Children as Biomarker Orphans: Progress in the Field of Pediatric Biomarkers

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Biomarkers are incorporated ubiquitously into clinical practice as surrogate endpoints of physiologic and pathologic processes that cannot be measured directly. For example, a lipid panel is used to evaluate cardiovascular disease but does not measure vascular heath directly. Biomarkers monitor health, detect exposures, diagnose disease, predict disease severity and outcome, and monitor treatment effects. The potential utility of biomarkers in pediatrics is high. Children are not only at risk of developing unique illnesses, but prevalent chronic diseases previously thought of as "adult" illness, including obesity, cardiovascular disease, and type 2 diabetes, have their origins in childhood.[1,2] In an era in which precision, or personalized, medicine is becoming a priority, testing that leads to early intervention and curbs the severity of disease may have an immense impact on population health and the use of healthcare resources. **Table 1** highlights examples of commonly used and recent biomarkers in pediatrics. Despite this potential, biomarker discovery in pediatrics has been limited. In 2010, the barriers to pediatric biomarker discovery were reviewed.[21] In this updated review, we will discuss the progress, as well as remaining challenges specific to pediatrics, and potential strategies for moving forward.

Definition

Biomarkers are defined by the Institute of Medicine as tests "that are objectively measured and evaluated as indicators of normal biologic processes, pathologic processes, or pharmacologic responses to therapeutic intervention."[22] Therefore, biomarkers may include biofluids (urine, blood, saliva, stool, cerebrospinal fluid), other tissue (including hair or nails), radiographic, genetic, or any other physiologic testing. The arena of biomarker discovery is moving toward proteins and other small molecule targets, as they provide sensitivity and specificity of current and emerging health status that genetic approaches cannot match.

Desirable Characteristics of Biomarkers

Several desirable characteristics have been defined for biomarkers.[23] New biomarkers need to be highly correlated with the current gold standard and should offer an improvement over what already is available. The sample must be both easy to obtain (referring to specimen collection) and easy to process and analyze in the laboratory. Both aspects are necessary for serial measurements to follow trends. Ideally, tests also should have high specificity and sensitivity and be inexpensive to perform.

New methods of noninvasive surrogate testing as an alternate to blood especially are important in pediatrics. Painful procedures are anxiety-producing for both patients and parents and often require sedation of the patient. Even imaging such as magnetic resonance imaging requires sedation in young children. Sedation adds cost and risk, making testing more difficult for patients and next-to-impossible to perform on healthy control subjects. Although invasive procedures may still be needed for confirmatory testing in some individuals, reliable noninvasive biomarkers from saliva, urine, stool, or hair may help avoid unnecessary procedures in many others.

Interest in Pediatric Biomarkers

Systematic literature searches were performed within the PubMed database to capture published pediatric clinical studies on biomarkers that use biospecimens and biobanks. The specimen categories were cerebrospinal, urine, blood, serum, plasma, saliva, stool, hair, and general/miscellaneous, and the search strategies included Medical Subject Headings vocabulary terms. The search query for biomarkers was combined with queries for all specified body fluids and for clinical studies. Searches were limited to the pediatric population and publication years 2012-2016. The biomarker queries were limited by language; biobank queries were not limited by language or publication status. Detailed search strategies and the complete list of references are provided in the **Appendix** (available at www.jpeds.com).

The search identified 1126 publications. Although many diseases have overlapping biological system involvement, the publications were categorized broadly (**Table 2**), with infection/sepsis, metabolic/nutrition, and kidney/urologic as the 3 most common systems. This is partially driven by the availability of high-quality inflammatory pathway multiplex immunoassays (including products from Meso Scale Discovery,

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Table 1. Examples of pediatric biomarkers in clinical use

