeps me going a few more years while I'm hanging on by my fingernails to keep working. And I'm developing more and more joint pain, muscle pain, not bone pain, and weakness, fatigue, hearing loss, vertigo attacks or dizziness with brain fog and loss of functional mobility.

Age 61 to 70: I've given up hanging on by my fingernails and retire on disability early in my sixties. I no longer have to visit medical land, I live there. Actually I'm in jail since I'm home

bound. I cannot perform or have trouble with almost all the basic activities of daily living and I can't do independent things such as shopping, meal preparation, etc. I use hearing aids. My hearing continues to worsen. I cannot watch TV as it makes me dizzy. I can barely use a computer or read for the same reason. And accessibility features on devices are still difficult. I only go out for medical appointments and almost always in an ambulance stretcher. So, I'm, now worried about having to live in a long term care facility in the future.

[JV] Sure, well thank you very much for sharing Elaine's story, and Elaine, if you're able to tune in by the webcast or you're seeing this as a recording, thank you for sharing your story, I think it's really a powerful description of the progression even in adulthood itself, and so, I would encourage you ... I think that might be a nice way to think about this is what might have been the thing that impacted your life most in your twenties and how does that compare to what is impacting you most now.

[Nancy Alauzen] My name is Nancy Alauzen. I have XLH, I just turned 60. When I had my osteotomies to correct the bowing I thought that was the end of it, but really the two things that have impacted me most over the last ten years, fifteen years, have been the hearing loss and the dental issues. And I've heard someone mention something about feet, and that's something I want to ask, maybe this isn't the right forum, but I find myself tripping over my own feet, I went to a podiatrist, they did some stuff, my massage therapist works through the stuff on my feet, and, but ironically, I didn't know this until I was fifty, that my feet are deformed too from the XLH. That was like a revelation at age fifty!

[JV] Quick follow up question for you, you mention that now the things that impact you most are hearing loss and the dental issues. Why is that that they now are the things that you're saying are the most burdensome?

[Nancy] The most worrisome?

[JV] Burdensome.

[Nancy] Burdensome.

[JV] Based, the most burdensome.

[Nancy] I mean the hearing loss, I quit going to movies just because I couldn't hear. Ironically, I've been probably wearing hearing aids for like thirty years, but I finally in the last year won some, bought some that are just wonderful. This morning before I put them in, I think my TV in my room was like fifty-five, when I put them in it was down to fourteen, so they're really kind of amazing. I still miss a little bit, and the dental issues it's every four months, which I'm sure everybody here can relate, so, that's my story.

[JV] Thank you so much.

[Carol Knight] Hi, my name's Carol Knight, the two things that impact me the most are kind of one blended into the other, and that is my bone pain and my muscle pain and stiffness. I'm

blessed to have a sit-down job and to work at home, but even when it's time for my fifteen-minute break, I've only been sitting, only, two hours, and when I try to stand up the muscles in my back, my lower back in particular, just tighten up like they're spasming, and I have to stand still for a few minutes just to get my back to straighten up so that my legs can engage so that I can walk to the bathroom for example. And then, as I'm walking, the pain in my ankles or my knees or my hips or all of the above causes me to stumble. It's like they're catching on something and not flexing, so I stumble. So I often use either a cane or a walker, sometimes a wheelchair. But the two things that are most detrimental for me are the muscle pain and back pain kind of combined together.

[JV] Thank you, Carol. Has that been a pretty steady issue that you had or has it been more recent?

[Carol] I've had the bone pain for as long as I can remember, even four or five years old, but it has gotten progressively worse. The muscle pain started probably about ten or fifteen years ago, and it's gotten severely worse.

[Ann] I'm Ann Lewis from Connecticut. My daughter has XLH. She's thirty-eight. She was diagnosed at Yale when she was two. Pain, pain, pain, pain, pain, has sucked the life out of her, a vibrant independent young woman, intelligent, educated, and she's now diminished so she has to live with her mother and father because she can no longer function.

What was the difference in her twenties and now? Her childhood was beautiful. She had doctors' appointments and a lot of medication, but the pain didn't start until she was in her mid-twenties. She tried everything, bee venom therapy, yoga, guided meditation, for those of you who don't know what that is, you hold on to crystals and they blow smoke in your face, to try and pretend the pain isn't there. They finally put her on steroids and it was beautiful, she had two beautiful months until her kidneys started to shut down. Medical marijuana didn't touch it.

I want to talk about the big elephant in the room here, is the new CDC guidelines, which are now interpreted as law, are preventing doctors from treating pain adequately. They're scared, they're being forced to diminish treatment for patients in pain clinics, it's not adequate, it's not fair, it's not legal, it's not right. My daughter is on the trial and that's questionable whether that's going to continue because of getting kidney problems. So what is she supposed to do? They're giving you the choice between taking illegal drugs and you're going to run into Fentanyl and that will kill you or commit suicide. I want to talk about suicide, that's what I want to talk about. I'm sorry if it's uncomfortable, her life is uncomfortable. Pain has cost her everything, jobs, relationships, children, everything, so where do you want to go with this?

[JV] You know, I think that's actually an extremely important perspective to share, your daughter, the impact that pain has had on her life. Is she ..., can you help me, paint a picture of that for me? You said she was very vibrant, was educated, successful.

[Karen Lewis] I can. I'm right here.

[JV] Oh, you're, this is you.

[Karen] I'm Karen Lewis.

[JV] Hi, Karen.

[Karen] I'm an autosomal dominant case. I think I maybe took an aspirin once every six months as a kid, totally normal childhood, couldn't run the mile in gym class but that kind of ruled, so I wasn't really complaining about that. It wasn't until I turned twenty-eight, and I don't know what it was, it was a switch flipped one day. And then it never got better, it's only ever decreased, and I was always told like you could do whatever you want, go to grad school, blah blah, so I decided that I wanted to do a physical job which in retrospect was stupid, but I'm a stage manager for music festivals and I was for fifteen years. I can't do that anymore. I set myself up to do big physical things because I was told that there were no limitations, you'll be over this when you're done growing, don't worry about it. So I was like, okay. So busted my butt, took all these crappy internships, eventually got recognized by the Grammys, got to do Lollapalooza, like really worked hard and now it's gone.

[JV] Now what is it that--

[Karen] Now I live with Mom and she has to help me put my bra on sometimes. It's really fun, so glad I went to grad school. Now my life revolves around, like can I walk my dog today, that would be cool, and when is my next dose of medication because the pain comes before the, you know, before the medication has run its course. So, that's...

[JV] Where is the pain, is it bone pain, muscle pain, what part of your body?

[Karen Lewis] Oh it's bone pain. My right hip, the head of my femur has been broken since February 2013 and there's sort of not a lot they can do about it at this point. Explored a whole lot of options but there's really nothing they can do. So it's hip pain, knee pain, ankle pain, feet pain, back pain. And the fatigue as well. I nanny sometimes, like four hours a day is about max I can do, so like Kelly [Topic 1 panelist] I've chosen not to have children because it's not fair and that's the one thing I get emotional about as well.

[Ann Lewis] We belong to a national organization called Don't Punish Pain. It's a grassroots project, it just started this spring, it's non-profit, we don't accept donations, it's trying to give doctors their power back to treat us instead of folding under the guise of the CDC guidelines. The rally's coming up, if you go to the website www.dontpunishpainrally, you'll find it. If there are medical people in the room there are ... there's a doctor's collaborative there too. We want to support doctors and let them treat at least this part of the disease.

