The Potential Role of Epigenetics in Asthma
Sample Scenario

1. Case

**History, Physical Examination, and ROS:**
- Infant Boy Smith weighed 6# 3 oz. (3.5 kg) at birth after 37 week gestation. His 27-year-old mother was primigravida, is 5 foot 3 inches and weighed 165 pounds prior to her pregnancy. She had pre-eclampsia and the child was at the 90th percentile by ultrasound early in pregnancy falling to 10-20th%ile by 3rd trimester. At age 12 months, the child developed RSV + viral pneumonia and was hospitalized for 4 days, but makes a seemingly full recovery. At age 4, the child had an episode of wheezing necessitating a visit to the ER.
- At age 5, a second wheezing episode occurred with an unknown trigger. He was hospitalized for 2 days and sent home on a regimen of Albuterol inhaler with spacer and short course of Prednisone.
- He has 3 more episodes in the next 18 months, successfully treated in your office and managed with a short course of prednisone. You see him at his age 7 visit.

**Family and Social History:**
Mother did not smoke but father did during pregnancy. The family lived in New York City until the child was 2 months old then moved to the suburbs. Mother and father are now separated. Mother reveals there is a restraining order against Dad, but that he never hit or physically abused the baby. No labor or delivery complications were noted. The newborn exam was normal. There is a family history of asthma on the father’s-side-only per mother.

2. What Role Does Epigenetics Play in this Case?
The possible reasons for the asthma/wheezing are considered to be a combination of:

- Maternal obesity
- Exposure to air pollution (once thought to be only an asthma trigger)
- Exposure to stress
- Previous bronchiolitis
- Fetal growth restriction

These factors are associated with a variety of health issues later in childhood and adulthood, and can be considered to be of significant importance for the overall health of the individual.

These factors can also alter epigenetic marks that in-turn can alter the short-term and long-term of expression of genes and have a dramatic effect on the expression of various disease states. Candidate genes include growth factors (impacting lung growth), immunomodulatory factors, stress impacting cortisol metabolism, previous RSV infection perhaps producing inflammatory airway damage, and second hand smoke exposure in pregnancy. Virtually all of these risk factors have been associated with various changes in epigenetic marks.
Remember, the genes have not been altered. The expression of the genes is potentially altered and that may be as important as inheriting a genetic predisposition for a certain problem. It actually may prove to be more important.

a. Diagnosis

- The proper documentation of the information in this case scenario can assist the pediatrician in the diagnosis of disorders that might be associated with the risk factors noted. While these risk factors might not appear to be relevant in early-life when the child appears healthy, the epigenetic marks have been set to program asthma and they will be very important later.
- Is it appropriate to test the methylation status of the glucocorticoid receptor in a blood draw? At present, no. Epigenetics is tissue specific. The relevant tissue may not be the blood, at least for the glucocorticoid receptor and asthma. A change in DNA methylation in blood may have no relationship to DNA methylation in the cells of the small airway. Note how this is different than a genetic test in which the tissue from which the DNA is obtained is irrelevant.

b. Treatment

No specific therapeutic intervention currently exists for the information documented in this scenario, yet it is reasonable to surmise that in the future various modalities will be available to alter epigenetic risks (expressed as epigenetic marks). The goal at present is to recognize that we can prevent not just childhood disease but also adult diseases, perhaps even neurodegenerative disease, by the counseling and interventions we provide to patients when they are children.

3. Epigenetic and Prevention Messages

Epigenetic susceptibility should not be thought of as deterministic, instead it should be considered a trajectory. Changes that can have positive influences (cleaner air, less stressful home environment, less secondhand smoke exposure, etc.) can influence epigenetic marks such as DNA methylation toward more favorable gene expression profiles.

As noted above, knowledge of epigenetic risk factors going forward will assist the pediatrician in their anticipatory guidance and prevention of various problems for their patients. This means that recognizing and preventing even teenage and adult disease is part of our role as pediatricians, and that this role begins even before birth. These risk factors are just as important as the standard risk factors (past medical history and social history, to name a few) currently used in office visits. In fact, many of the standard risk factors we think about work through epigenetics, we just didn’t realize it. Prenatal and perinatal risk factor information can have a significant impact for the rest of a patient’s life.

Messages for the Family:

The prenatal circumstances for Infant Boy Smith could potentially affect his care in his school-age years. The mother must be counseled about the impact of her weight on her child’s health, on the risk of smoking and air pollution, and she must be assisted in her home social situation.
(If this counseling and help had occurred during or before pregnancy, the child’s asthma may have been prevented.)

With regard to counseling a father who smokes, pediatricians can offer to help him quit through an effective 30-second intervention, 2 As + R (Ask, Advise, Refer): Physicians Ask patients if they smoke, Advise them to quit, and Refer them to cessation services (1-800-QUIT NOW or to community/internet quit resources).

Note that some interventions (air pollution and perhaps family violence) will require pediatricians to work at the level of pediatric community public health rather than individually, but that does not mitigate the importance of such measures. The pediatrician and the health care team must be cognizant of all these factors and how they play a role in the health and development of their patients.