Authors	Year	Test	Screening/diagnostic utility	Comments	Biospecimen
Bortolotti et al[3] Roberts[4]	2003 2011	anti-LKM	Autoimmune hepatitis, chronic hepatitis C	Positive in type 2 autoimmune hepatitis and in 10% of hepatitis C	Serum/blood
Dalrymple and Moore[5] Breda et al[6]	2015 2010	ANA	Multiple rheumatologic and autoimmune disorders: systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, idiopathic thrombocytopenic purpura, autoimmune hepatitis, and thyroiditis	Low titers in up to 20% healthy children; Positive in >90% of connective tissue disorders; elevations can occur with drug reactions and some viral infections	Serum/blood
Nir et al[7]	2009	BNP	Heart disease and failure	Normally elevated in the first few days of life then decrease; levels correlate with pulmonary-to-systemic flow and vascular resistance ratios, mean pulmonary artery pressure, obstructive lesions, and allograft disease after transplant	Serum/blood
Henderson et al[8] Zoppelli et al[9]	2014 2012	Calprotectin	Intestinal inflammation	Used for screening and treatment response in inflammatory bowel disease; also may be elevated with intestinal infection, cystic fibrosis, and juvenile polyps. Normal values are highly variable in infants born premature	Stool
Jones and Hattersley[10]	2013	C-peptide	Diabetes mellitus	Approximates endogenous insulin production, helps differentiate type	Serum/blood
Breda et al[6]	2010	CRP	Acute and chronic inflammation from severe bacterial infection, tissue injury, autoimmune disease	Highly sensitive, but not specific, increases more quickly compared with ESR	Serum/blood
Elsayed and Reilly[11] Gatheridge et al[12]	2010 2016	CK	Muscle injury	Elevated in rhabdomyolysis, myopathies, and myositis	Serum/blood
Breda et al[6] Malope et al[13]	2010 2011	Ferritin	Iron deficiency anemia (low) Hemophagocytic lymphohistiocytosis (high)	May be elevated as an acute-phase reactant in sepsis and shock	Serum/blood
Tang et al[14] Petsky et al[15]	2016 2016	FENO	Asthma	Marker of eosinophilic inflammation used for diagnosis and treatment response	Breath test
Lehrnbecher et al[16]	2016	Galactomannan	Aspergillus infection (immunocompromised patients)	Less sensitive for other fungal infections	Serum/blood
Copeland et al[17]	2013	Hemoglobin A1C	Diabetes mellitus	Used for diagnosis and to guide dosing of insulin	Serum/blood
Fine-Goulden and Durward[18]	2014	Lactate	Ischemia, sepsis, lactic acidosis/ metabolic crisis	Elevation may predict mortality in acutely ill or trauma patients	Serum/blood
Breda et al[6] Lautz et al[19]	2010 2016	Procalcitonin	Sepsis/severe bacterial infection, shock	More specific to bacterial sepsis than CRP in children	Serum/blood
Breda et al[6]	2010	ESR	Acute and chronic inflammation from autoimmune disease or infection	Acute-phase reactant with high sensitivity but low specificity for any one disease, increases more slowly compared with CRP	Serum/blood
Kelly et al[20]	2015	TTG	Celiac disease	Highly sensitive and specific; used for screening and treatment response	Serum/blood

ANA, Antinuclear antibody; *anti-LKM*, Anti-liver kidney microsomal antibody; *BNP*, Brain natriuretic peptide; *CK*, Creatine kinase; *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *FENO*, Fractional exhaled nitric oxide; *TTG*, Tissue transglutaminase.

Table 2. Proportion of publications by body system

System	Proportion, %
Allergy	2
Cardiovascular	3
Endocrine	6
Gastrointestinal/Liver	10
Hematologic	1
Immune	1
Infection/Sepsis	18
Inflammation	8
Kidney/Urologic	11
Metabolic/Nutrition	14
Neurologic	8
Oncologic	9
Pulmonary	5
Toxin/Environmental	4

Gaithersburg, Maryland, and Luminex Corporation, Toronto, Ontario, Canada) and the recent discovery of acute kidney injury biomarkers with clinical utility.[24-26] The majority of publications (75%) described diagnostic biomarkers, recognizing, however, that biomarkers may have both diagnostic and prognostic utility; 70 publications (6%) were dedicated specifically to the discovery of new biomarkers for diagnosing and monitoring pediatric diseases. The most common biofluid used was blood (**Figure**). The number of open and closed pediatric biomarker trials registered on ClinicalTrials.gov increased to 568 as of December 2016.[27] Even though the increase in publications and trials is encouraging, the pace of studies in pediatric subjects pales in comparison with studies in adults, where the number of annual biomarker publications in 2010 was

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