[Natascha Allen] My name's Natascha. I just turned thirty last year and up until thirty I felt like I had a very, very mild case of XLH, it wasn't even really in my mind when I was picking my career, anything. Almost right after I turned thirty I started getting really bad pains in my knees, and I went to the doctors and I've had an osteotomy that went bad and I haven't had it fixed yet but it's rebowed, my leg's rebowed. And I need double tibial osteotomies now, and I can't keep a job. I just got married two years ago so my husband and I have been trying to get off the ground, we bought a house, and now that all these medical things have come up, losing my job, having

health insurance. It's really hard to have health insurance when you can't keep a job, and my husband just changed careers and doesn't have great insurance and so, I think the financial burden of it causes a lot of stress and losing everything because of the disease. And that's my biggest fear, is that I'll lose my ability to have kids and that the surgeries won't go well because you hear so many times that you've got the rebuilding and things like that. So just the stress of everything I think has affected me a lot more than, I mean that's affected me a lot mentally.

[JV] Sure.

[Natascha] Yeah, so.

[JV] These are very important aspects of living with hypophosphatemia to share, not only the direct, ...

[Natascha] Yeah.

[JV] ...physical burden, but the emotional,

[Natascha] So much mental.

[JV] ,, mental burden as well,

[Natascha] Yeah.

[JV] So thank you. And you also mentioned things that worried you the most about your future and I want to encourage people to also share their concerns as part of this discussion.

[Robin Courtney] Hi, I'm Robin Courtney, I am the mom of a twenty-six-year-old who has a sporadic case of XLH. We live in Florida so we flew to Saint Louis Shriners Hospital twice a year for fifteen years to have him treated, because we couldn't find a physician in Florida that had really taken care of anybody. We went with one endocrinologist to start and he said, I've seen one case in twenty-five years, so we'll just treat it the same way. So he was on medicines at eighteen months old, eight times a day, taking a powder, and you know, everybody's been through it probably with their kids. So he's twenty-six years old now. He did pretty good. We kinda gave him two choices: "Honey, it's not going away, so either you embrace it and try to figure out how to live with it, or you be miserable because it's going to be problems. It's just part of this disease unfortunately." So he did pretty good. He was able to play lacrosse in high school. He was the slowest kid on the team, but his high school coach was nice enough to keep him in there until his senior year and then he said he was too embarrassed because he was too slow to do it. He managed through. I don't know if anybody else had Arnold Chiari syndrome, which is not uncommon with some of these XLH kids. He's had brain decompressions and he's been through challenges, but he is in the middle of medical school right now and that's why he couldn't be here. But one of the things he asked that I would please communicate is the bone pain. He's got the joint pain, the stiffness, the muscle pain, and the other thing that isn't brought up and I don't think your medications can help, but short stature, you know that's, at least for some boys especially, that's a big deal, so that was probably his number two issue with it. He has

changed his type of medicine that he's decided to get into. He thought he was going to be anesthesia or surgical, but when he was rotating he realized there's no way that he can stand as many hours. So he's decided to go to emergency medicine where they let them sit to talk to the patients. So that's probably been the biggest impact and it's getting worse. At twenty-six now he's noticing it's getting progressively worse. No sport. As far as team activities he just can't keep up with kids his age, but he does do a lot of gym, so he's a weightlifter and he tries to balance it to try and keep that mental health that goes along with the issues that you have with a chronic illness. So he's trying to balance it that way, but I just heard about the new drug for adults, so I said I'm coming and I'm going to listen to it, and we're going to see about getting you on it because, you know, you need to be on something to help him get through this.

[Sunindiya Bhalla] My name is Sunindiya Bhalla and I'm on the afternoon panel so I'm not going to share my story right now, but one of the things that's really striking me as I sit here is that it's so nice for me to hear from people who are in their late twenties, early thirties, late thirties. One of the most isolating things is to be in this age range, be a Gen-Xer or whatever you call it. We're the forgotten ones when it comes to XLH. I've felt that way for years. There's so much for the children, and when you're an older adult you don't get told you can't have a hip replacement or a knee replacement because you're too young. But then there's this group of us who ... no one tells us if we should have children, what we can expect, how to take care of our bodies. There's just been no support or treatment for us, and so I appreciate everyone telling their stories.

[Sandy Briscan] My name is Sandy Briscan and we're some of the Pacific Coast people. My main problem, because I was born with it ... my mother had it and she was spontaneous ... I had it and before I knew what was going on I had children and now they have children and now I have great grand children. So I'm along with the ones that are over the seven number. But anyway, I think one of the most disastrous problems we have is that we can't get medical care in the Pacific Coast. I did the Sacramento, San Francisco searching all of my life and now I've moved to Montana. I hide in the woods, which everybody teases me about. That's my choice with my husband to be rural. I've had more care and attention from this little rural doctor that lives where we are than I ever have. The insurance for instance in Sacramento that my daughter has: they sent her to UC Davis. I went the whole UC Davis route. They always tell you they know what's going on. None of them have a clue. San Francisco I was at Shriners San Francisco since my children were tiny. They did more damage to my son. My son actually passed away from poor medical care, some of the things they did. So how do we find people on the west coast that can help us, that's my big question, I mean, it's not like we're not trying. I've been as far as Salt Lake now, been to the university hospitals, gone to many orthopedic doctors and endocrinologists. None of them pay attention, and I'm sure all of you know that feeling, but it makes you crazy after a while. I had two parathyroid glands that had huge tumors on them. I needed them removed because I was having terrible problems with my parathyroid and the doctor in Utah recently diagnosed me with vertigo because he wouldn't take out the parathyroid glands. That wasn't the problem. So I got them done somewhere else by my own research. I just need to know how do you go about finding somebody that knows what they're talking about?

[JV] Hopefully one of the goals of today is by sharing your experiences and not only with the disease but especially in the afternoon session we'll be talking about approaches to treatment or

lack of treatment for particular symptoms and burdens, what really are the unmet needs that you have. That information is going to allow the XLH Network to help not only the people that we have in the room today be better educated about these issues, but be able to advocate more broadly. And that includes with the healthcare system, so thank you for sharing. I want to encourage everyone to keep sharing their own experiences because that's what it is that's going to help really educate the entire system.

[Kelly Rushing] My comment is more about the burden of care. It seems that my XLH has progressed as I've gotten older, and it's more about the burden of care for me or my husband and the impact it makes on our relationship. The more my physical demands are on him, or the more things that I can't do, the more stress it makes on our relationship, and surely we're not the only ones who have that.

PANEL 2

[Introduction by James Valentine] Now we want to explore with all of you, what are the different treatments that you utilize to try to help treat and manage and live with those various symptoms and burdens, as well as what are some of the downsides of those various treatments? So I will invite my second panel up onto the stage. In this topic, when I refer to treatments, I mean that in a very broad sense. Not only do we want to hear, of course, about medicines that you might use, whether medicines to directly treat your condition, or medicines that you might use to treat and manage certain symptoms that you are living with, but also surgeries, other medical procedures, also medical devices that you use, perhaps mobility assistance devices that you utilize in daily life. But also think even more broadly than just medical products. This might be different techniques that you use in daily life, whether it's an exercise regime, a diet, really anything, even like a lifestyle modification that just helps make your day a little bit easier. We really want to hear about this whole range of things, approaches that you use to treat, manage, and live with your condition. As you share each of those things and our panel shares each of those things, we're going to ask you to tell us how well those things are working. What are the downsides? And ultimately, looking toward the future, short of a cure for your condition, what specifically would you look for from a future treatment? So we want to know really, what's that gap that's left? Given everything that you do have, what is it, looking towards the future, that you would most want? And try to be as specific as you can in explaining that, since we're talking about things that are short of a full-blown cure. So to get us started on this topic, we have another great panel for you. We have Sunindiya, Billy, Gin, Brent, and Theresa who are going to share their experiences and preferences. And I'll go ahead and turn it over to Sunindiya to kick it off.

[Sunindiya Bhalla] Good afternoon. My name is Sunindiya Bhalla. I am thirty-six years old. I live just outside of Boston, Massachusetts, and I am the senior director of community impact at the United Way of Massachusetts Bay.

