Clinical Utility of Chromosomal Microarray Analysis

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**KEY WORDS:** microarray analysis, clinical utility, DNA copy number variants

**ABBREVIATION**

BAC—bacterial artificial chromosome

**WHAT’S KNOWN ON THIS SUBJECT:** Chromosomal microarray analysis offers a superior diagnostic yield over karyotyping for the evaluation of individuals with developmental disabilities. Many third-party payers, however, do not reimburse for microarray testing, citing a lack of evidence that patients benefit from testing.

**WHAT THIS STUDY ADDS:** This study demonstrates that microarray testing frequently identifies conditions that include features requiring specific medical follow-up and that referring physicians respond to abnormal test results with appropriate clinical actions. Microarray testing, therefore, provides direct benefits to patients.

**OBJECTIVE:** To test the hypothesis that chromosomal microarray analysis frequently diagnoses conditions that require specific medical follow-up and that referring physicians respond appropriately to abnormal test results.

**METHODS:** A total of 46 298 postnatal patients were tested by chromosomal microarray analysis for a variety of indications, most commonly intellectual disability/developmental delay, congenital anomalies, dysmorphic features, and neurobehavioral problems. The frequency of detection of abnormalities associated with actionable clinical features was tallied, and the rate of physician response to a subset of abnormal tests results was monitored.

**RESULTS:** A total of 2088 diagnoses were made of more than 100 different disorders that have specific clinical features that warrant follow-up. The detection rate for these conditions using high-resolution whole-genome microarrays was 5.4%, which translates to 35% of all clinically significant abnormal test results identified in our laboratory. In a subset of cases monitored for physician response, appropriate clinical action was taken more than 90% of the time as a direct result of the microarray finding.

**CONCLUSIONS:** The disorders diagnosed by chromosomal microarray analysis frequently have clinical features that need medical attention, and physicians respond to the diagnoses with specific clinical actions, thus arguing that microarray testing provides clinical utility for a significant number of patients tested. *Pediatrics* 2012;130:e1085–e1095
In recent years, chromosomal microarray analysis has had a large impact on the genetic evaluation of patients with intellectual disability/developmental delay, multiple congenital anomalies, and/or autism spectrum disorder. For these clinical indications, microarray testing has a significantly higher diagnostic yield than conventional karyotyping analysis. This superior diagnostic utility has led to recommendations that genomic microarray analysis be the first-tier test over karyotyping for the genetic evaluation of patients with these indications. Yet, whereas karyotyping is routinely reimbursed by third-party payers, often microarray testing is not. A major reason given for denial of coverage is that microarray testing is not medically useful. Many payers have indicated that there is an inadequate amount of published evidence that microarray testing offers clinical utility defined as a positive effect on patient management and/or clinical outcomes.

To assess the degree to which microarray testing provides medically useful information, we examined genomic copy number abnormalities detected in our laboratory to determine how often these abnormalities reveal diagnoses that warrant specific clinical follow-up. In a subset of cases, we tracked the clinical actions taken by referring physicians in response to the abnormal test result. Our findings indicate that disorders diagnosed by microarray testing often include clinical features that need to be directly addressed and that referring physicians frequently initiate specific and appropriate clinical actions.

METHODS

Our database of 46,298 postnatal patients tested by microarray analysis at Signature Genomic Laboratories from April 29, 2004, through October 21, 2011, was searched for abnormalities associated with specific clinical disorders, the diagnosis of which would likely lead to changes in patient management. The disorders comprised 3 categories: (1) established microdeletion and microduplication syndromes with clinical features that require specific medical follow-up, (2) conditions associated with increased cancer susceptibility, and (3) phenotypes for which obvious medical intervention is indicated and that are caused by copy number changes in individual dosage-sensitive genes. A few cases were listed in more than 1 category, but each was counted only once when performing the detection rate calculations.

For a subset of cases with abnormal results (n = 122), the referring physicians were queried as to whether they responded by taking specific clinical action(s) pertaining to the disorder identified by the microarray finding. Obvious and straightforward clinical actions for each diagnosis were the criteria used to select the disorders within this subset. Individuals in this study for whom additional clinical information was obtained provided written informed consent using an Institutional Review Board Spokane–approved consent form. For all other cases, clinical outcomes were not addressed, and no additional patient information was sought beyond the indication for testing noted on the test requisition form received by the laboratory. This form lists the following test indications: developmental delay, dysmorphic features, multiple congenital anomalies, seizure disorder, autism spectrum disorder, and “other” with details to be filled in by the physician.

