Deliverable

D5.4 Guidelines for molecular genetics of rare disorders	
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Explanation according to GA Annex I:

The final guideline and its impact will be presented at international meetings, published in the scientific literature, and via digital media.

Abstract: New diagnostic whole genome sequencing (WGS) guidelines for rare genetic disorders have been prepared and published (https://doi.org/10.1038/s41431-022-01113-x).

Introduction: In 2016, guidelines for diagnostic next-generation sequencing had been published by Gert Matthijs et al. in EJHG on behalf of EuroGentest and the European Society of Human Genetics (ESHG). Since then, WGS has been increasingly introduced in the diagnosis of rare diseases and the use of WGS in diagnostics warrants re-evaluation and update of the previously published guidelines. This has been done by EuroGentest and the Horizon 2020 project Solve-RD. Solve-RD has the ambition to elucidate the genetic cause of the majority of currently unsolved rare genetic disorders by a variety of analytical techniques. WGS and uniform clinical and genomic data-analysis are central in this project. To provide the link to reliable clinical application of the obtained information, EuroGentest had the task to update and produce diagnostic WGS recommendations.

The aim of these recommendations is primarily to list the points to consider for clinical (laboratory) geneticists, bioinformaticians, and (non-)geneticists, to provide technical advice, aid clinical decision-making and the reporting of the results.

Report: The task to re-evaluate and update the previously published guidelines has been undertaken by organizing expert meetings in February 2019 and September 2019. Colleagues with different fields of expertise and backgrounds from different countries across Europe and beyond were involved, as well as representatives of the European Reference Networks (ERNs, https://ec. europa.eu/health/ern_en). ERNs are virtual networks involving healthcare providers across Europe. They aim to tackle complex or rare diseases and conditions that require highly specialized treatment and a concentration of knowledge and resources. The following ERNs were represented: genetic tumor risk syndromes (GENTURIS), congenital malformations and rare intellectual disability (ITHACA), neuromuscular diseases (NMD), neurological diseases (RND), immunodeficiency, autoinflammatory and autoimmune diseases (RITA), urogenital diseases and conditions (UROGEN), eye diseases (EYE), inherited and congenital anomalies (ERNICA), rare bone diseases (BOND) and rare and complex epilepsies (EpiCARE). The recommendations have been finalized in May 2021 and endorsed by the Solve-RD Steering Committee, the representing ERNs, the European Board of Medical Genetics (EBMG) and the ESHG.

The recommendations focus on diagnostic NGS sequencing including WGS in a clinical setting for rare disease diagnostics, although most of the statements also apply to the identification of somatic variants in cancer diagnostics. The aim of moving to WGS is to be able to simultaneously detect CNVs and chromosomal anomalies, as well as SNVs for monogenic and oligogenic diseases and cancers. Applications of the different NGS approaches to multifactorial disorders and pharmacogenomics are not included. The use of tools to determine polygenic risks scores (PRS) and to calculate relative risks on the basis of association studies, is not covered in these recommendations. The recommendations cover aspects from the evaluation and rationale to set up diagnostic NGS applications, including quality control of the different aspects of the laboratory (wet work) procedure and bioinformatics pipelines, variant interpretation and data banking, to reporting of NGS results. The use of WGS for research is not addressed specifically, but quality rules will equally apply to such analysis. The requisites for providing NGS diagnostics are of course its clinical utility, the use of state-of-art sequencing technologies, diagnostic routing (i.e. routing of genetic tests within the laboratory for a specific disease) and variant analysis, and the generation of reports in a diagnostic setting.

Conclusion: These novel diagnostic WGS guidelines have been published online at May 22nd 2022 in the EJHG, https://doi.org/10.1038/s41431-022-01113-x.