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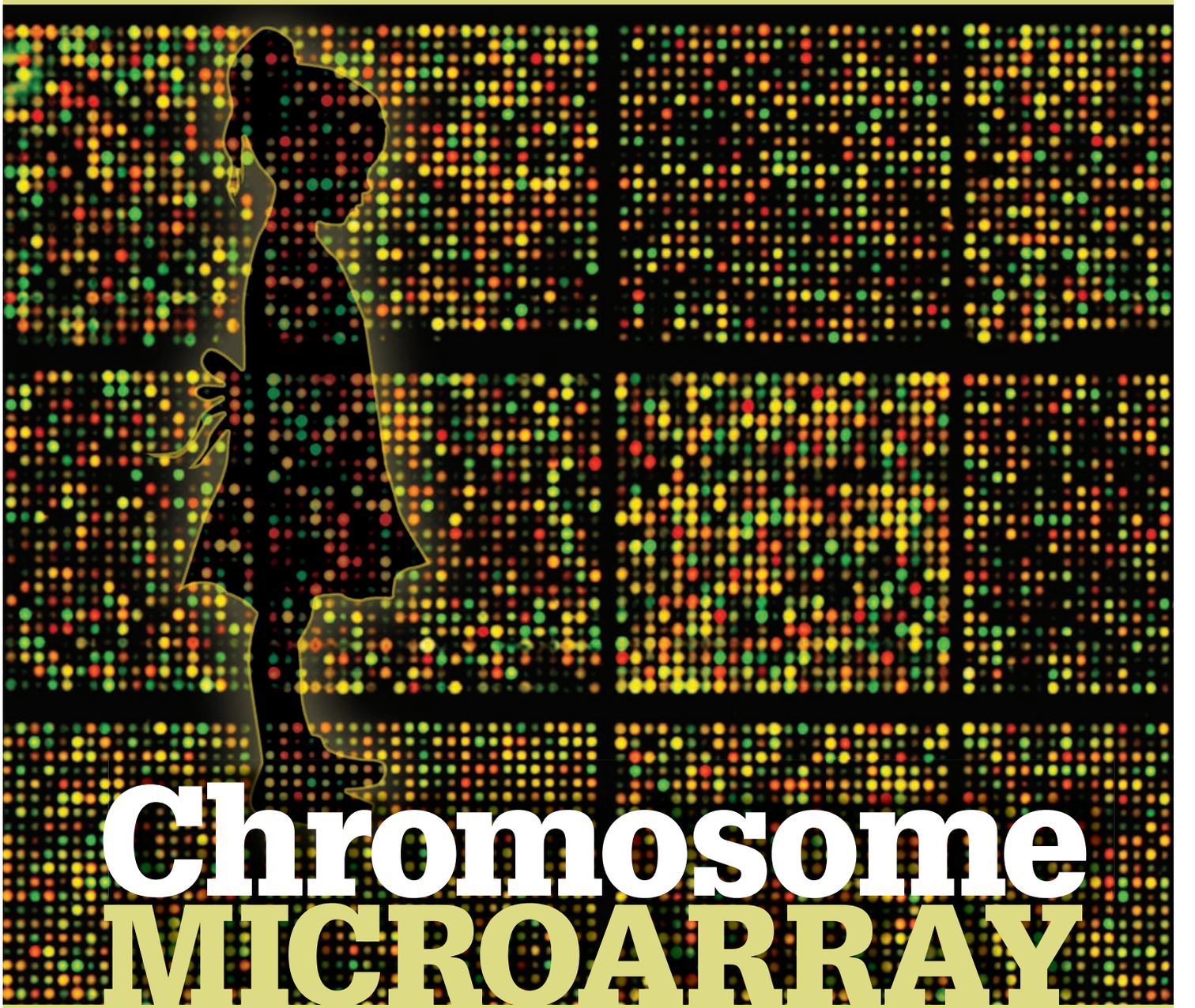

Chromosome MICROARRAY

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Abstract

Over the last half century, knowledge about genetics, genetic testing, and its complexity has flourished. Completion of the Human Genome Project provided a foundation upon which the accuracy of genetics, genomics, and integration of bioinformatics knowledge and testing has grown exponentially. What is lagging, however, are efforts to reach and engage nurses about this rapidly changing field. The purpose of this article is to familiarize nurses with several frequently ordered genetic tests including chromosomes and fluorescence in situ hybridization followed by a comprehensive review of chromosome microarray. It shares the complexity of microarray including how testing is performed and results analyzed. A case report demonstrates how this technology is applied in clinical practice and reveals benefits and limitations of this scientific and bioinformatics genetic technology. Clinical implications for maternal–child nurses across practice levels are discussed.

