Type 1 diabetes is the most common metabolic disease in childhood . It is caused by the destruction of pancreatic beta cells by one's malfunctioning immune system. The lost beta cells are responsible for the production of insulin – an essential hormone in blood glucose levels regulation. Currently, treatment of type 1 diabetes demands life-long subcutaneous insulin supplementation and requires dose adjustments to the ever-changing blood glucose level. The therapy aims to control blood glucose levels close to those observed in healthy peers and thus circumvent the development of severe, long-term diabetes complications that affect eyesight, kidneys, and the cardiovascular system. **Optimal treatment is crucial to safeguard patients from complications, which are a growing problem due to the increasing incidence of type 1 diabetes.**

However, **not only treatment intensity but also its timing** are critical for the development of long-term diabetes complications. Extensive clinical trials reported that better glycemic control in the first years after diabetes diagnosis was associated with a lower risk of complications development. This effect persisted for over 16 years after the trial's completion despite the diminished difference in blood glucose levels on follow-up. This phenomenon was dubbed **"metabolic memory" – the effect of early intervention and better glycemic control on risk reduction of long-term diabetes complications.** This project focuses on the mechanisms of its development.

A possible explanation of metabolic memory is connected with epigenetic modifications of human DNA. These modifications affect how the genetic code (DNA) is "understood" and acted upon by the different cells in our organism. Thus, even though all cells possess the same DNA data, epigenetic changes modify the availability of its fragments and activate or suppress the production of specific proteins. One of the most extensively studied epigenetic modifications is DNA methylation, which is the focus of this project. The addition of methyl group to cytosine may result in the different affinity of DNA binding factors, acting as an "on/off switch" for the gene expression. The methylation process is affected by external stimuli – stress, nicotine exposure and many others. Moreover, epigenetic modifications can be passed down through cell division, even if the initial stimuli that caused them are no longer present. As such, **early exposure to high glucose was associated with epigenetic changes that could persist, resulting in altered cell function and increasing the future risk of complications.**

In this project, we aim to investigate how the DNA methylation pattern (which fragments are methylated and how much) changes during the first years of type 1 diabetes treatment. To do so, we plan to recruit children and young adults aged 7-16 with confirmed type 1 diabetes duration for 12 to 24 months, which reflects the early intervention period in past trials. We plan to focus primarily on patients with poor glycemic control and to evaluate the changes due to their clinical improvement. All participants will be monitored using the continuous glucose monitoring (CGM) systems, allowing glucose measurement with unprecedented resolution (up to 288 measures per day). CGM will allow for much better patient glucose exposure assessment and clinical improvement than with methods available in the past. Genetic material will be isolated from blood samples drawn at the beginning and follow-up observations, and the DNA methylation patterns will be measured. Collected methylation and clinical data will allow for the evaluation of changes in the epigenetic patterns of DNA methylation during metabolic memory formation.

The prospective observation of patients will allow us to inspect if the observed methylation patterns associated with increased risk of complications may be reversed or exacerbated in patients that don't improve or worsen their glycemic control. Additionally, expression of few selected proteins associated with diabetes complications will be measured on samples from the subset of patients with the most defined changes in DNA methylation and glycemic control. Direct data from protein expression will confirm if observed methylation patterns directly alter genetic material availability and modulate cell functions.

The results of this project will allow us to better understand the mechanisms and dynamics of metabolic memory formation and identify how this process can be modulated by treatment and glycemic variability. The project's results could also help define the optimal timing for future clinical trials with new therapeutic interventions targeted at metabolic memory. By better understanding of the underlying molecular mechanisms, we thus hope to aid doctors and patients facing the challenges of optimal treatment of type 1 diabetes, one of the most challenging childhood chronic diseases.