ScientistSpotlight

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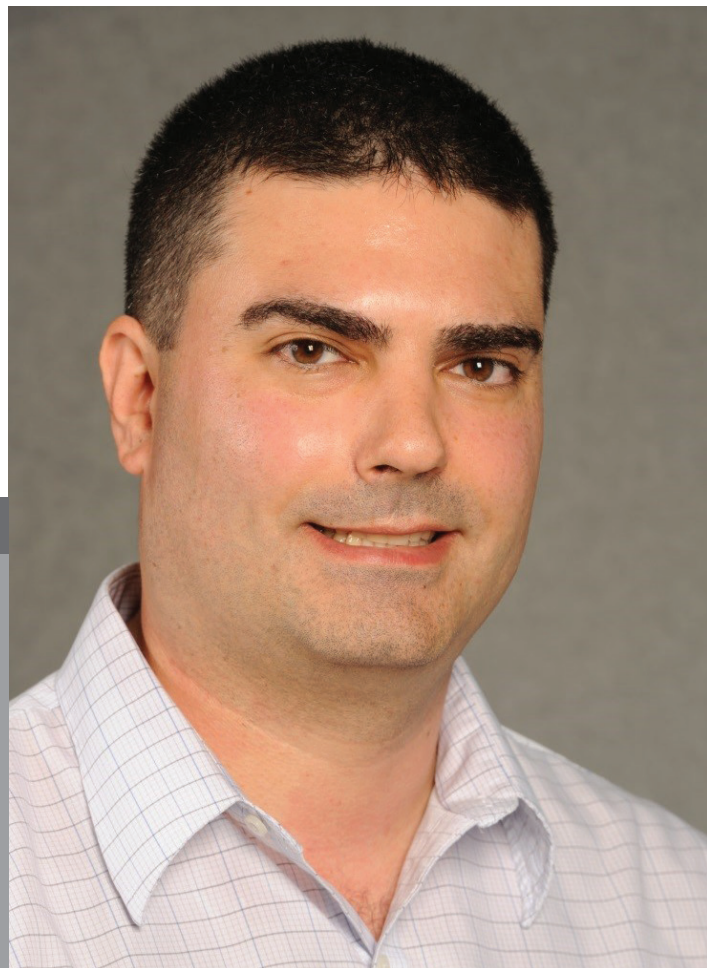
Flipping the switch: extinguish the chaos, save money and improve patient access

Introduction

The Division of Genetics and Metabolism at Children's National Health System is the largest clinical genetics program in the United States with over 7,000 patient encounters a year. The team consists of 12 medical geneticists, 1 nurse practitioner, and 10 genetic counselors. Evaluation of a patient in the Genetics clinic often includes a recommendation for genetic testing. Children's National Molecular Diagnostics Laboratory offers a wide range of genetic tests, including chromosomal microarray analysis (CMA), next-generation sequencing (NGS) of over 4,800 genes that can be ordered as fixed preconfigured panels or custom personalized sequencing panels, Fragile X by triplet—primed PCR, cystic fibrosis common mutation panel, prothrombin, and factor V Leiden mutation detection.

Affymetrix: Recently, your laboratory made some significant changes in regards to genetic testing, please tell us about it and the driving factors behind your decision.

Hofherr: Prior to June 2013, greater than 90% of genetic test requests were sent to outside laboratories resulting in disorganized, chaotic processes that were expensive. In July of 2013, we brought microarray testing in-house, which was a huge success. This one assay decreased our send-out testing by 50%. In August 2014, the Clinical Molecular Diagnostics Laboratory transitioned to the CytoScan® Dx Assay, which is the first FDA-cleared microarray test to aid in identifying the underlying genetic cause of developmental delay, intellectual disability, congenital anomalies, or dysmorphic features in children. A driving factor for adoption of the assay was to combat the high rate of insurance pre-authorization denials. A common reason for denials is that a given test is not FDA-cleared. Now we can move past this point, and anecdotally it has been beneficial not only to our patients but also to our physicians and genetic counselors who spend a huge amount of non-billable time obtaining authorization. In addition, every molecular diagnostics laboratory around the country is concerned about how the FDA involvement in laboratory developed tests (LDTs) will affect their operations, and having an FDA-cleared test will make this transition significantly easier.



