Inborn errors of metabolism in the 21st century: past to present

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Abstract: The 21st century is an exciting time to be in the field of metabolic medicine. As with many fields, one of the keys to anticipating the future is to understand the past. The term "inborn error of metabolism" was first coined in 1908 by Sir Archibald Garrod, in reference to four disorders (alkaptonuria, pentosuria, cystinuria and albinism). The first (and still most definitive) textbook on the subject, "The Metabolic Basis of Inherited Disease" was initially published in 1960 and covered 80 disorders in 1,477 pages. After the eighth edition of this text became unwieldy at 6,338 pages in 4 volumes covering more than 1,000 disorders, the book was changed to an online reference text with 259 chapters and is still growing. Current newborn screening on a few dried blood spots on filter paper identifies more than 1 in 2,000 newborns as having a metabolic disorder. The availability of metabolomic and genomic analyses is resulting in the diagnosis of many new disorders. Enzyme replacement therapy (ERT) has provided treatments for previously untreatable metabolic disorders, and the promise of gene therapy on the near horizon will certainly revolutionize the field.

Keywords: Inborn error of metabolism; newborn screening; enzyme replacement therapy; gene therapy

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Historic roots in classic biochemistry

The concept of inborn errors of metabolism was born about a century ago, when a mother brought her infant to Sir Archibald Garrod to investigate why the urine in her child's diapers turned black. As he found other affected patients and studied the disorder in families, he worked out the metabolic pathway leading to alkaptonuria and its relationship to Mendelian inheritance (1). This leads us to two important themes in the development of the study of inborn errors. One is the growing importance of biochemistry in medicine in the early part of the last century. The other is the importance of the role of advocacy by parents (2). Together these led to another important milestone in the developing field, the "discovery" of phenylketonuria (PKU).

In 1934 another mother sought the help of Dr. Følling to explain why her two children had intellectual disability and an unusual odor. Dr. Følling's son has given an account of his father's discovery of PKU and its subsequent impact as a model disorder in the study of inborn errors, including revolutionary treatment and development of newborn screening (3). Other disorders, such as maple syrup urine disease, were subsequently elucidated through classic biochemistry, and later better understood as technology advanced.

The description of PKU was a landmark event in metabolic history. The disorder was found to be a relatively frequent cause of intellectual disability in Dr. Følling's native Denmark, and eventually worldwide. Two decades later, Dr. Bickel *et al.* introduced the treatment of restricting dietary phenylalanine (4), the novel dietary restriction concept which became the standard of treatment for intoxicating inborn errors of metabolism. The realization that intellectual disability could be prevented by early diagnosis and dietary treatment led to the development of the first newborn screening program in the 1960's using a bacterial inhibition assay develop by Dr. Guthrie *et al.* (5). Worldwide, newborn screening has since been expanded by new technology, and can now detect more than

Table 1 Saudubray's classification of inborn errors of metabolism (10)

Disorders	Description	Examples
Intoxication	Acute or progressive accumulation of toxic compounds	(I) Urea cycle defects (NH3); (II) organic acidemias; (III) aminoacidopathies
Energy deficiency	Deficiency in energy production or utilization	(I) Gluconeogenic disorders; (II) glycogenosis disorders; (III) fatty acid oxidation defects
Complex molecules	Disturbances in synthesis or catabolism of complex molecules	(I) Lysosomal disorders; (II) peroxisomal disorders; (III) CDG

CDG, congenital disorder of glycosylation.

50 metabolic disorders.

The recognition and diagnoses of inborn errors of metabolism were further propelled by advances in chemistry and technology. Krebs worked out the urea cycle (the first biochemical cycle described), as well as the citric acid cycle that bears his name (Kreb's Cycle) (6,7). Amino acid analysis by simple paper chromatography, and later by automated individual amino acid quantification led to more widespread description and recognition of inborn errors. In the late mid-century the development of organic acid analysis was a major breakthrough, expanding the number of patients as well as identifying new disorders (8). Categories of disorders such as ketotic hyperglycinemia could now be more definitively classified as propionic acidemia or methylmalonic acidemia. Complementation analysis enabled important separation and sub-classification of disorders, for example the distinction between the various forms of methylmalonic acidemia and homocystinuria due in many cases to defects in sequential steps in the processing of cobalamin (vitamin B12). Another major breakthrough in diagnosis in the late 20th century was the development of tandem mass spectrometry (TMS) (9). This technology allows the identification of more than 50 inborn errors of metabolism in a single sample. Its application in dried blood spots paved the way toward expanded newborn screening using biochemical markers. Parental advocacy played a significant role in the expansion of newborn screening using TMS technology, particularly for the disorder medium chain acyl-CoA dehydrogenase deficiency (MCAD deficiency or ACAD-M).

