



# Defining Pathways for Development of Disease-Modifying Therapies in Children With Type 1 Diabetes: A Consensus Report

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**Emerging data suggest that type 1 diabetes is a more aggressive disease in children than in adults, with important differences in pathophysiology and clinical course. Therefore, the efficacy of disease-modifying therapies may be different in the two populations. Understanding the developmental and regulatory pathways for type 1 diabetes—modifying therapies in children will enable industry, academia, funders, advocacy groups, and regulators to translate new science to clinical care. This consensus report characterizes the fundamental differences in type 1 diabetes between children and adults and proposes a thoughtful approach to better understand the development and regulatory pathways for type 1 diabetes therapies.**

Despite advances in the treatment of type 1 diabetes, the disease remains a significant burden for individuals, especially for children and their families. Preventing or halting  $\beta$ -cell destruction—that is, using disease-modifying therapy, instead of just managing symptoms of hyperglycemia—could alleviate this burden. In recent years, potential treatments to alter the course of the disease via targeting the immune response or directly impacting  $\beta$ -cell health have multiplied. The challenge remains to bring such disease-modifying therapies into clinical use, particularly in children.

For diseases that occur in both children and adults, the pathway of pediatric drug development often relies on the concept that the impact of the disease, disease pathophysiology, clinical course, and response to therapy are essentially the same in the adult and pediatric populations. Under this assumption, clinical trials are usually conducted in adults first, with the intent of protecting children from the risks of new therapies. This approach could lead to delays in getting these therapies to children. In addition, if the outcome of such trials successfully leads to approval in the adult population, clinical use in children may occur prior to definitive studies demonstrating safety and efficacy in the pediatric population. Conversely, if the outcome of such trials in the adult population is negative, a therapy that could be efficacious in the pediatric population may never be tested.

Emerging data have increasingly highlighted the differences between type 1 diabetes diagnosed in children as compared with those in adults. Such differences imply that the requirement to first demonstrate efficacy and safety in adults may not be appropriate for type 1 diabetes, indicating that a different pathway should be considered when developing disease-modifying therapies in children with type 1 diabetes.

The American Diabetes Association (ADA), in conjunction with JDRF, the T1D Exchange, and the Benaroya Research Institute, convened a consensus conference in January 2015 entitled “Defining Pathways for Development of Disease-Modifying Therapies in Children With Type 1 Diabetes” to consider how differences in

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\*The complete list of the Type 1 Diabetes TrialNet Study Group and Affiliate Investigators can be found in the Supplementary Data.

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pediatric- and adult-onset disease should be incorporated when weighing the risks and benefits of each potential clinical trial and therapy. Speakers described the current understanding of the burden of the disease, its clinical course, and responses to therapy in the context of differences in pediatric- and adult-onset type 1 diabetes. Additional speakers discussed the ethical and regulatory framework for conducting studies and developing therapies in children. The meeting concluded with an open session in which all participants discussed pathways to engage children in clinical research as well as unmet research needs. This discussion resulted in a series of recommendations for future research directions.

## CLINICAL BURDEN OF TYPE 1 DIABETES

### Epidemiology

Continued increases in the global incidence and prevalence of type 1 diabetes indicate that the disease is an expanding problem. As defined by the U.S. population-based SEARCH for Diabetes in Youth (SEARCH) study, approximately 22 out of every 100,000 children aged <20 years develop type 1 diabetes annually in the U.S. (1). Incidence rates in most countries are steadily rising, particularly in the youngest children (2,3); data from the U.S. suggest that this increase is ~2.7% per year (4). The prevalence of type 1 diabetes in U.S. children aged <20 years is approximately 1 per 526 children (4), translating to just less than 200,000 affected youth (5). Modeling suggests that the number of children with type 1 diabetes will nearly triple between 2010 and 2050 (6).

Data on type 1 diabetes incidence in adults are less clear due to difficulties in defining and recognizing type 1 diabetes in adults. It has been estimated that 5% of all cases of diabetes diagnosed in adults may be type 1 diabetes (7). As is true for incidence data, precise prevalence estimates in adults are lacking. According to survival data and estimates of incident cases, when both children and adults are considered, 900,000 to 1.25 million Americans live with type 1 diabetes (7,8).

### Glycemic Control

Glycemic control is the foundation of type 1 diabetes care due to its role in prevention of acute and long-term complications.

