Sonographic Indications for Molecular Genetic Testing

Kenneth Ward

Professor and Chair, Department of Obstetrics and Gynecology, and Women's Health Director, Pacific Research Center for Early Human Development, John A Burns School of Medicine, University of Hawaii, Honolulu, Hawaii, USA

Correspondence: Kenneth Ward
University of Hawaii, Department of Obstetrics and Gynecology, and Women's Health, c/o Kapiolani Hospital
1319 Punahou Street, Room 824, Honolulu, HI 96826
Phone: 808-203-6528, FAX: 808-955-2174, e-mail:ken.ward.hi@mac.com

Abstract: There are many well-accepted indications for cytogenetic testing indicated by the detection of a fetal abnormality on prenatal ultrasound. Over the last decade, the molecular bases for thousands of single gene disorders have been elucidated, molecular cytogenetic tests have been created, and molecular assays for most infectious agents have been developed—potentially improving our ability to make accurate prenatal diagnoses. This review describes the role of molecular diagnostics in detecting chromosomal microdeletions and microduplications, single gene disorders, and infectious diseases. We show that molecular genetic testing is now frequently indicated in the evaluation of abnormal ultrasound findings. A significant educational effort will be necessary to incorporate new molecular knowledge into obstetric ultrasound practice.

Key words: DNA testing, molecular diagnostics, fetal dysmorphology, microarray, polymerase chain reaction.

Learning objectives

- To increase the reader's awareness of the emerging technologies to detect genetic abnormality
- To provide extensive tables to suggest clinical scenarios in which molecular genetic testing may be indicated
- To suggest the emerging role for molecular testing for infectious agents in prenatal diagnosis.

INTRODUCTION

Cytogenetic testing is routinely offered whenever certain fetal anomalies are seen on a prenatal ultrasound examination. "Molecular cytogenetic" tests have expanded our capacity to make a definitive prenatal diagnosis (i.e. fluorescence *in situ* hybridization (FISH) for 22q11 deletion when conotruncal or aortic arch abnormalities are seen). Over the past decade, the molecular bases for thousands of single gene disorders have been elucidated, potentially improving our ability to make accurate prenatal diagnoses of hundreds of single gene disorders as well. Now, polymerase chain reaction (PCR)-based tests are improving our capability to screen for *in utero* infections suggested by ultrasound findings.

Both as a clinician and a director of a diagnostic laboratory, I have observed that an increasing number of DNA based tests are being ordered solely because of a prenatal ultrasound finding (Table 1). The literature provides relatively little guidance on accepted indications for molecular genetic testing in contrast to the widely-used standard indications for prenatal cytogenetic testing. This review is intended to serve as a preliminary map for this rapidly-emerging but largely-uncharted complement to modern prenatal diagnosis by sonography.

Table 1: Examples of molecular genetic tests ordered because of an abnormal prenatal ultrasound

Ultrasound finding		*Molecular test performed*
Conotruncal heart defect	:	Deletion 22q11.2
Kleeblattschadel deformity	:	FGFR mutations
Meconium ileus	:	Cystic fibrosis
Skeletal dysplasia	:	FGFR mutations
Fetal cord vessel thrombosis	:	Factor V Leiden
Ambiguous genitalia	:	Y chromosome, 21-hydroxylase deficiency
Aqueductal stenosis	:	L-1 CAM
Polyhydramnios + clubbed feet:		Congenital myotonic dystrophy
Ascites, hepatic calcifications :		Microarray for TORCH and other perinatal infections

CASE EXAMPLE A

An ultrasound performed at 20 weeks' gestation ordered as an "anatomic screening exam" revealed that the fetus had tetralogy

of Fallot and possibly a cleft palate. Amniocentesis was performed for karyotype analysis and for fluorescence *in situ* hybridization (FISH) using a chromosome 22 probe. The FISH results confirmed that the fetus had a submicroscopic deletion of chromosome 22(del 22q11.2). Individuals with this deletion syndrome have congenital heart disease (74%), particularly conotruncal malformations (tetralogy of Fallot, interrupted aortic arch, ventricular septal defect, and truncus arteriosus) and palatal abnormalities (69%).[1] The syndrome can also include characteristic facial features, learning difficulties, an immune deficiency, hypocalcemia (50%), significant feeding problems (30%), renal anomalies (37%), hearing loss, laryngo-tracheoesophageal anomalies, autoimmune disorders, seizures, and skeletal abnormalities. In this instance, the parents were appreciative of the specific information we were able to provide as a result of the microdeletion diagnosis. They elected to carry the pregnancy to term. Knowledge of the deletion allowed anticipatory care during the pregnancy and proper neonatal testing and care after birth.

Microdeletions, Microduplications, and Microarrays

In Case Example A, a fluorescence *in situ* hybridization (FISH) probe was used to detect a specific suspected microdeletion syndrome because of the prenatal ultrasound findings. Many prenatal observable defects have been associated with microdeletions or microduplications (Table 2). A new technology now allows easy and conclusive screening for these previously under-appreciated genetic underpinnings for human malformation.

Chromosomal microarray (CMA) chips have hundreds to millions of molecules (oligonucleotides, cloned DNA, etc.) arrayed on a surface.[2] The attached molecules are used to probe a variety of chromosomal regions simultaneously. Manufacturers can place picogram amounts of a probe at defined locations, and each probe can be just a few micrometers apart. The molecular probes may be attached to plastic, glass, nylon, or even silicon wafers. Each individual probe is placed at a precisely defined location on the array support, which is usually a flat, two-dimensional surface. The identity of the molecule fixed to each spot for any particular array design never changes. The microscopic scale of the array keeps assay costs lower and allows high-throughput "parallel" testing of clinical samples.

