

Congenital forms of diabetes: the beta-cell and beyond

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The majority of patients diagnosed with diabetes less than 6 months of age, and many cases diagnosed between 6 and 12 months of age, have a gene mutation that causes permanent or transient hyperglycemia. Recent research advances have allowed for the discovery of new causes of congenital diabetes, including genes involved in pancreatic development (*GATA4*, *NKX2-2*, *MNX1*) and monogenic causes of autoimmune dysregulation (*STAT3*, *LRBA*). Ongoing follow-up of patients with *KCNJ11* and *ABCC8* mutations has supported the safety and efficacy of sulfonylureas, as well as the use of insulin pumps and continuous glucose monitors in infants with insulin-requiring forms of monogenic diabetes. Future studies are needed to improve clinical care and outcomes for these patients and their families.

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Introduction

Congenital diabetes, also called neonatal diabetes, describes a heterogeneous group of conditions that cause hyperglycemia within the first 6–12 months of life through defects in genes that are critical for beta-cell function, development, or autoimmunity. Although relatively rare, affecting approximately 1 out of every 100 000 births, knowledge of the specific gene cause will inform personalized treatment and prognosis, and may direct genetic counseling for other family members. Overall, the study of these monogenic forms of diabetes is fairly young. The discovery of the most common cause, mutations in the Kir6.2 subunit of the ATP-sensitive potassium channel (*KCNJ11*

mutations) was published less than 15 years ago [1]. Within this time, there have been significant advances in identifying and treating an increasing number of forms of congenital diabetes. This review will focus primarily on publications from 2014 to the present, with special emphasis on nomenclature, prevalence, identification and diagnosis, new gene causes, clinical updates to previously discovered gene causes, and updates to genetic testing.

Definition of neonatal diabetes

The term neonatal diabetes is frequently used, but is a misnomer; while the actual definition of ‘neonatal’ refers to the first month of life, the intended meaning of ‘neonatal diabetes’ usually stretches beyond this time frame. Six months of age is the most common cutoff in the literature, but variable definitions up to nine months or even 1 year of age have been given. Regardless of whether there is a precisely defined age cut-off, it is crucially important to recognize that these forms of diabetes are present from birth. Thus, we suggest that standardizing the definition may be a valuable addition to the field, and that a more appropriate name could be ‘congenital diabetes’, which we will use throughout this review, or ‘diabetes in infancy’.

Selecting who to test

Diagnosis age

A monogenic cause can be found in approximately 80–85% of cases diagnosed between birth and six months [2**] while early-onset type 1 diabetes predominates from six months to 1 year of age [3]. However, many publications report monogenic cases diagnosed after 6 months of age, and our Registry data suggests as many as 5–10% of those diagnosed between 6 and 12 months of age may have an underlying monogenic cause (University of Chicago Monogenic Diabetes Registry, data unpublished). The presence of islet autoantibodies at diagnosis may help to distinguish some of these 6–12 month onset cases as likely type 1 diabetes, but the discovery of monogenic forms of autoimmune diseases who would likely have positive antibodies (discussed further in ‘Newly discovered gene causes’ section) decreases the utility of using antibody status as an exclusion criteria. Use of a type 1 diabetes genetic risk score to discriminate likely monogenic cases may be helpful [4**], although this tool has not been used clinically and has been validated primarily in a Caucasian population, and thus may not be as useful in diverse patients or those with monogenic autoimmune syndromes.

Gestational age

Transient hyperglycemia occurs not infrequently in premature infants due to illness, stress, and/or glucocorticoid treatment and this may be related to immature pancreatic development, immaturity of beta-cell response to glucose elevation, and/or insulin resistance [5]. Distinguishing transient hyperglycemia related to prematurity from actual diabetes can be difficult. One study has shown that an underlying monogenic cause is more likely in patients who are >32 weeks gestational age (83%); however, a very significant 31% of those <32 weeks gestational age also had a monogenic etiology [6^{*}]. Congenital diabetes patients may have higher day-1 glucose levels and higher insulin requirements than transient hyperglycemia of prematurity [7]. We would suggest having a low threshold for performing genetic testing in any infant with hyperglycemia if it is significant (>250 mg/dL), persistent (more than a few days), or requires insulin treatment, especially if there is no other likely apparent cause.