Expanding the range of metabolic disorders

Given the nature of standard biochemical technology in the early 20th century, the inborn errors of metabolism initially described were generally disorders of intoxication (*Table 1*), in which the pathophysiology of the various disorders included a defect in an enzymatic pathway leading to accumulation of an abnormal metabolite having an intoxicating effect (10). The intoxication was typically manifest in the central nervous system or other end-organ effects. Classic intoxicating disorders include inborn errors of the urea cycle (leading to ammonia intoxication), amino or organic acidemias (leading to intoxication with specific amino or organic acids), as well as other non-protein intoxicating metabolites such as galactose (galactosemia) or fructose (hereditary fructose intolerance). But the pathophysiology of metabolic disorders includes other mechanisms as well as intoxication, including disorders of energy deficiency, and disorders of complex molecules (*Table 1*).

By the end of the past century, disorders of energy deficiency were being described with increasing frequency. These include, among others, disorders of fatty acid oxidation and disorders of mitochondrial function or of creatine metabolism.

The most common disorder of fatty acid oxidation, MCAD deficiency, was described in the 1980's, initially as familial Reye's syndrome (11) Affected individuals have impaired ability to break down medium chain fat stores for energy, and are at risk for hypoglycemia or death during periods of significant catabolism. With an incidence of about 1 in 15,000 births, it is one of the most common inborn errors of metabolism, but also one for which morbidity and mortality are most easily preventable by preventing fasting and providing alternate sources of energy (such as intravenous glucose) during intercurrent illnesses or other catabolic events. The recognition that the life-threatening effects of this disorder were potentially preventable profoundly changed the nature of newborn screening. Existing bacterial inhibition or enzyme assays had a limited range disorders suitable for screening. Parents

of children affected with MCAD deficiency pushed for the adoption of a new technology, TMS for newborn screening to enable pre-symptomatic detection of this disorder. TMS enabled early detection of not just MCAD deficiency, but also of a much larger range of inborn errors of metabolism. This technology greatly expanded the range of newborn screening from a few to as many as 50 disorders, virtually overnight.

The final decades of the past century also saw the recognition of mitochondrial disease, due to disorders of energy production at the mitochondrial level. Although clinical criteria were established to assist in diagnosis (12), it was still often difficult to make a diagnosis with certainty, and mitochondrial disease was frequently a clinical diagnosis of exclusion. In some cases, diagnostic patterns of mitochondrial dysfunction were recognized (e.g., Mitochondrial Encephalopathy with Ragged Red Fibers, aka MERRF, among others). In other cases, the symptoms were less well defined and even more difficult to characterize. Inheritance appeared complex; most disorders were caused by defects in nuclearly-encoded proteins that acted in the mitochondria. However, an independent genome was also identified within the mitochondria themselves that is maternally inherited, giving rise to maternal inheritance for some mitochondrial disorders. Prior to genomic diagnostic technology, mitochondrial disorders were both over and under-diagnosed. Given the profound variability in expression, the recognition that functional studies in tissues were sometimes inconclusive, and that inheritance patterns were not always clear, before genomic testing diagnosis of mitochondrial disorders was quite challenging.

Disorders of creatine metabolism are another example of energy deficiency disorder, leading to inadequate cellular energy in the brain. The X-linked creatinine transporter deficiency, in which creatine is unable to be transported into the brain, is now described as one of the most common causes of intellectual disability and seizures in boys (13). It is likely that current genomic technology will identify even more energy deficiency disorders.

The inborn errors of metabolism causing intoxication or energy deficiency are generally located in the cytoplasm or the mitochondria. The end of the 20th century also saw rapid evolution of understanding of metabolic disorders in other cellular organelles giving rise to disorders of complex molecules. Examples include inborn errors of metabolism affecting the peroxisome, the lysosome, and endoplasmic reticulum/Golgi.

