

LONG QT SYNDROME

Definition

Inherited long QT syndrome (LQTS) is characterized by a prolonged QT interval, syncope, and sudden cardiac death due to ventricular tachyarrhythmias, typically torsades de pointes.¹ A prolonged QTc, defined as a QTc value >450 ms in males and >460 ms in females measured preferably in lead II or V5 on a standard 12-lead ECG, predisposes to functional reentry, torsades de pointes, and sudden cardiac death (SCD).² Acquired LQTS is mainly drug-related.

Epidemiology

LQTS has variable penetrance and the estimated prevalence is 1:2000 apparently healthy births, whereas the probability of diagnosis according to the HRS/EHRA/APHRS criteria in children aged 12 years is 1:1000.³ Symptomatic patients without therapy have a high mortality rate, approximately 20% within 1 year from the first syncope.¹ There are longer QT intervals in healthy women compared to men, and among LQTS variant carriers, the clinical penetrance of disease is higher in women than in men.⁴

Genetics and Pathophysiology

The genetic basis of the LQTS is mutations or polymorphisms in genes encoding proteins that form ion channels affecting repolarization (Table 1). Nearly 1000 mutations have been identified in 17 distinct LQTS-susceptibility genes. However, in a study by the International, Multicenter LQTS ClinGen Working Group, only 3 genes (*KCNQ1*, *KCNH2*, *SCN5A*) were definitive genes for typical LQTS. Another 4 genes (*CALM1*, *CALM2*, *CALM3*, *TRDN*) had strong or definitive evidence for causality in LQTS with atypical features, including neonatal atrioventricular block, and the remaining gene (*CACNA1C*) had moderate level evidence for causing LQTS.⁵ It should be noted that a causal rare genetic variant with large effect size is identified in up to 80% of probands (genotype positive) and cascade family screening shows incomplete penetrance of genetic variants.⁶ Furthermore, in an analysis in the UK Biobank and TOPMed cohort, individuals in the population with QTc prolongation were more likely to have a common polygenic risk equivalent (21%) than a rare monogenic variant (3.4%) in an established QTc prolonging gene.⁷

Most of LQTS are due to loss-of-function mutations in the genes *KCNQ1*, and *KCNH2* encoding for voltage-gated potassium channels that affect the repolarizing currents I_{Ks} (LQT1, 30-35% of all LQTS) and I_{Kr} (LQT2, 25-40% of all LQTS), respectively.^{1, 8}

Mutations, usually in *KCNH2* are also found in one third of patients with drug- or hypokalaemia- or bradycardia-induced LQTS.⁹

LQT1 is the most common type of LQTS, and is due to heterozygous gene mutations of *KCNQ1* (encoding the alpha subunit of the I_{Ks} channel). I_{Ks} reduction increases transmural dispersion of repolarization and sensitivity to catecholamine stimulation. Mutations of *KCNQ1* reduce I_{Ks} but I_{Kr} (ie, the rapid component of the delayed rectifier K^+ current) could maintain a near-normal duration of action potentials, concealing LQT1. In this case, I_{Kr} blockade (eg, by drugs) or inactivation (eg, by hypokalaemia) can induce substantial QT prolongation, and trigger torsades de pointes.

LQT2 is the second most common genotype of LQTS, and is associated with reduced I_{Kr} by gene mutations (*KCNH2*) that encode the α -subunit (HERG) of the I_{Kr} channel. Reduced I_{Kr} slows repolarization, and increases the transmural dispersion of repolarization. I_{Kr} is unaffected by catecholamine stimulation.¹⁰ Emotional stress and sudden loud noises can cause a rapid increase in heart rate from sympathetic discharge, which acutely prolongs the action potential before subsequent shortening by a slowed enhancement of I_{Ks} . Bradycardia reduces I_{Kr} , delays repolarization, and increases transmural dispersion.

Up to 10 % of LQTS (**LQT3**) are due to gain-of-function mutations of the gene *SCN5A* (mostly missense, ie, single amino acid substitutions) encoding for the sodium channel, I_{Na} . In patients with such mutations, the channel fails to close properly after initial depolarization and continued leakage of sodium into the channel results in prolongation of the action potential, long ST segments and late appearance of T wave in the ECG, which are the characteristics of the LQT3 syndrome. These patients may have bradycardia, and the first cardiac event is more likely to be lethal and seems to occur later in childhood.¹¹ LQT3 results in cardiac events leading to sudden death occur usually at night or rest without arousal and occasionally follow sympathetic stimulation. Typical ECG in LQT3 shows a flat, long ST segment with late appearance of a narrow-peaked T wave.