Keywords: Comparative genomic hybridization; Databases; Genetic; Genetic testing; Molecular diagnostic techniques.

Not long ago, genetics was a field of clinical practice that combined expertise in dysmorphology assessment, knowledge of genetic syndromes, and patient history-taking skills to target testing by chromosome or single gene analysis to confirm or refute a genetic diagnosis. Since the completion of the Human Genome Project in April 2003, the genetics specialty has exploded. The field is evolving exponentially to one that relies less on clinical expertise and more on laboratory and bioinformatics technology. Routine genetic testing has grown to include high-resolution chromosome analysis, fluorescence in situ hybridization (FISH) and more recently, chromosome microarray. Although whole-exome and whole-genome (next generation) sequencing is one of the fastest-growing genetic technologies, at present it is cost prohibitive and prescribed sparingly. Therefore, chromosome microarray remains a highly relevant genetic test in prenatal, neonatal, and pediatric settings.

Nurses may hear the term chromosome microarray, microarray, array, or array comparative genomic hybridization or see a microarray result in clinical practice. Few outside the field of genetics have a thorough understanding of when it should be prescribed, how it is performed, and its benefits and limitations. Maternal–child nurses should have a basic understanding of the test. A brief overview of genetic testing methods is presented, including chromosome analysis and FISH followed by a focused discussion about chromosome microarray. Table 1 lists commonly used genetic terms and definitions.

Chromosome microarray can help reveal genetic changes missed by chromosome analysis and fluorescence in situ hybridization (FISH).

Chromosomes

Chromosome analysis is ordered to identify large losses or gains in genetic material through numeric or structural changes. In prenatal and perinatal settings, chromosomes may be performed in cases of spontaneous abortion, stillbirth, or unexplained newborn death. In pediatric settings, chromosomes are often prescribed to identify a diagnosis for children with two or more dysmorphic features and/or with a known or suspected chromosomal defect.

In clinical genetics, routine chromosomes have largely been replaced by high-resolution chromosomes (expanding chromosomes to better visualize banding patterns) improving test detection rate and accuracy. Although the technology has advanced, high-resolution chromosomes cannot detect changes in genetic material smaller than approximately 5 million base pairs (5 Mb). The human genome is approximately 3.2 billion (~3,200 Mb) base pairs long and contains 20,000 to 25,000 distinct protein-coding genes. Genetic changes are reported based on size with the unit of measure in comparison to the size of a base pair. A kilobase (kb) contains 1,000 base pairs and denotes small losses and gains of genetic material. In contrast, a megabase (Mb) contains 1,000,000 base pairs and denotes larger losses and gains.

Fluorescence in Situ Hybridization

Fluorescence in situ hybridization heightens detection of small genetic changes by taking chromosome analysis one step further. This process uses fluorescence-tagged probes specific to chromosome regions to improve resolution beyond what can be seen with high-resolution chromosomes to detect submicrodeletions and microduplications. Because FISH targets a specific chromosome region, the test must be ordered based on clinical findings suspicious of a specific disorder, for example, DiGeorge (22q11.2 deletion) syndrome. It can also be used to rapidly identify trisomy and sex in interphase cells. A FISH probe can look for a specific genetic change in a fetus (trisomy 21) and may be ordered with chromosomes because laboratory turn-around-time is faster.

Chromosome Microarray

Although chromosome analysis and FISH continue to have clinical relevance, chromosome microarray is a newer, more sophisticated genetic diagnostic process that combines the ability to simultaneously hybridize multiple DNA probes and analyze those findings using bioinformatics and informational database technologies. This method provides 10 to 100 times greater resolution than chromosomes, providing more detail to improve diagnostic and predictive clinical information (Palmer, Peters, & Mowat, 2012).

