Patients' recruitment and data collection Patients were recruited through the nationwide German SCD registry (NCT03327428) which collects prospective and retrospective data on patients with SCD in Germany.All patients for whom the complete set of genetic traits of interest (a− thalassemia, HBG2−polymorphism rs7482144, BCL11A poly− morphisms rs1427407 and rs7606173, HMIP polymorphism rs66650371) was available in combination with the respect− ive laboratory parameter (n=121 for HbF to n=164 for MCV) (Table 2) were included in the analyses that correlated gen− etics with laboratory parameters and clinical course.Data on complications and treatment of SCD were documented annually, together with routine laboratory parameters (hemoglobin, mean corpuscular vol− ume [MCV], reticulocytes, lactate dehydrogenase [LDH], bili− rubin and HbF) (Table 1).In the case of insuf− ficient efficacy, a dose escalation up to the maximum tol− erated dose or to 35 mg/kg/day is recommended.In order to investigate geographic and ethnic differences in the phenotypic expression of SCD, we categorized patients according to the origins of their parents from one of the three regions Mediterranean Sea, Sub−Saharan Africa and "rest of the world".Treatment guidelines implemented in 2014 recommend parental education, the use of penicillin prophylaxis at least until the age of 5 years, and annual screening with transcranial Doppler ultrasound starting from 2 until 18 years of age.The data collected included demographic information, di− agnosis and genotype, treatment, laboratory parameters and clinical events.For the analysis of the frequency and distribution of genetic modifiers, patients with homozygous SCD of all ages and ir− respective of treatment were included.For the analysis of laboratory parameters and complications of SCD, only patients at least 2 years of age and with ongoing treatment with hydroxyurea were con− sidered.The study was performed according to the Declaration of Helsinki and approved by the institutional review board of the Medical Faculty of Heidelberg University (S 416/2014).At the time of the data cutoff, May 13, 2020, 425 patients with homozygous SCD from 28 different institutions were enrolled in the registry.