SUBSPECIALIST CONSULT

Genetic Evaluation of Children

Genetic testing has entered a new era in the past few years. Our ability to perform DNA-based tests and identify an individual's susceptibility to cancer, heart disease, diabetes, and so many other conditions is beginning to have a major impact on our practice of medicine.

ROBERT MARION, M.D.

Experts predict – thanks to advances in technology we already have – that in a few years we will be able to screen during the newborn period and identify every mutation and polymorphism present. This screening will permit us to predict a child's "medical life" through identification of individual susceptibilities to disease likely to develop during his or her lifetime. Although still in its infancy, this technology would revolutionize pediatrics from a field in which we *wait* for the child to develop symptoms and signs of disease and then *react* with medication and other treatments, to one where we can *predict* disease. This will give us the opportunity to help our patients in a whole new way: to prevent the symptoms and signs from arising in the first place.

With the good comes the bad, as with any new technology. For example, interpretation of results with this advanced testing will require special expertise in genetics and genomics. Unfortunately, interpretation of genetic findings often is not as "black and white" as diagnosis of anemia based on serum hemoglobin and hematocrit levels. Genetic test results often include polymorphisms, and most of these variations of normal are benign and not associated with disease. Subspecialist consultation may be needed to make these important distinctions.

General pediatricians play an essential role in interpretation of newborn screening tests. Fortunately, results are normal for the majority of children and no further follow-up is indicated. However, if an abnormality is detected, referral to a specialist is warranted to facilitate an early intervention that, in some cases, can make a difference in the long-term health of the child. You also can refer families who request consultation with a geneticist to discuss recurrence risk in future progeny and for additional genetic testing, as indicated.

Beyond standard newborn genetic screening, the role of the pediatrician is somewhat limited regarding the screening and testing for specific genetic disorders. However, there are situations in which the pediatrician should feel comfortable in ordering and interpreting genetic tests.

For example, testing in children with intellectual disabilities and autism spectrum disorder has become standard. As tier 1 testing in such children, I usually order a microarray-based comparative genomic hybridization (array CGH), a test that has largely replaced high-resolution chromosome analysis in this population. I also perform DNA testing for fragile X syndrome, the most common inherited cause of intellectual disabilities. Because the results of this testing will be normal in 80%-90% of these children, I encourage pediatricians to order these tests themselves. I then make myself available if genetic evaluation reveals an abnormality.

Another factor to consider is the recent direct-to-consumer marketing of genetic testing that expands standard newborn screening or uses genetic markers to predict susceptibility to specific conditions. These tests often require the family, with or without the assistance of the pediatrician, to send a sample of DNA to a reference lab. The lab returns the results directly to the family. Again, the laboratory results are difficult to interpret, and you may be called on to provide guidance. Sometimes interpretation is straightforward, but in other cases it can be tricky, and if you are uncomfortable you might want to refer them to a medical geneticist or genetic counselor.

When you refer a child to a geneticist, include all results of your previous testing, those performed by other specialists, and newborn screening. Genetic tests performed on the mother during the pregnancy (for example, amniocentesis, chorionic villus sampling, sonograms, and/or biochemical screening tests) also are important. Provide any imaging findings, including MRIs or CT scans.

Proceed cautiously when counseling families regarding results of genetic testing. It can be trickier than you might think. For example, results of a test for a single gene disorder might uncover a previously unknown change in the child's DNA. The finding could be a benign polymorphism that has no clinical consequences or it could be a pathogenic mutation responsible for the child's signs and symptoms.

Simply informing the family about this finding is inadequate. To be certain, the parents need to be tested. If one or both of them has the same genetic change, the polymorphism might be benign. In contrast, if neither parent has the mutation, the child's test result might reflect a spontaneous genetic change and increase the likelihood you have discovered the cause of the clinical condition.

In general, there are three categories of children who may require genetic testing. First, there are those children who have multiple congenital anomalies or dysmorphic features. These findings could be caused by chromosome abnormalities, single gene mutations, or teratogenic agents. In these children, in order to ensure that the appropriate tests are ordered, a genetic consultation is important.