Population-based approaches

A systematic approach, such as screening all newborns, is one method that may be less biased. A recent study in the United Kingdom suggested that measuring glucose levels from a newborn screening card on day 5 of life (DOL 5) is feasible. Among their diverse group of 11 participants with known congenital diabetes, all had significantly elevated screening card glucose levels on DOL 5, regardless of their eventual diagnosis age (ranging from 2 to 112 days after birth) or genetic cause (6q24, *ABCC8*, *GATA6*, *GCK*, *GLIS3*, or *KCNJ11*) [8^{*}]. Different countries perform newborn screening on different days (e.g., in the United States, newborn screening is typically done within the first 24–48 hours of life), so further research is needed to perform country-specific validation studies.

Due to the ambiguous definition of neonatal diabetes, along with the critical importance of correctly diagnosing these conditions, we support genetic testing for anyone diagnosed with diabetes less than 1 year of age [9].

Incidence

The incidence of congenital diabetes varies by country. The highest incidence rates have been reported in countries with higher levels of consanguinity, such as Turkey (1 in 30 000 births [10]) and the United Arab Emirates (1 in 29 241 births [11]). Other recent incidence reports include Ukraine (1 in 126 397 births [12]) and Japan (1 in 89 000 births [13]). Overall, the incidence rate in most non-consanguineous populations appears to be on the order of 1:100 000, but the true incidence may be underestimated due to reporting, misdiagnoses, or deaths.

Onset and presentation

Although diagnosis ages can vary, the majority of infancy-onset cases have a severe presentation. The frequency of diabetic ketoacidosis (DKA) at presentation for infants

diagnosed less than one year of age may be up to 66%, higher than onset DKA rates for any other age group in the United States [14^{*},15,16]. This increased severity may be at least partially due to a delay in diagnosis. In a cohort of 88 cases diagnosed at one year of age or less, the odds of presenting in DKA increased with age at diagnosis (OR per 1 month increase 1.23) [14^{*}]. Infants with diabetes frequently present with vague signs and symptoms that may overlap with more common, less severe conditions (such as viral infections), which can make an accurate diagnosis challenging for healthcare providers [14^{*}]. Educating pediatric providers on congenital diabetes, as well as implementing system-wide screening measures (such as newborn screening or mandatory glucose check in any severely ill infant), will help to decrease delays in diagnosis, as well as morbidity and mortality.

Updates on existing gene causes

Figure 1 includes phenotypic information on new and known causes of congenital diabetes.

KCNJ11 and *ABCC8*

KCNJ11 encodes for the inward-rectifying potassium pore (Kir6.2) of the ATP-sensitive potassium channel, while *ABCC8* encodes for the outer regulatory subunit (SUR1). Activating mutations in either gene inhibit the closure of the channel, thereby causing permanent or transient congenital diabetes. Mutations in the *KCNJ11* gene are the most common cause of permanent congenital diabetes, whereas *ABCC8* mutations are more likely to have a transient phenotype. Importantly, 90–95% of these mutations are responsive to treatment with oral sulfonylurea medications, which facilitate closure of mutated channels and allow for endogenous insulin secretion [17,18^{*}]. In the past few years, several clinically important updates for patients with *KCNJ11*-related diabetes have arisen. Treatment with sulfonylureas for these patients is fairly straightforward, but research on safety and long-term efficacy is still needed. Perhaps even more importantly are the updates quantifying the existence of a variety of features beyond the beta-cell, such as neurodevelopment, sleep, and psychiatric disturbances that often accompany diabetes in these cases.

