A Practical, Systematic Approach to Genetic Diagnosis in a Fetus or Neonate with Congenital Anomalies

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EDUCATIONAL GAPS

Genetics is a rapidly evolving branch of medicine with a plethora of tests being added frequently to the diagnostic armamentarium. Clinicians need to be well-informed about all the available diagnostic tests to choose the best one for each specific case to provide maximum diagnostic yield.

OBJECTIVES *After completing this article, readers should be able to:*

1. Classify congenital anomalies based on morphology.
2. Describe a systematic algorithm for evaluating a fetus or neonate with congenital anomalies.
3. Determine the best genetic test to order when faced with a fetus or neonate with congenital anomalies.

ABSTRACT

Congenital anomalies contribute significantly to perinatal, neonatal, and infant morbidity and mortality. The causes of these anomalies vary, ranging from teratogen exposure to genetic disorders. A high suspicion for a genetic condition is especially important because a genetic diagnosis carries a risk of recurrence in future pregnancies. Various methods are available for genetic testing, and each plays a role in establishing a genetic diagnosis. This review summarizes a practical, systematic approach to a fetus or neonate with congenital anomalies.

INTRODUCTION

Normal morphogenesis is an organized process that combines several physiologic stages at the cellular or molecular level that can occur either concurrently or sequentially. (1) These stages include cell migration, cell-cell adhesion, apoptosis,

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and hormonal influences. (1) An abnormality in 1 of these phases could lead to a congenital anomaly. (2) Although aberrant morphogenesis can result from environmental or teratogenic exposures, genetic factors often play an essential role in fetuses/neonates with anomalies.

A significant congenital anomaly or structural malformation affects approximately 3% to 6% of all live births. (3)(4)(5) Congenital anomalies are emerging as one of the major causes of neonatal and infant mortality in countries with improved neonatal outcomes from other causes. (4)(6) With advances in fetal ultrasonography techniques, most of these anomalies can now be identified in the prenatal period. This review summarizes a practical, systematic approach to a fetus or neonate with anomalies.

GENERAL APPROACH TO ANOMALIES IDENTIFIED IN THE FETUS OR NEWBORN

Causes of congenital anomalies are diverse and multifactorial and can be categorized as a chronic disease in the pregnant person (eg, diabetes), an exposure to teratogens (eg, anticonvulsants), a genetic condition (either a chromosomal abnormality or a single gene etiology), or an infection (eg, rubella) or radiation exposure in the pregnant person. (7) The same congenital anomaly may have different etiologies in different cases (eg, cleft lip/palate, ventriculomegaly). Therefore, a multidisciplinary approach should be used when organizing the care, diagnostics, and counseling of parents who are expecting a fetus or neonate with an abnormality.

Identifying genetic conditions in the fetus can lead to lifesaving interventions, which can occur antenatally or during the immediate postdelivery period. Various gene modification therapies are currently being investigated for monogenic disorders. For example, Schneider et al's (8) groundbreaking study introduced recombinant ectodysplasin A protein into the amniotic fluid of 3 human fetuses diagnosed as having X-linked hypohidrotic ectodermal dysplasia at the end of the second trimester. After birth, these infants exhibited normal sweating abilities, and the associated condition had still not manifested at follow-up (14–22 months of age). (8) A prenatal diagnosis can also help prepare for urgent interventions in the immediate postdelivery period, such as a diagnosis of an obstructive neck mass that may require extracorporeal membrane oxygenation. (9)

Certain congenital anomalies (eg, anencephaly) are not compatible with survival. In such instances, when a termination of pregnancy is being considered, genetic testing is important because congenital anomalies due to a genetic etiology can recur in subsequent pregnancies. Invasive procedural testing, a targeted genetic evaluation, and, if relevant, a fetal autopsy can help determine the diagnosis and approach to the present and future pregnancies.

Previous studies have shown that genetic aberrations are considerably high in fetuses with structural malformations. Approximately 2% to 18% of fetuses with an isolated anomaly and almost 13% to 35% with multiple anomalies have an abnormal karyotype. (10)(11)(12) The diagnostic yield is considerably higher if chromosomal microarray or genomic techniques such as exome sequencing are used as diagnostic tests instead of a karyotype. (13)(14)(15)(16)(17) In a study by Pasternak et al, (18) chromosomal microarray yielded 23.9% of pregnancies terminated due to fetal malformations. In structurally abnormal fetuses, exome sequencing provides an additional yield of 31% when chromosomal microarray is normal. (19) Exome sequencing abnormalities were found more often in fetuses with multiple anomalies and skeletal anomalies, followed by those with cardiac anomalies. (19)(20)(21)

Genetics is a rapidly evolving branch of medicine, with a new plethora of tests being added frequently to the diagnostic armamentarium. Genetic evaluation for fetal anomalies is recommended only if there is a high suspicion of a genetic disorder and if the appropriate genetic testing has a high yield. Therefore, families and clinicians need to be well-informed about all the available diagnostic tests to choose the best one in each specific case and provide maximum diagnostic yield. Often, clinicians face challenges in deciding, and counseling pregnant patients and their partners about, which test would best suit a particular condition. A stepwise approach to the evaluation of a fetus or neonate with structural anomalies is recommended.

