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The Laboratory-Clinician Team: A Professional Call to Action to Improve Communication and Collaboration for Optimal Patient Care in Chromosomal Microarray Testing

Karen E. Wain¹, Erin Riggs², Karen Hanson³, Melissa Savage³, Darlene Riethmaier⁴, Andrea Muirhead^{1,5}, Elyse Mitchell¹, Bethanny Smith Packard⁶, and W. Andrew Faucett⁶

¹Mayo Clinic, Rochester, MN

²Emory University, Atlanta, GA

³Columbia University, New York, NY

⁴GeneDx, Gaithersburg, MD

⁵Boston University, Boston, MA

⁶Geisinger Health System, Danville, PA

Abstract

The International Standards for Cytogenomic Arrays (ISCA) Consortium is a worldwide collaborative effort dedicated to optimizing patient care by improving the quality of chromosomal microarray testing. The primary effort of the ISCA Consortium has been the development of a database of copy number variants (CNVs) identified during the course of clinical microarray testing. This database is a powerful resource for clinicians, laboratories, and researchers, and can be utilized for a variety of applications, such as facilitating standardized interpretations of certain CNVs across laboratories or providing phenotypic information for counseling purposes when published data is sparse. A recognized limitation to the clinical utility of this database, however, is the quality of clinical information available for each patient. Clinical genetic counselors are uniquely suited to facilitate the communication of this information to the laboratory by virtue of their existing clinical responsibilities, case management skills, and appreciation of the evolving nature of scientific knowledge. We intend to highlight the critical role that genetic counselors play in ensuring optimal patient care through contributing to the clinical utility of the ISCA Consortium's database, as well as the quality of individual patient microarray reports provided by contributing laboratories. Current tools, paper and electronic forms, created to maximize this collaboration are shared. In addition to making a professional commitment to providing complete clinical information, genetic counselors are invited to become ISCA members and to become involved in the discussions and initiatives within the Consortium.

Keywords

chromosomal microarray; array CGH; clinical utility; ISCA Database; phenotype information

The Evolution of Cytogenetic Testing

The history of cytogenetics illustrates how technological abilities and clinical knowledge evolve together over time. Cytogenetic testing became cemented in the routine medical evaluation of individuals with intellectual disability and/or congenital anomalies when banding patterns unique to each metaphase chromosome were discovered using Giemsa stain (Shaffer, et al. 2006). This technique, G-banded chromosome analysis, has historically been the gold standard for detecting large chromosomal imbalances, generally those larger than about 5–10 megabases (Mb) depending on the region and sample type, and has provided the genetic etiologies needed to understand and define such syndromes as Down syndrome, Cri-du-chat syndrome, and Smith-Magenis syndrome (Shaffer, et al. 2006). However, while G-banded chromosome analysis provides a look at the entire genome, it does so at very low resolution and techniques to detect smaller imbalances were desired. Fluorescence in situ hybridization (FISH) was the next major advance in cytogenetic testing and provided a means to detect deletions or duplications as small as approximately 100 kilobases (kb), which were not visible by routine chromosome analysis (Bejjani and Shaffer 2008; Shaffer, et al. 2006). This high resolution technique allowed for the characterization of several microdeletion/microduplication syndromes that are now well-known, such as 22q11.2 deletion (DiGeorge/Velocardiofacial) syndrome, Williams syndrome, and subtelomeric deletions/duplications (Bejjani and Shaffer 2008; Shaffer, et al. 2006). Excluding the subtelomeric regions, the clinical use of FISH testing requires an *a priori* knowledge of which genomic region to test based on the patient's clinical features. Thus, patients with nonspecific clinical features caused by a microdeletion or microduplication syndrome not well described or easily recognized would go undiagnosed (Bejjani and Shaffer 2008). Additionally, progress was limited in clearly defining and describing new microdeletion and microduplication syndromes characterized by variable or overlapping clinical features or which exhibited incomplete penetrance or variable expressivity (Bejjani and Shaffer 2008; Slavotinek 2008).

