Appendix G: Syndromes Terms and Definitions

Alagille Syndrome (intrahepatic biliary duct agenesis)
Alagille-Watson syndrome, is an autosomal dominant condition [mapped to 20p12 & 1p13-p11] of intrahepatic biliary duct agenesis or arteriohepatic dysplasia. Incidence is 1:70,000 births. The 20-year predicted life expectancy is 75% for all patients, 80% for those not requiring a liver transplant, and 60% for those requiring a liver transplant. Typical manifestations include intrahepatic cholestasis, distinctive facies, anterior chamber abnormalities of the eye, and butterfly hemiverterbrae. The most common cardiovascular abnormality is peripheral pulmonary artery stenosis. Additional defects include ASD, VSD, coarctation of the aorta and TOF.

Apert Syndrome
Also known as Apert-Crouzon disease or Vogt cephalodactyly, is an autosomal dominant condition [mapped to 10q26] of acrocephalosyndactyly. Incidence is 1:65,000-88,000 births; it occurs in strong association with advanced paternal age at conception. Apert syndrome is similar to Crouzon and Pfeiffer syndromes. Cardiovascular abnormalities include pulmonic stenosis, VSD, overriding aorta, and endocardial fibroelastosis.

Brugada Syndrome
Also known as sudden unexplained nocturnal death syndrome (SUNDS), is an autosomal dominant condition [mapped to 3p21, 3p22.3, 12p13.3 & 10p12], occurring in 1:2000 births. Brugada syndrome is associated with the risk of sudden cardiac death. Mean age of sudden death is approximately 40 years. Symptoms include right bundle branch block and ST segment elevation on ECG, idiopathic ventricular fibrillation, and cardiac arrest. Brugada syndrome, in its typical form is sinus rhythm with anterior raised ST segment in V1 and V2 due to a genetic ion-channel defect involving a sodium-channel defect isolated to SCN5A gene. Brugada syndrome is a type of “Channelopathy”. A ventricular tachycardia due to a genetic ion-channel defect is also known as a "Channelopathy" or "Ion channelopathy". This diagnosis is most commonly Long QT syndrome, but also includes Brugada syndrome, Jervell and Lange-Nielsen syndrome, Romano-Ward syndrome, Andersen syndrome, etc.

Cardiofaciocutaneous Syndrome
Cardiofaciocutaneous syndrome (CFC) is a sporadic condition [mapped to 7q34] affecting the heart, face, skin and hair. Incidence is 1:333,000-500,000 births. CFC is similar to Noonan and Costello syndromes. Cardiovascular abnormalities include pulmonary valve stenosis, ASD and hypertrophic cardiomyopathy.

Carpenter Syndrome
An autosomal recessive condition [mapped to 6p11] of acrocephalopolysyndactyly, type II. Incidence is 1:1,000,000 births. Cardiovascular abnormalities in 50% of cases include ASD, VSD, pulmonic stenosis, TOF, TGA and PDA.

Cat-eye Syndrome
Also known as Schmid-Fraccaro syndrome, is an autosomal dominant condition [mapped to 22q11], associated with coloboma of the iris. Incidence is 1:50,000-150,000 births. The classic pattern of malformations includes mild mental deficiency, hypertelorism, down-slanting palpebral fissures, iris, coloboma, pre-auricular pits or tags, and anal and renal malformations. Cardiovascular abnormalities in 40% of cases include TAPVC, ASD, VSD, persistent left superior vena cava, TOF, interruption of the inferior vena cava, and tricuspid atresia.
**Charge Association**
Also known as Hall-Hittner syndrome, is an autosomal dominant condition [mapped to 8q12.1 & 7q21.11]; some sporadic cases have been reported. Incidence is 1:8500-10,000 births. CHARGE syndrome is a nonrandom association of congenital anomalies which may include Coloboma, Heart defects, Atresia choanae, Retarded growth and development and/or central nervous system anomalies, Genital anomalies and/or hypogonadism and Ear anomalies and/or deafness. Diagnosis is made if 4/6 major (or 3 major & 3 minor) defects are present. Heart defects are present in 75% to 80% of cases. Of those with heart defects, most have conotruncal anomalies (TOF, DORV, truncus arteriosus) and aortic arch anomalies (vascular ring, aberrant subclavian artery, IAA, coarctation of the aorta, right aortic arch, aortic valve stenosis). Other cardiovascular abnormalities include PDA, AVSD, VSD, and ASD.

