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Hypoparathyroidism – The Critical Role of Genetics in Your Differential Diagnosis

Announcer:
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Dr. Shoback:
Hello, everyone, and welcome to this educational activity on hypoparathyroidism. We're going to focus today on the critical role of genetics in making the differential diagnosis in this condition. This is an educational activity that was developed by the France Foundation for your knowledge.

My name is Dolores Shoback. I'm an endocrinologist and Professor of Medicine at the University of California, San Francisco. And I'm joined in this educational activity by Dr. Collins.

Dr. Collins:
Hi, I'm Michael Collins. I'm an endocrinologist as well, and I'm a Senior Clinical Advisor at the National Institutes of Health in Bethesda, Maryland.

First, I'd like to review the learning objectives of this program, and they are to apply appropriate diagnostic strategies for suspected autosomal dominant hypocalcemia type 1, ADH1, including key considerations related to genetic testing. Next, recognize the importance of identifying ADH1 as a cause of hypoparathyroidism, abbreviated hypoPT. And finally, to explain to the patient the role of genetic testing in the diagnostic process for ADH1.

By way of outline, first, we'll do welcome and identify the unmet needs, when and how to test, clinical decision-making, recognizing ADH1, the differential diagnosis and clinical presentation patterns, genetic testing, supporting your patient with a wrap-up, resources, and next steps for change.

I'd like to point out to keep an eye out for this little brain symbol you see at the bottom because this identifies content that will be related to the pre- and post-test questions.

So first, let's go through the unmet needs. I'd like to highlight the unmet needs in these patients first with a patient story. This is a story of a 50-year-old man who was referred for chronic hypocalcemia. He had a very illustrative history, and that is, at the age of 6, he was evaluated for learning difficulties. He was running behind in school. It was then he was noted to be hypocalcemic with a low PTH and given the diagnosis of hypoparathyroidism.

At that point he started treatment with conventional therapy which included calcium and active vitamin D, in this case calcitriol. By the age of 14, though, he had developed nephrocalcinosis with very significant calcification of his kidneys and stage 3 kidney disease. And then at the age of 20, he had a hospitalization for hypercalcemia, which is also typical of these patients, who are just in general more difficult to manage than patients with postsurgical hypoparathyroidism.

Dr. Shoback:

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So, what I'd like to turn our attention to now is why does knowing about this condition in particular matter for your clinical practice?

Well, first of all, this is a rare disease, and it's underrecognized in clinical practice, even in the practice of endocrinologists. Many of these patients are labeled idiopathic or nonsurgical hypoparathyroid patients, and this can lead to a delay in diagnosis and a delay in best treatment.

There are several complications we need to think about in ADH1. It can cause renal complications, as you've just heard in the case Dr. Collins presented. It can cause neurologic problems and learning difficulties, ocular calcifications, and cardiovascular disease. And overall, there's a high burden to the quality of life of these patients.

And part of the reason it matters so much is the care of these patients often is quite fragmented. Because the diagnosis can be missed for years, these patients may be going to many different specialists, and preventable complications of renal disease and just the lack of a diagnosis to the family can have very significant consequences. So, making the correct diagnosis has implications for the management of the patient, for the patient's prognosis, and for the efficiency and effectiveness of family evaluation.

So, when should we suspect ADH1 in our patients? Well, some of the key features are that this is a form of nonsurgical hypocalcemia along with low or inappropriately normal PTH levels. Patients often have hypercalciuria or renal calcifications, and this is often out of proportion to the treatment expectations in a patient with hypoparathyroidism.

The onset is generally in childhood, and they may have very longstanding and unexplained hypocalcemic symptoms when their diagnosis is made. The family history is often suggestive of autosomal dominant transmission, or there may be unexplained neonatal or infant events that suggest hypocalcemia. The average age of diagnosis of hypocalcemia in these patients is 4 years of age, but the average age at the diagnosis of ADH1 is 25 years of age, so there's a big gap during which these patients remain undiagnosed.

So, let's turn now to some of the clinical decision-making that one would need in evaluating patients with hypoparathyroidism.

So, when I think of a patient with hypocalcemia in my differential diagnosis, my very first step is always to check the intact PTH level. If that level is low or inappropriately normal in a patient with hypocalcemia, I'm thinking hypoparathyroidism. And then I think about either acquired forms of hypoparathyroidism or the idiopathic or genetic forms of this disease.