Currently in cytogenetics, we are in the era of high resolution, whole-genome testing via chromosomal microarray, which combines the advantages of G-banded chromosomes and FISH into one assay. While microarray techniques themselves have evolved, testing platforms now most commonly utilize oligonucleotide and/or single-nucleotide-polymorphism (SNP) based array technology to detect very small copy number changes throughout the genome. This ability has increased the detection rate for patients with intellectual disability and/or congenital anomalies from 4% (with G-banded analysis) to 15–20% (Miller, et al. 2010). In some patients, microarray testing has identified large genomic rearrangements that were missed by previous G-banded analysis, illustrating the variability in clinical sensitivity with traditional G-banded analysis (Slavotinek 2008). These advantages have led to the recommendation that chromosomal microarray be considered a “first-tier test” for individuals with multiple congenital anomalies, apparently non-syndromic developmental delay/intellectual disability, or autism spectrum disorders (Manning, et al. 2010). Additionally, the use of chromosomal microarray in postnatal care has prompted interest in incorporating the technology into prenatal applications. Reports of increased detection rates by microarray testing compared to G-banded chromosome analysis in prenatal diagnosis have been published (Coppinger, et al. 2009, Maya, et al. 2010). The American Congress of Obstetrics & Gynecology (ACOG) has recommended microarray testing specifically for fetuses with abnormal ultrasound findings and normal karyotype as well as for fetal demise when anomalies are present but a karyotype cannot be obtained (ACOG Committee 2009). While the recommendation states that microarray should not replace G-banded chromosome analysis in prenatal diagnosis at this time, these recommendations may change over time as the results of the recent clinical trial, funded by

the National Institute of Child Health and Human Development (Wapner, RO1 HD055651-04), are released and as further research studies are conducted.

The “genotype-first” approach that microarrays provide has allowed for the characterization of multiple new syndromes (Bejjani and Shaffer 2008; Slavotinek 2008). However, it has also resulted in an increased appreciation for the amount of copy number variants (CNVs) in humans, a phenomenon that can often complicate the clinical interpretation of chromosomal microarray test results (Bejjani and Shaffer 2008; Wong, et al. 2007). While databases, such as the Database for Genomic Variants (DGV) (<http://projects.tcag.ca/variation>) and peer-reviewed publications have been helpful for cataloguing common genomic variation (CNVs present in more than 1% of the general population), there is often not enough data available from a single laboratory or a single clinician to readily classify many rare or novel copy number changes found in patients tested. Therefore, the laboratory and clinician are faced with the difficult challenge of knowing how to interpret and act on these CNVs of uncertain significance and how to help patients and families understand and cope with the ambiguity they can bring. To provide guidance for these interpretive challenges, professional recommendations for interpretive categories were published by the American College of Medical Genetics (ACMG) (Kearney, et al. 2011). These outline a five category system where CNVs are considered pathogenic, likely pathogenic, uncertain, likely benign, or benign based on available published literature, the gene content and size of the CNV, and information available in intra-laboratory and public databases (Kearney, et al. 2011). However, despite this guidance, many CNVs are not uniformly classified into one of these categories and additional research and resources are needed.

The International Standards for Cytogenomic Arrays (ISCA) Clinical CNV Database

In recognition of these challenges, the International Standards for Cytogenomic Arrays (ISCA) Consortium, a worldwide collaboration of independent cytogenetic laboratories and experts, was formed in 2008 to promote advances in chromosomal microarray testing and improve overall patient care (www.iscaconsortium.org). The ISCA Consortium members are a diverse group, including genetic counselors, laboratory directors, industry partners, bioinformatics experts, and other clinicians. Genetic counselors, in particular, have been instrumental in accomplishing the ISCA Consortium’s goals and engaging the broader genetics community. These initiatives include, among others, an evidence-based dosage-sensitivity rating system for genes throughout the genome to aid in microarray result interpretation and design (Riggs, et al. 2011) and working with the insurance industry to improve reimbursement for microarray testing. However, one of the most important initiatives of the ISCA Consortium is the ISCA Clinical CNV Database, which contains genotype and phenotype data to be used as a resource for the clinical and research communities and is publicly available through the Database of Human Variation (dbVar) (<http://www.ncbi.nlm.nih.gov/dbvar/studies/nstd37/>) at the National Center for BioInformatics (NCBI) (Church et al. 2010). Raw data files are also available for researchers with approved access in the Database of Genotypes and Phenotypes (dbGaP) (http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000205.v3.p2). All ISCA member laboratories are encouraged to submit de-identified data from every patient tested. An opt-out model of consent is utilized for this effort since risks of privacy breaches are very low. Patients may opt-out by contacting the participating laboratory at any time without impacting their clinical testing (Faucett, et al. 2008).

