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The fault…is not in our stars, but in ourselves

— William S. Ferguson, MD

Thiopurines, including mercaptopurine, are a cornerstone of modern maintenance therapy for childhood acute lymphoblastic leukemia (ALL) and various other diseases. Thiopurine methyltransferase (TPMT) is a pivotal enzyme in the degradation of toxic thiopurine metabolites. Individuals heterozygous for inactivating TPMT variants (about 10% of the European and American population) require modest decreases in thiopurine dosing, whereas those with homozygous defects tolerate only about one-tenth the conventional dose. Preemptive testing for TPMT variants prior to exposure to mercaptopurine is now common practice; however, even in patients with wild-type TPMT there remains significant variability in tolerated dose, suggesting that additional factors influence thiopurine metabolism.

In this volume of *The Journal*, Berggren et al report on a retrospective analysis of 2 additional genes implicated in thiopurine metabolism, Nudix hydrolase 15 (NUDT15) and inosine triphosphatase (ITPA), in Swedish children treated for ALL. Initial dosing of mercaptopurine was based on upfront TPMT testing, with ongoing dose adjustments based on blood counts every 2 weeks during treatment.

As might be expected given the frequent monitoring, none of these gene variants were associated with excessive neutropenia. However, presence of the NUDT15 variant was correlated with receiving a lower dose of mercaptopurine, suggesting that like TPMT, deactivating variants of this gene can have clinically relevant effects on thiopurine metabolism. In contrast, the presence of ITPA variants did not influence mercaptopurine dosing, and indeed were unexpectedly associated with a *lower* incidence of febrile neutropenia.

The relevance of this study is not limited to those who prescribe thiopurines. Balancing drug toxicity and efficacy is a quite common issue: adverse drug events occur in an estimated 15% of hospitalized children, while variations in metabolism can also decrease drug efficacy. Although expense and turn-around time would make routine genetic testing for most short-term drug therapies impractical, this balance may be quite different for children receiving long-term or chronic therapy. The lessons to keep in mind from the current study are not just that multiple genes are likely to influence drug metabolism, but that confirmatory investigations are required to determine the actual clinical effects resulting from gene variants and to define those situations where genetic testing could effectively guide clinical practice.

Article page 150►

Mucopolysaccharidoses newborn testing

— Thomas R. Welch, MD

Physicians who care for newborns are aware of the rapid expansion of the disorders for which newborn blood-spot based screening is employed. Inclusion of a specific test on a state's panel is the final step in a process that begins with basic science studies followed by feasibility testing in sample populations. A host of considerations go into the decision to screen presumably normal newborns for a disease. In addition to the disease having severe consequences and the potential for successful therapy, considerations of the overall "burden" of such testing are crucial. If, for example, a test has so many false positives that many healthy children will be subject to unnecessary, costly, and anxiety-provoking testing for every affected child identified, one might argue that the burden of testing outweighed the benefit.

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Lately, a lot of attention has been paid to newborn screening for the mucopolysaccharidoses (MPS). Recent developments in enzyme replacement therapy and bone marrow transplantation have made these rare but devastating diseases appropriate targets for screening. The current volume of *The Journal* includes a very important report from a group of investigators in Seattle examining the "real world" performance of a single-spot testing procedure for 5 MPS. Previous studies from the group described the technical aspects of the procedure, and this study shows the experience using it on over 100 000 newborns. Not surprisingly, given the rarity of these conditions, there were apparently only 2 clinically affected children identified. Importantly, however, the numbers of children who were positive in the initial screen but not affected were quite modest. Most of these initial screen positive children underwent additional testing on other available blood spots, so they would not have needed to be "recalled" for definitive testing.

This study does not constitute a definitive statement on this test. Ultimately, that is a decision for professional organizations and state health departments. Readers should understand, however, that one of the roles of journals such as ours is to offer a forum for studies such as this. Decision-makers and the public rely on our scientific review, editing, and publication as important resources in making major public policy determinations.

Article page 204 ▶

Algorithm-driven electronic health record notification enhances detection of Turner syndrome

— Hans C. Andersson, MD, FACMG

Causes for short stature in females are numerous; Turner syndrome is among the commoner etiologies. A simple blood test, array comparative genomic hybridization (aCGH, commonly called "microarray") or karyotype, can typically identify partial or complete absence of the second sex chromosome. Chromosome analysis has been a standard recommendation in evaluating idiopathic proportional short stature in females (*J Clin Endocrinol Metab* 2008;93:4210–7) (*Genet Med* 2009;11:465–70). In this volume of *The Journal*, Alexandrou et al used an algorithm-driven review of electronic health records (EHRs) to identify 216 females with idiopathic short stature, of which 72 females had never received chromosome analysis. Interestingly, the females who received chromosome analysis were significantly shorter with a greater mid-parental height deflection than those who had not received either microarray or karyotype. Of the 72 patients initially identified without chromosome analysis, 32 were successfully studied with aCGH. Of these, 2 new cases of Turner syndrome were identified and 1 new patient had a chromosome copy number variant associated with short stature.

