Prenatal Diagnosis and Genetic Counseling

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R. Douglas Wilson

Birth defects are increasingly being identified prenatally, allowing the pediatric surgeon to become involved before presentation in the neonatal intensive care unit. Congenital malformations are the most frequent cause of mortality during the first year of life, accounting for approximately 20 % of all infant deaths in the USA. The overall risk of birth defects for any couple undertaking a pregnancy is estimated at 3–5 %, with 2–3 % of those infants having major structural abnormalities identified prenatally and requiring evaluation and treatment as a newborn (Table 2.1). More functional birth defects and developmental changes, not recognizable as structural anomalies, can make up the additional 2–3 % by the end of the first year of life. Minor birth defects are estimated at 8–10 % but generally are not associated with significant morbidity.

The principal causes of birth anomalies are (1) chromosome abnormalities, such as microdeletion and microduplication syndromes, (2) single-gene disorders, (3) multifactorial disorders involving both genetic and environmental factors, (4) teratogenic exposure, and (5) idiopathic.

The most common prenatal diagnosis procedure is ultrasound (US), which is recommended as a routine evaluation for all pregnancies in the 18–22 weeks' gestational age range. First trimester US is becoming more common for screening of pregnancies to identify early risks for aneuploidy and structural defects, but this is not as frequently utilized as the second trimester US. The classification of fetal and birth defects has developed over the years with the Royal College of Obstetricians and Gynaecologists in the United Kingdom looking at four specific subgroups: (1) lethal anomalies, (2) anomalies associated with possible survival and long-term morbidity, (3) anomalies that may be amenable to intrauterine therapy, and (4) anomalies associated with possible immediate or short-term morbidity.

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Genetic Inheritance Mechanisms and Other Etiologies

Autosomal recessive inheritance is common as all individuals are carriers for up to five recessive genetic conditions. For common recessive conditions, the survival advantage conferred by being heterozygous is usually much more important than incidence of new mutations for maintaining the diseased gene at high frequency, the most obvious example being sickle cell disease, in which carriers are less susceptible to malaria. Heterozygotes do not usually manifest a phenotype or, if they do, it is a mild form of the disease. Affected siblings often follow a similar clinical course—more similar in fact than for many autosomal dominant disorders. Once a diagnosis of a recessive disorder is made, the parents are considered obligate carriers, and the risk of another affected child is 25 %. The healthy siblings of the affected individuals have a two-thirds risk of recessive carrier status.

Autosomal dominant diseases require a single mutant allele to be manifested and are characterized by significant clinical variability. Factors influencing this variability include penetrance, expressivity, somatic mosaicism, germline mosaicism, reproductive ability of the affected individual, new mutation rate, paternal age effect (new mutations occur with age greater than 50), and anticipation (worsening of the disease severity in successive generations). Carriers of autosomal dominant conditions have a 50 % chance of passing the condition on to their offspring.

X-linked recessive disorders usually manifest in males who are hemizygous for the X chromosome but generally not in carrier females. The exception is the rare situation in which, rather than the usual 50–50 inactivation pattern, the inactivation of one X chromosome predominates, allowing an X-linked recessive condition to be clinically expressed. Mosaicism may also occur, as in Duchenne muscular dystrophy and androgen insensitivity syndrome. When a female X-linked recessive carrier has a pregnancy, there are four possible outcomes that occur in equal proportion: normal

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Table 2.1 Congenital anomalies: classification and frequency

Classification		Frequency (per 1000)	
		Isolated	Multiple
A	Major malformations (mortality; severe morbidity)	30	7
B	Deformations (mechanical; intrinsic or extrinsic)	14	6
C	Minor malformations (limited or mild morbidity)	140	5

Source: Data from Connor and Ferguson-Smith (1993), p. 193

daughter, carrier daughter, normal son, and affected son. When an affected male initiates a pregnancy, all of his daughters will be X-linked carriers and none of his sons will be affected.

X-linked dominant disorders affect males more severely and often lead to pregnancy loss or neonatal death. When a heterozygous affected female has an offspring, there are four equally likely possibilities: normal daughter, affected daughter, normal son, and severely affected son. When an affected male has a child, the daughters will inherit the mutation with some clinical features while none of the sons will be affected.