Regardless of the array design, hybridization (the ability of two complementary nucleic acid molecules to lock together based upon Watson-Crick base-pairing) is the critical feature. Single-stranded DNA probes will hybridize or "stick" to the strands of DNA sample to be tested following the usual rules of base pairing (A to T, C to G). Complementary DNA sequences have incredibly high affinity for each other and thus the target DNA in a solution literally "find" and attach itself to the immobilized probe DNA. Probes as short as 20 nucleotides in length can be highly specific; while even a single mismatched base will greatly reduce the strength and likelihood of hybridization. Thus, highly specific DNA capture molecules can be designed and prepared either by chemical synthesis or by using PCR.

The probes which are fixed onto the array surface capture the nucleic acid to be tested which is in a solution applied to the array. Most microarrays use fluorescent tags as the means of identifying whether hybridization has occurred (whether the target molecule is stuck to the probe molecule on the array). Array scanners can rapidly detect very low levels of fluorescence and map the signal to its source on the array with great certainty. Usually the fluorescent tags are excited by a laser and the signal captured by a high-resolution 'digital' camera. Most protocols improve sensitivity of detection by chemically attaching more than one copy of fluorescent tag per target molecule detected.

With chromosomal microarrays, it is possible to perform a "molecular karyotype".[3] The resolution of a CMA is better than the resolution of conventional cytogenetics and no culture time is required. Furthermore, probes can be included for all of the microdeletion regions commonly tested by ancillary fluorescent *in situ* hybridization (FISH) tests (i.e. Di George syndrome caused by a chromosome 22 microdeletion). Moreover, all of these common microdeletion regions can be tested in parallel, rather than one at a time. The patterns obtained on arrays are easier to read by computer compared to G-banded metaphase spreads. Although CMAs cannot detect low-level mosaicism or balanced rearrangements, it can detect many important abnormalities missed by conventional cytogenetics. A CMA is such a sensitive test for small duplications and microdeletions, genetic variants of unknown clinical significance will be detected. Blood from both parents will usually be requested to help determine the significance of these findings. Prenatal CMA can detect the disorders that are usually identified by karyotypic analysis, including Down syndrome, trisomy 13, trisomy 18, sex chromosomal abnormalities.

A CMA testing can be performed on CVS, amniocentesis, or fetal blood. It is likely that CMA will become the preferred method for the prenatal diagnosis of chromosomal abnormalities.

CASE EXAMPLE B

An ultrasound performed because the patient was measuring "large-for-dates" at 20 weeks' gestation showed isolated idiopathic polyhydramnios. A karyotype was performed and it was normal. Subsequently, positional deformities of the fetal hands and feet were observed. The fetus had congenital myotonic dystrophy by DNA triplet repeat mutation analysis.

Table 2: Examples of microdeletions/duplications associated with anomalies observable using prenatal sonography (derived from Appendix 1 in Jones[5])

- **Microcephaly**
  - — Deletion 1p36
  - — Deletion 3p
  - — Deletion 4p
  - — Deletion 5p
  - — Deletion 18p
  - — Deletion 11q
  - — Deletion 13q
  - — Deletion 18q
  - — Deletion 22q11.2
  - — Duplication 10q
- **Craniosynostosis**
  - — Deletion 9p (metopic)
- **Cleft lip/palate**
  - — Deletion 4p
  - — Deletion 22q11.2
  - — Duplication 3q
  - — Duplication 10q
- **Micrognathia**
  - — Deletion 3p
  - — Deletion 4p
  - — Deletion 5p
  - — Deletion 9p
  - — Deletion 18p
  - — Deletion 4q
  - — Deletion 11q
  - — Deletion 13 q
  - — Deletion 22q11.2
  - — Duplication 3q
  - — Duplication 15q
- **Ear anomalies/malformed auricles**
  - — Deletion 1p36
  - — Deletion 3p
  - — Deletion 9p
  - — Deletion 18p (prominent, protruding)
  - — Deletion 4q
  - — Deletion 11q
  - — Deletion 13q (prominent, slanting)
  - — Deletion 18q (prominent antihelix and antitragus)
  - — Deletion 22q11.2
  - — Deletion 22q13 (prominent and dysplastic)
  - — Duplication 3q
  - — Duplication 9p
  - — Duplication 10q
- **Hypertelorism**
  - — Deletion 4p
  - — Deletion 9p
  - — Deletion 4q
  - — Deletion 11q
  - — Deletion 13 q
  - — Deletion 22q11.2
  - — Duplication 9p
- **Cardiac malformation**
  - — Deletion 1p36
  - — Deletion 4p
  - — Deletion 9p
  - — Deletion 4q
  - — Deletion 11q
  - — Deletion 13q
  - — Deletion 18q
  - — Deletion 22q11.2 S (conotruncal defect)
  - — Duplication 3q
  - — Duplication 10q
  - — Duplication 15q
- **Ambiguous genitalia/hypospadias/bifid scrotum**
  - — Deletion 4p
  - — Deletion 11q
  - — Deletion 13q
- **Clubfoot**
  - — Deletion 4p
  - — Deletion 9p
  - — Deletion 13q
  - — Deletion 18q
  - — Duplication 3q
  - — Duplication 9p
  - — Duplication 10q
- **Syndactyly**
  - — Duplication 10q
- **Clinodactyly of fifth fingers**
  - — Deletion 4q
  - — Deletion 13q
  - — Duplication 9p
  - — Duplication 3q
- **Arthrogryposis**
  - — Deletion 11q
  - — Duplication 10q (camptodactyly)
  - — Duplication 15q (camptodactyly)
- **Kidney malformation**
  - — Deletion 4q
  - — Deletion 18q
  - — Duplication 3q
  - — Duplication 10q