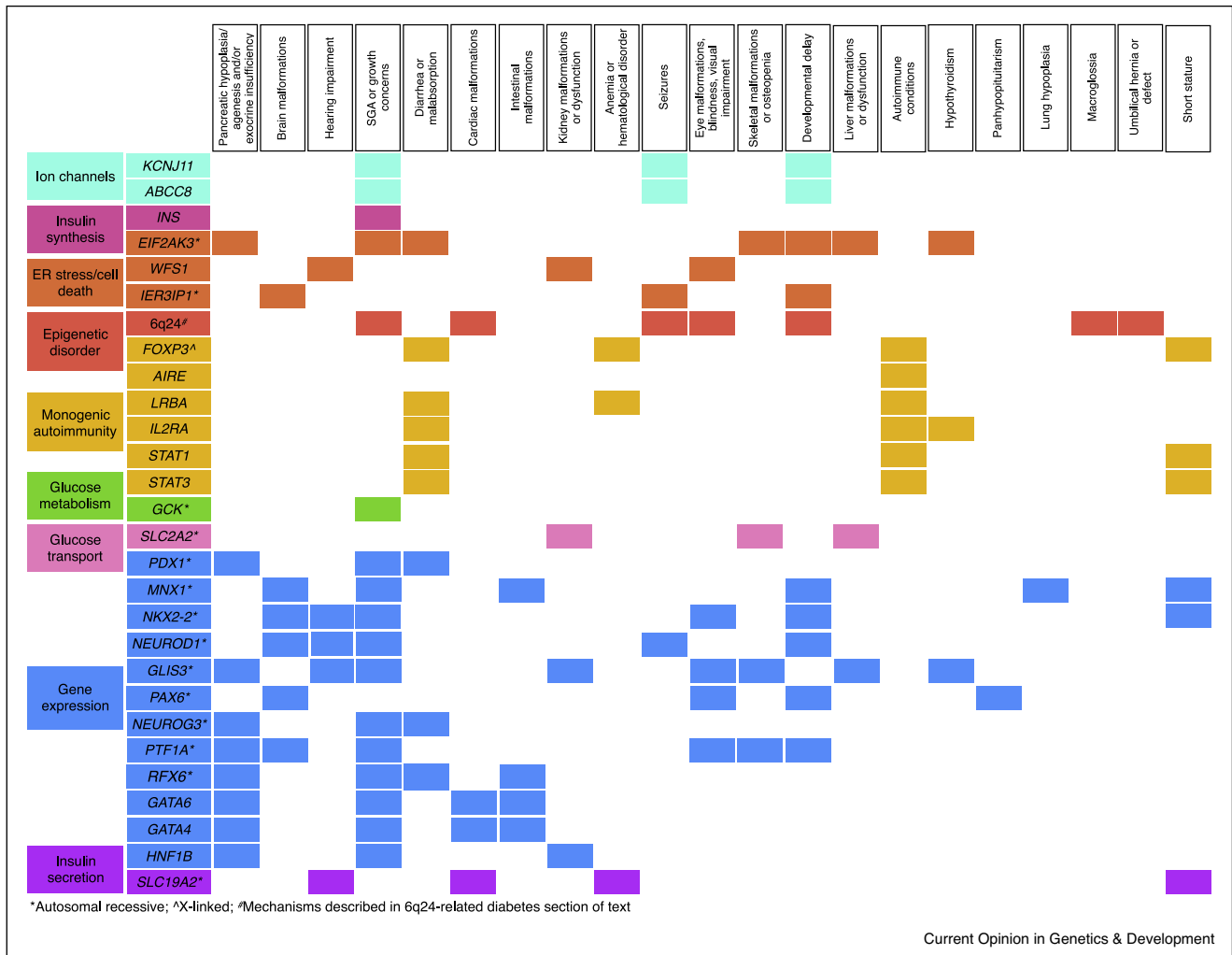
Effects of sulfonylureas on neurodevelopment and glycemic control

Sulfonylureas (SU) continue to support improvements in HbA1c measurements, neurodevelopment, and behavior in children with *KCNJ11*-related diabetes. Further details on safety and efficacy can be found in the ‘Treatment of Congenital Diabetes’ section.