**Cornelia de Lange Syndrome**
Also known as de Lange or Brachmann-de Lange syndrome, is an autosomal dominant condition [mapped to 5p13.1, Xp11.22-11.21 & 10q25]; some X-linked and sporadic cases have been reported. Incidence is 1:10,000-30,000 births. Cardiovascular abnormalities in 25% of cases most commonly include VSD and ASD.

**Costello Syndrome**
An autosomal dominant condition [mapped to 12p12.1 & 11p15.5]; some sporadic cases have been reported. Incidence is 1:1,000,000 births. Cardiovascular abnormalities include ASD, VSD, pulmonic stenosis, mitral valve prolapse, hypertrophic cardiomyopathy and arrhythmias.

**Cri-du-chat Syndrome**
Also known as LeJeunesyndrome, is a chromosome deletion syndrome [mapped to 5p15.2]. Incidence is 1:20,000-50,000 births. Cri-du-chat refers to the distinctive cry of children with this disorder, caused by abnormal larynx development. Cardiovascular abnormalities in 30% of cases most commonly include VSD and ASD. Rare defects include TOF and AVSD.

**Deletion 10p Syndrome**
Deletions on the short arm of chromosome 10 are associated with septal defects, particularly ASDs, and DiGeorge/velocardiofacial 2 syndrome.

**Deletion 8p Syndrome**
Deletions on the short arm of chromosome 8 are associated with ASD, AVSC, conotruncal abnormalities, pulmonic valve stenosis and Tetralogy of Fallot.

**DiGeorge Syndrome**
Also known as Shprintzen, Takao, velocardiofacial, or conotruncal anomaly face syndrome, is an autosomal dominant condition [mapped to 22q11.2]. Incidence is 1:4000 births. Cardiovascular abnormalities are seen in association with hypoplasia or aplasia of the thymus and parathyroid gland, which are derivatives of pharyngeal pouches III and IV, and which can result in abnormalities of the immune system and calcium metabolism respectively. Cardiovascular abnormalities include conotruncal or outflow tract defects of the heart, such as tetralogy of Fallot, truncus arteriosus, and interrupted aortic arch, particularly type B IAA. Additional defects include VSD, right aortic arch, aberrant right subclavian artery, and PDA.

**Down Syndrome**
Also known as Trisomy 21, is the most frequent chromosomal abnormality. Incidence is 1:600-1000 live births. Sporadic cases of Down syndrome occur in strong association with advanced
maternal age at conception. Affected individuals have an extra (or third) copy of chromosome 21. Cardiovascular abnormalities in 40-50% of cases, in decreasing order of frequency, include AVSD, VSD, TOF and PDA. Left-sided obstructive defects, such as coarctation and aortic valve stenosis, are rare.

Edwards Syndrome
Also known as Trisomy 18, is a chromosomal abnormality. Incidence is 1:3000-5000 births. Sporadic cases of Edwards syndrome occur usually in association with advanced maternal age at conception. Affected individuals have an extra (or third) copy of chromosome 18. Approximately 50% of infants with Trisomy 18 die within the first week of life, approximately 40% die within the first month of life, only 5-10% survive beyond the first year. Cardiovascular abnormalities in more than 50% of cases include VSD, ASD and PDA; bicuspid aortic and/or pulmonic valves, nodularity of valve leaflets, pulmonic stenosis, coarctation of the aorta in 10-50% of cases; and anomalous coronary artery, TGA, TOF, dextrocardia and aberrant subclavian artery in less than 10% of cases.

Ehlers-Danlos Syndrome
Is a group of inherited disorders marked by extremely loose joints, hyperelastic skin that bruises easily, and easily damaged blood vessels. A variety of gene mutations involve collagen of the skin, bone, blood vessels, and internal organs. The abnormal collagen leads to the symptom which can include rupture of internal organs or abnormal heart valves.