Single Gene Disorders

The Online Mendelian Inheritance in Man database now lists over 10,000 human diseases which are caused by defects in single genes.[4] Most of these monogenic disorders are individually very rare but they affect about 1 percent of the population as a whole. The DNA testing is clinically available for several hundred of these disorders (see www,genetests.org for current information about available tests).[1]

Many of these monogenic conditions can cause significant anatomic findings on prenatal ultrasound. The DNA testing in response to some ultrasound findings has become routine. For instance, testing for thalassemia has been part of the evaluation of the fetus with non-immune hydrops for decades now. Similarly, since the discovery of the cystic fibrosis gene in 1988, an ultrasound suggesting meconium peritonitis usually prompts cystic fibrosis mutation testing.

Unfortunately, most monogenic conditions need to be screened for one at a time depending upon the anatomic findings. Our knowledge of human single gene disorders is still developing. As a result, for some disorders, the available DNA test cannot give a conclusive answer (i.e. when the disease is caused by more than one gene and only one of the causative genes has been discovered) or it cannot suggest severity or extent of the disease. This list of potential ultrasound findings caused by single gene disorders and the list of associated genes is very long. Table 3 lists several common neonatal or prenatal ultrasound findings, and suggests a differential diagnosis of syndromes and single gene disorders in which that particular finding as a common feature of the genetic disorder. [5] Table 3 also indicates whether clinical DNA testing is available for the disorder in the United States as of October 2006.[1] In the near future, panels will be developed to test for all of the conditions associated with a particular ultrasound finding. This should increase utilization of DNA testing to diagnose important but uncommon conditions associated with isolated ultrasound findings.

CASE EXAMPLE C

A TORCH infection was suspected when a fetus was found to have ascites and hepatic calcifications. In addition to sending maternal serologies, amniotic fluid cultures, and amniotic fluid for various PCR-based assays for individual pathogens, amniotic fluid was also tested using a prototype microarray designed to screen for all common infectious agents capable of impacting a fetus. The microarray showed the offending organism to be cytomegalovirus (CMV) in just a few hours, long before the other test results were available. The patient received extensive counseling about CMV infections late in gestation.

Table 3: Expanded differential diagnosis of sonographic observations (derived from Appendix 1 in Jones[5] and Genetests database[1])

Observable anomalies and associated syndromes	*DNA testings available?*
Encephalocele	
Meckel-Gruber syndrome	N
Walker-Warburg syndrome	N
Aqueductal stenosis/hydrocephalus	
Hydrolethalus syndrome	N
Osteopetrosis: Autosomal recessive-lethal	N
Shprintzen-Goldberg syndrome	N
3C syndrome	N
Walker-Warburg syndrome	N
X-linked hydrocephalus spectrum	N
Dandy-Walker malformation	
3C syndrome	N
Walker-Warburg syndrome	N
Agenesis of the corpus callosum	
Acrocallosal syndrome	N
Cerebro-oculo-facio-skeletal (COFS) syndrome	N
FG syndrome	N
Fryns syndrome	N
Marden-Walker syndrome	N
Meckel-Gruber syndrome	N
Microphthalmia-linear skin defects syndrome	N
Miller-Dieker syndrome	N
Neu-Laxova syndrome	N
Septo-optic dysplasia sequence	N
Toriello-Carey syndrome	N
Walker-Warburg syndrome	N
Zellweger syndrome	Y
Microcephaly	
Angelman syndrome	Y
Aniridia-Wilms tumor association	N
Autosomal recessive chondrodysplasia punctata	N
Bloom syndrome	Y
Borjeson-Forssman-Lehmann syndrome	N
Cerebro-oculo-facio-skeletal (COFS) syndrome	N
Cockayne syndrome	Y
Coffin-Siris syndrome	N
de Lange syndrome	N
Dubowitz syndrome	N
Dyggve-Melchior-Clausen syndrome	N
Johanson-Blizzard syndrome	N
Langer-Giedion syndrome	N
Lenz microphthalmia syndrome	N
Marden-Walker syndrome	N
Meckel-Gruber syndrome	N
Meier-Gorlin syndrome	N
Miller-Dieker syndrome	N
Mowat-Wilson syndrome	Y
New-Laxova syndrome	N

Contd...

Contd...

Observable anomalies and associated syndromes	*DNA testings available?*
Oto-palato-digital syndrome, type II	N
Roberts-SC phocomelia	N
Rubinstein-Taybi syndrome	N
Seckel syndrome	N
Septo-optic dysplasia sequence	N
Smith-Lemli-Opitz syndrome	Y
Thanatophoric dysplasia	Y
Toriello-Carey syndrome	N
Williams syndrome	Y
X-linked μ-thalassemia/mental Retardation (ATR-X) syndrome	N
Yunis-Varon syndrome	N
Craniosynostosis	
Antley-Bixler syndrome	N
Apert syndrome	N
Baller-Gerold syndrome	N
Carpenter syndrome	N
Craniofrontonasal dysplasia	N
Crouzon syndrome	N
FGFR3-associated coronal synostosis syndrome	Y
Pfeiffer syndrome	N
Saethre-Chotzen syndrome	Y
Shprintzen-Goldberg syndrome	N
Kyphosis, scoliosis	
Angelman syndrome	Y
Bannayan-Riley-Ruvalcaba syndrome	N
Beals syndrome	N
Chondrodysplasia punctata, X-linked dominant type	N
Coffin-Lowry syndrome	Y
Cohen syndrome	Y
Dystrophic dysplasia	N
Dyggve-Melchior-Clausen syndrome	N
Fibrodysplasia ossificans progressiva syndrome	Y
Freeman-Sheldon syndrome	N
Gorlin syndrome	N
Kabuki syndrome	N
Kniest dysplasia	N
Larsen syndrome	Y
Lenz Microphthalmia syndrome	N
Limb-Body wall complex	N
Marden-Walker syndrome	N
Marfan's syndrome	Y
Maroteaux-Lamy mucopolysaccharidosis syndrome	N
Metaphyseal dysplasia, McKusick type	Y?
Metatropic dysplasia	N
Morquio syndrome	N
Proteus syndrome	N
Pseudoachondroplasia	Y
Robinow syndrome	N
Shprintzen-Goldberg syndrome	N
Smith-Magenis syndrome	Y
Spondylocarpotarsal synostosis syndrome	Y

Contd...

