Tracking and Monitoring Patients With Genetic Conditions

ACGME Sub-competencies / Developmental Milestones Addressed

**Patient Care**: Gather essential and accurate information about the patient; Make informed diagnostic and therapeutic decisions; Develop and carry out management plans

**Practice-based Learning and Improvement**: Identify strengths, deficiencies, and limits of one’s knowledge

**Professionalism**: Develop awareness of limitations to engage in help-seeking behaviors

**Systems-based Care**: Coordinate patient care within the health system

Overview
As a pediatrician, you are at the forefront of pediatric primary care and may have the opportunity to diagnose a child with a genetic condition at any time—at an acute-care visit or at a well-child check (WCC). You need to be tuned in to this possibility at each encounter with a patient, because early diagnosis and intervention may prevent complications. The diagnosis of genetic disorders can also be a significant benefit to any members of the patient’s family who are still in their reproductive years, in that a diagnosis can give the family members the opportunity to obtain reproductive counseling.

While serving as a medical home provider and interacting with children and their families, you can track and monitor patients, remaining aware of the natural history of the condition, including any complications that might arise. Understanding the natural course of genetic disorders and knowing when, and to whom, to refer your patients will allow you to provide them with the optimal care.

Learning Objectives
Upon completion of Tracking and Monitoring Patients With Genetic Conditions, residents should

- recognize the need for surveillance of children with genetic conditions to address health and developmental concerns,
- know how to locate health supervision guidelines for specific genetic conditions, and
- be able to identify key features of specific genetic conditions and be aware of the potential need for referrals to specialists.
Case Presentation

Presentation, Physical Examination, and Family History at the Newborn Follow-Up Visit

JT is a new patient to your practice. You saw her in the hospital after an uncomplicated 40-week gestation and vaginal delivery. Today she is in your office accompanied by her 27-year-old mother and 28-year-old father. JT is the couple’s first child, and they are excited and anxious about your assessment of their baby.

JT was discharged home yesterday and is 3 days old today. She is breast-feeding, and her mother's milk has just come in. JT’s weight is down approximately 6% from her birth weight. She is waking on her own to feed and is voiding and stooling appropriately. The parents' only concern is about the number of "birth marks" she seems to have on her back and legs.

Your physical exam reveals a vigorous 3-day-old female infant in no distress. Overall the examination is within normal limits, except for skin findings: on her back and upper legs, JT has 7 flat hyperpigmented areas varying in size from 5 to 7 mm. The macules have smooth (not irregular) borders. No other abnormalities are noted.

You take an expanded family history and note that the parents report no inherited diseases or disorders. Both parents are healthy, and the only positive family history reported is adult cardiovascular disease.

Question 1. Which of the following statements about the skin findings noted above is correct?

(A) The macules are located in areas of little concern (the back and upper legs)
(B) The presence of 6 or more café-au-lait spots (CLSs) with diameters equal to or greater than 5 mm is cause for concern
(C) Macules in 3-day-old infants are usually benign and are not worthy of further investigation
(D) Macular changes in infants are usually hypopigmented, so hyperpigmented changes are of little consequence

The presence of 6 or more CLSs with diameters equal to or greater than 5 mm warrants consideration for a neurocutaneous disorder such as neurofibromatosis type 1 (NF1). The location of the macules can be quite variable in NF1, but their presence warrants further evaluation, even in a 3-day-old infant. A variety of disorders present with macular changes, which can be either hypopigmented or hyperpigmented, and both types can be diagnostically significant. Irregular borders can be a sign of other conditions, such as McCune-Albright syndrome.

Question 2. You can be confident that your patient has NF1. True or false?

The correct answer is “false.” Diagnosis of NF1 requires 2 or more of the following clinical criteria:

- Six or more CLSs with diameters equal to or greater than 5 mm in prepubertal patients and 15 mm in postpubertal patients
- Two or more neurofibromas of any type, or one plexiform neurofibroma
- Freckling in the axillary or inguinal regions
- Optic glioma
- Two or more Lisch nodules
• Distinctive osseous lesion—sphenoid wing dysplasia or thinning of the cortex of long bones with or without pseudoarthrosis
• First-degree relative with NF1

At this point, JT meets just one of the above criteria; the presence of CLSs alone is not sufficient to allow you to diagnose NF1. It is important to emphasize that a more-thorough family history should be taken to be sure that no other family members are affected. Examination of the parents is recommended to rule out subtle manifestations.

A thorough family history is negative for any of the problems associated with NF1. The parents have no cutaneous changes.

**Question 3.** Which of the following statements is correct?

(A) A negative family history rules out NF1 in the patient.
(B) **A negative family history does not rule out NF1 in the patient.**
(C) Taking a thorough family history is unnecessary, because molecular testing can be done.
(D) Even though NF1 can result from a spontaneous mutation, this occurrence is so infrequent that you do not need to consider it.