The ADA recommends an HbA<sub>1c</sub> target of <7.5% (<58 mmol/mol) for youth

aged <18 years and an HbA<sub>1c</sub> target of <7.0% (<53 mmol/mol) for adults (9). Unfortunately, these targets are infrequently met. Data from the T1D Exchange clinic registry, which includes ~26,000 participants with type 1 diabetes seen at ~70 adult and pediatric diabetes specialty centers in the U.S., show mean HbA<sub>1c</sub> levels well above targets at all ages, particularly in teenagers (Fig. 1) (10). Population-based data from the SEARCH study also reflect significant hyperglycemia; nearly 17% of youth with type 1 diabetes have HbA<sub>1c</sub> >9.5% (>80 mmol/mol), with higher HbA<sub>1c</sub> levels observed in children from ethnic minority populations (4). Data from other countries indicate suboptimal glycemic control as well (11). These rates persist despite the availability of comprehensive care recommendations and advanced technology.

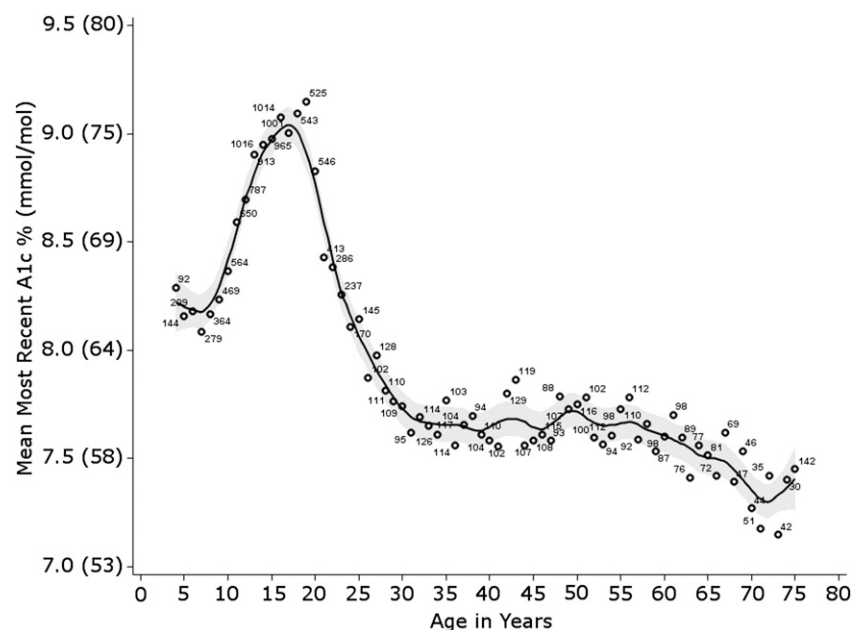
In addition to the failure to meet glycemic targets, current care also fails to prevent severe hypoglycemic episodes. In 2015, the T1D Exchange found that up to 6% of individuals had reported a seizure or loss of consciousness attributable to hypoglycemia in the previous 3 months (10). The previously well-recognized relationship between better glucose control and higher rates of hypoglycemia was not seen in the T1D Exchange clinic registry data;

similar rates of severe hypoglycemia were seen across all HbA<sub>1c</sub> values (Supplementary Table 1) (10). These data indicate that factors beyond glycemic control, such as endogenous insulin secretion, may be important in preventing severe hypoglycemia.

Diabetic ketoacidosis (DKA) also remains a common acute complication. In the U.S., the SEARCH study reported that ~30% of participants younger than 20 years of age with type 1 diabetes presented with DKA (12). Recent data noted that 46% of newly diagnosed children had DKA at onset in 2012 (13). Outside of diabetes onset, 3% of the T1D Exchange participants reported experiencing at least one episode of DKA requiring a visit to a hospital or other medical facility within the prior 3 months. DKA rates were generally highest in children (10).

### Neurocognitive Effects

Studies have shown that both children and adults with type 1 diabetes may have evidence of cognitive dysfunction and structural changes within the central nervous system. Differences between people with and without diabetes are most apparent on measures of psychomotor speed, cognitive flexibility, intelligence, attention, and visual perceptual ability, whereas learning, memory, and



**Figure 1**—Mean HbA<sub>1c</sub> levels by age. Circles represent mean HbA<sub>1c</sub> values for each year of age from 16,057 T1D Exchange registry participants. Participants aged <4 years were grouped as age 4 and those aged ≥75 years were grouped as age 75. Shaded area represents the 95% CI around smoothed line. Numbers next to circles are the N for each year of age. Reprinted with permission from Miller et al. (10).

language skills are usually unaffected. Effect sizes are moderate (14) and are somewhat lower in children (15), with one important exception. Some children who developed type 1 diabetes early in life, before the age of 6 or 7 years, not only perform more poorly on virtually all cognitive tests—including measures of learning and memory—but also are more likely to meet diagnostic criteria for clinically significant impairment (16).