Development, behavior, and sleep

The neurological sequelae in patients with *KCNJ11* and *ABCC8* mutations is likely related to the widespread expression of KATP channels in the brain. Compared

Figure 1



Genetic causes of congenital diabetes and associated clinical features.

to their unaffected sibling controls, patients with *KCNJ11* mutations performed worse in areas such as academic achievement, executive functioning, and IQ [19*,20]. Participants with the most severe *KCNJ11* mutations, often associated with DEND syndrome (development delay, epilepsy, and neonatal diabetes), consistently scored the lowest, while some were unable to perform the measures at all [19*,20]. Parents and teachers of children with *KCNJ11*-related diabetes reported high levels of psychiatric morbidity [21*]. Nearly all participants required some level of educational or developmental intervention. Developmental, anxiety, and behavioral disorders were present in 80% of participants, with ADHD, autism, and anxiety disorders being the most common. However, many of these disorders had gone undiagnosed by their healthcare team [21*]. A separate study found similar results — patients with *KCNJ11* were more likely than their sibling controls to be diagnosed

with ADHD, have behavior difficulties, struggle with social awareness and academic achievement, utilize an Individualized Education Plan (IEP), and have sleep difficulties [22]. All patients with *KCNJ11*-related or *ABCC8*-related diabetes should have access to an interdisciplinary healthcare team to allow for screening of, and early intervention in, developmental, behavioral, and sleep disorders.

Complications of DKA at diagnosis

In a report of two cases with KATP mutations (Case 1: compound heterozygous *ABCC8* mutation; Case 2: heterozygous *KCNJ11* p.S3C mutation), the authors suggest that the severity of DKA at diagnosis led to significant long-term neurological disability, since other patients with the same mutation did not have similar neurological dysfunction [23]. However, study of long-term neurological outcome in greater numbers of patients with diabetes

due to all gene causes is needed in order to determine whether those with KATP mutations may be more susceptible to such injury.

INS

Mutations in the proinsulin gene (*INS*) most frequently create misfolded insulin products that can cause endoplasmic reticulum stress, and thus beta-cell death [24]. Patients with *INS* mutations are insulin-dependent.

Insulin treatment and using new diabetes technologies

Early identification and treatment of elevated blood sugars in patients with *INS* mutations may preserve beta-cell function and improve outcomes. In two sisters (*INS*: p.Gly32Ser), earlier identification and insulin treatment in sister two was associated with lower insulin requirements, lower HbA1c values, and higher c-peptide levels at age-matched time-points [25]. New diabetes technologies, such as continuous subcutaneous insulin infusions (CSII; insulin pumps) and continuous glucose monitoring, may be especially useful in managing insulin-dependent forms of congenital diabetes such as *INS* mutations. A sensor-augmented pump with threshold-suspend features was successfully used in a 3 month old (*INS*: p.Tyr108Cys). Importantly, this case also describes the difficulties in obtaining insurance approval for new diabetes technologies, and how the authors overcame these obstacles [26].

Novel mechanism in homozygous case

By studying a case with a novel deep intronic homozygous mutation (*INS*: c.187 + 241G > A), a novel mechanism of diabetes was discovered [27]. This also supports how regulatory regions that are often not covered by genetic testing, such as deep introns, may be important in finding a genetic cause for the remaining ‘unknown’ infancy-onset cases.

6q24-related diabetes

6q24-related diabetes is the most common cause of transient congenital diabetes and is caused by overexpression of the genes *PLAGL1* and *HYMAI*, whose shared promoter overlaps with the 6q24 differentially methylated region that is normally methylated when maternally inherited, thus suppressing transcription. Diabetes is usually diagnosed shortly after birth, with remission sometime during the first year of life, then reoccurrence later in life [28]. There are three main mechanisms that lead to overexpression of two imprinted genes on chromosome 6q24 (*PLAGL1* and *HYMAI*): (1) uniparental paternal disomy (UPD6), (2) paternal inheritance of a duplication in this region, or (3) defects in maternal methylation. Patients may have hypomethylation only at this locus, while others may have multiple areas of hypomethylation due to mutations in *ZFP57* [29].

Areas affected by ZFP57 mutations

A novel region within the *PPP1R13L* gene was found to be hypomethylated in patients with transient congenital diabetes and *ZFP57* mutations through genome-wide methylation analysis. This finding may help to explain the mechanism by which hypomethylation causes transient hyperglycemia [30].

