Legacy LabAdvisor

Quarterly laboratory and pathology update from Legacy Laboratory Services in collaboration with Cascade Pathology Edition 5

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Legacy Laboratory Services brings cytogenetics into the new genomic era

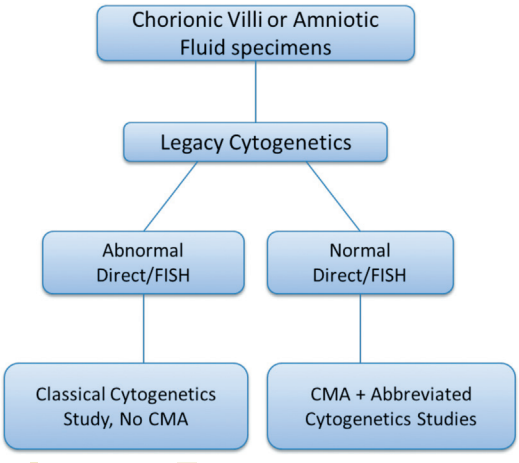
By Yassmine Akkari, Ph.D., FACMG

The ability to visualize the genome has undergone a dramatic change over the last half of the century. It began with the elucidation of the number of chromosomes in human cells, and continued with the identification of chromosomes, recognition of specific chromosomal bands and the introduction of fluorescence in situ hybridization (FISH). The latest advance in genome analysis, namely chromosomal microarray analysis (CMA), has enabled health professionals to view the hereditary material at a much higher resolution.

Since this revolution in genome analysis, we have been able to describe multiple disease entities based on specific phenotypes and accurate correlation with a genotypic change. Having the ability to examine increasingly larger proportions of a patient's genome has revolutionized the field of cytogenetics.

Legacy Cytogenetics Laboratory offers CMA testing in prenatal diagnosis, and as first-line testing for all cases referred for mental retardation of unknown etiology, autism spectrum disorders and developmental delay.

CMA testing in prenatal diagnosis, the first of its kind in Oregon, uses an algorithm that serves our patients both medically and economically. The use of CMA in prenatal diagnosis is supported by data from the National Institutes of Health (NIH). In prenatal CMA trial studies, the NIH showed that 6 percent of cases referred for prenatal diagnosis through an amniocentesis or chorionic villi sampling revealed a clinically relevant abnormality using CMA. This occurred when a structural abnormality was found by ultrasound and when classical cytogenetic analysis revealed a normal karyotype (data presented at the Society for Maternal Fetal Medicine and American College of Medical Genetics 2012 annual meetings).



Prenatal testing algorithm

Figure 1. Prenatal testing algorithm at Legacy Heath

This is a significant percentage given that little is known about the actual phenotype of the fetus after birth. To better serve our patients financially, CMA testing is initiated only if abnormalities are not found with conventional preliminary tests. In short, once a structural abnormality is found on ultrasound, a preliminary study is initiated. This study

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is a FISH screening test looking for common aneuploidy in the case of amniocentesis or a direct preparation following chorionic villi sampling. If the results from this preliminary study are abnormal, CMA becomes unnecessary and the long-term cultures are analyzed with classical cytogenetics. If the preliminary results are normal, CMA is initiated from amniotic fluid or villi. A back-up of long-term cultures is analyzed through a limited study to check for balanced rearrangements.

Legacy Cytogenetics has offered CMA for all cases referred for mental retardation of unknown etiology, autism spectrum disorders and developmental delay since 2010. Although routine conventional karyotyping has been the standard of care, the diagnostic yield does not exceed 5–10 percent. The American College of Medical Genetics has issued a practice guideline (Manning M. and Hudgins L., 2010), recommending the use of chromosomal microarrays as a first-line test in the initial postnatal evaluation of individuals with nonsyndromic developmental delay/intellectual disability, autism spectrum disorders and multiple congenital anomalies.

Although truly balanced rearrangements, such as reciprocal translocations and inversions, are not detected by arrays, these are relatively infrequent causes of abnormal phenotypes in this population (<1 percent). Therefore, available evidence in the literature strongly supports the use of CMA in place of G-banded conventional karyotyping as the first-tier cytogenetic diagnostic test for patients with the above described phenotypes. G-banded karyotype analysis should continue to be reserved for patients with obvious chromosomal abnormalities (such as common aneuploidies), a family history of chromosome rearrangement or a history of multiple miscarriages.

