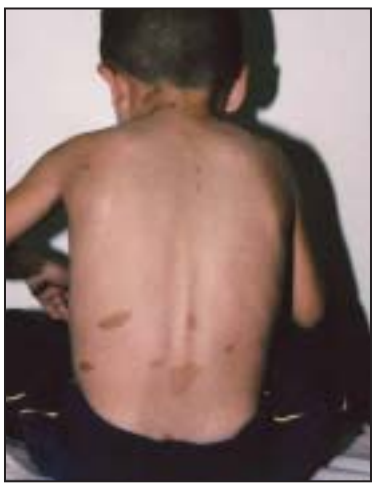
Watchful Waiting Best in Kids' Neurofibromatosis

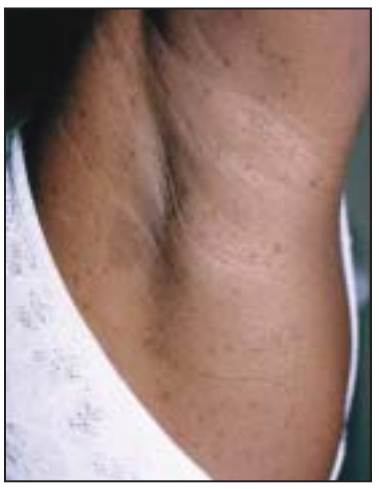
BY DOUG BRUNK
San Diego Bureau

LA JOLLA, CALIF. — The way Dr. Lynne M. Bird sees it, the $1,500 gene sequencing test for neurofibromatosis type 1 in children is rarely necessary because it usually does not change clinical management.

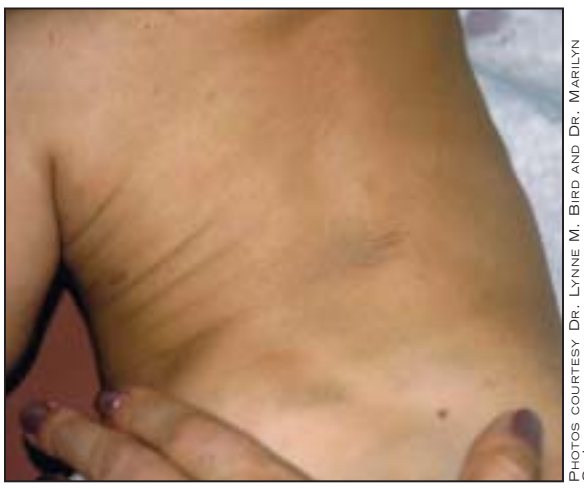
She favors a watchful waiting approach in children who present with the hallmark symptom of at least six café au lait macules that are at least 5 mm in size, "and [I] wait for the second criterion to appear," she said at a meeting sponsored by Rady Children's Hospital and the American Academy of Pediatrics. "I follow these children as if I already knew they had NF1, monitoring them for potential complications without doing gene testing."



Cafe au lait macules, shown here, are usually the first sign of NF1.



Axillary freckling is often evident later in the school-age child.



The Riccardi sign, a tuft of hair near the spine, may be present at birth and may even precede macules.

Photos courtesy Dr. Lynne M. Bird and Dr. Marilyn C. Jones

The prevalence of neurofibromatosis type 1 (NF1) is 1:3,000, making it the most common neurocutaneous disorder in children. Diagnosis is made if the child meets two of seven criteria: café au lait macules; axillary or inguinal freckling; two or more neurofibromas or one plexiform neurofibroma; optic nerve glioma; two or more Lisch nodules of the iris; a distinctive osseous lesion such as pseudarthrosis or sphenoid wing dysplasia; or a family history of the disease.

About of half of cases with no family history meet criteria for the disorder by 1 year of age; 97% meet the criteria by 8 years of age.

NF1 is an autosomal, dominantly inherited disorder due to mutations in a gene on chromosome 17, which encodes the protein neurofibromin, a tumor suppressor. "Finding a mutation of the gene would also allow you to make this diagnosis," said Dr. Bird of the division of genetics and dysmorphology at Rady Children's Hospital, San Diego. "If you have a parent with NF1 and you can determine their mutation through genetic testing, then you can offer them prenatal diagnosis. In my experience, most parents aren't concerned enough about passing NF1 on to their children that they would consider interrupting a pregnancy. But some families have experienced major complications associated with NF1, and they are very interested in not passing the gene on to their children."

A study of nearly 1,900 patients with NF1 found that the features of the disease typically appear in a characteristic order, beginning with café au lait macules (Pediatrics 2000;105:608-14).

Sometimes macules are present at birth "but others will appear in the first few months of life and certainly by the first couple of years of age," Dr. Bird said. "Typically the next feature is axillary freckling, which is usually evident in the school-age child. Lisch nodules will appear gradually after that, followed by neurofibromas as a sign that the child is entering puberty."

Another clue is the presence of the Riccardi sign, a tuft of hair along the back near the spine. "This sign will often be present at birth and may be there before any of the café au lait macules show up, so you will look really smart if you make a tentative diagnosis upon seeing this," Dr. Bird said.

Optic glioma almost always appears by 3 years of age "and certainly by 6 years of age," she said. "In addition, there is frequent thickening of the optic nerves, which is asymptomatic and doesn't cause disease."