Multifactorial inheritance is the result of environmental interactions with genetic alleles at many loci and is the cause of a large number of common birth defects, such as cleft lip and palate, congenital dislocation of the hip, congenital heart disease, and neural tube defects. The risk of the specific defect is greatest among close relatives and decreases with increasing distance of relationship. The risk is also higher when the proband is severely affected and if two or more close relatives demonstrate the defect. When there are several affected close relatives, the possibility of an autosomal dominant disorder with incomplete penetrance should be considered.

Genomic imprinting is when one allele is inactivated in utero by an epigenetic mechanism such as histone modification or DNA methylation. The imprint is maintained throughout the life of the organism. Imprints previously established are removed during the early development of male and female germ cells and thus reset prior to germ cell maturation. About 50 genes are known to be imprinted, and these genes have important roles in growth and development as well as in tumor suppression. One additional aspect of imprinting is inheritance by uniparental disomy, in which one of the chromosome pairs has been inherited exclusively from one parent. If two identical homologues are inherited, this is called isodisomy; if nonidentical homologues are inherited, this is called heterodisomy.

A trisomic zygote is then formed at fertilization and trisomic rescue with loss of the "paired" chromosome from the other parent. If uniparental disomy occurs in an imprinted region of the chromosome, this could determine a specific disease. Some diseases that are a result of an imprinting effect are transient neonatal diabetes, Russell–Silver syndrome, Beckwith–Wiedemann syndrome, Prader–Willi syndrome, Angelman syndrome, and Albright hereditary osteodystrophy.

Chromosomal mosaicism is the presence of two or more cell populations derived from the same conceptus that are genetically disparate. Mosaicism can occur prenatally or postnatally, due to mitotic nondisjunction, trisomy rescue, or a new mutation. Prenatal chromosomal mosaicism is increasingly identified by invasive prenatal diagnostic studies and is found in 0.3 % of amniocentesis specimens and approximately 2 % of chorionic villi specimens. In chorionic villi, this is usually confined to the placenta with true fetal mosaicism occurring in less than 10 % of cases. The morbidity from mosaicism is difficult to predict and may require analysis of more than one cell source from the fetus, such as amniocytes or fetal blood.

When evaluating a child with an anomaly, it is important that the appropriate terms be used so that a clear understanding of the etiology will be conveyed (Table 2.1). The causes of birth defects include multifactorial inheritance in 25 %, familial disorders in 15 %, chromosomal defects in 10 %, teratogens in 3 %, single mutant genes in 3 %, uterine factors in 2.5 %, twinning in 0.4 %, and unknown in 40 %.

The four defined terms that should be used to describe birth anomalies are malformation, deformation, disruption, and dysplasia. The term *malformation* is used for intrinsic abnormalities caused by an abnormal completion of one or more of the embryonic processes. These anomalies are usually limited to a single anatomical region, involve an entire organ, or produce a syndrome affecting a number of different body systems. *Deformations* are secondary events that can be extrinsic or intrinsic to the fetus, such as mechanical forces that alter the shape or position of a normally formed body structure. Deformations usually occur during the fetal period. Intrinsic deformations are secondary to other malformations or neuromuscular disorders. *Disruption* is a structural defect of an organ, part of an organ, or larger region of the body that is caused by an interference with or an actual destruction of a previously normally developing organ or tissue. Disruptions result from mechanical forces as well as events such as ischemia, hemorrhage, or adhesion of denuded tissues. Disruption anomalies are commonly involved with teratogen exposure. *Dysplasia* occurs when structural changes are caused by abnormal cellular organization or function within a specific tissue type throughout the body. Except for hamartomatous tumor development (hemangioma, nevi), this is usually caused by a primary defect caused by a major mutation.

Additional terms used in describing birth defects include syndrome, sequence, and association. A *syndrome* is a particular set of developmental anomalies occurring together in a recognizable and consistent pattern and known or assumed to be the result of a single etiology. A *sequence* is a pattern of devel-

opmental anomalies consistent with a primary defect but often with a heterogeneous etiology (oligohydramnios sequence). An *association* is a nonrandom collection of developmental anomalies not known to represent a sequence or syndrome that are seen together more frequently than would be expected by chance, such as the VACTERL association.

