ALAN MARMORSTEIN: Hi, I'm Alan Marmorstein, I'm a professor of ophthalmology at the Mayo Clinic.

JOSE PULIDO: And I'm Jose Pulido, professor in departments of ophthalmology and molecular medicine at the Mayo Clinic.

ALAN MARMORSTEIN: And today we're going to discuss the importance of genetic testing and diagnosing macular degeneration, with some emphasis on vitelliform dystrophies and Best Disease.

JOSE PULIDO: And the reason we think this is important, is because just looking at the fundus, the back of the eye, and doing electrical testing including electrooculography is insufficient nowadays to make the diagnosis. And we are showing three cases here. They've been variably called adult onset foveomacular dystrophy, they've been called macular degeneration, they've been called Best Disease. And only by doing genetic testing, which we can do nowadays in a very quick and very almost inexpensive way in comparison to older days, we can make these diagnoses. The importance is that now, we're at the threshold of treatments. And Dr. Marmorstein is going to explain to you some new and exciting treatments that we might have in the future, and some important early studies that are ongoing right now at the Mayo Clinic.

ALAN MARMORSTEIN: So here is the first case Dr. Pulido was referring to. This is a case where there are several different possibilities. Obviously adult vitelliform dystrophy and Best Disease would be considered for the differential diagnosis there. In this case, genetic testing ruled out Best Disease. Now vitelliform dystrophies like this-- we know from our own research in the Rochester Epidemiology Project-- occur in about one in 5,500 patients, at least in Olmsted County, Minnesota, which is probably representative of the United States as a whole.

Our next case here is a little bit different though. This is an example where we had a patient who came in and-- I don't know if you would like to comment on some of the possible diagnoses for this?

JOSE PULIDO: Dr. Marmorstein, thank you. So this has been thought to be possibly Best Disease, macular degeneration. And really, the genetic testing was what made the diagnosis. Dr. Marmorstein?

ALAN MARMORSTEIN: Right. In this instance, the patient was found to have a mutation in the gene BEST1. That mutation, A243V, has been found in patients who have both adult vitelliform dystrophy as well as Best vitelliform macular dystrophy. And in this particular instance, even without electrophysiologic testing, then we can assign this patient to the category of Best vitelliform dystrophy.

JOSE PULIDO: Which totally changes how we've been able to diagnose these patients nowadays.

ALAN MARMORSTEIN: Indeed. This third case was originally presented in the clinic as macular degeneration, as I understand it. And following genetic testing, the patient was found to have a mutation as well in the gene BEST1. And in this particular case, it's in an amino acid that has previously been shown to cause Best Disease. And so this patient's diagnosis went from macular degeneration to Best vitelliform macular dystrophy. Now what are the implications of this within your practice?

JOSE PULIDO: The implications are now important because we are at the threshold of being able to make changes in how we help the lives of these patients.

ALAN MARMORSTEIN: In consideration of these three cases, if you had done electrooculogram testing on these patients combined with electroretinogram testing, you would have had a similar ability to diagnose. Our first patient, with AVMD, would presumably have had a normal EOG and ERG. The second patient, who actually had what would be AVMD due to a BEST1 mutation, would have had a normal EOG and a normal ERG. And the third patient, who had Best Disease, if you had thought from the fundus photo that was Best Disease and ordered the EOG and ERG, would have had an abnormal EOG, a ratio under 1.55, and a normal ERG.

But instead of undergoing that testing, which is somewhat uncomfortable for the patient because they have to have the electrodes placed on their temples for the EOG and the bridge of the nose and the contact lens electrodes for the ERG, if they get genetic testing, this involves, in the worst case scenario, a blood draw. And many cases today, it can be done simply using a mouthwash. And it can be done at home if the patient desires. So it strikes me that we could replace the electrophysiologic testing using genetic testing. Would you agree with that?

JOSE PULIDO: I agree. And interestingly enough, many of these companies that now can do the genetic testing will actually call their insurance companies of the patients to determine whether insurance will pay. And many times, insurance companies will pay for this.

ALAN MARMORSTEIN: So in most cases, then, your patients are finding that their out-of-pocket expense is actually pretty limited. In the last couple of years, our laboratory at the Mayo Clinic has begun a clinical trial. It's listed on clinicaltrials.gov, and the information for this trial is shown on the slide that you're looking at. What we're doing is we're collecting DNA as well as skin fibroblasts from patients who have Best Disease or any of the other forms of Bestrophinopathy, and there are five.

The most common, of course, is Best Disease. We're also taking adult vitelliform dystrophy patients, patients with the recessive forms of Best Disease, including autosomal recessive bestrophinopathy, and then patients who have peripheral retinal disorders due to mutations in BEST1, and those are autosomal dominant vitreoretinochoroidopathy, as well as the very rare cases of retinitis pigmentosa. With the skin fibroblasts, we're preprograming them into induced pluripotent stem cells, which we can then differentiate into retinal pigment epithelial cells. That's the cell where Bestrophin, the product of the BEST1 gene is expressed, and that's where the pathogenic problem that results in these diseases occurs.

Now this allows us to do a number of things. From a therapeutic perspective, there are already phase 1 clinical trials using IPS-derived retinal pigment epithelial cells for the treatment of macular degeneration going on in several countries. Japan and there should be one going on in the United States shortly. But the bigger issue here is that it allows us to consider the same process to therapeutically treat Best Disease, potentially adult vitelliform macular dystrophy, autosomal recessive Bestrophinopathy, and we can generate models of these diseases in the laboratory. Those models allow us to understand the processes that have gone awry to cause the disease, and they allow us to test potential therapeutic compounds to determine whether they actually have effect on these specific patients.

There are over 200 different mutations that cause these diseases in the BEST1 gene, And so having the widest array of stem cells that we can representing the widest number of mutations is critical, because some patients may respond differently, dependent on their mutation, to different drugs that we test in the laboratory, that we hope to bring to the clinic in the not terribly distant future. So on that note, if the criteria for enrollment in our trial happens to be that you have genetically tested, genetically confirmed Best Disease or Bestrophinopathy, and that means that you have to have had that genetic testing done. And your patients have to have that genetic testing done in order to enroll in our trial, and probably any other trial that's going to come down the road using these therapies. And those trials are not far off.

JOSE PULIDO: It's a brave new world, and I suspect that in the not too distant future, we will be using these cells that are already growing in Dr. Marmorstein's labs, to help our patients with these forms of diseases. Specifically starting with Best Disease, but also going further than that.

ALAN MARMORSTEIN: Once again, I'm Alan Marmorsteing from the Department of Ophthalmology at the Mayo Clinic, and we've been discussing the use of genetic testing and diagnosis of Best Disease, vitelliform dystrophies, and macular degeneration.

JOSE PULIDO: And I'm Jose Pulido from the Department of Ophthalmology also at Mayo Clinic. Thank you for watching.