Public databases similar to the ISCA Clinical CNV Database have been utilized effectively by molecular genetic laboratories for numerous conditions and have been an important component of translational research as large amounts of data on both disease-associated

mutations and unclassified variants are identified. Examples of such databases include those for pseudoxanthoma elasticum (http://www.ncbi.nlm.nih.gov/lovd/home.php?select_db=ABCC6), Cornelia de Lange syndrome (<http://www.lovd.nl/NIPBL>), and muscular dystrophy caused by mutations within the *DMD* gene (<http://www.umd.be/DMD/>) (Oliveira, et al. 2010; Tuffery-Giraud, et al. 2009). These types of public genetic databases that capture phenotypic information provide additional insight into the spectrum of clinical features and range in severity seen in individuals with a given genetic disorder. They have helped laboratories assess the clinical significance of sequence variants, allowed access to a standardized collection of high-quality, disease-specific information, have been a useful tool for genotype-phenotype correlations, and serve as an excellent model for addressing the interpretive challenges facing the genetics community.

The ISCA Clinical CNV Database is a valuable resource for clinical laboratories as it allows each to benefit from the others' experience. Any CNV reported on a clinical basis is submitted to the database using the interpretive categories outlined by ACMG (Kearney, et al. 2011), which allows for greater intra- and inter-laboratory consistency. For example, if a small, novel copy number change of unknown inheritance is identified in a patient that has not been reported in the literature or found previously within the laboratory, this change would likely be considered of uncertain significance. However, if this same change was found by other laboratories to be *de novo* in multiple patients with similar phenotypes, this could dramatically change the test interpretation and report. The database also provides participating laboratories with the quality control opportunity of automatic curation reports. This is invaluable as variation in reporting practices has been found to raise the potential for confusion for clinicians, patients, and researchers (Tsuchiya, et al. 2009). With each data submission, a laboratory will receive a report of any individual copy number changes whose assigned interpretive categories conflict with its own previous submissions or with the ISCA curated list of known pathogenic and benign regions (<http://www.ncbi.nlm.nih.gov/dbvar/studies/nstd45/>). Expert curation of the entire database will also be performed on a routine basis. This process will help maintain consistency within and between laboratories and will identify genomic regions that are not well understood and require expert discussion about clinical significance. Additionally, this database is available publically to all clinicians as they make their own clinical interpretations of microarray reports for their patients. As with all such database efforts, the quality of the data contained within a database dictates its true utility. Since all testing is completed within CLIA-certified laboratories, the quality of the genotype data is held to a high standard; the corresponding phenotypic data, however, is subject to individual clinician effort and, as such, is quite variable in its completeness.

The Importance of Phenotypic Data

The challenge of obtaining clinical information on patients has long been recognized by genetic laboratories as it directly impacts the interpretation of each patient's result and is often used to determine if the appropriate testing was ordered. The Centers for Disease Control and Prevention (CDC) and the Clinical Laboratory Improvement Advisory Committee (CLIA) have published recommendations and guidelines for quality assurance in clinical genetic testing laboratories with the ultimate goal of improving healthcare outcomes (Chen and Greene 2010; Chen, et al. 2009). In addition to recommendations related to the availability of test information, analytic performance, sample requirements, clinical validity, and quality control processes, CLIA-approved laboratories are responsible for ensuring that test requisitions allow for the collection of necessary clinical information relevant to test interpretation (Chen and Greene 2010; Chen, et al. 2009; CLIA 42 C.F.R. Part 493 2004). This pre-analytic variable is considered necessary for optimal result reporting and a reasonable effort is needed to obtain it.

