Acute lymphoblastic leukemia (ALL) is the most common malignancy in childhood. It represents a group of clinically and biologically heterogenous malignancies that can be subclasified into several subtypes according to the presence of recurrent genetic aberrations. The typical genetic aberrations in childhood ALL are chromosomal translocation, that often result in creation of fusion genes encoding either chimeric kinases or chimeric transcription factors. These recurrent genetic aberations are aquired lesions, they are supposed to be the initial hits (that may arise even prenataly) with a causal role in the process of leukemogenesis, which is, however, in the majority of them not yet fully understood. They further represent specific markes used for the detection of leukemic cells and some of them have also prognostic significance and belong among the factors used for risk group stratification in treatment protocols. Risk group stratification and subsequent risk-adapted therapy together with introduction of new therapeutic approaches (intensive chemotherapeutic regimens involving intrathecal application, hematopoetic stem cell transplantation (HSCT), supportive therapy) account for the significant improvement of the treatment outcomes of childhood ALL in the last decades. In addition to genotype, several clinical and laboratory factors such as age, white blood cell count (WBC), immunophenotype and CNS involvement are used for risk group stratification at the beginning of the treatment. Patients are further stratified according to the therapy response at the specific timepoints during the course of the treatment, particularly during its initial phase. Quantitative monitoring of minimal residual disease (MRD) is a fundamental tool for the assessement of therapy response. MRD represents the pool of surviving leukemic blasts that escaped the therapy and their amount is below the detection limit of standard morphologic methods.