STEP 1: DETAILED ASSESSMENT—HISTORY AND PHYSICAL EXAMINATION

The evaluation of a fetus/neonate with a congenital anomaly based on prenatal ultrasonography or postnatal examination should start with a detailed history, including a detailed history of the parents, with particular attention to their age, ethnicity, consanguinity, previous obstetric history (including any history of terminations, stillbirths), previous history or family history of a birth of an infant with a congenital anomaly, or any other significant pregnancy-related complications. The clinician should elicit a history of intake of over-the-counter medications in the pregnant person, with a special note of intake of drugs for seizure disorders, acne, or illicit drugs. Clinicians also need to ask about any history of prolonged radiation exposure and fever with rash during the first trimester of pregnancy. Providers need to inquire about the pregnant person's vaccination status,

with particular attention to rubella and chickenpox vaccinations. Whenever possible, a detailed history of extended family and pedigree, up to 4 generations, should be taken to evaluate for genetic causes.

Identification of the index case (ie, the first affected member of the family) is an important step in the evaluation. If an index case is identified, a detailed history regarding the age at onset of symptoms or delay in growth or development should be noted. The nature of the progression of the disease and, if the index case is no longer alive, details of how and what led to the death are critical pieces of information. Photographs of the index case should be taken and kept in the record as these may be helpful in the future. Photographs should include the front and back of the affected person's entire body, as well as the facial profile, hands and feet, and detailed photographs of the anomalies of the affected person. Videotapes should be made if the family member has abnormalities in gait, speech, or behavior. Any abnormal limb and body movements should also be recorded.

When an anomaly is detected on antenatal ultrasonography, the expectant parents should be initially counseled by a multidisciplinary team composed of an obstetrician, a fetal medicine specialist, a neonatologist, a medical geneticist, a social health worker, and relevant allied specialists (eg, a pediatric surgeon, a pediatric nephrologist, a pediatric cardiologist). The focus of the counseling includes several factors. First, the expectant parents must be prepared for the birth of a neonate with anomalies, if the infant were to survive to delivery, with an explanation of the possible postnatal outcomes. Second, the management plan, including various prenatal and postnatal (if relevant) diagnostic tests and therapeutic measures (medical or surgical), should be clearly outlined. Offering the appropriate prenatal testing (ie, chorionic villus sampling, amniocentesis, or cord blood sampling) and a detailed discussion regarding its benefits, risks, and limitations is important. Third, parents should be counseled regarding different genetic tests that are available, the limitations of each test, and what to expect if, even after invasive testing, the results are inconclusive. The antenatal counseling should be staged, with the first counseling scheduled as soon as possible after the antenatal diagnosis. This helps convey basic details of the anomaly and possible pregnancy outcomes and can alleviate anxiety in the expectant parents. (13) Subsequent counseling can be scheduled as per family request, and vetted web-based materials can be shared with the expectant parents. Another counseling session closer to the expected delivery date is very important, where the family is given a detailed explanation of the postnatal course and management plan. If severe congenital anomalies that are not compatible with life are recognized on antenatal scans, offering the option of termination (if available) and/or the possibility of comfort care measures after birth is crucial. It is essential that the counselor is knowledgeable and empathetic to the family and uses understandable language rather than technical jargon.

After the neonate is born, the initial focus will be on the stabilization of the neonate and the need for any medical or surgical interventions if the infant is receiving full resuscitative measures. Once stabilized, a focused approach is required to make a genetic diagnosis if it was not made antenatally. This includes a detailed physical examination of the neonate, requesting additional diagnostic tests targeted to the patient's findings (eg, hematologic or biochemical tests, brain ultrasonography, echocardiography, ultrasonography of the abdomen/renal system, radiography of the spine, etc), and determining the ideal genetic testing to establish a definitive genetic diagnosis. A detailed eye examination can offer critical diagnostic clues. All dysmorphic neonates should undergo diagnostic audiologic testing with brainstem auditory evoked potentials. Assessment of thyroid function is essential because several genetic disorders have an increased incidence of congenital hypothyroidism. (22) A systematic approach to examining the neonate with a possible genetic diagnosis is provided in Table 1.

STEP 2: MORPHOLOGIC CHARACTERIZATION OF DETECTED ANOMALIES

The next important step is the morphologic characterization of the anomalies into malformation, deformation, disruption, or dysplasia. Table 2 describes the terminology used to describe aberrant phenotypes. Examples of anomalies within each group are depicted in Figure 1. The morphologic characterization guides the need for genetic evaluation and relevant test(s) to be sent.