Using quantitative measures and sophisticated statistical programs, microarray analyzes thousands of DNA segments simultaneously. It may be used to identify chromosome imbalances in individuals with a normal karyotype or as the initial test to detect microdeletions and/or microduplications in individuals with minor physical findings and developmental delays.

How Microarray is Performed

Chromosome microarray is used to measure the copy number of thousands of fragments of DNA simultaneously. By comparing sample and control DNA, it identifies a greater or smaller number of copies per genome (copy number variants) in regions too small to see using a microscope. It does not require prior knowledge of chromosomal location of any variant such as with FISH.

After isolating patient DNA from a blood sample, it is tagged with a green fluorescent label (fluorochrome) and a reference (control) DNA is tagged with a red fluorochrome. Equimolar amounts of patient and reference

Table 1. Commonly Used Genetic Terms and Definitions

Term	Definition
Copy number variants	Duplicated or deleted sections of gene or segment of DNA (from a few base pairs to megabases) present with a different number of copies in different individuals. Most copies are present as tandem repeats, but they can be dispersed. These may or may not be pathogenic. Many, in fact, are nonpathogenic common variants.
Deletion	Loss of genetic material such as a gene/genes or chromosome.
***De novo* mutation**	A gene alteration that presents for the first time in a family.
Duplication	Segment of genes or chromosome that repeats itself resulting in extra copies of those genes.
Exome	A part of the genome formed by exons (functional protein-coding regions).
Exome sequencing	Selectively sequencing a part of the genome (exons).
Genome	All the genetic material of a cell.
Genome sequencing	Sequencing the entire genome (exons and introns). Introns are a nonprotein-coding region of the gene housed between the exons.
Genotype	The genetic material (make-up) of an individual. It explains why individuals with the same genetic change may show a feature (or features) of varying degrees.
Karyotype	Arrangement of paired chromosomes by centromere location and length.
Microdeletion	Small losses of genetic material, too small to be noticed by standard chromosomes.
Microduplication	Small gains in genetic material, too small to be noticed by standard chromosomes.
Mosaicism	Two or more genetically different cell lines (single gene or chromosome) are present. Mosaicism can occur within the blood or when different cell lines appear in the same individual but in different organs.
Pathogenic	A condition or genetic change that is disease causing.
Phenotype	Physical characteristics or differences in a person. It is the physical traits observed based on genotype.
Polymorphism	DNA change with a population frequency of 1%.
Single gene defect	A change in the DNA that alters the gene product, thus altering function. The function may range from deficient or reduced, absent, and even, a change that causes no discernable effect.
Translocation	A structural abnormality when a chromosome segment becomes attached to another chromosome. These can be balanced (where there is reciprocal exchange of material) or unbalanced (where the material is lost or gained during the process).

DNA are mixed and hybridized to thousands of reference DNA fragments on the microarray slide. Typically, normal hybridization appears as yellow (equal intensity; a balance of red and green fluorescence), whereas an imbalance of fluorescence intensity will appear as a red or green signal. Because there is more control present, results that fluoresce red indicate where one or both copies of patient DNA are deleted. Alternately, duplications emit a green signal. Once complete, arrays are computer scanned and images analyzed to quantify the intensity (hybridization) of each probe (National Coalition, n.d.).

Microarray is an innovative, bioinformatics genetic technology used to identify copy number variants.

Raw images of these fluorescent patterns of red, green, and yellow dots are organized, aligned to the corresponding DNA sequence, and translated into a map that iterates any losses (deletions) or gains (duplications) in genetic material (copy number). To compare subtle losses or gains of genetic material among unaffected and affected individuals and help determine significance and/or classify disease, after scanning and analysis, results are recorded and entered into a computer database. Unfortunately, when reported, there is not always a clear interpretation of results. It is, therefore, at this point when the work of (and challenges for) genetic providers begins.