Dysfunction may appear soon after the diagnosis. For example, young children who had diabetes for less than 2 or 3 years, were diagnosed early in life, and had elevated HbA<sub>1c</sub> values performed poorly on multiple cognitive tests and manifested widely distributed microstructural white matter changes (17,18). A recent report demonstrated that older children and adolescents studied within 3 days of the diagnosis performed significantly below average on tests of psychomotor speed, and those scores predicted HbA<sub>1c</sub> values 1 year later (19).

Longitudinal studies have demonstrated that cognitive function may decline somewhat over time when children with type 1 diabetes are followed from childhood into early adulthood (20). Over a 12-year period, children followed since diagnosis showed only a 1-point decrease in intelligence quotient scores compared with demographically similar subjects without diabetes. However, when patients with an earlier onset of diabetes were compared with those with a later onset, a greater decline over time was observed (~4 points), and when those who experienced severe hypoglycemia at any age were compared with those who never experienced hypoglycemia, an even greater decline was seen (~6 points) (21).

The pathophysiological basis for neurocognitive changes in children with type 1 diabetes remains poorly understood, but it appears that the development of diabetes early in life is an important risk factor, as is a history of chronically elevated hyperglycemia and/or severe hypoglycemia. Interventions that can delay the onset of diabetes (for example, shift its onset beyond the first 6–7 years of life) or that can reduce the occurrence of glycemic extremes may lead to marked reductions in the risk of cognitive dysfunction in children and adolescents.

### Long-term Consequences

The long-term prognosis for those with childhood-onset type 1 diabetes has

greatly improved over the last 30 years (22). Advanced chronic complications are now rarely seen in the U.S. during childhood or adolescence, although early signs of complications can still be detected (4).

Indeed, recent data from the Pittsburgh Epidemiology of Diabetes Complications (EDC) study suggest that for those who were diagnosed with type 1 diabetes in childhood between 1965 and 1980 life expectancy is now only 3.8 years less than what might be expected (23). Furthermore, as suggested by the Finnish Diabetic Nephropathy Study (FinnDiane) (24) and confirmed in the EDC over a 20-year follow-up (25), there appears to be no excess mortality in those who avoid increased albuminuria. Although rare, when death does occur in children with diabetes, it is usually (~80% in one recent analysis [26]) due to acute complications (hypoglycemia or DKA).

In contrast, two national databases in Scotland (27) and Sweden (28) showed that mortality rates still appear to be greatly increased in adults with type 1 diabetes relative to individuals without diabetes. Interestingly, both of these studies included those with adult-onset type 1 diabetes. This raises the issue as to whether the natural history differs in childhood- versus adult-onset cases. It has long been thought by some that the prepubertal years of type 1 diabetes are less “damaging” than the years after the onset of puberty. A recent study from Sweden supports this concept (29), but the tenet remains controversial. Death due to DKA or hypoglycemia among adults with type 1 diabetes is less common, proportionately, than in children and accounts for between 10% (26) and 18% (30) of all deaths.

The 30-year cumulative incidence of complications in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) conventional treatment group and in the DCCT “eligible” participants from the EDC study showed similar rates (31). In the DCCT conventional treatment group, 50% developed proliferative retinopathy, 14% had cardiovascular disease, and 25% had nephropathy. Despite significant changes in clinical care, among the major complications, only end-stage renal disease showed a major fall in the EDC after

30 years’ duration (22). As shown by the DCCT, improved glycemic control is likely the most critical risk factor in terms of reducing complication rates in type 1 diabetes; the inability to achieve glycemic targets as outlined above is therefore one explanation for the persistence of complications in type 1 diabetes. However, even with improved glucose control and potential reductions in other factors, such as smoking, insulin resistance (32), hypertension (33), and hyperlipidemia (33,34), the increasing incidence of type 1 diabetes combined with the increased survival of those diagnosed in childhood noted above portends an increasing burden on society with respect to care of adults with long-standing type 1 diabetes.

