INTRODUCTION

“You will remember the stone bricks which were so popular as children’s toys some years ago. They were of different colors, shapes and sizes, and with them could be constructed a variety of buildings of different kinds—houses, churches, temples and the like. However, if the bricks of some particular kind had been lost, as was often the case, although abundance of others were available, one could not construct some special kind of building which was wanted”—Sir Archibald Garrod, Where Chemistry and Medicine Meet (Garrod, 1911).

This statement from Sir Archibald Garrod in 1908, who introduced the concept of inborn errors of metabolism in his Croonian lectures to the Royal College of Physicians of London in 1908, eloquently describes the basic pathophysiology of biochemical defects of the cell (Garrod, 1908). From Garrod’s initial description of albinism, alkaptonuria, cystinuria, and pentosuria, to the translation of these concepts into the discipline of medicine dedicated to inborn errors of metabolism by such luminaries as Harry Harris and Barton Childs (Valle & McInerney, 2010), to today, the field of human genetics has evolved from disease description to mechanistic discovery to targeted treatment, and continues to march onward as advances in molecular biology enable manipulation of basic processes of the cell.

In this review, we will give an overview of therapeutic approaches for treating inborn errors of metabolism, which center on subverting biochemical defects by reducing upstream substrate accumulation, replacing abnormal enzymes and/or cofactors, and supplementing deficient products. We will follow the path of discovery in biochemical genetics over the past six decades that brought us to where we are today (Figure 1), and examine major milestones in the diagnosis and management of inborn errors of metabolism through illustrative patient cases.

THERAPIES FOR INBORN ERRORS OF METABOLISM

2.1 A patient presents with classical phenylketonuria (PKU) in 1960: Dietary therapy

A 5-year-old girl with severe intellectual disability had a positive test for phenylpyruvic acid in the urine via a ferric chloride assay (Allen, 1960) and was diagnosed with PKU. She was started on a low phenylalanine formula and protein-restricted diet, resulting in
decreased blood phenylalanine levels and mild behavioral improvements. Her parents had another child that year, who was tested early in the newborn period due to her sister’s diagnosis. She was diagnosed with PKU and immediately treated with a low phenylalanine formula. Her development was in the typical range.

Dietary modification, focused on the limitation of substrates upstream of a biochemical enzymatic defect thereby reducing accumulation of toxic metabolite(s), was the earliest successful treatment approach for inborn errors of metabolism. This approach was first successfully employed in PKU, which was described by Dr. Asbjorn Folling in 1934 (Folling, 1934). PKU is caused by a defect in phenylalanine hydroxylase that results in an abnormal elevation of phenylalanine, and which causes seizures and intellectual ability among other features if untreated. Not long after it was recognized that deficiency of the enzyme phenylalanine hydroxylase caused PKU, the first phenylalanine-restricted formula as developed and improved outcomes were reported in patients who were treated at an early age (Bickel, 1954; Jervis, 1953). Dietary management for other disorders of amino acid metabolism, including maple syrup urine disease and homocystinuria, was developed shortly thereafter (Gentz et al., 1967; Snyderman et al., 1964).

2.2 | A patient has a positive newborn screen for PKU in 1965: Newborn screening

A newborn baby boy born in 1965 in the state of Massachusetts received a newborn screen, and elevated phenylalanine was detected via a bacterial inhibition assay. PKU was diagnosed, and he was immediately treated with a low phenylalanine formula. His development was in the typical range.

Massachusetts began the first universal newborn screen for PKU in 1963 using a phenylalanine-specific bacterial inhibition test to detect elevated levels of phenylalanine in dried blood spots (Guthrie & Susi, 1963). While early in the development of dietary therapy practices for PKU, it was thought that diet could be discontinued in childhood; it was later found that elevated maternal phenylalanine levels during pregnancy had a teratogenic effect, leading to Maternal PKU syndrome (Levy & Ghavami, 1996). Additionally, neurocognitive effects of low-phenylalanine diet discontinuation were recognized, and lifelong treatment is now recommended (Vockley et al., 2014).

2.3 | A patient presents with a urea cycle defect in 1988: Ammonia scavengers

A 6-year-old girl with a partial argininosuccinic acid synthase deficiency was presented to the emergency room with vomiting, fever, and decreased consciousness. Laboratory test showed a plasma ammonia level of 250 μmol/L. She was treated with intravenous arginine, sodium benzoate, and sodium phenylacetate and her plasma ammonia level normalized.

