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MEDICAL GENETICS

Contributors

2 Unraveling the Mystery
A brief history of medical genetics and Emory's team
By Michael J. Gambello, MD, PhD

3 When Does My Patient Need a Medical Geneticist?
By Rossana Sanchez, MD

6 Genetics in Pediatrics
Genetic diseases that affect child health and development
By Suma Shankar, MD, PhD

10 Inborn Errors of Metabolism at a Glance
From newborn screening to multidisciplinary adult care
By Hong Li, MD, PhD

18 Single Gene Disorders with Presentation in Adulthood
By Jaime Vengoechea, MD

23 Treatment of Genetic Diseases: The Future is Here
By William R. Wilcox, MD, PhD

SPECIAL FEATURE

26 Where Cardiology and Vascular Care Go Hand in Hand
By Helen K. Kelley

SPOTLIGHT

30 Bariatrics
By Helen K. Kelley
CONTRIBUTING WRITERS

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Hong Li, MD, PhD, Dr. Li is an assistant professor of the Department of Human Genetics and Pediatrics at Emory University. As a board certified clinical and biochemical geneticist, she specializes in the diagnosis and treatment of inherited metabolic disorders, lysosomal storage diseases, genetic disorders with dysmorphic features and intellectual disability and extensively involved in the NBS follow up care for IEMs. She is also the medical director of the Genetic Counseling Training Program at Emory University School of Medicine. She completed her combined Pediatrics and Medical Genetics Residency at Wayne State University and Medical Biochemical Fellowship at Harvard Medical School. She is the PI for several clinical trials including PEG-PAL therapy for patients with PKU.

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Medical genetics is a relatively new subspecialty that is a mystery to many healthcare providers as well as the general public. We hope to unravel some of this mystery in this issue of Atlanta Medicine and enlighten you on some aspects of our practice at Emory.

At Emory, we do diagnose and manage rare diseases, which collectively are not that rare – but this is not exclusively so. Medical genetics involves the diagnosis and management of hereditary diseases, or the “science of human biologic variation as it relates to health and disease,” to quote Victor McKusick1, one of the fathers of medical genetics.

In spite of these definitions, our daily role is still not clear. However, by looking at the history of medical genetics and Emory’s role in this fascinating and technology-laden world, perhaps these definitions can be put in a better perspective.

A Brief History of Medical Genetics

Many clinicians noted familial segregation of disease before medical genetics surfaced as a young specialty in the 1950s. Over the next several decades, major discoveries in the basic science of human genetics led to the development of medical genetics. Noteworthy areas of discovery occurred in cytogenetics (the study of chromosomes), inheritance of discrete traits (sometimes called Mendelism, after Gregor Mendel’s studies on wrinkled and round peas), biochemical, population and molecular genetics.

The 1950s were transformative years. In 1953, Watson and Crick, using important data from Franklin and Wilkins, discovered the double helical structure of DNA, noting “it has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.”2

In 1956 Tjio and Levan developed a novel method to analyze chromosomes under the microscope and determined that humans have 46 chromosomes.3 In 1959 Lejeune showed that an extra chromosome 21 was the cause of Down syndrome, soon to be followed by the chromosomal nature of Turner syndrome and Klinefelter syndrome.1 During this time, the central dogma of molecular biology was also established: DNA is transcribed into RNA that is translated into protein.
The genetic code was “broken” in 1966 by the combined work of Holley, Khorana and Nirenberg and others. A three nucleotide codon specifies which amino acid will be incorporated into a protein. The first World Congress of Human Genetics was held in Copenhagen in 1956. The first chair of Medical Genetics, Maurice Lamy, was appointed in Paris. In 1957, specific medical genetics departments open in Baltimore (Victor McKusick at Johns Hopkins) and Seattle (Arno Motulsky at the University of Washington).

Victor McKusick, considered the father of medical genetics by many, published Mendelian Inheritance in Man (MIM), a catalogue of autosomal dominant, autosomal recessive and X-linked phenotypes. The exponential increase in genetic knowledge has transformed MIM to OMIM – Online Mendelian Inheritance in Man – A catalogue of Human Genes and Disorders (http://www.omim.org).

In 1977, Sanger developed a novel method of sequencing DNA, and the molecular era was full speed ahead. Using families and linkage analysis, gene identification and mapping for many Mendelian disorders were accomplished. In 1991, the American Board of Medical Genetics (ABMG), became the 24th organization to join the American Board of Medical Specialties. This board gives oversight to the training and practice of medical genetics.

By 1984, plans were underway to determine all the A’s, T’s, G’s and C’s that comprise the human genome, called The Human Genome Project. The project began in 1990 and was finished in 2003. It is amazing that only about 1 percent of the genome actually codes for genes (termed the exome) and that we only have about 20,000 genes. (Given the size of our genome, it was thought that we had at least 100,000.)

The remaining 99 percent of our genome appears to regulate gene expression, but there is still much research to be done.

Over the past 10 years, DNA sequencing technologies (called massively parallel sequencing) have improved tremendously, permitting whole exome sequencing (only 1 percent of the genome, i.e. coding genes only) for diagnostic testing in medical genetics. The next technology challenging medical genetics is whole genome sequencing. While The Human Genome Project cost $2.7 billion and took 13 years, a whole human genome now costs about $2,000 and can be done within a week.

Indeed we are in the genomics age, where we are now sequencing, assembling and analyzing the function and structure of genomes. Recently the ABMG changed its name to the American Board of Medical Genetics and Genomics to reflect the importance of genomics in our practice.

Medical genetics has indeed evolved quickly in just over 60 years. Today, there are many Medical Genetics Departments and Divisions throughout the U.S. that assist healthcare givers and patients navigate the rapidly advancing field of medical genetics.

The next technology challenging medical genetics is whole genome sequencing.
The Division of Medical Genetics at Emory

The Division of Medical Genetics at Emory University School of Medicine (genetics.emory.edu) was founded in 1970 by Louis “Skip” Elsas II, MD. Medical genetics was then part of the Department of Pediatrics to reflect a heavy emphasis on pediatric medicine. In 2001, Stephen Warren, Ph.D., founded the Department of Human Genetics at Emory. By 2002, the Division became formally affiliated with the Department of Human Genetics. This structure reflects an important historical and synergistic relationship between the clinical and basic sciences. While we certainly still care for many children, our practice has a much larger scope. The Division is composed of a variety of genetic providers, including physicians (the medical geneticists), genetic counselors, metabolic nutritionists, nurses, psychologists, a developmental pediatrician and other support staff.

Medical geneticists are physicians who have completed a two-year ACGME (Accreditation Council for Graduate Medical Education) accredited program in medical genetics. Typically, physicians who train in medical genetics have already completed a residency in a primary care specialty such as pediatrics, internal medicine, family medicine or obstetrics-gynecology.

Medical geneticists are encouraged to become Board Certified by the American Board of Medical Genetics and Genomics. The Board exists to protect the public by maintaining high standards for the practice of medical genetics. Emory has an ACGME-accredited training program in medical genetics (genetics.emory.edu/education). We provide inpatient consultation for Children’s Healthcare of Atlanta at Egleston/Scottish Rite and Emory University Hospital.

We have about 4,000 outpatient visits a year, and we anticipate 5,000 next year. Our patient population is diverse, and the subsequent sections of this issue will help you understand the scope of our practice and when your patient might need a consultation with the medical genetics team. Keep in mind that our mission is not only excellent patient care, but also research and teaching. Many of us are involved in discovering the genetic causes of new disease, conducting clinic trials, and teaching in the classroom and clinic.

Genetic counselors are health professionals who form an integral part of the medical genetics team. They complete a two-year ACGC (Accreditation Council for Genetic Counseling) accredited graduate program to gain experience in medical genetics, research and counseling. Students come from a variety of disciplines such as biology, nursing, social work, psychology and public health. The National Society of Genetic Counselors states that “genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease.”

In practice, their role varies widely. Some functions include taking medical and family histories, coordinating and interpreting genetic testing to patients and healthcare providers, coordinating clinical trials and teaching. Emory has an ACGC-accredited training program (genetics.emory.edu/gc_training) and is always looking for enthusiastic students.

