Diagnosing Disease: The Past, Present and Future with Dr Michele Gregorini and Dr Tobias Schindler

[Vicky Edkins]
Welcome to the Science Speaks: Conversations on Health podcast. This podcast series has been developed by the Basel Research Centre for Child Health in Switzerland to share some of the great work that is taking place and to look at what it means to be a scientist within the various disciplines that are represented by the Centre.

In this episode, we are delighted to be talking to Dr Michele Gregorini and Dr Tobias Schindler from ETH Zurich. Michele and Tobi are both postdoctoral researchers at the Institute for Chemical and Bioengineering at ETH Zurich and the co-founders of the ETH spin-off company Diaxxo.

Michele and Tobi, thank you very much for joining us.

[Dr Michele Gregorini]
Thank you for inviting me to the podcast. It's an honour to be here and I'm very excited to dive into our discussion today.

[Dr Tobias Schindler]
Thanks Vicky. I'm grateful to be on your podcast. It's a pleasure to be here alongside Michele and I can't wait to explore the topics we have lined up.

[Vicky Edkins]
Thank you.

During this podcast, we're going to take a whistle-stop tour through time to look at the ways in which diagnosing common diseases have changed over the past few decades, the developments that were made specifically by Michele and Tobi's team during and following the COVID-19 pandemic and also what the future of disease diagnosis might look like.

Tobi, take us back 50 years, if you will, and give us an insight into the ways in which common infectious diseases were diagnosed and how these methods have evolved over time.

[Dr Tobias Schindler]
Over the past decades, the diagnosis of infectious diseases has undergone a significant evolution, driven mostly by technological advancements and a deeper understanding of pathogens. For example, prior to the discovery of HIV as the cause of AIDS, diagnoses were made solely based on symptoms and epidemiological links, leading to widespread misinformation about the disease and its transmission. Today, we know that among many other reasons, the lack of a reliable diagnostic test for HIV most likely contributed to the spread of the HIV-AIDS pandemic in the early days.

A significant advancement in diagnostic testing came with the development of immunoassays in the late 1950s. This technology enables the detection of antigens from pathogens and in the case of serological tests, the identification of antibodies

against these pathogens. The ability to detect pathogen-specific proteins revolutionised diagnostics because, before that, it took a very long time, sometimes days to weeks, to grow the pathogens in a lab and then identify them by microscopy.

Very often, the results were actually inconclusive. So if we go back to our example of HIV, the widespread introduction of antigen and antibody-based diagnostic tests in the late 1980s and in the 1990s enabled diagnosis well before the onset of symptoms and therefore helped a lot in understanding and managing the spread of HIV-AIDS.

Another very important step in technological development was in the 1990s. The so-called polymerase chain reaction, or short PCR, technology completely revolutionised diagnostics by detecting the pathogen's DNA and RNAs, so its nucleic acids, providing and that provided a level of sensitivity and especially flexibility which surpassed that of antigen-based diagnostic tests.

[Vicky Edkins]
Thank you. And Michele, can you explain what has happened more recently?

[Dr Michele Gregorini]
In recent years, the focus has shifted towards rapid point-of-care diagnostics and this was driven by the need for immediate decision-making, especially in clinical settings. Technologies like CRISPR-based diagnostics and portable devices have emerged, offering quick and accurate results without the need for sophisticated lab facilities. The COVID-19 pandemic accelerated all of this, highlighting the importance of rapid, accessible and reliable diagnostic methods in managing infectious diseases.

However, it's important to note that despite this advancement, the majority of diagnostic tests today are still performed in centralised laboratories and major hospitals only. This reliance on centralised facilities can lead to delays in diagnosis and treatment, particularly in remote or underserved areas where access to such infrastructure is very limited.

Over the last 50 years, new diagnostic technologies have not completely replaced older methods. Instead, I would say they have complemented them, expanding the toolkit available to the diagnostic community. As a matter of fact, indeed, it's common to find PCR and microscopy being used side by side in today's diagnostics laboratories. And this shows how these tools collectively enhance our capabilities.

[Vicky Edkins]
Thank you. You mentioned in your answer COVID, and of course, COVID has kind of monopolised discourse on disease diagnosis over the past few years. When we first started to hear about this new coronavirus disease at the end of 2019, what methods and technologies were available to diagnose the disease at that point?

[Dr Michele Gregorini]
Yeah, you said it correctly. At the end of 2019, when COVID came, the primary and mostly only method to diagnose the infection was real-time reverse transcript polymerase chain reaction, or PCR, as everybody knows it. This was a molecular technique, which was a cornerstone in infectious disease diagnostics for years, and it was rapidly adapted to detect the novel coronavirus.

Other methods like serological testing to detect antibodies were still under development and they were not immediately available.

[Dr Tobias Schindler]
Yeah, I would probably add that major benefit of PCR-based diagnostics lies in their rapid development. So thanks to the technique, simplicity, and especially universality.

So for instance, after the first genome sequence of SARS-CoV-2, the virus causing COVID-19, was shared in January 2020, it took less than two weeks for a group of European researchers to design and publish a complete PCR test for detecting this new virus. So they did not only design the test, but they also tested it actually under lab conditions. So they made sure that it's working reliably and the performance is good.