The urea cycle, discovered by Hans Krebs and Kurt Henseleit in 1932 (Krebs & Henseleit, 1932), is responsible for the disposal of waste nitrogen in the form of ammonia as urea in humans and other
ureogenic organisms. The urea cycle consists of five enzymes (Carbamoylphosphate synthetase I [CPS1], Ornithine transcarbamylase [OTC], Argininosuccinic acid synthetase [ASS1], Argininosuccinic acid lyase [ASL], and Arginase [ARG1]), a cofactor-producing enzyme (N-acetylglutamate synthetase [NAGS]), and two amino acid transporters (ornithine translocase (ORNT1; ornithine/citrulline carrier) and citrin (aspartate/glutamate carrier; solute carrier family 25, member 13). Defects in the urea cycle result in hyperammonemiac disorders with a high morbidity and mortality, which can present in the neonatal period (the most severe forms) through adulthood (milder, later-onset forms) (Matsumoto et al., 2019). Since the earliest report of an infant with ornithine transcarbamylase deficiency in 1963, therapeutic approaches to ammonia detoxification were attempted in defects of the urea cycle (Russell et al., 1962).

In 1982, Batshaw et al. showed effective ammonia reduction in 26 infants with urea cycle defects by employing nitrogen scavenger therapy with daily administration of sodium benzoate and arginine (Batshaw et al., 1982). This therapy takes advantage of alternative mechanisms of waste nitrogen disposal, thus subverting the primary biochemical abnormality. Soon afterward, intravenous administration of sodium benzoate, sodium phenylacetate, and arginine was shown to be effective in the treatment of acute hyperammonemiac episodes in urea cycle defects (Brusilow et al., 1984), expanding the treatment toolkit for treatment in these disorders. Starting in the late 1980s and early 1990s, introduction of liver transplantation as a long-term, effective therapy for urea cycle defects provided a significant therapeutic option for affected individuals, particularly in those where dietary or medical management resulted in suboptimal ammonia management (Matsumoto et al., 2019; Whitington et al., 1998).

Prior to the introduction of newborn screening for distal urea cycle defects, including argininosuccinic acid synthase deficiency and argininosuccinate lyase deficiency, via tandem mass spectrometry in the 2000s, patients were either identified and treated early due to known family history of a urea cycle defect or were treated after presenting symptomatically. Introduction of newborn screening for these disorders has allowed for presymptomatic detection of some affected infants, thus increasing the likelihood of an improved outcome (Posset et al., 2016; Sun et al., 2012). Screening for proximal urea cycle defects has been implemented in several states in the United States, although methodologies and approaches are still being refined and optimized to improve sensitivity and specificity (Vasquez-Trincado et al., 2016).

2.4 A patient presents with Gaucher disease in 1993: Enzyme replacement therapy

A 22-year-old man presented to a hematologist with splenomegaly and easy bruising. Laboratory testing revealed thrombocytopenia and a bone marrow aspirate revealed Gaucher cells. Sequencing of the GBA gene revealed homozygosity for a p.N370S pathogenic amino acid variant. He was diagnosed with Gaucher disease type I and started treatment with enzyme replacement therapy (ERT) with alglucerase. This therapy resulted in the reduction of spleen size and the improvement of thrombocytopenia over the course of several months of treatment.

Gaucher disease type I, the visceral form of Gaucher disease, is a clinically variable lysosomal storage disorder with complications that can include hepatosplenomegaly, thrombocytopenia, anemia, tendency for bleeding, and bone disease, caused by a deficiency of lysosomal glucocerebrosidase (Whittington & Goa, 1992). In 1977, Belchetz et al. treated an adult with Gaucher disease type I with placental derived lysosomal glucocerebrosidase packaged in liposomes over the course of 13 months, resulting in decreased liver size and reduction of liver-derived transaminases (Belchetz et al., 1977). Over the ensuing decade and a half, numerous studies showed the effectiveness of ERT in improving visceral symptoms of Gaucher type I disease. In 1991, the FDA approved Ceredase® (alglucerase), a modified, placental-derived, macrophage-targeted β-glucocerebrosidase ERT for Gaucher disease type I (Parker et al., 1991). Three years later, Cerezyme® (miglustase), a recombinant analog of the human enzyme β-glucocerebrosidase, was approved, thus subverting the need for placental tissue as a source of the enzyme (Weinreb et al., 2013). Additional recombinant ERT products to treat Gaucher disease type I were approved in ensuing years. Currently, ERT is available for nine lysosomal storage disorders as well as several other disorders (Table 1) (Li, 2018), with clinical trials ongoing for additional enzyme replacement therapies and disease targets.