So, in the acquired forms of hypoparathyroidism, the most common etiology is some form of neck surgery that led to this complication, and that explains hypoparathyroidism in 75% of patients with that diagnosis. And then everything else in the differential diagnosis pretty much occupies the other 25%. So, rarely irradiation to the neck, rarely infiltration by iron, copper, or granulomatous processes like sarcoidosis. Hypomagnesemia can cause either transient or chronic hypocalcemia and hypoparathyroidism.

And then finally, there's a large category of patients that are characterized by idiopathic hypoparathyroidism or genetic etiologies. Those include the DiGeorge syndrome, the autosomal polyglandular endocrinopathy syndrome type 1 with hypoparathyroidism as one form of it. And then there are many other etiologies that are genetic in origin for this condition. And importantly, on that list is ADH1, wherein 40% of them have calcium-sensing receptor mutations, and 40% of them in that idiopathic category and genetic category are due to ADH1.

So, what clinical clues should trigger the consideration of the diagnosis of ADH1? Well, as we've just said, nonsurgical hypocalcemia with a low or inappropriately normal PTH level. As Dr. Collins described, childhood-onset, seizures in childhood, paresthesias, muscle cramping, neurocognitive symptoms, all of those should enable the clinician to think about ADH1 as the explanation for the hypopara and the hypocalcemia. Hypercalciuria or renal calcifications disproportionate to what we typically see in hypoparathyroidism are also an important clue that you might be dealing with ADH1. And then finally, that strong family history of hypocalcemia, seizures in childhood, kidney stones, or some kind of parathyroid disease in that patient's family should trigger us to think about ADH1.

Some of the key features of ADH1 include, if it's acute, the carpopedal spasms that occur with hypocalcemia, the tetany, the paresthesias, and the muscle cramping can all be part of the acute presentation. And then the complications of hypocalcemia, the seizures that can occur, the choking sensation, laryngospasm, altered mental status, all of those can be features and complications of ADH1. And then chronically we think about cataracts, cardiovascular adverse events, arrhythmias, heart failure, fractures, renal disease, seizures, depression, bipolar disease. All of these are potential complications of ADH1.

These patients typically have no history of neck surgery to explain any of their hypoparathyroidism, and they have no other autoimmune disease features. The family history may be positive for hypocalcemia. It may be positive for chronic kidney disease that is unexplained and kidney stones. And on exam in the office, the patient should not have a neck scar. They shouldn't have the dysmorphic features of some of the other genetic etiologies of hypoparathyroidism, and there should be no cardiac abnormalities, hearing loss, or any of the autoimmune features like mucocutaneous candidiasis.

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The laboratory findings include the low serum calcium and often an inappropriately normal or an elevated urinary calcium when that serum calcium is low.

Now, in ADH1, when patients have a severe form of this disease, their average serum calcium is 6.8 mg/dL. We classify that as severe. When they have moderate hypocalcemia, the average serum calcium is 7.4 mg/dL. And in those patients who are asymptomatic—and there's a proportion of them that are—the serum calcium averages 7.6 mg/dL. In patients with ADH1, if they're given conventional therapy, as Dr. Collins mentioned in his patient, urinary calcium is often high, and that happens in 90% of these patients. So that's a very important tip-off.

The intact PTH, as I've said, is low or low-normal and is frankly low in nearly 60% of patients with ADH1. Serum phosphorus is elevated, again in about 60% of the time of diagnosis, and that is often the case with moderate or severe ADH1.

Serum magnesium can be low in these patients, and the fractional excretion of magnesium is often increased. Now, this is linked typically to how active that calcium-sensing receptor variant is in ADH1, how active it is functionally. So some of the strongly activating mutations can lead to a low serum magnesium and an increased fractional excretion of magnesium in these patients. And then those with the more mild variants in the calcium-sensing receptor may have normal magnesium levels.

The imaging can be quite dramatic in these patients. And if you do a noncontrast CT scan of the head, for example, you can see calcifications almost throughout the brain with a special emphasis on the basal ganglia calcifications. And those are about fivefold times more common in patients with ADH1 versus other forms of hypoparathyroidism, where they can have brain calcifications as well.

The kidney can also show lots of calcifications as time goes on in these patients. They may have nephrocalcinosis, they may have kidney stones present, and that's seen in about 75% of patients with ADH1 on conventional therapy. And the presence of these renal calcifications and these renal complications are strongly associated with the presence of hypercalciuria on the measurements that you make, and the rate of that, the odds ratio, the risk of that is ninefold greater than in patients with other forms of hypoparathyroidism.