Peroxisomal disorders can manifest as a global failure of peroxisome assembly (in which case the peroxisomal structure and all peroxisomal functions are disturbed), or as a single enzyme defect in only one peroxisomal function (e.g., as in X-linked adrenoleukodystrophy). Complementation analysis was instrumental in distinguishing the numerous genes involved in peroxisomal assembly and functioning. As with many inborn errors of metabolism, early diagnosis can be important. For example, in X-linked adrenoleukodystrophy pre-symptomatic stem cell bone marrow transplantation may arrest disease progression, and many newborn screening programs are now adding this disorder to their screening panel.

Interest in lysosomal storage disorders has been growing and evolving over the last few decades. Lysosomes are responsible for degradation of cellular waste, and an inborn error in a degradative enzyme results in waste metabolites accumulating within the lysosome (a "storage disorder"). The discovery that lysosomal enzymes carry a post-translational mannose 6-phosphate "tag" that directs the enzyme's uptake into the lysosome revolutionized the development of ERT (14). ERT has greatly improved the morbidity and mortality associated with many lysosomal storage disorders, and a number of these disorders are now on the newborn screening panel to enable earlier detection and treatment e.g., MPS-1 (Hurler syndrome) and GSD-2 (Pompe disease).

The first congenital disorder of glycosylation (CDG) was described in 1980 by Grunewald and colleagues (15). The CDG are disorders of post-translational glycosylation of proteins and some glycolipids, a process that takes place in the endoplasmic reticulum and Golgi. As of this writing, there are more than 100 inborn errors of glycosylation described, and given the large number of enzymes involved in the glycosylation pathway it is likely the 21st century will see many more described. Although originally diagnosed by observing the electrophoretic pattern of sialic acids on glycoproteins, many of the more recently discovered CDG have been identified by molecular sequencing. At present, only two of the more than >100 forms have a definitive treatment, but experimental treatments are coming available at this time for others as the metabolic and molecular pathways are elucidated.

Obviously, this short review cannot begin to describe more than a sampling of the variety inborn errors of intoxication, energy production or complex molecules. For additional detail, the reader is referred to the excellent and comprehensive online text "Online Metabolic and Molecular Bases of Inherited Disease" for a more thorough

review. Although perhaps intimidating at first glance, this exceptionally well written reference is considered the predominant metabolic reference text, and chapters are quite user friendly when read from beginning to end.

The "-omics" revolution

Inborn errors in the 20th century began as the era of the biochemist, but the century's closing was marked by the beginning of the era of the "-omics' revolution, particularly genomics and metabolomics. Metabolomics is the culmination of a century of biochemistry on a scale that would likely not have been imaginable to Garrod or Følling. It enables the laboratory to analyze the chemical fingerprints of multiple metabolites in body tissues and fluids, typically with small sample sizes and rapid speed. In addition to the identification of individual metabolites, the functioning of entire pathways and their interactions can be assessed. In 2012 the National Institutes of Health developed a Metabolomics program to establish six Metabolomic resource cores around the United States, support development of new tools and technology as well as a national data repository, and to promote community engagement in the technology. Although metabolomics technology is not yet ready to replace traditional biochemical methods for the diagnosis of inborn errors of metabolism, the influence of this technology is likely to be defining as we move along in this century.

Genomics is the penultimate "-omics" of the 21st century. Clinical exome sequencing is becoming standard of care for patients with unexplained genetic or metabolic disorders, and will be followed in short order by clinical genome sequencing as the bioinformatics evolve. Historically, as individual genes were cloned, sequencing was particularly helpful in identifying individual metabolic disorders for which the enzymes are not expressed in easily accessible tissues—for example disorders with enzyme activity typically expressed in hepatocytes but not leukocytes (e.g., fructose 1-6 bisphosphatase or ornithine transcarbamylase activity). In the early years of genetic testing, it was necessary to have clinical suspicion for a specific diagnosis to select that gene for analysis. "Panel" testing has become more popular and can sequence an entire range of genes specific to a metabolic symptom (e.g., hypoglycemia or neonatal seizures).

Exome or genome sequencing technology has tremendous potential to identify a wider range of disorders. In some cases, sequencing identifies specific metabolic diagnoses that had not necessarily even been previously suspected. It has been particularly helpful in bridging the gap between dysmorphology and metabolism. Numerous inborn errors of metabolism have been identified which can also result in structural birth defects or dysmorphic features. The classic example of a metabolic disorder causing birth defects, Smith-Lemli-Opitz syndrome (a defect in cholesterol synthesis associated with structural abnormalities including polydactyly, and other birth defects), has been joined by a number of other disorders such as D-2-hydroxyglutaricaciduria or congenital disorders of glycosylation. In the absence of typical metabolic signs such as acidosis or hypoglycemia, these and similar metabolic disorders might be missed on traditional genetic testing, but are likely to be found with increasing frequency on genomic sequencing.

