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Approval of the First CRISPR-Cas9 Gene Editing Therapy for Sickle Cell Disease

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Guest: Dr. Sean Campbell from the Chemistry and Immunology Laboratories at Montefiore Medical Center in New York City.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. Sickle cell disease, an inherited condition caused by a variant form of hemoglobin that results in anemia and impaired blood flow, affects an estimated 100,000 people in the United States alone. Because the variant hemoglobin is encoded by the patient's DNA sequence, standard pharmaceutical treatments temporarily alleviate symptoms but do not address the underlying cause.

As a consequence, affected patients experience repeated sickle cell crisis and often require repeated transfusions. Stem cell transplantation can cure some patients and may be appropriate in cases of severe disease, but this is not a viable option for all individuals. This all changed in 2023 when the FDA approved a new therapy for the treatment of sickle cell disease, the first to use CRISPR/Cas9 genome editing. A News & Views article, appearing in the October 2024 issue of *Clinical Chemistry,* highlights this new therapy, describes how it works, and summarizes the expected downstream impact on the clinical laboratory.

In this podcast, we're excited to welcome the article's author. Dr. Sean Campbell is a co-director of the chemistry and immunology laboratories at Montefiore Medical Center in New York City. Dr. Campbell's research focuses on hemoglobinopathies, diabetes, and other topics. Dr. Campbell, let's start out here. It is clear that the first approved CRISPR therapy would be a big deal but the fact that it was for sickle cell anemia, that is a bit unexpected. Could you tell us why that is?

Sean Campbell: Absolutely. So, like you said, it's clear why CRISPR becoming a therapeutic is a big deal. But sickle cell disease is actually the most common monogenic disorder in the US, but it receives a fraction of the funding of other similar monogenic disorders. So, the fact that this big breakthrough was made on sickle cell disease was little unexpected and fantastic. And actually, the approval of this treatment brings the number of approved therapies for sickle cell disease only to six overall. So, yeah, very unexpected but very welcome.

Bob Barrett: Six? That is amazing after all this time.

Sean Campbell: Yeah.

Bob Barrett: Could you briefly explain how this therapy works?

Sean Campbell: Yeah. In brief, a person's stem cells are harvested from their blood and then edited with CRISPR to damage a protein called BCL11A. And the important thing with that is that's what shuts off the fetal hemoglobin production in adults. And so, when you damage that, it actually allows fetal hemoglobin to be produced again. Fetal hemoglobin is really good for stopping sickle's hemoglobin from sickling, as its namesake. And once you stop that, you stop most of the problem with the disease.

So, once that's edited, once those cells are growing well, you actually remove the rest of the patient's marrow, bring back in these new healthier cells that can then be producing both this fetal hemoglobin as well as sickle hemoglobin. Once that fetal hemoglobin is around, you can stop the problems, and then the patient has healthy red blood cells.

Bob Barrett: What effect could this have on laboratories? Should we alter our practices as a result of this?

Sean Campbell: So, yeah, testing for hemoglobinopathies and diagnosing hemoglobinopathies can already be pretty complicated. And so, this is going to add to that. there's already a genotype called hemoglobin S and hereditary persistence of fetal hemoglobin. This is kind of a natural mutation that occurs. And patients that have this therapy are going to look a lot like that. It may also look like patients that are on one of the other approved drugs called hydroxyurea, which has very similar effects. And so, we are really going to have to be careful with patient histories when we're diagnosing to know when patients are presenting to our centers that we have all the information as to if this is a patient undergoing treatment, which treatment, and their genotype. So, it will make things a little more complicated I think, but we can figure it out.

Bob Barrett: So, doctor, do you foresee many patients receiving this treatment?

Sean Campbell: I do think eventually, but it will take us a lot of time to get there. One of the major things of course is insurance coverage. These treatments can cost them into the millions of dollars. And so, having insurance approve this is already a challenge. And once the patient is approved, you have to go to an approved center that's been approved by one of these pharmaceutical companies to make the drug. Also, after that, it takes multiple months, between four to six months, to go through the entire process.

So, I do think we will see patients getting this, in time, but I think it's going to take us quite a few years before we see many, many patients getting it.

Bob Barrett: Finally, Dr. Campbell, looking ahead, where do you predict CRISPR treatments going next?

Sean Campbell: So, there's a lot of interesting research into CRISPR, of course. CRISPR is really interesting, because we think of it as an editing tool, but actually it's really the best at breaking things.

It is originally from kind of a bacterial immune system. And so, disorders where removing a broken gene from the system is going to be the best place. So, that's one of the reasons why it came up in sickle cell disease, because if we can break that BCL11A, that actually leads to a healthier patient. So, any disorder we can see where stopping a single gene from working is going to be curative. I think we're going to see a lot of progress. So, I'm not quite sure where that is yet, but I do think that we're going to see quite a few more coming down the pike.

Bob Barrett: That was Dr. Sean Campbell from Montefiore Medical Center in New York City. He wrote a News & Views article describing gene editing therapy for sickle cell disease in the October 2024 issue of *Clinical Chemistry*, and he's been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.