A second group of children who may require genetic testing are those in whom deviation from typical development or "normal" growth parameters occur during the first few years of life. Such children may have chromosome abnormalities, single gene mutations, and/or an underlying metabolic disorder. Keep in mind seizures, developmental regression, failure to thrive, and respiratory disturbances can bolster the likelihood of a genetic or metabolic etiology.

Before ordering any genetic testing, it is essential to take a complete patient and family history and to perform a complete physical exam. Children with a family history of a first- or second-degree family member with a genetic disorder also might benefit from genetic evaluation, comprising the third group. For example, even before symptoms are present, testing a child who has a brother with Duchenne muscular dystrophy or a relative with cystic fibrosis may prove life saving if it uncovers a similar diagnosis. ■

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New Combo Acne Treatments 'Powerful,' but Costly

BY LAIRD HARRISON

EXPERT ANALYSIS FROM A PEDIATRIC UPDATE

LAS VEGAS – New combination drugs have given clinicians powerful weapons against acne, according to Dr. Lawrence Eichenfield, assistant chief of pediatric and adolescent dermatology at the University of California, San Diego.

"I can wipe out virtually anyone's acne," he said at the update, sponsored by the American Academy of Pediatrics California District 9. "We are capable of doing it with the broad range of medications we have."

The condition varies widely in the number of lesions, the amount of scarring, and the patient's perception. "There are some teenagers who might have one pimple, but to them it's like a volcano," he said.

Retinoids are considered the base therapy for any significant acne because they target microcomedos, the precursors to acne lesions. Topical retinoids are usually enough for comedonal acne. Benzoyl peroxide can be used as an alternative. For more moderate cases, a topical antibiotic may be needed.

The bacterium implicated in acne, *Propionibacterium acnes*, can develop resistance to topical antibiotics. But combining antibiotics with benzoyl peroxide minimizes this resistance. So some of the new gels combine benzoyl peroxide with clindamycin. There are also tretinoin-clindamycin and adapalene–benzoyl peroxide combinations.

"These are excellent products," said Dr. Eichenfield. "Probably the only negative is the cost." Some can run as much as $160 a tube, he noted.

If these treatments fail or if the acne is very severe, an oral antibiotic may be needed, but should be used only in combination with topical retinoids. Finally, if these fail, he said, you can prescribe isotretinoin.

Once the acne is under control, the medication can be scaled back and should be predominantly topical. In older adolescent females, hormonal therapy may be an alternative. "We try to minimize the use of systemic antibiotics," said Dr. Eichenfield. "Get control over 2-3 months, and then try to back down."

No medication is approved for acne in patients under age 12 years, he said. But acne vulgaris is reported in more than three-quarters of children in this age range, so it's not unreasonable to think about treating them with a topical retinoid. Dr. Eichenfield and his colleagues investigated this possibility in an open-label study of 40 patients aged 8-12 years with mild to moderate acne (Pediatrics 2010;125:e1316-23). After 12 weeks of treatment with 0.04% tretinoin microsphere gel supplied in a pump, 75% of cases were graded as almost clear or mild. The total lesion count decreased 49.8%, and there were significant improvements in the Evaluator's Global Severity Score and the Alternative Evaluator's Global Severity Score.

'We try to minimize the use of systemic antibiotics. Get control over 2-3 months, and then try to back down.'

DR. EICHENFIELD

Patients had only mild adverse reactions, mostly skin irritation in the first 3 weeks of therapy. One patient discontinued use of the medication.

Such data have made Dr. Eichenfield an advocate of taking acne seriously. "It's much easier to prevent scarring than to get rid of it later," he concluded.

Dr. Eichenfield disclosed ties to the following companies: Astellas Pharma, Coria Laboratories, Galderma, Ortho Dermatologics, GlaxoSmithKline (Stiefel), Sanofi-Aventis, and Johnson & Johnson. ■