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The Use of Arrays to Detect Copy-Number Variations in Clinical Practice

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For the Focus on CNV Detection with Diagnostic Arrays

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Since their introduction, array-based detection techniques have flooded diagnostic practice worldwide. Technical innovation and commercialization of array platforms have brought down their costs and put them within reach of many diagnostic laboratories. Array diagnostics are, therefore, rapidly replacing traditional karyotyping techniques for a range of indications. Such innovations give rise to many questions related to indications for testing, test outcome interpretation, quality control, and the ethics of using arrays for particular applications. There is a growing need for guidelines on these topics. To address the key issues in this field, an international workshop was organized in Amsterdam in 2011 under the auspices of the Genetic Services Quality Committee of the European Society of Human Genetics. The aim was to explore whether consensus could be achieved on the major quality issues and to produce recommendations for the use of arrays to detect copy-number variations (CNVs) in a diagnostic setting. The outcome of the workshop has been summarized in five articles that formulate recommendations and guidelines to cover the different aspects of CNV detection using diagnostic arrays in genetics.

In general, it can be concluded that genome-wide array analysis is well established in postnatal cytogenetics. Most commercially available platforms and data analysis software packages are of high quality and relatively easy to use. The article by Vermeesch et al. (2012) aims to guide laboratories in assuring the quality of their array experiments, by suggesting standards for the minimal resolution of the platform used, and for the interpretation and reporting of the results. Unfortunately, the interpretation of CNVs is not always straightforward since the distinction between pathogenic and benign variants can be difficult as, for example, CNVs with a highly variable phenotype and incomplete penetrance are common. Web-based databases, especially when used in combination, can be helpful in interpreting CNVs. A general clinical interpretation strategy for CNVs is presented by de Leeuw et al. (2012). Because of the genome-wide nature of the use of arrays, clinically relevant CNVs will be detected that are not related to the patient's known phenotype. This clearly raises ethical questions, which may be especially complex if the tested individuals are children, investigated prenatally or postnatally. Dondorp et al. (2012) discuss these ethical issues, trying to find a solution to possible "information overload" in counseling, and exploring the balance between the "right to know" and the "right not to know" in different situations.

Two particular clinical applications of array diagnostics are discussed in more detail. Vetro et al. (2012) explore the use of arrays in prenatal diagnosis and provide recommendations for the various steps of the process, starting with pretest counseling. In their opinion, array diagnostics have a place in the case of abnormal ultrasound findings as long as local guidelines have been established, whereas the value of offering array diagnostics to all pregnant women is highly debatable. Changing focus from constitutional to acquired chromosomal abnormalities, Simons et al. (2012) review the clinical value of array-based genome-wide screens in leukemia. The genetic complexity of cancer cells requires the detection of small genomic changes in a mixed cell population, as well as the ability to detect regions of homozygosity. The authors discuss these technical challenges and, again, stress the need for international data sharing.

We are proud to present this special collection of articles that report on a set of recommendations and suggested guidelines for CNV array diagnostics. They are meant to encourage further discussion, development, and implementation of local, national, and preferably, international guidelines. The development of such guidelines will not only be important for the use of array diagnostics as part of good clinical and laboratory practice. There should be important spin-off as well. In the rapidly changing landscape of genetic diagnostics, other genome-wide techniques are being introduced as well, including whole-exome sequencing and whole-genome sequencing. Those who endeavor to apply these new technologies to standard clinical use will likely face many challenges similar to those faced in the routine application of array diagnostics.

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