Data from the DCCT highlight the important role of residual endogenous insulin secretion in microvascular complications and hypoglycemia. For patients receiving exogenous insulin therapy, measurement of C-peptide reflects endogenous  $\beta$ -cell secretion. Patients with a stimulated C-peptide  $>0.2$  nmol/L had a 62% lower risk for severe hypoglycemia and a 79% lower risk for progression of retinopathy (35) (Supplementary Fig. 1), indicating that C-peptide  $>0.2$  nmol/L is a clinically significant threshold. Even lower, but measurable, amounts of C-peptide were recently reported to confer protection from long-term complications (36). The value of small amounts of endogenous  $\beta$ -cell function is also highlighted in islet transplantation literature. Most patients undergoing islet transplantation have recurrent severe hypoglycemia as a result of hypoglycemic unawareness—a severely debilitating consequence of type 1 diabetes. Although only 44% of patients remain insulin independent 3 years after transplant, almost all subjects with modest C-peptide production after transplant have complete resolution or significant reduction in severe hypoglycemia (37).

### Quality of Life

Quality of life (QOL) is recognized as a central outcome for health care and health care policy and is increasingly considered as an important outcome measure in clinical trials evaluating interventions to improve diabetes management. The construct includes both general well-being and health-related QOL, encompassing the disease state and physical symptoms, functional status,

psychological and social functioning, and neurocognitive functioning.

Factors related to the QOL of individuals with type 1 diabetes include medical, demographic, and psychosocial components. In addition, the QOL of parents and other family members is also affected, particularly for those with childhood type 1 diabetes, because many parents experience increased psychological distress as well as the burden of caregiving related to diabetes management.

There are a number of reliable and valid measures of both child self-reported and parent proxy-reported generic and diabetes-specific QOL for children and adolescents with type 1 diabetes (38–40). These measures typically provide an overall score and scale scores for the domains of QOL, and because they are fairly brief, they have good utility for use in clinical trials. Comparisons of QOL cannot be made between adults and children in the same study because there are no standardized QOL measures that are appropriate for both populations.

Although some individual studies showed small to moderate effect sizes based on several standardized measures, weighted effect sizes across studies suggest that scores are more similar than different across QOL domains between children with type 1 diabetes and healthy peers. Interestingly, however, parents tend to rate their children's QOL as lower compared with healthy peers (41). Numerous studies have documented that many parents report significant distress after their child's diagnosis of diabetes, with significant symptoms of depression and posttraumatic stress disorder evident in up to one-third and with ~20% reporting distress up to 4 years later (42). Fear of hypoglycemia is also common among parents of children with type 1 diabetes and is related to their own increased emotional distress as well as poor glycemic control in their children (43,44). Thus, it is clear that the QOL of parents and caregivers is affected by type 1 diabetes in their children.

There is conflicting literature about the relationship of QOL with factors such as age of onset or duration of the disease in childhood (45). One study was unique in examining diabetes-specific QOL in a sample of 59 adults with type 1 diabetes, including 16 diagnosed before the age of 5 years (46). Those

diagnosed very early in life reported better QOL than those with later diagnoses; however, these results are limited by the small study sample size. Similarly, there appears to be a limited effect of treatment regimens or use of glucose-sensing technology on QOL in both children and adults (41,47,48).

Multiple studies have demonstrated that lower HbA<sub>1c</sub> is associated with better QOL (48–50). A recent prospective study showed that poor QOL predicted later poor glycemic control (51). Both pediatric and adult studies reveal a reduced QOL with respect to the consequences of the disease. SEARCH results reveal that in children reduced QOL is associated with the presence of comorbidities and early health complications, greater frequency of serious hypoglycemic episodes and emergency department visits, and hospitalizations for poor metabolic control (48,49). Similarly, studies in adults with type 1 diabetes find that QOL is adversely impacted by lower socioeconomic status, longer duration of diabetes, presence of health complications, comorbid psychiatric disorders, less social support, decreased physical activity, obesity, more hypoglycemic episodes, and perceived sense of burden related to diabetes self-management (52–54).