Variable presentation

Recent publications suggest that other presentation patterns may be possible. Three patients from Japan were found to have paternal uniparental isodisomy of chromosome 6q24, but although all three patients were born small-for-gestational age (SGA), they did not have any evidence of hyperglycemia in the neonatal phase [31]. Conversely, a separate case report described a patient who was born SGA, developed hyperglycemia on DOL 2, was found to have paternal uniparental isodisomy of chromosome 6q24, but remained on insulin at 5.5 years old [32].

Non-insulin therapies

Although the optimal treatment for 6q24-related diabetes remains unknown, studies have shown that these patients are capable of endogenous insulin production and thus insulin may not necessarily be the most appropriate treatment. Four patients in the reoccurrence phase (age range 20–29 years old) were able to transition off of insulin and onto glyburide with a corresponding increase in c-peptide level. All four participants were insulin-independent at a follow-up 5 months later. One subject continued only on glyburide, while one required the addition of metformin, and the remaining two required the addition of metformin and sitagliptin [33]. Some patients may respond to sulfonylurea therapy during the neonatal period instead of subcutaneous insulin therapy without adverse events [34,35].

FOXP3

Mutations in *FOXP3* have previously been associated with Immunodysregulation Polyendocrinopathy Enteropathy X-linked (IPEX) syndrome [36]. Males with these mutations typically present with diabetes and other autoimmune conditions during infancy or early childhood. However, not all cases develop severe IPEX syndrome, and cases with mild phenotypes have been previously described [37]. A recent study of six males with *FOXP3* mutations and variable phenotype severity supports this finding [38].

NEUROG3

Patients with homozygous *NEUROG3* mutations most often present with infancy-onset diabetes and malabsorptive diarrhea. An expanded phenotype was found in a Turkish patient with a novel homozygous nonsense mutation (p.Q4*), including thyroid gland hypoplasia,

reduced intrahepatic biliary tracts, and neuromotor retardation due to bilateral ventriculomegaly [39].

EIF2AK3 (Wolcott–Rallison syndrome)

EIF2AK3 encodes for eukaryotic translation initiation factor 2- α kinase 3 (also called PERK) and plays an important role cellular management of misfolded proteins. Mutations in this gene lead to a build-up of misfolded proteins in the endoplasmic reticulum that ultimately triggers cell death [40,41]. PERK expression in multiple tissues helps to explain the range of clinical manifestations, typically including infancy-onset diabetes, skeletal dysplasia, and liver dysfunction. Evidence of endoplasmic reticulum stress was found in autopsy specimens (liver, pancreas, kidney, and myocardium) from two patients with *EIF2AK3* mutations [42]. This condition is the most common recessive cause of congenital diabetes and is more common in countries with high rates of consanguinity. However, as noted in a recent Iranian cohort of patients, clinical features other than diabetes often develop outside of the infancy period [43]. *EIF2AK3* should be included in any panel of congenital diabetes genetic testing and should especially be tested in any patient with known or suspected consanguineous family, even if skeletal dysplasia and liver dysfunction are not present during infancy.

GLIS3

Mutations in *GLIS3* most frequently lead to infancy-onset diabetes, congenital hypothyroidism, glaucoma, kidney abnormalities, and liver disease. A facial phenotype was recently described which included an elongated philtrum, vermilion outline of upper lip, low-set ears, and a sunken nasal bridge with upturned nose [44]. This may assist in identifying patients who are likely to have *GLIS3*-related diabetes.

RFX6 (Mitchell–Riley syndrome)

Homozygous mutations in *RFX6* can cause a severe syndrome of diabetes, intestinal atresia, gallbladder hypoplasia, and diarrhea. Most cases have diabetes onset shortly after birth. Two cases in which compound heterozygous nonsense mutations near the end of the *RFX6* gene (p.Arg726X/p.Arg866X) were recently described to have intestinal atresia diagnosed at birth, whereas diabetes was not diagnosed until ages 3 and 6 years [45], thereby expanding the phenotype of *RFX6* mutations.

Treatment in congenital diabetes

Treatment options for congenital diabetes usually include either insulin or sulfonylureas (SU).