Metabolic dietitian is another highly specialized profession. These healthcare providers help care for patients with inborn errors of metabolism, or biochemical genetic disorders. Some of these disorders result from a genetic defect in an enzyme that is important for detoxifying too much of a metabolite, or making energy. Most readers are familiar with phenylketonuria (PKU) – the inability to breakdown excess phenylalanine. Adherence to a strict diet from infancy prevents severe intellectual disability. In fact, the success of dietary treatment for PKU was a major impetus for the introduction of newborn screening programs that will be discussed in a subsequent section. We now screen for more than 30 disorders and identify many children and families who benefit from the expertise of a metabolic dietitian.

In this issue of Atlanta Medicine, you’ll find articles by many of my colleagues about various aspects of medical genetics, from infancy to adulthood. We hope that these brief articles will better define what we do and how we might be able to help you and your patients. Rossana Sanchez, MD, is a trainee in our medical genetics residency. She gives you a concise description of when your patients might benefit from a medical genetics consultation. Suma Shankar, MD, Ph.D., reviews aspects of medical genetics and pediatrics. Hong Li, MD, Ph.D., gives an excellent description of newborn screening programs and biochemical genetics. Jaime Vengoechea discusses some genetic disorders of adult medicine. Bill Wilcox, MD, Ph.D., demonstrates that we are not merely diagnosticians, but do indeed treat many genetic diseases.

References
Medical Genetics is a vast and rapidly advancing field. With an estimated 20,000 to 25,000 genes in the human genome, mutations in these genes give rise to many disorders. The scope of practice of a geneticist is necessarily broad, encompassing inpatient and outpatient consultations for inherited conditions and congenital malformations, for genetic counseling and risk assessment, for treatment of genetic diseases and prevention of complications, as well as for ordering genetic and genomic testing.1 The focus of genetics as a science is not solely on the patient, either, but also the patient’s family.

Preconception and Prenatal

The need for a medical geneticist may arise very early, sometimes even prenatally. As the science advances, mothers-to-be are offered special screening options for genetic conditions, such as the first and second trimester screen and the newer noninvasive prenatal testing (NIPT).2 These tests are designed to screen for aneuploidies (abnormal chromosomal numbers) of select chromosomes in the fetus via maternal blood. Common disorders caused by aneuploidies are trisomy 21 or Down syndrome, trisomy 13 and trisomy 18. It is common to offer this testing to mothers who are over 35 years of age, which is called “advanced maternal age.” The reason this age was originally chosen as an ideal screening time is because the risk of having a baby with Down syndrome was comparable to the risk of having a miscarriage as a result of an invasive procedure like amniocentesis to confirm this same diagnosis.

Usually, a certified genetic counselor explains all testing to parents and discusses age-related chromosomal problems when presenting results. If any of the screening tests are positive, then the mother should be offered confirmatory testing via amniocentesis. If an aneuploidy is diagnosed, then she and her partner will receive further genetic counseling so they have adequate information about the disease and understand their options. Confirmatory testing may also be offered if there are any fetal abnormalities seen on the ultrasound, including abnormal nuchal (posterior neck) translucency. Prenatal testing via amniocentesis or chorionic villus sampling (CVS) can also be offered for other genetic conditions that are present in the family if the mutations for a disease are known. Antenatal testing may also be offered to couples who have a family history of a disorder and wish to know if they are carriers and to couples with multiple (more than two) miscarriages or multiple stillbirths.

Some couples may also need preconception genetic testing. This is known as carrier testing or a carrier screen.3 Most people are carriers of genetic disorders that are recessive, and females can be carriers of X-linked disorders. Carriers do not usually have any signs or symptoms; however, if both partners in a couple are carriers for the same recessive condition, then the chances of a child being affected are 25 percent for each pregnancy. If a mother is a carrier of an X-linked disorder, then males have a 50 percent chance of being affected, and females have a 50 percent chance of being carriers. Ethnicity may also affect the chances of being carriers of certain disorders. For example, cystic fibrosis is well known to be more common in Caucasians, Tay-Sachs is more common in the Jewish population, and sickle cell disease is more common in African Americans. This is why initiatives like the Jewish Screen, or JScreen (www.jscreen.org), started. It initially screened for common mutations in genes that caused diseases in this population, but it has now expanded to include more genes and full gene sequencing to detect mutations in other populations, becoming a pan-ethnic carrier screen.

Couples who are carriers of a known genetic disorder and whose mutations are known also have a chance to deliver healthy children via pre-implantation genetic diagnosis, or PGD.4 This is a procedure used to screen embryos made via in vitro fertilization for genetic conditions, and then only unaffected embryos are implanted in the mother.

Neonatal

After birth, if any malformation is noted in a baby, a geneticist should be consulted. Common birth defects include cleft lip and palate or a congenital heart defect, which may
be isolated and nonsyndromic, meaning it is not related to other findings. These defects may also be seen as part of other disorders. A geneticist might recognize patterns that lead to a specific diagnosis or suggest a need for testing. It is common to order a chromosomal microarray when there are multiple congenital anomalies that are not explained by maternal exposures or deformations in utero. This test helps uncover missing or extra copies of genetic material, known as deletions and duplications, respectively, which may explain the myriad of signs and symptoms. If a diagnosis is confirmed, then there will be counseling with the family to discuss the diagnosis, possible complications and risks of recurrence.

In the neonatal period also comes the challenge of positive newborn screens. In the state of Georgia, we currently screen for more than 30 conditions. The false-positive rate tends to be high, so we must follow many children until confirmatory testing is complete. Some of the babies who are true positives appear clinically ill, even before the screen is back. Thus, inborn errors of metabolism should be considered in cases of suspected sepsis, seizures, lethargy, hyperammonemia or an anion gap acidosis, amongst other findings. In all these cases, a biochemical geneticist and metabolic nutritionist should be consulted. If a metabolic condition is diagnosed, then the patient will be followed by geneticists throughout his or her lifetime.

**Infancy and Childhood**

During infancy and childhood, common reasons for a genetic referral include developmental delay or regression and autism spectrum disorder (ASD). Developmental regression tends to be a more ominous sign but can be seen in many different disorders, including some inborn errors

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<th>Table 1. Indications for Medical Genetics Referral</th>
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<td><strong>Antenatal/Prenatal</strong></td>
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<td>Abnormal findings in prenatal screen</td>
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<td>Advanced maternal age</td>
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<td>Abnormal prenatal US</td>
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<td>IUGR</td>
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<td>Exposure to teratogens</td>
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<td>Mother with AFLP</td>
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<td>Recurrent miscarriages or stillbirths</td>
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<td>Carrier of a genetic condition</td>
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of metabolism like Tay-Sachs, neurological conditions like neuronal ceroid lipofuscinosis or Rett syndrome. Developmental delay may be fairly nonspecific and common in many disorders. A thorough history, physical exam and pedigree can help focus the diagnosis and target the testing strategy. Moreover, ASD may have an underlying genetic cause, and genetic testing is warranted in the initial stages of evaluation.

Another concern at this age is muscle weakness or hypotonia; again, this may be due to a number of different disorders, and it is important to rule out spinal muscular atrophy, Prader-Willi syndrome, and muscular dystrophy, amongst other disorders. A simple blood creatine phosphokinase level (CPK) can help differentiate a muscular dystrophy from other disorders.

Abnormal growth patterns may also indicate a genetic disorder. Such patterns include both short and tall stature or failure to thrive. Many skeletal dysplasias present with disproportionate short stature, so measuring a patient’s limbs and obtaining the height of other family members are recommended. Overgrowth syndromes, such as Sotos syndrome, are also seen and usually present with increased weight, height and head circumference that may be present from birth.

Evidence of congenital or early-onset blindness or deafness warrants a genetics consult. It is important to rule out syndromic causes for these and assess for family history of potentially inherited conditions. One common autosomal dominant trait, for instance, is congenital cataracts. When signs and symptoms of an unknown disease follow a Mendelian pattern of inheritance or there is a family history of a known condition, patients should also be referred to genetics.

Adolescence and Adulthood

We customarily see patients during adolescence who have abnormal growth patterns. Patients with tall stature and other findings of common disorders like Marfan syndrome or Klinefelter syndrome should be assessed by a clinical geneticist. Many of these patients present with other findings, and the work-up may be started by the primary care physician. If, for instance, a diagnosis of Marfan syndrome is considered, then an eye exam and an echocardiogram should be ordered. Another common reason for referral is abnormal sexual maturation. It is important in these cases to rule out disorders of sex development or intersex conditions. Chromosomes should be analyzed for both growth abnormalities and sexual maturation anomalies.

