It is becoming more evident that epigenetics plays an important role in health and development, making this an essential technology for primary care providers to understand in order to, in the future, provide effective medical care to patients over a lifetime. This was part of the discussion during the webinar, “Epigenetics–What Your Patients are Asking, What You Need to Know,” held on December 20, 2012. The webinar, which featured Robert Saul, MD, FAAP, FACMG, and Robert Wright, MD, MPH, FAAP, was part of the Time Out for Genetics webinar series hosted by the Genetics in Primary Care Institute (GPCI).

**What is Epigenetics?**
Epigenetics is “the study of changes in gene function that occur without a change in DNA sequence.”

**Why is Epigenetics Important?**
- There is a misconception that epigenetic diseases are rare. While it is true that epigenetics causes some rare diseases, epigenetics plays an important role in almost every disease, including common diseases.
- Epigenetics performs a major function in the development of the human system.
- There is a mistaken belief that epigenetics is like genetics and cannot be changed, but epigenetics is actually modifiable. The likelihood that epigenetics will be used in the treatment of childhood diseases and developmental disorders in the future is greater than that for genetics.
- DNA methylation, histone modifications and microRNA are epigenetic mechanisms.
- Epigenetics regulates which genes get turned off and on for differentiation into specific cells.

**DNA Methylation Responds to the Environment**
- DNA methylation plays a role in development and responsiveness to the environment. For example, during the first year of life, identical twins have similar DNA methylation patterns, suggesting that these patterns are inherited. However, as identical twins age, their methylation patterns begin to change, most likely from environmental factors. In adulthood, differences in the DNA methylation patterns of identical twins are evident.
- Researchers examined the Agouti mouse which is sensitive to epigenetic changes to determine if diet can affect DNA methylation patterns. The mice fed a diet low in folic acid became obese, while the mice fed a diet high in folic acid was thin. This outcome suggests that DNA methylation regulates expression of this part of the health outcome and that diet was the determining factor in the expression of this particular phenotype. It also provides evidence that environmental health factors, such as diet, can help determine whether or not genes get expressed. If the mice were fed the exact same diet, they would look identical, but because they are fed different diets, they had different health outcomes despite having the exact same genotype.

**Histone Modification and MicroRNA: Important Epigenetic Factors**
- DNA is wound around histone proteins, and these proteins play a role in gene expression regulation. Histone modifications not only affect chromosome function but also the expression of specific genes.
- MicroRNA is critical in the development of organisms, differentially expressed in tissues, involved in viral infection processes and associated with oncogenesis. MicroRNA also regulates the expression of genes.
- Both histone modifications and microRNA respond to the environment just as DNA methylation does. These factors work in tandem.
Disorders with Epigenetic Etiology

- Angelman syndrome
- Autism spectrum disorders
- Beckwith-Wiedemann syndrome
- CHARGE association
- Fragile X syndrome
- Maternal duplication 15q11-13
- Metabolic syndrome
- Prader-Willi syndrome
- Rett syndrome
- Russell-Silver syndrome
- Common adult disorders believed to be caused by epigenetic changes that occurred in childhood include:
  - Heart Disease
  - Hypertension
  - Neurodegenerative diseases
  - Obesity

Epigenetics and Assisted Reproductive Technology

Although rare, there is evidence that suggests that assisted reproductive technologies might predispose a fetus to epigenetic conditions because of early methylation changes of zygotes around fertilization and implantation. Following are some of the epigenetic conditions that are possibly associated with assisted reproductive technologies:

- Angelman syndrome
- Beckwith-Wiedemann syndrome
- Maternal hypomethylation syndrome
- Retinoblastoma
- Russell-Silver syndrome

Epigenetics Can Have a Delayed Effect

Epigenetic changes can occur in utero and affect the postnatal development of the infant and child. In fact, historical evidence indicates that children conceived during famines in China and the Netherlands had a two-fold risk of schizophrenia as a result of intrauterine nutritional deficiency. There is some other evidence to suggest that epigenetic changes to environmental influences may be passed on to subsequent generations.

Key Factors That Cause Epigenetic Changes

There are many environmental health factors that affect epigenetic changes:

- asthma
- chemical exposures
- diet during slow growth period (SGP [ages 9-15 in males])
- endocrine disrupting compounds
- hypoxia
- maternal diabetes
- maternal physical state and age
- placenta size
- maternal smoking
- psychosocial stress
- psychological trauma
At this time, it is unknown how to apply information about environmental factors to epigenetic outcomes, but it is important to be aware of these factors because they will grow to be more important as they become better understood.

**Disease Prevention**

Understanding how to control epigenetics has the potential to prevent diseases because epigenetic changes early in life affect the onset and severity of diseases that occur later in life. As influences on DNA methylation, histone modification, and microRNA are better defined, more of these factors will be discovered and our understanding of how to prevent and treat diseases will improve.

**Diagnosis and Treatment**

Epigenetics will play a key role in diagnosis and treatment of many diseases in the future. Using epigenetics for diagnosis will help primary care providers understand the causes of the disease and to provide appropriate medical care, counseling, and anticipatory guidance for disease that may occur later in life. In some cases understanding epigenetics might assist in reproductive counseling. In addition, the future of epigenetic treatments may include methods to alter epigenetic marks toward better health and/or using our understanding of epigenetic mechanisms that affect DNA to more effectively diagnose patients.

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**About the Presenters**

Dr. Saul is a pediatrician, clinical geneticist, and medical director of General Pediatrics at the Children’s Hospital, Greenville Health System, Greenville, SC. He is also co-medical director of the GPCI, and chair of the American Academy of Pediatrics (AAP) Committee on Genetics.

Dr. Wright is a pediatrician, epigeneticist and environmental epidemiologist at Mount Sinai School of Medicine in New York, where he is also a professor of pediatrics and preventive medicine. He is also director of the Mount Sinai School of Medicine Division of Environmental Health, Department of Preventive Medicine and Director of the Molecular Environmental Health Lab.

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**About GPCI**

The GPCI was established to increase primary care providers’ knowledge and skills in the provision of genetic-based services. The GPCI is a cooperative agreement between the US Department of Health and Human Services, the Health Resources & Services Administration, the Maternal & Child Health Bureau and the American Academy of Pediatrics.

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