Sequencing has also expanded the range of genotype-phenotype correlations. In some cases, individuals can have two pathogenic gene variants for a metabolic disease, but appear to be asymptomatic or to have a phenotype not previously associated with the disease in question. For example, many infants diagnosed with very long chain acyl CoA dehydrogenase deficiency appear completely asymptomatic at birth, and some, though certainly not all, remain so for many years. Some urea cycle disorders have had their initial symptomatic presentations in adults undergoing bariatric surgery (due to the profound catabolism associated with the surgery) (16). Polymorphisms or carrier status for certain urea cycle enzymes are associated with increased risk for pulmonary hypertension (17). Other disorders now appear potentially to be biochemical abnormalities evident on genotyping, but without a specific phenotype. Thus, genotyping alone is not always sufficient for prediction of phenotype or to dictate treatment regimens.

New metabolic disorders are revolutionizing the way we think of inborn errors of metabolism. One of the classes of newly recognized disorders includes more than 40 distinct defects in the synthesis and remodeling of complex lipids, including phospholipids, sphingolipids, and complex fatty acids (18). Aminoacyl-tRNA synthetases are vital in charging transfer RNA's with their amino acids, and their defects have been linked to a number of metabolic and neurologic disorders (19). Epigenetic mechanisms are an under-explored area of metabolic disease that is likely to be of interest in the near future.

Evolution of treatment

Treatment of inborn errors of metabolism in most of

the 20th century was largely aimed at reducing abnormal metabolites. The first treatments involved dietary restriction of metabolites prior to the metabolic block to decrease production of offending metabolites. Later methods included diverting abnormal metabolites or creating alternate pathways to eliminate potentially toxic metabolites (e.g., dialysis or ammonia scavenger drugs in urea cycle disorders or organic acidemias).

PKU again serves as a model disorder for tracing the advancement of treatments over the past century. The original therapy was dietary restriction of phenylalanine, with supplementation of the deficient end product tyrosine. This diet is cumbersome and difficult to follow, and there was an ongoing effort for improvements. One attempted improvement included supplementation with large neutral amino acids in attempt to block entry of phenylalanine into the brain, with limited success. Another improvement for PKU treatment was supplementation of the enzyme's cofactor, tetrahydrobiopterin. A subset of responsive patients having residual enzyme activity had improved quality of life and dietary relaxation with this therapy. The concept of treatment by cofactor supplementation has also been successful in patients with some other forms of inborn errors, e.g., B12 supplementation in some cases of methylmalonic acidemia, B6 in some cases of homocystinuria, and riboflavin for glutaric aciduria type 2, to name a few.

Treatments in the 21st century have become aimed at more directly correcting the underlying metabolic defect. Orthotopic liver transplantation is now a treatment of choice for a number of severe inborn errors of metabolism, particularly severe urea cycle defects. In some cases, less drastic measures have been attempted by transplanting cells instead of the entire organ, such as muscle cell transplantation for neuromuscular disorders, or liver cell transplantation for PKU and a number of other metabolic disorders. Stem cell bone marrow transplantation can be therapeutic, particularly in some storage disorders (e.g., Hurler Syndrome), and pre-symptomatically in some degenerative white matter leukodystrophies (e.g., adrenoleukodystrophy). Other therapies showing promise include chaperonins to optimize protein folding, enzyme replacement therapies, and therapeutic mRNA. Microbiome alteration using antimicrobial agents is in common use to reduce propionate production in methylmalonic or propionic acidemia, or trimethylamines in trimethylaminuria. Other microbiome manipulation is likely to be developed in the coming years. Finally, the promise of gene therapy is on the very near horizon. The first experiment with gene therapy for urea cycle defects led to the death of a study subject, apparently due to issues with the gene-delivery vector (20). Improved vectors have renewed the promise for gene therapy and current trials are again beginning.