STEP 3: RECOGNITION OF PATTERNS

The next step involves the recognition of patterns wherein clinicians determine whether the anomaly is isolated or there are multiple anomalies and whether the anomalies are consistent with a specific chromosomal or single gene disorder. Aneuploidies of chromosomes 21, 13, and 18 and sex chromosomes constitute the most common genetic abnormality detected prenatally. (28) Together, they constituted approximately 85% of all chromosome abnormalities in the European Surveillance of Congenital Anomalies database of patients diagnosed prenatally and before 1 year

Table 1. A Systematic Approach to Examining the Neonate with a Possible Genetic Diagnosis (16)(23)(24)(25)(26)(27)

BODY PART	SPECIFIC POTENTIAL FINDINGS
Scalp and skull	Head size (microcephaly and macrocephaly), sutures (craniosynostosis), head shape (dolichocephaly and brachycephaly), aplasia cutis congenita, anterior hairline, posterior hairline, sparse hair
Face	Eye abnormalities: microphthalmia/anophthalmia, shape (eg, almond shape), hypertelorism/hypotelorism, telecanthus, up slant/down slant, epicanthal folds, long eyelashes, strabismus/nystagmus Ear abnormalities: low-set ears, preauricular tag/pit, postauricular tag/pit, microtia or anotia, simplified ears, posteriorly rotated ears Nose abnormalities: nasal bridge (flat/depressed), the shape of the nasal tip, alae nasi, columella, choanal patency Oral abnormalities: lip pits, cleft lip/palate, shape of palate/uvula, natal teeth, tongue abnormalities (lobules), frenula Micrognathia/retrognathia
Neck	Increased nuchal fold, cystic hygroma, short/webbed neck
Trunk	Pectus excavatum/carinatum, widely spaced/inverted/accessory nipples, organomegaly, hernial orifices, umbilical cord abnormalities
Spine	Kyphosis and scoliosis, midline defects (tuft of hair, hemangioma, lipoma, abnormal sacral dimple: closer to anal verge [<2.5 cm] or deeper [>2.5 mm])
Upper and lower limbs	Acromelia, mesomelia, and micromelia, polydactyly (preaxial or postaxial), syndactyly (fusion of the digits), clinodactyly (incurving of the digits), arachnodactyly
Skin and nails	Skin (hyperpigmentation/hypopigmentation, ichthyosis, café-au-lait spots, ash-leaf spots, shagreen patches, adenoma sebaceum, neurofibromas, hyperextensibility) Nails (convex, deep-set, dystrophic, longitudinal ridges)
Genitalia	Hypospadias, chordee, cryptorchidism, microphallus, ambiguous genitalia
Anus	Anal tags, anal placement (anogenital ratio), anal patency
Palms and soles	Dermal ridge patterns, or dermatoglyphics, transpalmar crease, sandal gap, overlapping fingers/toes, keratoderma

of age. (16)(29) Because a considerable proportion of affected fetuses result in spontaneous abortions or induced pregnancy terminations due to multiple malformations, diagnosis of chromosomal abnormalities based solely on prenatal genetic testing is even higher. (30) Table 3 shows the common anomalies found on antenatal ultrasonography that suggest a possible genetic condition, and Table 4 lists the prenatal sonographic anomalies noted in the common aneuploidies.

STEP 4: ESTABLISHMENT OF DIAGNOSIS—CHOOSING THE BEST GENETIC TEST FOR THE FETUS/NEONATE

After the initial assessment (history and examination) of a fetus/neonate with an anomaly, clinicians should assess for the need to obtain genetic testing and, if required, the type of test to be performed. Genetic testing is usually not warranted for deformations (eg, clubfoot or arthrogryposis due to oligohydramnios), disruptions (eg, loss of digits attributable to amniotic bands), a teratogen exposure, or an environmental explanation for the anomalies. Common teratogens include uncontrolled diabetes of the pregnant person in the first trimester, radiation exposure, alcohol exposure, certain drugs, and intrauterine infections due to rubella, cytomegalovirus, toxoplasmosis, and varicella. However, if the clinical manifestations do not fit one of these categories, it is prudent to consider genetic testing.

Before proceeding with genetic evaluation, an initial assessment for a potential genetic cause is recommended. Although not common, a few genetic diagnoses can be determined based on the specific anomalies and dysmorphisms that have been identified. Some user-friendly databases aid in diagnosing syndromes using specific phenotypic abnormalities, including the Winter-Baraitser Dysmorphology Database, the Baraitser-Winter Neurogenetics Database, Online Mendelian Inheritance in Man, Pictures of Standard Syndromes and Undiagnosed Malformations, and Phenomizer.