Ellis-van Creveld Syndrome
Also known as chondroectodermal dysplasia, is an autosomal recessive condition [mapped to 4p16] of skeletal dysplasia. Incidence is 1:60,000-200,000 births. Major features include short stature of prenatal onset (short limbs), hypoplastic nails and dental anomalies, postaxial polydactyly, narrow thorax, and cardiac defects. Cardiovascular abnormalities in more than 50% of cases most commonly include ASD or common atrium. Additional defects include PDA, persistent left superior vena cava, hypoplastic left heart defects, coarctation of the aorta, TAPVC, and TGA.

Fetal Alcohol Syndrome
Indicate whether the patient has a history of Fetal alcohol syndrome (FAS). Fetal alcohol syndrome (FAS) is a condition that results from prenatal alcohol exposure. FAS is a group of problems that can include mental retardation, birth defects, abnormal facial features, growth problems, problems with the central nervous system, trouble remembering and/or learning, vision or hearing problems, and behavior problems. Mothers who consume large quantities of alcohol during pregnancy may have babies who are born with Fetal Alcohol Syndrome (or FAS). A diagnosis of FAS is based on three factors: 1) prenatal and postnatal growth retardation; 2) central nervous system abnormalities, and, 3) abnormalities of the face.

Fetal Drug Exposure
Indicate whether the patient has a history of Fetal drug exposure. Fetal drug exposure can lead to numerous problems including low birth weight, prematurity, small for Gestational Age (SGA), failure to Thrive (FTT), neurobehavioral symptoms, infectious diseases, and Sudden Infant Death Syndrome (SIDS).

Fetal Rubella Syndrome (Congenital Rubella Syndrome)
Indicate whether the patient has a history of maternal rubella virus infection during first trimester of pregnancy. Fetal rubella syndrome is associated with PDA, peripheral pulmonary stenosis, fibromuscular and intimal proliferation of medium and large arteries, VSD and ASD.
Goldenhar Syndrome
Also known as hemifacial microsomia, oculoauriculo-vertebral dysplasia or spectrum, and facioauriculovertebral sequence, is an autosomal dominant condition [mapped to 14q32]. Incidence is 1:3000-5000 births. Cardiovascular abnormalities include VSD, PDA, TOF and coarctation.

Heterotaxy Syndrome
Synonymous with ‘visceral heterotaxy’ is defined as an abnormality where the internal thoraco-abdominal organs demonstrate abnormal arrangement across the left-right axis of the body. By convention, heterotaxy does not include patients with either the expected usual or normal arrangement of the internal organs along the left-right axis, also known as ‘situs solitus’, nor patients with complete mirror-imaged arrangement of the internal organs along the left-right axis also known as ‘situs inversus’.

Heterotaxy Syndrome, Asplenia
Is defined as a subset of heterotaxy with components of bilateral right-sidedness, usually associated with absence of the spleen.

Heterotaxy Syndrome, Polysplenia
Is defined as a subset of Heterotaxy with components of bilateral left-sidedness, usually associated with multiple spleens.

Holt-Oram Syndrome
Also known as heart-hand syndrome is an autosomal dominant condition [mapped to 12q24.1]. Incidence is 1:100,000 births. Holt-Oram syndrome was first described in 1960 by Holt and Oram who noted the association of radial anomalies with atrial septal defects. Cardiovascular abnormalities in 75% of cases most commonly include ASD. Additional defects include first degree AV block, bradycardia, fibrillation, AVSD, VSD, HLHS and PDA.

Jacobsen Syndrome
Jacobsen syndrome is a chromosome deletion syndrome [mapped to 11q23]. Incidence is 1:100,000 births. Associated cardiovascular abnormalities include VSD and ASD.

Kabuki Syndrome
Kabuki, or Niikawa-Kuroki, syndrome is an autosomal dominant condition. Incidence is 1:32,000 births. Affected individuals have a facial appearance similar to Japanese Kabuki theatre actors. Cardiovascular abnormalities in 50% of cases include ASD, VSD, coarctation of the aorta, bicuspid aortic valve, mitral valve prolapse, TOF, single ventricle with common atrium, DORV, TGA, and pulmonic, aortic and mitral valve stenosis.

Kartagener Syndrome
Kartagener syndrome, also known as Siewert syndrome or primary ciliary dyskinesia, is an autosomal recessive condition [mapped to 9p21-p13]. Incidence is 1:30,000 births. Features include situs inversus and asplenia. Cardiovascular abnormalities include dextrocardia.