SU treatment for *KCNJ11*-related diabetes

The majority of patients with *KCNJ11*-related diabetes will be responsive to SU treatment, although the dose required can be variable (usually within 0.5–2.0 mg/kg/day) [18*]. Older studies showed promising reductions in

HbA1c [17] with SU treatment, while a recent study concurred by demonstrating a decrease on average from 8.5% (69 mmol/mol) before transition to 6.2% after initiation of SU therapy [18*]. Importantly, this study also suggested that those who were transitioned to SU therapy at a younger age needed a lower dose of the medication and were more likely to remain well controlled on monotherapy, while those who transitioned at a later age (after 13 years of age) were more likely to need additional glucose-lowering medications. Several case reports of patients at various ages and one study of 18 patients before and after initiation of SU treatment strongly suggest improvements in neurological and psychomotor function [46*]. Initiating SU at a younger age may result in greater overall improvement; however, further study is needed to define the degree to which neurodevelopmental disability may be prevented [47]. Significantly, use of sulfonylureas in those with *KCNJ11* mutations does not seem to cause severe hypoglycemia, even at the high doses required by some patients (~2.0 mg/kg/day in some cases). A cohort of 30 patients with *KCNJ11*-related permanent diabetes reported no episodes of severe hypoglycemia while maintaining HbA1c in goal range (166 patient-years, median recent HbA1c 5.7%) [48**]. These findings support the need for early genetic testing in all patients with infancy-onset diabetes to allow for personalized treatment and improvements in prognosis.

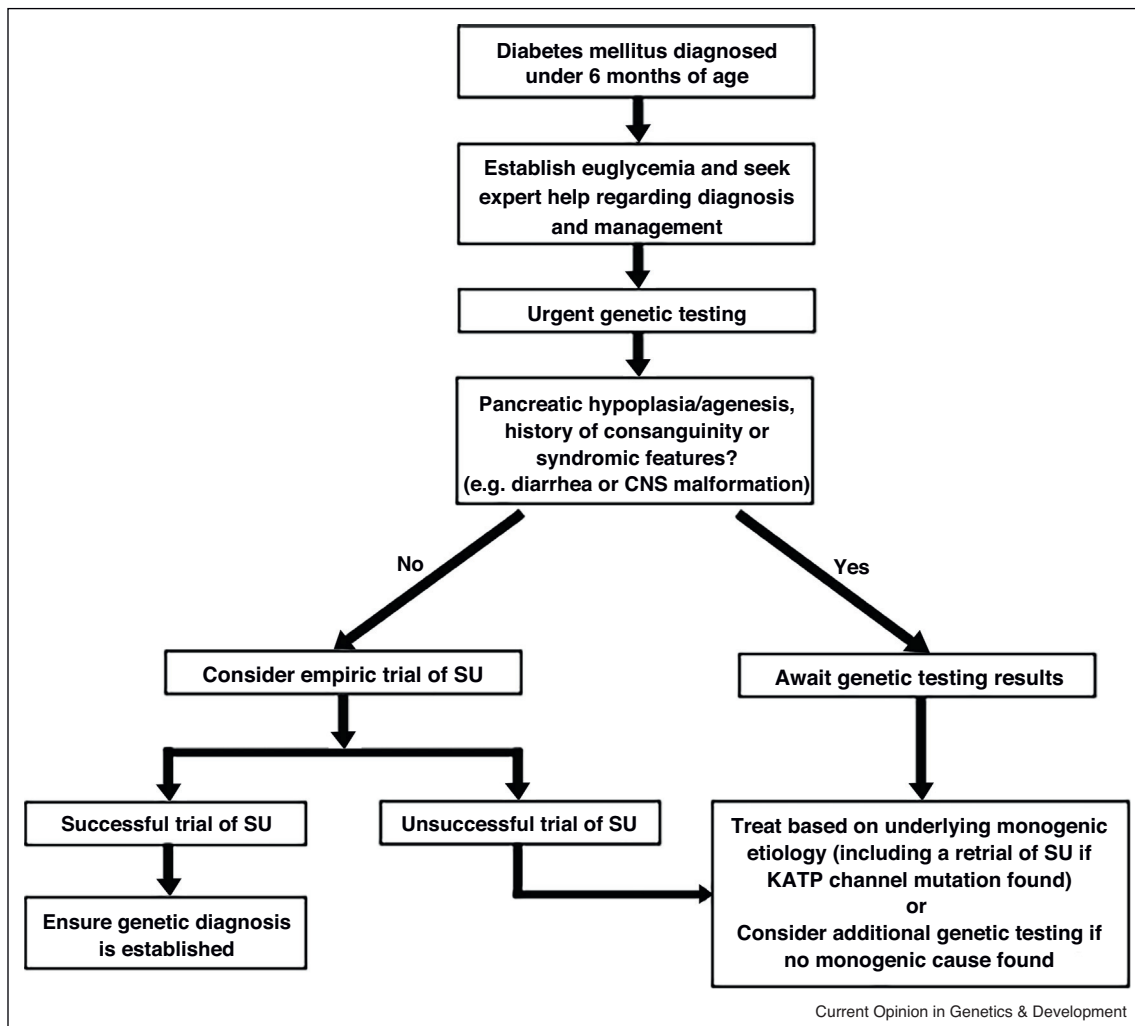
Empiric SU treatment before genetic testing

