required for the determination of fetal aneuploidy. Studies to date have shown the sensitivity and specificity of this technology for the screening of cfDNA in composed study populations with known karyotypes with very high prevalences of aneuploidies.[5,6] This study method, however, has made it impossible to calculate the positive and negative predictive values of cfDNA screening at prevalences of aneuploidies that would be encountered in a generally representative obstetric population.

In this issue of the *Journal*, Bianchi et al.[7] describe how cfDNA screening is also useful in women at low risk for carrying an aneuploid fetus. The investigators compared the performance of cfDNA screening with that of standard screening (serum biochemical assays with or without measurement of nuchal translucency) in singleton pregnancies. The primary outcome was the comparison of false positive rates for identifying trisomy 21 (Down's syndrome) and trisomy 18 (Edwards' syndrome). They observed that cfDNA screening had a greater specificity than the standard biochemical and imaging methods of screening in that it had a significantly lower false positive rate than standard screening (0.3% vs. 3.6% in detecting trisomy 21 and 0.2% vs. 0.6% in detecting trisomy 18). In addition, they reported a lower rate of false positives with cfDNA screening for trisomy 13 (Patau's syndrome) than with standard screening (0.1% vs. 0.7%), although the difference was not statistically significant.

The positive predictive values of the assay — 45.5% for trisomy 21 and 40.0% for trisomy 18 — underscore the conclusion that assaying fetal DNA is a screening tool and not a diagnostic intervention. As the investigators acknowledge, women who receive a positive result on cfDNA screening must be counseled to have a diagnostic test — for example, through karyotype analysis of cells obtained by amniocentesis or chorionic villus sampling — to determine whether their fetus is one of the approximately 60% of fetuses that are falsely identified on cfDNA screening as having a chromosome 18 or 21 trisomy.

The observed negative predictive values of 100% with 95% confidence limits down to 99.8%, combined with the significantly and substantively lower false positive rates with cfDNA screening than with standard screening, augurs well for pregnant women and their fetuses: a negative result on cfDNA screening obviates the need for invasive testing and thus the discomfort and risk to the pregnancy incurred by such testing.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Department of Obstetrics and Gynecology, Massachusetts General Hospital, Boston (M.F.G.).

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New Diagnostics for Common Childhood Infections

Kathryn Maitland, M.B., B.S., Ph.D.

The implementation of preventive strategies and effective treatment has substantially reduced the incidence of malaria across many parts of Africa.[1] The introduction of *Haemophilus influenzae* type b vaccine and, more recently, pneumococcal conjugate vaccine should dramatically reduce the incidence of serious bacterial infections among children.[2] Historically, these pathogens

accounted for a substantial proportion of childhood deaths in regions of Africa where malaria is endemic. High coverage with these measures will also affect the burden and spectrum of the common childhood febrile diseases. Consequently, case-management guidelines[3] — which are currently designed to maximize sensitivity over specificity, resulting in widespread use of low-cost antimalarial or antimicrobial agents to avert adverse outcomes — will need to be revised.[4] However, most research underpinning such guidelines was undertaken two to three decades ago. The advent of rapid diagnostic tests and molecular diagnostics has expanded the potential to identify causes of disease and may inform future management strategies for common childhood diseases.[5] Nevertheless, few such pathogenic data are available from sub-Saharan Africa.

In this issue of the *Journal*, D'Acremont and colleagues[6] report the results of their study of 1010 pediatric outpatient visits to two clinics in Tanzania, both located in communities of low endemicity for malaria. Included were children 2 months of age or older who had an acute febrile illness (temperature, ≥38°C) of 1 week or shorter duration and had not been treated with antimicrobial or antimalarial agents during the week before the clinic visit. Children with World Health Organization–classified emergency signs, severe malnutrition, or trauma were excluded. For each child, a standardized clinical history was obtained, and physical examination and a systematic set of investigations were performed, including blood cultures; rapid diagnostic testing for malaria, typhoid fever, group A streptococcus, adenovirus, and rotavirus; serologic testing for other conditions; and molecular testing of blood and nasopharyngeal specimens for potential pathogens. Supplementary investigations were guided by a complex decision tree and were based on clinical presentation. In total, 1232 clinical or microbiologic diagnoses were made; 227 children (22.6%) had multiple conditions diagnosed, and in 32 children, no infectious cause of illness was found. A total of 70 children were hospitalized; 4 of these children died. Most of the diagnoses involved upper or lower respiratory tract infections: acute respiratory tract infection accounted for 51% of diagnoses, and nasopharyngeal infection accounted for another 10%. A virus was detected in 81% of children with acute respiratory tract infection. Systemic infections, *Plasmodium falciparum* malaria, gastroenteritis, and urinary tract infection accounted for 11%, 9%, 8%, and 5% of diagnoses, respectively. More than 50% of children with malaria, irrespective of parasite density, had a secondary pathogen or diagnosis.

The authors make two important observations. First, interpretation of the infectious cause of illness based solely on laboratory testing is potentially misleading. Bacterial, viral, and parasitic pathogens were identified in 87%, 81%, and 11% of patients, respectively. However, when laboratory data were combined with predefined clinical criteria to determine each diagnosis, the disease burden was significantly rebalanced (bacterial, 22%; viral, 71%; and parasitic, 11%). Although the authors ensured internal consistency and external validity by using previously defined definitions of clinical disease, the lack of a control group (i.e., nonfebrile children) meant that they were unable to verify the clinical significance of most viral pathogens and, to some extent, other pathogens identified with the use of serologic or molecular markers.[7] The importance of a case–control design was recently exemplified in a hospital study of causes of severe and very severe pneumonia among Kenyan children younger than 5 years of age,[8] which included outpatient children without pneumonia as control patients. Respiratory viruses were present in nasopharyngeal swabs from 60% of case patients and 47% of control patients. With the exception of respiratory syncytial virus, no nasopharyngeal viral infection was found to be associated with hospitalization for pneumonia in the case–control analysis. Interpretation of test results therefore remains challenging in the context of nasopharyngeal colonization[8,9] and the persistence of genetic material in the nasopharynx — or in blood, in the case of rapid diagnostic tests for malaria.[7]

The second observation is that in the absence of critical illness and once malaria has been ruled out, most febrile outpatient children can be treated conservatively without antibiotics. The most common bacterial isolates found by blood culture in this study were enteric gram-negative bacteria; thus, once pneumococcal vaccine is widely used, treatment with recommended first-

line antibiotics will probably be ineffective. Targeting of high-risk subgroups (e.g., patients with human immunodeficiency virus infection, sickle cell disease, malnutrition, or severe illness) and associated likely pathogens on the basis of the presenting syndrome should be considered in future efforts to refine guidelines for prescribing antimicrobial agents.

New diagnostics have considerable potential to improve care, target treatment, and reduce the cost of unnecessary prescriptions and the downstream effects of antimicrobial resistance. However, a trial investigating the effect of rapid, point-of-care malaria diagnostics on case-management decision making, in which pretrial training of clinical staff emphasized that a negative test result should lead to consideration of an alternative diagnosis, did not show reduced rates of malaria treatment.[10] Ninety percent of antimalarial agents prescribed in the trial were for children with negative test results. As the epidemiologic landscape evolves, updated guidelines based on evidence such as that generated in the study by D'Acremont and colleagues are welcome; however, experience suggests that changing current practice will not be a straightforward process.

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From the Wellcome Trust Centre for Clinical Tropical Medicine, Faculty of Medicine, Imperial College, London; and the Kenya Medical Research Institute Wellcome Trust Research Programme, Kilifi, Kenya.

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