Substrate reduction therapy (SRT), a type of small molecule therapy (Table 2), is another approach for the treatment of lysosomal storage disorders. The strategy of SRT is to reduce the synthesis of the substrate (or substrate precursors) of the defective lysosomal enzyme. Oral treatment with N-butyldeoxynojirimycin (Zavesca®, miglustat), a small molecule that competitively inhibits glucosylceramide synthase and reduces cell storage of glucosylceramide, was approved as a SRT for Gaucher disease type I in 2002 (Ficicioglu, 2008). There is also evidence that miglustat can cross the blood brain barrier, and possibly stabilize the CNS manifestations of some LSDs including Neimann Pick type C (Patterson et al., 2020; Pineda et al., 2018).

2.5 A baby is born with medium-chain acyl-CoA dehydrogenase (MCAD) deficiency in 2006: Expanded newborn screening

A newborn boy born in 2006 in the state of Massachusetts received an expanded newborn screen. Abnormal acylcarnitines, including elevated octanoylcarnitine (C8) and decanoylcarnitine (C10), were detected via tandem mass spectrometry. Molecular testing revealed that he was homozygous for a c.985A>G pathogenic variant in the ACADM gene resulting in a Lys304Glu amino acid substitution, and MCAD deficiency was diagnosed. With avoidance of prolonged fasting and prompt management during times of illness, he remained asymptomatic throughout childhood.
**TABLE 1** Enzyme replacement therapies

| Disorder                                      | Drug name             | Trade name | FDA approval year |
|-----------------------------------------------|-----------------------|------------|-------------------|
| Adenosine deaminase-SCID                      | Pegademase            | Adagen     | 1990              |
| Gaucher disease type I                        | Alglucerase           | Ceredase   | 1991              |
|                                               | Imiglucerase           | Cerezyme   | 1994              |
|                                               | Velaglucerase alfa    | VPRIV      | 2010              |
|                                               | Taliglucerase alfa    | Eleyso     | 2012              |
| Fabry disease                                 | Agalsidase beta       | Fabrazyme  | 2003              |
| Mucopolysaccharidosis type I, Hurler/Scheie   | Laronidase            | Aldurazyme | 2003              |
| Mucopolysaccharidosis type VI, Maroteaux-Lamy Syndrome | Galsulfase | Naglazyme   | 2005              |
|                                                    | Idursulfase           | Elaprase   | 2006              |
| Pompe disease                                 | Alglucosidase alfa    | Myozyme    | 2006              |
|                                               | Alglucosidase alfa    | Lumizyme   | 2010              |
| Mucopolysaccharidosis type IVA, Morquio s      | Elosulfase alfa       | Vimizim    | 2014              |
| Lysosomal acid lipase deficiency, LAL-D        | Sebelipase alfa       | Kanuma     | 2015              |
| Mucopolysaccharidosis type VII – Sly syndrome | Vestronidase alfa     | Mepservii  | 2017              |
| Batten disease (CLN2)                          | Cerliponase alfa      | Brineura   | 2017              |
| Phenylketonuria                               | Pegvaliase-pqoz       | Palynziq   | 2018              |
| Adenosine deaminase-SCID                      | Elapegademase-lvr     | Revcoyi    | 2018              |
| Homocystinuria                                | Cystathionine Beta-Synthase | OT-58 | NCT03406611  |
| Arginase deficiency                           | Peglarginase          | CAEB1102-300A | NCT03921541 |