Interpreting the Results: A Case Report

Chromosome microarray is considered a first-tier test when evaluating infants and children with unexplained congenital anomalies, neurodevelopmental disorders such as intellectual disability, autism spectrum disorder, and epilepsy, and can detect genetic changes in up to 20% of children for which a routine karyotype is normal (de Vries et al., 2005; Howell et al., 2013; Manning & Hudgins, 2010; Miller et al., 2010; Stankiewicz & Beaudet, 2007; Thorland & Wain, 2011). Positive microarray

Table 2. Genetic Resources for Providers, Patients, and Families

Database	Summary
Providers	
Genetic Testing and Information	
Genetic Testing Registry® (GTR)	NCBI* genetic testing resource
GeneReviews®	NCBI* resource of expert-authored summaries about genetic conditions, genotypes, phenotypes, testing, and management
Genetic Test Results: Interpretation and Education	
ClinVar	NCBI* publically available laboratory data warehouse and database resource created and maintained for cytogenetic array data from clinical testing laboratories focused on clinical utility of microarray technology
DECIPHER (DatabasE of genomiC varlation and Phenotype in Humans using Ensembl Resources)	Interactive, web-based clinical data warehouse that helps researchers and clinicians interpret genomic variants and correlate genotypes with phenotypes
OMIM®	NCBI* compendium of genes and genetic phenotypes
Unique	Rare chromosome disorder computerized database, education, and support group information
Providers, Patients, and Families	
Genetic Information, Education, and Resources	
Genetic Alliance	Disease InfoSearch is a resource for patients, clinicians, and researchers. Other features include BioTrust that promotes individuals, families, and communities to actively participate in translational research. Expecting Health is a tool to facilitate informed decision making and navigate complex healthcare systems.
Genetics Home Reference: Your Guide to Understanding Genetic Conditions	Presents information about the effects of genetic variations on human health in a consumer-friendly manner. Available information includes a comprehensive library of genetic conditions as well as a handbook of genetics, genetic terms, and resources.
National Institutes of Health, National Human Genome Research Institute	Compendium of on-line genetics resources ranging from health, education, and issues in genetics for healthcare professionals, patients, and the public.
National Organization for Rare Disorders	Comprehensive information, support, and services provided to patients and their families, healthcare professionals, and those seeking to take part in or develop new diagnostic or treatment interventions for rare diseases. They provide information, state health insurance information, and connect individuals with rare diseases to one another.

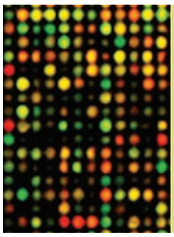
*NCBI = National Center for Biotechnology Information

results are usually defined by the following parameters: (a) a DNA copy gain or loss of greater than or equal to 50 kb in a clinically significant gene; (b) a DNA copy loss of greater than 200 kb; and/or (c) a greater than 500 kb loss in a gene of known unknown clinical significance. With established criteria in hand to evaluate a positive test result, the following case report exemplifies how chromosome microarray is applied in clinical practice.

Patient History

"Robert" is a 12-month-old, nondysmorphic male with developmental delay, growth failure, and microcephaly who presented to the genetics center for evaluation. He was born by spontaneous vaginal birth at term to his nonconsanguineous 25-year-old mother and 26-year-old father of mixed European descent. Prenatal, perinatal, and immediate postnatal courses were noncontributory. His birth weight was 5 pounds 7 ounces.

A three-generation pedigree was obtained and reviewed. Maternal family history was remarkable for Turner syndrome in a maternal aunt. Paternal history included cognitive impairment for the father's brother and maternal aunt.



Microarray can detect between 7% and 20% of chromosome abnormalities including imbalances and microdeletions and/or microduplications.