## CLINICAL COURSE

Type 1 diabetes starts long before the clinical onset of hyperglycemia, progressing through multiple stages of the disease (55). In relatives of individuals with type 1 diabetes and those without relatives tested due to high genetic risk, islet autoantibodies can be identified, signaling that the immune system is inappropriately sensing and damaging  $\beta$ -cells. Those confirmed to have multiple antibodies are considered to have "islet autoimmunity"; the vast majority of these individuals will develop diabetes over time (56,57). Prior to clinical diagnosis, impaired insulin secretion and eventual abnormal glucose tolerance are evidence of  $\beta$ -cell injury and death. After clinical diagnosis,  $\beta$ -cell destruction continues, with the majority of individuals eventually having minimal or no detectable endogenous insulin secretion. Although this overall picture of the disease course has been confirmed in multiple studies over the past decades, there are now considerable data highlighting significant differences in the

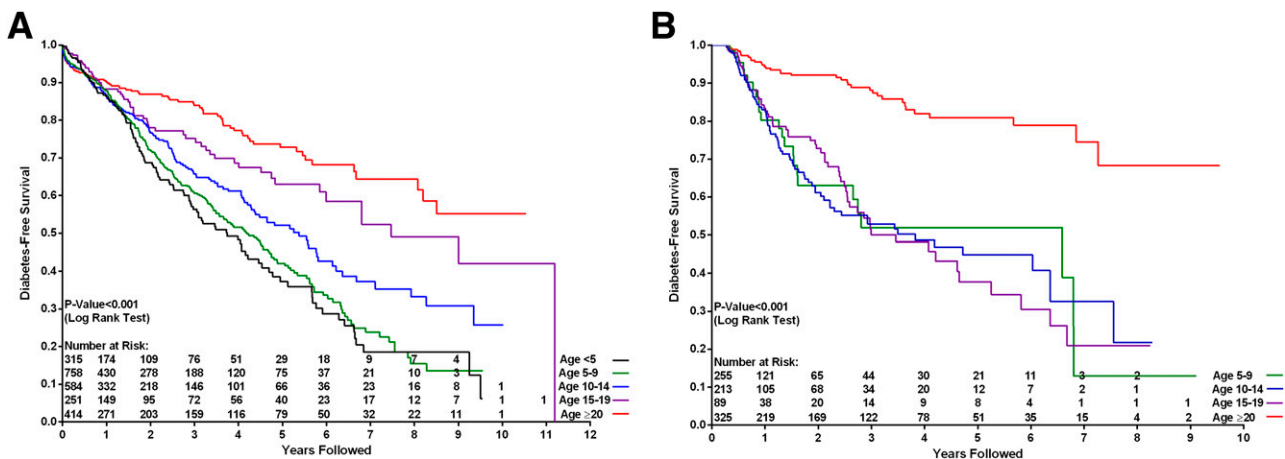
clinical course of the disease and rate of the disease progression in children compared with adults.

## Effect of Age on Progression From Risk to Onset of Clinical Disease

Prior to diagnosis, important information about the age at which  $\beta$ -cell autoimmunity first appears has been gleaned from genetically at-risk cohorts followed from birth. These include the Diabetes Autoimmunity Study in the Young (DAISY) in Colorado, the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) study, the BABYDIAB studies in Germany, and the international The Environmental Determinants of Diabetes in the Young (TEDDY) study. Data from the National Institutes of Health (NIH)-sponsored Diabetes Prevention Trial–Type 1 (DPT-1) (58,59) and the Type 1 Diabetes TrialNet Pathway to Prevention Study (60) ([www.diabetestrialnet.org](http://www.diabetestrialnet.org)) also provide evidence on the effect of age on progression from autoimmunity to clinical disease.

Children with high genetic risk based on HLA haplotype have been followed from birth for the development of autoantibodies and type 1 diabetes. Combined data from DAISY, DIPP, and BABYDIAB suggest that nearly all children who develop multiple autoantibodies go on to eventually develop childhood type 1 diabetes (>85% risk at 15 years) (61). Developing multiple autoantibodies prior to age 3 years further increased the rate of progression compared with children who developed antibodies at older ages. These cohort studies in children followed from birth indicate that the disease process starts very early in life. The DIPP study found that 65% of those who developed clinical disease before puberty had antibodies before age 2 years and 95% before age 5 years (62). The DPT-1 and the TrialNet Pathway to Prevention Study screened first- and second-degree family members (1–45 years of age) of probands with type 1 diabetes for the presence of autoantibodies. Data from these studies also suggest that the vast majority of relatives with two or more antibodies eventually develop clinical disease at a rate of ~10–12% per year (57). TrialNet found that the most important factor associated with a more rapid rate of progression is age; children with multiple antibodies progress to clinical disease much more rapidly than adults ( $P < 0.0001$ ). These dramatic differences are illustrated in





**Figure 2**—Impact of age on risk for disease progression in antibody-positive relatives participating in TrialNet Pathway to Prevention Study. *A*: Life table of progression to diabetes according to age in double antibody-positive relatives. *B*: Life table of progression to diabetes according to age in double antibody-positive subjects from time of abnormal glucose tolerance.