The microarray platforms used to test samples evolved during the reporting period of 2004 to 2011. Initial platforms (SignatureChip versions 1–4, Signature Genomic Laboratories, Spokane, WA) used bacterial artificial chromosome (BAC) probes with targeted coverage of the genome. Subsequent BAC-based arrays (SignatureChip OS versions 1–2, Signature Genomic Laboratories) featured whole-genome coverage and were used from 2007 to 2009. Oligonucleotide-based whole-genome arrays (SignatureChip OS versions 1–3, Signature Genomic Laboratories) have been offered since February 2008; the current version is a 135K array custom designed by Signature Genomic Laboratories and manufactured by Roche NimbleGen (Madison, WI). Abnormalities detected on all array platforms were tallied for this report. For the measurement of detection rate, only cases tested on oligonucleotide platforms were included in the calculations because the lower-resolution BAC-based platforms did not assay all of the genes reported here.

RESULTS

Known Microdeletion and Microduplication Syndromes

On searching our database, we identified 1733 individuals who were found to have genomic copy number changes that encompassed regions corresponding to established microdeletion and microduplication syndromes that were selected for this study (Table 1). These disorders have complex phenotypes that typically include developmental and/or neurologic abnormalities, often accompanied by congenital malformations and other medical problems. Each of the 40 listed disorders shows a significant incidence of at least 1 clinical feature (eg, cardiac, renal, eye, or endocrine abnormalities) that requires specific medical follow-up. Note that these clinical features may not have been evident at the time of testing and, in fact, only rarely were they mentioned as an indication for testing.

The following case example illustrates the utility of microarray testing in directing the clinical care of a patient. A 6-year-old boy was tested because of
developmental delay and dysmorphic features. Microarray analysis revealed a 1.3-megabase deletion of chromosome band 17q12 that includes the gene HNF1B, which is associated with a recurrent microdeletion syndrome called renal cysts and diabetes. Following the test result, he had a renal ultrasound that showed the presence of multiple cysts and was referred to a nephrologist for follow-up. He continues to be monitored periodically for elevated blood glucose levels.

**Hereditary Cancer Predisposition**

A search of our database found 189 patients who have copy number changes detected by microarray analysis of genes associated with hereditary cancer risk (Table 2). Based on the indication for testing, only 16 patients had a known or suspected tumor risk before testing; for the remaining 92% of patients, the indications for testing were not related to cancer predisposition. In all cases, the referring physician was informed of the association...
of the abnormality with cancer risk. It should also be noted that for 2 of the probands a parent was found to carry the same abnormality; therefore, risk was identified not just for the proband but also for other family members. Letters that specifically addressed the risk to these relatives were sent to referring physicians.

The patient reported by Heald et al.\textsuperscript{16} provides a dramatic example of how microarray analysis can benefit patients. This patient was a 22-year-old woman who was tested in our laboratory as part of an evaluation for developmental delay and other features. She was found to have a 5q22.1–q22.2 deletion that included \textit{APC}, the causative gene for familial adenomatous polyposis. Although she had not previously had suggestive symptoms, a diagnosis of familial adenomatous polyposis was confirmed when colonoscopy revealed hundreds of adenomatous polyps. A thyroid scan led to a finding of papillary thyroid cancer. She subsequently underwent the life-saving measures of \textsuperscript{131}I therapy and a total colectomy.

\textbf{Other Actionable Conditions Associated With Dosage-Sensitive Genes}

We searched our database of abnormal microarray results for an additional set of 74 genes that are associated with a specific actionable phenotype when functional gene dosage is altered. Almost all of the phenotypes are associated with haploinsufficiency for the relevant gene, as evidenced by published reports of heterozygous whole-gene deletions or other null alleles in affected individuals. A total of 252 cases of copy number abnormalities representing these genes were detected in our laboratory. The conditions, corresponding genes, relevant clinical actions pertaining to the diagnosis, and numbers of cases diagnosed are listed in Table 3. We identified a number of patients who were at risk for more than one actionable phenotype as a result of a deletion that includes multiple dosage-sensitive genes. These cases included the following: (1) a patient with deletions of \textit{EDNRB} and \textit{RB1}, which put the patient at risk for hearing loss, Hirschsprung disease, and retinoblastoma; (2) 12 patients with deletions of \textit{MNX1} and \textit{KCNH2}, thus putting them at risk for urologic, spinal, and anal abnormalities, as well as cardiac arrhythmia; (3) 9 patients with deletions of \textit{GATA3} and the DiGeorge 2 critical region, which put them at risk for hearing loss, renal anomalies, and cardiac abnormalities; (4) 4 patients with deletions of \textit{LHX4} and \textit{SERPING1}, putting them at risk for pituitary insufficiency as well as a clotting predisposition; and (5) 14 patients whose deletions encompassed the 10q22–q23 microdeletion critical region, as well as the gene \textit{BMPRIA}. The 10q deletion