So I think that shows very nicely that the speed, like from obtaining a genomic sequence of a completely new virus to deploying a ready-to-use test for even mass screening is unmatched by any other diagnostic technology.

[Vicky Edkins]
Two weeks seems incredibly fast. Can I just ask, what is that process? What did those scientists do in those two weeks?

[Dr Tobias Schindler]
Yeah, so as soon as they had access to the genomic sequences, they were able to compare this new virus with similar viruses, other coronaviruses, also especially the coronavirus number one, which caused the pandemic 20 years earlier, and also drew a lot of experience from that epidemic and used comparative genomics to identify regions which were perfect for designing a PCR assay. And another big advantage was that this team of researchers from different European institutions also had access to a lot of samples for different viruses. So they could also test cross-reactivity to other coronaviruses.

So the combination of having access to the genomic sequences and a big biobank or a large biobank of lab-cultivated viruses helped them a lot to be so fast.

[Vicky Edkins]
Great. And what were the major problems or deficiencies that were associated with those diagnosis methods that were already available during the pandemic at the beginning?

[Dr Tobias Schindler]
Yeah, while PCR is in general a great technology, it requires quite some specialised laboratory equipment and also skilled personnel. So we saw it, especially during the early days of the pandemic, that the reliance on PCR also meant that there were also constraints in terms of laboratory capacities. That also was leading to challenges in accessibility to testing and turnaround times were sometimes also rather long.

[Vicky Edkins]

And did that lead to inequalities between different places, particularly geographically in terms of accessibility to accurate testing?

[Dr Tobias Schindler]
Yeah. In December 2019, while I was still engaged in malaria research, I was asked to help with setting up SARS-CoV-2 diagnostic capacities in some of our partner labs in sub-Saharan Africa, just in case this new virus would turn to be a problem, right?

So this required also coordinating a lot of supply chain mechanisms. So I had to purchase PCR machines and reagents. But then as soon as the situation escalated into a global health crisis, securing tests and equipment, swabs and even protective gear became increasingly difficult due to export restriction in some countries and also the overall holding in global logistics because of widespread lockdowns. So in the early 2020s, there was a significant shortfall in diagnostic tests worldwide, with lower-income countries often facing neglect from major suppliers.

[Vicky Edkins]
And how do you think people's expectations and demands of healthcare, specifically in diagnostics, changed during the pandemic?

[Dr Michele Gregorini]
I think that throughout the COVID pandemic, there was a notable shift in how people perceived and demanded healthcare diagnostics. The urgency of the situation led to an increased expectations for swift and easily accessible diagnostic methods, notably the rapid antigen test for home or immediate use. Convenience in testing, along with the ability to access and interpret results digitally, became paramount.

People also grew more concerned about the accuracy and the reliability of the diagnostic test, driving a demand for high quality but yet accessible testing methods. Additionally, there was more awareness of preventing healthcare, with more individuals seeking regular health screenings. The pandemic also improved health literacy, as people sought to understand more about the diagnostic process and their health in general.

However, this pandemic also catalysed a shift towards more rapid, user-friendly, and transparent diagnostic services in healthcare.

[Dr Tobias Schindler]
Yeah, and I would say the good thing is like today a vast number of people are familiar with PCR. Even my daughter, who lived through the pandemic and had to participate in mass testing at school, also knows what a PCR test is. So this is amazing, right? But I think it's also very important to mention here that PCR is more than just a vehicle for testing COVID. You can basically diagnose any disease, whether it's a bacterial or viral infection.

[Vicky Edkins]
You were both part of a team of scientists that developed a new technology for diagnosing COVID-19, and as you've already highlighted, potentially other diseases. Can you tell us what is unique about the technology that you developed, and what the advantages of this technology are?

[Dr Michele Gregorini]
Yeah, sure. So we have developed an entirely new technology with the goal of making diagnostics faster and more accessible, and also affordable, especially in point-of-care settings. The whole idea is based on a small cartridge, which we call pod, that has everything needed for a PCR test inside it. All the chemicals, all the reagents within the same cartridge. And this pod can be stored at normal room temperature for more than 12 months. And obviously this makes it much easier to handle and ship it around the world, compared to traditional PCR tests, which often need to be kept cold at low temperature. Therefore, you need a cold chain, both for shipping and storage. And with the support of the Basel Research Centre for Child Health, we were able to enhance this technology significantly and finalise our point-of-care platform, capable of detecting a variety of viral and bacterial infections based on our unique pods.

[Dr Tobias Schindler]
Yeah, and the second major milestone was the development of our own small-size, low-cost PCR device. So our compact device can quickly analyse the pods Michele just described and deliver fast and accurate PCR results, and this even in very remote locations. So our innovation brings precise PCR testing from specialised labs to where it's needed most, making in the end PCR more accessible.

[Vicky Edkins]
It sounds like an incredibly impactful development that you produced, this technology. Are you able to describe the process that you underwent to develop this technology? And in addition to that, kind of who was involved in that process as you went along?