Fig. 2A. The path from islet immunity to clinical disease includes an interim stage of metabolic decompensation manifested as impaired glucose tolerance. Overall, more than 85% of antibody-positive relatives with impaired glucose tolerance will have clinical disease within 5 years. Strikingly, even at this stage of the disease progression, younger age markedly increases the rate of the disease development compared with older age (Fig. 2B).

#### Effect of Age on Residual Insulin Secretion After Clinical Diagnosis

Similar data are now available regarding the rate of decline of endogenous insulin secretion, measured by C-peptide, after the onset of clinical disease. A series of recent studies provide new insights; detectable C-peptide secretion persists longer after the type 1 diabetes diagnosis than is commonly appreciated, and age is the most important factor impacting the rate of decline of C-peptide post diagnosis.

Greenbaum et al. (63) studied residual insulin secretion within 2 years of diagnosis in subjects from the TrialNet's new-onset intervention trials. C-peptide at the start of the study was driven by age, with the youngest cohort (Fig. 3A) exhibiting the lowest C-peptide. Age was also highly correlated with loss of C-peptide over time: subjects aged 7–21 years demonstrated rates of decline in stimulated C-peptide secretion that were similar over time, whereas participants aged >21 years manifested a significantly slower rate of C-peptide decline.

Persistence of C-peptide secretion also varies between those diagnosed as children and those diagnosed as adults, with more adults retaining C-peptide production longer after the diagnosis than is commonly appreciated. Davis et al. (64) measured C-peptide in 919 subjects characterized by the duration of the disease and whether they were diagnosed as children or as adults. Although the fraction of individuals with detectable random C-peptide diminished over time as expected, there was a dramatic difference in persistence of C-peptide according to age at diagnosis (Fig. 3B). For a given duration of the disease, the odds for having C-peptide were estimated as 6% higher for every 1-year increase in the age of diagnosis. The same difference between children and adults was observed for C-peptide  $\geq 0.2$  nmol/L.

#### RESPONSE TO THERAPY

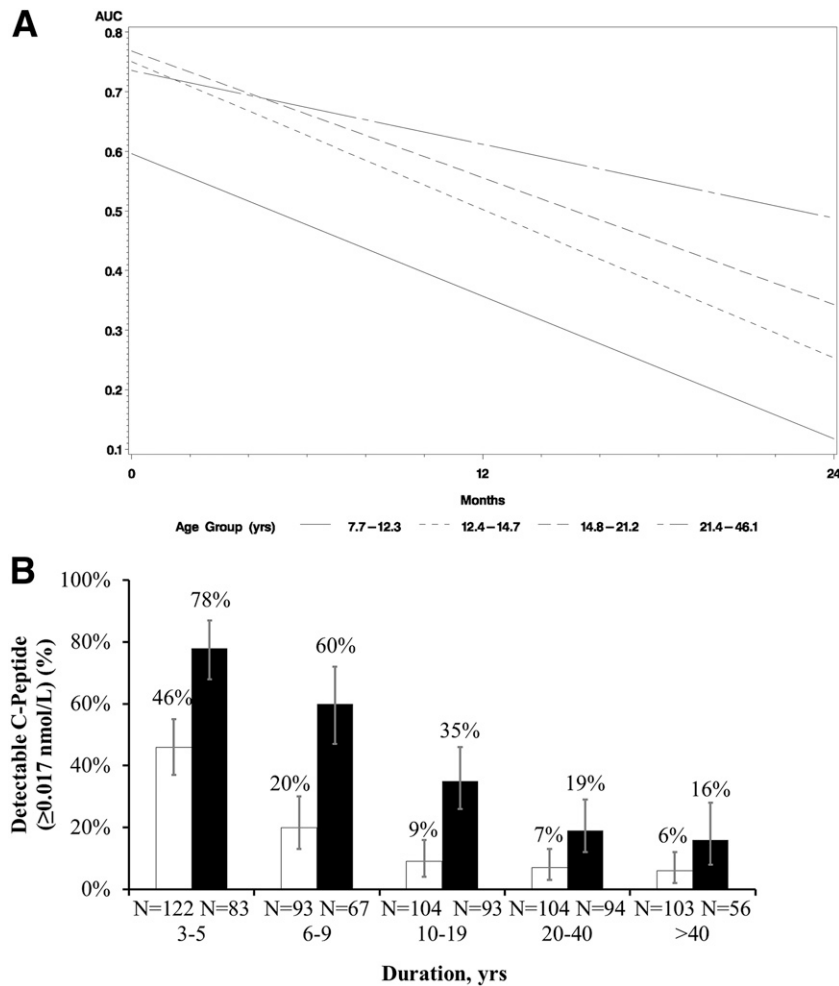
Type 1 diabetes in children and juvenile idiopathic arthritis (JIA) have striking similarities, including similar prevalence and effect on families. Both diseases affect children and adults, and the course is notably different in the two age-groups (Table 1). Disease-modifying therapy has transformed the lives of children with JIA; instead of treatment focused on symptom management of pain or disability, treatment changing the course of the disease, although not yet curative, has markedly improved the daily lives of these families. Differences in response to therapy between pediatric and adult rheumatic disease have