In this age group, it is also common to receive referrals for a strong family history of cancer or when the types of cancer are rare. Usually, these patients are seen by a certified counselor in the Cancer Genetic Counseling Clinic who obtains a family history and orders testing for known cancer syndromes. Depending on which genes are found to have mutations, the risks for different cancers increase in different percentages, and follow up with counselors is warranted to explain recurrence risks, practice guidelines and to offer testing to other relatives at risk.

We commonly receive referrals for mutations in the MTHFR gene, which has been linked to mildly elevated homocysteine levels in blood. Hyperhomocysteinemia has been associated with increased risk of developing cardiovascular disease and venous thrombosis. That said, a person with the common polymorphisms in the MTHFR gene, even in the homozygous state, but with a normal homocysteine level does not require management or referral to genetics. All women regardless of MTHFR status should take folic acid supplements preconceptionally and during pregnancy to lessen the risk for neural tube defects at the recommended daily allowance of folate (0.4 mg/day).

References:
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Genetic diseases may be congenital (present at birth) and include multiple birth defects and distinct clinical features or present later affecting growth and development. Although individual genetic diseases are relatively rare, collectively, the prevalence of genetic diseases in the pediatric population is considerable and accounts for a large percentage of hospital admissions and mortality.

Many genetic diseases are chronic and impact child health and development tremendously, but a medical geneticist can help. Some of the most common clinical presentations in pediatric genetics include birth defects and dysmorphic/distinct facial and clinical features, abnormal growth (failure to thrive, overgrowth, short or tall stature), developmental delays, intellectual disability, distinct behavior, multisystem involvement and finally as a “diagnostic Odyssey.”

We begin by taking a detailed medical history, including prenatal, birth and postnatal history that is essential in evaluating the etiology of birth defects. Family history is crucial and may provide the most important clue to a genetic diagnosis. The pattern of disease occurrence in a family by a detailed three-generation pedigree helps in determining the mode of transmission of a disease as autosomal dominant, autosomal recessive, X-linked or mitochondrial and can direct one to a single gene.

Clinical diagnosis may be obtained by a thorough physical exam with attention to major and minor traits followed by confirmatory genetic testing. Based on the clinical symptoms and assessment, options for genetic testing include karyotype, chromosomal microarray, methylation testing for imprinting disorders, single gene testing, targeted next generation sequencing, exome or genome analysis. Here’s how we approach some of these common clinical presentations in our pediatric genetics clinic.

**Birth defects, multiple congenital anomalies and dysmorphic features**

A baby with multiple birth defects, unusual or distinct facial features in the nursery may be suspected as having a genetic disorder. While evaluating a baby with multiple birth defects, one has to determine whether a single early morphogenic event lead to several later in a sequence. The underlying problems in morphogenesis generally fall into one of these four categories:

1. **Malformation**: Poor formation of tissue because of an abnormal developmental process (Figure 1a).

2. **Deformation**: Distortion by unusual forces on normal tissue (Figure 1b).

3. **Disruption**: A breakdown/destuction of normal tissue, such as in amniotic band sequence (Figure 1c).

4. **Dysplasia**: Abnormal organization of cells in tissue resulting in structural changes, such as in achondroplasia (Figure 1d).

These birth defects may provide a clue to an underlying diagnosis or may be isolated and only related to an issue during gestation. In order to distinguish among different etiologies, clusters of birth defects are grouped into the categories listed below:

- **Sequence**: A pattern of developmental anomalies consequent upon a primary defect, often with heterogeneous etiology. For example Pierre-Robin syndrome, which includes hypoplasia of mandibular development, posterior displacement of tongue and a posterior cleft of palate.

- **Association**: A non-random collection of developmental anomalies not known to represent a sequence or syndrome that are seen together more frequently than expected by chance. For example, VATER/VACTERL Association (Vertebral anomalies, Anal atresia, Cardiac defects, Tracheo Esophageal fistula with esophageal atresia, Renal anomalies, Limb defects).

- **Syndrome**: A particular set of developmental anomalies occurring together in a recognizable and consistent pattern and known or assumed to be the result of a single etiology.

While a major birth defect may bring the baby to attention, one has to remember that it may be three or more minor anomalies occurring in a consistent recognizable pattern that leads to a specific diagnosis.
Syndromes are caused by any one of the following genetic defects: chromosomal abnormalities, abnormal gene expression (called imprinting disorders) and single gene defects.

It is important to differentiate sequence or association from syndromes to provide accurate recurrence risk for families.

**Abnormal growth (failure to thrive, overgrowth, tall or short stature)**

Some children are referred to genetics because of abnormal growth. We need to investigate specific genetic diseases depending on whether the child is too big or too small. All such children would have X-rays to examine for disorders of skeletal development.

Some other disorders we might consider are Beckwith Wiedemann syndrome (BWS) (for overgrowth) and Russell-Silver syndrome (RSS) (for short stature). Very tall children with easy bruising or frequent joint dislocations may have Marfan syndrome or Ehlers-Danlos syndrome. Marfan syndrome is caused by mutations in a single gene *FBN1*, whereas both clinical and genetic heterogeneity are present in Ehlers-Danlos syndromes.

**Developmental delays, intellectual disability and autism spectrum disorders**

Children with global, motor or speech delays, intellectual disability and autism spectrum disorders may be either isolated/non-syndromic or syndromic. Detailed family history and attention to dysmorphic features may point towards specific diagnosis. Regardless, chromosomal microarray identifies genetic etiology in 15 to 20% of children with developmental disability and associated multiple congenital anomalies or dysmorphic features. Fragile X syndrome is the leading cause of intellectual disability in males often suggested by family history of affected males through maternal lineage and characteristic facial appearance. Genetic testing for Fragile X syndrome to identify trinucleotide repeat expansion would confirm clinical suspicion. Other genetic testing options include single gene testing, next generation sequencing panels and exome analysis.

**Children with specific organ system involvement in a recognizable pattern**

Some genetic conditions affect specific organ systems, and patients may present with vision loss due to retinitis pigmentosa, hearing loss due to Usher syndrome or hypotonia due to congenital muscular dystrophies. These are genetically heterogeneous with multiple genes causing similar disorder and are best tested by next generation sequencing (NGS) panels. Metabolic work up and mitochondrial DNA analysis is recommended if multi-system involvement and a mitochondrial condition or inborn error of metabolism is suspected.

**Family history of a certain genetic condition, including childhood cancers such as retinoblastoma or APC-associated polyposis conditions**

In these instances, asymptomatic children may present to the pediatric genetic clinics. Careful clinical examination and targeted genetic testing is recommended in conditions that necessitate medical action. For example, in those with positive family history of the APC gene mutation, screening for hepatoblastoma by liver ultrasound and measurement of serum alpha-fetoprotein concentration (until age 5 years) and sigmoidoscopy or colonscopy beginning at age 10 to 12 years is recommended. Targeted molecular genetic testing if negative reduces anxiety and the need for costly screening procedures in those at-risk family members.

**Diagnostic Odyssey**

It is not uncommon for patients to be referred as “Diagnostic Odyssey” to genetics clinic. These are individuals who have multiple non-specific symptoms and organ system involvements that do not fit into any recognized clinical disease, syndrome or condition. They would have often undergone multiple investigations and extensive testing for more recognizable clinical conditions. In this instance, an exome analysis as a clinical test or genome analysis on a research basis is often considered. An algorithm for work up of a genetics patient is proposed in the accompanying flow chart. (Figure 2)

**Clinical Genetic Evaluation and Testing**

The ultimate goal of a genetics consultation is to identify a unifying diagnosis for a patient. This may necessitate a more extensive exam of the patient and at many times other family members. Two very reliable resources regarding genetic conditions that are freely accessible

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**FIGURE 1: Problems in morphogenesis**

1A. Malformation causing cleft palate.
1B. Deformation causing club feet.
1C. Disruption from amniotic bands causing finger constrictions.
1D. Dysplasia causing trident hand in achondroplasia
are OMIM (www.OMIM.org) and Genereviews (www.ncbi.nlm.nih.gov/books/NBK1116/).

Based on clinical diagnosis, several options for genetic testing are available. The number of clinically available genetic tests is rapidly expanding. A compendium of laboratories and genetic tests that are available can be obtained at the Genetic Testing Registry, www.ncbi.nlm.nih.gov/gtr.

Points to remember about genetic testing:
1. Genetic testing often provides more accurate unifying diagnosis, ending the “diagnostic odyssey.” Many families may feel empowered knowing the underlying etiology for their child’s disorder and being able to develop the best possible monitoring and treatment plan.