However, despite laboratory efforts to make test requisitions and instructions as user-friendly as possible, many test specimens arrive in laboratories with little to no clinical information. Laboratories employ various methods to try to obtain this information as the test specimen is processed, and sometimes testing is placed on hold to ensure that the appropriate test was ordered. Several laboratories employ genetic counselors to help with this process, as their clinical training makes them familiar with the presenting clinical features in most patients as well as other conditions potentially included in a differential diagnosis. Laboratory genetic counselors often initiate conversations regarding a patient's clinical presentation at the time the testing is ordered to ensure appropriateness of testing. This practice, as illustrated by one laboratory genetic counselor team, significantly reduces the number of erroneous test orders, thereby saving healthcare expense and preventing incorrect conclusions from being drawn clinically (Miller, et al 2011). Laboratory genetic counselors can also intercede at any point in the test process if additional information is needed to fully interpret the patient's results or make additional testing recommendations. This practice of open communication and collaboration has been standard in traditional cytogenetic testing of both prenatal and postnatal specimens and has informed our understanding of clinical outcomes in rare situations such as de novo translocations and insertions and rare mosaic trisomies (Hsu, et al. 1997; Warburton 1991). A team approach to genetic testing between the clinician and the laboratorian has served the field of clinical genetics well, and now, with increasing test specimen volumes and competing research or academic responsibilities for laboratory directors, laboratory genetic counselors are helping to ensure this team approach remains.

As described above, the ISCA database will improve clinical laboratory reports and patient care by fostering consistency in the interpretation of rare CNVs between laboratories and by facilitating intra- and inter-laboratory curation. However, providing complete clinical information also improves a patient's microarray report by allowing the laboratory to specifically recommend additional testing that may lead to a complete diagnosis, point out medical management implications, or include information about a CNV that is particularly relevant for a given phenotype. The clinical information provided can also directly influence the interpretation of a CNV. For example, if a small deletion in a child with developmental delay and dysmorphic features is found to be paternally inherited, informing the laboratory of a paternal history of developmental delay could change the interpretation of that deletion from uncertain or likely benign to potentially likely pathogenic.

The impact of adequate clinical information on test interpretation and, subsequently, on patient care, is illustrated by the following postnatal case examples. In Case 1 (Sebold, et al. 2009), microarrays were ordered on two twin boys who presented with hypotonia, developmental delay, and feeding difficulties. The array detected a small deletion (176 kb) in the *VPS13B* gene. Mutations in this gene are associated with Cohen syndrome, a rare autosomal recessive condition with clinical features including: failure to thrive, early-onset hypotonia, developmental delays, acquired microcephaly, moderate to profound intellectual disability, progressive retinchoroidal dystrophy, and characteristic facial features (Falk, et al. 2011). This particular deletion fell below the laboratory's standard reporting threshold based on its size. Also, laboratories often do not comment specifically on the involvement of a gene for a recessive condition because detecting carriers of recessive conditions is not the goal of microarray testing. However, because of the clinical information provided by the ordering clinician, the laboratory was able to recommend sequencing of *VPS13B* to look for a mutation on the other chromosome, which confirmed the diagnosis of Cohen syndrome in both twins. This diagnosis impacted medical management and led to the initiation of an ophthalmology examination, which diagnosed high myopia and ensured screening for the development of retinchoroidal dystrophy. The diagnosis also facilitated enrollment in

social and therapeutic services, prevented other unnecessary invasive procedures, and guided genetic counseling for future pregnancies for the family.

Case 2 is that of a 6-year old girl whose microarray testing was performed in an ISCA member laboratory (personal communication, K.E. Wain). The laboratory was informed that the clinician was considering a diagnosis of incontinentia pigmenti, although specific details of her clinical presentation were not shared. She was found to have a duplication of approximately 331 kb at Xq28 which was of uncertain significance. However, this duplication lay within about 40 kb of the *IKBKG* gene which is responsible for incontinentia pigmenti. While it cannot be determined from the microarray data whether or not this duplication disrupts *IKBKG* function, it is certainly important that the clinician realize the proximity of this duplication to the gene causing the suspected diagnosis, as gene function could be impacted by position effects. Since the duplication did not directly overlap the *IKBKG* gene, this proximity would likely not have been explicitly discussed in the laboratory report had the clinical information provided not made it clear that it was relevant.