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|}
\hline
\textbf{Disorder* (OMIM No.)} & \textbf{Gene(s)$^b$ (Chromosome Band)} & \textbf{No. of Cases$^{cd}$} \\
\hline
Juvenile polyposis (174900) & \textit{BMPRIA} (10q23.2) & 15$^e$ \\
Beckwith-Wiedemann (130650) & \textit{IGF2} (11p15.5) & 13 \\
Familial adenomatous polyposis (175100) & \textit{APC} (5q22.2) & 13 \\
Lynch (613437, 614350) & \textit{MSH6} (2p16.3) & 2 \\
Neurofibromatosis 1 (162091) & \textit{NF1} (17q11.2) & 19 \\
Paraganglioma, pheochromocytoma & \textit{SDHB} (1p36.13) & 8 \\
(168000, 115300, 171300) & \textit{SDHD} (11q23.1) & 3 \\
VHL & \textit{VHL} (3p25.3) & 10 \\
Rubinstein-Taybi (180849, 613684) & \textit{CREBBP} & 15 \\
\textit{EPC3} (22q13.2) & 1 \\
Retinoblastoma (194070) & \textit{RB1} (13q14.2) & 12 \\
(180200) & \textit{CREBBP} (18p13.3) & 15 \\
\textit{EP300} (22q13.2) & 1 \\
Leiomymatoses and renal cell cancer (150800) & \textit{FH} (1q43) & 7 \\
Wilms tumor (120470) & \textit{WT1} (11p13) & 6 \\
Monosomy 7 mosaicism (252270) & unknown & 5 \\
Basal cell nevus (109400) & \textit{PTCH1} (9q22.32) & 6$^i$ \\
Hereditary breast and ovarian cancer (612555) & \textit{BRCA2} (13q11.2) & 3 \\
Peutz-Jeghers (175200) & \textit{STK11} (19p13.3) & 5 \\
Tuberous sclerosis (162200) & \textit{TSC2} (16p13.3) & 4 \\
Simpson-Golabi-Behmel (312870) & \textit{GIPC3} (10q26.2) & 1$^d$ \\
\textit{PTEN} hamartoma (601728) & \textit{PTEN} (10q23.31) & 3$^i$ \\
Li-Fraumeni and Li-Fraumeni-like (151623, 609265) & \textit{CHD7} (17p13.1) & 1 \\
& \textit{CHEK2} (22q12.1) & 1 \\
Neurofibromatosis 2 (101000) & \textit{NF2} (22q12.2) & 1 \\
Hereditary diffuse gastric cancer (137215) & \textit{CDH1} (16q22.1) & 1 \\
Multiple exostoses (133700, 133701) & \textit{EXT1} (8q24.11) & 9 \\
& \textit{EXT2} (11p11.2) & 4 \\
Hyperparathyroidism-jaw tumor (145001) & \textit{CDCC7} (1q31.2) & 2 \\
Acute myelogenous leukemia (601628) & \textit{RUNX1} (21q22.12) & 8 \\
Melanoma (156801, 155755) & \textit{CDKN2A} (9p21.3) & 1 \\
Rhabdoid predisposition (609322) & \textit{SMARCBL} (22q11.23) & 7 \\
Schwannomatosis (120621) & & \\
\hline
\end{tabular}
\caption{Detected Copy Number Changes of Cancer Susceptibility Genes in Postnatal Cases}
\end{table}