A rare feature of NF1 is juvenile xanthogranuloma, which occurs in 1%-2% of cases. This skin lesion usually resolves spontaneously but is associated with an increased incidence of juvenile myeloid leukemia (JML). "When you see this, you want to at least do a complete blood count and be thinking about JML, and maybe contact your local oncologist to see if they have further recommendations for monitoring," she advised.

In most cases, the diagnosis of NF1 is made on clinical exam, including a careful evaluation of both parents. "This condition is present in 1 in 3,000 in the general population, but I don't see anywhere near the equivalent number of kids in my clinic," Dr. Bird said. "That tells me there is a lot of undiagnosed NF1 out there. Most parents [with NF1] are healthy; they just have spots and a few lumps on their skin."

The best way to follow children with NF1 is to see them regularly for a complete physical examination and review of systems. There is no way to screen for every single complication of NF1 except by talking to families, said Dr. Bird, who is also with the department of pediatrics at the University of California, San Diego. "Families should be told that symptoms which are not self-limited need to be brought to your attention," she said

Basic follow-up tests should include checking blood pressure and monitoring for scoliosis as well as an ophthalmology evaluation and an assessment of developmental skills. "Learning disabilities are common," she said. "Expressive language delay is the area of development most commonly affected."

NF1 patients with neurofibromas have a 10% lifetime risk of developing a malignant peripheral nerve sheath tumor within one of the lesions. Signs of malignant degeneration include persistent pain, a change in texture, a rapid increase in size, or development of a neurologic deficit associated with the neurofibroma.

Dr. Bird said she had no relevant disclosures to make. ■

Follow-Up Surveillance for Primary Melanomas Often Overdone

BY BRUCE JANCIN
Denver Bureau

WAIKOLOA, HAWAII — Dermatologic surveillance following diagnosis of a primary melanoma is often overly intensive, Dr. Daniel G. Coit asserted at the annual Hawaii dermatology seminar sponsored by Skin Disease Education Foundation.

"The key recommendation for melanoma patients is that they ought to go on lifetime dermatologic surveillance. … We find a lot of patients who are fairly low risk undergoing dermatologic surveillance every 3 months for the rest of their lives," said Dr. Coit, a surgeon who is coleader of the Melanoma Disease Management Team at Memorial Sloan-Kettering Cancer Center in New York and a member of the American Joint Committee on Cancer melanoma staging committee. "You don't need to follow up everybody three or four times a year."

Annual skin surveillance is entirely appropriate in melanoma patients who are not in a subgroup at elevated risk for another primary melanoma, he said. These high-risk subgroups include melanoma patients who have dysplastic nevi, who have a positive family history for melanoma, or who have already been diagnosed with a second primary tumor, he continued.

Several years ago Dr. Coit and his Sloan-Kettering colleagues examined this issue of second primary melanomas in detail. They reported on 4,484 patients with primary melanoma who were followed prospectively at the tertiary cancer center; 8.6% went on to have two or more primary melanomas. Patients with more than one primary melanoma averaged 2.3.

The estimated cumulative 5-year risk of a second primary melanoma was 11.4%. Fifty-nine percent of patients presented with their second primary tumor within 1 year of their first. After that first year, the incidence in patients without a family history of dysplastic nevi leveled off at about 0.3% a year, less than many physicians might expect. That low long-term annual rate was quite similar to the figure reported in an earlier analysis of the Duke University (Durham, N.C.) melanoma database, he noted (Surgery 1993;113:330-9).

Not only were most of the second primary melanomas detected during the first year of surveillance in the Sloan-Kettering series, but most of those diagnosed in the first year were found when the initial primary was diagnosed. "With the heightened awareness created by finding a primary melanoma, these patients undergo a complete and very thorough review, and other suspicious lesions are biopsied. After that, the slope of the curve [of incident second primary melanoma] is actually pretty flat." But this was not the case in the high-risk subgroups. In such patients, a case can be made for lifetime dermatologic surveillance more often than annually, Dr. Coit said.

In the Sloan-Kettering study, the subgroup of melanoma patients at highest risk of another primary tumor consisted of patients who had already been diagnosed with a second primary melanoma; they had a 15.6% incidence of a third primary tumor within 1 year of their second and a 31% probability of developing a third primary within 5 years (JAMA 2005;294:1647-54).

Forty-nine percent of patients had their second primary melanoma on the same body site as their first. The greatest site concordance was 60% for lesions on the extremities.

Dysplastic nevi, which for the most part were diagnosed clinically rather than histologically in this study, were present in 18% of patients with a single primary melanoma and 38% with multiple primary tumors.

Dr. Keith T. Flaherty, a medical oncologist at the University of Pennsylvania, Philadelphia, noted the risk over time is not linear, depending instead on the stage of the first primary melanoma. The risk is greatest early on for those with high-risk disease and much more spread out over time in patients with early-stage disease. "That needs to inform our surveillance," he said.

Dr. Coit concurred. "Almost no one with early-stage disease recurs early, and almost no one with late-stage disease recurs late."

The Skin Disease Education Foundation and this news organization are wholly owned subsidiaries of Elsevier. ■