Background: Primary ciliary dyskinesia (PCD) is a heterogeneous disorder of dysfunctional motile cilia. PCD is characterized by severe recurrent otosinopulmonary infections, male infertility due to abnormal spermatozoa motility, situs inversus totalis, complex situs abnormalities such as situs ambiguous (heterotaxy) and associated congenital heart disease. Identification of ultrastructural defects in the cilia based on electron microscopy has been the traditional test to confirm the diagnosis, but this approach is no longer the sole “gold standard”. The clinical use of exome sequencing (ES) has increased the diagnostic yield in patients with heterotaxy PCD.

Methods: ES data of > 146 proband (and when available their parents) were analyzed for a panel of 148 heterotaxy PCD related genes from 2019 until now at the Center of Medical Genetics in Ghent. Variant classification was based on ACMG/AMP and ACGS guidelines.

Results: We identified multiple class 4 or 5 variants explaining the clinical presentation in 21% of the cases. The majority (97%) of the cases have an autosomal recessive inheritance. In our cohort, 70% of the class 4 or 5 variants were loss-of-function variants and DNAH11 was the most affected gene. Furthermore, we reported variants of unknown significance (class 3) in an additional 6% of the probands. Hence more genetic testing is required to solve these cases (panel updates, phenotypic spectrum, and familial segregation).

Conclusion: With a diagnostic yield between 21-27%, we confirm that ES can be used as a second “golden standard” for the diagnosis of heterotaxy PCD.