You are unable to make the diagnosis at this point with just CLS noted. Fifty percent of the time, NF1 is the result of a spontaneous mutation, so you cannot reassure the parents that NF1 is not present. A negative family history and lack of physical signs in the parents makes a heritable mutation unlikely but does not rule it out in the infant. JT will need to be monitored closely at follow-up WCCs for other criteria that would allow you to make the clinical diagnosis of NF1. A clinical diagnosis will be based on 2 or more of the above mentioned criteria. Molecular testing can detect 95% of mutations in NF1, but such testing is typically not indicated, because in 95% of cases, the diagnosis can be made on the basis of clinical findings alone.

Providing the parents with anticipatory guidance about the importance of complying with routine well-child care and reporting any new or unusual findings is necessary. Additionally, you should reassure the parents that CLSs are cosmetic findings without clinical significance and that they may increase in number and size throughout JT’s childhood.

**Presentation and Physical Examination at the 2-Week and 2-Month WCCs**

At JT’s 2-week WCC, you find that she is growing well. Your exam reveals no new findings, and there are no new reports from her parents. At the regularly schedule 2-month WCC, her parents report a “bump” that seems to have gotten larger since birth, and a few more “birth marks” have developed. JT is otherwise well.

Review of her growth charts at the 2-month WCC reveals normal weight and length curves (50th percentile), but you note that her head circumference is approaching the 90th percentile. Your exam confirms the addition of 2 more CLSs with diameters of >5 mm. You appreciate the “bump” described by the parents on her back near the midline, and this “bump” is under a hyperpigmented area that was initially documented as a CLS.

**Question 4.** What concerns, if any, do you have in light of your new exam findings?

(A) The nodule under the hyperpigmented macule could be a cutaneous neurofibroma.
(B) **The nodule under the macule could be a plexiform neurofibroma.**
(C) The nodule under the macule could be a central nervous system tumor.
(D) You have no concerns. The nodule under the macule is probably just a hemangioma that has yet to emerge.

Cutaneous neurofibromas are highly unusual at this age, and it is unlikely that the nodule is a central nervous system tumor. A hemangioma could be present but typically is not a part of the NF1 complex. Plexiform neurofibromas are found in 25% of individuals with NF1 and typically are congenital. This finding (which will need to be confirmed by tissue biopsy), along with the number of CLSs previously documented, now leads you to the clinical diagnosis of NF1. Plexiform neurofibromas can involve multiple organ systems and can give rise to complications if they impinge upon or penetrate underlying structures (the spinal canal, in this case).

Referral to genetics should be considered to assist in the diagnosis and to provide counseling about the disorder, the mode of inheritance, and the risk of recurrence.

**Question 5.** Is there anything different that you should do regarding JT’s routine health supervision visits now that you suspect NF1?

(A) No, because NF1 is typically a mild disorder, no special health supervision measures are necessary.
(B) No, because if anything out of the ordinary develops, it will be easily identified and treated.
(C) Yes, following specific health supervision guidelines for children with NF1 might be helpful.
(D) No, because health supervision guidelines for NF1 are applicable only to adults.

There are specific health supervision guidelines for children with NF1.1 These guidelines outline additional screenings and treatments that may be needed for these individuals. Additionally, there are NF1-specific growth charts to track growth.

On average, children with NF1 have larger heads than children without NF1; the increased size is likely secondary to increased brain volume rather than to hydrocephalus. These children are often shorter than non-NF1 children as well. Plotting growth on NF1-specific growth charts will allow you to appropriately monitor growth.

JT will also need to be referred to a pediatric ophthalmologist. The presence of Lisch nodules (small clinically insignificant nodules on the iris) can be another diagnostic sign. Other findings around the eye and optic tract can include optic gliomas and proptosis caused by sphenoid wing dysplasia. The former are present in up to 15% of children with NF1 and can cause various problems but are typically asymptomatic. Yearly eye exams are recommended.

Careful physical exams should be completed at each of JT’s future visits, and any new findings should be carefully documented to track and monitor new skin findings, eye findings, growth parameters, and skeletal findings.

Other specialists might be needed to assist with various complications that can occur in NF1.

**Presentation and Physical Examination at the 18-Month WCC**

JT has done well over the past year. Her parents have adhered to the schedule for health supervision visits, and she has been evaluated by a pediatric ophthalmologist and has a routine follow-up scheduled. Parents report noting freckling in her underarm area and are worried that she is not talking as well as other 18-month-old children they know.
Case 2

Review of NF1-specific growth charts shows that JT is following her curves. You confirm the presence of bilateral axillary freckling on exam. JT is shy in the office, and you are unable to accurately assess her speech. No other abnormalities are noted on exam. Both the number and size of the CLSs are stable. There are no new palpable lesions, and no proptosis is noted on exam. Her skeleton appears normal.

**Question 6.** What concerns, if any, do you have in light of your new exam findings?

- (A) Axillary freckling is a new and potentially troublesome sign.
- (B) Speech delay is not worrisome and can just be followed.
- **(C) Speech delay should be evaluated.**
- (D) Speech and shyness go hand-in-hand and can just be followed.

Delayed development can occur in children with NF1. Referral to early intervention at this point is warranted. Both motor and speech delays may be present.

Axillary freckling is a cosmetic finding, just like CLSs, but is another diagnostic criterion. Sunscreen should be recommended, as for any child, but there is no increased risk of melanoma associated with CLSs.

