Question #1 from the viewership: I joined USA fb soft bones group...there they put my daughters genetic sequence into their data base...unequivocally was told my daughter has two variants and has infantile HPP. My son as well....then only couple of days ago doctor told my daughter she is a carrier and does not have HPP....I've been taught via sue Krug from HPP USA patient advocate there is no such thing as a carrier anymore. Can you discuss the issue of someone being a "carrier"?

Dr. Leanne Ward response: Thank you for your question. The definition of a "silent carrier" is an individual who has a known, pathogenic variant in the *ALPL* gene, but no signs or symptoms of the disease *despite thorough and repeated testing.* The latter part of this definition is extremely important, because signs and symptoms of the condition may be so subtle, that highly specialized testing may be needed to determine whether an individual has features of HPP.

The other aspect of this conversation, is that an individual can test negative for signs and symptoms of the condition at one time point, but may show signs or symptoms consistent with HPP later in life. Both of these facts challenge the notion of "silent carriers" in HPP.

To address this point, I mentioned on the webinar that "carriers" (i.e. individuals with only one copy of the abnormal *ALPL* gene), have traditionally been considered 'silent carriers". Their child/children with two copies of the abnormal gene have traditionally been said to have "autosomal recessive HPP". We now understand that the individual with only one abnormal copy of the gene, previously thought to be a carrier, may actually have signs or symptoms of HPP upon thorough testing. If so, such a patient is not a carrier, after all.

We are appreciating more and more in HPP that individuals who were initially considered to be carriers, may in fact show signs of the condition at some point in their lifetime, in which case they are not carriers in the true sense of the definition. The situation is further complicated by the fact that an individual may initially lack any signs or symptoms of HPP, and then later (in adulthood) develop HPP-related health problems. This "variable expressivity" of the condition, including the age at which signs and symptoms present, can lead to under-diagnosis of HPP in certain kindreds, and mis-diagnosis of the inheritance pattern.

Therefore, our understanding of HPP is evolving, and the use of the terms autosomal dominant, autosomal recessive, and carriers, are therefore also evolving.

The main take-home messages from this question are the following:

1. An individual with one, or two, abnormal copies of the *ALPL* gene, should undergo thorough investigations, in search of signs or symptoms of HPP. These investigations should be repeated periodically, since the signs and symptoms of HPP can surface later in life. The use of the term "carrier" is therefore difficult,

because an individual with only one abnormal copy of the *ALPL* gene can lack signs or symptoms of HPP at one time point, but develop them later on.
2. Based on current knowledge, it is most informative to describe patients as having one, or two, abnormal copies of the *ALPL* gene, and to describe whether they are symptomatic or not (recognizing that symptoms can evolve over time). It should be recognized that individuals require thorough, and repeated, testing in order to understand whether they show signs of the condition.

What does all of this mean for you and your family, in practical terms?

We were taught in medical school that "when in doubt, look at and listen to the patient". This is so relevant today with the rapidly changing knowledge about HPP. You did not say in your question whether or not either of you children actually have any signs or symptoms of HPP, or if you yourself do. But the important points for you to consider are:

1. Understand what we mean by an *ALPL* variant. This is a change in the letter sequence of the DNA that makes up the gene coding for alkaline phosphatase. A variant may or may not have any consequence or medical significance. By this we mean that a) the variant can be completely benign (i.e. a normal variant), b) it may be known to be associated with HPP (i.e. a known pathogenic variant), or c) we may not know the significance of the variant yet (i.e. a variant of unknown significance). It may be that with time, the interpretation of the variants found in your daughter changed. This can be discussed with someone who is part of a child's care team, such as a genetic counselor.

2. Individuals who have 1 or 2 variants in the *ALPL* gene that are felt to be "disease-causing" should be followed yearly, as such individuals may develop signs or have symptoms of HPP. The terms carrier, dominant, and recessive as related to HPP do not necessarily fit perfectly for some families with HPP. Understand that people who have only one copy of their *ALPL* gene with a miss-print, may develop symptoms with time. However, many people with variants will not develop any symptoms. This can be confusing, and anxiety-provoking. While there is some uncertainty about how to best interpret genetic findings in some situations, whether an individual has signs or symptoms of the condition is still the most important part of making a diagnosis of HPP.

Question #2 from the viewership:

My son, age 4, has a very mild case of HPP. He lost 3 teeth at age 2 and otherwise seems to be healthy. Strensiq has not been prescribed. What kind of ongoing monitoring should I expect when there is no immediate need for treatment?