2. Genetic counseling prior to a genetic test is highly recommended to explain the outcomes of a test.

3. A positive genetic test can have implications for the entire family and can cause anxiety and depression among other asymptomatic relatives.

4. A negative genetic test result does not override a clinical diagnosis. (Many inherited diseases may not have a gene identified yet.)

5. Uncertainty about the significance of a genetic change due to lack of functional data or sufficient information are reported as “variants of unknown significance” and may be confusing to patients and families.

6. Clinical exome sequencing and chromosome microarrays have the potential of identifying changes in genes that are potentially unrelated to the presenting features, and patients and families should be appropriately counseled about these incidental findings.

7. Although diagnosing a genetic condition may not alter management of patients, clinical trials and treatment options are emerging and available for lysosomal storage disorders and inborn errors of metabolism.

8. Supportive management, including referrals to improve patient’s quality of life and availability of support groups, are valuable to patients and families.

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![Algorithm for Genetic Work Up](image-url)
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Inborn Errors of Metabolism at a Glance
From Newborn Screening to Multidisciplinary Adult Care

By: Hong Li, MD, Ph.D.

Inborn errors of metabolism (IEMs) are individually rare, but collectively the incidence is close to one in 1,500 persons. IEMs are no longer considered rare diseases.1 The recent application of tandem mass spectrometry (TMS) to expanded newborn screening (NBS) has provided the opportunity to detect an IEM at an asymptomatic phase and perform medical interventions that positively alter the natural history of the disease.

IEMs have become more important in the routine care of pediatric patients. Therapeutic advances have improved the prognosis of children with IEMs; however these children grow up and face challenges in transitioning to multidisciplinary adult care.

The individual rarity of IEMs means limited exposure for most physicians, and so experience and confidence in dealing with such patients may not be well developed. These frequently asked questions can help address the many practical issues and advancements in the field of IEMs.

Why is it important for primary care physicians to learn about IEMs?

With expanded NBS and advanced molecular diagnosis, more and more IEMs can be identified early and will be encountered in your daily practice. Some IEMs can present with life-threatening events. Without prompt diagnosis and appropriate management, they can lead to fatal decompensation or significant neurological damage. Early recognition is critical. Many IEMs are treatable. As healthcare providers, we should make every effort not to miss a treatable disorder. Therefore all primary care providers should be familiar with the basics of IEMs.

What are the pathophysiological mechanisms of IEMs?

From a pathophysiological perspective, IEMs can be divided into the following three categories,2 which form the basis for better understanding and recognizing of the signs and symptoms of IEMs:

1) Intoxication: This includes inborn errors of intermediary metabolism that lead to acute or chronic intoxication from a) the accumulation of toxic upstream compounds, b) the effects of reduced downstream essential compounds or c) abnormal alternative substrate metabolism. This includes aminoacidopathies (phenylketonuria [PKU], maple syrup urine disease, homocystinuria, tyrosinemia, etc), organic acidurias (methylmalonic and propionic aciduria etc.), urea cycle defects (UCD), and sugar intolerance (galactosemia, hereditary fructose intolerance).

2) Energy defect: This group of diseases is caused by a deficiency in energy production or utilization and primarily affects tissues with high energy requirements, such as the brain, liver, muscle and heart. These include defects in the synthesis or breakdown of glucose, glycogen and fatty acids as well as mitochondrial disorders. Hypoglycemia and lactic acidosis are commonly seen.

3) Cellular organelle defect: This group of diseases disturbs the synthesis or the catabolism of complex molecules and includes lysosomal storage disorders, peroxisomal disorders, congenital disorders of glycosylation (CDG), and cholesterol metabolism defects. Symptoms are permanent, progressive, independent of intercurrent events and unrelated to food intake.

What are the clinical presentations of IEMs?

The clinical presentations of IEMs can be non-specific, vague and variable. The key to recognizing and diagnosing IEMs is to maintain a high index of suspicion, especially in an unexplained acute or chronic setting with a negative evaluation. IEMs can present at any age, from fetal life to adulthood. Because most IEMs are inherited in an
Autosomal recessive pattern, it is very common that family history is negative for IEMs, although consanguinity increases the risk. Some points to remember:

- **Acute presentation**: poor feeding, vomiting, lethargy, respiratory distress, ataxia, coma.
- **Chronic presentation**: food intolerance, failure to thrive, developmental delay, seizures.

**What are the red flags for IEMs?**

- Unexplained recurrent episodic symptoms
- Decompensation during stress or illness (triggers for catabolism)
- Unexplained failure to thrive/developmental delay
- Symptoms in high energy utilizing organs such as brain, heart, liver, muscle
- Avoidance of certain foods
- Family history of symptoms or early childhood death

**What are the life-threatening metabolic crises in IEMs?**

In the acutely ill patient, do not forget IEMs. Especially do not miss treatable IEMs!

- Coma/Encephalopathy caused by acute neuron intoxication and cerebral edema
- Hyperammonemia: commonly seen in UCD and organic acidurias
- Hyperleucinemia: seen in maple syrup urine disease (MSUD)
- Subdural hemorrhage, seizure and dystonia caused by the decompensation in glutaric aciduria type I, which can be misdiagnosed as child abuse
- Stroke-like episodes in mitochondrial disorder, like MELAS
- Hypoglycemia
- Metabolic acidosis with elevated anion gap (AG)
- Acute liver failure

**What is the basic work up for IEMs?**

This includes general labs, which are immediately available in primary or emergency care settings, and specialty labs, which are performed in specialized biochemical genetic labs with results available within several days.

**General Labs:**

- Blood gas with pH: Look for respiratory alkalosis (hyperammonemia) and metabolic acidosis
- Electrolytes: Look for CO2 and calculate AG
- Glucose: It is important to collect critical labs in the setting of hypoglycemia, including 3-hydroxybutyrate and lactate along with endocrine labs.
- **Urinalysis**: Used to check for ketones in urine. It is an immediately available critical test in the setting of hypoglycemia and helps in differentiating the etiology of hypoglycemia.
- **Liver/renal function**
- **Ammonia**: Order this test for patients with neurological presentation, especially with encephalopathy. The specimen is best collected from free-flowing blood, put on ice and sent for analysis immediately. Poor sample processing can lead to a falsely elevated result.
- **Lactate/pyruvate**

**Specialty labs for common IEMs:** Ideally collected in the sick setting if possible because a typical biochemical profile for some IEMs can be normalized when patients are well.

- Plasma amino acids
- Urine organic acids
- Acylcarnitine profile
- Carnitine profile

When suspecting cellular organelle defects, you should consider referring patients to metabolism specialists for further work up.

**How many IEMs are screened by NBS?**

More than 30 IEMs are being screened by the Georgia NBS program, which expanded in 2007. Most aminoacidopathies, organic acidurias and some of the urea cycle defects are detected by TMS. Biotinidase deficiency and galactosemia are detected by enzymatic analysis. A pilot study of Pompe disease and mucopolysaccharidosis type I (MPS I) will be initiated at Emory in early 2016. Remember that a normal NBS result for IEMs does not rule out the possibility of IEMs; there are disorders for which we do not yet screen, and there can be false negatives.

**How does the NBS program work for IEMs in Georgia?**

All NBS specimens are sent to the Georgia State Public Health Laboratory. The screening result is usually available two to three working days after the specimen is received. Abnormal results are handled by the metabolic follow-up team at Emory University Division of Medical Genetics. The NBS team is responsible for reporting abnormal results to the appropriate healthcare provider, aiding in the location of the newborn, and making recommendations for follow-up testing. Additionally, follow-up staff helps coordinate confirmatory testing and ensures that all diagnosed newborns are referred to the Emory Division of Medical Genetics for treatment and long-term management.

As there are around 9,000 positive NBS results every year, it is important to triage these results and report them according to severity. As a primary care physician, you may receive a borderline abnormal result by fax requesting a repeat NBS. You may receive a routine or critical abnormal result by both phone and fax requesting a confirmatory test.
In any situation, when you receive a positive NBS result, the first step is always to assess the patient first to ensure the baby is clinically doing well. If you have any concerns about the patient, please communicate in a timely manner with our metabolic NBS follow-up team or consult the on-call medical geneticist immediately.

What documents are included in the abnormal NBS result reporting package?