\textit{OMIM No.}, Online Mendelian Inheritance in Man reference number.
\textit{*} Disorders taken from Lindor et al.\textsuperscript{24}
\textit{b} Other genes were queried, but no pathogenic abnormalities were found in our database. These genes are \textit{MSH2}, \textit{MLH1}, \textit{SDHC}, \textit{BRCA1}, \textit{TSC1}, \textit{PRKAR1A}, and \textit{MEN1}.
\textit{c} The GIPC3 and \textit{SMAD4} cases are also included in Table 3.
\textit{d} The 14 cases reported by Adams et al.\textsuperscript{22} are included among these cases.
\textit{e} Fourteen of these patients have a deletion of the 10q22–q23 microdeletion critical region, and one of these 14 patients also has a deletion of \textit{PTEN}. These patients are also listed in Table 1.
\textit{f} These cases are also presented in Table 3.
\textit{g} Duplications, rather than deletions, are associated with tumor risk.
\textit{h} These patients have the 9q22.3 deletion syndrome and are included in Table 1.
\textit{i} One of these patients has the 10q22–q23 deletion syndrome and is included in Table 1.
\textit{j} One of these patients also has a deletion of \textit{BMPRIA}.

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TABLE 3 Conditions Caused by Dosage-Sensitive Genes for Which Specific Clinical Actions Are Indicated

