

MULTI-CANCER GENE PANEL TESTING IN 1255 DUTCH FAMILIAL CANCER PATIENTS: SINGLE NUCLEOTIDE AND COPY NUMBER VARIANT ANALYSIS

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Abstract:

Next Generation Sequencing (NGS) allows diagnostic testing of many genes simultaneously and the use of NGS gene panels is now common in familial cancer diagnostics. In diagnostics, these panels usually target particular tumour types or combination of tumour types, e.g. colorectal cancer, or breast and ovarian cancer, deliberately limiting the chance of unsolicited findings. However, the systematic use in familial diagnostics of broader, multi-cancer gene panels, including new candidate cancer predisposing genes, could potentially help identify expansions of the currently known tumour syndrome phenotypes and could help define the phenotypes of mutations in newly postulated genes. This might, in time, increase the diagnostic yield in patients as most of them are currently left without a molecular diagnosis. Another reason for using broader gene panels is that it would allow for screening of actionable mutations in cancer predisposing genes as has for example been advocated by the American College of Medical Genetics and Genomics. Although such screening, as opposed to diagnostics, is currently not part of Dutch genetic counselling and testing services, the potential benefits of such screening warrant further study. With all these considerations in mind, we developed an 85-gene multi-cancer NGS panel including well-known as well as, for research only, some newly postulated tumour syndrome genes, and implemented it in our diagnostics lab. For diagnostic purposes, clinicians can order reports on particular cancer specific subsets of the panel data, whereas for research purposes, all panel genes can be analysed anonymously in all patients. We analysed the yield of variants in 1,255 patients referred to our clinic for familial cancer diagnostics, and to try to match those variants with the tumour types that had prompted referral for testing. Those that would not match could be regarded as secondary findings and/or as suggestions for future expansions of the known tumour gene phenotypes. In analysing our NGS panel data we aimed to analyse all 85 panel genes for CNVs as well, which is not yet common diagnostic practice. We were interested to know how much CNV analysis in the NGS data for all genes, rather than of selected ones using the traditional Multiplex Ligation-dependent Probe Amplification (MLPA), would add to the single nucleotide variant (SNV) analysis in terms of mutational yield. In order to get an estimate of what to expect in frequency of secondary findings, we analysed both SNV and CNVs in the dataset of all 498 non-related individuals from the Dutch population whole genome sequencing project GoNL. Results will be presented at the meeting.