Next Generation Mapping: karyotyping revival with molecular banding

Since its first use in 1959 to unravel trisomy 21 (Down Syndrome), karyotyping has been the single pan genome method of analysis to decipher both numerical and structural abnormalities of the genome, balanced as well as unbalanced.
Its biggest drawback i.e. lack of sensitivity has been addressed by numerous improvements, almost one every 10 years: banding techniques in the 70s, high resolution banding technique in the 80s, FISH in the 90s, comparative genomic hybridization (CGH) in the beginning of the new century, and finally microarray analysis (either based on CGH or SNPs) in the 2010s. All of these improvements led to largely improved sensitivity, with increasing knowledge of cryptic rearrangements (nowadays called CNVs: Copy Number Variants). However, none of them could supersede the old Karyotype because of one or more of several limitations. It was either not a pan genome analysis method (FISH) or there was loss of paramount topographic information on the location of the abnormal segments (CGH or SNP arrays). Even the rise of various applications of massively parallel sequencing techniques, once a promise of an all-in-one tool for genetic analysis, was hardly convincing as a soon-to-become replacement for visual inspection of the chromosomes. This was because of the low sensitivity and specificity of current bio informatics tools for the detection of structural variants (SVs) and inherent limitation of short-read sequencing to overcome the preferential location of many breakpoints in difficult to sequence, repeat rich regions.
However, in keeping with the 'once every decade' path of innovation in cytogenetics, a new promising method has emerged; it could replace both Chromosome Microarray Analysis (CMA) and the karyotyping in patients referred for various reasons.
This technology, named Genome Optical Mapping (or NGM for Next Generation Mapping as opposed to NGS for Next Generation Sequencing), relies on the imaging of very long DNA molecules that have been labeled at specific sites after linearization in a microfluidic device. Without any sequencing (which may in some cases be an advantage by limiting the amount of information that one is not looking for), the labels on the DNA molecules are used as a molecular banding to reconstruct the genome by recognizing the identical patterns on the millions of molecules analyzed.
This paper which was recently published in BioRxiv https://www.biorxiv.org/content/10.1101/2020.07.15.205245v1.full addresses for the first time the performance of the Bionano's optical mapping technology to decipher known chromosomal abnormalities previously identified with either karyotyping or CMA. Several teams were involved in this large study which shows a 100% concordance between standard clinical technologies and optical mapping. In some cases that were also analyzed with whole genome massively parallel sequencing technique, Bionano's optical mapping could even find new, unforeseen rearrangements or reveal very complex abnormalities that had been overlooked by CMA or NGS.
Further blind studies are required to test this approach against the current state-of-the-art techniques. However, it already holds the promise of becoming a first tier test for both Intellectual Deficiency / Developmental Disorders and reproductive disorders, although it may not be able to totally eclipse the old karyotype because of its inability to recognize breakpoints located in large heterochromatic regions (for example, whole-arm translocations and Robertsonian translocations).