<table>
<thead>
<tr>
<th>Disorder/Phenotype (OMIM No.)</th>
<th>Gene(s) (Chromosome Band)</th>
<th>Relevant Clinical Actions</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long QT (613688)</td>
<td>KCNH2 (1q23.1)</td>
<td>ECG, cardiology referral</td>
<td>14</td>
</tr>
<tr>
<td>Brugada (601144)</td>
<td>SCN5A (3p22.2)</td>
<td>ECG, cardiology referral</td>
<td>1</td>
</tr>
<tr>
<td>Waardenburg (various types; 193500, 193510, 277580)</td>
<td>PAOX (2q31.1)</td>
<td>Audiology, ENT referral</td>
<td>4</td>
</tr>
<tr>
<td>Axenfeld-Rieger type 1 (180500)</td>
<td>MITF (5p14.1)</td>
<td>Audiology, ENT referral</td>
<td>2</td>
</tr>
<tr>
<td>Hyperparathyroidism, deafness, renal anomalies (148255)</td>
<td>EDNRB (13q22.3)</td>
<td>Audiology, ENT referral, gastroenterology referral</td>
<td>13</td>
</tr>
<tr>
<td>Seizures (300672, 604403, 612164, 613720, 613721)</td>
<td>GATA2 (10p14)</td>
<td>Audiology, ENT referral</td>
<td>12</td>
</tr>
<tr>
<td>Thrombocytopenia (188025)</td>
<td>F11R (11q24.3)</td>
<td>Check platelet count, monitor closely pre-op</td>
<td>22</td>
</tr>
<tr>
<td>Pituitary hormone deficiency (500123)</td>
<td>SOX3 (Xq27.1)</td>
<td>Endocrine referral</td>
<td>6</td>
</tr>
<tr>
<td>Simpson-Golabi-Behmehl (512870)</td>
<td>GCPC (Xq26.2)</td>
<td>Echocardiogram, tumor surveillance</td>
<td>2</td>
</tr>
<tr>
<td>Branchiootorenal (113650)</td>
<td>EYA4 (8q13.3)</td>
<td>Audiology, ENT referral, specialist referral</td>
<td>4</td>
</tr>
<tr>
<td>Axenfeld-Rieger type 1 (180500)</td>
<td>PITX2 (4p25)</td>
<td>Ophthalmology referral</td>
<td>5</td>
</tr>
<tr>
<td>Axenfeld-Rieger type 3 (602482)</td>
<td>FOXC1 (9p21.4)</td>
<td>Ophthalmology referral</td>
<td>12</td>
</tr>
<tr>
<td>MOYD (125850, 125851)</td>
<td>HNF4A (7p13)</td>
<td>Glucose monitoring, endocrine referral</td>
<td>2</td>
</tr>
<tr>
<td>Holt-Oram (142390)</td>
<td>TBPX5 (1q24.21)</td>
<td>Glucose monitoring, endocrine referral</td>
<td>7</td>
</tr>
<tr>
<td>Stickler (108300, 600491)</td>
<td>COL2A1 (12q13.11)</td>
<td>Ophthalmology referral, audiology</td>
<td>1</td>
</tr>
<tr>
<td>Pseudohypoparathyroidism (103580, 603233, 612462)</td>
<td>COL11A1 (1p21.1)</td>
<td>Ophthalmology referral</td>
<td>3</td>
</tr>
<tr>
<td>Otodental (with coloboma; 188750)</td>
<td>GJB3 (11q13.3)</td>
<td>Ophthalmology referral, audiology</td>
<td>2</td>
</tr>
<tr>
<td>GLUT1 deficiency (606777, 612126)</td>
<td>SLC2A1 (1p34.2)</td>
<td>Neurology referral, ketogenic diet</td>
<td>3</td>
</tr>
<tr>
<td>Familial cavernous hemangioma (118860, 603284)</td>
<td>KRIT1 (1q31.1)</td>
<td>Brain MRI, avoidance of NSAIDs</td>
<td>4</td>
</tr>
<tr>
<td>Poly cystic kidney disease (173900, 613085)</td>
<td>CCM2 (7q13)</td>
<td>Brain MRI, avoidance of NSAIDs</td>
<td>3</td>
</tr>
<tr>
<td>Pituitary insufficiency (262700)</td>
<td>LHX4 (1q21.2)</td>
<td>Endocrinology referral</td>
<td>9</td>
</tr>
<tr>
<td>Adrenal hypoplasia congenital (300200)</td>
<td>NR0B1 (1q13.3)</td>
<td>Ophthalmology referral</td>
<td>5</td>
</tr>
<tr>
<td>Alport syndrome (301050)</td>
<td>COL4A5 (Xq22.33)</td>
<td>Ophthalmology referral</td>
<td>4</td>
</tr>
<tr>
<td>Heart malformations (193900)</td>
<td>CHD7 (3q26.2)</td>
<td>Cardiology referral</td>
<td>1</td>
</tr>
<tr>
<td>Choroideremia (303100)</td>
<td>CHM (7q36.3)</td>
<td>Urology, neurosurgery referral</td>
<td>27</td>
</tr>
<tr>
<td>Currarino (118450)</td>
<td>MNX1 (7q13.2)</td>
<td>Endocrinology referral, audiology</td>
<td>9</td>
</tr>
<tr>
<td>Infantile spasms (806582)</td>
<td>MAG2 (7q21.11)</td>
<td>Neurology referral, specific therapy</td>
<td>3</td>
</tr>
<tr>
<td>Kalhmann (308700)</td>
<td>KAL1 (11q11)</td>
<td>Endocrinology referral, renal ultrasound</td>
<td>1</td>
</tr>
<tr>
<td>Immune deficiency (308240)</td>
<td>SH2D1A (Xq25)</td>
<td>Immunology referral</td>
<td>1</td>
</tr>
<tr>
<td>Ornithine transcarbamylase deficiency (311250)</td>
<td>OTC (Xp11.4)</td>
<td>Specific medical and dietary therapy</td>
<td>8</td>
</tr>
<tr>
<td>Marfan (154700)</td>
<td>FBN1 (15q21.1)</td>
<td>Cardiology and ophthalmology referral</td>
<td>2</td>
</tr>
<tr>
<td>Proteins S deficiency (613238)</td>
<td>PROS1 (3q12.1)</td>
<td>Hematology referral</td>
<td>1</td>
</tr>
<tr>
<td>Antithrombin III deficiency (613118)</td>
<td>SERPINC1 (1q25.1)</td>
<td>Hematology referral</td>
<td>$3k$</td>
</tr>
<tr>
<td>CHARGE syndrome (214800)</td>
<td>CHD7 (8q12.2)</td>
<td>Cardiology, ophthalmology, ENT referral</td>
<td>7</td>
</tr>
<tr>
<td>Diamond-Blackfan anemia (612528)</td>
<td>RPL35A (3q28)</td>
<td>Hematology referral</td>
<td>2</td>
</tr>
</tbody>
</table>

*CHARGE, coloboma, heart defect, atresia choanae, retarded growth and development, genitai hypoplasia, ear anomalies/deafness; ECG, electrocardiogram; ENT, ear, nose, and throat; GI, gastrointestinal; HHT, hereditary hemorrhagic telangiectasia; MOYD, maturity-onset diabetes of the young; NSAID, nonsteroidal anti-inflammatory drug; OMIM No., Online Mendelian Inheritance in Man reference number.

* Other dosage-sensitive genes were queried, but no pathogenic abnormalities were found in our database. These genes are CDKL5, TBX5, LIMK1, ENG, F8, F9, HAMP2, HPRT1, DNA2, ATPTA, NDUFS4, CSF2, RPS10, RPS19, RPS24, RPS26, RPL5, RPL11, and RPL22.

