Top Ten Things to Know
Genetic Basis for Congenital Heart Disease: Revisited

1. This Scientific Statement has been compiled to provide updated information for clinicians about new developments in our understanding of the genetic contributions to the etiology of congenital heart disease (CHD), providing an update of the 2007 American Heart Association Scientific Statement on this subject.

2. Our understanding of the role of genetics in the etiology of CHD has advanced at a rapid pace over the past 10-15 years. The availability of new molecular techniques has facilitated gene discoveries, which have changed the medical and cardiologic care of many individuals with CHD. CNVs detection and next generation sequencing (NGS) gene panels are now in widespread use by geneticists, genetic counselors and cardiologists for accurate diagnosis of CHD patients.

3. For clinicians caring for a child or adult with CHD, important reasons for determining the genetic cause can include: a) Assessing recurrence risks for the offspring of the CHD survivor, additional offspring of the parents or other close relatives; b) Evaluating for associated extra-cardiac involvement; c) Assessing risk for neurodevelopmental delays for newborns and infants; and d) Providing more accurate prognosis for the CHD and outcomes for CHD-related interventions.

4. As genetic testing technologies have evolved to offer higher resolution and higher diagnostic yields than those provided by conventional chromosomal analyses, CNVs have emerged as important causes of both syndromic and non-syndromic CHDs. Moreover, an increasing recognition of contributing environmental and epigenetic factors has revealed a previously unanticipated breadth to CHD etiology.

5. Recent human genetic studies have identified subclasses of CHDs which show strong familial clustering in first-degree relatives, ranging from 3-fold to 80-fold compared to the prevalence in the population, or are more likely associated with underlying genetic causes.

6. Genetic counselors skilled in cardiovascular genetics have become an invaluable clinical asset, helping not only to provide accurate recurrence risks, but also to obtain family and medical histories, facilitate appropriate genetic testing, interpret test results, make necessary subspecialty referrals, and provide attendant psychosocial support for patients and their families. Physicians with subspecialty training in medical genetics are trained in dysmorphology, metabolism, monogenic conditions, genomics, and diagnostic testing and are able to generate a differential, determine a diagnostic evaluation approach, and provide specific management and treatment recommendations for patient care.

7. The advances in the understanding of CNVs, syndromes, RASopathies and heterotaxy/ciliopathies are examined in this Scientific Statement. Insights into new research with CHD models including genetically manipulated animals such as mouse, chick, and zebrafish as well as human induced pluripotent stem cell-based approaches are provided to allow an understanding of how future research breakthroughs for CHD are likely to happen.

8. During the last 10-15 years, a period of active gene discovery, the molecular basis of many syndromes has been identified. Numerous syndromes due to single gene variants (traditionally referred to as mutations) have additionally been found to be genetically heterogeneous, meaning that an individual variant in more than one gene is capable of causing a similar condition.
9. Cardiovascular genetic clinics are now available in many major medical centers in the United States. Accurate diagnosis of CHD etiology is allowing for determination of familial recurrence risks, providing reproductive options, identifying extracardiac manifestations of the genetic diagnosis that may affect clinical care, and improving long-term medical decisions in the care of CHD.

10. Uncovering a genetic etiology for CHD is increasingly clinically relevant, in part because of improved survival and improved CHD-related health interventions.