- **A copy of the lab report**: Note: Authorized providers can access newborn screening results through the State Electronic Notification Surveillance System SendSS at https://sendss.state.ga.us/sendss/login.screen.
- **Written recommendations**
  1) The concerning signs and symptoms that need to be assessed
  2) What testing is required: either repeat NBS or confirmatory testing
- **Test requisitions for Emory Genetics Lab including specific test information**
- **Educational information**
  1) NBS ACT sheet, which can also be found at www.acmg.net/ACMG/Publications
  2) Parents’ Fact Sheet, which can also be downloaded at www.newbornscreening.info/Parents/facts.html
- **Contact information for metabolic specialist**

Why is the rule of “Assess the Patient First” so important in the process of NBS?

In many situations, the abnormal NBS result can be caused by multiple metabolic disorders, including either severe disease that can lead to a life-threatening crisis if not treated promptly or a benign biochemical profile abnormality. In other cases we see false positive results. To help distinguish the two, a careful assessment is very important and can prevent a metabolic decompensation.

Why are you sometimes asked to collect a mother’s specimen for testing in the process of NBS?

The level of some metabolites on the NBS can reflect the mother’s blood levels in the first few days of life, just like a creatinine level in newborns. As such, it is not surprising that “asymptomatic” maternal metabolic defects can be detected via an abnormal NBS result of the unaffected baby. This is common in maternal 3-methylcrotonyl-coenzyme A carboxylase (3MCC) deficiency, maternal carnitine deficiency, and maternal B12 deficiency. It is therefore sometimes important to investigate NBS-positive infants and their mothers simultaneously in this follow-up process.

What does the Emory metabolism team do to take care of patients with IEMs?

The Emory metabolism team consists of three physicians who are board-certified in medical biochemical genetics, four dedicated metabolic dietitians, genetic counselors and metabolic research staff involved in clinical trials of lysosomal storage diseases and other IEMs. We not only evaluate and diagnose patients with IEMs, but also provide long-term management. Currently more than 500 patients are followed in our clinic.

What are the advances in managing patients with IEMs?

New therapeutic treatments are constantly being developed for IEMs. For example, in addition to traditional dietary management for patients with PKU, a wide array of novel treatments are currently in clinical use. These include a) new, more palatable foods using glycomacropete; b) large neutral amino acids; c) Kuvan™, the orally active synthetic form of cofactor tetrahydropterin (BH4); d) clinical trials of enzyme substitution therapy with subcutaneous PEGylated Phenylalanine Ammonia-Lyase (PEG-PAL). Many enzyme replacement therapies and substrate reduction therapies have been developed for lysosomal storage diseases.

What are the challenges in transitioning patients with IEMs to adult care?

Improved therapeutic efficacy combined with earlier diagnosis has dramatically changed the prognosis of many IEMs. These children grow up and should transition to specialized adult care. Adult patients with IEMs are a relatively new phenomenon in medicine. We have limited knowledge about their continued complex management at this time. Extrapolated pediatric guidelines are applied to the adult population taking into account adult life stages (social independence, pregnancy, aging process and potential long-term complications).

Today, adult patients with IEMs, due to the complexity of their management, need to be looked after by a multidisciplinary team of physicians (metabolic specialist, primary care physician), dietitians, social workers, psychologists and variety of other specialists. It is also essential, in this complex and rapidly expanding field, that experiences should be shared at both a national and international level in order to provide the most adequate care for patients.

References:
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The recent advances in clinical molecular genetic testing technology that have revolutionized the practice of medical genetics are also applicable to the realm of adult medicine. Geneticists help the patient understand his disease and the risks and benefits of genetic testing, and solve questions about ethical and privacy issues.

A medical geneticist can help the consulting physician by narrowing or expanding the differential diagnosis, confirming or ruling out a particular diagnosis using genetic testing, and use genetic testing results to guide therapy when possible. In medical genetics, we also take into account other relatives who may be impacted and can help identify and test at-risk individuals.

There are several relatively common adult onset single-gene conditions that can impact health significantly: familial hyperlipidemia, familial thoracic aneurysm and aortic dissection (TAAD), hypertrophic cardiomyopathy and inherited cancer syndromes. There are also several novel applications of genetic testing for somatic mutations in tumors and transcriptome-based prediction of outcomes in oncology.

FAMILIAL HYPERLIPIDEMIA (FH)

This autosomal dominant condition has a prevalence of 1 in 500.1 The great majority of cases are caused by mutations in a gene called LDLR encoding the low-density lipoprotein (LDL) receptor, which is used by the liver to process LDL cholesterol. Individuals with FH are at a 100-fold risk of developing coronary artery disease compared to the general population.2 The clinical presentation of FH often includes physical exam signs such as xanthomas, xanthelasmas (yellow plaques on eyelids) and the presence of corneal arcus. The absence of such signs does not rule out the possibility of FH.2 Although clinical guidelines for the diagnosis of FH exist, including the MEDPED and Simon Broome criteria developed in the U.S. and UK respectively2, clinical molecular genetic testing has been shown to be a
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A medical geneticist can help the consulting physician by narrowing or expanding the differential diagnosis, confirming or ruling out a particular diagnosis using genetic testing, and use genetic testing results to guide therapy when possible.

FAMILIAL TAAD
Another relatively common genetic condition is familial TAAD. Of all TAAD, 20 percent are familial. It is an autosomal dominant condition that can be caused by mutations in one of several genes. It can present in an isolated form, in which dilation and/or dissection of the thoracic aorta is the only sign, or it could be a part of a genetic syndrome such as Marfan syndrome, Loeys-Dietz or Ehlers-Danlos.

Currently, there is no consensus as to whether all patients with TAAD should have genetic testing. However, a reasonable approach is to refer all patients to a geneticist to evaluate for signs of another syndrome, look closely at the family history and decide if genetic testing is required. If a mutation is identified, it may change the threshold for surgical management of the aneurysm.

For example, in Marfan syndrome, the cutoff for surgery is generally thought to be when the aorta reaches 50 mm in size. Dilation of the aortic root is defined as an aortic root diameter with a Z score above 2.5, so reporting the actual diameter of the aortic root in an echocardiogram is important, so that the Z score can be calculated. Other features of Marfan syndrome include lens dis-
Marfan syndrome is diagnosed using the Ghent criteria. In the absence of family history, aortic root dilation is necessary to establish the diagnosis. Therefore, it is possible for a patient to have a mutation in the causative gene (FBN1) and yet not fulfill the diagnostic criteria for Marfan. Thus, the first step in evaluation of any patient with suspected Marfan syndrome (because of features such as tall stature or marfanoid habitus) is to obtain an echocardiogram. Establishing a specific diagnosis is important for management decisions regarding aortic root dilation. Clinical trials suggest high-dose beta-blockers and losartan may delay progression of the aortic root dilation.

Loeys-Dietz syndrome was first described 10 years ago. It is characterized by aortic root dilatation with risk of dissection at smaller diameters when compared to Marfan syndrome, arterial tortuosity and aneurysms, distinct craniofacial anomalies, bifid or short uvula, skeletal anomalies, osteopenia and a higher frequency of food allergies. Mutations in four different genes have been identified as causative: TGFBR1 (Type 1), TGFBR2 (Type 2), SMAD3 (Type 3) and TGBF2 (Type 4).

Because of the distinct risk of developing aortic rupture at a smaller diameter and the possibility of aneurysms in arteries, making a specific diagnosis of Loeys-Dietz syndrome directly impacts the clinical management of the patient. For instance, surgery would be recommended at a diameter of 40 mm (vs 50 mm for most TAAD), and CT/MRA imaging of the full arterial tree is needed to identify other aneurysms that may require pre-symptomatic intervention.

The genetics of isolated TAAD is still in its infancy, as only 20 percent of cases have an identifiable genetic cause. The ACTA2 gene is the most frequently affected. Several other causative genes have been identified, with each gene accounting for 1 percent or less of TAAD. Sequence variants are occasionally identified when gene sequencing is performed, but it is not clear if these are benign or disease causing. Geneticists call these “variants of uncertain significance,” and they pose a clinical challenge. Such variants cannot be used to exclude the possibility of developing aortic dilation. Therefore, careful pre-test counseling is important. In general, screening for TAAD in at-risk relatives can be accomplished by echocardiogram only, and if the individual is older than 21, no further screening is necessary if the initial echocardiogram is normal.

INHERITED CANCER SYNDROMES
One of the greatest advances in clinical adult genetics has been in the area of inherited cancer syndromes. The most frequent of these is Hereditary Breast and Ovarian Cancer (HBOC). HBOC is caused by mutations in the BRCA1 and BRCA2 genes. It confers a risk of 50-80 percent of breast cancer by age 80, and an approximately 20 percent risk of ovarian cancer. There is also an increased risk of pancreatic cancer, prostate cancer and melanoma.