Contd...

Observable anomalies and associated syndromes	*DNA testings available?*
Cleft lip, palate	
Branchio-oculo-facial syndrome (pseudocleft)	N
Ectrodactyly-ectodermal dysplasia-clefting syndrome	N
Fryn's syndrome	N
Hay-Wells syndrome of ectodermal dysplasia	N
Holoprosencephaly sequence (midline)	Y?
Miller syndrome	N
Mohr syndrome (midline)	N
Oral-facial-digital syndrome (midline)	N
Popliteal pterygium syndrome	N
Rapp-Hodgkin ectodermal dysplasia	N
Roberts-SC phocomelia	N
Short rib-polydactyly syndrome, type II (Majewski type) (midline)	N
van der Woude syndrome	N
Cleft palate or bifid uvula without cleft in lip	
Catel-Manzke syndrome	N
Cerebro-costo-mandibular syndrome	N
Distal arthrogryposis syndrome, type 3	N
Dubowitz syndrome	N
Escobar syndrome	N
Femoral hypoplasia-unusual facies syndrome	N
Fibrochondrogenesis	N
Hay-Wells syndrome of ectodermal dysplasia	N
Hydrolethalus syndrome	N
Kabuki syndrome	N
Kniest dysplasia	N
Marden-Walker syndrome	N
Meckel-Gruber syndrome	N
Nager syndrome	N
Oral-facial-digital syndrome	N
Oto-palato-digital syndrome, type I	N
Oto-palato-digital syndrome, type II	N
Popliteal pterygium syndrome	N
Retinoic acid embryopathy	N
Robin sequence	N
Short rib-polydactyly syndrome, type II (Majewski type)	N
Spondyloepiphyseal dysplasia congenita	Y?
Stickler syndrome	Y
Toriello-Carey syndrome	N
Treacher Collins syndrome	Y
van der Woude syndrome	N
Micrognathia	
Achondrogenesis, types 1A and 1B	N
Amyoplasia congenita disruptive sequence	N
Aniridia-Wilms tumor association	N
Atelosteogenesis, type I	Y
Baller-Gerold syndrome	N
Bloom syndrome	Y
Branchio-oculo-facial syndrome	N
Campomelic dysplasia	Y
Catel-Manzke syndrome	N

Contd... *Contd...*

Contd...

Observable anomalies and associated syndromes	*DNA testings available?*
Cerebro-costo-mandibular syndrome	N
Cerebro-oculo-facio-skeletal (COFS) syndrome	N
Cohen syndrome	Y
de Lange syndrome	N
Dubowitz syndrome	N
Escobar syndrome	N
Femoral hypoplasia-unusual facies syndrome	N
Frontometaphyseal dysplasia	N
Fryn's syndrome	N
GAPO syndrome	N
Hajdu-Cheney syndrome	N
Hallermann-Streiff syndrome	N
Hurler-Scheie syndrome	N
Hydrolethalus syndrome	N
Langer mesomelic dysplasia	Y?
Lethal multiple pterygium syndrome	N
Mandibuloacral dysplasia	Y
Marden-Walker syndrome	N
Marshall-Smith syndrome	Y?
Meckel-Gruber syndrome	N
Meier-Gorlin syndrome	N
Melnick-Needles syndrome	N
Metaphyseal dysplasia, Jansen type	Y?
Miller syndrome	N
Miller-Dieker syndrome	N
Moebius sequence	N
Mohr syndrome	N
Nager syndrome	N
New-Laxova syndrome	N
Oculo-auriculo-vertebral spectrum	N
Opitz G/BBB syndrome	N
Oral-facial-digital syndrome	N
Oromandibular-limb hypogenesis spectrum	N
Oto-palato-digital syndrome, type II	N
Pallister-Hall syndrome	Y
Pena-Shokeir phenotype	N
Peters'-plus syndrome	N
Progeria syndrome	N
Pyknodysostosis	N
Restrictive dermopathy	N
Retinoic acid embryopathy	N
Roberts-SC phocomelia	N
Robin sequence	N
Russell-Silver syndrome	Y
Schwartz-Jampel syndrome	N
Seckel syndrome	N
SHORT syndrome	N
Shprintzen-Goldberg syndrome	N
Smith-Lemi-Opitz syndrome	Y
Stickler syndrome	Y
Toriello-Carey syndrome	N
Treacher Collins syndrome	Y
Tricho-rhino-phalangeal syndrome	N
Triploidy syndrome	N
Weaver syndrome	N
Yunis-Varon syndrome	N
Zellweger syndrome	Y

Contd...

Contd...