Klinefelter Syndrome (XXY)
Klinefelter, or 47XXY syndrome, is a sporadic chromosomal abnormality in which males have at least two X chromosomes and at least one Y chromosome. Incidence is 1:500 males or 1:1000 births. Klinefelter syndrome occurs usually in association with advanced maternal age at conception. It is the most common sex chromosome disorder and the most common cause of
hypogonadism and infertility. Cardiovascular abnormalities in more than 50% of cases include mitral valve prolapse, varicose veins and deep venous thrombosis.

**Leopard Syndrome**
LEOPARD is an acronym for multiple Lentigines, Electrocardiographic conduction abnormalities, Ocular hypertelorism, Pulmonic stenosis, Abnormal genitalia, Retardation of growth, and sensorineural Deafness. LEOPARD syndrome is an autosomal dominant condition [mapped to 12q24.1 & 3p25]. Cardiovascular abnormalities include pulmonic stenosis in 40% of cases, and hypertrophic cardiomyopathy in 20% of cases. Additional defects include subaortic stenosis, complete heart block, bundle branch block, prolonged P-R and QRS, and abnormal P waves.

**Loeys-Dietz Syndrome**
Loeys-Dietz syndrome is an autosomal dominant condition [mapped to 3p22 & 9q22]. Cardiovascular abnormalities include aortic and arterial aneurysms/dissections with tortuosity of the arteries, PDA, ASD, bicuspid aortic and pulmonic valves, and mitral valve prolapse.

**Long QT Syndrome (Ward Romano Syndrome)**
Long QT syndrome (LQTS), or Ward Romano syndrome, is an autosomal dominant condition [LQTS1 mapped to 11p15.5]. There are at least 11 known mutations for LQTS which have been mapped to at least 7 chromosomes. Long QT syndrome is characterized by a prolonged QT interval on EKG and is associated with the risk of sudden cardiac death. Incidence is 1:2000 births. Symptoms include ventricular arrhythmias, recurrent syncope, ventricular fibrillation, torsade de pointes, and cardiac arrest. Long QT syndrome (Ward Romano syndrome) is a ventricular tachycardia occurring in the setting of prolonged Q-T interval. Long QT syndrome is a type of “Channelopathy”. A ventricular tachycardia due to a genetic ion-channel defect is also known as a "Channelopathy" or "Ion channelopathy". This diagnosis is most commonly Long QT syndrome, but also includes Brugada syndrome, Jervell and Lange- Nielsen syndrome, Romano-Ward syndrome, Andersen syndrome, etc.

**Marfans Syndrome**
The most common connective tissue disorder, and is associated with the risk of sudden cardiac death. Cardiovascular abnormalities include aortic root dilation, aortic dissection and rupture, aortic regurgitation, ascending aortic aneurysm, mitral valve prolapse, mitral regurgitation, tricuspid valve prolapse, premature calcification of the mitral annulus, pulmonary artery dilatation and CHF.

**Mucopolysaccharidosis Syndrome**
A group a disorders, including Hurlers syndrome, Hurler-Scheie syndrome, Hunter syndrome, and Scheie syndrome of lysosomal storage. Cardiovascular abnormalities include valve disease, coronary artery narrowing, and ventricular hypertrophy. Survival varies depending on the particular genetic configuration.

**Noonan Syndrome**
Noonan syndrome is an autosomal dominant condition [mapped to 12q24.1]. Incidence is 1:1000-2500 births. Major features include short stature, seen in about half, mental retardation (usually mild), characteristic facial features, a shield chest deformity, cubitus valgus, and a short webbed neck. Cardiovascular abnormalities occur in at least 50% of cases and include pulmonary valve stenosis (75%) secondary to a dysplastic pulmonary valve with thickened valve leaflets, ASD (30%) usually associated with pulmonary stenosis, PDA (10%), VSD (10%), and
hypertrophic cardiomyopathy (10-20%) that can involve both ventricles. Rare lesions include TOF, coarctation of the aorta, subaortic stenosis, and Ebstein malformation.

