P8- The bigger the better? Evaluation of the value of large multi-gene panels in Portuguese cardiomyopathy genetic testing

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Introduction: Genetic testing of cardiomyopathies went through major changes in the last few years, from sequential Sanger sequencing of the most likely gene candidates, to multigene panels by NGS, with an ever increasing number of genes analyzed. Since only a few genes account for the majority of hereditary cardiomyopathies, the increase in the number of genes evaluated is largely accompanied by adding less relevant or penetrant genes to existing panels, which may translate in minor benefits in terms of diagnostic yield but a significant increase in the number of variants of uncertain significance (VUS). In order to access the pros and cons of larger gene panels, the results of different cardiomyopathy gene panels used in our laboratory were reviewed, taking into account current ACMG classification criteria. Methods: All results of different cardiomyopathy panels performed between 2011 and 2018 at Ipatimup Diagnostics were retrieved (n=1781 index cases). We calculated the diagnostic yield of each gene panel at the time they were used in the laboratory. Moreover, we compared the results before and after applying ACMG guidelines. Results: Before ACMG guidelines were adopted, a case was considered positive whenever a rare variant was identified. With the adoption of the ACMG guidelines, several variants previously considered relevant were classified as VUS, which lead to a drop in the diagnostic yield of the test (from 68% in 2011 to 37% in 2018). This drop is even increasing over time, as a result of the adoption of ever larger gene panels. Conclusions: The increase in the number of genes in cardiomyopathy gene panels does not necessarily mean an increase in the diagnostic yield of genetic tests. There is an increment in the number of variants detected, however most of them are VUS, some of which in genes of current limited value for cardiomyopathy genetic testing. Nevertheless, if we look at genetic testing as a tool to better understand a disease, the study of these variants (namely with functional assays and segregation studies) might help in the future to better understand some cases, which remain uncertain with the current available information.