There is controversy as to who should be tested for mutations in BRCA1/2, with some authors advocating for population-wide screening, others for testing any individual affected by breast cancer or any of their relatives.
The National Comprehensive Cancer Network has published narrower guidelines for testing.\textsuperscript{19}

Currently, any woman diagnosed with breast cancer younger than age 50, or with estrogen, progesterone and HER2/neu receptor-negative (“triple negative”) cancer younger than 60 should be offered BRCA1/2 testing. Women with breast cancer at any age and at least one relative with either early-onset breast or invasive ovarian cancer and any man with breast cancer should also be offered testing. First- and second-degree relatives of those meeting guidelines can be offered testing only if their affected relative cannot be tested.

Medical geneticists can help establish whether genetic testing for BRCA1/2 is necessary and whether other genes need to be tested as well. We can also assist patients in making decisions to manage their high risk for cancer. For breast cancer risk, one of two approaches is generally used: heightened screening with breast MRI every year and mammogram every year, in such a way that one test or the other is performed every six months; or a risk-reduction mastectomy.\textsuperscript{18, 19} For the ovarian cancer risk, the current recommendation is to perform a risk-reduction oophorectomy after age 35 or when childbearing is completed. Oophorectomy also further decreases the risk of breast cancer.\textsuperscript{18, 19}

It is important to note that there are several other genes that are known to increase the risk of developing breast cancer. In some instances, this is part of a broader inherited cancer syndrome, such as Li-Fraumeni Syndrome, PTEN hamartoma syndrome or Hereditary Diffuse Gastric Cancer (HDGC). Clinical geneticists can help identify these patients, who will need additional genetic testing and if positive should undergo a different screening program. Also, several genes have recently been found to be associated with an increased risk of breast cancer, but are not part of a recognizable hereditary cancer syndrome.

There is considerable controversy as to the clinical applicability and utility of testing for mutations in these genes.\textsuperscript{20} Individualized assessment and genetic counseling is key in deciding whether a genetic test for these lower penetrance genes should be done.

Clinical genetics can also impact the management of colon cancer. In familial adenomatous polyposis, a highly penetrant autosomal dominant condition caused by truncating mutations in the APC gene\textsuperscript{21}, patients develop usually innumerable polyps in their colon and rectum, although an attenuated variant with a lesser polyp burden also exists.\textsuperscript{22} Extra-colonic manifestations include osteomas, soft tissue tumors and CNS tumors. The lifetime risk of developing colorectal cancer is virtually 100 percent, therefore a prophylactic total colectomy is recommended for those with a confirmed diagnosis.\textsuperscript{21}

Lynch syndrome is another autosomal dominant disorder in which patients are at risk of developing colorectal, endometrial, ovarian, renal and CNS cancer.\textsuperscript{22} It is caused by a germ-
line mutation in one of several genes controlling mismatch repair: MLH1, MSH2, MSH6, PMS2 or EPCAM. Somatic mutations in MLH1 are fairly common in non-Lynch colorectal tumors. Immunohistochemistry staining of colorectal and endometrial cancers for mismatch repair genes is now advocated. Depending on the results of the staining, a patient may need to consider having a genetic test to establish a diagnosis of Lynch, which is important because this allows for other screening measures to be implemented.

Management of patients with confirmed Lynch syndrome includes annual colonoscopy starting at age 25 and recommendation for risk-reducing total hysterectomy with salpingo-oophorectomy after completing childbearing. There is no firm consensus regarding screening for extracolonic tumors – annual office endometrial sampling, upper endoscopy, capsule endoscopy and annual urinalysis with cytology to screen for transitional cell cancer are possible strategies, currently only supported by expert opinion.

A fairly recent advance in genetic testing is oncoyping. This differs from germline genetic testing in that the DNA being analyzed is that of the tumor, not the patient's leukocytes.

The purpose is to identify tumor-specific mutations that can drive therapeutic decisions. For example, whether to use EGFR tyrosine kinase inhibitors for lung cancer depends on whether the tumor harbors mutations in EGFR, with activating mutations being a predictor of response to therapy.

Also, clinical applications for tumor transcriptome are emerging, in which based on the specific "signature" of the tumor, predictions about tumor aggressiveness and response to therapy can be made, such as in node-positive breast cancer and response to tamoxifen.

References

**General Principles**

Treating genetic diseases is neither new nor unfamiliar: physicians treat common diseases with a heritable genetic component every day – including diabetes, hypertension, atherosclerosis, some forms of cancer, etc.

Specialists in medical genetics focus on the diagnosis and treatment of disorders that are predominantly due to the effects of a single dysfunctional gene (i.e. Mendelian with autosomal dominant, autosomal recessive or X-linked inheritance), mitochondrial DNA mutations (maternal inheritance) or are chromosomal in nature (such as Down syndrome). (See Table 1 for features of specific disorders.)

The goals of treatment are to prevent morbidity and mortality and ensure better developmental outcomes through disease-specific therapies, symptomatic treatment and anticipatory guidance and surveillance. Our success in achieving these goals varies greatly depending on the given disorder.

In general, treatment outcomes are better the earlier a diagnosis can be made and require coordinated, multidisciplinary care and compliance with recommendations by the patient and family. Unfortunately, except for some disorders detected by newborn screening, a correct diagnosis is often delayed for many years or made post-mortem.

Current treatment for genetic disorders is usually lifelong. With few exceptions, treatments are not curative but only modify the course of the disease. For disorders with a pediatric onset, the lack of medical coverage for many adults often leads to a cessation of proper treatments, with disastrous and expensive consequences.

The number of specific therapies for genetic disorders is increasing, but there is a substantial lag between advances in the laboratory, clinical trials and approval by the FDA. In part, this is due to the relative rarity of the disorders, the lack of good natural history data, a paucity of surrogate markers for the efficacy of treatment, the expense of clinical trials for rare disorders and a regulatory structure that, in spite of the orphan drug pathway, is really designed for common diseases.

Fortunately, pharmaceutical companies are showing more interest in orphan diseases, and the regulatory framework is evolving due to the advocacy of patient organizations. A major problem in the future will be affordability of these treatments for any health system. In the absence of any pricing regulation, most treatments are extremely costly.

For best outcomes and quality of life, the healthcare team cannot forget the importance of symptomatic therapies (e.g. occupational, physical and speech therapies, pain control, gastrostomy tubes for feeding, etc.), anticipatory guidance and surveillance for complications of the disorder (e.g. hypothyroidism, strabismus and hearing loss in Down syndrome; hepatic tumors in tyrosinemia), and treatment of diseases unrelated to the primary genetic diagnosis (e.g. obesity and hypertension in a dwarf).

The specific ways we treat genetic disorders include decreasing the amount of toxins; increasing the amount of functional protein; providing what is lacking; and modifying the disease pathogenesis. Gene therapy can theoretically result in a permanent cure, but that has been difficult to successfully accomplish. While there have been some promising clinical trials and a few regulatory approvals in other countries, no gene therapy is currently approved by the FDA.

**Specific Treatments**

- Decrease the amount of toxins: Many disorders of intermediary metabolism cause an increase in toxic metabolites that can increase further during intercurrent illnesses with concomitant catabolism. A variety of strategies exist for decreasing the amount of toxins.
  - **a. Limit intake of the toxin or its precursors:** Phenyketonuria (PKU) is a classic example wherein a deficiency of phenylalanine hydroxylase leads to increased phenylalanine in the brain disrupting normal function at all ages and brain development in young children. Restriction of dietary phenylalanine can successfully reduce phenylalanine to levels that are not harmful. Supplementation with special formula and other medical foods containing the other amino acids and calories are essential for treatment to be successful.

Pregnancies in women with PKU present a particular challenge because phenylalanine is teratogenic to the developing fetus. Failure to adequately treat women during pregnancy leads to microcephalic, intellectually disabled children. However, when properly treated, PKU patients and their children can be normal. In that sense, PKU has been a great success story for newborn screening, but adherence to diet can be difficult, especially for older patients.