The classic LQTS is being transmitted as an autosomal dominant trait (initially described by **Romano** and by **Ward**). A less common but more severe form is transmitted as an autosomal recessive disease (patients carry two abnormal LQT genes), and is associated with neurosensory deafness and higher risk of sudden death (**Jervell and Lange-Nielsen syndrome type 1**).¹² Jervell and Lange-Nielsen syndrome occurs in 1-7% of patients with LQTS and is an autosomal recessive condition due to loss of function *KCNQ1* variants. Diagnosis is considered on the basis of the established diagnostic criteria for LQTS and on the presence of congenital neurosensory deafness. A milder form (JLN type 2), due to loss of function *KCNE1* variant has also been described.¹³ **Andersen-Tawil Syndrome type 1** is caused by loss-of-function mutations in the *KCNJ2* gene and associated with facial

dysmorphism and a high risk of life-threatening ventricular arrhythmias. Patients can have a normal QT interval but marked Q-U prolongation with biphasic and/or enlarged U waves. Amiodarone is proarrhythmic and should be avoided in these patients.¹⁴ An **autoimmune-associated** form of LQTS has also been recently described. Anti-Ro Abs from patients with autoimmune diseases inhibit I_{Kr} by cross-reacting with the HERG channel.¹⁵ **Bradycardia-induced, post-tachycardia** and **post-infarction** forms as well as **drug-** and **hypokalemia-induced** long QT syndrome, have also been described.¹⁶

Polygenic risk score analyses based on common genetic variants that modulate the QT interval in the general population provide evidence for a polygenic architecture in LQTS patients that remain genetically elusive despite genetic testing of established genes (i.e. genotype negative). Polygenicity in genotype negative LQTS patients implies that risk is not primarily attributable to one genetic factor inherited from one of the biological parents as is the case for autosomal dominant LQTS.⁶

The QT interval on the ECG represents the longest repolarization in the mid-myocardial M-cell region, ie a physiological transmural dispersion of repolarization. Gene mutations or medications that cause selective action potential prolongation in the M-cell region can lead to increased transmural repolarization gradients, and thus create the conditions for functional reentry and subsequent torsades. A net decrease in repolarizing currents prolongs actions potentials in LQTS, and subsequently promotes the L-type Ca^{2+} current ($I_{Ca,L}$) and phase-2 early afterdepolarisations.¹⁰ Prolonged action potentials cause Ca^{2+} overload, leading to the activation of the inward Na^+-Ca^{2+} exchanger current that causes phase-3 early afterdepolarizations. Early afterdepolarizations (phase 2 and phase 3) and dispersion of repolarization contribute to torsades de pointes.¹² The trigger for TdP is thought to be a PVC that results from an early afterdepolarization generated during the abnormally prolonged repolarization phase of the affected myocardium. A long preceding pause increases the amplitude of early afterdepolarizations, which makes them more likely to reach the threshold necessary to produce a PVC or ventricular couplet (short-long-short RR intervals sequences mode of TdP onset). Torsades de pointes therefore is triggered by early afterdepolarizations and can be maintained by repetitive, multifocal early afterdepolarizations, as well as re-entry around shifting pathways.¹⁷ Pause-dependent torsades de pointes is seen in LQT2 and perhaps LQT3, but not in LQT1, in which sympathetic activation is the usual trigger.¹⁸ Sympathetic activity is an important modulator of the disorder and can further delay repolarization, induce early afterdepolarizations, and trigger sudden arrhythmic death in patients with LQTS, especially LQT1.