become apparent during the conduct of more than a dozen studies in children in recent years. As a result of these studies, many of these therapies now carry approval for use in pediatric rheumatic disease (65). As described below, a similar story is emerging with respect to the effect of age on response to disease-modifying therapy in type 1 diabetes.

#### Participation of Children in Type 1 Diabetes Trials

Children with recent-onset type 1 diabetes have been enrolled in trials of disease-modifying therapies since the early 1980s and constitute the majority of participants in many trials. The proportion of subjects aged <16 years enrolled in 10 NIH- and industry-sponsored multicenter clinical trials conducted since 2001 has ranged between 24% and 84% (Supplementary Table 2). Similarly, the majority of participants are children in 10 trials of disease-modifying therapies given prior to the onset of clinical disease (that is, type 1 diabetes prevention trials) that were or are being performed in the U.S. and Europe (Supplementary Table 3).

It is important to recognize that parents and children are eager to participate in type 1 diabetes studies, such that the pace of enrollment is markedly greater in trials open to pediatric participants. For example, the rate of enrollment markedly increased in both the TrialNet abatacept (66) and GAD65 (67) trials once the enrollment age was reduced (Supplementary Fig. 2). This is in marked contrast to studies enrolling adults only, some of



**Figure 3**—Impact of age on C-peptide after diagnosis. *A*: Model-based estimates of average slopes of C-peptide area under the curve (AUC) over time according to age quartiles (age-groups 7.7–12.3 years, 12.4–14.7 years, 14.8–21.2 years, and 21.4–46.1 years). Data from 191 TrialNet clinical trial participants. Reprinted with permission from Greenbaum et al. (63). *B*: Proportion of participants with detectable ( $\geq 0.017$  nmol/L) nonfasting C-peptide according to age at diagnosis and duration of type 1 diabetes. White bars, those diagnosed at age  $\leq 18$  years; black bars, those diagnosed at age  $> 18$  years. Data from the T1D Exchange residual insulin study. Reprinted with permission from Davis et al. (64).

which are unable to fully complete enrollment in the planned time period (68).

#### Effect of Age on Efficacy

Of all the fully powered multicenter clinical trials in recently diagnosed type 1 diabetes conducted since 2001, three therapeutic approaches had positive outcomes, with active drug-treated subjects experiencing significant reductions in the rate of decline in C-peptide compared with placebo-treated subjects. These therapies are rituximab (anti-CD20 monoclonal antibody) (69), abatacept (CTLA4-Ig) (66), and the anti-CD3 monoclonal antibodies teplizumab (70,71) and oteelixumab (72). All of these trials included many pediatric participants. Most importantly, the significant effect

of drug treatment in the rituximab and abatacept trials was largely driven by the positive response noted in the pediatric population (Fig. 4). In two trials of an anti-CD3 monoclonal antibody (71,73), subjects younger than 15 years of age had a more robust response compared with those who were older. The effects of young age were not limited to change in C-peptide: the treatment effect on insulin use was significantly different in subjects younger than 15 years of age ( $P = 0.02$ ), but not in older subjects ( $P = 0.8$ ). If enrollment in these studies had been limited to adults, then the study results would have likely been negative, and promising therapies for children would have been inappropriately discarded. In most of the clinical trials in which the overall

result was negative, neither the pediatric nor adult populations had any benefit, as illustrated by the results from the GAD trial (67). In contrast, in the Study of Antithymocyte Globulin for Treatment of New-onset T1DM (START) (ClinicalTrials.gov identifier NCT00515099), which only enrolled subjects 12 years of age or older, post hoc analysis pointed to improved C-peptide responses after 12 months in older (aged  $> 22$  years) but not younger subjects ( $P = 0.04$ ) (74).