A preventable source of difficulty for patients is that of access to treatment. In many states, there are laws mandating insurance coverage for medical foods and insurance coverage for

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**Treating Genetic Disease**

1. Specific treatments are available for many genetic conditions with many more on the horizon.
2. Symptomatic treatments, surveillance, anticipatory care and treatment of unrelated medical conditions can help improve outcomes and quality of life.
3. All patients with genetic diseases need multidisciplinary care.
4. A correct and early diagnosis is essential for the best outcomes.
adults with PKU, but not in Georgia in spite of advocacy by genetics and the families. Consequently, many cannot afford the formula with tragic and permanent consequences for themselves and their offspring.

b. Use alternate pathways to eliminate the toxic metabolites: Ornithine transcarbamylase (OTC) deficiency is a disorder of the urea cycle leading to elevations in ammonia. In addition to limiting protein in the diet, the amount of toxic ammonia the patient has to contend with can be decreased by giving phenylbutyrate, which is conjugated with the amino acid glutamine in the liver and excreted in the urine, eliminating the two ammonia molecules contained within glutamine.

c. Block production of toxic metabolites: Deficiency of the last step of tyrosine degradation, fumarylacetoacetate hydrolase, causes hepatorenal tyrosinemia. Much of the pathogenesis of the disease is to the formation of a toxin formed by alternate pathways, succinylacetone. Inhibition of a proximal step in the pathway with nitisone markedly decreases the production of succinylacetone thus decreasing hepatocellular damage and malignant transformation, neurologic crises and renal tubular dysfunction.

Increase functional protein: Increasing the amount of functioning protein to a sufficient level to ameliorate or prevent disease progression can be accomplished by the use of chemical chaperones, which help mutant protein fold correctly. We have done this for many years with increased doses of vitamin cofactors. Tetrahydrobiopterin administration, for example, can increase phenylalanine hydroxylase activity in some patients with PKU, increasing the amount of phenylalanine they can tolerate. Non-vitamin chaperones are currently in clinical trials for other disorders.

Another way of increasing the amount of functional protein is enzyme replacement therapy. Gaucher disease type I, due to a deficiency of the lysosomal enzyme glucocerebrosidase, causes accumulation of glucocerebroside in macrophages with resultant hepatosplenomegaly, hypersplenism, and bone disease. Gaucher can be effectively treated with biweekly infusions of recombinant enzyme. Enzyme replacement therapy is currently approved for several other diseases.

Transplantation is used for a few disorders, albeit with the mortality and morbidity associated with transplantation for any condition. For example, males with OTC deficiency who survive...
the neonatal period without severe brain injury can receive a liver transplant, which provides functioning OTC enzyme thereby preventing future hyperammonemic crises. Hematopoietic stem cell transplantation is used not just for hematologic genetic disorders but also as a means for delivery of enzyme into the brain. In severe mucopolysaccharidosis type I, transplantation before 2 years of age can allow transplanted cells to migrate to the CNS, becoming microglial cells that can release enough enzyme to correct the storage found in other cells, preserving cognitive abilities. New means of delivery of enzyme to the CNS may eliminate the need for transplantation in the future.

3. Provide what is missing: The pathogenesis of some disorders is due to the lack of production or recycling of something essential. Biotinidase deficiency, for example, is due to a defective ability to recycle the essential vitamin biotin, leading to progressive deficiency after birth and damage to the CNS. We now detect this condition by newborn screening. Supplementation with biotin completely prevents the manifestations of the disease and is as close to a cure as we have in genetics.

4. Modify the disease pathogenesis: The pathogenesis of genetic disorders is complex and generally imperfectly understood. Marfan syndrome’s most serious manifestation is aortic aneurysms leading to fatal dissection and rupture. For many years, beta-blockers were used to decrease the stress on the aorta, slowing down the rate of progression, but a more effective medication is used now. Marfan is caused by mutations in the gene for fibrillin, leading to decreased fibrillin microfibrils in the extracellular matrix. The damaging effect on the aorta is not predominantly due to some mechanical property of microfibrils, however. Instead, one of fibrillin’s functions is to sequester transforming growth factor beta (TGFβ). Excess action of TGFβ leads to damage to the aorta. Losartan, an angiotensin receptor blocker, is also able to inhibit the intracellular actions of TGFβ, more effectively slowing the progression of the disease.

The Future
This is a hopeful time for patients with genetic disease and their families. An astonishing array of treatments for genetic disorders is currently being developed in the laboratory and tested in the clinic.

The genetic clinical trials unit in the Department of Human Genetics at Emory University is one of the most capable in the world. We are currently conducting clinical trials for Down syndrome, Fragile X, PKU, mucopolysaccharidoses types I and II, and Fabry disease; we will soon begin enrolling patients in trials of treatments for osteogenesis imperfecta, achondroplasia, and Niemann-Pick Disease type B and pre-FDA approval expanded-access studies for hypophosphatasia and cholesterol ester storage disease. In addition to these clinical trials, we participate in many disease registries that yield new insights into specific genetic diseases.

The trials are directed by the physicians Joseph Cubells, Michael Gambello, Hong Li, Suma Shankar, Amy Talboy, Jaime Vengoechea-Barrios, and the author along with a team of experienced coordinators led by Dawn Laney, metabolic dieticians directed by Rani Singh and adult and pediatric psychologists Nadia Ali, Debra Hamilton and Sarah McMurty.
The statistics on cardiovascular disease are startling. It is the leading cause of death for both men and women and for most ethnicities in the United States — according to the Centers for Disease Control, approximately 610,000 Americans die of cardiovascular disease every year, accounting for one in every four deaths. In fact, cardiovascular diseases claim more lives than all forms of cancer combined.

Faced with the formidable challenge that cardiovascular disease presents, Northside Hospital’s team is comprised of board-certified cardiologists, vascular surgeons, cardiovascular trained nurses and technicians who are leaders in the field of the treatment and prevention of heart disease, stroke and vascular diseases. Their integrated approach includes the latest technologies and surgical techniques, along with a comprehensive network of preventive, diagnostic, medical and support services, for treating patients with cardiovascular disease.

Expansion, research, technology offer new options in cardiology

Northside’s cardiologists are dedicated to providing leading treatments for patients with cardiac conditions such
as arrhythmias, coronary artery disease and heart failure, as well as early detection, diagnosis and management of other conditions that could potentially affect the heart, like high blood pressure, high cholesterol, diabetes and obesity. Using advanced technology, the staff of cardiologists teams up with radiologists and technicians to diagnose and treat various cardiac conditions. They also perform invasive procedures to correct heart abnormalities, including pacemaker implementation, defibrillators, cardiac catheterization and stent placement.

Recently, expanded lab capabilities and the addition of staff have increased the Heart & Vascular Institute’s ability to diagnose and treat patients with cardiac issues, according to Michael Balk, MD, Medical Director, Northside Heart and Vascular Institute. “We’ve expanded our interventional and invasive labs, and we’ve added additional physicians,” he said. “As a result, we’re able to do more procedures. Plus, we now have a dedicated electrophysiology lab, where our electrophysiologists use the latest techniques to treat arrhythmias.”

As part of its mission to identify and treat heart disease earlier, Northside is participating in the National Heart, Lung and Blood Institute’s new research program involving low dose methotrexate. The drug, which has been used successfully to reduce inflammation in people who have arthritis, is currently being studied to see if it is effective in reducing cardiovascular inflammation.

“Doctors who were using methotrexate to treat patients for arthritis noticed that these patients also had fewer coronary events. Once this was discovered, it became important to determine whether or not the drug also could be effective in people with cardiac issues,” Balk explained.

The participants in this clinical trial are people who have experienced a heart attack or major blockage and who have additional comorbidities like diabetes or metabolic syndrome.

“We are looking at methotrexate as a treatment that can reduce inflammation and therefore, reduce the chance of a future heart attack or stroke in these individuals,” Balk explained. “If found to be effective, this drug may change how we treat patients in the future.”

Across the board, the Institute’s physicians are continuously seeking out ways to improve diagnoses and treatments.

“For example, our electrophysiologists are trained in techniques like cryoablation, which uses extreme cold to treat cardiac arrhythmias by ablating tissue. This technique can lower the risk of procedure-related complications in some patients,” Balk said. “Whether it’s electrophysiology, cardiology, nuclear cardiology, CT, angiography or vascular and interventional procedures, we’re always working to reduce risks and improve outcomes for our patients. Therefore, about 90% of our catheterization procedures are now done radially, a less-invasive approach,” Balk added.

Emphasis on early detection

Balk stresses that early detection of cardiovascular disease is a major focus for the Northside Heart & Vascular Institute, and that an aging baby boomer population has offered new reasons for changing the way cardiac problems are diagnosed. “As the demographic changes across the country, we will see larger numbers of age-related illnesses like atrial fibrillation, which is still on the rise,” he said.