**Presentation and Physical Examination at the 6-Year WCC**

JT continues to do well. She is receiving services through early intervention and has made progress. You have seen her routinely, and no complications have been noted. She is in 1st grade, and her parents report that she is falling behind in school. The problems in school are worrisome to her and her family. She seems to struggle with reading, and her teachers report that she often loses focus. Today’s physical exam reveals no new findings, and previously noted findings are stable. She continues to track appropriately on her growth charts. Her blood pressure is noted to be in the 90th percentile today.

The problems in school are concerning to the patient and the family.

**Question 7.** Which of the following statements is incorrect?

- (A) Learning disabilities can occur frequently in children with NF1.
- (B) All children are at risk for learning disabilities.
- (C) Learning disabilities are infrequently in NF1.
- (D) Poor school performance should be evaluated in the context of NF1.

Attention deficit hyperactivity disorder occurs frequently in children with NF1. Specific learning disorders are also seen in 40–60% of children with NF1. Appropriate screening and evaluation are needed at this time.

**Presentation and Physical Examination at the 12-Year WCC**

JT was diagnosed with attention deficit hyperactivity disorder and a specific reading learning disorder. She is receiving accommodations in the classroom and is managed with stimulants. Overall, she is doing well in school. Her blood pressure has remained stable while on the stimulant. She is concerned because she is not as tall as the other girls in her class, and she is not as “developed” as the other girls. JT’s mother reports that her own menarche occurred at age 12. Both JT and her mother report a few more CLSs and new skin tags that have developed over the past several months.
Review of her growth charts reveals that JT is continuing to follow her curve and that she is on the smaller side even on the NF1-specific curves. Physical exam reveals Tanner 2 breast development and Tanner 1 pubic hair. You confirm the findings of new “skin tags.” Otherwise her exam is unremarkable. No scoliosis is noted.

Factors to be considered at this age include the following:

- Delayed pubertal development is not a rare finding in NF1. You can reassure JT and her mother that she is beginning to show signs of sexual maturity. She will likely be shorter than most of her peers, and in individuals with NF1, it is not rare for the pubertal growth spurt to be reduced. You will continue to follow her development at WCCs.
- Dermal neurofibromata are found frequently in NF1 patients and may initially present as skin tags. They can increase in size and number as JT goes through puberty.
- Scoliosis is noted in 10–30% of patients with NF1.
- Elevated blood pressure should be monitored closely. Although essential hypertension is the most common form noted, the risks of renovascular disease, vasoactive secreting tumors, and coarctation of the aorta are increased in children with NF1.

**Presentation and Physical Examination at the 15-Year WCC**

JT has progressed through puberty normally. She has some mild developmental delays, and her mother is concerned about risk-taking behavior in her adolescent daughter. JT is concerned about the “bump” on her back because it seems to be getting bigger. She has been routinely followed by the ophthalmologist. School is going okay.

Physical exam reveals normal blood pressure and normal growth patterns. You confirm the increase in size of the previously diagnosed plexiform neurofibroma on her back. You do not note any new skin findings today. No scoliosis is noted on exam.

Factors to be considered at this age include the following:

- Enlargement of plexiform neurofibromata can occur at any time during childhood. Further evaluation may be necessary to ensure that infiltration of underlying tissue does not occur. The local effects of the tumor should be monitored as well as a potential transformation into a malignant tumor. The latter transition is unusual but can occur and deserves close attention.
- Anticipatory guidance regarding sexuality and risk-taking behaviors should be provided. Birth control and effects of pregnancy on NF1 should be discussed. Discussion of the transition of care should be a part of all future WCCs.
- Because of the autosomal dominant inheritance of NF1, JT has a 50% risk of having an affected child, even given the negative family history.

**Summary**

This report of a patient with NF1 emphasizes the need to observe and document abnormal physical findings over time. Such findings might be insignificant (such as skin birth marks), or they might be clues to a more widespread condition with multiple manifestations (growth, cardiovascular, central nervous system, development, school performance, and further skin changes, to name just a few). Referral to a geneticist for diagnostic confirmation and counseling should be strongly considered.
The primary care provider can manage NF1 with appropriate assistance from subspecialists as needed, along with health supervision guidelines.

The multiple features of NF1 exemplify 2 other genetic principles—pleiotropy (the various features and systems affected by a single genetic mutation) and expressivity (the variability of expression of NF1 features from patient to patient; i.e., not all family members with the same mutation will have identical expression). These principles can be exhibited in many other disorders and are always worthy of consideration during any evaluation of a genetic disorder.

The diagnosis of a genetic disorder, the treatment of its manifestations, and the prevention of any complications continue to be the mainstays of “thinking genetically” for the primary care provider. JT’s case emphasizes the need for constant attention to any atypical physical signs and for subsequent monitoring for changes over the life of the child, the hallmark of the medical home model. Close collaboration between the primary care provider and medical specialists will be necessary to optimize the child’s care and to ease the burdens of the parents as they maneuver through the health care system.

References

Resources for Parents and Caregivers