When evaluating a fetus or child, parents will want to know several things about the anomaly: the etiology, the genetics, the prognosis, the risk of recurrence in subsequent pregnancies, and what further studies might be available to better answer these questions. The history is very important and includes the family history for at least three generations, pregnancy history and exposures, neonatal history, and, if the child is older, developmental milestones and current school level. The physical examination will allow classification of the birth anomalies into the descriptive terms of malformation (multiple or isolated), deformation, and disruption. The pattern of the birth defects, both major and minor, will assist in syndrome identification as well as considering the possibilities of a sequence or an association pattern. This type of evaluation will assist in the investigations and directed diagnostic testing required (Table 2.2).

Genetic Analysis and Techniques

The screening and diagnostic techniques to evaluate the genetic status of the fetus are changing rapidly (Tables 2.3 and 2.4). Appropriate pretest counseling and maternal informed consent are required. Prenatal/genetic assessment can be considered as:

1. Screening (ultrasound; noninvasive maternal plasma cell-free fetal DNA (cffDNA))
2. Diagnostic (detailed fetal ultrasound assessment (fetal echocardiography/Doppler), MRI, invasive needle-based fetal diagnostic techniques amniocentesis/chorionic villus sampling/cordocentesis)

National guidelines/recommendations for screening and diagnosis by ultrasound have been published in 2014 by National Institute od Child Health and Disease (NICHD), Society of Maternal Fetal Medicine (SMFM), American Institute of Ultrasound in Medicine (AIUM), American College od Obstetrics and Gynecology (ACOG), American College od Radiology (ACR), Socirty of Perinatal Research (SPT), Society of Radology (SR). The practices reviewed are fetal US (first trimester, second trimester, ultrasonographic aneuploidy or structural "soft markers" in the second trimester), US in specific subgroups and conditions (obese women, twin gestation, placenta previa, placenta accreta, amniotic fluid volume), safety of ultrasound in pregnancy, and fetal MRI.

Noninvasive prenatal screening (NIPS) using maternal plasma cell-free fetal DNA (cffDNA) is becoming the primary screen or used as a secondary screen tool (after traditional aneuploidy screening by ultrasound and maternal serum analyses but before invasive testing) for fetal aneuploidy screening/assessment for trisomy 13, 18, and 21. National Societies are summarizing the use of NIPS and the precautions:

1. NIPS is not a diagnostic test and requires confirmatory needle-based invasive testing.
2. The positive predictive value of NIPS is better in high-risk populations rather than general "all risk" populations.
3. Accuracy for twin pregnancies (dichorionic twins) requires further investigation.
4. Pretest counseling for screening and subsequent diagnosis is very important (Table 2.4).

The traditional tissues required for the invasive/definitive/diagnostic analysis have not changed (amniocytes, chorionic tissue, fetal lymphocytes), but the methods to analyze the cells have become more sophisticated and detailed (Table 2.4).

Diagnostic fetal chromosome analysis is commonly performed for prenatal diagnosis when there is increased genetic risk due to screening risk, ethnicity, birth defects, multiple malformations, familial disorders, risk of neonatal mental retardation, infertility, or a history of recurrent miscarriages (Table 2.3). Cytogenetic testing requires the cells that are replicating, including blood lymphocytes, bone marrow cells, skin fibroblasts, amniocytes, chorionic villus, or solid tumor cells.

Standard chromosome analysis using staining methods (G-banding, Q-banding, C-banding) is being replaced by molecular chromosomal analysis techniques. G-banding combines the use of trypsin to denature associated proteins and a green dye. This produces the characteristic dark and light bands as seen on a standard karyotype. Q-banding uses fluorescent microscopy, while C-banding is used to enhance the centromeric regions and areas containing heterochromatin. Standard chromosome analysis can identify fetuses with trisomy 21 (1 in 800), trisomy 18 (1 in 5000), and trisomy 13 (1 in 15,000), as well as sex chromosome abnormalities such as Klinefelter syndrome 46XXY (1 in 700 males), 47XYY syndrome (1 in 800 males), 47XXX syndrome (1 in 1000 females), and Turner's syndrome 45X or mosaics (1 in 1500 females).