* Listed references provide evidence for functional dosage sensitivity of the phenotype for the corresponding gene.

* Twelve of these patients also have Currarino syndrome owing to deletion of MKX.

* Six of these patients are at risk for retinoblastoma due to deletion of RB1.

* Nine of these patients also have deletions of the DiGeorge 2 critical region and are included in Table 1.

* Both SCN1A and SCN2A are deleted in 8 of these cases.

* These patients represent a subset of patients with Jacobsen syndrome (Table 1).

* Duplications, rather than deletions, result in the phenotype.

* These patients all have the 6p21.3 deletion syndrome (Table 1).

* Four of these patients also have deletions of SERPINC1.

* Four of these patients also have deletions of LHX4.
predisposes these patients to cardiac abnormalities, whereas deletion of BMPR1A puts them at risk for juvenile polyposis; 1 of these 14 patients also had a deletion of PTEN; therefore, greatly increasing the risk of developing numerous tumor types, including thyroid, breast, and endometrial malignancies. These examples clearly illustrate the nature of disorders caused by copy number abnormalities: they often have multiple clinical features resulting from altered doses of multiple genes.

Another example of a patient who benefited from the information given by microarray analysis was the case of a patient who was referred for microarray testing because of developmental delay, dysmorphic features, and multiple congenital anomalies. This 3-month-old infant was one of the patients noted previously with a deletion of 7q36 that included the MNX1 and KCNH2 genes. These findings not only provided a diagnosis of Curranario syndrome as a result of the MNX1 deletion (with its predisposition to urologic, spinal, and anal anomalies), but also susceptibility to long QT syndrome (owing to deletion of KCNH2). Following the array result, the patient had an electrocardiogram that showed an elongated QT interval, and prophylactic medical therapy was subsequently instituted.

**Physician Responses to Microarray Results**

Our data clearly show that microarray testing can identify individuals at risk for specific medical problems that warrant follow-up care. To determine whether these risks are in fact being addressed, for a subset of cases we queried referring physicians as to whether they took specific actions pertinent to the particular diagnosis made by microarray testing. Of the 122 inquiries made, we received 81 responses (from 46 different clinicians), which are tallied by gene in Table 4. In 76 (94%) of the 81 cases, at least 1 of the appropriate clinical actions was taken by the referring physician after the receipt of the microarray result. Examples of these actions included an electrocardiogram and cardiology referral for those at risk for long QT syndrome; glucose monitoring and endocrine referral for those at increased risk of diabetes; renal ultrasound for those at risk for renal pathology; and platelet count monitoring for those at risk for thrombocytopenia.

**Detection Rate of Clinically Actionable Abnormalities**

A total of 46,298 microarray analyses were performed during the reporting period on postnatal proband samples, with nearly equal numbers tested on BAC and oligonucleotide array platforms (23,142 and 23,156, respectively). Of the 151 clinically actionable disorders reviewed, we detected pathogenic abnormalities for 118, resulting in a total of 2088 diagnoses. Of these cases, 1968 (94%) involved DNA segments that were shorter than 10 megabases and so would likely be missed by routine karyotyping. Our initial BAC arrays were targeted and did not probe the entire genome, and later BAC platforms did not provide the resolution necessary to detect all small copy number alterations that we currently address. Therefore, to obtain a more accurate estimate of our current detection rate of actionable conditions, we separately tallied cases tested on higher-resolution oligonucleotide arrays. The total number of diagnoses made using these arrays was 1259, giving a detection rate of 5.4%. We previously determined that our rate of detection of clinically significant alterations on oligonucleotide arrays is 15.4%. Therefore, 35% of all pathogenic copy number changes found in our laboratory identify conditions for which specific clinical actions are warranted.