**Patau Syndrome (Trisomy 13)**
This is a disorder with an Incidence is 1:5000-10,000 births. Sporadic cases occur usually in association with advanced maternal age at conception. Affected individuals have an extra (or third) copy of chromosome 13. More than 90% of individuals with Trisomy 13 die within their first days or weeks of life. Only 5-10% survive beyond 1 year of age. Cardiovascular abnormalities in 80% of cases include VSD, PDA, ASD; dextrocardia in more than 50% of cases; and anomalous pulmonary venous connection, overriding aorta, pulmonary stenosis, hypoplastic aorta, mitral valve atresia, aortic valve atresia, and bicuspid aortic valve in fewer than 50% of cases.

**Pierre Robin Syndrome**
Characterized by an unusually small mandible (micrognathia), posterior displacement or retraction of the tongue (glossoptosis), and upper airway obstruction. Incomplete closure of the roof of the mouth (cleft palate) is present in the majority of patients, and is commonly U-shaped.

**Prune Belly Syndrome**
Characterized by three main features: Anterior abdominal wall musculature ("stomach muscles") deficient or absent, urinary tract anomalies (such as a very large bladder) and bilateral cryptorchidism (two undescended testicles.) The incidence of prune belly syndrome is about 1 in 40,000 births; 95% of cases occur in males. It is thought that prune belly syndrome is a multisystem disease complex that derives from a primary defect in mesodermal development at about 8 weeks’ gestation. The major prognostic factor is the degree of dilation of the urinary tract; 20% of patients are stillborn, 30% die of renal failure or urosepsis within the first two years of life, and the remaining 50% have varying degrees of urinary pathology.

**Rethore Syndrome (Trisomy 9)**
A rare chromosomal abnormality, which is a frequent cause of first trimester spontaneous abortions. Incidence is 1:100,000 births. Affected individuals have an extra (or third) copy of chromosome 9. Most affected individuals die during infancy or early childhood. Cardiovascular abnormalities occur in 75% of cases and include VSD, ASD, PDA, valve defects, DORV, persistent left SVC, and endocardial fibroelastosis.

**Rubinstein-Taybi Syndrome**
An autosomal dominant condition [mapped to 16p13.3 & 22q13]. Incidence is 1:100,000-125,000 births. Cardiovascular abnormalities occur in 30% of cases and include ASD, VSD and PDA.

**Short QT Syndrome**
Short QT syndrome appears to be an autosomal dominant condition [mapped to 7q35-q36, 11p15.5, 17q23.1-q24.2]. Short QT syndrome is characterized by a shortened QT interval on EKG and is associated with the risk of sudden cardiac death. Symptoms include episodes of syncope, palpitations, paroxysmal atrial fibrillation, ventricular fibrillation, and cardiac arrest. Short QT syndrome is a ventricular tachycardia occurring in the setting of short Q-T interval. Short QT syndrome is a type of "Channelopathy". A ventricular tachycardia due to a genetic ion-channel defect is also known as a "Channelopathy" or "Ion channelopathy". This diagnosis is most commonly Long QT syndrome, but also includes Brugada syndrome, Jervell and Lange-Nielsen syndrome, Romano-Ward syndrome, Andersen syndrome, etc.
Sickle Cell Disease
An autosomal recessive genetic blood disorder with over dominance, characterized by red blood cells that assume an abnormal, rigid, sickle shape. Sickling decreases the cells' flexibility and results in a risk of various complications. The sickling occurs because of a mutation in the hemoglobin gene. Sickle-cell disease occurs more commonly in people (or their descendants) from parts of tropical and sub-tropical regions where malaria is or was common.

Sickle Cell Trait
A condition in which a person has one abnormal allele of the hemoglobin beta gene (is heterozygous), but does not display the severe symptoms of sickle cell disease that occur in a person who has two copies of that allele (is homozygous). Those who are heterozygous for the sickle cell allele produce both normal and abnormal hemoglobin (the two alleles are co-dominant). Sickle cell disease is a blood disorder in which the body produces an abnormal type of the oxygen-carrying substance hemoglobin in the red blood cells. Sickling and sickle cell disease also confer some resistance to malaria parasitization of red blood cells, so that individuals with sickle-cell trait (heterozygotes) have a selective advantage in some environments.

Situs Inversus
Defined as an abnormality where the internal thoraco-abdominal organs demonstrate mirror-imaged atrial arrangement across the left-right axis of the body.

Smith-Lemli-Opitz Syndrome
An autosomal recessive condition [mapped to 11q12-q13]. Incidence is 1:20,000-40,000 births. Cardiovascular abnormalities include VSD, ASD, coarctation of the aorta, and PDA.