LQTS is not considered a pure electrical disease. Patients with LQTS, despite a normal LVEF, have significantly longer contraction duration and greater indices of regional and transmural inhomogeneous contraction times as assessed by strain echocardiography.¹⁹

LQTS is also associated with an increased risk of AF.²⁰ In the general population, an increased risk of cardiovascular disease has been observed for both very short and long QT interval.²¹ In the MESA trial, prolongation of the corrected QT interval was associated with an elevated risk of arrhythmic and sudden death, as well as incident stroke, heart failure, and ischemic cardiovascular events in patients with and without ischemic heart disease.^{22, 23} QTc prolongation is also associated with an increased risk of stroke independent of traditional risk factors and this also true for drug-induced prolongation.²⁴

Presentation

Patients may be entirely asymptomatic. The term “torsades de pointes” was introduced by Dessertenne in 1866 when he described polymorphic ventricular tachycardia occurring in the setting of bradycardia due to complete heart block. Symptoms caused by this tachyarrhythmia range from dizziness and syncope to cardiac arrest and death in up to 16% of patients.

Because torsades de pointes can cause seizures due to cerebral anoxia, LQTS is important to consider in patients with apparent drug-resistant seizure disorders. Bidirectional ventricular tachycardia suggests Andersen-Tawil syndrome. Both exercise (especially swimming), and emotional stress (sudden loud noise, anger) can trigger syncope in patients with LQTS, possibly via an increase in catecholamine concentrations. There is an increased arrhythmia susceptibility in the 9-month period of postpartum, especially in patients with LQT2, whereas pregnancy-related hormones are protective, probably due to estradiol—mediated enhancement of KCNH2 membrane trafficking.²⁵ β blockers reduce the occurrence of cardiac events post-partum. LQT2 patients display increased incretins and insulin secretion and defective glucagon secretion, causing decreased plasma glucose and thus increased risk of hypoglycemia.²⁶ Triggers for events are:

- LQT1: exercise (especially swimming), emotional stress
- LQT2: Emotional stress, sudden noise
- LQT3: Rest, sleep
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Diagnosis

The QT interval must be measured accurately, excluding the U wave.²⁷ The modified diagnostic criteria for the LQTS score are provided in (Table 2). Diagnosis is mainly based on this score (Table 3). Inherited LQTS is considered when electrolyte- or drug-induced QT prolongation has been excluded. The most important diagnostic and prognostic characteristic is QT-interval prolongation, although it might not accurately reflect prognosis in LQT3 (Figure 1). The QT interval should be determined as a mean value derived from at least 3 to 5 heart beats, and is measured from the beginning of the earliest onset of the QRS complex to

the end of the T-wave in leads II and V5 or V6, with the longest value being used. Manual measurement using either the tangent or threshold method are acceptable (Figure 2). In addition, a freely accessible online probability calculator for LQTS (www.QTcalculator.org) has been made available as an aid in the interpretation of the QT interval.²⁸ In AF the average of the QTc values of the shortest and longest R-R intervals is used. If the interval from R wave to the peak (or nadir) of the T wave is more than 50% of the R-R interval, there is an indication that it would be longer than the critical threshold of 500 ms, if measured. The QT interval is usually corrected for heart rate, because the QT interval shortens at fast heart rates, and prolongs at slow heart rates using the Bazett formula ($QTc = QT/\sqrt{RR}$, with all intervals in seconds) which remains the standard for clinical use despite some limitations at particularly fast or slow heart rates in which the formula may over-correct or under-correct, respectively. Another method is the Framingham linear regression formula. Diagnostic criteria for LQTS carry a high specificity but low sensitivity.^{1, 29} Artificial intelligence-enabled mobile ECG devices may accurately detect QTc prolongation when obtaining a traditional 12-lead ECG is not feasible.³⁰

Normal QTc values are <440 for age 1-15 yrs, <430 for adult males, and <450 ms for adult females.¹²

A **QTc value of ≥ 430 ms** distinguishes carriers from non-carriers (<430 ms), with a 72% sensitivity and 86% specificity.³¹

Increased **QT dispersion** (>100 msec), measured as the difference between the minimum and maximum QT intervals in the 12-lead ECG, indicates ventricular repolarization heterogeneity, is increased in symptomatic patients and reduced by beta blockers.

Prominent **U waves** and T-U complexes are frequently seen.

T-wave alternans, ie a beat-to-beat alternation in T-wave morphology, is a marker of high cardiac electrical instability.

Notches on the T-wave are rather typical for LQT2 and are associated with a higher proarrhythmia risk.¹

Sinus bradycardia may be present, and **sinus pauses** are mainly seen in LQT3. Long sinus pauses favor early afterdepolarizations.

Response to exercise or catecholamine injection In healthy individuals, acute sympathetic stimulation increases inward Ca^{2+} currents, shortens the RR interval, and initially prolongs and then shortens the QT interval by activating the delayed rectifier K^+ current (slow component, I_{Ks}).