**TABLE 2** Selected small molecule therapies

| Disorder                                      | Drug name                                         | Trade name | FDA approval year |
|-----------------------------------------------|---------------------------------------------------|------------|-------------------|
| Wilson’s disease                              | Penicillamine                                     | Cuprimine  | 1970              |
| Primary carnitine deficiency                  | Levocarnitine                                     | Carnitor   | 1985              |
| Wilson’s disease                              | Trientin HCl                                      | Syprine    | 1985              |
| Acute hyperammonemia                          | Sodium benzoate/phenylacetate                      | Ammonul    | 1987              |
| Cystinosis                                    | Cysteamine (enteric coated and ophthalmic drops)  | Cystagon, Procysbi, Cystadrops | 1994–2013–2020 |
| Urea cycle disorders                          | Sodium phenylbutyrate                             | Buphenyl   | 1996              |
| Homocystinuria                                | Betaine                                           | Cystadane  | 1996              |
| Wilson’s disease                              | Zinc acetate                                      | Galzin     | 1997              |
| Hereditary tyrosinemia-type 1                 | Nitisinone                                        | Orfadin    | 2002              |
| Gaucher disease type 1                        | Miglustat                                         | Zavesca    | 2003              |
|                                               | Eliglustat                                        | Cerdelga   | 2014              |
| Hereditary orotic aciduria                    | Uridine triacetate                                | Xuriden    | 2015              |
| Phenylketonuria                               | Sarpropterin dihydrochloride                      | Kuvan      | 2007              |
| N-acetylglutamate synthase deficiency         | Carglumic acid                                    | Carbaglu   | 2010              |
| Urea cycle disorders                          | Glycerol-phenylbutyrate                            | Ravicti    | 2013              |
| Fabry disease                                 | Migalastat                                        | Galafold   | 2018              |
| Long-chain fatty acid disorders               | Triheptanoin                                      | Dojolvi    | 2020              |
| Molybdenum cofactor deficiency type A         | Fosdenopterin                                     | Nulibry    | 2021              |
| Congenital disorders of glycosylation         | D-galactose, mannose, fucose                      | CERC-801-3 |                   |
| Menkes disease                                | Copper histidinate                                | CUTX-101   | NCT04074512       |
| Thymidine kinase 2 deficiency                 | Deoxycytidine, deoxythymidine                     | MT1621     | NCT03639701       |
| Niemann-Pick disease type C                   | Arimocmol                                         | BRX-345    | NCT02612129       |
| Galactosemia                                  | Aldose reductase inhibitor                        | AT-007     | NCT04117711       |
| Propionic, methylmalonic acidemia             | CoA decrease                                      | HST5040    | NCT04732429       |
MCAD deficiency is a disorder of fatty acid oxidation that is detectable on the newborn screen as elevations of medium chain acylcarnitines identified via tandem mass spectrometry (MS/MS). Undiagnosed individuals can remain asymptomatic for long periods of time until faced with an episode of increased energy demand and fasting, which can result in severe metabolic decompensation and death (Schatz & Ensenauer, 2010). Introduction of newborn screening for MCAD deficiency led to a massive decrease in mortality, as great as a decrease from 55% to 4% mortality in one study, associated with this disorder (Wilcken et al., 2007).

High-throughput, multianalyte analysis via MS/MS in a blood spot was introduced in the early 2000s, allowing newborn screening to include many more disorders then were previously included (Wilcken et al., 2003). Upon initial introduction of this expanded screening modality, there was significant variation in disorders screened between different states in the United States. To help address this issue, in 2006 the American College of Medical Genetics recommended a panel of 29 disorders to be included in newborn screening panels, known as the Recommended Uniform Screening Panel (RUSP) (American College of Medical Genetics Newborn Screening Expert Group, 2006). The RUSP is revised by the federal Advisory Committee on Heritable Disorders in Newborns and Children on an ongoing basis to consider inclusion of additional disorders based on new developments. Currently, the RUSP includes 35 core disorders and 26 secondary disorders (https://www.hrsa.gov/advisory-committees/heritable-disorders/).

2.6  |  An adolescent with PKU in 2008: Enzyme cofactor therapy

A 14-year-old boy with PKU required a diet highly restricted in natural protein and supplemented with synthetic protein in order to keep his plasma phenylalanine in the therapeutic range. This diet was extremely limiting and unpalatable for him, and his compliance was consequently poor. He began taking sapropterin dihydrochloride (Kuvan®), a synthetic form of the tetrahydrobiopterin cofactor of phenylalanine hydroxylase, and was able to maintain a plasma phenylalanine level in the therapeutic range with more permissive diet allowing increased natural protein intake.

Vitamin cofactors are utilized as treatment for inborn errors of metabolism that involve the uptake, synthesis, or transport of enzymatic cofactors, or to stabilize the function of their cognate mutant enzymes. Sapropterin dihydrochloride (Kuvan®), a synthetic form of the tetrahydrobiopterin cofactor of phenylalanine hydroxylase, increases the phenylalanine hydroxylase activity in a subset of individuals with PKU by augmenting and/or stabilizing the mutant phenylalanine hydroxylase enzyme (Erlandsen et al., 2004; Erlandsen & Stevens, 2001). Multiple clinical trials showed effectiveness of Kuvan in treating PKU in affected children and adults (Blau, 2013). Response rates and strength of response to Kuvan were shown to vary based on the underlying severity of disease, but were as high as 27% in individuals with classical PKU, and higher in individuals with variant forms of PKU (Vernon et al., 2010).