I was diagnosed with XLH when I was sixteen months old, after spending months in the hospital because my parents noticed that I was very bow-legged and not walking straight. I am a spontaneous case. I have taken medication to manage my XHL ever since I was diagnosed. I say manage instead of treat because there has been no treatment from my perspective until recently.

For the past two and a half years, I've been on burosumab, the recently approved treatment for XLH. It is different from other medications that have been available in the past because it is not just supplementing the vitamins and minerals missing from my body, but is preventing my body from getting rid of them. So it feels to me that it's getting at the root cause of the disease, my body's overproduction of the hormone FGF23.

Until I started burosumab, I was taking active vitamin D and phosphate, which were constantly being fine-tuned throughout my life. As a child, I could not stomach the form of phosphate that was available, so my parents drove down to New York once a month to get a medication that was shipped all the way from France called Foslymar. It had to be dissolved in water and tasted horrible. For many years, I had to take this four times daily, being called out of class, and therefore singled out in school, skipping doses whenever I could get away with it.

Because of my XLH, I missed a significant amount of school for appointments and surgeries, and while I kept up with my schoolwork and was fortunate to be surrounded by caring and compassionate adults and peers, I was bullied, almost did not graduate because I did not fulfill the physical education requirements, missed graduations and special events, and had to find new hobbies and interests that were less physical. I also had to look for a college that was near enough to my doctors.

During early adulthood when I stopped growing, I stopped treatment. However, the pain was even worse as I started to get calcifications and enthesopathies, develop arthritis, and I quickly resumed my treatment. I now have the added stress of being my own advocate, managing my own medications, and having new physicians who knew little about XLH as I transitioned to adulthood.

Around this time, I found the XLH Network, which ultimately led me to burosumab. Although burosumab is not a cure, nor does it reverse the impact the disease has already had on my body, it is definitely controlling my XLH. For the first time in as long as I can remember, I have moments of being pain-free. Since being on the drug, I haven't seen significant progression in my disease. This is confirmed by how I feel, what I'm able to do, and by x-rays.

In terms of the physical aspects of my current treatment, I have yet to encounter many downsides. One significant downside is not knowing about any long-term side effects and what to expect. However, I am willing to take this risk since this disease is all about not knowing what the future will bring.

Along those lines, stress is a constant downside of this and any treatment for XLH. It is really stressful navigating things like building my career, while needing high quality and comprehensive health insurance coverage to be a strong factor in any decision I make. I struggle with how and when to discuss my disease with my employers, often waiting until I have no choice and need surgery again, not wanting my XLH to define me. All of this is in addition to the increased complexities of someone living with XLH and navigating relationships, wanting children, and everything else that comes with living my life.

The most significant thing I look for in managing my XLH is pain management. XLH is not a

visible disease, nor is it life-threatening, but it is chronically debilitating and life-altering. One thing I've learned as I've met more and more people with this disease is that we have a high tolerance for pain. That does not make it okay for us to have to tolerate so much constant pain. I will randomly wake up with excruciating joint pain when osteophytes dig into my muscles in my hips or knees. I know I need knee and hip replacements, but I'm told I'm too young, so I work through this pain as best I can.

I have an uncanny ability to know when I need to listen to my body and see a doctor. I'll often get an urgent call after an x-ray or MRI from a radiologist who looks at my spine and thinks I should go to the emergency room ASAP because my spinal cord is about to be crushed. For the first time in my life, I found myself going against medical advice. Fortunately, since starting burosumab, I now have a physician, Dr. Insogna, who is knowledgeable about XLH, trusts me, and takes me seriously, does not jump to conclusions, is collaborative and willing to take some risks, and who is eager and willing to learn with and for me.

I hope that future treatments can more significantly stop the progression of this disease, and even reverse some of the painful effects. For someone like me who cannot take stronger pain medication than ibuprofen, pain management is crucial. Being on this drug has opened my eyes to the complexities and benefits of the medical and pharmaceutical industries, and the infrastructure we have here in the US, and how committed these industries are to find treatments and cures for people like me. Thank you for letting me share my perspective.

[Billy Branch] My name is Billy Branch. I am fifty-six years of age and a typical case of X-Linked Hypophosphatemia. I acquired this condition from my mother, who has dealt with this debilitating disease for seventy-nine years and continues to struggle daily. I am sorry to say that now I have passed this condition to my daughter, who will inevitably pass it to my grandchildren.

As a teenager, I was diagnosed with hypophosphatemia, but was never started on a regimen of medications. I experienced some issues with bone pain and I tried playing sports, but due to the bone pain, I was not able to continue. After high school, I joined the Navy, and still my XLH was left untreated. Despite the pain of physical limitations, I was able to get through six years of physical training, the demands of being in confined quarters, and working as a mechanic in the engine room. I now remember this time when I was working below the deck plates of the ship. I had to spend extra time lying on the deck because I was in such a tight space, and I became so stiff, I could barely move. Somehow I managed to get myself out of those tight spots and to continue to move forward in the service.

It wasn't until after my years in the Navy that I started experiencing more issues that were related to XLH. Again, I tried playing softball, but after one particular game I could barely walk, and the next morning was hell. It was after this incident that I found an endocrinologist that was able to prescribe calcitriol and phosphorus. The large doses of phosphorus cause terrible stomach issues and so I had to reduce the number of doses. When I reduced the number of doses, I felt that I wasn't getting any benefits from the medications, so I quit taking them.

It was in my early to mid-thirties when the symptoms became unbearable. I couldn't drive long distances due to the pain and stiffness. I could only drive for an hour or two before needing to

stop and change position due to the pain and stiffness in my hips. A four-hour road trip could take six hours and with young kids, it seemed even longer. Are we there yet?

During this time, I started having trouble walking. After thirty minutes or more, when I stood up and tried to walk, I had excruciating pain in the Achilles tendon area of my feet. I had to find the problem, and that led to finding an orthopedic surgeon who, after examining my x-rays, recommended I get back on my meds in preparation for my upcoming surgery and the healing I would need to do.

I had calcium depositing into my Achilles tendon and every time I walked, it rubbed against the tendon causing it to deteriorate. The need for surgery was urgent, as my doctor was concerned my Achilles would snap. I first had to get through a trip to Disney World with my daughter that I could not delay. I wore a walking boot to immobilize my right foot and to prevent any further damage to my Achilles throughout Disney World. Once I returned, a plan was formulated to repair my Achilles by removing it, grinding the calcium away, and reattaching the Achilles. This process did not work, as the calcium started returning quickly. One more attempt was made to clean the calcium out and again it did not work. The third time, a surgeon decided to do an FHL transfer, which did work. If you don't know what this entails, please look it up. It's no fun.

After two surgeries for the same issue on my left foot, I was finally able to get around, although there are still days when I can't help but limp. While recovering from surgery, and a period afterward, I was on two to three Vicodin daily just to be able to move. I had five surgeries in two years. This included three stints of eight weeks at a time in a cast, multiple walking boots, and along with months of physical therapy.

After I hit my thirties, the issues and procedures just seemed to keep coming. I had to have my thumb fused together because I could barely hold a pen. A lateral release on my kneecap due to calcium scar tissue binding my kneecap up after an accident. There was a time when I stepped in a hole and fractured my femur. I had no idea I'd fractured my bone. I just knew it hurt. As with many of my fellow XLHers, the tolerance for pain is very high, and we grow to expect it daily.

Approximately ten years ago, I heard about a clinical trial for burosumab, or at that time, KRN23. I didn't know if it would help me, but I wanted to give it a try in hopes that it would help my daughter and the rest of future generations. I was in the initial study and have continued participation and have just completed the final phase a month ago. There were times when there were delays in getting to another phase of the study and my body would let me know I need to get back on meds.