**DISCUSSION**

Karyotype analysis has long been used for the genetic evaluation of individuals with developmental abnormalities. The

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**TABLE 4 Responses to Abnormal Microarray Results for Specific Genes**

<table>
<thead>
<tr>
<th>Disorder/Phenotype</th>
<th>Gene (Chromosome Band)</th>
<th>Cases Queried</th>
<th>Responses Received</th>
<th>Appropriate Action Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>17q12 deletion/renal cysts and diabetes</td>
<td>HNF1B (17q12)</td>
<td>28</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Long QT</td>
<td>KCNH2 (7q36.1)</td>
<td>13</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Waardenburg</td>
<td>PAX3 (2q36.1)</td>
<td>7</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>MIIF (5p14.1)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Hyperparathyroidism, deafness, renal anomalies</td>
<td>GATA3 (10p14)</td>
<td>6</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Miller-Dieker/loissencephaly, seizures</td>
<td>PAFAH1B1 (17p13.3)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>SCN1A/SCN2A (2q24.3)</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>SCN2A (2q34.3)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>STXB1 (9q34.11)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HHT</td>
<td>ENG (8q43.11)</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>HHT plus juvenile polyposis</td>
<td>SMAD4 (18q21.2)</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>11pter deletion/ thrombocytopenia</td>
<td>FLJ1 (11q24.3)</td>
<td>9</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Pituitary hormone deficiency</td>
<td>SOX3 (Xq27.1)</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Cardiomyopathy, tumor risk</td>
<td>GPC3 (Xq26.2)</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Williams</td>
<td>ELN (7q11.23)</td>
<td>20</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>and others</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DiGeorge/velocardiofacial</td>
<td>TBX1 (22q11.21)</td>
<td>26</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>and others</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td></td>
<td>122</td>
<td>81</td>
<td>76</td>
</tr>
</tbody>
</table>

*SCN1A and SCN2A genes were both deleted in the cases.

HHT, hereditary hemorrhagic telangiectasia.
diagnostic yield of this testing for patients with developmental delay/mental retardation varies in different studies, but the average is 4% to 5%.\textsuperscript{16,18,19} Karyotyping has been consistently reimbursed by third-party payers, but current concerns about health care costs are leading to higher expectations for the usefulness of laboratory tests, beyond simply providing a diagnosis.\textsuperscript{20} It is increasingly expected that testing provide clinical utility, in the form of changes in patient management and improved clinical outcomes.

The first reported examples of the clinical utility of microarray testing were descriptions of deletions of tumor suppressor genes, which put the patients at a high risk of developing hereditary cancer syndromes.\textsuperscript{16,21,22} Such patients benefit from awareness of tumor risk and appropriate clinical surveillance.\textsuperscript{23–26} Other studies showed that clinical actions were taken after abnormal microarray results,\textsuperscript{27–30} although these studies were limited in scope and/or did not tie specific actions to diagnoses. These reports have not provided sufficient evidence to universally convince third-party payers that microarray testing is worthy of reimbursement.

The goal of our study was to examine the evidence for the clinical utility of chromosomal microarray analysis, which has already been demonstrated to have a superior diagnostic yield over karyotyping for similar clinical indications.\textsuperscript{14,15} Our approach was to identify specific diagnoses made by microarray testing, which are expected to lead to specific clinical actions and improved patient care. We identified more than 100 such disorders, ranging from complex syndromes involving multiple organ systems, to disorders with discrete problems that need obvious and specific medical follow-up. Admittedly, some of the patients may have displayed such problems before testing, but many of the disorders diagnosed have variable features that frequently are not evident or suspected. The test result thus serves to alert physicians to the possibility of these treatable problems. We showed that these actionable diagnoses constitute a significant proportion (35%) of all pathogenic abnormalities detected by microarray analysis and that the detection rate of these disorders is greater than the overall detection rate of karyotype analysis for similar testing indications. We can expect the frequency of actionable diagnoses to increase in the future as we learn more about the clinical consequences of copy number abnormalities. Finally, we showed that physicians respond to abnormal microarray results with specific and appropriate clinical actions and noted several illustrative cases where the clinical outcome was optimized. Our findings, therefore, argue strongly that chromosome microarray analysis provides clinical utility for a significant number of tested patients.

**CONCLUSIONS**

Our data show that the diagnoses made by chromosomal microarray analysis frequently involve specific clinical features that may have been present but not apparent or were not yet manifest at the time of testing. Alerting physicians and families to these potential problems leads to optimal health management of patients, as demonstrated in the cases in which we queried the referring physicians. It is expected that anticipatory medical care of children and adults with developmental disabilities will lead to improved outcomes in terms of both general health and fulfillment of their developmental potential. Long-term follow-up studies could be performed to confirm this assumption, but in the meantime, our data show that microarray testing provides immediate clinical utility for patients and such testing should be considered worthy of reimbursement by insurers.

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