If the anomalies are consistent with a common trisomy on prenatal ultrasonography or after examination of a neonate, and in cases with ambiguous genitalia, a karyotype is recommended. Fig 2 lists the conditions when a karyotype is usually recommended, and also notes a few commonly encountered congenital anomalies (especially if it is an isolated anomaly) when a karyotype is usually not required. Chromosomal microarray is the preferred genetic test for fetuses or neonates with multiple anomalies. It does not require culture and has the advantage of identifying microdeletions and microduplications that cannot be detected by traditional karyotype; whereas the detection yield with

Table 2. Terminology Used to Describe Congenital Anomalies (2)(17)

TERMINOLOGY	DESCRIPTION	EXAMPLES
Normal variation	A small departure from the reference population present in healthy people, but can be associated with major congenital anomalies	Low-set ears, hypertelorism
Malformation	A congenital nonprogressive abnormality of an organ or tissue due to interference with the primary developmental program of morphogenesis Categorized into major malformations or minor malformations	Major malformations • Central nervous system anomalies • Congenital heart disease Minor malformations • Polydactyly • Single transpalmar crease
Deformation	Abnormality in the shape and size of a normally formed structure due to intrinsic/external mechanical forces	Congenital talipes equinovarus Arthrogryposis due to oligohydramnios
Disruption	Normal initial development of an organ followed by interference with its development due to either vascular interruption, teratogen exposure, or amniotic bands resulting in nonprogressive abnormality	Missing limbs or digits
Dysplasia	A morphologic aberration caused by abnormal proliferation and organization of cells in the tissue	Skeletal dysplasia Ectodermal dysplasia
Syndrome	Single etiology leading to a group of major and minor anomalies due to either malformation or dysplasia	Edward syndrome (trisomy 18), Cornelia de Lange syndrome
Sequence	A cascade of ≥1 secondary morphologic anomalies that arise from a single abnormality that is either a malformation or a deformation	Pierre Robin sequence
Association	The presence of multiple abnormalities that occur together more frequently than would be predicted by chance with no clear cause	VACTERL association, OEIS complex

OEIS=omphalocele, exstrophy of bladder or cloaca, imperforate anus, and spinal defects, VACTERL=vertebral anomalies, anorectal anomalies (anal atresia), cardiac anomalies, tracheoesophageal fistula or atresia, renal anomalies, and limb anomalies.

conventional chromosomal analysis is 5%, the yield is increased to 12% to 15% with microarray. (13)(14)(15)(16)

The introduction of molecular genetic techniques such as next-generation sequencing, which can pick point mutations and tiny deletions and duplications, has significantly advanced the field of genetic testing. Next-generation sequencing is a cost-effective technique with a fast turnaround time. (38)(39) It is routinely used in clinical settings for sequencing multiple genes at one time, sequencing

Figure 1. Examples of various anomalies.
Upper left. Variant—low-set ear. Upper right. Malformation—meningoencephalocele. Lower left. Deformation—talipes. Lower right. Disruption—limb reduction.

Table 3. Common Fetal Abnormalities Identified by First- and Second-Trimester Ultrasonography that Warrant Further Testing

First trimester	• Increased nuchal translucency • Absent nasal bone • Cystic hygroma • Structural anomalies in the fetus: holoprosencephaly, facial clefts, abdominal wall defects, megacystis, limb anomalies
Second trimester	• Second-trimester soft markers (usually a combination of multiple soft markers is suggestive of a genetic etiology) ○ Choroid plexus cysts ○ Mega cisterna magna ○ Mild ventriculomegaly ○ Absent or hypoplastic nasal bone ○ Thickened nuchal fold ○ Echogenic intracardiac focus ○ Single umbilical artery ○ Hyperechoic bowel ○ Urinary tract dilation ○ Shortened long bones (humerus, femur) • Fetal growth restriction • Structural anomalies

Table 4. Prenatal Sonographic Structural Anomalies Found in Common Aneuploidies (14)(18)(19)(20)(21)(22)(28)(29)(31)(32)(33)(34)(35)(36)(37)