While still in use for chromosomal deletion and duplication screening/diagnosis, fluorescence in situ hybridization (FISH) is a sensitive and relatively rapid method for direct visualization of specific nucleotide sequences. Single-stranded DNA is annealed with specific complementary probes tagged with fluorescent markers. One of the major advantages of FISH over the standard cytogenetic techniques is the ability to recognize subtle chromosomal changes such as deletions or duplications. FISH probes are used to recognize specific microdeletions that may be suspected due to the pattern of congenital anomalies. An example of this is the 22q deletion sequence (DiGeorge syndrome or velocardiofacial syndrome).

Table 2.2 Differential diagnosis of congenital anomalies based on results of screening studies

Neck
Cystic hygroma
Isolated (sporadic)
Trisomies 21 or 18
45X
Noonan's syndrome (AR)
Hemangioma
Isolated (sporadic)
Klippel–Trenaunay–Weber syndrome
Proteus syndrome (somatic mosaicism)
Teratoma
Isolated (sporadic)
Chest
CCAM
Isolated (sporadic)
Genetic mutations reported for growth control
CPL
AR associated with pleural effusions
CDH
Isolated (60 %)
Trisomy 18, 21; tetrasomy 12p
Chromosomal deletions (15q, 8p, 8q, 4p, 1q)
Cornelia de Lange syndrome (AD, XL); craniofrontonasal dysplasia (XL)
Donnai–Barrow syndrome (AR); Fryns syndrome (AR); Matthew–Wood syndrome (AR)
Multiple vertebral segmentation defects (AR)
Jarcho–Levin syndrome (AD); Simpson–Golabi–Behmel syndrome (XL)
WT1 mutations
TEF/EA
Trisomy 18, 21
del22q11; 17qdel
VATER/VACTERL (sporadic)
Goldenhar syndrome (sporadic)
CHARGE sequence (sporadic)
OEIS (sporadic)
Feingold syndrome (AD)
Opitz syndrome (XL, AD)
AEG syndrome (SOX2 mutation)
Martinez–Frias syndrome (AR)
CHARGE sequence (sporadic)
OEIS syndrome (sporadic)
Feingold syndrome (AD)
Opitz syndrome (XL, AD)
AEG syndrome (SOX2 mutation)
Martinez–Frias syndrome (AR)
Abdomen
Gastroschisis
Isolated (sporadic)
Omphalocele
Trisomy 13 or 18
Beckwith–Wiedemann syndrome
OEIS syndrome
Cloacal exstrophy
OEIS syndrome
Bowel obstruction
Miller–Dieker syndrome; duodenal atresia; deletion 17p
Short rib-polydactyly syndrome (Type I, III—AR)
Trisomy 21 or 22
Cystic fibrosis (AR)
Fryns syndrome (AR)
Feingold syndrome (AD)
Martinez–Frias syndrome
Ascites
Perlman syndrome (AR); Fraser syndrome (AR)
Trisomy 21; 45X; alpha-thalassemia (AR)
OEIS syndrome
CHAOS syndrome
Cystic fibrosis (AR)
Infection (CMV, parvovirus, toxoplasmosis, syphilis)
Hyperechogenic bowel
Intra-amniotic bleeding
IUGR
Trisomy 21
Cystic fibrosis (AR)
Alpha-thalassemia (AR)
Infections (rubella, CMV, varicella)
Absent stomach
CDH
Trisomy 9 or 18
Tetrasomy 12p
Deletion 4p (Wolf–Hirschhorn syndrome)
VATER/VACTERL sequence
Tracheoesophageal fistula
Distended bladder
Cloacal exstrophy sequence
Megacystis-microcolon-intestinal hypoperistalsis syndrome (AR)
PLUTO (posterior urethra valves, urethral hypoplasia/atresia)
Bladder hypotonia

AR autosomal recessive, *AD* autosomal dominant, *XL* X-linked

Another advantage of FISH is that it can be applied to interphase nuclei of nondividing cells, thereby minimizing the need for cell culture. A disadvantage of FISH is that certain structural chromosome abnormalities cannot be detected with this technique.

In addition to FISH, other molecular genetic methods are used for rapid aneuploidy detection and include quantitative fluorescence polymerase chain reaction (QF-PCR) and multiplex ligation-dependent probe amplification (MLPA), which is replacing standard cytogenetics due to their sensitivity, specificity, and cost saving compared to the full karyotype if aneuploidy (large chromosome defect) testing is the primary reason for the prenatal diagnosis.