The amount of time required to receive genetic testing results can vary by country, healthcare insurance policy, and healthcare provider knowledge. The risks and benefits of trialing SU before genetic testing results are returned were assessed. In the cohort studied, which was mainly from the United States, there was frequently a significant delay in the availability of genetic testing results, whereas empiric SU treatment appeared to be safe and often successful [35]. Positive results of trialing SU were also found in a cohort of infancy-onset diabetes patients from China [49]. Genetic testing is always recommended, even if the SU appears to be successful. Caution should be taken in situations where a *KCNJ11/ABCC8* mutation is less likely (such as a consanguineous family or when extra-pancreatic manifestations are present), and efforts to guard family expectations should be taken (Figure 2).

Insulin therapy

Many patients with congenital diabetes will require long-term insulin therapy. These patients can benefit from advancing diabetes technology such as diluted insulin, continuous subcutaneous insulin infusions (CSII; including those with advanced automated features, as discussed in the updates to INS-mutations section above), and continuous glucose monitors (CGM). Four cases of infancy-onset diabetes utilized CSII, CSII and CGM, or CSII and CGM with threshold suspend to introduce

Figure 2



Decision algorithm for an empiric trial of sulfonylurea. CNS, central nervous system; SU, sulfonylurea. International monogenic diabetes registries can be contacted (<http://monogenicdiabetes.uchicago.edu> and <http://www.diabetesgenes.org>) if local expert help is unavailable. (Previously published in Carmody *et al.*, Sulfonylurea Treatment Before Genetic Testing in Neonatal Diabetes: Pros and Cons, JCEM, Dec 2014).

insulin therapy [50]. Due to the small insulin requirements and frequent feeding of infants, using CSII allowed for more accurate dosing, and was safe without any episodes of DKA or severe hypoglycemia. Suggestions on initial insulin dosing in neonates and infants using CSII were created after analysis of a cohort of German patients [51]. A helpful comprehensive review of the literature on insulin therapy in infancy-onset diabetes was recently published [52*].

Although the majority of insulin types are not approved in the United States for use in children under 2 years of age, newer insulins that have become the standard of care in diabetes can still be used off-label, just as many drugs are routinely used off-label to treat neonates and infants for a variety of conditions. Continued research in this area will

help to provide the needed data for updated safety approvals in the United States.

Newly discovered gene causes

It has been difficult to find new monogenic causes for the remaining patients with unclassified infancy-onset diabetes. As mentioned above, some of these patients will have early-onset type 1 diabetes [4], however, a few new gene causes have been described in patients who ultimately developed syndromic features.

Monogenic causes of autoimmunity — *STAT3* and *LRBA*

In addition to mutations in *FOXP3*, studies have described other gene causes of early-onset autoimmune diabetes (*STAT1*, *AIRE*, *IL2RA*), usually in association with other autoimmune problems [36,53–55]. Recently,

activating *STAT3* mutations were found in multiple patients with early-onset polyautoimmune disease, the majority of whom were diagnosed with permanent diabetes (diagnosis age range: birth–43 weeks) [56]. Nine patients with diabetes diagnosed before 12 months of age were found to have compound heterozygous or homozygous mutations in *LRBA*. Of these nine, eight had at least one other immune dysregulatory feature [57].