When I first started burosumab, I only had minor side effects, such as terrible back pain. There were times if I jarred my spine, or even just initially lying in the bed, I would get excruciating pain until I felt a little pop, and then it would subside. After several injections, that all disappeared, and I didn't have any other issues.

I hope that continued study can be accomplished to figure out how to alleviate some of the other issues with XLH, one being teeth issues. This has always been a big and expensive issue for me and hope some studies can be completed on this issue as well.

I am worried that insurance won't pay for these meds and that is a fight I'm having right now. I need to make sure that my daughter has access to burosumab so she can lead a normal, or as normal of life as possible.

I never knew how bad I felt until I felt better on burosumab.

[Gin Jones] My name is Gin Jones. I'm sixty-three and I have spontaneous XLH. I lived through the whole range of approaches to treatment, starting with massive doses of vitamin D, plus calcium in the 1960s, and then a brief stint with phosphorus and calcitriol. Nothing helped until I started the clinical trial for burosumab.

Despite the ineffective treatment, my childhood symptoms were not terribly bad. My legs were not visibly bowed, and while I was short, I was still taller than many XLHers, due to my extremely tall parents. I was taken off treatment. such as it was. at the age of sixteen.

What wasn't visible then from the outside was the weakness in my bones and muscles. As time went on, my body deteriorated. I first sought adult treatment in my late twenties, when I developed serious knee pain. The osteoarthritis and osteomalacia were diagnosed, but there was no effective treatment so the damage continued to progress. Of even more concern was something I didn't even know was happening. My soft tissues, ligaments, and tendons were calcifying. This is, and continues to be, the most debilitating symptom for me, with much of my spine so calcified ...you can probably see ... that I can barely move my torso or my neck. I also have calcifications in my feet, knees, hips, and they all affect mobility and range of motion.

Between the mobility restrictions and related pain and fatigue, I was unable to continue working as a lawyer, which is generally not a physically demanding career, but I had to stop by the age of fifty-three, and had only been able to work part-time for ten years before that. So it was fairly restrictive of my career.

There is no current treatment that can reverse these calcifications once they occur. It was once believed that phosphorus supplementation might help, and as a result, I went on treatment in my late forties, but I couldn't tolerate it. Phosphorus supplements, as others have mentioned, are known for causing gastrointestinal distress. In my case, even the lowest dose of the phosphorus, which Dr. Insogna was always telling me wasn't clinically significant, still caused such serious gastrointestinal pain that I thought I had appendicitis. Keep in mind that I've had a broken arm and didn't even realize it, and it didn't bother me. So it takes a lot for me to notice pain. So I persisted with an extremely low dose of phosphorus in the hope of stabilizing my calcifications, which didn't happen, and over just a few years, the supplements kicked my parathyroids into high gear and I needed to take yet another medication to bring the parathyroid levels back to normal.

It appears that burosumab can at least stop the progression of these calcifications. It just can't reverse them.

At age sixty, I started in the phase three trials for burosumab, which normalized my phosphorus levels, and seems to have halted the progression of calcifications. I used to have spinal spasms

that would literally paralyze me, leaving me unable to breathe for a few seconds whenever my spine was jarred. Like when I hit a pothole, was hugged by a friend, or simply turned over in bed. I no longer have those spasms and can do a lot more in a day before my fatigue and pain kick in to stop me. Unlike with the phosphorus supplements, I haven't experienced any significant side effects with burosumab. The regimen is simple, with a single dose once a month.

I am, of course, grateful for what burosumab is doing for me, but it can't undo the existing calcification and joint damage from before I started the treatment, and the challenge for the future is that by the time adult patients notice the calcifications and seek out treatment (and remember we deal with pain pretty well, so we often delay treatment), by the time that happens, significant damage has already been done, and it's too late to treat them effectively. The only way to prevent the calcifications is to go on effective treatment *before* they form, and it's still not known for sure whether even the best current treatment will be effective in stopping them. While burosumab is a life-changing improvement over both the earliest ineffective treatments of my childhood and the more recent marginally effective treatments with phosphorus, there is still more work to be done. We're getting closer to the source of the problem, but it's still not currently known why it is that the genetic mutation leads to the excessive production of FGF23 or why the tumors create excessive production of FGF23. If that process were better understood, a treatment might be developed to prevent the overproduction rather than simply blocking it once it's produced. And that, of course, is the ideal treatment, a cure, something that could be done once allowing the patient to live a normal life without the need for ongoing treatment and dealing with insurance issues.

Short of a cure, the keys to an ideal treatment, I believe, are 1) it enables strong, straight, properly mineralized bones that are less prone to osteoarthritis, 2) it prevents calcifications, 3) it enables proper dental structure to form, 4) it provides adequate phosphorus for muscle function, and, 5) it doesn't trigger hyperparathyroidism or nephrocalcinosis.

We've come a long way since the 1950s, but there still needs to be work to be done in making the whole life, whole body treatments more effective and less burdensome.

[Brent Davidson] My name is Brent Davidson and I turned forty in March of this year. But if you were judging by my x-rays alone, you'd probably think I was in my eighties.

My birth mother, several of her siblings, and her father all had XLH. I was adopted immediately after birth and though my birth mother informed the adoption agency that I would likely have XLH, the adoption agency unfortunately decided that the rarity of the condition was a potential breach of anonymity and chose to withhold the medical information from my adoptive parents. They were simply told I might have an inherited vitamin D deficiency and would probably need a supplement.

It was not until I started walking and my legs bowed that I was finally diagnosed with what was at the time called vitamin D resistant rickets by Shriners Hospital in Houston, Texas. It wasn't until my biological mother managed to track me down around 2010 that I learned the term X-linked hypophosphatemia, or XLH.

Through the years, I've dealt with multiple problems resulting from XLH, including many dental abscesses, spinal stenosis, hyperparathyroidism, bone spurs, soft tissue calcification, chronic bone, joint, and muscle pain, and limited range of motion in my back and legs. I wore leg braces for several years as a toddler to correct the bowing that occurred before the medications were started.

Growing up, I was treated with calcitriol and phosphate supplements. Initially, the phosphate was in the form of Fleet Phospho-Soda. My parents learned when I was a baby that the easiest way to get the medicine down me was to measure it in a syringe and squirt it down my throat. As I got older, we continued to use a syringe as a convenient way to measure and transport individual doses, which made for many embarrassing conversations with friends and teachers once I started school and had to carry my noon dose with me.

I was eventually switched to K-Phos tablets, which made the dosing much easier and more palatable, but still caused relentless gastrointestinal issues. I always dreaded the first day of school and explaining to teachers that if I had a stomach attack, I wouldn't have time to ask permission before heading to the restroom. Most of my teachers were understanding, but it was still upsetting every time I'd feel that rumbling, cramping feeling in my stomach and having to jump up mid-lesson, head for the restroom, grab my backpack on the way out the door, just in case I need the spare set of clothes I kept with me.

In addition to the digestive issues, calcitriol and phosphate therapy was always a delicate balance between receiving enough medication to keep the XLH under control and keeping the dosage low enough to prevent runaway parathyroid enlargement. My parathyroid levels began to rise to the point that calcium was being removed from my bones. Medication dosages were reduced to try to compensate, but my XLH then became more active and my legs began to bow again, and my parathyroid levels continued to rise. In 1986, before starting fifth grade, I had my first parathyroid surgery.

Since that time, I've had 12 more surgeries to correct problems caused either directly by XLH, by side-effects of treatments of XLH, or by incorrect treatment prescribed by doctors unfamiliar with XLH. The doctors at Shriners Hospital in Houston did an excellent job with my treatment, but since reaching adulthood, it has been a struggle to find a doctor who has even heard of XLH, and the few that have, most only recognize it from older papers they read during medical school.