Providing detailed phenotypic information is essential not only for the interpretation of individual test results; it is also crucial for the clinical utility of databases for future patients and the whole genetics community through the development of research initiatives. Compiling data from numerous patients, potentially from other public databases as well, provides an opportunity to refine and more fully characterize the clinical implications of both novel and previously described microdeletion/microduplication syndromes, such as the frequencies, penetrance, and variable expressivity of these disorders. Historically, individual laboratories or small collaborations have published case series of patients with novel or rare microdeletion/microduplication syndromes which typically include clinical information to further define the syndromes. The large quantity of cases within the ISCA database has the potential to drastically increase the rate at which this type of knowledge can be generated and disseminated to the medical community. For example, one recent large case-control study that utilized the ISCA data, using a genotype-first approach, has led to a more confident interpretation of 14 microdeletion/microduplication regions, as well as frequency estimates (Kaminsky, et al. 2011). Researchers can also take a phenotype-first approach by searching the database using specific phenotypic terms, such as autism, to identify clusters of genomic regions associated with a particular phenotype for future research (Riggs, et al. 2012). Additionally, genotype-phenotype correlations can be used to better understand gene function and the pathophysiology of disease (Goh, et al. 2006; Groth, et al. 2008; Perez-Iratxeta, et al. 2002).

The Collection of Phenotypic Data: A Call to Genetic Counselors

As discussed above, a major challenge in the creation and maintenance of the ISCA Clinical CNV Database is the collection and organization of patient phenotypic data. In order for the available phenotypic information to be useful for the varied functions of the database, it is important that a standardized vocabulary is utilized. Employing a standardized vocabulary allows for the database to be easily indexed and searched, alleviates confusion from the use of acronyms, and removes the risk of potentially identifying patients through free text descriptions entering the database. The standardized terms and organizational structure of terminology used for the ISCA Database comes from the Human Phenotype Ontology (HPO), a system developed to describe the concepts and attributes of terms, and the relationships between terms, frequently encountered in human genetic disease (Robinson, et al. 2008). Initially developed using terms found in OMIM, the HPO currently has over 9,500 terms and over 50,000 annotations between these terms and specific diseases within OMIM, allowing for the generation of differential diagnoses lists based on the relationships between terms and diseases (Kohler, et al. 2009; Robinson and Mundlos 2010). These relationships

can also be used to explore associations between phenotypic traits and gene families, possibly revealing clues about gene function and interactions. Terms are associated with parent terms in an “is_a” type of relationship, and the “true-path” rule is applied so that phenotype terms provided are annotated both to the most specific HPO term available and automatically to the more general terms in that term family (Gkoutos, et al. 2009). For example, “tetralogy of Fallot” (HP: 0001636) is related to the parent term “complex cardiac malformation” as well as to further removed ancestor terms such as “cardiac malformation,” “abnormality of the heart,” and “abnormality of the cardiovascular system.” Using HPO terms in this way allows for database searches to be at least somewhat informative regardless of the level of specificity available for a given clinical feature.

To facilitate the provision of phenotype information during the course of clinical laboratory testing, the ISCA Consortium has developed one-page phenotype collection forms for use by clinicians in both the prenatal and postnatal settings. Each form includes phenotype terms (each annotated to a specific HPO term) organized by organ system, with space for the user to include free text descriptions of other phenotypic characteristics present in the patient that are not represented on the forms. The current versions of these forms are available for download on the ISCA website (www.iscaconsortium.org) and can be modified to be consistent with standard requisition forms for any contributing laboratory. Online versions of the forms can be generated free of charge for member laboratories in partnership with Cartagenia (www.cartagenia.com), a company that specializes in web-based software and database platforms for genomic variation.

Genetic counselors are a core group of individuals to engage in the important effort for collecting this information. Genetic counselors are familiar enough with their patients’ presentations and histories to be able to fill out the form completely, and are frequently the member of the clinical team completing laboratory requisition paperwork. They can also be effective at training other clinical or laboratory staff to ensure that completed forms either are faxed directly to the laboratory or accompany the testing specimen as intended. Educational initiatives of the ISCA Consortium will continue to focus on informing the genetic counseling community and other clinicians of both the immediate (individual patient care through laboratory results) and long-term (global patient care through the ISCA Database) impacts of their efforts to report detailed clinical information to their laboratory partners.