Observable anomalies and associated syndromes	*DNA testings available?*
Macroglossia	
Athyrotic hypothyrodism sequence	N
Beckwith-Wiedemann syndrome	Y
Costello syndrome	Y
Generalized gangliosidosis syndrome, type I (Severe infantile type)	N
Hunter's syndrome	N
Simpson-Golabi-Behmel syndrome	Y
X-linked μ-thalassemia/mental Retardation (ATR-X) syndrome	N
Ear anomalies/malformed auricles	
Aarskog syndrome	Y
Acrocallosal syndrome	N
Anencephaly sequence	N
Antley-Bixler syndrome	N
Baller-Gerold syndrome	N
Beals syndrome (crumpled)	N
Beckwith-Wiedemann syndrome (creased lobes)	Y
Blepharophimosis syndrome	N
Borjeson-Forssman-Lehmann syndrome (large)	N
Branchio-oculo-facial syndrome	N
Cardio-Manzke syndrome	N
Cerebro-oculo-facio-skeleton (COFS) syndrome (large)	N
CHARGE syndrome	Y
Coffin-Lowry syndrome (prominent)	Y
Cohen syndrome (large)	Y
Costello syndrome	Y
Dystrophic dysplasia (cysts)	Y?
Dubowitz syndrome	N
Ehlers-Danlos syndrome (hypermobile)	Y?
FG syndrome (small)	N
Fibrochondrogenesis	N
Floating-Harbor syndrome (posteriorly rotated)	N
Fragile X syndrome (large)	N
Fraser syndrome	N
Fryn's syndrome	N
GAPO syndrome	N
Hydrolethalus syndrome	N
Kabuki syndrome (large)	N
Killian/Teschler-Nicola syndrome (large)	N
Langer-Giedion syndrome (large, protruding)	N
Lenz microphthalmia syndrome	N
Lethal multiple pterygium syndrome	N
Levy-Hollister syndrome (cupped)	N
Meckel-Gruber syndrome	N
Meier-Gorlin syndrome (small)	N
Melnick-Fraser syndrome	N
Miller syndrome	N
Mowat-Wilson syndrome	Y
Multiple lentigines syndrome (prominent)	N
Nager syndrome	N
Neu-Laxova syndrome (large)	N
Noonan syndrome	N
Oculo-auriculo-vertebral spectrum	N
Opitz G/BBB syndrome	N

Contd...

Contd...

Contd...

Observable anomalies and associated syndromes	*DNA testings available?*
Pallister-Hall syndrome	Y
Pena-Shokeir phenotype	N
Peters'-plus syndrome	N
Restrictive dermopathy	N
Retinoic acid embryopathy (anotia, microtia)	N
Roberts-SC phocomelia	N
Rubinstein-Taybi syndrome	N
Saethre-Chotzen syndrome	Y
Schinzel-Giedion syndrome	N
Smith-Lemli-Opitz syndrome	Y
Smith-Magenis syndrome	Y
SHORT syndrome	N
E-M syndrome	N
Toriello-Carey syndrome	N
Townes-Brocks syndrome	Y
Treacher Collins syndrome	Y
Tricho-rhino-phalangeal syndrome (prominent)	N
Triploidy syndrome	N
Weaver syndrome (prominent, large)	N
X-linked μ-thalassemia/mental retardation (ATR-X) syndrome	N
Yunis-Varon syndrome	N
Midface hypoplasia	
Atelosteogenesis, type I	Y
Bloom syndrome	Y
Chondrodysplasia punctata, X-linked dominant type	N
Ectrodactyly-ectodermal dysplasia-clefting syndrome	N
Hajdu-Cheney syndrome	N
Hallermann-Streiff syndrome	N
Marshall syndrome	Y
Miller syndrome	N
Mohr syndrome	N
Nager syndrome	N
Oculo-auriculo-vertebral spectrum	N
Oto-palato-digital syndrome, type I	N
Oto-palato-digital syndrome, type II	N
Pallister-Hall syndrome	Y
Pyknodysostosis	N
Seckel syndrome	N
Shprintzen syndrome	N
Spondyloepiphyseal dysplasia congenita	Y?
Stickler syndrome	Y
3-M syndrome	N
Treacher Collins syndrome	Y
Hypotelorism	
Holoprosencephaly sequence	Y
Hypertelorism	
Aarskog syndrome	Y
Acrocallosal syndrome	N
Acrodysostosis	N
Apert syndrome	N
Atelosteogenesis, type I	Y
Cardio-facio-cutaneous (CFC) syndrome	Y

Contd...

Contd...

Observable anomalies and associated syndromes	*DNA testings available?*
Cleft lip sequence	N
Coffin-Lowry syndrome	Y
Craniofrontonasal dysplasia	N
DiGeorge sequence	N
Escobar syndrome	N
FG syndrome	N
FGFR3-associated coronal synostosis syndrome	Y
Frontonasal dysplasia sequence	N
Greig cephalopolysyndactyly syndrome	Y
Hajdu-Cheney syndrome	N
Killian/Teschler-Nicola syndrome	N
Larsen syndrome	Y
Lenz-Majewski hyperostosis syndrome	N
Lethal multiple pterygium syndrome	N
Neu-Laxova syndrome	N
Noonan syndrome	Y
Opitz G/BBB syndrome	N
Oto-palato-digital syndrome, type I	N
Oto-palato-digital syndrome, type II	N
Pena Shokeir phenotype	N
Peters'-plus syndrome	N
Pfeiffer syndrome	N
Restrictive dermopathy	N
Retinoic acid embryopathy	N
Roberts-SC phocomelia	N
Robinow syndrome	N
Saethre-Chotzen syndrome	Y
Schinzel-Giedion syndrome	N
Shprintzen-Goldberg syndrome	N
Simpson-Golabi-Behmel syndrome	Y
Sotos syndrome	Y
3C syndrome	N
Triploidy syndrome	N
Weaver syndrome	N
Diaphragmatic hernia	
Fryn's syndrome	N
Cardiac malformation	
Aase syndrome	N
Acrocallosal syndrome	N
Alagille syndrome	Y
Athyrotic hypothyroidism sequence (patent ductus arteriosus)	N
Cardiofacio-cutaneous (CFC) syndrome	Y
Carpenter syndrome	N
Catel-Manzke syndrome	N
CHARGE syndrome	Y
CHILD syndrome	N
Chondroectodermal dysplasia (septal defect)	N
Costello syndrome	Y
Fryn's syndrome	N
Holt-Oram syndrome (septal defect)	N
Hydrolethalus syndrome (endocardial cushion defect)	N
Kabuki syndrome	N
Laterality sequences (complex)	N

Contd...

