Ehlers-Danlos Syndrome (EDS) is a common reason for consulting in clinical genetics. In our genetic consultations, we are confronted with an excessive numbers of patients referred for joint hypermobility and/or an electronic microscopy analysis of skin biopsies. In many cases, a dermatologist or a physiotherapist has already established a clinical diagnosis of hypermobility type EDS. As recently published by Malfait et al. 1, EDS hypermobility type diagnosis is based on clinical findings. Only in this context, a genetics consultation does not seem to be of additional value since no additional analyses are indicated to confirm the diagnosis.

The aim of this study was to characterize patients referred to clinical genetics consultations for EDS suspicion and evaluate the utility of genetics analysis.

Methods
We performed a retrospective observational study of the patients from the University Hospital of Liège who had come to a genetic consultation for Ehlers-Danlos syndrome or other collagenopathies between March 2016 (date of creation of the consultation dedicated to EDS) and December 2017. We performed a descriptive statistical analysis of demographic and clinical characteristics including reason for referral, referee, age, gender, Beighton score, Ehlers-Danlos syndrome associated clinical signs, family history, as well as the prescribed complementary tests (heart ultrasound, aortic angio MRI/scan, genetic testing).

Results
From March 2016 to December 2017, we have seen 143 patients in the collagenopathies consultation : 123 women and 20 men, with a mean age of 35.9 (± 14.1) years old.

111 patients (78.2%) were referred for an Ehlers-Danlos syndrome suspicion based on joint hypermobility. The other 32 patients were referred for collagenopathy suspicion (personal or family history of aneurysms), 5 of whom presented a marfanoid habitus.

Only two thirds of the patients presented joint hypermobility as assessed by the Beighton score : 60.8% (n=87) had a positive Beighton score higher than 5 (mean of 4.95 ± 2.90). This was associated with joint instability in most of the cases and generalized arrhythmia. Only 19% (n=27) of the patients presented skin hyperextensibility, 28% (n=40) skin fragility with enlarged scars and only one case presented atrophic panniculosis scars. Among the other clinical signs, 11% (n=16) presented arachnodactyly and 14% (n=20) a high palate (Table 1).

Regarding family history, 81 patients (57.0%) had at least one relative with joint hypermobility. In 20 patients (14.1%) the family history was positive for vascular problems, five patients (3.5%) had a family history positive for auto-immune disorders and one patient (0.7%) had a relative with polycystic kidneys.

We have diagnosed one patient with classical EDS with so far no molecular confirmation and we have diagnosed a familial Loey-Dietz syndrome (mother and daughter). In three patients (2.2%), the genetic results were not conclusive (variants of unknown significance). Except for these rare cases where the consultation confirmed the presence of pathology, the majority of the evaluations only confirmed the already established diagnosis of benign hypermobility syndrome (57.0%) or excluded the presence of a collagenopathy (40.8%).

Conclusion
The vast majority (98.7%) of the patients referred for an EDS suspicion presented a hypermobility type or another non-genetic disorder, and a genetic consultation did not have any additional value. Since the diagnosis of hypermobility type of EDS is based on clinical findings, it is essential to make physiotherapists, rheumatologists and general practitioners aware of this. Specialized training regarding signs or symptoms suggestive of rare EDS type or other collagenopathies that can be diagnosed genetically, is essential. Referral criteria should be defined in order to select cases needing a clinical genetic evaluation.