So, what our diagnostic workup is, is can be quite complex. It includes both clinical features and it includes laboratory determinations. So we want to first confirm that the patient has persistent hypocalcemia over time, so repeated measurements of the biochemical parameters. And then we want to carefully review the medical and surgical history. Just convince yourself there's been no neck surgery. Convince yourself there's been no radiation to the neck for any condition. Look for autoimmune-associated conditions that can be seen and other forms of infiltrative disease that can lead to hypoparathyroidism. And take a careful medication history from your patient.

Then you want to look carefully at the family history, and you want to try to get at least a three-generation family history, if you can, from your patient.

And then we want to look at the PTH carefully. We want to look at the phosphorus, the magnesium. We want to make sure we're not dealing with vitamin D problems, so measure a 25-hydroxy vitamin D. We want to measure renal function by a serum creatinine and an estimated GFR. And then we want to determine that 24-hour urinary calcium excretion along with creatinine.

And so, it's a very detailed and thorough both clinical and biochemical examination of the patient.

Let's turn now to what genetic testing will show us. These are data from Dr. Mannstadt and his colleagues presented at the 2026 European Congress of Endocrinology. In this study, they tested nearly 450 patients with nonsurgical hypoparathyroidism over the period of 2020 to 2025, and they found that a variant—a genetic variant—explaining the hypoparathyroidism, was present in nearly 50% of their patients. When you look at those variants and the commonness of the different variants, the calcium-sensing receptor was found in 40% of those patients. The next couple of commoner diagnostic variants were in the AIRE gene, the GATA3, and the TBX1. So, doing genetic testing in these patients definitely pays off. You come up with a genetic etiology in approximately 50% of patients.

When should we order genetic testing in our patients with nonsurgical hypoparathyroidism? Dr. Roszko and her colleagues, in a very comprehensive review of this topic, recommended pretty much that all patients with idiopathic hypoparathyroidism should undergo genetic testing, and I strongly agree with that recommendation.

So now let's turn to our first polling question: Who should be tested? And our question is: Which patient with hypoparathyroidism has the strongest indication for genetic testing? Answer A: Postsurgical hypocalcemia after thyroidectomy with improving labs; Answer B: Nonsurgical hypocalcemia, low PTH, hypercalciuria, nephrocalcinosis, and a sibling with kidney stones; Answer C: Transient hypocalcemia during acute pancreatitis; Answer D: Isolated vitamin D deficiency with secondary hyperparathyroidism.

So the best answer to this polling question, which patient with hypoparathyroidism has the strongest indication for genetic testing, the best answer is B, nonsurgical hypocalcemia, low PTH, hypercalciuria, nephrocalcinosis, and a sibling with kidney stones. That's the best answer because, as you've just heard, this really is the hallmark of ADH1, and ADH1 patients, the diagnosis is best made by genetic

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testing.

Genetic testing: What to order. So, what testing should we consider ordering when we are evaluating a patient with nonsurgical hypoparathyroidism? Well, we want to use a targeted hypoparathyroidism gene panel as our first-line test. We want to make sure that the calcium-sensing receptor gene is included in that panel. So we want to look at the menu, if you will, of the genes that are involved in that panel. And I would strongly recommend that you consider using the free testing available through PreventionGenetics. And it's available to all patients who meet the eligibility criteria as outlined on that website.

If, after you do that testing, the suspicion still remains high and you don't have a genetic etiology, then I think it's very important to consider a genetics clinic consult and potentially genetic counseling for that patient.

Dr. Collins:
Thank you, Dr. Shoback.

And with that, I'd like to return to the case that we discussed earlier of the 50-year-old man who was referred for chronic hypoparathyroidism, who had symptoms that started at the age of 6, had nephrocalcinosis at age 14, and had a number of complications, including hospitalization for hypercalcemia.

And that brings us to poll question #2, which deals with a case decision point. And the question is: What would you do next for our 50-year-old male patient referred for chronic hypocalcemia? Option A: Increase calcium, calcitriol, and monitor.

Option B: Pursue genetic testing for nonsurgical hypoparathyroidism that includes the calcium-sensing receptor; Option 3: Refer to nephrology first because of nephrocalcinosis.

