PublicationSummary

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Pfundt R., *et al.* Clinical performance of the CytoScan Dx Assay in diagnosing developmental delay/intellectual disability *Genetics in Medicine* advance online publication (April 16, 2015). doi:10.1038/gim.2015.51 **OPEN ACCESS**

Purpose: The prevalence of developmental disabilities in the United States is reported to be 13.87% across all racial, ethnic, and socioeconomic groups. Microarrays have been recommended as first-tier tests for these patients. This study reports the diagnostic yield and potential actionability of findings using a high-density chromosomal microarray (CMA).
Methods: The diagnostic yield of CytoScan Dx Assay in 960 patients was assessed with the Riggs criteria of actionability to evaluate predicted clinical utility.
Results: Eighty-six percent of the subjects were assessed using a microarray as part of historical routine patient care (RPC). The rate of pathogenic findings was similar between RPC (13.3%) and the CytoScan Dx Assay (13.8%). Among the 138 patients who did not receive microarray as RPC, the diagnostic yield for CytoScan Dx Assay was 23.9% as compared with 14.5%, indicating a 9.4% improvement when using higher-resolution methods. Thirty-five percent of patients with abnormal findings had predicted clinical management implications.
Conclusions: This is the first study to assess the clinical performance of CytoScan Dx Assay. The assay's diagnostic yields are similar to those found in other studies of CMAs. Thirty-five percent of patients with abnormal findings are predicted to have clinical management implications that may improve health outcomes.

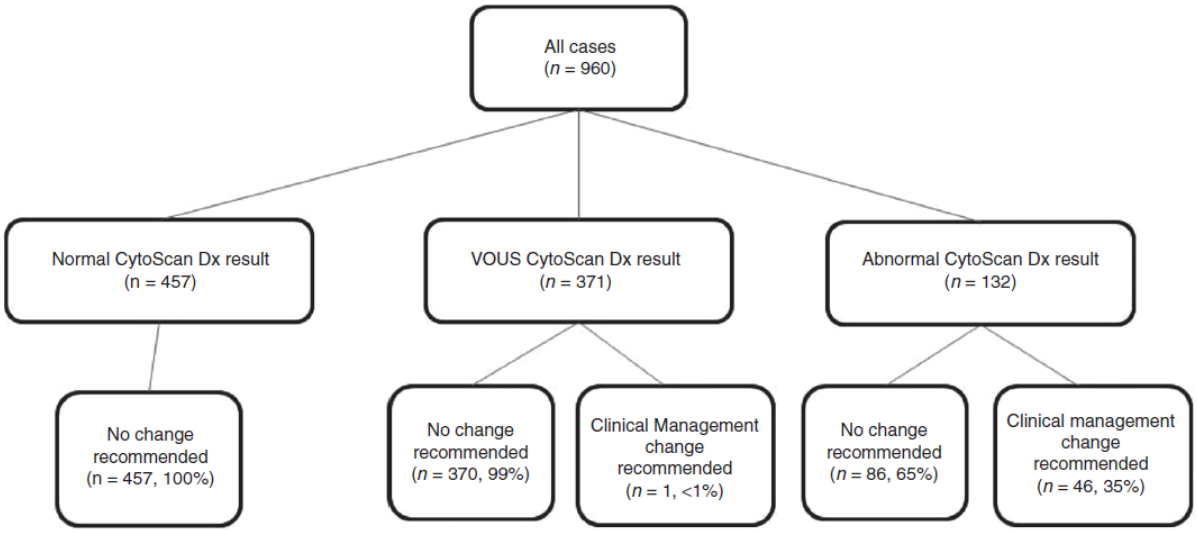
Key points

This is the first study to assess the clinical performance of CytoScan® Dx Assay in a consecutive cohort of patients with developmental delay (DD), intellectual disability (ID), and/or congenital anomalies who were referred for whole-genome chromosomal testing.