Dr. Leanne Ward response: Thank you for your question. There are two main points to this answer. First of all, some children with dental signs of HPP (odonto-HPP) have no signs of the condition otherwise, and some children with the dental form actually DO have some other signs of HPP. For children with odonto-HPP, we recommend periodic

evaluations with an HPP physician to inquire about how the child is doing, a thorough physical examination to assess the child's function (walking, running, climbing stairs, fractures, etc), blood and urine testing, and possibly other testing such as x-rays, depending on how the child is making out overall.

The second part of the answer to this question is that if a child ONLY has the dental form of the condition, without any evidence of HPP otherwise despite thorough and repeated testing, then such a child does not qualify for enzyme replacement therapy (asfotase alfa). Currently asfotase alfa is indicated for children who have more than ondonto-HPP, who have a confirmed abnormality in the *ALPL* gene, and who are symptomatic. By symptomatic, we mean that they have signs or symptoms of HPP that are interfering with their day to day life.

As an aside, the situation is a little different in adults. Adults may be eligible for treatment via different mechanisms:

1. Public funding is not available for adults, unless they were on asfotase alfa as children, they continued on asfotase alfa into adulthood, and they did so without stopping the medication.
2. Private insurance companies may opt to follow the same guidelines for public funding, or they may choose to fund some adults with significant symptoms. This can only be known following application on a case-by-case basis.
3. If an adult is in need of treatment, and public or private funding is not available, access through a "compassionate use program" may be explored.

Question #3 from the viewership: What if they were never diagnosed as child but now have been diagnosed as infantile. And has never had enzyme replacement. Should she receive it now?

Dr. Leanne Ward response: The definition of "infantile HPP" is that the symptoms and/or signs were present in the first year of life (i.e. in the first 12 months). As I mentioned on the webinar, this is a more severe form of HPP, and we would anticipate that children with HPP who had symptoms starting in infancy would undergo a thorough evaluation in consideration for asfotase alfa treatment. Another way to say it, is it that we would indeed anticipate that children with infantile HPP would be potential candidates for asfotase alfa therapy.

Question #4 from the viewership: Dr Ward- you mentioned that the physician is an important advocate for the specialized treatment with asfotase alfa- but should all children with HPP be treated with enzyme? what are the indications to start treatment?

Dr. Leanne Ward response: Indeed, an HPP physician is an important advocate for a child with the condition, not only in terms of enzyme replacement therapy, but also in terms of supportive care such as access to allied health professionals including as physiotherapists, experts in pain management, and psychologists (as needed). Where

enzyme replacement therapy is concerned, not all children require this specialized treatment.

First of all, children with HPP who have more than just the dental form, who have a confirmed mutation in the *ALPL* gene, and who have symptoms or signs of HPP interfering with their day to day life, are typically eligible for asfotase alfa.

Secondly, not all children with symptoms that started in childhood necessarily need enzyme replacement therapy. Some children may experience such mild symptom that highly specialized treatment may not be required. The decision to treat a child with HPP depends on the child's symptoms and signs of the condition, the child's physical activity goals, and the family's comfort with undertaking three to six times per week injections. I would anticipate that the family of a child with HPP would collaborate with their HPP physician to arrive at a decision with which everyone is comfortable (the child, the parents, the physician).

In my experience, following thorough evaluation, and with an informed discussion about anticipated benefits, and potential side effects, children and families will make the best decision for them in the setting of drugs for rare diseases. These decisions can always be re-visited over time, which underscores the need to stay in touch with your HPP physician on a regular basis, as your child gets older.

Question #1 from the viewership - I'm in the process of being diagnosed, with no severe symptoms. My diagnosing doctor is suggesting that since I'm not a candidate for Strensiq, they'll just add me to their database and call me if any new treatments become available in the future. What kind of ongoing health monitoring should I expect? Would it be my family doctor who takes responsibility for that?

Dr. Aliya Khan response - I believe you should see an expert in metabolic bone disease at least at the beginning to ensure the correct diagnosis is made - after that your family doctor can do monitoring if that would be appropriate based on the complete assessment.

Question #2 from the viewership - I'm dealing with fatigue, brain fog, and anxiety, and my family doctor is exploring several reasons for why that might be. My family doctor has almost zero knowledge of HPP, and my HPP doctor has no knowledge of any HPP symptoms outside of bone and dental symptoms. Thus far we have found no good explanation for my symptoms and I'm wondering about the possibility of HPP being a factor but no doctors who are able to speak to that. What can I do? I'm located in Vancouver.

Dr. Aliya Khan response - I suggest you see my colleague Dr David Kendler at University of BC.

Question #3 from the viewership - Does Stensiq help with dental issues in children and adult patients? If so, what have the outcomes been?

Dr. Aliya Khan response - there is limited information about dentition - in the adults they have usually lost all their teeth - we can ask Dr Leanne Ward about the pediatric aspect.