The answer, of course, is Option B: Pursue genetic testing for nonsurgical hypoparathyroidism that includes the calcium-sensing receptor.

Dr. Shoback:
So, when we obtain the genetic testing, we have to interpret the results, and we have to explain them to our patients. So, there are three options for the results that come from genetic testing. You may get a positive result, you may get a variant of unknown or unclear significance, and you may get a negative but suspicious result from the genetic test that you order.

So, the positive result means that you have identified a pathogenic or likely pathogenic calcium-sensing receptor gain-of-function variant that supports the diagnosis of ADH1 in a patient with the right phenotype. And we've talked about that phenotype. So that's straightforward. That's a positive result.

The VUS, when we get that result, we need to go back and look at the clinical phenotype. We need to correlate that with the variant. We need to then do family studies when it's feasible, and we need to exercise caution so that we don't overcall clinical significance to this variant of unclear significance. If the result is negative, it doesn't completely eliminate all genetic etiologies, and one may need to pursue further testing if your suspicion remains high.

So, we want to always correlate the results of genetic testing with the biochemical phenotype, the patient hands, the family history. And if we need to, we need to get our genetics colleagues involved by consultation.

So, let's turn now to poll question #3: The positive genetic test. So, a patient with hypoparathyroidism is found to have a gain-of-function calcium-sensing receptor mutation, or ADH1. Which of the following statements best reflects the clinical implication of this genetic diagnosis for management? Answer A: The serum calcium should be aggressively normalized to the upper limit of normal to prevent symptoms; Option B: It's usually not difficult to titrate calcitriol and calcium to achieve both normal serum and urine calcium values; Option C: Raising the serum calcium with treatment will disproportionately increase renal calcium excretion, increasing the risk of nephrocalcinosis; or Option D: The genetic diagnosis confirms that standard hypoparathyroidism treatment protocols can be applied without modification.

So the best answer to poll question #3 is Option C: Raising the serum calcium with treatment will disproportionately increase renal calcium excretion, increasing the risk of nephrocalcinosis. Again, we reviewed nephrocalcinosis in the prior slides, and it's clear that this is a definite complication of this disease. So that's the best answer to this question.

So, the genetic diagnosis, if you can make it, can really change the management of patients with hypoparathyroidism. For the patient, it confirms the mechanism of their disease. It may explain why conventional treatment can worsen the hypercalciuria that they might have. It really refocuses them and us on monitoring for renal outcomes, and it has significant family implications. And it also creates a rationale for considering new and emerging therapies and future therapies for mechanism-based treatment options, since the genetic diagnosis in these patients matters a great deal.

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Dr. Collins:
So now let's turn to the importance of identifying ADH1. So, addressing the issue of underdiagnosis, what do the data tell us about that?

This was a recently published paper, this 2025, that really outlines the importance of this. The symptom burden of ADH1 was greater than twofold higher than previously appreciated. This was a study that involved large databases: the UK database, the *All of Us* database, and the Mass General database. As you can see, hundreds of thousands of patients were assessed. And they assessed the relative prevalence, penetration, and expressivity of ADH1 CASR gain-of-function variants.

And what they found was that in patients who had ADH1 variants in the UK database, 63% of those patients had hypocalcemia, and in the *All of Us* database, 89% of those patients had hypocalcemia. So, you can see it was really quite penetrant if you had that variant.

What was also important, too, is that it also showed that relatively few of those patients who had ADH1 variants had the appropriate diagnosis. Only 17% in the UK database, and only 44% in the *All of Us* database. So, the majority had hypocalcemia, and less than 50% were diagnosed.

Why is this diagnosis often missed? And that is, one, because the biochemical overlap with other etiologies of hypoparathyroidism is common. There may be fragmented care across neurology, nephrology, pediatrics, and adult endocrinology. There's a general perception that ADH1 is just too rare to test for, and there's uncertainty about what panel to order and how to interpret the results.

But we have to keep in mind the consequences of a misdiagnosis. There are long-term complications that can progress and will not be addressed, and these include, as Dr. Shoback and I pointed out, nephrolithiasis, nephrocalcinosis, and chronic kidney disease.

There's also a missed opportunity to advise pregnancy planning and the diagnosis of other family members. Importantly, conventional therapy in the US with calcium/calcitriol does not address the underlying pathophysiology and can, in fact, worsen the renal complications.

