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Future Prospects for Biomarkers in the Management and Development of Novel Therapies for Pediatric Heart Disease

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Broadly defined, a biomarker can be any quantifiable, patient-derived characteristic that provides insight into the presence or absence of disease, the severity of the disease, or the patient's prognosis. This can include assays measured in the clinical laboratory, imaging endpoints measured using echocardiography, cardiac magnetic resonance imaging, and positron emission tomography, and imaging measures ascertained by cardiopulmonary exercise testing.

In the field of pediatric cardiology there is a specific need for biomarkers to guide patient care, since many pediatric patients cannot express their symptoms precisely, and the symptoms and signs of heart disease may overlap with those of other disease. For example, infants with heart disease and deteriorating myocardial function commonly present with non-cardiac symptoms like irritability, respiratory distress, or gastrointestinal upset. It is often difficult for the clinician to differentiate on clinical grounds between early cardiac decompensation and intercurrent illnesses. In addition, the conduct of clinical outcome trials for novel therapeutic interventions in children are hampered by the small number of available study subjects compared to adult heart disease, and the heightened sensitivity to risk when studying the pediatric population. Sensitive biomarkers that predict outcomes could facilitate the design of smaller, informative trials in children.

We recently described the use of biomarkers in certain clinical scenarios for which they have shown utility in children and adolescents [1]. The applications of these surrogate observations have mainly focused on distinguishing cardiac from non-cardiac disease, anticipating outcomes for patients with dilated cardiomyopathy, monitoring deterioration in children after heart transplant, establishing prognosis in repaired congenital heart disease, such as tetralogy of Fallot, and staging intervention in patients with complex, univentricular cardiac disease.

Despite the current array of biomarkers, many knowledge gaps remain. However, technological advances in molecular biology, biochemistry, and cell biology, as well as anatomic and metabolic imaging, and physiological testing, bring opportunities for new biomarkers to emerge. Specifically, work on imaging the myocardial stress-strain relationship, evaluation of cardiac function using 3D echocardiography, and understanding the biology of fibrosis is likely to provide additional biomarkers for use in children as well as adults with cardiac disease.

Biomarkers currently being tested in adults are likely to be tested in children, although given the different etiologies and pathophysiologies of pediatric versus adult heart disease, adult biomarkers may not be readily translatable to childhood disease. While the number of randomized controlled trials to assess biomarker-guided therapy in children is small, these will hopefully increase with funding initiatives such as the U.S. National Heart, Lung, and Blood Institute-sponsored Pediatric Heart Network [2] and the Biomarkers Consortium of the Foundation for the National Institutes of Health [3]. Such work would also enable the development of novel therapies for children, and facilitate the extension of registered drugs to pediatric populations as mandated by regulatory agencies such as the U.S. Food and Drug Administration [4] and the European Medicines Agency [5].

References

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