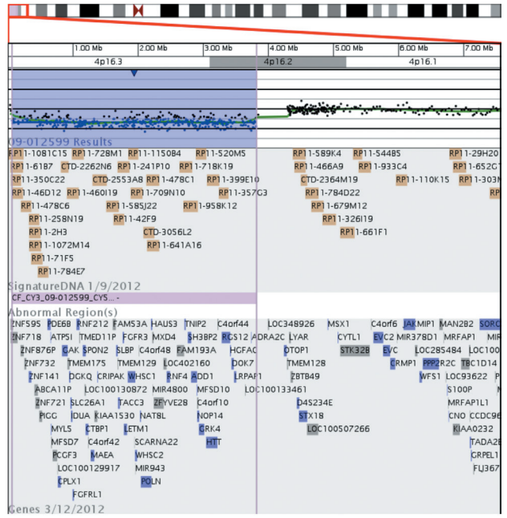

Figure 2. CMA Results from (a) a newborn girl referred for multiple congenital anomalies and found to have a 3 Mb deletion on the short arm of chromosome 4; and (b) a 6-year-old boy referred for developmental delay and found to have a deletion in the Neurexin gene predisposing to autism spectrum disorders. The data is analyzed using the Genoglyphix software from Signature Genomics.

Legacy Medical Group–Maternal-Fetal Medicine, genetics and biochemical clinics, and the Legacy Cytogenetics Laboratory collaborated to successfully implement this new prenatal diagnosis and existing pediatric program. The Legacy Cytogenetics Laboratory offers state-of-the-art chromosome testing and personal interaction with referring clinicians and genetic counselors to assure patients have the best information available when making decisions during an emotional and vulnerable time. A team of expert genetic counselors who pursue the intricate task of guiding our patients through this process help to strengthen this program.

We use sophisticated microscopes equipped with high-resolution cameras, advanced chromosome analysis software and tissue culture technology. Advanced technology in tissue culture and automatic harvesting enables consistent high-quality and efficient testing strategies. Each specimen is processed with care and expertise, and the patient story remains personal. We follow patients from prenatal testing through delivery and from diagnosis through treatment. Referring physicians personally interact with patients, providing both continuity of care and proper follow-up during an emotional and vulnerable time.

Our ability to offer our patients the best available genetic testing will help them make decisions about their pregnancies that best suit their needs. We now can also allow for equal treatment and management of the emotions and vulnerability of those needing CMA for mental retardation and autism diagnoses.

New Testing developments at Legacy Laboratory Services

Clinical updates for the tests described below are available on our website: **www.legacyhealth/labservices** or by calling Client Services at 877-270-5566.

New! Quantiferon Gold is an alternative to TB skin testing

Legacy Laboratory Services is now performing the QuantiFERON®-TB Gold In-Tube test (QFT-GIT), an interferon-gamma release assay. QFT-GIT aids in the diagnosis of tuberculosis by measuring immune reactivity to M. tuberculosis and, with few exceptions, is an acceptable or preferred alternative to tuberculin skin testing (TST). Unlike TST, QFT-GIT requires only a single patient visit, eliminates subjective interpretation errors associated with TST and avoids false positive results from prior BCG vaccination.

Because of limited data for interferon-gamma-release assays and a greater risk of progression from latent to active TB, TST remains the preferred test for assessing children less than 5 years of age. To avoid false positive results, as with TST, QFT-GIT testing generally should not be used for testing persons who have low risk for both infection and progression to active tuberculosis if infected, except for those likely to be at increased risk in the future.

New comprehensive respiratory virus panel

Legacy Laboratory Services is now offering a comprehensive respiratory virus panel, FilmArray RP, targeting Adenovirus, Coronavirus HKU-1, Coronavirus NL63, Influenza A (including targets for H1, H3, and H1N1), Influenza B, Rhinovirus, Human Metapneumovirus, Respiratory Syncytial Virus, Parainfluenza 1, Parainfluenza 2, Parainfluenza 3, and Parainfluenza 4. FilmArray RP, manufactured by BioFire Diagnostics (formerly Idaho Technology, Inc.) utilizes nested multiplexed polymerase chain reaction technology to amplify and simultaneously detect multiple viral targets.

Testing will be performed in the Legacy Central Microbiology Laboratory, and turn-around time is up to 24 hours, dependent on time of specimen receipt. Sample types accepted include **nasopharyngeal swabs, nasal washes and bronchial washes**. The FilmArray RP is recommended for inpatients being served by infectious disease spectialists, pulmonologists, pediatricians and ICU specialists.

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Celebrating 20 years together

Serving patients, physicians, hospitals and employers since 1992, Legacy Laboratory Services remains committed to quality, service and innovation. Thank you for your continued support.

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