There is a great need for clinical trials to define evidence-based therapies. Although inborn errors of metabolism are collectively frequent, most disorders are individually relatively rare. In some cases, it is ethically challenging to assign a placebo group when no other treatment is available, such that many treatments are offered open label on a compassionate use basis. As a result, traditional placebo-controlled trials are difficult to conduct. This has additional consequences in that evidence-based clinical practice protocols are lacking, and without these third-party payors are often reluctant to cover many therapies. The National Institutes of Health in the United States has worked to develop Rare Disease consortia, as well as alternative mechanisms such as "n of 1" trials. The problem of the pace of diagnoses outstripping the pace of evidence-based therapies will be an important problem in the next years.

Newborn screening, a work in progress

A commentary on advancements in inborn errors of metabolism would not be complete without reviewing the impact newborn screening. Newborn screening itself has undergone significant revolution since its introduction in the 1960's as a way to screen for PKU. The first government-mandated newborn screening program originated in the state of Massachusetts (United States of America) (21). The original concept of population-based mandated newborn screening was quite controversial when first proposed (amid concerns about "socialized medicine"). However, parent advocacy groups were instrumental in the adoption of Dr. Guthrie's test as a mandated newborn screening test (2). As new disorders were added to the screen it became apparent that the process of expanding the screening panel required considerable thought. Wilson and Jungner proposed what became the official standards for newborn screening for the World Health Organization in 1968 (22). These included basic concepts such as: the disorder should be an important health problem whose natural history is well understood, it should be detectable at an early stage and early treatment should be beneficial, risks should be less than benefits, and the program should be cost effective.

The development of TMS meant that a significant

number of new disorders could be added to a single blood spot analysis, adding 40–50 or more disorders to the screening process. In many cases these were not primary target disorders that would independently meet Wilson and Jungner screening criteria for panel inclusion, but were detectable on the same instrumentation and single blood spot analysis as the primary target disorders. Not all these disorders were well understood, and not all were treatable. It became clear that technology had outstripped the utility of the Wilson and Jungner criteria, requiring a new approach.

In the United States, in 2006 the American College of Medical Genetics developed an updated panel of recommendations to determine which disorders are appropriate for newborn screening, establishing a list of "primary" metabolic targets which meet more traditional criteria for screening, and "secondary" targets, which are found incidentally in testing for primary targets (23). Although similar in scope to the Wilson and Jungner criteria, the updated ACMG criteria reflect more inclusiveness regarding the addition of many disorders diagnosable by TMS, recommending reporting of readily detectable primary target disorders that might not necessarily be common or cost effective, as well as the reporting of secondary targets. The US Secretary of Health and Human Services also convened an advisory panel (now called the Advisory Committee on Heritable Disorders in Newborns and Children) to establish evidence-based criteria to determine which additional disorders would be recommended for addition to the Recommended Uniform Screening Panel (aka the RUSP) (24). The panel has made recommendations in support of and against a number of inborn errors of metabolism. However, in the United States, newborn screening is administered by individual states and not by the federal government, thus the recommendations of this panel are advisory only with no legal strength.

Worldwide, the conduct and content of most newborn screening panels are administered by countries, regions or provinces, with each program administering their own screening panel and regulations. For example, a standardized panel across the United Kingdom includes only 9 disorders, while other countries may screen for more (or fewer) disorders (25). Many have mechanisms to remove a disorder from their panel after review.

There remain a number of controversies affecting newborn screening programs. The status of some biochemical disorders is now questionable. Expanded screening programs have demonstrated that the vast majority of infants found to have certain biochemical "disorders" on newborn screening such [e.g., 3-Methyl-CoA carboxylase deficiency (3-MCC), short chain acyl CoA dehydrogenase deficiency (SCAD), or 2-Methylbutyryl-CoA dehydrogenase deficiency] are completely asymptomatic. This has given rise to the question of whether some disorders might be simply metabolic phenotypes rather than actual diseases. Evidence based data are needed to evaluate whether affected patients require any treatment, if these disorders should be on the screening panel at all, and particularly if broad application of restrictive dietary treatments for biochemical disorders that might not actually be diseases could be harmful. Some newborn screening programs have now stopped screening for SCAD and/or 3MCC deficiency and other more controversial disorders.