Pancreatic development – *GATA4*, *NKX2-2*, and *MX1*

Mutations in at least 12 genes affecting pancreas development have been described as causes of congenital diabetes. *GATA6*, *PDX1*, and *PTF1A* are characterized by pancreatic hypoplasia or agenesis [58–63], whereas others appear to predominantly affect the beta-cell lineage, although in some cases the pancreas may appear small on imaging (see Figure 1). Mutations in *GATA4* have recently been shown to cause infancy-onset diabetes and variable levels of exocrine insufficiency [64]. Homozygous mutations in *NKX2-2* were identified in two families with diabetes and severe developmental delay, hypotonia, cortical blindness, impaired visual tracking, and hearing impairment [65]. A more variable phenotype was found in two families with homozygous *MX1* mutations; while both patients presented with diabetes, one patient had additional features such as severe neurological complications, hypoplastic lungs, and sacral agenesis [65].

Cell stress – dominant *WFS1*

Dominant, heterozygous mutations in *WFS1* that cause syndromic congenital diabetes, and are clinically and genetically distinct from recessive Wolfram Syndrome, have been recently identified [66]. All five patients were diagnosed with diabetes less than 12 months of age (2/5 diagnosed <6 months of age) and sensorineural deafness. The majority (4/5) also had congenital cataracts and hypotonia. This severe syndrome is likely caused by significant endoplasmic reticulum (ER) stress causing cell death [66].

Updates to genetic testing

In previous years, the clinical phenotype of a patient would inform the decision about which genes to test. Based on diagnosis age, response to sulfonylureas, and syndromic features, one could narrow the list of possible genes, and perform single-gene sequencing to identify the monogenic cause. As the cost of genetic testing has fallen — while the number of known gene causes has risen — a shift from single-gene sequencing to more comprehensive, next-generation sequencing methods has occurred. This includes targeted panels, whole exome sequencing, and whole genome sequencing [67–71]. Performing wider-reaching genetic testing at the outset allows for a better chance of making a genetic diagnosis early on. This can guide personalized treatment and improve prognosis [72]. Amidst these scientific advances,

unique practical challenges remain for obtaining genetic testing. For example, even in the United States, coverage of genetic testing by health insurance companies is still variable, and even with coverage, tests can take a month or longer to be approved, performed and result. Families and healthcare providers often find this ordering process frustrating, and results can be jargon-filled and difficult to understand. Increased genetic testing knowledge of healthcare providers and better cooperation from insurance companies would help to improve care quality for patients with congenital diabetes.

Cell-free fetal DNA analysis

Prenatal cell-free DNA analysis was successfully performed on a sample of maternal plasma in order to rule out a paternally-inherited *KCNJ11* mutation in the fetus at 12–16 weeks' gestation [73]. This non-invasive testing is of great interest to many families with monogenic diabetes, and as the technology improves it will be an important tool for helping to guide family expectations and clinical management.

Conclusions

The field of congenital diabetes is quickly advancing. Knowledge gained in the last few years has allowed for improvements in comprehensive genetic testing and interdisciplinary clinical care, improving overall quality of life for patients and their families. We are able to provide patients with earlier diagnoses, make personalized treatment plans for diabetes and associated conditions, and utilize the newest pump and sensor technologies to improve outcomes. Patients with insulin-dependent congenital diabetes will continue to benefit from these technological advances, such as improved 'artificial pancreas' pumps. Further research on the efficacy of sulfonylureas and related drugs may help to improve neurodevelopment for patients with *KCNJ11*-related and *ABCC8*-related diabetes. Continued efforts at gene discovery may help reveal mechanistic secrets of the more common forms, type 1 and type 2 diabetes. At some point in the not-too-distant future, advances in the areas of gene editing and induced pluripotent stem cells (iPSCs) may even allow for a 'cure' for some forms of congenital diabetes that only involve hyperglycemia, such as *INS*-related diabetes. Progress in discovery is likely to yield better treatments and outcomes for those affected by congenital diabetes and their families.

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Conflict of interest statement

Nothing declared.

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- of special interest
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