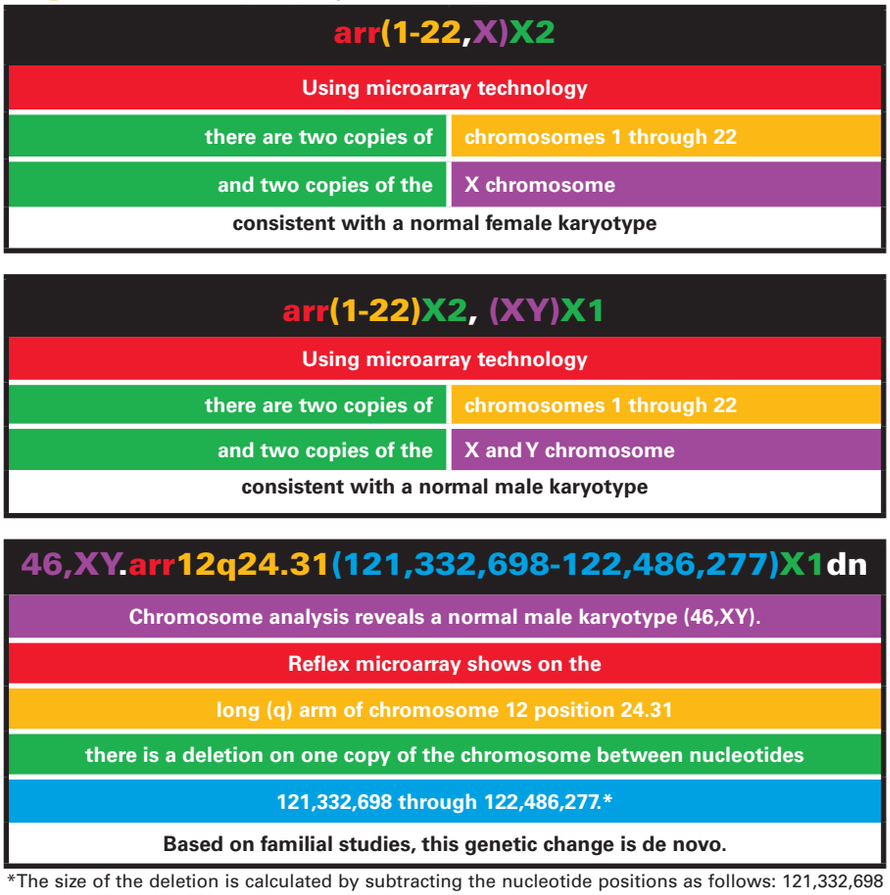
Robert developed failure to thrive and growth failure, microcephaly, and gross developmental delay by several months of age that prompted referral to a number of pediatric specialists. The endocrinologist was carefully monitoring his growth and the gastroenterologist was managing gastroesophageal reflux and feeding problems. Because of microcephaly and gross developmental delay, he was followed by a neurologist and receiving early intervention services. Neuroimaging studies to date were negative. Because of persistent nasal congestion and noisy breathing, Robert was seen by an otolaryngologist. His assessment identified small ear canals, hearing deficit, and tonsillar and adenoid hypertrophy. He was referred by his primary care provider for genetic consultation to determine if the constellation of findings were consistent with a specific genetic condition.

Genetic Testing Recommendations and Results

In addition to several biochemical tests to screen for inborn errors of metabolism (unremarkable), testing recommendations included routine chromosomes and if normal, microarray testing. Chromosomes revealed a normal karyotype (46,XY) but reflex microarray revealed the following genetic changes: a) 3q29 (194,814,775-197,751,986)X3 and b) 12p13.33p13.31 (191,040-5,406,692)X1 (Figure 1 shares examples of how microarray results are read). To most, this test result is written in a genetic code that is unfamiliar. Although a microarray result may be followed by a paragraph of interpretive information, at times it can be quite vague. It may suggest possible genes in the region and if known, the function of those genes. It does not always, however, delineate a clear diagnosis or prognosis for the patient, family, or provider. So what does this result mean for Robert and his parents? And, where do providers and families turn for additional information, interpretation and support?

The chromosome microarray identified two genetic changes. First, 3q29 (194,814,775-197,751,986)X3 reveals a 3 Mb gain of genetic material on the long arm of chromosome 3 (3q29 microduplication syndrome). In addition, there is a 5.2 Mb loss on the short arm of chromosome 12 (12p13.3 3p13.31[191,040-5,406,692]

Figure 1. Demystifying Microarray Results



*The size of the deletion is calculated by subtracting the nucleotide positions as follows: 121,332,698 -122,486,277 = 1,153,579 base pairs ÷ 1,000,000 (1 Mb) = 1.2 Mb in size.