LQT1: Prolongation of both QT and QTc interval during and after cessation of exercise or catecholamine injection (paradoxical QT response).

LQT2: Initial prolongation followed by shortening of the QT and QTc, and promotion of the notch on the descending T wave.

LQT3: Shortening of the QT interval. The QTc is slightly prolonged at the peak effect of exercise and returns to baseline at steady state.

The presence and genotype of LQTS can be established by **exercise testing** that may reveal features such as inadequate QT shortening, postural T-wave change, and exercise-related T-wave notching.^{32, 33} The post-recovery QTc may also be helpful. LQT1 patients begin the recovery period at a very prolonged QTc that decreases during recovery, whereas the LQT2 patients begin recovery at a lower QTc that increases during recovery. At the end of recovery, a QTc cut-off value of 445 ms indicates LQTS, while a start-of-recovery QTc > 460 ms suggests LQT1, and <460 ms LQT2.³⁴ Symptomatic LQT1 patients have a greater heart rate reduction ($\geq 17\%$) at the first minute of recovery phase from the peak heart rate during exercise when compared with asymptomatic LQT1 patients, regardless of the use of beta blockers. This does not occur in LQT2 and LQT3 patients. Thus, heart rate reduction immediately after exercise, a marker of vagal reflex response, can be used for risk stratification in LQT1.³⁵

Isolated long QT <500 ms in **athletes** may resolve with deconditioning.²⁷ A newly described form exercise-induced QT prolongation in athletes has been described. They are genotype-negative, and 40% of them normalize their ECG after detraining. Probably, they should be managed as if they had drug-induced LQTS, ie allow them to practice their sport, but at an intensity that does not trigger reappearance of repolarization abnormalities, and avoid taking I_{Kr} blocking drugs if possible.³⁶

Other provocative tests are absence of QT shortening (but prominent QTc increase) with tachycardia induced by standing,³⁷ and QT prolongation (15%) by adenosine boluses of 6-24 mg.³⁸ Data from the CASPER Registry have shown that epinephrine challenge at doses of 0.05, 0.10, and 0.20 $\mu\text{g/kg}$ per minute may also disclose LQTS in unexplained cardiac arrest. A test is considered positive for long-QT syndrome if the absolute QT interval prolonged by ≥ 30 ms at 0.10 $\mu\text{g/kg}$ per minute and borderline if QT prolongation is 1 to 29 ms.³⁹

LQTS may be responsible for >10% of unexplained fetal death, and QTc ≥ 490 ms assessed by fetal magnetocardiography identifies LQTS in utero.⁴⁰

Risk stratification

1. A history of **aborted cardiac arrest** and/or ECG-documented episodes of **torsades de pointes**, particularly with β -blocker treatment indicates high risk.⁴¹ Children and adolescents who present after an episode of syncope that has occurred after the first year of life should be considered to be at a high risk of the development of subsequent syncope episodes and fatal/near-fatal events, regardless of QTc duration.⁴²

2. In **genotype-confirmed** patients, the cumulative probability of aborted cardiac arrest or sudden death at age of 40 years is 4% for those with a normal QTc intervals, and 15% for those with prolonged QTc, as compared to 0.4% for unaffected family members.⁴³ There is a gradual increase in risk for TdP as the QTc increases. High-risk patients usually have QTc intervals of at least 500 ms, and can also show T-wave alternans. In a series of 1710 carriers of a single mutation in one of the major LQTS genes (*KCNQ1*, *KCNH2*, or *SCN5A*), the risk of life-threatening arrhythmias increased by 15% for each 10-ms increment in QTc duration, and arrhythmic risk for those with the LQT2 and LQT3 genotypes was 130% and 157% greater, respectively, than for those with LQT1.⁴⁴

3. Patients with **LQT3, QTc ≥ 500 ms and a history of syncope** are at high-risk.¹¹ A risk stratification scheme has also been proposed for LQTS 2: Females >13 years or males with mutations in the pore-loop region of *KCNH2*, and QTc ≥ 500 ms indicate intermediate risk, while the presence of syncope in this category indicates high risk.⁴⁵ Asymptomatic patients at first evaluation (in a series of patients aged 31 ± 16 years), have an extremely low chance of having an LQTS-triggered cardiac event (<1%).⁴⁶