Turner Syndrome (45XO)
A chromosomal deletion abnormality, which occurs in 1:5000 live female births. Although common in first trimester, most 45XO conceptuses are spontaneously aborted. Affected individuals are missing one X chromosome. The major features include short stature, primary amenorrhea due to ovarian dysgenesis, webbed neck, congenital lymphedema, and cubitus valgus. Cardiovascular abnormalities occur in 20-40% of cases, the most common of which is coarctation of the aorta (70%). Additional defects include bicommissural aortic valve, aortic stenosis, a spectrum of left-sided obstructive defects and/or hypoplastic defects, hypoplastic left heart syndrome; aortic dilation, dissection, and rupture.

VACTERL Syndrome (VACTER/VATER/VATERR Syndrome)
A nonrandom association of defects, including Vertebral anomalies, Anal atresia, Cardiovascular anomalies, Tracheoesophageal fistula, Esophageal atresia, Renal and/or Radial anomalies, and Limb anomalies. Diagnosis is made if 3/7 defects are present. Incidence is 1:6000 births. Cardiovascular malformations include VSD, TOF, TGA and PDA.

Von Willebrand disease (vWD)
The most common hereditary coagulation abnormality described in humans, although it can also be acquired as a result of other medical conditions. It arises from a qualitative or quantitative deficiency of von Willebrand factor (vWF), a multimeric protein that is required for platelet adhesion. There are three forms of vWD: inherited, acquired and pseudo or platelet type. There are three types of hereditary vWD: vWD Type I, vWD Type II and vWD III. Within the three inherited types of vWD there are various subtypes. Platelet type vWD is also an inherited condition. vWD Type I is the most common type of the disorder and those that have it are
typically asymptomatic or may experience mild symptoms such as nosebleeds although there may be severe symptoms in some cases. There are various factors that affect the presentation and severity of symptoms of vWD such as blood type.

**Williams Syndrome (Williams-Beurn Syndrome) (7q11/7q11.23)**
An autosomal dominant condition [mapped to 7q11.23]. Incidence is 1:7500 births. Williams syndrome was initially described by Williams and colleagues in four unrelated children with mental retardation, an unusual facial appearance, and supravalvar stenosis. Cardiovascular abnormalities occur in at least 50% of cases and include supravalvar aortic stenosis, bicuspid aortic valve, mitral valve prolapse, mitral regurgitation, coronary artery stenosis, pulmonary valve stenosis, ASD, VSD and peripheral pulmonary artery stenosis. Supravalvar aortic stenosis is the most frequent single defect, but any of the systemic or pulmonary arteries can be affected.

**Wolff-Parkinson-White Syndrome (WPW Syndrome)**
A condition in which there is an extra electrical pathway or circuit in the heart. Incidence is 1:500. WPW is one of the most common causes of tachycardia in infants and children. Symptoms may include chest pain, syncope, palpitations, shortness of breath, and can lead to episodes of tachycardia with heart rate >230 bpm. The “Wolff-Parkinson-White Syndrome (WPW syndrome)” is an "accessory connection-mediated tachycardia". An “accessory connection-mediated tachycardia” is a tachycardia secondary to accessory connection(s) or pathway(s). Typical accessory pathways are extra nodal pathways that connect the myocardium of the atrium and the ventricle across the AV groove and are classified by location, type of conduction (decremental versus nondecremental), and whether they are capable of anterograde (manifest, demonstrating pre-excitation on standard ECG) or retrograde (concealed) conduction, or both. The “Wolff- Parkinson-White Syndrome (WPW syndrome)” diagnosis is reserved for patients who have both pre- excitation on ECG (manifest conduction) and tachyarrhythmias.

**Wolf-Hirschhorn Syndrome**
A chromosome deletion syndrome [mapped to 4p16.3]. Incidence is 1:96,000 births. Affected individuals have a 35% risk of mortality prior to age 2. Cardiovascular abnormalities include ASD and VSD.

**Other Syndrome**
Select if patient has a syndrome other than those listed above.

**Q:** Does a syndrome like Tourette’s belong in the syndrome field, the pre-operative factor field (as a neurological deficit), or in both?  
**A:** Enter as Other Syndrome.