While calcitriol and phosphate therapy seem to have done an adequate job of facilitating proper bone development, there were many symptoms it could not treat, and the side effects range from inconvenient to potentially dangerous. I've already mentioned the numerous surgeries I've undergone and the digestive issues. I also have continuing dental issues. The majority of my adult teeth have abscessed and have either been root-canaled or pulled and replaced with implants. I began walking with a cane before I turned 30 and have had to deal with moderate to severe chronic pain throughout my body. There's also the emotional toll, the frustration and anger at my own body when it refuses to cooperate with projects and activities my heart and mind choose to undertake.

Fortunately, time and technology have given us burosumab. I've been taking burosumab since the first open-label human trials. Since starting burosumab, I've gone from needing the 0.75

microgram per hour fentanyl patches to keep my pain marginally bearable to needing no pain meds apart from cyclobenzaprine for muscle spasms and duloxetine for nerve pain, both of which stem from spinal stenosis. It's also enabled me to increase my physical activity enough to have lost forty pounds, and thus stand to resume my hobbies. This January, I finally retired my cane, at least until bone spurs around the base of my little toe and my right foot tore through the plantar fascia last Friday while moving some file cabinets.

All those changes have come without any side effects for me, and for someone who has lived their whole life dealing with XLH and the side effects of traditional treatments, burosumab is truly a welcome change. But there's still work to be done. Burosumab requires a doctor or nurse visit for administration. Self-administration would be much more convenient. Burosumab can't reverse the abnormal tooth development that causes our dental issues, and we don't yet know if it'll lessen those issues for children.

An ideal adult treatment for XLH would be able to reverse the spinal stenosis, bone spurs, and other physical deformities that go along with XLH. There's also still data to be collected to determine whether burosumab will lessen the impact of XLH on adults who were treated with burosumab as children.

Compared to treatments of the past, burosumab is a giant leap forward, but it's just one small step on the long road to complete understanding of and ultimately a cure for XLH.

[Theresa Harnar] My name is Theresa Harnar. I was diagnosed with XLH when I was nine years old. My parents were concerned because my legs were extremely knock-kneed and they took me to Children's Hospital to find out why.

Calcium and phosphorus pills were the standard treatment in the 1970s, and I took those several times a day, along with wearing straight leg braces at night and eventually at school. I hated those braces because they made me look different than all the other kids, and it was always a fight to make me wear them. Eventually, I stopped wearing them and just took the pills.

When I was fifteen, I had surgery at Shriners Hospital in St. Louis to finally straighten my legs. Growing up, I played softball and basketball on our small town leagues. After my operation, a friend told me how her mom thought I was so brave to play in front of the whole school when my legs looked like that. I was shocked. That was the first time I realized how different I must look to people. Of course, I knew I was different. I was much shorter than everyone else and didn't have a lot of stamina. Gym class did a great job of pointing that out. We would strength train by jumping on and off the bleachers and I was allowed to jump on the lower step since the seat part where everyone else jumped came all the way up to my thigh and I couldn't jump that high. I also was the only kid who didn't have to run the hurdles. They came almost to my shoulders. I was allowed to run beside them, and at the time, I thought it meant I was lazy and weak, and I realized later it was just a physical impossibility. You can't jump over something you can walk under.

I've always had pain. Growing up, my knees would hyperextend if I did nothing more than stub my toe. There was nothing I could do, but sit and hold my leg until the agonizing pain went

away. Then I would get back up and continue the game of tag or whatever I was playing.

In my twenties, the waddle in my gait became very pronounced. I would swing my legs around instead of pulling forward with my thigh. I couldn't understand why at the time. I know now that XLH affects my muscle tone a lot. Even though I walked and exercised consistently, my muscles just weren't strong enough to support correct walking. The waddle caused pain in my hips and back and really affected my self-esteem.

By the time I was in my thirties, working and doing common household chores were becoming difficult. I was having more pronounced symptoms of XLH. There was bone pain, constant ringing in my ears, pronounced fatigue, multiple stress fractures, dental abscesses, and one episode where my leg muscles refused to work correctly.

I had gone off treatment when I was twenty-one. At the time, the doctors thought most people did not need treatment once they reached adulthood. I even put off looking into treatment or resuming it for as long as possible. I was willing to deal with the issues because the side-effects of using K-Phos and calcitriol tablets scared me. They were kidney stones, calcification of your organs, and renal failure, and that was very scary.

I finally sought treatment in my forties when my legs stopped working correctly and I was using a walker and a wheelchair. Within two weeks of starting treatment, my muscles responded and I was walking again. The pills dealt with the most severe symptoms, but I still had a waddle, muscle weakness, bone pain, and ringing in my ears.

I've been on the drug burosumab now for several years. Most of my symptoms are gone. The biggest improvement has been in my muscle tone. I no longer waddle or have back pain or get fatigued easily. I'm able to work a full day and walk several miles without distress.

Some of the things the drug still does not address and that I deal with are the extra bone my body made and deposited in random places in my neck and back, the ringing in my ears, and the things that can't be undone, my short stature and my teeth that had to be pulled because the bone was too weak to hold them in, or they were infected because the dentin wasn't mineralized correctly and bacteria got into the root.

There are two areas I struggle with in managing my disease. One is the cost of treatment. This disease requires ongoing medication and ongoing monitoring through doctor visits and lab work. Co-pays, deductibles, travel to a specialist, and other out-of-pocket expenses add up quickly.

The second is finding a doctor who knows about or is willing to learn about XLH. I've had doctor's offices tell me that their doctors do not talk to specialists outside their practice, even if those specialists could give them vital information about me and my disease. Right now, I travel three and a half hours to see Dr. Insogna at Yale. I have an appointment with a doctor this month who's closer to where I live and I'm hopeful that he's willing to talk with Dr. Insogna and learn about and manage my XLH.

[JV] Sorry to end this. So, so tough to dig deep and bring up and share so many of these

experiences from throughout your life. So let's give this panel a round of applause.

DISCUSSION 2nd topic

What we want to do now is dive in deeper, just like we did this morning, and hear about those treatments that are most important to you, either because they've really helped, or maybe, it would be also, I think it's equally important to discuss those things that have not helped so much. In either case, whether the product or approach, strategy, again, when we talk about treatments we're being very broad here, we're not talking just about medicines, but also medical procedures, maybe medical devices that you use, like mobility assistance devices, canes, walkers, wheelchairs, scooters, and then even things we've heard about, physical therapy, occupational therapy, exercises being some other strategies. So, how well have they worked? Maybe starting with those things that have worked the most for you as well as those things that have worked least well for you. Any time you talk and share an experience with a therapy, I want you to also let us know if there were any downsides to that. Was it pretty easy to utilize that strategy or take that product, whether that be the number of times you need to take it a day, side effect profile, the amount of time that it took? Is that part of the burden of taking that product or was it relatively easy, whether or not the product actually significantly improved your symptoms and burdens of the disease? So I want to start out broad, although I'm going to try to work us through a lot of the different categories of treatments that we have, but I want to first see what experiences in the audience might be most burning, where you really want to share something that has really either worked, or not worked, paint a little bit of a picture for us about, showing us how that treatment did or did not work.

[Anne Lewis] One of the requirements, I guess, for being on Crysvida was that there was supposed to, at least for my daughter, was physical therapy, and she went to one and they actually hurt her, again, illustrating the fact that they don't know how to handle XLH patients. So she was in bed three days on that one. So that was a non-starter, right there. So it was like, I didn't know if they thought they were dealing with a football player or what, I don't know. But she crunched pretty good.

[Nancy Alauzen] I just want to share two things that have been really helpful. I've been working with a personal trainer for the last eight years, three days a week, and it's really been very helpful in terms of my strength and mobility. That's number one, and I treat myself now to a monthly massage to work out all the kinks in my body and that's been very helpful too.

[JV] And what have been the impacts that you've noticed on maybe what you've been able to do because of these things?