4. The presence of **missense mutations** in distinct functional domains of the *KCNQ1* protein, the S2-S3 and S4-S5 cytoplasmic loops (C loops), is associated with a significantly increased risk for life-threatening cardiac events compared with other mutations, and these patients gain greater benefit when treated with β-blockers compared with patients having other *KCNQ1* mutations independently of clinical risk factors.⁴⁷ Mutations in these regions are responsible for the condition in 7–15% of patients with LQT1. LQT2 as well as multiple mutations occur in 5% of LQTS patients, and are associated with increased risk.^{41, 48} **LQT1** carriers of a mutation located in the S6 segment are also regarded as at higher risk.⁴⁹

5. The assessment of regional heterogeneity of LV contraction by the '**electromechanical window**' (EMW: duration of LV-mechanical systole on echocardiography as assessed by the duration of Q-onset to aortic-valve closure minus QT interval) is also useful. EMW negativity is most pronounced in patients with documented arrhythmic events.^{50, 51}

6. A family history of premature SCD is not an independent risk factor for subsequent lethal events in an affected individual.

7. Identification of LQT2 or LQT3 genotypes does not by itself constitute an indication of ICD implantation.^{48, 52}

8. Two well-defined malignant variants are the **Jervell and Lange Nielsen syndrome** and **LQT8** due to mutations in *CACNA1C*. In Jervell and Lange Nielsen syndrome the first cardiac event often occurs in the first year of life, and 90% of patients have syncope during their early lifetime, usually induced by exercise and emotional stress. Subgroups at relatively lower risk for sudden death are females, patients with a QTc < 550 ms, those without events in the first year of life, and those with mutations on *KCNE1*.¹²

Genetic Testing

Apart from risk stratification purposes, genetic testing is useful for the identification of concealed LQTS, because individuals with genetically proven LQTS may have a nondiagnostic QTc (Table 4 and Figure 3).⁵³ Incorporation of polygenic risk assessment may aid in increasing the yield of genetic testing for QTc prolongation.⁷ However, no treatment decision should be influenced solely by either the genotype or the specific LQTS-causative mutation that was identified. In cases where only the proband in the family has a clear phenotype, even in cases where a positive genotype is identified in the LQTS genes, there is the possibility that the given genetic variant might not necessarily be related to clinical LQTS.^{54, 55} In particular, a decision to implant an ICD prophylactically in an asymptomatic LQT3 host must include risk factors besides LQT3 genotype status.⁵³ Genetic testing may also be considered for patients with drug-induced torsade, and a 12-lead ECG is recommended for first-degree relatives.

Therapy

With the implementation of appropriate therapy, the annual cardiac event rate has been reduced to 3.7% in symptomatic, and 0.3% in asymptomatic patients.⁴⁸ However, an observation-only strategy may be considered in LQTS patients with a clinical profile including asymptomatic status, older age at diagnosis (>38 years), and QTc < 470 ms.⁵⁶ **Beta blockers** should be administered to all intermediate- or high-risk affected individuals and considered in low-risk patients unless there is a contraindication. β -adrenergic blockade may not shorten QTc at rest but suppresses cardiac events in LQT1 and LQT2, although the efficacy of β blockade is reduced in LQT2 possibly due to the resultant bradycardia. **Nadolol** (1-1.5 mg/kg/day) is the preferred beta blocker.^{44, 57} When nadolol is not available, **propranolol** is theoretically more efficacious than selective β_1 selective blockers. Interestingly, in a recent registry propranolol was found the least effective beta blocker in patients who already had experienced a cardiac event, whereas nadolol was found the only effective beta blocker in LQT2.⁵⁸ In asthmatic patients, **bisoprolol** or **metoprolol** may be used.²⁷ Targeting of the pathologic, LQT3-associated late sodium current with propranolol with or without **mexiletine** (that blocks the recently reported late sodium current I_{NaL}) represents the preferred pharmacotherapeutic option for LQT3.^{11, 59} Mexiletine may be useful to treat both LQTS 2 and LQTS3 and drug-induced torsades de pointes.^{60, 61} Although **flecainide** prolongs the QT interval, it may be useful in the Andersen-Tawil syndrome which is usually due to mutations in KCNJ2 (LQTS7),⁶² or in patients with LQTS3 and the D1790G SCN5A mutation.⁶³ Potassium supplements shorten QT interval by increasing the I_{Kr} that is inversely regulated by the concentration of extracellular potassium. This approach has been

proposed for LQT2, although it has the potential to shorten QT interval in all patients with at least 1 KCNH2 wild-type (functional) allele.⁶⁴ The problem is that in the presence of normal renal function, the additional dietary potassium load typically may be excreted without clinically significant increases in serum potassium levels. In the Jervell and Lange Nielsen syndrome, beta blockers have limited efficacy and early ICD implantation must be considered.