So, I want to return again to the case that we talked about earlier and point out the importance of this by highlighting the family history. This patient had two older siblings who had died in infancy with hypocalcemic seizures. The father, who had had lifetime symptoms, was not evaluated till his son was diagnosed, and now had an explanation for the symptoms that he had had across his life span. They were also able to identify cousins and additional family members who were affected and had the diagnosis of ADH1. So early genetic clarification could have changed care for multiple relatives. Important to test family members once a patient is identified.

So this brings us to poll question #4: What raises your suspicion? So the question is this: Which single feature below most strongly raises suspicion for ADH1? Option A: Chronic low calcium alone; B: low calcium with low PTH; C: Low calcium with low PTH plus nephrocalcinosis and hypercalciuria; D: Prior need for calcium and calcitriol; E: No history of neck surgery or autoimmune disease.

So, the answer to poll question #4 is low calcium with low PTH plus nephrocalcinosis and hypercalciuria.

So, let's review how calcium-sensing receptor activating variants cause ADH1. So, at the tissue level, activating variants in the calcium-sensing receptor increase tissue sensitivity to calcium. So, in the case of the parathyroid and the kidney, the dose-response curve to calcium is essentially shifted to the left, and that results in less PTH secretion at lower blood calcium and more calcium excretion at lower blood calcium.

The results are there's a decrease in PTH secretion, there's a decrease in blood calcium, and there's an increase in urinary calcium. The clinical manifestations of this begin in the acute phase are hypocalcemic seizures, paresthesias, tetany, and muscle cramps. Long-term complications include nephrolithiasis, nephrocalcinosis, and chronic kidney disease. And a very important point of all of this is that conventional therapy—calcium and calcitriol—does not address the underlying pathophysiology and can worsen renal complications.

The good news is that from this disease mechanism we can go to targeted treatment. Can we address the underlying receptor defect? And the answer is yes. There's a class of drugs called calcilytics that are a potential treatment for ADH1.

So, what are calcilytics? Calcilytics are negative allosteric modulators—antagonists of the calcium-sensing receptor—that decrease calcium-sensing receptor sensitivity to extracellular calcium. Normalizing calcium-sensing receptor sensitivity could correct hypocalcemia, hypercalciuria, and the low PTH in individuals with ADH1.

What they do essentially is shift the dose response group both the parathyroid gland and the kidney back towards normal. Allowing for the normalization of blood calcium, urine calcium, and PTH. So, the CALIBRATE trial was the phase three trial used to test the efficacy of encaleret in patients with ADH1. It was a controlled trial where two to one patients received encaleret to standard of care. 45 patients received encaleret, 22 patients received standard of care. Through 20 weeks of study, 4 weeks of maintenance, and a 48-month long-term extension.

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The primary endpoint was a proportionate patients who achieved normalization of blood calcium and simultaneously urine calcium as well. This is the first study in hypoparathyroidism where both normalization of blood and urine calcium is the primary endpoint. The secondary endpoints included proportion to achieve intact PTH above normal, proportion to achieve 125 vitamin D, magnesium phosphate within range, bone turnover markers, and renal ultrasound calcification. So, the efficacy of the phase 3 trial is shown in this slide, and it shows that blood calcium on encaleret very quickly rose within the normal range, in patients on standard of care the blood calcium remained low. When patients on standard of care wwere crossed over to encaleret they rapidly achieved normalization of blood calcium as well. And this was maintained throughout the entire trial through the long-term extension.

At the same time, the 24-hour urine calcium, which was high at baseline, rapidly normalized in patients on encaleret. And when patients on standard of care crossed over to encaleret they also normalized their 24-hour urine calcium throughout the duration of the study. In terms of the secondary endpoints, blood phosphate, which was on the high side, high in some patients, rapidly came down into the normal range and remained within the normal range throughout. As did magnesium, it was on the low end at the beginning of the study, and it normalized into the normal range you know crossing over, phosphate and magnesium maintained within the normal range as well.

So, in terms if efficacy, encaleret met all primary and secondary efficacy endpoints, about 76 percent of the patients on encalerent achieved a normal serum and urine calcium. 91 percent of the patients on encalerent achieved restoration of PTH levels and encalerent corrected main serum and phosphate magnesium to the target normal range. As far as safety, encaleret appeared to be quite safe as far as treatment emergent adverse events, we see that the primary treatment emergent adversement was hypercalcemia. It was seen in about 22 percent of the patients on encaleret. This also counted for the headaches that these patients experienced, but it was really those two that were the only ones that were different between encaleret and standard of care. So overall, encaleret was safe and effective in patients with ADH1.