Trisomy 21 (Down syndrome) (31)	• Craniofacial (eg, cystic hygroma, brachycephaly) • Central nervous system (eg, mild ventriculomegaly) • Cardiovascular, notably endocardial cushion defects and ventricular septal defects (40%–50%) • Gastrointestinal system (eg, duodenal atresia) • Hydrops fetalis
Trisomy 18 (Edward syndrome) (14)	• Strawberry-shaped calvarium • Central nervous system anomalies (neural tube defects, ventriculomegaly, agenesis of the corpus callosum, cerebellar anomalies) • Facial anomalies (clefts, micrognathia) • Nuchal fold thickening or cystic hygroma • Cardiovascular anomalies (complex congenital heart defects, ventricular septal defects, and valvular defects) • Gastrointestinal anomalies (omphalocele, diaphragmatic hernia) • Urogenital anomalies (horseshoe kidney, hydronephrosis) • Limb abnormalities (upper limb reduction [eg, radial ray defect]), clenched hands with the overlapping index finger, club feet, rocker bottom feet) • Fetal growth restriction
Trisomy 13 (Patau syndrome) (32)(33)	• Central nervous system (ventriculomegaly, alobar holoprosencephaly, neural tube defects, posterior fossa abnormalities, agenesis of the corpus callosum) • Severe midline facial abnormalities (anophthalmia/microphthalmia, cyclopia, midline facial clefts, hypoplastic nose) • Cardiac anomalies (complex congenital heart defects, ventricular septal defects) • Gastrointestinal anomalies (omphalocele, diaphragmatic hernia) • Renal anomalies (polycystic kidneys, enlarged echogenic kidneys, horseshoe kidneys) • Skeletal anomalies (postaxial polydactyly, club feet, rocker bottom feet)
Triploidy (34)(35)	• Central nervous system anomalies (ventriculomegaly, posterior fossa malformations, holoprosencephaly neural tube defects) • Facial defects • Cardiac anomalies (complex congenital heart defects, tetralogy of Fallot, and transposition of the great arteries) • Renal anomalies (renal agenesis and multicystic kidneys) • Clenched hands, congenital talipes equinovarus
Monosomy X (Turner syndrome) (36)(37)	• Large septate cystic hygroma • Hydrops fetalis • Cardiac abnormalities (bicuspid aortic valve, coarctation of aorta, aortic stenosis) • Short femur

specific genes (targeted sequencing predominantly for well-known gene mutations involved in the pathogenesis of any disease), sequencing coding regions (exons) of all genes (known as whole exome sequencing), and sequencing coding and noncoding regions (exons and introns) of all genes (known as whole genome sequencing).

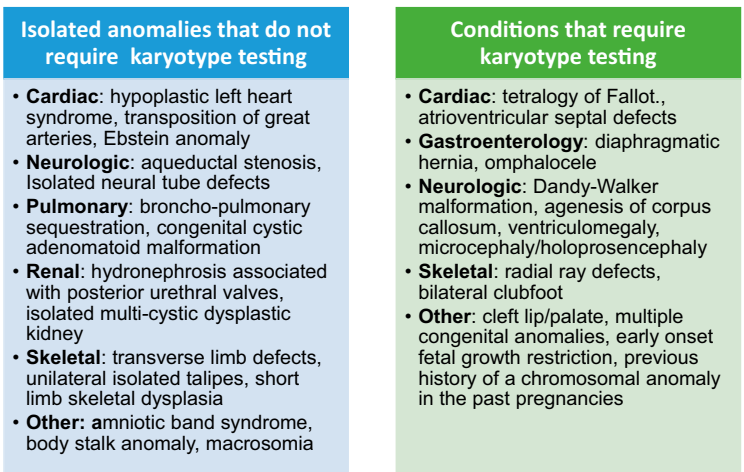

Figure 2. Karyotype: When to do? When not to do?

Next-generation sequencing is the recommended test when the pattern of anomalies is consistent with a monogenic disorder or when the karyotype and/or microarray is not informative in a fetus/neonate with multiple anomalies. The yield is especially good if the anomalies are consistent with skeletal dysplasia or a neuromuscular disorder or involve multiple systems. (40) A guide to choosing the best test and its indications, resolution, turnaround time, advantages, and limitations is provided in Table 5.

Expectant parents who have a fetus with a concern for a genetic diagnosis should be counseled in detail regarding the indication for testing, the specific genetic test that is being performed, the cost and turnaround time, the reliability of the test, the possibility of ambiguous results, and the need for repeated or further testing. After the report is available, the couple should be educated about the plan for the current pregnancy as well as subsequent pregnancies.

STEP 5: GENETIC COUNSELING—ASSESSMENT OF PROGNOSIS AND RECURRENCE RISK

After the identification of a fetus/neonate with anomalies, the prognosis depends on the type of congenital anomaly and the genetic diagnosis. In the case of common chromosomal aneuploidies, the recurrence risk is 0.5% to 2%. (41) If 1 parent is a carrier of a balanced reciprocal chromosomal translocation, the offspring's risk of an unbalanced translocation varies from 5% to 30%. (42) If 1 parent is a carrier for a balanced Robertsonian translocation, the offspring risk of an unbalanced translocation is 1% to 5% if the expectant father is a carrier and 5% to 10% if the expectant mother is a carrier. (43)

If a fetus/child is diagnosed as having a microdeletion or duplication syndrome, a parental microarray is needed in some cases, such as DiGeorge syndrome, to determine recurrence risk. This is because if the abnormality is absent in both parents, the risk of recurrence is less than 1%. (44)(45) But, if 1 parent is found to have the same abnormality, irrespective of whether they are symptomatic or asymptomatic, the recurrence risk may be as high as 50%. (45)(46)

In cases with single gene etiology, the chance of recurrence risk is 25% for autosomal recessive disorders. For autosomal dominant disorders, if inherited from 1 of the parents, the recurrence risk is 50%, and if it is de novo, the risk is less than 1%. (47)(48) The recurrence risk of some congenital anomalies is variable and depends on various factors, including genetic and environmental. Table 6 can be used as a reference guide for counseling parents regarding the risk of recurrence of common congenital anomalies with a multifactorial etiology.