Concluding Remarks

The current approach in clinical genetics of testing and analyzing one or a few genes at a time is becoming dated, and new approaches to genomic analysis are needed (Berg, et al. 2011). The challenge of classifying variants of unknown clinical significance is not unique to chromosomal microarray and is expected to increase significantly as many individuals begin having their entire genome sequenced, resulting in the identification of thousands of variants in a single individual (Bale, et al. 2011). Berg and colleagues (2011) have proposed a categorical framework to help manage sequence data and to provide initial criteria for how variants should be interpreted and reported which relies on accurate phenotypic information. As the realities of clinically available whole-genome or whole-exome sequencing are realized, such proposals will likely be refined and collaborative clinical efforts similar to that of the ISCA Consortium will be invaluable. ISCA has begun collaborations with the molecular laboratory community and plans to develop joint databases to capture all types of genomic changes. Future ISCA endeavors will be closely paired with the emerging ClinVar database which will hold publicly available sequence data, and the successes and experiences of the ISCA Consortium will certainly serve as models for these translational efforts. We anticipate that the importance of collaboration with clinical genetic counselors,

as with the ISCA Clinical CNV Database, will be recognized in the context of whole-genome and whole-exome sequencing. Therefore, incorporating practice changes to provide more complete clinical data with the ISCA phenotype form for chromosomal microarray testing has the potential to pave the way for additional clinical benefits in other areas of genetic testing.

The translation of genetic testing from the research or diagnostic laboratory to clinical care is a team-based effort requiring close relationships and good communication between involved parties (Das, et al. 2008; Zierhut and Austin 2011). Zierhut and Austin (2011) recently argued for the inclusion of genetic counselors on research teams to maximize translational research efforts. We would like to extend this idea further to acknowledge the importance of clinical genetic counselors in the process of optimizing the clinical utility of chromosomal microarray testing, particularly in their ability to provide complete and accurate phenotypic information about patients. Regardless of their specialty, clinical genetic counselors are accustomed to collaborating with other health care professionals, researchers and laboratories on a regular basis. They make a difference in the lives of patients every day in a variety of ways, whether by providing psychosocial support and resources, ensuring accurate and appropriate testing is completed, facilitating insurance coverage, or helping with decision-making. Many also make additional contributions through published case reports, original research, coordination of programs and services, or other research-related activities. The consistent use of the ISCA phenotype form to provide detailed and accurate phenotypic information when ordering a chromosomal microarray is yet another opportunity for genetic counselors to provide high-quality patient care. Professional commitment to the concepts of open communication and collaboration with this larger definition of the “patient care team” is required for the best care possible for current and future patients and has the potential to significantly impact the continuous evolution of scientific knowledge available to our profession. We encourage all genetic counselors to support the efforts of the ISCA Consortium, and other similar clinical databases, and are eager for the feedback, ideas, and collaborations that our colleagues have to offer.

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References

- American College of Obstetricians and Gynecologists (ACOG) Committee. Array comparative genomic hybridization in prenatal diagnosis. ACOG Committee Opinion No. 446. *Obstet & Gynecol.* 2009; 114:1161–1163.
- Bale S, Devisscher M, Van Criekinge W, Rehm HL, Decouttere F, Nussbaum R, et al. MutaDATABASE: a centralized and standardized DNA variation database. *Nat Biotechnol.* 2011; 29(2):117–118. [PubMed: 21301433]
- Bejjani BA, Shaffer LG. Clinical utility of contemporary molecular cytogenetics. *Annu Rev Genomics Hum Genet.* 2008; 9:71–86. [PubMed: 18949852]
- Berg JS, Khoury MJ, Evans JP. Deploying whole genome sequencing in clinical practice and public health: Meeting the challenge one bin at a time. *Genet Med.* 2011; 13(6):499–504. [PubMed: 21558861]
- Chen B, Gagnon M, Shahangian S, Anderson NL, Howerton DA, Boone DJ. Centers for Disease Control and Prevention, Good Laboratory Practices for Molecular Genetic Testing for Heritable Diseases and Conditions. *MMWR Recomm Rep.* 2009; 58(RR-6):1–37. [PubMed: 19521335]
- Chen B, Greene C. Promoting quality of genetic testing with guidelines for good laboratory practices. *Mol Genet Metab.* 2010; 99:238–243. [PubMed: 20196208]
- The Clinical Laboratory Improvement Amendments (CLIA) regulations; laboratory requirements, 42 C.F.R. Part 493. 2004. Available at <http://www.cdc.gov/clia/regs/toc.aspx>