So this brings us to poll question #5: Response to calcilytics. The question is: What lab profile would result from treatment of ADH1 with an antagonist of the calcium-sensing receptor? Option A: Reduction in serum PTH with elevation in serum calcium; Option B: Lowering of serum magnesium and phosphate; Option C: Improvement in urinary calcium and normalization of serum calcium; Option D: Improvement in renal function and reduction in urinary calcium.

And so the answer to poll question #5 is C, improvement in urinary calcium and normalization of serum calcium.

So, what's the evidence shaping ADH1-related practice? So the best practice recommendation: Genetic testing is advised for all patients with idiopathic hypoparathyroidism, especially if family history is positive or the patient is under the age of 40.

Calcium-sensing receptor variants in ADH1: There's over 121 calcium-sensing receptor variants have been described in patients with ADH1, and hypoparathyroidism due to gain-of-function variants in the calcium-sensing receptor with ADH1 is associated with more symptoms and is often underdiagnosed.

And ADH1 impacts hypoparathyroidism management. Conventional therapy can exacerbate hypercalciuria and increase risk for renal complications in patients with ADH1. So, if you're giving conventional therapy to patients with ADH1, you have to be more conscientious and test laboratory values more often.

To me, this slide really is the bottom line on this. If your patient doesn't have a scar, you have to do genetic testing. No scar. Check the CASR.

And this brings us to the next section: Genetic testing, supporting your patient.

So, let's review the genetic testing results in the case that we've been talking about.

The test that was ordered was a hypoparathyroidism gene panel, and the results identified a pathogenic variant in the calcium-sensing receptor. The specific variant was arginine 825 histidine. It was a heterozygous variant, and it was classified according to the American Congress of Medical Genetics as pathogenic, the gain-of-function missense variant.

So our interpretation of this: It confirms the diagnosis of ADH1. It explains the patient's triad of hypocalcemia with low or inappropriately normal PTH and disproportionate hypercalciuria. It also explains why his conventional calcium and calcitriol therapy does not correct the calcium-sensing receptor defect and may worsen renal calcium deposition, as it did in this patient, and that this patient, as other patients with ADH1, will require more frequent monitoring and dose adjustments than the normal postsurgical hypo patient.

Because this is autosomal dominant transmission, there's a 50% risk of first-degree relatives having this same thing, and testing of the at-risk relatives is recommended.

Dr. Shoback:
So we need to do quite a bit of education when we're doing genetic testing in patients with nonsurgical hypoparathyroidism, and we

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need to use language that patients can understand and appreciate.

So, the key message when going after the genetic testing is to explain how it will impact our management of their kidney disease and explain the kidney findings, how it may really provide clarity about the diagnosis that they have, and it may impact which family members need to be evaluated and the family members need to be evaluated.

So, when we talk to patients, we want to tell them this is going to help us explain the cause for the low blood calcium and the low PTH. It may explain the kidney findings if we have a positive genetic result, and it may again help with guiding us to evaluating other members of the family. We want to remind them that the results can be positive, which is a clear-cut result. They can be uncertain, or they can be negative at the point in time when the testing is done. And then we want to also remind them that in the future we may do this testing again. The testing may or may not change the therapy that we use today, but it may improve our understanding of their diagnosis, may help with family planning, and may lead to the application of future new therapies that come up as research is being done that may impact the management of their condition.

So, when do we bring up the issue of testing family members in patients who are at risk for ADH1 or have ADH1? We want to discuss it after we confirm that a pathogenic or likely pathogenic variant has been found in a patient. We want to do a very careful, at least three-generation family history. We want to explain autosomal dominant inheritance in the plain language we just, you know, practiced. We want to prioritize the screening of first-degree relatives, and then that can be extended based on how many relatives are available for screening and what the family tree looks like. And then often we come to referring an affected patient and other family members to genetics consultants and a genetic counseling service, if that's available to you.

And in general, family members should be advised to undergo targeted or site-specific genetic testing for the known variant, rather than undergoing the entire hypoparathyroidism gene panel. And so that means once a proband is identified, other family members can then undergo targeted testing for that particular variant.