ROLE OF FETAL/NEONATAL AUTOPSY

Investigations of second-trimester fetal loss, stillbirths, and neonatal mortality linked to nonchromosomal fetal abnormalities should ideally include a fetal/neonatal autopsy. The main goals of the fetal or neonatal autopsy are to provide the family with precise information by establishing gestational age, documenting growth and development, validating prenatal ultrasonography findings, identifying congenital abnormalities not detected by ultrasonography, and establishing the cause of death. If a fetal abnormality is present when there is no obvious clinical diagnosis, autopsy results are more likely to be helpful. A fetal autopsy is particularly recommended when fetal anomalies are detected but no chromosomal diagnosis is evident. (59)

In most cases, information from a fetal autopsy modifies or greatly improves the clinical diagnosis. (60) Studies have shown that a new finding was more likely if the infant was born between 28 and 36 weeks' gestation, if prenatal care was lacking, or if the infant died within 6 hours after birth. (60)(61) Although most significant abnormalities may be detected by prenatal ultrasonography, several studies have found that the prenatal diagnosis often differs from the results of a fetal autopsy. (62)(63)(64)

Autopsy also allows for the confirmatory documentation of defects that are suspected on ultrasonography. Dysmorphology, inspection of external orifices, and confirmation of bowel, ureter, and esophageal patency, as well as evaluation of the extremities, including the fingers, are helpful in determining the phenotype. Several findings (such as a band between fingers, colonic atresia, bifid thymus, lung lobulations, absence of ureters, and hypertrichosis), which are difficult to detect by ultrasonography, are easy to document by autopsy. (65) A few abnormalities (such as popliteal pterygium, hexadactyly of all 4 limbs, sirenomelia, and cloacal anomalies) could be suspected on ultrasonography but are readily apparent on autopsy. (66)(67) Although autopsy is the best method for evaluating dysmorphology and anomalies involving the ears, limbs, and genitals, ultrasonography and/or echocardiography are more useful when evaluating the heart because they allow for a functional examination. Hence, for evaluating internal organs such as the heart, autopsy has a complementary role to sonography. (68)

The results of fetal autopsy provide more accurate genetic counseling to the family about the possibilities of prevention or risks of recurrence. One study found that in approximately 20% of cases, the fetal autopsy changed genetic counseling about subsequent pregnancies. (69) Even when the autopsy does not uncover any new anomalies, it nevertheless makes it possible to draw conclusions (eg, the

Table 5. Indications, Resolution, Turnaround Time, Advantages, and Limitations of Genetic Tests

TYPE OF GENETIC TEST	INDICATIONS	RESOLUTION	TURNAROUND TIME	ADVANTAGES	LIMITATIONS
Karyotype	• Clinical findings suggestive of a trisomy • Disorder of sex development • Couple with multiple first-trimester miscarriages (≥2) to look for balanced chromosome translocations that cannot be detected by chromosomal microarray	4–5 Mb (million base pairs)	14–21 d	Can diagnose common chromosomal abnormalities	Will not be able to detect submicroscopic abnormalities such as microdeletions and duplications
FISH	• Common chromosomal aneuploidies • Common microdeletions/ duplication syndromes such as DiGeorge syndrome and Williams syndrome	–	48–72 h	No need for live cells or cell culture	Clinical suspicion of a specific disorder is the prerequisite
MLPA	• Common chromosomal aneuploidies • Common microdeletions/ duplication syndromes such as DiGeorge syndrome and Williams syndrome	–	48–72 h	No need for live cells or cell culture	Clinical suspicion of a specific disorder is the prerequisite
QF PCR	• Common chromosomal aneuploidies	–	48–72 h	Does not require cell culture	• Rapid prenatal testing of common chromosomal aneuploidies • Cost-effective
CMA	• Multiple malformations • Unexplained intellectual disability with or without dysmorphic features or other anomalies • Unexplained growth restriction or failure to thrive	Deletions up to 50–100 kilobase (kb) and duplications up to 400 kb	10–14 d	• Covers the entire genome • Does not require live cells or cell culture	• Cannot detect balanced chromosomal rearrangements and CNVs <50 kb • Variants of uncertain significance are identified
WES	• Monogenic disorders (eg, inborn errors of metabolism) • Suspected skeletal dysplasia • Suspected neuromuscular disorder • Karyotyping and/or CMA is not diagnostic in the presence of multiple anomalies	Point mutations	4–6 wk	Detects sequence variants	Variants of uncertain significance are identified
WGS	• A genetic etiology is suspected based on phenotype, although all previous tests/targeted genetic panels were inconclusive • Monogenic and polygenic disorders	Capable of detecting nearly all DNA variation in a genome	10–12 wk	Can diagnose most of the >6,000 conditions, listed in the OMIM database	• Variants of uncertain significance are identified • Tendency to uncover unsought secondary findings, leading to ethical issues

CMA=chromosomal microarray, CNV=copy number variant, FISH=fluorescence in situ hybridization, MLPA=multiplex ligation probe amplification, OMIM=Online Mendelian Inheritance in Man, QF-PCR=quantitative fluorescence polymerase chain reaction, WES=whole exome sequencing, WGS=whole genome sequencing.