Sean Hofherr, PhD, is director of the Children's National Molecular Diagnostics Laboratory in Washington, District of Columbia. He is board-certified by the American Board of Medical Genetics in Clinical Molecular and Clinical Biochemical Genetics. Sean holds a PhD in Molecular and Human Genetics from Baylor College of Medicine and completed fellowships in Molecular Genetics and Biochemical Genetics at the Mayo Clinic.

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Affymetrix: What guidelines did you follow for laboratory validation, training, and certification, and what was the process?

Hofherr: We validated this assay according to Clinical Laboratory Improvement Amendments (CLIA) standards. However, since it was an update to an already validated method and FDA-cleared, it was a fast and painless process. Affymetrix has an excellent track record in assisting with training, and with the FDA clearance, this process was even more clearly defined.

Affymetrix: How many cases have you reported out, and what are the findings thus far?

Hofherr: Since bringing microarray testing in-house we have completed over 1,000 cases. After transitioning to CytoScan Dx Assay for suspected chromosome disorders in individuals with findings such as developmental delay, intellectual disability, multiple congenital anomalies, and dysmorphic features, we have run and reported 346 patients and identified 99 cases with clinically relevant aberrations, including 74 copy number variations (CNVs) and 25 cases with absence of heterozygosity (AOH) for a diagnostic yield of 28%. As for the CNVs detected, quite a few of them are the well-known microdeletion syndromes. For example, we see a deletion of 22q11.21 about once a month, and several of them are considered atypical and would have been missed had the physician ordered fluorescent *in situ* hybridization (FISH) instead of CMA.

"…bringing CMA in-house saves our institution over $250,000 every year."

Affymetrix: What impact does this testing have on the workflow in your laboratory?

Hofherr: Recently we introduced NGS for over 4,800 genes. Aside from the ability for physicians to order preconfigured panels, they also can now order personalized sequencing panels specific to the patient's clinical presentation. An integral part of this offering is the ability to feed the CMA data into our NGS pipeline to target the analysis to regions of interest, mostly areas of homozygosity.

Affymetrix: Do you have any advice or recommendations to other laboratories considering implementation of microarray testing?

Hofherr: I recommend you take the time to explore all the options, but to not consider the FDA clearance of the system and the assay would be a mistake.

28% diagnostic yield

346
Patient run and reported on CytoScan® Dx Assay

74
Cases with clinically relevant copy number variations (CNVs)

25
Cases with clinically relevant absence of heterozygosity (AOH)

"We have noticed a significant decrease in the number of insurance denials, written appeals, and peer-to-peer requests for CMA testing since offering the FDA-cleared assay."

Affymetrix: How have you educated the ordering physicians about your new CMA technology?

Hofherr: Because we are an in-house genetics laboratory, we have the luxury of gauging physician and stakeholder interest prior to developing a new assay. The physicians were kept in the loop from the very beginning, and since there was little to no impact to their standard workflow, it was well received.

Affymetrix: What financial impact does this new FDA-cleared microarray test have on your institution?

Hofherr: Given our history of disorganized, chaotic, and costly send-out genetic tests, bringing CMA in-house saves our institution over $250,000 every year.

Affymetrix: What impact does this new FDA-cleared microarray test have on your patients and families?

Hofherr: As previously stated, the families that were unable to get their respective insurance companies to approve coverage now have a very useful tool in their arsenal.

Affymetrix: What has been the response from insurance companies thus far?

Hofherr: Although it is too soon to quantify, we have noticed a significant decrease in the number of insurance denials, written appeals, and peer-to-peer requests for CMA testing since offering the FDA-cleared assay. We have examples where the insurance company denied coverage, but when resubmitted once we transitioned to the FDA-cleared CMA test, the patient was approved for testing. We are seeing many similar situations where there is improved patient access with the FDA-cleared microarray, and patients previously denied coverage can now get the testing.

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