SPEAKER 1: One of the key questions in treating a lifelong disease is, at what point should we start treatment? And who are good candidates for treatment?

In Fabry Disease there is not universal agreement for this. But some guidelines have been developed. For classical Fabry Disease, at least in the United States, the recommendation is to start treatment as soon as any symptoms are defined, regardless of age or sex of the patient. However, in male patients with mutations that are associated with classical Fabry Disease, in the US we recommend consideration of pre-symptomatic treatment, if a patient gets to be beyond age 10. Because we know that all males with classical Fabry Disease will develop a significant disease. And the vast majority will become symptomatic early in life.

The reason for wanting to start treatment before they become symptomatic is that, in Fabry Disease one of the effects of the storage is cell death. And when the functional cells die, they are often replaced by a fibrous tissue. And the implication of that is that you will not be able to recover all of the lost function if you wait until you have a noticeable loss of function in the key organ systems.

So for example, if you wait until you have decreased cardiac function, it is unlikely that you would be able to recover that. Or if you wait until a patient has proteinuria or renal insufficiency, it is unlikely that with treatment, you will see reversal of that. At that point, the goal of therapy becomes stabilization at the current level of function.

So in the US, the desired strategy has been to start treatment early on patients, where you can be confident that they will have progressive Disease. So far that has all focused on the men. You may be wondering what's different about the women?

So in women, even with classical mutations, up to 30% will not become symptomatic. This is thought to be related to X-inactivation. So if you have some skewing of X-inactivation, so that the healthy copy of the alpha-galactosidase A gene is the active one, those women will often not become symptomatic. And because the burden of care for Fabry Disease is quite high, we would like to not treat the patients who will not become symptomatic.

In the US, the published guidelines have focused on treatment for any symptoms. So even the non-specific symptoms, if they are thought to be attributed to the Fabry Disease. So a woman, for example, who has hand or foot pain, or chronic fatigue as the primary manifestation of her Fabry Disease, would still qualify for treatment.

Some of the European guidelines however, have suggested that in Europe, the non-specific symptoms may not be adequate for treatment. That they would prefer that the patients-- that the treatment be held off either until it is so severe that it absolutely requires treatment, or until you see some evidence of involvement of the kidneys, heart, or brain, in the patients with Fabry Disease.