[Nancy Alauzen] I can get up if I'm taking a bath, I can get up from the sitting position at the bottom of the bathtub, and my sisters noticed a lot of ... I call them baby exercises they have me doing, and lifting weights, but it's been really, really positive.

[JV] Wonderful, thank you. I don't know that we necessarily have anyone, but we did hear in our presentation this morning about TIO tumor removal, and so if anyone has any experience with that we'd love to hear those experiences.

[Carol Knight] One thing that helped me tremendously for my stiff muscles, which is one of my major issues, is we have a hot tub. We live in Texas so I can't use the hot tub in the summertime because the outside temperature is sometimes 113 degrees. But in the wintertime, using the hot tub and finding one that is not where everybody sits on the floor of it, with a little bump for your seat, but rather where the seat is up eight to twelve inches from the floor, so that I can put my short legs down in the center and ride bicycle or what have you. It makes a huge difference in my flexibility for the entire day. We have one that has jets where I can put my wrists on them or my hands, move them toward my back, needs the right amount of pressure that day, it's just astounding the difference it makes.

[JV] Helps with the stiffness?

[Carol] Yes.

[JV] Great, thank you. Is there any takers on the tumor removal? Either experience with it or maybe perspectives on having tumors and not having undergone tumor removal? I figure we probably don't. Maybe Jim is our only TIO patient in the room, but I wanted to at least put it out there.

[Jamie DiBlasi] I'm Jim's mom and... if you know anyone that has a tumor, that's having trouble with bone things, that just isn't generally connected. The neurologists we worked with were great, the endocrinologists we worked with were very, very helpful, but those two fields are not connected at all, so if you know of anybody, just tell them to just keep searching. If they think there's a connection, keep searching. Keep listening to little tidbits or ideas that your doctors will say and then you kind of add them all up and you're thinking, well these kind of match.

[JV] Can you tell us a little bit about Jim's experience with tumor removal?

[Jamie DiBlasi] Well. Jim can probably talk more about that.

[Jim DiBlasi] I have been through a lot. I had two tumor surgeries. On my second tumor surgery, this is when we all found out that I was really having different qualities after, well, before and after I had my surgery too. And we just need more information about, about, like, bone pain, and my osteomalacia,. It's just not a whole lot information out there. I went through a ton of doctors and they didn't know a whole lot of why I was having balance issues. It was very frustrating to me. And I just want, it's just not enough questions that you can ask your doctors the questions that you need to, ... there's just not enough answers out there and they just don't know what... is out there, so I just, you can't just ask enough questions. I'd just put it that way. Because I've been through a whole lot and we need to have a lot more answers about TIO, and tumor-induced that causes osteomalacia and rickets in your bones. Once they figured it out, I was... Happy. That's when they finally narrowed it down. But it took a very, very long time and stuff, too. But I don't want to hold you guys up anymore, but I can just go on and on, but. It's just not a whole lot of information out there. And on other bone cases also, too.

[JV] Thank you, Jim. And it sounds like your experience is actually quite similar to what we've

heard a lot of in the room, about not having all the questions answered. And thank you for representing the TIO patient voice. So we have a comment right here in the back?

[Gin Jones] I obviously can't talk to TIO, so I wanted to go back to what Carol said about using heat therapy for relaxing muscles. And I think this speaks to the fact that there's so much variability across the patients because I find if I use heat therapy I get worse. I'll feel better temporarily, while the muscles relax and everything, but the next day I'll be in significantly more pain. That's just me. I know plenty of people like Carol said, within our community, that find that useful, but in my case I have to use ice. Which is great in the summertime, but if you're doing it in January or February in Massachusetts, it's not a lot of fun. But for me, it works longer term because it reduces the inflammation, because we're of course at more risk of arthritis and things like that, that is inflammation-based. So I'm just throwing that out there. I keep meaning to do a little survey someday on it, saying do you use ice or heat? And I have a feeling we'd end up with a 50/50 mix, but like I said, there is variability there, but that is another option.

[Athina Kinsley] One of the questions that are up there is basically if there's no cure for our condition, what specific things would help us? For treatment and options, I think, what I'm learning as growing into an aging adulthood, I think it's so important to get the physical therapy and prevention of certain limited range of motions and how we can really impact the aging process, and taking for granted riding a bike, that's not an option for me anymore. So I think there needs to be more providers who can help the community and prevent those things as we get adults and understanding the manifestations with calcifications.

[JV] So can you tell me a little, you mentioned that using physical therapy, has that been something that's been helpful for you? And can you tell me --

[Athina Kinsley] When I went through that horrible experience in my life, the physical therapy, I was still in a walker after surgery, I had rigorous therapy three times a week, even after the rehab facility, and without that and the continuous care, I wouldn't be where I'm at today. So physical therapy was a huge impact in my life. For the better.

[Tonya] Hi, my name's Tonya, I'm some type of spontaneous hypophosphatemia, we're not sure if it's XLH or a dominant case. Treated with phosphorous and calcitriol as a child, did well, went on and off treatments sort of, through young adulthood, actually made it through medical school and into practice, met my husband, had two children. But what I want to talk about just a little bit is the burden of treatment. For me, I changed jobs, went to a new place, a smaller practice. My boss decided that Obamacare would be what we should have. And I live in a community where I had to choose a plan where I would either be able to see the practitioner across the state in Philadelphia, or one that would not. So I chose the one where I could keep my practitioner that knew what was going on, but hence, Obamacare allowed them to put calcitriol as a vitamin. After multiple times trying to work through the insurance industry, my senator's office, and even as a physician trying to talk to the CMO of the insurance agency, who refused to talk to me, I had to change jobs to get better health insurance for my family. With the flux in the health care system that has led to three jobs in a twenty-six-month period. So just trying to get basic treatment has been a stressor on my family.

[JV] How well the calcitriol and phosphorous was working for you, obviously it was important because you were pursuing it, and changing jobs even to get access to it, so can you tell us a little about that?

[Tonya] Actually, as a child, within one year of treatment ... so I was diagnosed at seven, at eight there were no physical signs of the rickets and probably within shortly of that, the bowing had completely resolved. So for me, the calcitriol and phosphorous worked well. I had bone pain here and there as an adult, had to go back on treatment having to use both rails on a set of stairs to get up the stairs because of knee and muscle pain. But going back on treatment, I do a pretty rigorous lifestyle. I mean, there's three days in a row I won't be home. I go from hospital to office and back to hospital. And I'm able to keep up. I've had to give up running because some of the... pain, and it's not the day of. It's actually pain the day after in joints and ligaments. But I'm still able to exercise on a regular basis so for me, again, we can't tell what type I have, but the calcitriol has worked well, the calcitriol and phosphorous has worked well for my son too.

[Roy Smith] I'd just like to say thank you to the doctors that have been so instrumental in developing this drug that is such a breakthrough. My daughter has had both back surgery and been part of that clinical process. It really has helped her a lot. It was too late, I mean, even after the back surgery, and the clinical help with the monthly shots, she's been told now that her back is not operable by the spine people, and so she's got to live with being hunched over and... I just want to express thank you to the doctors for all the help they've been. I'm so grateful for that.

[Brent Davidson] I'd like to elaborate a little bit on the surgeries, and this goes into the calcitriol and K-phos treatments as well. As I mentioned, I've had parathyroid surgery. First one, they removed parathyroid glands, left a small portion in my neck and did the implant into the arm. The second time I had to have parathyroid surgery, they were thinking it was going to be the one in the arm, but it was actually the remainder that they had left in the neck that had enlarged again, so they went in and took that out. So the only remaining parathyroid I have is now in my left arm. But that has to do with the K-phos and the phosphates, calcitriol. But, you know, we think of our bones as being soft. I've had surgery on both of my legs, tibial osteotomies. And the first surgery I went in, they had planned to do both legs at one time, supposed to be, I think, a three-hour surgery. I ended up in the operating room for six hours. They only got one leg done, the rod jammed up shortly above my ankle and they had to go in and cut the ankle to finish driving the rod out. And they told me after the fact that they broke four saw blades and two drill bits during that operation. They said that the bones were extremely dense, and extremely hard, at least in my case. So I'm guessing that's an indication of how well the calcitriol and K-phos worked for the bone mineralization, at least for me. The other leg they went in and did with a plate at a later date, but I, after being under the tourniquet for so long that first surgery, developed compartment syndrome in that leg and actually came within an hour of losing the leg, the swelling reached that point. Ended up with five surgeries over the course of nine days, to relieve the pressure and then go back and have the wounds closed up, because of the amount of swelling that was present.

