Hello my name is Linzy Elton and I'm a postdoctoral research associate at the Centre for Clinical Microbiology at University College in London. I'm going to talk about how genomics is being applied to tuberculosis and drug resistance. What is tuberculosis? So tuberculosis, or TB, is a bacterial infection that's spread via air droplets and can cause weight loss, fever, and a cough. Around 10 million people a year, mostly in low- and middle-income countries, are diagnosed with TB, and around 1.5 million people die, despite it being treatable. This is due to the difficulties with diagnosing people appropriately and starting them on treatment on time.

In 2020, it was estimated that 4.1 million TB cases went undiagnosed. Why is it so difficult to diagnose and treat? Whilst access to diagnostic and treatment facilities is a major factor in mismanaged cases, the bacteria that causes TB, mycobacterium tuberculosis, can make it more complicated. Many diagnostic laboratories, especially in resource-constrained settings, use culturing methods. And MTB is a slow-growing organism, which makes diagnosis a long, slow process and can take weeks and also requires high-safety laboratories. Once a patient is diagnosed with TB, they will then begin treatment.

Mycobacteria have a thick cell wall, making it hard for antibiotics to penetrate and kill the bacteria. Even with straightforward cases, it can take six months of treatment. What if you don't, then, respond to treatment? Whilst many people do respond well there are increasing numbers of patients who still have the TB bacteria in their bodies after their course of treatment ends. There are several reasons someone might still be infected, the most common of which is drug resistance and drug resistance can occur when antibiotics are mismanaged.

How can sequencing help? Sequencing is being integrated into more tuberculosis diagnostic and research laboratories. Looking at the bacteria's genome can identify which drug resistance mutations might be present. Whole genome sequencing, or WGS, can also help spot new potential drug resistance mutations which is vital for keeping drugs working into the future.

Sometimes patients can catch a new strain of TB whilst they're being treated for the original one. This is known as a reinfection. Sometimes the original bacteria aren't completely eliminated and cause infection again, which is known as a relapse. Comparing before and after treatment TB samples can show you whether they are genetically identical and therefore a relapse of the original bacteria or genetically different, which means somebody has been reinfected with a different strain.

TB is very slow-growing, and sometimes the difference between patient strains can be as few as tens of SNPs within a genome of 4.4 million bases. We're becoming increasingly aware as well that TB, as the disease, isn't just caused by one species but also a whole group of other organisms, too, collectively called the non-tuberculous mycobacteria. These different species respond to different drugs differently, and without looking at their genomes it can be very hard to tell them apart.

Is it difficult to sequence TB? The cost of sequencing is continually decreasing, and for TB whole genome sequencing it's around $100 depending on the platform and the scale of your sequencing. But there are still some issues when sequencing the mycobacteria. Because of its thick cell wall, it can be hard to extract enough high-quality DNA and currently this makes sequencing directly from a patient's sputum unrealistic on a large scale, so scientists have to rely on culturing, which can take time to grow.

The genome itself also makes it tricky to sequence as it's very GC rich and it has many repeated regions, too, which can make it difficult to assemble the genome correctly, like putting the pieces of a puzzle together. What does the future look like? Whilst at the moment sequencing is unlikely to replace traditional diagnostic methods such as culturing, it's a powerful complementary tool to help understand difficult-to-treat cases. As the cost reduces and technologies advance, it will become more widely available, not only helping with routine diagnosis but also in surveillance and research to help reduce TB burden for future generations.