- Church DM, Lappalainen I, Sneddon TP, Hinton J, Maguire M, Lopez J, et al. Public data archives for genomic structural variation. *Nat Genet.* 2010; 42(10):813–814. [PubMed: 20877315]
- Coppinger J, Alliman S, Lamb AN, Torchia BS, Bejjani BA, Shaffer LG. Whole-genome microarray analysis in prenatal specimens identifies clinically significant chromosome alterations without increase in results of unclear significance compared to targeted microarray. *Prenat Diagn.* 2009; 29(12):1156–1166. [PubMed: 19795450]
- Das S, Bale SJ, Ledbetter DH. Molecular genetic testing for ultra rare diseases: models for translation from the research laboratory to the CLIA-certified diagnostic laboratory. *Genet Med.* 2008; 10(5): 332–336. [PubMed: 18496031]
- Falk, MJ.; Wang, H.; Traboulsi, EI. Cohen Syndrome. In: Pagon, RA.; Bird, TD.; Dolan, CR.; Stephens, K., editors. *GeneReviews* [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2006 Aug 29. [updated 2011 Mar 10]
- Faucett WA, Hart S, Pagon R, Neall L, Spinella G. A model program to increase translation of rare disease genetic tests: Collaboration, education, and test translation program. *Genet Med.* 2008; 10(5):343–348. [PubMed: 18496033]
- Gkoutos GV, Mungall C, Dolken S, Ashburner M, Lewis S, Hancock J, et al. Entity/quality-based logical definitions for the human skeletal phenome using PATO. *Conf Proc IEEE Eng Med Biol Soc.* 2009; 2009:7069–7072. [PubMed: 19964203]
- Goh CS, Gianoulis TA, Liu Y, Li J, Paccanaro A, Lussier YA, et al. Integration of curated databases to identify genotype-phenotype associations. *BMC Genomics.* 2006; 7:257. [PubMed: 17038185]
- Groth P, Weiss B, Pohlentz HD, Leser U. Mining phenotypes for gene function prediction. *BMC Bioinformatics.* 2008; 9:136. [PubMed: 18315868]
- Hsu LY, Yu M, Neu RL, Van Dyke DL, Benn PA, Bradshaw CL, et al. Rare trisomy mosaicism diagnosed in amniocytes, involving an autosome other than chromosomes 13, 18, 20, and 21: karyotype/phenotype correlations. *Prenat Diagn.* 1997; 17(3):201–242. [PubMed: 9110367]
- Kaminsky EB, Kaul V, Paschall J, Church DM, Bunke B, Kunig D, et al. An evidence-based approach to establish the functional and clinical significance of copy number variants in intellectual and developmental disabilities. *Genet Med.* 2011; 13(9):777–784. [PubMed: 21844811]
- Kearney HM, Thorland EC, Brown KK, Quintero-Rivera F, South ST. Working Group of the American College of Medical Genetics Laboratory Quality Assurance Committee. American College of Medical Genetics standards and guidelines for interpretation and reporting of postnatal constitutional copy number variants. *Genet Med.* 2011; 13(7):680–685. [PubMed: 21681106]
- Kohler S, Schulz MH, Krawitz P, Bauer S, Dolken S, Ott CE, et al. Clinical diagnostics in human genetics with semantic similarity searches in ontologies. *Am J Hum Genet.* 2009; 85(4):457–464. [PubMed: 19800049]
- Manning M, Hudgins L, Professional Practice, Guidelines Committee. Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. *Genet Med.* 2010; 12(11):742–745. [PubMed: 20962661]
- Maya I, Davidov B, Gershovitz L, Zalstein Y, Taub E, Coppinger J, et al. Diagnostic utility of array-based comparative genomic hybridization (aCGH) in a prenatal setting. *Prenat Diagn.* 2010; 30(12–13):1131–1137. [PubMed: 20925131]
- Miller, CE.; Krautscheid, P.; Baldwin, EE.; LaGrave, D.; Openshaw, A.; Hart, K., et al. White paper. ARUP Laboratories; 2011. Value of Genetic Counselors in the Laboratory. www.aruplab.com
- Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet.* 2010; 86:749–764. [PubMed: 20466091]
- Oliveira J, Dias C, Redeker E, Costa E, Silva J, Reis Lima M, et al. Development of NIPBL Locus-Specific Database Using LOVD: From Novel Mutations to Further Genotype –Phenotype Correlations in Cornelia de Lange Syndrome. *Hum Mut.* 2010; 31(11):1216–1222. [PubMed: 20824775]
- Perez-Iratxeta C, Bork P, Andrade MA. Association of genes to genetically inherited diseases using data mining. *Nat Genet.* 2002; 31:316–319. [PubMed: 12006977]