Patricia Tyson, Administrative Director of Northside Heart & Vascular Institute, adds that early detection is especially...
beneficial to patients who are pregnant or looking to become pregnant.

“Nationally, the number one reason for maternal death and complications during the pregnancy and postpartum is cardiac-related such as embolism, preeclampsia and cardiomyopathy,” she said. “Therefore, we are working to identify those patients early and have specialists on our staff that focus on these complications in women during pregnancy and can intervene to prevent major issues and/or death.”

On the vascular side of early detection and treatment, the Northside Heart & Vascular Institute has a process called Code Rupture that alerts the hospital’s Emergency Department to the impending arrival of a patient experiencing a ruptured aortic aneurysm.

“Ruptured aortic aneurysm has one of the highest mortality rates for any health issue in the country. Our Code Rupture system is active and alerts the full ED team in advance to prepare for the patient who is being transported,” Tyson explained. “Through this effort, we’ve vastly improved the mortality rate from a ruptured aortic aneurysm at Northside; in fact, it’s lower than the national average.”

Access to clinical trials, research devices offers benefits in treatment of vascular diseases

The vascular surgeons of Northside’s Heart & Vascular Institute are all academically trained physicians who have an interest in clinical research. Their education and training have provided the perfect set-up for the Institute to participate in clinical trials involving new, investigational devices that are undergoing testing, according to Siddharth Patel, a surgeon in the Department of Vascular Surgery and Endovascular Therapy.

“There are some clinical trials accessible to us that can potentially have significant benefits for our vascular patients. For example, there are drug-coated balloons and stents that were formerly available only in the cardio arena and are now available to the patient with peripheral arterial disease, or PAD,” he said. “Additionally, many of these trials were formerly available only in the university setting. Now, the Northside Heart & Vascular Institute is able to access these trials and we are excited to bring these treatments to our community.”

Patel cites two clinical trials currently underway for technologies that may soon benefit Northside patients — the
“Northside is the only health system in Georgia with the Magellan endovascular robotic system. This technology delivers therapy with increased precision and efficiency for a wide range of procedures, from carotid stenting to visceral and renal procedures in the lower extremity interventions.”

Gore branched stent graft, used to treat iliac artery aneurysms while maintaining pelvic perfusion, and Bolton’s Treovance endograft, which has a smaller caliber that may be useful in delivering treatment to patients with smaller arteries, particularly females. He adds that Northside’s vascular team has an interest in participating in several upcoming trials, including a bedside intravascular ultrasound-guided vena cava filter for patients who are too unstable to transport to the fluoroscopy suite or patients with renal insufficiency who cannot receive contrast, and a drug-coated balloon catheter that can be used to treat lesions in the tibial arteries below the knee.

Dr. Patel also described an exciting new technology available at Northside, the Magellan endovascular robotic system. “This new robotic tool will allow us to deliver therapy with increased precision and efficiency for everything from carotid stenting to visceral and renal procedures to lower extremity interventions, thereby reducing the radiation dose for both the patient and the endovascular team. We are very excited to be the only health system in Georgia with the robot. In fact we have two, one at Northside Atlanta and one at Northside Forsyth, which is amazing considering there are only 14 total in the entire country. This speaks volumes about how committed Northside Hospital is to improving the care of the vascular patient.”

Collaboration reaches patients far beyond metro Atlanta

The Northside Heart & Vascular Institute’s network of cardiologists and vascular surgeons extends well outside the walls of Northside’s flagship hospital in Atlanta. Many physicians located throughout Georgia utilize the vast network of specialists and leverage the Institute’s services for their patients.

Utpal H. Pandya, MD, Chief of Cardiology with Kaiser Permanente’s Southeast Permanente Medical Group, says his association with the Northside Heart & Vascular Institute has provided a critical partnership.

“We [Southeast Permanente Medical Group] perform a wide range of diagnostic and interventional procedures, and many of our cases are at Northside,” he said. “They provide good service to our patients; moreover, they assist us in areas such as documenting heart failure readmissions and medication compliance. This collaboration is, in fact, critical to our success.”

Additionally, the collaboration offers access to the latest technologies and clinical trials to a wider patient base.

“The physician’s struggle in any highly expensive field of medicine, like cardiology, is the desire to treat patients with the newest tools available. But we always have to face the economic realities,” said Pandya. “However, the Northside Heart & Vascular Institute works very hard to bring those tools to us. They welcome our input and decision-making is collaborative. This partnership has worked very well.”
According to the Centers for Disease Control and Prevention (CDC), more than one-third (34.9 percent) of all adults in the U.S. are obese, and the rate of adult obesity in the U.S. nearly tripled from 1960 to 2010.

Many individuals who fall into the overweight or morbidly obese categories are desperately searching for a “magic” solution that will take away the pounds permanently. Frustrated with diets and pills that often provide only temporary results, thousands of people are lining up for bariatric procedures, which may provide the closest thing to the permanent solution they seek.

According to the American Society for Metabolic and Bariatric Surgery, bariatric surgery has been shown to be the most effective and durable treatment for morbid obesity, and it helps prevent, improve or resolve more than 40 obesity-related diseases or conditions, including type 2 diabetes, heart disease, obstructive sleep apnea and some cancers.

Atlanta Medicine recently spoke with two Atlanta-area bariatric physicians, who shared their knowledge of how the bariatric landscape has changed over the past several years.

Surgical and non-surgical options improve patients’ weight loss success

According to Fritz Jean-Pierre, MD, a bariatric surgeon with WellStar Health System, improvements in both surgical and nonsurgical options over the past 10 years have resulted in both giving patients better weight loss and giving physicians the ability to better predict that weight loss.

He says the most notable change has been an increase in the selection of a more invasive surgery, the gastric sleeve, over the once-popular lap band and other procedures. The gastric sleeve (sleeve gastrectomy) actually removes approximately 80 percent of the stomach, leaving a tubular pouch that resembles a banana. This procedure, which is less complicated than many other types of bariatric surgery, now comprises over 60 percent of all weight loss surgery procedures performed in the U.S.

“There has been a huge switch in choice of surgeries today. We’ve seen a large increase in patients selecting the sleeve gastrectomy in the past five years,” says Dr. Jean-Pierre. “In addition, we are better able to evaluate our patients’ metabolic conditions today, which helps us in making recommendations for the most appropriate weight loss option.”

Dr. Jean-Pierre adds that non-surgical options can also be very good solutions for some patients who desire to lose weight, especially children and adolescents.

“One of the partners in our practice is an obesity specialist who helps patients determine the weight-loss options available to them and which of those options is best suited. Sometimes, diet and exercise are a better approach,” he says. “For young patients, this is often the first and best choice rather than a surgical intervention, which causes lifelong changes.”

For the patient with a very high Body Mass Index (BMI) and/or various comorbidities like diabetes and high blood
pressure, Dr. Jean-Pierre says the more aggressive gastric bypass (Roux-en-Y Gastric Bypass) may be the best option.

“The gastric bypass is still considered the ‘gold standard’ of weight loss surgeries,” he says. “While it’s more invasive, it has a high rate of success for significant long-term weight loss.”

Lifestyle change is key part of solution

Christopher J. Hart, MD, chief of staff and medical director of the Atlanta Bariatric Center at Emory Johns Creek Hospital, says that long-term weight loss success depends on the patient’s commitment to making permanent lifestyle changes to ensure that success after surgery.

“Once a person’s BMI rises above the 30-35 percent range, long-term weight loss with just diet and exercise becomes much harder; it becomes about deprivation,” he says. “So the nice thing about bariatric surgery is that it results in the patient being able to eat less and still feel satisfied.”

However, to obtain lasting results, the patient still has to make lifestyle changes after surgery.

“I tell my patients, ‘I can do a technically perfect surgery, but you will still not lose the weight and get healthy unless you hold up your end of the deal – which means good nutrition and exercise,’” he says.

Dr. Hart adds that data compiled over the years for different bariatric procedures is an important tool in developing treatments that can help patients achieve permanent weight loss.

“For example, in the early days of the lap band procedure, there was some experimentation – after a patient reached his or her goal weight, the band was removed. The hope was that the patient had made lifestyle changes that would keep the weight off and would no longer need the band for continued support. The data showed that patients regained the weight because their hunger drive returned,” he says. “It’s important to follow our patients throughout the course of their lives so that we can monitor their progress and success as well as compile data that will be helpful in the future. We can use that data to determine success rates and complications, as well as see how we compare against national statistics.”
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