This study demonstrates the power of EHRs in capturing signs and symptoms of unrecognized diseases. As the completeness of EHRs becomes widespread, the strategy of recognizing overlooked healthcare needs by searching for signs in the EHR may be more frequently used. This strategy can also identify deviation from disease-specific guidelines and help to create systematic compliance with standards of care. In this study, one-third of females with idiopathic short stature did not receive the recommended (10 years ago) chromosome analysis in their initial evaluations. EHR-driven strategies could help compliance with disease-specific guidelines and serve as a focus for quality improvement.

Article page 227 ▶

It's time to detect kids' brain attacks early

— Paul G. Fisher, MD

We are now well past a simple awareness that strokes are not just for old folks. Yes, children have strokes, too, and the incidence may exceed 1 per 100 000 or even 10 000 annually (*Emerg Med Int* 2011;2011:734506), more common than many childhood cancers. But, can we detect these brain attacks sooner and save brain?

In this volume of *The Journal*, Harrar et al deploy an historical cohort study in a single tertiary center to determine whether a stroke alert system decreased the time to diagnosis of children presenting to the emergency department with acute-onset

focal neurologic deficits. After implementation of a stroke alert system, the median time from emergency department arrival until neuroimaging for children with acute-onset focal neurologic was 82 minutes, significantly less compared with the median 196 minutes before the alert system. Interestingly, as a secondary finding, this coordinated pediatric stroke protocol also led to more children being carefully evaluated for stroke. At the same time, the treating physicians were unable to distinguish who would or would not ultimately benefit from an intervention such at tissue plasminogen activator, although they did identify perceived potential candidates even more quickly than the median 82 minutes.

The take-home message of this study is that we can and should do better identifying strokes in children. Such timely diagnosis is prerequisite to applying interventional therapies. Identification and treatment will also lead eventually to better primary and secondary prevention in those children at risk for stroke. It's time for us to save more children's brains.

Article page 136 ▶

Ambulatory blood pressure variability

— Thomas R. Welch, MD

The recent release of new guidelines for pediatric hypertension (*Hypertension* 2014; 63:1116–35) has had broad implications for providers of child health care. One of the major consequences of the recommendations is the increasing use of ambulatory blood pressure monitoring (ABPM) in the evaluation and management of children with elevated blood pressure. Interestingly, this recommendation was made in the absence of data on the stability of ABP measurements in children over time.

In the current volume of *The Journal*, a group including investigators from Seattle and Pittsburgh examined changes in ABP phenotypes in 124 children for whom 2 studies 6 months apart were available. Readers may find it curious that this is the first study in which such data are available for this number of children. The bottom line of the study is that, like office casual blood pressures, ABP patterns are not fixed over time. Nearly one-half of the children studied underwent a change in their ABP classification after 6 months. These changes were not unidirectional; one-third worsened and two-thirds improved. Note that none of these children were receiving any drug therapy between the 2 periods.

As the use of this diagnostic technology increases, we must recognize that we still have a lot to learn about it.

Article page 37 ▶

HbA1c and pre-diabetes in youth: More data needed

— David M. Maahs, MD, PhD

Kelsey et al performed a secondary data analysis on 8 814 youth in the HEALTHY study, which included ethnically and racially diverse 11- to 15-year-olds with a range of body mass index (BMI) and risk for type 2 diabetes (T2D). The American Diabetes Association uses hemoglobin A1c (HbA1c) as a test to screen and diagnose pre-diabetes based on data in adults. These criteria have been extrapolated to youth despite a lack of data on how a pre-diabetes HbA1c in youth predicts risk of future T2D or diabetes complications. Kelsey et al report that 2% of normal weight youth, not at risk for T2D, had an HbA1c in the pre-diabetes range (5.7-6.4%) and that the distribution of HbA1c overlaps in the normal and overweight cohorts. The authors emphasize that a pre-diabetes HbA1c should be interpreted with caution and that more data are needed on measures of glycemia during puberty with attention to the impact of race/ethnicity on HbA1c distribution. Given the continued increase in obesity in youth in the US and globally, an improved ability to assess risk and predict progression to diabetes is an important research focus. On a public health level, efforts to prevent obesity need to be a priority.

Article page 232 ▶