Table 2.3 Informed consent (benefit/risk) for ultrasound-guided invasive acquisition of fetal tissue for genetic and other fetal laboratory investigations

Benefit: diagnosis, possible treatment, prognosis		
Risk: spontaneous loss with no procedure; loss (added or total) for invasive acquisition technique		
1. Spontaneous fetal death (FD)/loss rate after 10 gestational weeks		
Evidence-based etiology/cause		
(a) Fetal	25–40 %	(Chromosomal; birth defect NTD/CNS, cardiac, immune/nonimmune hydrops, infection)
(b) Placental	25–35 %	(Abruption, PROM, implantation/growth issues, chorioamnionitis)
(c) Maternal	5–10 %	(Diabetes, hypertension, obesity, thyroid, renal, APA, thrombophilia)
(d) Unexplained	15–35 %	
2. Amniocentesis	Estimated total singleton procedure loss risk is 0.5–1.0 % (range 0.17–1.5 %)	
Risk of miscarriage above the estimated background rate or as the loss rate (total or at a specific GA beyond procedural related affect)		
(Related to maternal age, gestational age at procedure, indication for procedure, provider experience)		
3. CVS (TC/TA)	Estimated added postprocedure loss rate of 0.5–1.0 %	
Risk of miscarriage above the estimated background rate or as the loss rate (total or at a specific GA beyond procedural related affects)	(Total spontaneous and procedure loss rate of 1.9–2.0 %)	
(Related to maternal age, gestational age at procedure, indication for procedure, provider experience)	Total fetal loss rate for TA CVS = second trimester amniocentesis rate RR 0.9 (0.66–1.23)	
	TA 1–2 %	
	TC 2–6 %	
	(TC increased fetal loss OR 1.40 (1.09–1.81)	
4. Cordocentesis	18–24 weeks increased risk	
Total risk of miscarriage	No anomalies 1 %	
	Anomalies 7 %	
	IUGR 14 %	
	Hydrops 25 %	

Source: Reprinted with permission from Wilson RD. Fetal Hydrops: An Evidenced Based Triage, Diagnosis, and Treatment Approach. In: *High-Risk Pregnancy*: *Management Options*, *5th Edition*, ed. David James et al. Cambridge: Cambridge University Press. Forthcoming 2016

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Table 2.4 Checklist for depth of genetic analysis/information available based on techniques, infectious, and body cavity fluid analysis *Source*: Reprinted from Wilson RD et al. Prenatal Diagnosis Procedures and Techniques to Obtain a Diagnostic Fetal Specimen or Tissue: Maternal and Fetal Risks and Benefits J Obstet Gynaecol Can 2015;37(7):656–668, by permission of the Society of Obstetricians and Gynaecologists

Indication for Invasive Prenatal Testing

- ❑ *Past obstetrical history (fetal chromosomal anomaly / genetic syndrome) specify:* _____
- ❑ *Positive family history (translocation carrier; genetic carrier AR/AD/XL) specify:* _____
- ❑ *+ aneuploidy screening test (first +NT/second trimester; maternal age>35) specify:* _____
- ❑ ***Fetal anomalies identified by ultrasound imaging specify: NIFH***

_____

Depth / Complexity of Fetal Testing: Patient informed consent counselling

Genetic Complexity Level I-V

- ❑ *I. Fetal karyotype only*: for the number of chromosomes / chromosome pairs and large chromosome re-arrangements / large deletion / duplication detection

- ❑ *II. Fetal karyotype plus selected molecular deletion / duplication testing*
  Specify molecular del /dup test:
  Deletion interstitial p or q chromosome arm location
  Deletion terminal or subtelomeric location
  Duplication interstitial direct 'abab' or inverted 'abba'
  Duplication terminal or subtelomeric location

- ❑ *III. Fetal karyotype plus array CGH (comparative genomic hybridization)*
  CGH analysis with fetal anomalies identifies 6% more genetic pathology not seen by karyotype alone (additional findings vary based on anomalies)

