Voice of the Patient Report
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The Symposium on Hypophosphatemia:
Past, Present, and Future

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Baltimore, Maryland

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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.

The Patient-Focused Drug Development meeting was attended by officials from the U.S. Food and Drug Administration (FDA), 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 grew 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. (Links in Appendix 8.)

C. Overview of Available Treatments

According to the panelists, audience participants and survey respondents, three different pharmacological treatments have been available over the course of their lives, leading to different patient experiences. The first, beginning in the 1950s, was high doses of inactive vitamin D, which had serious side-effects (i.e., vitamin D toxicity) and minimal, if any, effectiveness, so orthopedic surgery was often required. Second, beginning around 1980, was a combination of phosphorus supplements and active vitamin D (calcitriol). It too had serious side-effects, including nephrocalcinosis, hyperparathyroidism, and gastrointestinal distress, and required close monitoring (lab tests, x-rays, kidney scans). It offered some benefits for bone and dental health, but it was a burdensome regimen, patients still did not reach their height potential and often required surgical intervention, and the most debilitating adult-onset symptoms such as osteoarthritis, spinal stenosis and enthesopathy still occurred.

A new treatment, burosumab (marketed as Crysvita), was approved by the U.S. Food & Drug Administration in April 2018 for XLH patients, and a clinical trial is underway for its safety and effectiveness in treating Tumor-Induced Osteomalacia. Burosumab is a monoclonal antibody rather than a supplement, and it is the first treatment to address the excess FGF23 levels of chronic hypophosphatemia. Several of the panelists were in the clinical trials for burosumab (including both the XLH trials and the TIO trial), and reported significant improvement in their adult symptoms, with minimal, if any, side-effects. While this treatment appears to be highly effective, it is not a true cure, since the effects last only about two to four weeks.

For more information on the history of these treatments and their effectiveness, with journal citations, please see Appendix 9.

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.

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 a 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 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 like 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 [medical[career] 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.

Another example of patients having high pain tolerance came from those who had had significant bone damage, but were unaware of it. Gin found out during the screening for the burosumab clinical trial that she had a still-healing upper-arm fracture from three months earlier that she'd been paid no attention to, since 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. On audience member said:

> 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 XLH 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." Gale reported she had her first abscess in her early teens, and she has had "many more since, so I'm missing teeth and have numerous root canals with crowns." 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. Similarly, one audience member said the two symptoms that were most burdensome for her were dental issues and hearing loss, rather than the more commonly cited pain and mobility challenges.

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 (and sometimes vertigo or tinnitus) at a much earlier age than the general population is a common symptom in this community. 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. Theresa's tinnitus began in her thirties. Elaine's hearing loss and vertigo also began in her thirties, as did that of an audience member. Gale, who was a switchboard operator, said she lost her hearing in one ear right when she first retired and is currently losing it the second ear.

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. She explained:

> 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.

An audience member also talked about the need for more transition education:

> 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.

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, as described in the overview of the condition, that were not of primary concern to the representatives of the community who were able to attend the event, and therefore were not addressed. And there are many unknowns, which could not be addressed.

The bottom line 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, needing to repeat surgery: "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. 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.

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.

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 [with supplements]."

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.

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.

Some patients stated they did find relief from the worst of bone pain with supplements, but others did not, or still needed other forms of pain management. See also Carpenter, et al, 2011.

Burosumab provided the panelists with 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."

According to the panel patients who had participated in the burosumab clinical trials, they experienced a significant lessening of pain and fatigue while on that treatment. (See also Insogna, et al, 2018.) Brent reported discontinuing his fentanyl patches after going on burosumab. He also regained mobility (and retired 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, as Gin noted, burosumab cannot reverse structural problems that occurred before the treatment begins, like malformed teeth and bones, or the pre-existing enthesopathy and calcifications.

Alternative treatments may provide some relief. Audience members suggested a variety of alternative treatments that, while not a cure, did provide some relief for them. 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.

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 which 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.

Treatment of Calcifications and Enthesopathy is critical to adult quality of life.

These symptoms lead to mobility restrictions, which are reported by patients to have the most negative impact on 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 as Gin noted, 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 it was just a subjective impression, not objective data. As Elaine said, "the progression is gradual like watching grass grow. Eventually, you know something is happening, but [having lost hope for effective treatment], I simply adjust to the challenges and keep on going."

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. (See the discussion above on pain tolerance and delaying treatment.) 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 the treatments available 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.

Several patients mentioned having difficulty finding a specialist qualified to treat adults with XLH. Susan said she "was told at age nineteen that I no longer needed to be treated for my XLH [and] was told the same thing repeatedly over the years whenever I sought help for what I knew were XLH-related challenges. [I] didn't meet a doctor with any real experience in XLH until I was 54 years old." Brent said, "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." An audience member expressed her frustration over not being able to find a doctor able to treat her. She said, "I think one of the most disastrous problems we have is that we can't get medical care in the Pacific Northwest." She chronicled her experiences at various sites on the west coast, including with places reputed to understand XLH, but she concluded, "None of them have a clue." She went on to say, "I've been … 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." Theresa had similar experiences, describing the challenge of "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."

Because 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. Brent noted that this type of treatment "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."

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. See above, for Brent's experience with hyperparathyroidism while on supplement treatment.

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. Some patients, like Elaine, also experience kidney stones from treatment.

While supplements were burdensome and presented several serious health risks, the opposite was true of the panelists' experience with 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 very 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 all or even most insurers will cover burosumab, 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 purely scientific value, and 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.

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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 *Beyond*XLH, 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. *Beyond*XLH 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
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 2
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 WWll 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 3
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

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 4
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 our 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

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?	**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	**A. 59** **B.** 9 **C.** 17 **D.** 4 **E.** 4 **F.** 7
What is your experience in, and perception of, clinical trials for chronic hypophosphatemia?	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.	A. 10 B. 21 C. 8 **D. 23** **E. 26** F. 13 G. 0 H. 0
How has the impact of you/your loved one's chronic hypophosphatemia changed over time?	**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	**A. 84** **B.** 11 **C.** 0 **D.** 5

APPENDIX 5
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 6
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 7
ADDITIONAL RESOURCES AND WORKS CITED

The FDA has a great deal of information about Patient-Focused Drug Development meetings here: https://www.fda.gov/industry/prescription-drug-user-fee-amendments/fda-led-patient-focused-drug-development-pfdd-public-meetings

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), Twitter (@XLH_Network) and Instagram (xlhnetwork) or visit our website at xlhnetwork.org.

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Appendix 8

Expanded Overview of Available Treatments

For the Phosphate-wasting:

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.

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 hypophosphatemias 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 acupressure. There is no published research on the topic, however.