The options for genetic testing are really quite extensive. Just two options I would strongly recommend that you consider is the hypoparathyroidism gene panel that's available through PreventionGenetics. This is free, and this will test for calcium-sensing receptor mutations and 26 other genes that are involved in genetic forms of hypoparathyroidism. So, it really expands the access of our patients to genetic diagnosis of their hypoparathyroidism, and this is a sponsored, commercially sponsored program and is free to patients and families.

There's also testing offered through Invitae, which is another genetic testing company, and several other companies. These are fee-based testing and include a vast number of genes involved in hypoparathyroidism and help you in making the differential diagnosis for the etiology in your patient with nonsurgical hypoparathyroidism.

So, the options are extensive, and I refer you to the Clinical Companion that was developed for this educational activity that gives you more information about genetic testing options for patients.

So, when we make this diagnosis and we want to discuss it with the patient and we talk about treatment options, we want to bring up that standard of care is what we may apply in a given case, but it does carry some risks to that particular patient. And the important risk is that we'll often increase the urinary calcium excretion, so the amount of calcium in the urine is often going to go up, and that has potential consequences.

When we make this diagnosis, our goals are going to change with regard to the biochemical parameters. We're going to maintain the serum calcium at a level high enough to control symptoms, but we want to at the same time minimize the urinary calcium excretion that the patient has.

We may use PTH replacement therapy, and we now have an FDA-approved form of PTH for that, palopegteriparatide. It's an option, but it's not been extensively tested in patients with ADH1.

And then, as Dr. Collins has described to you already, there are emerging targeted therapies, the calcilytics, and one of them is encaleret, which can directly counteract that overactive gain-of-function calcium receptor mutation that patients with ADH1 have.

And so this drives home the point how important it is that we understand the genetic cause of hypoparathyroidism in our patients because it's going to change our monitoring, and it's potentially going to change our treatment options for that particular patient.

Dr. Collins:
Okay, let's return to the case that we've been discussing throughout this presentation after the content that we've gone through.

So, in regard to treatment goals, you want to minimize urinary calcium with the goal to slow renal disease progression. You want to

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maintain serum calcium sufficient for symptom control while minimizing the degree of urinary calcium.

So, the management plan could involve PTH replacement to be considered to reduce hypercalciuria. Again, there is an approved medication, but it hasn't been extensively tested in patients with ADH1. You could consider in the future targeted calcilytic therapy when it becomes available, and you should monitor renal function, urinary calcium, and nephrocalcinosis.

And of course, what's important in patients with ADH1 is to consider family counseling. Offer calcium-sensing receptor variant-specific cascade testing to any at-risk relative, to refer to genetic counseling as needed, and in the families, to screen potential carriers for renal involvement.

Dr. Shoback:
So I'd like us to wrap up now and look at some resources that are available to both physicians and to patients, and the next steps for change in your clinical practice. Okay, so let's review some key practical takeaways from this educational activity.

I'd like you to reconsider idiopathic or nonsurgical hypoparathyroidism through a genetic lens. I'd like you to suspect ADH1 when low serum calcium and low PTH coexist with hypercalciuria, renal calcifications, symptoms in early life, or a positive family history.

We should use genetic testing more routinely as part of our diagnostic strategy for unexplained hypoparathyroidism. We should pursue a confirmed diagnosis, which informs clinical monitoring, patient communication, and family testing. And we should be able to explain to patients what the information that we're going to gain will and will not be provided by genetic testing.

So, our poll question #6: Application to practice. Which of the following actions are you likely to take? Select all that apply. Option A: Review a patient panel to identify patients with nonsurgical hypopara who may benefit from evaluation for ADH1; Option B: Share with your colleagues how identifying ADH1 can change the management of hypoparathyroidism; Option C: Determine how to access genetic testing for hypoparathyroidism; Option D: Explain the importance of genetic testing to patients diagnosed with nonsurgical hypoparathyroidism; Option E: Share information about free genetic testing and counseling with patients diagnosed with nonsurgical hypoparathyroidism; Option F: Share the Clinical Companion with your colleagues; Option G: Use the Clinical Companion when discussing ADH1 hypoparathyroidism with patients.

So, choose which actions that you'll take in your practice based on what you've learned during this educational activity today.

In conclusion, thank you so very much for participating in this educational activity. Can you please complete the evaluation and claim your credit, and remember to download the Clinical Companion with lots of information that you can use in your clinical practice.

Dr. Collins:
Thank you. I hope you enjoyed the presentation, and please do download the Clinical Companion.

Announcer:
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