- ❑ *IV. Fetal karyotype plus whole genome sequencing* (genome and exome sequencing)
  Recurrence of anomalies; Limited use to date for prenatal assessment but increasing neonatal use

- ❑ *V. Fetal sexing only (molecular / ultrasound)* FISH or QF-PCR for sexing

- ❑ *Other amniotic fluid testing*
  Genetic DNA storage (future); FISH or QF-PCR trisomy only
  Infection culture; PCR (CMV, ParvoB12, toxoplasmosis) RPR syyphilis
  Fetal lung maturity (dependent on GA)
  fetal blood testing CBC , platelets, TORCH, liver, Hb electro
  cavity aspiration lymphocyte count, albumin, culture

The whole genome can be evaluated for copy number variation (CNV), indicating that there is too much or too little of a portion of a chromosome. This is known as array-based comparative genomic hybridization (array CGH) and is able to detect small changes in the amount of chromosomal material in the fetus but with the advantage of significant less analysis time than a standard karyotype. Studies that compare chromosomal microarray with standard karyotyping for prenatal diagnosis suggest that the microarray technology identifies an additional 6 % of clinically relevant deletions and duplications in fetuses with structural abnormalities and a standard normal karyotype. The microarray does not typically identify fetal-balanced translocations or triploidy. In prenatal diagnostic cases where fetal anomalies (isolated or multiple) are identified, the prenatal diagnostic standard of care is moving to the diagnostic molecular technology.

The limitations of array CGH are that it cannot detect chromosomal defects in which the total amount of chromosome material is unchanged. Therefore, it cannot be used to identify balanced rearrangements such as reciprocal translocations, Robertsonian translocations, or inversions.

Other molecular technology such as whole genome/exome sequencing is required for certain genetic diagnostic circumstances as array CGH cannot detect point mutations or small changes in the genes as it is designed to detect syndromes caused by duplications or deletions of large amounts of chromosome material.

Chromosomal mosaicism may or may not be more identifiable depending on the level of the mosaicism. The level of the mosaicism needs to be higher than 15–30 % of the cells. The array CGH analysis will also identify "normal variants" that are not associated with pathological changes. For this reason, when prenatal or neonatal array CGH testing is undertaken, parental bloods are used to compare for the presence of these "normal" variants. Other pediatric surgery issues are important to identify and include the appropriate evaluation of prenatally diagnosed structural congenital anomalies and the need for informed consent and recommendation for fetal and perinatal autopsy in prenatally diagnosed fetal abnormalities with normal karyotype.

A good understanding of prenatal diagnosis techniques, genetic counseling issues, and birth defect terminology and etiologies will assist pediatric surgical specialists in their daily role of caring for fetuses, newborns, and children with birth defects.

Editor's Comment

Prenatal testing continues to evolve as newer and less invasive technologies are developed. Many women in the USA undergo a quadruple screen (or "quad" screen, which has replaced the triple screen) in the second trimester, a test that measures serum levels of alpha-feto=protein (AFP), unconjugated estriol, human chorionic gonadotropin (hCG), and inhibin. It is more than 80 % sensitive for neural tube defects and certain chromosomal abnormalities (trisomies 18 and 21), but has a 5 % incidence of false-positive results. A positive screen is usually followed by more detailed imaging or, in some cases, amniocentesis or chorionic villus sampling (CVS). Imaging modalities, including 3-D ultrasound and fetal MRI, have also continued to improve significantly, allowing the prenatal characterization of complex structural anomalies such as heart defects and gastrointestinal abnormalities. There are now a number of fetal diagnostic and therapeutic specialty centers where the care of the high-risk pregnant woman and fetuses with congenital anomalies can be coordinated and planned, sometimes allowing in utero intervention.

What defines a pregnancy as high risk for birth defects is somewhat variable, but usually includes women who are over 35 years of age, women who have a history of miscarriages or premature births or have given birth to a child with cardiac defects or genetic abnormalities, parents with an ethnic background associated with a high risk of certain genetic syndromes, multiple fetuses, and women with certain medical conditions (diabetes, systemic lupus erythematosus, seizure disorder). Regardless of the calculated risk of a birth defect, national groups like the American College of Obstetricians and Gynecology often recommend that all pregnant women be made aware of the prenatal screening tests that are available to them.

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