[Patricia Kennedy-Stefanac] I have two questions for the room. First, regarding surgery, I had the spinal stenosis surgery maybe five or six years ago after needing it three or four years before that but didn't want to do it until I couldn't drive. And now all that pain has come back. Is that

happening to people? You have spinal stenosis surgery, then it gets better, then it gets worse again, and you're repeating the surgeries? Has anyone been through that?

[JV] I'm seeing heads nodding around the room, yeah.

[Patricia Kennedy-Stefanac] Okay. And then the other thing I have, this is a little unrelated but I haven't heard anyone refer to this. In my twenties, my jaw quit opening, I got TMJ and I've wondered all these years if the TMJ is related, I've always assumed it was, but I haven't read that anywhere, no one has mentioned it, do other people have TMJ? Yeah, how many people?

[JV] Is there a show of hands on TMJ?

[Patricia Kennedy-Stefanac] Not very many, actually, okay. All right. All right, thank you, that's it.

[Caroline] Hi, I'm Caroline. I'm going to stand so everyone can see me because we're short. I'm twenty-six, so kind of repping the younger adult generation. As far as surgeries, I had three surgeries to straighten my legs growing up. I had pretty severe bowing, my orthopedic surgeon said you can picture it like the McDonald's M, like your femur goes like that and then at the knee it goes like that again. Which I think can be a little different from what some other people experience. So I had the spatial frame to straighten my entire left leg when I was five years old, and then in fifth grade we did lower left and upper right, and in sixth grade, lower right and upper left. And then I stopped growing so they haven't rebowed again, thankfully. And then in high school, I stopped taking the phosphorous and calcitriol because no one really said to keep taking it, they didn't say to not take it, nor really emphasize anything. So after college, probably a couple years ago, I got back on meds, I live in Houston so Dr. Ruppe was there, so that was really great to meet her, which has really affected, my rickets is a lot more chill when I'm on meds, and is a lot less painful, but just kind of in general, and I know this is being talked about in community but I would love to see more emphasis on educating the teenagers, coming out of surgeries and out of pediatric care, and then going into young adult care and learning to take over your own care, and really emphasizing that it's important to keep taking care of your body because we do change. And hearing stories of everyone who's older than me and going through a lot, I'm taking notes from all of y'all for my own future. It's important to stay on meds and kind of educate our younger generation for their future.

[JV] We've been talking a lot about your experiences with what treatments, broadly defined, you currently have, now kind of fully extended into the future. We've been talking about the past and your experiences, but I want to know a little bit about your preferences. You're in a community, you heard Dr. Kempf say, in some ways you're at the cutting edge, you're in the five percent of rare diseases that have an approved treatment, but we also heard from Susan that the burden of the disease is shifting and there's still work to be done. We've heard that over and over throughout the day. So I think it's important that we make sure that we address this while we have this opportunity. So the question is, short of a cure for your condition, what specifically would you like from the next future therapy? This can be really described however you might like, it might be some improvement in a symptom. It might be related to your disease progression, whether you would like to see that be slowed, stopped, even improved upon,

reversal. It could even be more broadly defined in terms of activities that you would like to be able to do more of, or do more fully. There's a lot of opportunity here, to build on everything leading up right to this point and communicate what it is specifically you would like to see, short of a cure, from your next therapy.

[Gale Smith] I would like to see in the future a way to control the enthesopathy. It seems to me to be very debilitating. I'm seeing it particularly in my daughter with her elbows won't extend any more than this now. And apparently her longitudinal ligament posterior is being calcified, ossified, and she's being pushed forward to the point where she's like this. And she was my height and now she's down to about here. I don't know how much more she's going to lose.

[Kelly Rushing] In new treatment, if we could just ... this may be an impossibility because of the extent of our illness, but if we could just see some regression of our symptoms. That would be something that all of us could appreciate. If we could gain some height, if we could have our teeth just want to stay in our mouth, if our hearing could come back. So many things, just some regeneration of the symptoms that we had. That's what I would like to see, not that I'm not thankful for the treatment that we have now, but if we could just have regeneration or restoration of what we've lost already.

[Roy Smith] When my sister had her knees replaced in Phoenix, we heard about a process called ARP wave technology, that in two weeks, one of her knees was just tremendously fast-healing. And part of the gentleman who helped us with that was, he said that if you continue this on an ongoing basis, it would redistribute, because it stimulates the muscles, it makes them work, it would redistribute the blood in such a way that it takes away the calcium build-up between the bones. The question is, is this not an area that maybe we could explore the use of electro-pulses making the muscles work more? That makes the blood flow and maybe gets rid of the deposits of calcium? I don't know if that's a valid thing, but I thought I'd ask.

[JV] Yeah, good to throw it out there.

[Sunindiya Bhalla] I think it would be really helpful to see future treatments that encompass a lot of the related or, I don't know, co-morbid conditions that go with this. I know many of us have talked about having osteoarthritis. For me, that's a particular challenge, and it's hard to know where my joint pain is coming from or if it's coming from both things, and then manage the complexities of medications that address one or the other but then, I've had issues with liver enzymes being elevated and things like that, and so it's just such a big balance between different physicians, different treatments, and all of that to figure out what's coming from where and how to control all of it without it interfering with one another.

[Brent Davidson] One more thing I'd like to add. We need better pain management. You know, my pain is much better now than it used to be. I've found in talking with people that have XLH and from my own experience, pain medications, for one reason or another, don't work well for us. You know, things like morphine, hydrocodone, fentanyl, that would treat pain for a normal person, it seems like, I don't know if we burn through the pain medication faster or, you know, some of us have had so many surgeries and been on so many different treatments that maybe we've just adapted but there needs to be some investigation, number one, into why the pain

medication doesn't work for us and how to find something that does work. You know, it's not that our pain is so much worse than other people's, I think, and a lot of times, it's just incredibly frustrating that you try stronger and stronger and stronger pain medications to the point that you're walking through life like a zombie. And it doesn't do anything for the pain.

[JV] How would you define, you know, successful treatment of your pain? Is it some activity that you could do? Or is it, how would you describe that?

[Brent Davidson] Well, in my case, when my pain was at the worst, it would, it wasn't like constant. You know, it would be a certain movement would trigger just terrible pain, you know. Or when the spinal stenosis reached the point where I roll over in bed and it triggers, you know, massive back spasm. I almost caused my dad to have an accident one time, we were driving to a doctor's appointment in Houston. I was asleep in the passenger seat, we hit a bump, and hitting the bump in the car triggered a massive back spasm which woke me up with a scream, and of course he jerked the wheel and went across six lanes of traffic in the middle of downtown Houston. Finding something that would ease that pain, or prevent that. Some days you have just a general pain, like I was telling somebody earlier, I don't know if it's bone pain, I don't know if it's muscle pain. I don't know where the pain is coming from, but this hurts or that hurts. And nothing would stop it. Even when I was on the .75mg power Fentanyl patches, those are supposed to last you three days. I would get about a day and a half of marginal relief and then I'd have to go through another day and a half of withdrawal symptoms before I could change the patch because I could only change them out every three days. And you'd go to the doctor and you'd try to explain this, and they treat you like a criminal because that level of pain medication should put a horse to sleep. And it doesn't do anything. Well, you're just wanting pain meds. So that's kind of one of the areas that we need to look into.