Although newborn screening was originally intended for early-onset, treatable disorders, some of the recent additions appear to diagnose mostly later or adult onset variants, particularly for the lysosomal storage disorders. More concerningly, some screens cannot definitively differentiate affected from unaffected. For a number of lysosomal storage disorders such as Pompe Disease, it appears the majority of diagnoses are for later onset disease rather than infantile onset disease. Recent data from the Pennsylvania newborn screening program note that after screening several hundred thousand infants for Pompe disease, no infantile onset cases were identified. Forty-four infants were referred for follow-up DNA testing based on low enzyme activity, and twelve were diagnosed as likely having late onset Pompe disease. The status of the other 17 patients is uncertain at this time, with most having variants of uncertain significance that are potentially pathogenic (26). This creates medical and ethical dilemmas regarding who will require treatment and when such treatment should be started, or even who might never become symptomatic. The potential of conducting newborn screening by whole genome sequencing will likely raise additional ethical concerns, particularly regarding infantile diagnosis of untreatable adult onset disorders. Further, many of the screens identify unaffected disease carriers, although under non-screening conditions the diagnosis of carrier status in minors would be considered unethical.

The availability of ERT has led to heightened interest in adding more lysosomal storage disorders to the screening panel, again with the advocacy of parent organizations. Some of these additions have been controversial, given many unknowns. Concerns include difficulties in interpretation of borderline enzyme activities and/or novel

gene variants, lack of evidence-based data regarding which affected individuals require pre-symptomatic treatment, the efficacy of the treatment, cost-benefit, penetrance, and other issues. Newborn screening for Krabbe disease has been particularly controversial. The program originated in New York State in 2006 (27). After screening 2 million newborns, five newborns with infantile onset Krabbe disease were identified. Two underwent stem cell bone marrow transplantation and died of complications related to transplant. One did not undergo stem-cell bone marrow transplant and died of complications of Krabbe disease. Two other infants who underwent stem cell bone marrow transplantation have had the progression of their disease slowed significantly but remain with moderate to severe neurological deficits. Forty-six other newborns have uncertain status, either low enzyme activity (in some cases overlapping the carrier range) with two later onset-mutations or novel gene variants predicted to be pathogenic but without current evidence of disease. If all become symptomatic it would demonstrate a much higher incidence of Krabbe disease than previously known. Thus, the risk these 46 neonates identified by screening will ever become symptomatic is not known. The inability to clearly distinguish affected from unaffected newborns poses significant ethical challenges, particularly when treatments are not curative and inherently risky in themselves.

Genomics is also likely to transform newborn screening. In 2013 the National Institutes of Health funded a series of grants to explore the application of genomic technology to newborn screening. At present a number of obstacles must be overcome, particularly in the understanding of genotype-phenotype correlations. There is a need for better understanding of the role of epigenetic influences, pseudodeficiencies, imprinting, mutations outside of the gene coding sequence (promotor, etc.), improved variant prediction, detection of triplet repeat disorders, and other influences on gene expression and phenotype. There is also a need to develop better functional study assays to determine the pathogenicity of newly identified mutations or variants of unknown significance. Thus, it is likely that biochemical screening will remain a part of the newborn screening process for the near future. However, a combination of genomic and biochemical screening (metabolomics and or enzymatic) may be on the near horizon. Preliminary versions of this already exist in many newborn screening programs utilizing algorithms that use first tier biochemical testing and second tier mutation testing for some disorders.

The 21st century

The current status of the breadth and scope of the diagnosis and treatment of inborn errors of metabolism may have been barely imagined a century ago. But these advances also bring challenges for medicine and society. Available treatments are generally expensive; ERT can cost hundreds of thousands of dollars per year. Where limited funding is available, this cost might otherwise be applied to broader public health initiatives such as immunization programs. Not all insurance programs cover medical foods, and many do not cover expensive non-prescription supplements used in metabolic treatments. Screening for disorders without a commitment to provide affordable treatment for affected individuals is in itself ethically challenging.

In the 21st century, we look forward to the time when improved diagnosis and treatment make morbidity and mortality from inborn errors of metabolism a relic of the past. It is likely the nature of inborn errors of metabolism will continue to evolve as more complex metabolic mechanisms of lipids and other cellular processes are understood, and the role of epigenetics is explored. The future will be expected to bring advancements in detecting and correcting secondary metabolic disturbances caused by cancers, immune dysfunction, ageing, and other disorders. In anticipation of this time, the Online Metabolic and Molecular bases of Inherited Disease now include chapters on each of these topics to help us prepare for an exciting future.

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Footnote

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