Table 6. Empirical Recurrence Risk of Congenital Anomalies with a Multifactorial Etiology

CONGENITAL ANOMALY	STATUS OF AFFECTED PARENT/ SIBLINGS	EMPIRICAL RISK OF RECURRENCE (%)
Neural tube defect (49)	No siblings/neither parent	0.3
	No siblings/1 parent	4.5
	No siblings/both parents	30
	1 sibling/neither parent	4
	1 sibling/1 parent	12
	1 sibling/both parents	38
	2 siblings/neither parent	10
	2 siblings/1 parent	20
	2 siblings/both parents	43
Cleft lip/palate and cleft palate (50)(51)	1 sibling affected with unilateral cleft lip/ palate	2–3
	1 sibling affected with bilateral cleft lip/ palate/affected parent	5–6
	2 affected siblings/affected parent and sibling	10
Congenital heart disease (52)(53)	1 affected sibling	3.5
	2 affected siblings	4.5
	1 affected parent	5–8
		As high as 10% of relatives are also affected
Congenital diaphragmatic hernia (54)	1 sibling affected	1
	When a previous child has multiple congenital anomalies of unknown etiology	~5
Pyloric stenosis (55)	Mother affected	Males: 19 Female offspring: 7
	Father affected	Males: 5.5 Females: 2.4
	Sibling affected	To the next male child: 4 To the next female child: 2.4
Omphalocele, except if a part of a syndrome (56)	–	Usually sporadic, <1
Talipes equinovarus (57)(58)	If the first affected sibling is a male	2
	If the first affected child is a female	5
	1 parent and 1 child affected	25

abnormality is most likely sporadic and not syndromic and, thus, there is no reason to make a prenatal diagnosis for a future pregnancy).

The fetal autopsy also can lead to a recommendation for exome or genome sequencing provided there is a suspicion of a genetic pathology. Autopsy is also helpful in identifying cases that may benefit from additional testing as well as obtaining samples for this testing. For example, if a biochemical disorder has been observed, fibroblast culture may allow for future metabolic testing and DNA analysis. (70)

CONCLUSIONS

In summary, a systematic approach to the fetus and/or neonate with a congenital anomaly helps to determine a genetic diagnosis (Fig 3). Involvement of a multidisciplinary team very early in the management (ie, after the first recognition of the anomaly/ies) ensures that the expectant parents are well-informed and appropriate diagnostic tests are obtained. Because there are several genetic tests available, choosing the correct diagnostic test(s) can decrease the effort, time, and costs that are involved as well as minimize anxiety. A fetal autopsy and genetic testing can guide the management of future pregnancies.

KEY POINTS

- When encountering a fetus or neonate with anomalies, the multidisciplinary team consisting of an obstetrician, a fetal medicine expert, a medical geneticist, a neonatologist, a social health worker, and an allied specialist (depending on the anomaly) should follow a systematic approach to diagnosis, counseling, and management.
- Identification of the index case and assessment of exposures in the antenatal period are crucial components when gathering a history.
- A detailed clinical examination and morphologic characterization is important to guide genetic testing.
- Pattern recognition and establishing a differential diagnosis can help determine the appropriate genetic test.
- A fetal autopsy can help determine a diagnosis and, thus, assist families in planning for future pregnancies.