More recently, a subcutaneously administered ERT for the treatment of adults PKU was approved by the FDA. Pegvaliase (Palinziq®) is a PEGylated recombinant Anabaena variabilis phenylalanine ammonia lyase which converts phenylalanine to trans-cinnamic acid and ammonia, and has been shown to lower plasma phenylalanine in adults with PKU (Thomas et al., 2018). Despite the side effects profile, which includes a risk of anaphylaxis, Palinziq® has had successful introduction into the clinic, with success in management of plasma phenylalanine levels in adults with PKU (Sacharov et al., 2020).

Thus, effective management of PKU, first accomplished with dietary therapy, has evolved to include cofactor and ERT, allowing for a personalized management plan with a variety of effective treatment options for affected individuals.

2.7  |  A baby has a positive newborn screen for mucopolysaccharidosis type I (MPS I) in New York in 2018: Hematopoietic stem cell transplantation

A newborn girl has a positive newborn screen for MPS I (Hurler Syndrome). Follow-up testing showed elevated urinary glycosaminoglycans, absent α-L-iduronidase (IDUA) enzyme activity in leukocytes, and molecular testing revealed homozygosity for a Trp402Ter early termination mutation. These findings were predictive of a severe MPS I phenotype (Clarke et al., 2019). She received a hematopoietic stem cell transplant (HSCT) at 4 months of age from an HLA-matched donor.

MPS I is a lysosomal storage disorder caused by pathogenic variants in the IDUA gene which encodes for IDUA, resulting in accumulation of heparan and dermatan sulfate in multiple organs. There is a wide spectrum of clinical severity of MPS I, ranging from the most severe phenotype, MPS IH (Hurler Syndrome), with early-onset symptoms, severe neurocognitive effects, and multiorgan involvement, to a relatively milder disorder that has minimal CNS effects (Scheie Syndrome) (Beck et al., 2014).

The rationale for HSCT in the treatment of MPS IH and other LSDs is that donor-derived cells have the ability to migrate across the blood brain barrier and differentiate into microglia. These donor cells secrete the deficient enzyme, which can then be taken up by neighboring cells, thereby cross-correcting the metabolic defect (Fratantoni et al., 1969; Krivit et al., 1995). HSCT for MPS IH, first reported in 1981, has been shown to favorably alter the natural history of this disease, allowing for prolonged survival, preserved neurocognition, and slowing progression of visceral organ involvement, with the most significant effects in those transplanted the earliest in their disease course (Hobbs et al., 1981; Parini et al., 2017). MPS I was added to the RUSP in 2016, thus promoting the earliest identification of affected patients who may benefit from HSCT. However, despite HSCT, significant features of MPS IH do persist in affected individuals, emphasizing the need for additional treatment approaches (Parini et al., 2017).

HSCT has been employed in the treatment of multiple other inborn errors of metabolism, with varying effects (Tan et al., 2019).
For example, HSCT has been shown to significantly favorably alter the natural history of disease when performed in the early phase of childhood cerebral adrenoleukodystrophy, and is the standard of care (Raymond et al., 2019). HSCT has been shown to have less favorable results in other disorders (Tan et al., 2019).

### 2.8 A patient presents with methylmalonic acidemia (MMA) in 2021: Genomic therapies

A newborn presented on day of life 2 with lethargy, tachypnea, hypothermia, pancytopenia, metabolic ketoacidosis, and elevated ammonia. Treatment with intravenous sodium benzoate and phenylacetate was implemented, but ammonia increased rapidly to over 500 requiring hemodialysis. Urine organic acids showed massive elevations of methylmalonic acid, while hyperglycinemia was present in the plasma. N-carbamylglutamate was added with gradual decrease in the ammonia levels. Injectable vitamin B12 was administered daily with no lowering of serum MMA. Sequencing of the methylmalonic acidemia gene panel revealed two nonsense variants in MMUT, confirming the diagnosis of severe mut$^6$, non-B12 responsive MMA subtype (Manoli et al., 1993). The family is counseled about enrolling in one of several new clinical trials testing MMUT mRNA monthly infusion therapy versus GeneRide AAV-mediated genome editing therapy. They will need to weigh the risks and benefits of each option and compare to the alternative of a liver transplant.