[Ann Lewis] Just to speak to your comment on pain, yesterday, the House and the Senate passed the HR-6 Opioid Support Bill, so. We can kiss chronic pain management goodbye. The president's going to sign it into law this week, it's further going to punish chronic pain. So... what do we want to do about that?

[JV] This concludes what we really set out to do today, I know it's been long, very personal, definitely emotional at times. From my perspective, you all did what Susan asked you to do from the outset. You lifted the curtain, you spoke your truth, and I just want to thank each and every one of you for rising to this occasion. For me, I definitely witnessed each and every one of your courage, each and every one of your perseverance. I've certainly gotten to peek behind your curtain as someone that's an outsider to this community and it is incredible what you experience day in and day out. And if you didn't speak it today, it would not have been heard. So it's truly been my honor and privilege to have a part in what I think is a very monumental day for this community, and I just want to thank you again for letting me be part of that.

Erik Imel, MD

[Introduction by Susan Faitos] We're at the part of the agenda, where we're going to have some summary remarks, while probably an impossible task to fully recap everything that was shared today. We enlisted the best person that we could to make the best stab at it and that's Dr. Erik Imel. If you don't know him, he's an associate professor of medicine and pediatrics at Indiana

University School of Medicine. He completed his fellowship and is dual certified in both pediatric endocrinology and adult endocrinology. Dr. Imel conducts clinical and translational research in rare and common musculoskeletal diseases, including serving as co-investigator on multiple burosumab clinical trials. So, please join me in welcoming Dr. Erik Imel.

We started out today with Susan pointing out something that ... I don't know if this was the big thing she wanted to point out, but it was the first thing that my brain latched onto when she was talking, which was something that's also been in my mind a lot over the past few years, which is that there needs to be a greater recognition among both patients and doctors that XLH is not just a pediatric disease. This was a theme that was reiterated throughout the day in a lot of different comments.

As a personal aside to that, this is something that's probably an artifact of our understanding of the disease even going back thirty or forty years ago when the thing that we could measure the best, in terms of our outcomes, was height. So once kids were done growing, we knew that there might still be some benefit to being on treatment but we knew there were definitely some harms to being on treatment with Calcitriol and phosphate. Many of you have actually experienced some of those harms including problems with nephrocalcinosis, some patients with chronic kidney disease. People have had to have multiple parathyroid surgeries over time and some of these other problems that are a consequence of what's been conventional therapy for the last thirty years. This has influenced doctor's decisions about when do we treat and when do we not treat.

One side effect is that we've been communicating a message that, oh, you're fine now, and therefore, any problems that you're having can't possibly be due to XLH and we have to go think of something else. I've seen a lot of people get a lot of unnecessary evaluation for things that aren't really the problem and that maybe what needs to be done is address the XLH.

Now, some patients describe doing relatively well for a while after stopping therapy when they're done growing. But I also noted that most people who mentioned that, didn't describe having *no* symptoms, they described having *mild* symptoms, and somewhat manageable symptoms, for a period of time and then gradually getting worse. I think that's important to note, that even doing relatively well off therapy, may not mean being symptom free. That may have some impact as we think about how best to manage XLH.

Then of course, another big problem is access to clinical providers. Access to doctors, who have some experience with XLH, of which there are few of us. Even more so, access to people who are willing to take some extra time, and that's a challenge because a lot of doctors have a lot of time pressures and have difficulty stepping out of their comfort zone and doing that because of those time pressures.

I think we don't necessarily need to expect every doctor to be an expert in every rare disease, because that would be virtually impossible. But one single high yield thing that Dr. Jan deBeur and I were talking about that would probably have gotten many people to getting more treatments sooner, especially in the case of TIO patients, is if phosphorus were just routinely measured, and it's not. So many of you who may have seen delays in diagnosis and treatment,

that may be part of it.

As we went on throughout the day, we talked a lot about how you start to have symptoms again (or maybe your symptoms didn't go away completely) when you're a young adult. Once you start to have symptoms again, there's a gradual increase in disease burden over time that really just seems to increase with ongoing years, and that impacts a lot of things. It impacts things we would like to be doing that would be fun or meaningful, or sometimes things that have to do with being able to work or take care of your house or your family.

There was a lot of concern about what that impact would be as people developed more problems with their XLH. Mobility and pain control have certainly been big issues and I think that this really is a big unmet medical need, especially with the enthesopathy. A lot of the symptoms that you are describing as the most debilitating things in your life relate to this calcification that's in places it shouldn't be, leading to spinal stenosis surgery. And leading to joint immobility, and stiffness, and pain in many situations. I think these are all places that we need more research.

And these are places for which we don't have great information. We know for sure that calcitriol and phosphate, at this point in time, do not benefit the enthesopathy. We actually have no information to tell us whether burosumab is going to benefit the enthesopathy or not. There are some theoretical reasons that it might, but we have no evidence from any of our research trials. That's going to take a long time to actually develop because it's something that progresses slowly.

I also saw some hope today. There were a lot of people that are very hopeful in terms of their experience with therapy with calcitriol and phosphate when it's working well for them, and with burosumab when people have had the opportunity to experience that.

Finally, we need to increase awareness of what additional things we need to address, because I think that as we continue to learn more about XLH, we're going to need to try to address some of the other things that are sort of ancillary to the primary bone problem.

Elizabeth Olear

Good afternoon. My name is Elizabeth Olear, and I am Susan's Co-Chair of the Symposium Committee. And I know many of you from my work at the Yale Center for XLH, where I've been for over ten years.

I'd like to thank everyone who has traveled to Baltimore to be in attendance with us today, and those as well who've joined the Symposium online. We'd also like to thank all of our invited speakers, Doctor Lucas Kempf, and our expert clinicians, Doctor Karl Insogna, Doctor Eric Imel, and Doctor Susan Jan De Beur, who we'll hear from tomorrow.

We'd also like to thank the Food and Drug Administration representatives for being here, especially Doctor Theresa Kehoe, and those FDA reps who are watching through the webcast. We'd also like to thank the Food and Drug Administration for showing understanding of the needs of the patient community and for approving burosumab.

We'd like to thank our sponsors, Ultragenyx, Inozyme, Ionis, and the EveryLife Foundation. And I'd like to thank James Valentine, whose patience, expertise, and support preparing for this symposium, and for facilitating as moderator today, were invaluable to its success.

And I'd also like to thank Susan Faitos, whose long hours, long weeks, and long months went into planning and executing today's event. Susan brought her own experience as a patient with XLH into every detail, and she also brought her tremendous heart. So thank you on behalf of the Network, and on behalf of the patient community for all hypophosphatemic disorders.

And finally, both Susan and I would like to thank all of our panelists, without whom today would not have happened.

This meeting is only a piece of a year-long process, and I'd like to remind you that people can still submit written comments over the next thirty days, whether you've attended in person and have something more to add, or if you've been following along online, or you're listening at a later time to the recording. You can still contribute to our post-event survey at xlhday.org, or by submitting a written statement by e-mail at symposium@xlhday.org. This and all input today will be summarized in the Voice of the Patient Report, which The XLH Network will submit to the FDA and also put on its website.

So where do we go from here? As you've heard today, there's so much work to still be done. We're just finishing many of the clinical trials that I know some of you have participated in. And one of the questions that I've received recently is "What are you going to do now?"

We know that XLH, and TIO, and the other hypophosphatemic disorders are so variable. And as we've heard, patient experiences might have some similarities. But no two patients are exactly alike. There are so many more questions to ask and answers to find. We've only just begun.

So thank you again for everyone who came and participated today, and who will continue to participate online and on the webcast. And I hope that you will all enjoy the rest of your time in Baltimore.