Two fundamental observations were noted

- *CytoScan Dx Assay represented a **9.4% improved diagnostic yield** versus patients receiving routine patient care (RPC) such as karyotyping, FISH, and other CMA tests*
- ***One-third** of patients with abnormal findings had clinical management implications that may improve health outcomes*

Classification of CytoScan® Dx Assay results and predicted clinical management changes.



Additional copy number variations (CNVs) identified by CytoScan Dx Assay.
"Several microdeletion/microduplication syndromes were identified by CytoScan Dx (and missed by RPC) in this study, including (but not limited to) 3q29 microduplication, 22q11 microduplication, 16p11.2 microduplication, 16p11.2 microdeletion,KBG syndrome, and Floating-Harbor syndrome. ***Some of these cases would have warranted significant clinical management at the time of diagnosis***, whereas for others finding a genetic cause would have ended the diagnostic odyssey. However, because the RPC deemed these cases normal, no other follow-up information was provided..."

				Genomic coordinates (hg19)		Primary CNV/syndrome	Clinical management implication
Sex	Age	RPC method[a]	Chr	Stop	Stop	Identified by CytoScan Dx Assay	
F	2	Karyotype, methylation	chr5	88031638	88446608	5q14.3 deletion	No
F	5	Karyotype, PCR	chr22	18916843	21465659	22q11 microduplication	No
F	<1	Karyotype, PCR	chr16	29432245	30240227	16p11.2 microduplication	Yes
F	14	Microarray,[a] karyotype, PCR	chr3	195725291	197386180	3q29 microduplication	No
M	2	Microarray,[a] karyotype, FISH, PCR	chr16	30609032	30765430	Floating-Harbor syndrome	No
M	2	Karyotype, PCR, methylation	chr7	72691243	74141512	Williams-Beuren syndrome	Yes
M	2	Karyotype	chr12	19597206	21972819	2.5 Mb deletion on 12p	No
M	11	Karyotype	chr5	56561970	68212088	11 Mb deletion on 5q11.2-q13.1	No
M	14	Microarray,[a] karyotype, PCR	chr16	89376153	89490401	KBG syndrome or ANKRD11 (ankyrin repeat domain 11) gene deletion	No
M	3	Microarray,[a] karyotype, PCR	chr9	139907011	140180810	273 kb deletion on 9q34.3	No
M	3	Karyotype, PCR	chr16	29567296	30177916	16p11.2 microdeletion	No
F	6	Karyotype	chrX	31774321	31947969	Duchenne/Becker muscular dystrophy	No
F	7	Karyotype	chrX	168547	8393904	Turner syndrome	No
F	0	Karyotype	chr17	29356946	30386515	Neurofibromatosis 1 with intellectual disability	Yes
F	3	Karyotype	chr16	15364267	18231275	16p13.11 microduplication	Yes
F	0	Karyotype	chr12	173787	2121136	2 Mb loss 12pter; 9.3 Mb gain 21qter	No
F	28	Karyotype	chr16	29567296	30177916	16p11.2 microdeletion	No
F	0	Karyotype	chr22	18937513	21465659	22q11 microduplication	No
F	7	Microarray[a]	chr15	22752398	102429049	Angelman/Prader-Willi	No
F	0	Karyotype	chr22	18644791	21800797	DiGeorge/velocardiofacial/22q11.21 microdeletion	Yes

CNV, chromosomal copy-number variant; FISH, fluorescence in situ hybridization; PCR, polymerase chain reaction; RPC, routine patient care.
[a]Non-Affymetrix Microarray.

Conclusion

Early diagnosis has the potential to reduce health-care costs and provide physicians and families with information about the disorder affecting the child, prognosis, and comorbidity, all of which have implications beyond medical treatment. This study assessed the clinical performance of CytoScan® Dx Assay in a consecutive cohort of patients with DD, ID, and/or congenital anomalies who were referred for whole-genome chromosomal testing. The diagnostic yields are similar to those reported in previous studies, with 13.8% and 35% of patients with pathogenic CNVs identified by CytoScan Dx Assay predicted to have clinical management implications that may improve health outcomes.