Organic acidemias, including methylmalonic and propionic acidemia, are a heterogeneous group of inborn errors of metabolism presenting with severe hyperammonemic encephalopathy, often before the newborn screening results become available (Kolker et al., 2015). Prompt initiation of adequate metabolic emergency treatment is necessary to prevent the associated high morbidity and mortality (Remacle et al., 2018). In addition to classic ammonia lowering measures, carglumic acid (Carbaglu$^6$), a synthetic analog of N-acetylglutamate (NAG), facilitates ammonia detoxification and urea production by activating carbamoyl phosphate synthetase 1, thereby improving or restoring the function of the urea cycle. It has been used successfully for the treatment of NAG synthase deficiency and was FDA approved in January 2021 for use as an adjunctive therapy in the treatment of acute hyperammonemia in MMA and Propionic Acidemia (PA).

Patients with severe isolated methylmalonic acidemia are managed by orthotopic liver transplantation, increasingly at younger ages (Critelli et al., 2018; Niemi et al., 2015; Nyhan et al., 2002; Pillai et al., 2019), in order to achieve hepatic enzyme replacement from a healthy donor and lower the risk for recurrent acute metabolic decompensations, thus improving the significant morbidity and mortality associated with this disorder. Patients receiving liver transplant show no metabolic instability, a reduction in circulating methylmalonic acid, and improved protein tolerance, but remain at risk for extrapathic disease manifestations including chronic renal disease and neurological complications, including metabolic basal ganglia infarct. Moreover, organ availability, complications related to surgery, graft rejection and life-long immune-suppressive drug therapy are additional limitations that prompted studies toward alternative approaches.

Liver-targeted genomic therapies, including systemic canonical recombinant adeno-associated virus (rAAV) gene therapy (Chandler & Venditti, 2010), systemic mRNA replacement (An et al., 2017), and genome editing (Chandler et al., 2020; Chandler & Venditti, 2019), have shown significant promise in animal models and are reaching phase I/II clinical trials as promising alternatives to liver transplantation. Several rAAV8 or 9 vectors with strong liver tropism and various promoters (liver specific or ubiquitous) showed sustained therapeutic benefit in knockout or transgenic MMA mouse models using the human MMUT coding sequence. Despite the impressive efficacy in the mouse models, genotoxicity in the form of hepatocellular carcinoma was observed with certain vector enhancer–promoter combinations, decreased efficacy of early neonatal treatment due to liver growth over time, and preexisting immunity to AAV capsids and dose-dependent hepatotoxicity requiring immunomodulation, pose ongoing challenges for the field. Lipid nanoparticle mRNA therapy is not limited by preexisting immunity and has low risk for genotoxicity but needs repeat systemic/intravenous delivery for chronic efficacy every 10–14 days in mice. A new AAV-based technology, GeneRide, using nuclease-free, promoterless homologous recombination to achieve integration of the MMUT into the albumin locus in the liver provides a promising new approach to minimize genotoxicity and achieve increased expression over time due to survival advantage of the transduced hepatocytes. Each of the approaches has its own advantages and limitation and will need to be tested for efficacy and safety in the clinic (Chandler & Venditti, 2019) (Table 3).

Similar liver-directed gene therapies are being tested in a large number of inborn errors with the hope of providing a definitive therapy with a one-time intravenous infusion in early stages of diseases or even presymptomatically after newborn screening diagnosis (Piccolo et al., 2021). Incorporating Whole Exome Sequencing/Whole Genome Sequencing (WES/WGS) or targeted sequencing into newborn screening programs for Inborn Errors of Metabolism (IEMs) combined with effective genomic therapies will allow presymptomatic detection and treatment and could alleviate the morbidity and mortality and significantly alter the natural history for the most serious disorders.

### 3 SUMMARY

“We may reasonably hope that in due time the substances of which we are speaking will, in like manner, be brought within the grip of the chemist. Obviously, the realization of this dream will result in an immense extension of the field in which chemistry and medicine meet”—Sir Archibald Garrod (Garrod, 1911).

As Sir Archibald Garrod presciently expressed, the treatment of inborn errors of metabolism centers on understanding and subverting biochemical defects of the cell to treat an ever-growing category of
The expanding repertoire of therapeutic approaches for inborn errors of metabolism, ranging from dietary modification to cofactor therapy to genetic modification, offers hope for affected individuals. Continuing to advance therapies and diagnostics available for these individuals is the charge of the medical and scientific community entrusted with their care.

CONFLICT OF INTEREST
The authors declared no potential conflicts of interest.

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