[Dr Michele Gregorini]
Sure. So let's start from the beginning. So the first step in the journey is to develop a proof of concept of the technology.

The goal is to understand whether the idea would actually work. Can you actually make a PCR test on a sample holder that is completely new with different chemicals in a shorter time? So you go ahead and go to the lab and perform a lot of research and preliminary tests, often with state-of-the-art equipment.

And the goal is indeed to validate the underlying science and make sure that the technology at the end will deliver what you think. Once you confirm that the concept is viable, you move on and design and develop the prototype. And this required a multidisciplinary effort.

We had a team of engineers, scientists, designers, multicultural, multinational, all working together to create a functional model of a diagnostic device. After countless hours of tweaking and testing and fixing issues, we achieved a working device. But this is just a starting point because then you need to optimise the design to improve accuracy, usability, and reliability.

And this involves more rigorous testing, both in the lab and with initial user feedback to identify any potential issue or areas for improvement.

[Dr Tobias Schindler]

Thanks to numerous collaborations, we have often been able to deploy our devices in field tests in real-world settings with the aim to collect feedback on its performance, usability, and overall impact on diagnostic processes. Throughout this journey, we faced numerous challenges and learned valuable lessons.

But seeing our device make a difference in the field is always incredibly rewarding. In a remarkably short period, we managed to complete the CE certification process for our COVID-19 testing. That was a very critical step towards broader recognition and acceptance in the European market.

And furthermore, we established a spin-off company called Diaxxo to facilitate the distribution of our products, ensuring that our innovative diagnostic solutions could reach the market effectively and contribute to global healthcare needs.

[Vicky Edkins]
Sounds like a phenomenal process to have gone through. You mentioned some of the challenges that you faced during that process. What were the major challenges?

[Dr Tobias Schindler]
Yeah. The development of diagnostic tests, especially in the case of PCR tests, is a rather complex task. A PCR test is a very delicate system where each of the elements must align perfectly to ensure a robust and accurate performance.

The development of a complete PCR platform, as in our case, which also includes devices, not only the tests, presents further challenges. So it requires the optimisation across very distinct areas of expertise. So that includes more like from the lab side, biochemistry, molecular biology, but then also includes developments on hardware and software.

[Dr Michele Gregorini]
Right. And additionally to all this complexity, there were external factors that significantly impacted our progress. We all remember that the global supply chain was completely disrupted, and this was coupled with travel restrictions, lockdowns, and at the end for us, this was generating real substantial hurdles.

These issues not only affected the availability of the necessary materials, the components, the hardware parts, but they also hampered our collaboration efforts, as you could not meet in person and exchanges were severely limited. Navigating through these challenges required a lot of adaptability and resilience and a strong commitment to overcoming obstacles to finally achieve our objectives.

[Vicky Edkins]
Looking forward, how do you think the developments that you made, these new testing systems, will equip us better in the future?

[Dr Michele Gregorini]
So our mission extends beyond just bringing our diagnostic platform to decentralised settings. We aim to develop a comprehensive portfolio of diagnostic tests for both human and animal diseases, and maybe even more. We are focusing on the most common and critical needed diagnostics.

For human, this includes tests for influenza, malaria, and sexually transmitted infections, just for example. And in animal health, we are targeting prevalent and impactful diseases, such as avian influenza.

[Dr Tobias Schindler]
Yeah, we believe by covering a broad spectrum of both human and animal diseases, our platform, our ideas, seek to address key health challenges in a more holistic manner, providing a rapid and accessible diagnostic solution across various medical and veterinary contexts.

So this expansive approach not only promises to improve healthcare outcomes, but also supports a One Health perspective. So by acknowledging that there is a very strong link between human and animal health.

[Vicky Edkins]
So we've talked about diagnostics over the past 50 years, all the way through to the present, and also the potential that exists for the technology that you've developed. If we look forward into the future and look as far forward as you like in your response, and what are your predictions for what the diagnosis of common diseases might look like in the future?

[Dr Michele Gregorini]
I think that decentralised diagnostics in settings like doctor's office or pharmacy should be more than just a vision for the future. Actually, they should be a reality of the present today. We believe that over time, diagnostics should evolve into a widely accessible commodity available on a large scale at a minimal cost.

This approach will revolutionise healthcare and will allow us to identify diseases much faster and initiate the treatment sooner, often even before symptoms develop or before the illness has already a chance to spread. Such timely intervention is the key to improve health outcomes and control the spread of diseases. By making these diagnostic tools readily available in everyday healthcare settings, we can significantly enhance disease management and preventive care, and ultimately we can contribute to a healthier and more resilient society.

[Vicky Edkins]
Dr Michele Gregorini and Dr Tobi Schindler, thank you both for taking the time to talk with me. It's been an absolute pleasure speaking to you today. Thank you very much.

[Dr Tobias Schindler]
Thank you.

[Dr Michele Gregorini]
Thank you.

[Vicky Edkins]
Thank you for listening to the Science Speaks: Conversations on Health podcast. This podcast was produced by the Basel Research Center for Child Health in Switzerland and hosted by me, Vicky Edkins. Editing was carried out by Sebastian Schell at the University of Basel's New Media Centre.

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