- Riggs ER, Church DM, Hanson K, Horner VL, Kaminsky EB, Kuhn RM, et al. Towards an evidence-based process for the clinical interpretation of copy number variation. *Clin Genet*. 2011;110.1111/j.1399-0004.2011.01818.x
- Riggs ER, Jackson L, Miller DT, Van Vooren S. Phenotypic Information in Genomic Variant Databases Enhances Clinical Care and Research: The International Standards for Cytogenomic Arrays Consortium Experience. *Hum Mutat*. 2012; 00:1–10.
- Robinson PN, Kohler S, Bauer S, Seelow D, Horn D, Mundlos S. The Human Phenotype Ontology: a tool for annotating and analyzing human hereditary disease. *Am J Hum Genet*. 2008; 83(5):610–615. [PubMed: 18950739]
- Robinson PN, Mundlos S. The human phenotype ontology. *Clin Genet*. 2010; 77(6):525–534. [PubMed: 20412080]
- Sebold C, Graham L, McWalter K. Presented Abstracts from the Twenty-Eighth Annual Education Conference of the National Society of Genetic Counselors. *J Genet Couns*. 2009; 18(6):669.
- Shaffer, LG.; Ledbetter, DH.; Lupski, JR. Sriver CR, etc. MMBID Online. McGraw-Hill; New York: 2006. Molecular Cytogenetics of Contiguous Gene Syndromes: Mechanisms and Consequences of Gene Dosage Imbalance. <http://genetics.accessmedicine.com>
- Slavotinek AM. Novel microdeletion syndromes detected by chromosome microarrays. *Hum Genet*. 2008; 124(1):1–17. [PubMed: 18512078]
- Tsuchiya KD, Shaffer LG, Aradhya S, Gastier-Foster JM, Patel A, Rudd MK, et al. Variability in interpreting and reporting copy number changes detected by array-based technology in clinical laboratories. *Genet Med*. 2009; 11:866–873. [PubMed: 19904209]
- Tuffery-Giraud S, Beroud C, Leturcq F, Ben Yaou R, Hamroun D, Michel-Calemard L, et al. Genotype-phenotype analysis in 2,405 patients with a dystrophinopathy using the UMD-DMD database: a model of nationwide knowledgebase. *Hum Mutat*. 2009; 30(6):934–945. [PubMed: 19367636]
- Warburton D. De novo balanced chromosome rearrangements and extra marker chromosomes identified at prenatal diagnosis: clinical significance and distribution of breakpoints. *Am J Hum Genet*. 1991; 49:995–1013. [PubMed: 1928105]
- Wong KK, deLeeuw RJ, Dosanjh NS, Kimm LR, Cheng Z, Horsman DE, et al. A comprehensive analysis of common copy-number variations in the human genome. *Am J Hum Genet*. 2007; 80(1):91–104. [PubMed: 17160897]
- Zierhut H, Austin J. How Inclusion of Genetic Counselors on the Research Team Can Benefit Translational Science. *Sci Transl Med*. 2011; 3(74):74cm7.