Implantable cardioverter defibrillators are indicated in cardiac arrest survivors and patients with recurrent syncope despite β -blocker treatment, and for primary prevention in high-risk patients usually in combination with β blockers (Table 5, and Figures 4 and 5). In the past, ICDs had been implanted in some LQTS patients whose high risk now appears questionable.^{52, 65} ICD implantation for primary prevention without a β -blocker trial is rarely indicated, and evaluation of clinical indications of previously implanted devices should be thoroughly reconsidered.²⁷ Recommendations for management of patients with Andersen–Tawil syndrome, in particular, are presented in Table 6.

Left cardiac sympathetic denervation is considered in patients with recurrent syncope despite beta-blocker therapy and in patients who experience arrhythmia storms with an ICD, but does not offer full protection. Dryness on left side, unilateral facial flush, contralateral hyperhidrosis, and differential hand temperatures are common side-effects.⁶⁶

Permanent pacing may be needed for documented pause-dependent VT.

RF ablation of the torsade-triggering PVC has also been reported.⁶⁷

Gene-specific treatments are under study. A suppression-and-replacement *KCNQ1* gene therapy approach has successfully corrected type 1 long QT syndrome in human in vitro cardiac models.⁶⁸ Human induced pluripotent stem cell-derived cardiomyocytes obtained from LQT2 patients, have been used to validate a targeted pharmacological approach. KCNQ1 antibodies activate IKs channels, and suppress arrhythmias in an in vitro cellular model of long QT syndrome.⁶⁹ It has also been demonstrated that lumacaftor and ivacaftor, drugs in clinical use for cystic fibrosis, have mutation-specific anti-arrhythmic effects.^{70, 71}

All LQTS patients should avoid **drugs that block the I_{Kr} current** (www.torsades.org) (see also Chapter on VT).

Restriction of physical activities depends on the type of LQTS (Table 7). Asymptomatic patients with short baseline QTc intervals should not be significantly restricted.⁸ QTc >470 ms in male subjects, or QTc >480 ms in female subjects is an indication for low-intensity only competitive sports (36th Bethesda Conference), while the ESC recommends recreational only sports in QTc >440 ms in male subjects, and QTc >460 ms in female subjects.⁷² Low-risk patients, with genetically confirmed LQTS (especially not LQTS1) but with borderline QTc prolongation, no history of cardiac symptoms, and no family history of multiple sudden cardiac deaths (SCD), may be allowed to participate in competitive sports in special cases

after full clinical evaluation, utilization of appropriate LQTS therapy and when competitive activity is performed where automated external defibrillators are available and personnel trained in basic life support.⁷³ These precautions should be considered in the context of more recent data that indicate a reduced risk in appropriately treated patients. The risk of cardiac events among patients with LQTS or other inherited arrhythmogenic channelopathies need not preclude participation in sports after thorough evaluation, risk stratification, and tailoring of therapy.⁷⁴ In the LIVE-LQTS Study, among individuals diagnosed with phenotypic or genotypic LQTS who were risk assessed and treated in experienced centers, LQTS-associated cardiac event rates were low and similar between those exercising vigorously and those not exercising vigorously.⁷⁵

Avoidance of all QT-prolonging medications is advisable to all LQTS patients.

Pregnancy

The postpartum period in long QT syndrome (especially type 2) poses the greatest risk of arrhythmias.⁷⁶ Nadolol, metoprolol and propranolol are recommended in this setting.⁷⁷ No data exist on the effect of mexiletine on the fetus. Maternal blood for circulating fetal cells can be tested to determine the gene status of the fetus, but this is typically deferred to the postpartum period. An umbilical cord blood sample could be stored to obtain the genotype of the child.²⁷ General recommendations are presented in Figure 6 and Table 8.

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