The results of chromosome microarray results can be difficult to read, interpret and communicate. The above translates three microarray results with corresponding words to describe each result.

X1). Consistent with the genomic data sharing policy of the National Institutes of Health, there are a number of laboratory data warehousing, expert review, and educational resources to help make sense of microarray results (Table 2). To determine the significance of changes identified through chromosome microarray, it is not uncommon to review test results against several databases to elucidate more information, especially the pathogenicity of the change. Even with an identified genetic change and exhaustive search, the change may be of uncertain significance.

3q29 Microduplication

To determine the significance of the 3q29 microduplication, ClinVar was searched and revealed a total of 77 individuals with the 3q29 genetic change, of which 60 had gains in genetic material. Fourteen of the 60 changes were likely pathogenic or pathogenic, whereas the remaining were considered of uncertain significance, likely benign, or benign. Second, DECIPHER (DatabasE of genomiC varIation and Phenotype in Humans using Ensembl Resources) revealed the clinical features of affected individuals vary and the significance of this change remained uncertain or unknown. Third, Online Mendelian Inheritance of Man (OMIM) stated that in addition to mild-to-moderate intellectual disability, dysmorphic features for individuals with 3q29 included a round face with bulbous nose, short or down slanting palpebral fissures, excessive hand creases, and pes planus presented (Lisi et al., 2008). Robert, however, did not demonstrate these physical differences. Lastly, the Unique patient and provider Web site was accessed. An informational booklet about this genetic change showed the 22 genes in this region are believed to predispose affected individuals to overall developmental and learning difficulties including speech delay. Some children also have cardiac and/or ophthalmologic problems.

After review of the available evidence and resources, it was determined the 3q29(194,814,775-197,751,986)X3 may be pathogenic for Robert. Based on the reported cases, ongoing follow-up was recommended to address developmental delay and future learning difficulties. Because of risk for ophthalmologic problems including optic atrophy, ophthalmology consultation and follow-up were recommended.

12p13.11-31 Microdeletion

Once the research process was completed for the 3q29 microduplication, it was repeated for the second genetic change (12p13.33p13.31 [191,040-5,406,692]X1 microdeletion syndrome). Review of the same databases yielded less information regarding this change. ClinVar showed 16 individuals with similar genetic losses, of which four were pathogenic or likely pathogenic. No clinical overviews were available on DECIPHER. OMIM revealed a number of genes in this region that corresponded with problems such as microphthalmia, myeloid leukemic factor 2, and retinal cone dystrophy. Most significant, however, the *CACNA1C* and *BRGDA3* genes fall in this region. Changes in the *CACNA1C* gene cause Timothy syndrome that predisposes individuals to long QTc and syndactyly. A defect in the *BRGDA3* gene results in Brugada syndrome that causes ST segment elevation and a shortened QTc that can result in sudden death. There were no matches on the Unique Web site.

Test interpretation extends beyond the result to include information gathering and data mining.

There is less straightforward information surrounding pathogenicity and anticipatory guidance for the 12p13.11-31 microdeletion. By revealing potential risk for Timothy and Brugada syndromes, however, cardiology consultation, baseline electrocardiogram, and ongoing follow-up were recommended. In addition to continuing neurodevelopmental and ophthalmology previously discussed, parental studies were recommended to address the possibility these genetic changes occurred as a result of translocation.

Benefits and Limitations of Chromosome Microarray

Benefits of Chromosome Microarray

There are a number of benefits to chromosome microarray of which, the most important is often providing patients and parents with answers to questions regarding what "caused" the condition. Because the information obtained through testing and bioinformatics interpretation is so unique and new, diagnoses not previously identified through other genetic tests such as chromosome analysis and FISH may be revealed. Identifying minute losses or gains in genetic material is important when it confirms a diagnosis and allows healthcare providers to share information about the condition's natural history and offer specific anticipatory guidance and prognostic information. A shift in medical care may include: (a) eliminating ineffective or contraindicated treatments, (b) recommending additional or different medical surveillance, (c) optimizing educational planning, and at times, (d) redirecting care from a treatment to palliative focus. Even when information does not offer a change in treatment or outcome, when a firm diagnosis and inheritance is identified, recurrence risks for future pregnancies can be discussed.