Contd...

Observable anomalies and associated syndromes	*DNA testings available?*
McKusick-Kaufman syndrome	N
Miller-Dieker syndrome	N
Mowat-Wilson syndrome	Y
Mulibrey Nanism syndrome (pericardium)	N
Multiple lentigines syndrome	N
Noonan syndrome	N
Pallister-Hall syndrome (endocardial cushion defect)	Y
Peters'-plus syndrome	N
Radial aplasia-thrombocytopenia syndrome	N
Retinoic acid embryopathy (conotruncal defects)	N
Rubinstein-Taybi syndrome	N
Short rib-polydactyly syndrome, type I (Saldino-Noonan type)	N
Smith-Magenis syndrome	Y
3C syndrome	N
Toriello-Carey syndrome	N
VATERR Association	N
Wiedemann-Rautenstrauch syndrome	N
Williams syndrome	Y
Tachyarrhythmia/bradyarrhythmia	
Multiple lentigines syndrome	N
Myotonic dystrophy syndrome	Y
Simpson-Golabi-Behmel syndrome	Y
Tracheosophageal atresia	
VATERR association	N
Hepatomegaly, splenomegaly	
Achondrogenesis, types IA and IB	N
Berardinelli lipodystrophy syndrome	N
Geleophysic dysplasia	N
Generalized gangliosidosis syndrome, type I (severe infantile type)	N
Hunter syndrome	N
Hurler syndrome	N
Hurler-Scheie syndrome	N
Leroy I-cell syndrome	N
Maroteaux-Lamy mucopolysaccharidosis syndrome	N
Morquio syndrome	N
Mucopolysaccharidosis VII	N
Mulibrey Nanism syndrome	N
Osteopetrosis: Autosomal recessive-lethal	Y?
Sanfilippo syndrome	N
Zellweger syndrome	Y
Ambiguous genitalia/hypospadias/bifid scrotum	
Aniridia-Wilms tumor association	N
Exstrophy of bladder sequence (epispadias)	N
Exstrophy of cloaca sequence	N
Fraser syndrome	N
Fryn's syndrome	N
Lenz microphthalmia syndrome	N
Limb-body wall complex	N
Mowat-Wilson syndrome	Y
Opitz G/BBB syndrome	N

Contd...

Contd...

Observable anomalies and associated syndromes	*DNA testings available?*
Rapp-Hodgkin ectodermal dysplasia	N
Rieger syndrome	Y
Robinow syndrome	N
Schinzel-Giedion syndrome	N
Short rib-polydatyly syndrome, type II (Majewski type)	N
Sirenomelia sequence	N
Smith-Lemli-Opitz syndrome	Y
Triploidy syndrome	N
Urorectal septum malformation sequence	N
X-linked μ-thalassemia/mental retardation (ATR-X) syndrome	N
Clubfoot	
Amnion rupture sequence	N
Amyoplasia congenita disruptive sequence	N
Atelosteogenesis, type I	Y
Campomelic dysplasia	Y
Caudal dysplasia sequence	N
Dystrophic dysplasia	N
Distal arthrogryposis syndrome	N
Escobar syndrome	N
Femoral hypoplasia-unusual facies syndrome	N
Freeman-Sheldon syndrome (varus with contracted toes)	N
Hecht syndrome	N
Hydrolethalus syndrome	N
Larsen syndrome	Y
Lethal multiple pterygium syndrome	N
Limb-Body wall complex	N
Marden-Walker syndrome	N
Meckel-Gruber syndrome	N
Meningomyelocele sequence	N
Moebius sequence	N
Mucopolysaccharidosis VII	N
Oligohydramnios sequence	N
Oral-facial-digital syndrome	N
Pena-Shokeir phenotype	N
Schinzel-Giedion syndrome	N
Shprintzen-Goldberg syndrome	N
Zellweger syndrome	Y
Radial ray malformation/radius hypoplasia to aplasia	
Aase syndrome	N
Baller-Gerold syndrome	N
Fanconi pancytopenia syndrome	N
Holt-Oram syndrome	N
Levy-Hollister syndrome	N
Radial aplasia-thrombocytopenia syndrome	N
Roberts-SC phocomelia	N
Ulnar-mammary syndrome	N
VATERR association	N
Polydactyly	
Acrocallosal syndrome	N
Atelosteogenesis, type III	Y
Bardet-Biedl syndrome	Y
Carpenter syndrome	N
Chondroectodermal dysplasia	N

Contd..

Contd...