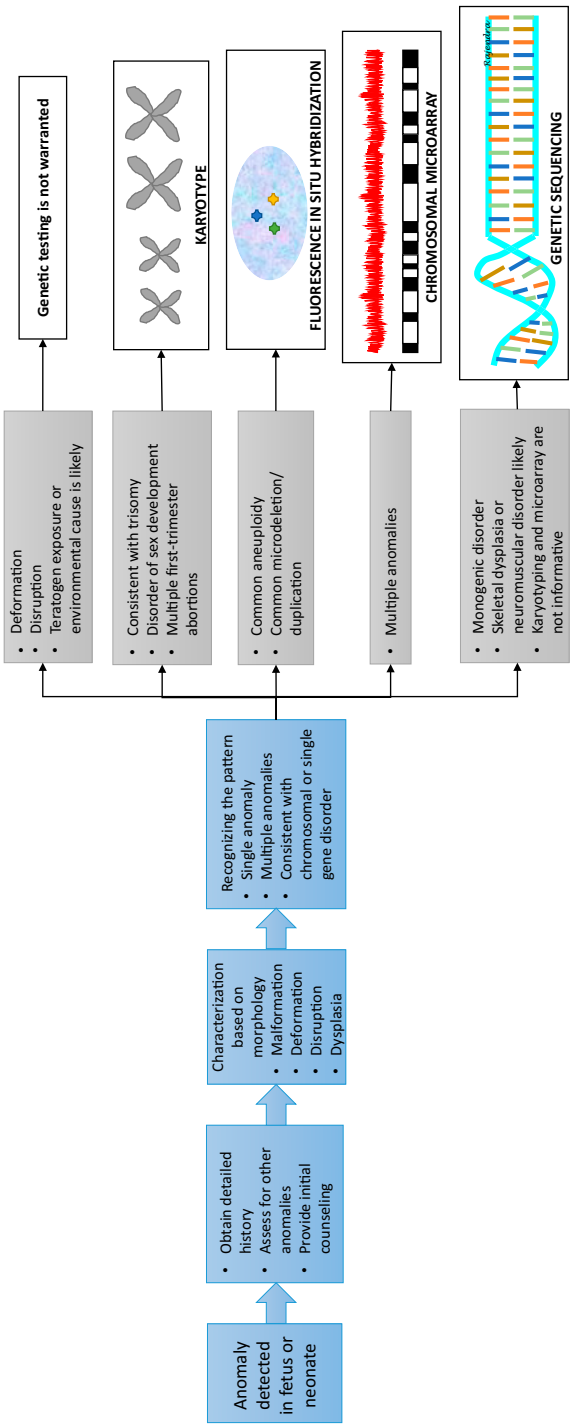

Figure 3. Pictorial representation of a systematic approach to choosing an appropriate genetic test in a fetus/neonate with congenital anomaly.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the components of a complete family history for genetic disorders.
- Know how age at presentation (in utero, neonate, infancy, or later) affects the differential diagnosis of the clinical presentation of genetic disorders.
- Know the relationship between the ethnic origin of the parents and the risk of specific genetic conditions.
- Recognize the diagnostic implications of single versus multiple anomalies.

- Know the frequency of minor congenital anomalies.
- Know the frequency of major congenital malformations.
- Know the clinical features and inheritance patterns of common syndromes or associations that can be recognized in the newborn period (eg, VATER association and DiGeorge syndrome).
- Know the disorders for which molecular genetic studies are clinically indicated, such as cystic fibrosis, and how to interpret test results.
- Know the indications and limitations of molecular cytogenetic studies (eg, fluorescence in situ hybridization) in the diagnosis of aneuploidy and microdeletion.
- Know when to obtain karyotypes on the subject, parents, or other family members.
- Know the indications for and utility of comparative genomic hybridization studies.
- Know the indications, limitations, and techniques for newborn screening for genetic disorders.

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NEO QUIZ

1. An infant of 38 weeks' gestation is born to a mother on anticonvulsants throughout her pregnancy and is found to have a neural tube defect in addition to several other structural malformations. It is known that significant congenital anomalies are one of the major causes of neonatal mortality. Up to what percentage of all live births are affected by a major congenital abnormality?

   A. <1%.
   B. 3%.
   C. 6%.
   D. 9%.
   E. 12%.

2. A term infant is being examined in the newborn nursery and is noted to have low-set ears. This type of anomaly is defined as a small departure from the reference population, although it can be associated with major congenital anomalies. Low-set ears can most accurately be described as a:

   A. Deformation.
   B. Disruption.
   C. Malformation.
   D. Normal variation.
   E. Syndrome.

3. Several fetal abnormalities that can be detected on prenatal ultrasonography warrant further testing. All of the following fetal anomalies are usually detected in the second trimester EXCEPT for:

   A. Cystic hygroma.
   B. Hyperechoic bowel.
   C. Single umbilical artery.
   D. Thickened nuchal fold.
   E. Urinary tract dilation.

4. An infant is born at 34 weeks of gestation via cesarean delivery for decreased fetal movement and is admitted to the NICU for respiratory distress. On further examination, the infant is found to have a posterior fossa malformation, multicystic kidneys, clenched hands, and congenital talipes equinovarus. What is the most likely diagnosis of the infant described?

   A. Monosomy X.
   B. Triploidy.
   C. Trisomy 13.
   D. Trisomy 18.
   E. Trisomy 21.

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5. An infant is admitted to the NICU for multiple congenital anomalies, including hypertelorism, flattened nasal bridge, postaxial polydactyly, and cardiac murmur. Given this presentation, the team decides to pursue further genetic testing. Which of the following statements describes testing with whole exome sequencing?

   A. A test requiring live cells and cell culture.
   B. A test with a resolution of 4 to 5 million base pairs.
   C. A test with a resolution of up to 50 kilobase (kb) for deletions.
   D. A test with a resolution of up to 400 kb for duplications.
   E. A test with the resolution to detect point mutations.