Limitations of Chromosome Microarray

Although microarray is an incredibly accurate genetic test that measures minute losses and gains in genetic

material, not all genetic differences can be identified. For example, because DNA probes identify copy number variants, truly balanced rearrangements are not revealed. Genomic imbalances in regions not on the microarray, low-level mosaicism and small DNA changes (single gene defects) may be missed. Therefore, microarray may need to be combined with chromosome and/or FISH technology based on patient clinical findings and test results (Crotwell & Hoyme, 2012; Stankiewicz & Beaudet, 2007).

When microarray identifies a copy number variant, the clinical significance of the change may be insignificant or not yet known. To help predict the effect in the affected individual when a previously unrecognized or equivocal genetic change is found, parental studies may reveal whether one of the parents has the same genetic change or a translocation led to the variant. For example, if a parent has the same genetic change and does not have a similar phenotype to the affected child, the change is likely benign. If, however, the genetic change is not identified in the parents, it may explain the child's phenotype. Of note, when parent samples are requested, it is important to disclose that regions of homozygosity suggestive of common ancestry, nonpaternity, and/or genetic abnormalities consistent with adult-onset disease may be exposed.

Maternal–child nurses at all practice levels should be familiar with this genetic test.

In the absence of available clinical, phenotypic, and outcome information, patients, parents, and providers can be left with equivocal test results and unanswered questions. This may prompt ongoing genetic follow-up and/or testing and highlights the importance of continuing to build data warehouses of clinical and genetic information to ensure a robust compendium of resources that, in the future, may be more meaningful than they are today.

Clinical Implications for Nurses

The field of genetics will continue to grow and as such, nurses require a basic understanding of genetics and genetic testing to provide competent care, participate in clinical conversations, and share current genetic education. To improve genetic literacy among nurses across various disciplines and levels of practice, essential care competencies for nurses have been established (Consensus Panel on Genetic/Genomic Competencies, 2009). These include making sure nurses have the skill and knowledge to interview patients to obtain a meaningful patient health history, elicit and document an accurate three-generation family history, identify key features of common genetic conditions and/or risk factors, and refer individuals for genetic evaluation and testing. It is important that nurses are able to discuss genetic testing and help set realistic expectations and implications for testing and test results with patients and parents, assess recurrence risk based on inheritance pattern, and provide appropriate individualized patient care based on genetic test results. On a broader perspective, with a greater understanding of genetics and genetic risk factors for disease and/or a confirmed diagnosis, nurses must be able to provide patient- and condition-specific health promotion, disease prevention, anticipatory guidance, and symptom management education. Nurses advocate for informed decision making and address ethical, legal, and social issues of genetic testing and implications of learning test results. Nurses understand the challenges of prescribing, interpreting, and conveying chromosome microarray and other genetic test results and improve communication skills to provide patients and parents with sensitive genetic information (Consensus Panel on Genetic/Genomic Competencies, 2009; Kirk, 2013; Kirk & Marshallsay, 2013). ✣

Clinical Implications for Nurses

- In combination with an astute clinician and other genetic tests, chromosome microarray can help reveal genetic changes missed by high-resolution chromosomes and FISH.
- Chromosome microarray may be ordered to identify chromosome imbalances in individuals with a normal karyotype or as the first-line test to detect microdeletions and/or microduplications in individuals with minor physical findings and developmental delays.
- In today's genetically-focused healthcare arena, nurses at all practice levels must learn, understand, and speak the language of genetics and genomics.
- Nurses must demonstrate confidence in their ability to reinforce and discuss information about genetics, genetic testing, and results including chromosome microarray.
- Nurses can have an important role in supporting patients and parents with decision making surrounding genetic testing and when receiving results.

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The author has no conflicts of interest and nothing to disclose.

DOI:10.1097/NMC.0000000000000260

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Disclosure Statement:

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