Observable anomalies and associated syndromes	*DNA testings available?*
Grebe syndrome	N
Greig cephalopolysyndactyly syndrome	Y
Hydrolethalus syndrome	N
McKusick-Kaufman syndrome	N
Meckel-Gruber syndrome	N
Mohr syndrome	N
Oto-palato-digital syndrome, type II	N
Pallister-Hall syndrome	Y
Short rib-polydactyly syndrome, type I (Saldino-Noonan type)	N
Short rib-polydactyly syndrome, type II (Majewski type)	N
Simpson-Golabi-Behmel syndrome	Y
Townes-Brocks syndrome	Y
Syndactyly	
Accocallosal syndrome (fingers and toes)	N
Apert syndrome (with synostosis)	N
Atelosteogenesis, type III	Y
Carpenter syndrome	N
Craniofrontonasal dysplasia	N
de Lange syndrome (second and third toes)	N
Ectrodactyly-ectodermal dysplasia-clefting syndrome	N
Escobar syndrome	N
FG syndrome	N
Fraser syndrome	N
Goltz syndrome	N
Greig cephalopolysyndactyly syndrome	Y
Holt-Oram syndrome	N
Jarcho-Levin syndrome	N
Lenz-Majewski hyperostosis syndrome	N
Lenz microphthalmia syndrome	N
Miller syndrome	N
Mohr syndrome	N
Neu-Laxova syndrome	N
Oculodentodigital syndrome (fourth and fifth fingers, third and fourth toes)	Y?
Oral-facial-digital syndrome	N
Oto-palato-digital syndrome, type II	N
Pallister-Hall syndrome	Y
Pfeiffer syndrome	N
Poland sequence	N
Popliteal pterygium syndrome	N
Roberts-SC phocomelia	N
Saethre-Chotzen syndrome	Y
Sclerosteosis	N
Short rib-polydactyly syndrome, type I (Sldino-Noonan type)	N
Short rib-polydactyly syndrome, type II (Majewski type)	N
Simpson-Golabi-Behmel syndrome	Y
Smith-Lemli-Opitz syndrome (second and third toes)	Y
Clinodactyly of fifth fingers	
Aarskog syndrome	Y
Acrocallosal syndrome	N
Atelosteogenesis, type III	Y

Contd...

Contd...

Observable anomalies and associated syndromes	*DNA testings available?*
Carpenter syndrome	N
Catel-Manzke syndrome	N
Craniofrontonasal dysplasia	N
de Lange syndrome	N
Escobar syndrome	N
FG syndrome	N
FGFR3-Associated coronal synostosis syndrome	Y
Fibrochondrogenesis	N
Floating-Harbor syndrome	N
Langer-Giedion syndrome	N
Lenz-Majewski hyperostosis syndrome	N
Lenz microphthalmia syndrome	N
Miller-Dieker syndrome	N
Mohr syndrome	N
Multiple synostosis syndrome	N
Oto-palato-digital syndrome, type I	N
Peters'-plus syndrome	N
Roberts-SC phocomelia	N
Russell-Silver syndrome	Y
Saethre-Chotzen syndrome	Y
Seckel syndrome	N
SHORT syndrome	N
X-Linked μ-thalassemia/mental retardation (ATR-X) syndrome	N
Arthrogryposis	
Achondroplasia (elbow)	Y
Acromesomelic dysplasia (elbow)	N
Amyolplasia congenita disruptive sequence	N
Antley-Bixler syndrome (hands, hips, knees, ankles, fused elbows)	N
Atelosteogenesis, type III	Y
Autosomal recessive chondrodysplasia punctata	N
Beals syndrome (knees, elbows, hands)	N
Catel-Manzke syndrome (camptodactyly)	N
Caudal Dysplasia Sequence (hips, knees)	N
Cerebro-oculo-facio-skeletal (COFS) syndrome	N
CHILD syndrome	N
Chondrodysplasia punctata, X-linked dominant type	N
Cockayne syndrome	Y
Diastrophic dysplasia	N
Distal arthrogryposis syndrome (camptodactyly)	N
Dyggve-Melchior-Clausen syndrome (elbow, hip)	N
Escobar syndrome	N
Femoral hypoplasia-unusual facies syndrome (elbow)	N
FG syndrome	N
Fibrochondrogenesis (camptodactyly)	N
Fibrodysplasia ossificans progressiva syndrome	Y
Freeman-Sheldon syndrome (fingers)	N
Frontometaphyseal dysplasia	N
Geleophysic dysplasia	N
Generalized gangliosidosis syndrome, type I (severe infantile type)	N
Hecht syndrome (jaw, hands)	N
Hunter syndrome	N
Hurler syndrome	N

Contd...

Contd..

Contd...

Observable anomalies and associated syndromes	*DNA testings available?*
Hurler-Scheie syndrome	N
Hypochondroplasia (elbow)	Y
Jarcho-Levin syndrome (camptodactyly)	N
Killian/TGeschler-Nicola syndrome (late onset)	N
Kniest dysplasia	N
Leri-Weill dyschondrosteosis (elbow, wrist)	N
Leroy I-cell syndrome	N
Lethal multiple pterygium syndrome	N
Mandibuloacral dysplasia	Y
Marden-Walker syndrome	N
Marfan syndrome (elbow)	Y
Maroteaux-Lamy mucopolysaccharidosis syndrome	N
Metaphyseal dysplasia, Jansen type	Y?
Metaphyseal dysplasia, McKusick type (elbow)	Y?
Metaphyseal dysplasia, Schmid type	Y?
Metatrophic dysplasia	N
Morquio syndrome (hips)	N
Multiple epiphyseal dysplasia (hip)	N
Multiple synostosis syndrome (fusion)	N
Nail-patella syndrome	Y
Neu-Laxova syndrome	N
Oligohydramnios sequence	N
Oto-palato-digital syndrome, type I (elbow, hip, knee)	N
Pallister-Hall syndrome (camptodactyly)	Y
Pena-Shokeir phenotype	N
Popliteal pterygium syndrome	N
Progeria syndrome	N
Pseudoachondroplasia (elbows)	N
Pseudo-Hurler polydystrophy syndrome	N
Restrictive dermopathy	N
Saethre-Chotzen syndrome (elbow)	Y
Sanfilippo syndrome	N
Scheie syndrome	N
Schwartz-Jampel syndrome	N
Shprintzen-Goldber syndrome (camptodactyly)	N
Seckel syndrome (knee)	N
Smith-Lemli-Opitz syndrome (hands)	Y
Smith-Magenis syndrome (elbows)	Y
Spondylocarpotarsal synostosis syndrome	Y
Spondyloepiphyseal dysplasia congenita	Y
Spondylometaphyseal dysplasia, Koslowski type	N
Stickler syndrome	Y
3-M syndrome (elbows)	N
Weaver syndrome (camptodactyly)	N
Wiedemann-Rautenstrauch syndrome	N
X-linked hydrocephalus spectrum (thumb)	Y
Single umbilical artery	
Exstrophy of cloaca sequence	N
Monozygotic (MZ) twinning and structural defects—general	N
Sirenomelia sequence	N
VATERR association	N

Contd..

Contd...

Observable anomalies and associated syndromes	*DNA testings available?*
Kidney malformation	
Aniridia-Wilms tumor association	N
Bardet-Biedl syndrome	Y
Beckwith-Wiedemann syndrome	Y
Carpenter syndrome	N
Congenital microgastria-limb reduction complex	N
Early urethral obstruction sequence	N
Ectrodactyly-ectodermal dysplasia-clefting syndrome	N
Exstrophy of cloaca sequence	N
Fanconi pancytopenia syndrome	N
Fryn's syndrome	N
Jeune thoracic dystrophy	N
Johanson-Blizzard syndrome	N
Klippel-Feil Sequence	N
Laterality sequences	N
Limb-Body wall complex	N
McKusick-Kaufman syndrome	N
Meckel-Gruber syndrome	N
Melnick-Fraser syndrome (bilateral renal agenesis)	N
Meningomyelocele sequence	N
Mowat-Wilson syndrome	Y
MURCS association	N
Oligohydramnios sequence	N
Oral-facial-digital syndrome	N
Pallister-Hall syndrome	Y
Peters'-plus syndrome	N
Rubinstein-Taybi syndrome	N
Schinzel-Giedion syndrome	N
Short rib-polydactyly syndrome, type I (Saldino-Noonan type)	N
Short rib-polydactyly syndrome, type II (Majewski type)	N
Sirenomelia sequence	N
Smith-Magenis syndrome	Y
Townes-Brocks syndrome	Y
Tuberous sclerosis syndrome	Y
VATERR association	N
Zellweger syndrome	Y
Macrosomia/Overgrowth	
Beckwith-Wiedemann syndrome	Y
Berardinelli lipodystrophy syndrome	N
Marshall-Smith syndrome	N
Simpson-Golabi-Behmel syndrome	Y
Sotos syndrome	Y
Weaver syndrome	N
Hydrops fetalis	
Achondrogenesis, type I	N
Fibrochondrogenesis	N
Monozygotic (MZ) twinning structural defects-general	N
Osteogenesis imperfecta syndrome, type II	Y

Infectious Pathogens

Diagnostic assays for acute infections are rapidly changing from antibody detection to pathogen detection, from slower culture based methods to rapid molecular methods, from clinical laboratory based to point-of-care (POC)-based tests, and from detection of only a few types of organisms at a time to simultaneous detection of multiple pathogens.[6] Microarrays have the ability to detect viruses, bacteria, and other microorganisms all on the same chip. They can detect the organisms even when they are no longer alive. Very rapid testing is possible and sample handling is very simple. Microarrays are also being used to monitor both innate and adaptive immunity; others are studying global gene expression of both the pathogen and the patient during the progression of an infection. In the near future, virulence factors, resistance factors, and host response to the pathogen will all be monitored in parallel. Rapid POC devices will allow rapid screens on amniotic fluid in the setting of a suspected TORCH infection or chorioamnionitis.

CONCLUSIONS

Molecular genetic testing frequently aids in the evaluation of abnormal ultrasound findings. Hundreds of new assays are being developed every year. A significant educational effort will be necessary to incorporate new molecular knowledge into obstetric ultrasound practice. It is hoped that these tables and their primary sources will be helpful references for all those involved in state-of-the-art prenatal diagnosis.

ACKNOWLEDGMENTS

This work was supported by grants from the National Institutes of Health (5 K24 HD01315-02 and 2 U 54 RR014607-06 from the Research Centers in Minority Institutions program in the National Center for Research Resources).

REFERENCES

1. GeneTests. Medical Genetics Informational Resource (database online). Copyright, University of Washington, Seattle, 1995-2006. Available at http//:www.genetests.org. Accessed October 18, 2006.
2. Lapierre JM, Tachdjian G. Detection of chromosomal abnormalities by comparative genomic hybridization. Curr Opin Obstet Gynecol 2005;17:171-7.
3. Dudarewicz L, Holzgreve W, Jeziorowska A, Jakubowski L, Zimmermann B. Molecular methods for rapid detection of aneuploidy. J Appl Genet 2005;46:207-15.
4. Online Mendelian Inheritance in Man, OMIM (TM). McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD), October 20, 2006. World Wide Web URL: http://www.ncbi.nlm.nih.gov/omim/.
5. Jones K. Smith's Recognizable Patterns of Human Malformation. Philadelpia: Saunders, 2005.
6. Bryant PA, Venter D, Robins-Browne R, Curtis N. Chips with everything: DNA microarrays in infectious diseases. Lancet Infect Dis 2004;4:100-11.