#### Effect of Age on Safety

Disease-modifying therapies that alter immune function share similar theoretical risks among each other: in the short term, risks of infection and, potentially in the longer term, additional adverse effects with chronic use or if there is persistence of immune modulation. Thus, careful monitoring of short- and long-term safety is imperative. It is reassuring that in the treatment of many rheumatologic disorders, the adverse event profile is similar between adults and children. Similar data have been seen in type 1 diabetes trials using disease-modifying therapies to date wherein the safety profiles have not differed between children and adults, including studies testing teplizumab (75), abatacept (66), and rituximab (69). Additionally, the effect of therapy on immunization was directly studied in some of these trials and demonstrated no compromise in efficacy (66,69).

#### REGULATORY ISSUES

Including children in product development trials is necessary to ensure effective dosing for the pediatric population (for example, to characterize differences in absorption, distribution, elimination, and metabolism between adults and children of different ages) and to address potential differences in the safety profile between the pediatric and the adult populations.

The U.S. Congress passed the Best Pharmaceuticals for Children Act (BPCA) in 1997 to encourage pharmaceutical makers to voluntarily conduct studies in children, providing sponsors with specific incentives. The Pediatric Research Equity Act (PREA) of 2003 mandates pediatric studies (76). As a result, more than 500 products were studied in U.S. pediatric populations and now carry pediatric information on the label. Similar pediatric legislation exists in the European Union (EU) (77).

**Table 1—Similarities between JIA and childhood-onset type 1 diabetes**

- Pediatric and adult forms of both diseases are similar to each other but not identical.
- Both diseases are chronic without known curative treatment and require ongoing therapy.
- Both diseases are associated with increased morbidity and mortality.
- Both diseases have complex and multifactorial effects on the lives of patients and their families requiring a multidimensional assessment of clinical effect of treatments (e.g., pain, health-related QOL, social function, school function, etc.).
- Prevalence:
  - JIA: 1 per 1,000 individuals (91).
  - Type 1 diabetes: ~2 per 1,000 aged ≤20 years (4).
  - Relatively rare diseases in which market incentives are unlikely to lead pharmaceutical firms to focus on them.
- Moderate polygenetic predisposition.
- Etiologic agent(s) unknown.
- Preclinical phase can extend over years, is poorly understood, and remains without therapeutic options.
- In JIA, time is critical in the clinical phase—each month of delay of treatment onset during the first 12 months after the disease onset decreases the ability to reach clinical remission by 1.7 fold (92). Analysis of teplizumab response in recently diagnosed type 1 diabetes showed better preservation of C-peptide if treatment was initiated <6 weeks after the diagnosis (74).

Government agency regulation of clinical research and drug development process is critical to ensure trial participant safety. Pediatric development is global in nature, but legal and regulatory differences exist. These include the timing of when the pediatric investigation plans should be submitted and who is responsible for approving the pediatric development plan. In the U.S., this is within the relevant U.S. Food and Drug Administration (FDA) division that may receive advice or guidance from the Office of Pediatric Therapeutics, whereas in the EU, an external group of advisors (Paediatric Committee [PDCO]) (78) has decision-making authority. Both the FDA and the European

Medicines Agency (EMA) recommend that industry should request early discussions with relevant regulatory agencies to enable a global discussion of drug development and study end points.

A pediatric investigative plan, although required by both the FDA and the EMA in any new drug submission, does not always necessitate a pediatric clinical trial. Both the FDA and the EMA support extrapolation of well-controlled adult efficacy data to the pediatric population when possible and relevant.

Guidance (EU [79]) and draft guidance (FDA [80]) on the development of disease-modifying therapies for type 1 diabetes are available. EU guidance specifically

recommends an approach whereby studies in younger age-groups require prior demonstration of efficacy and safety in older subjects.

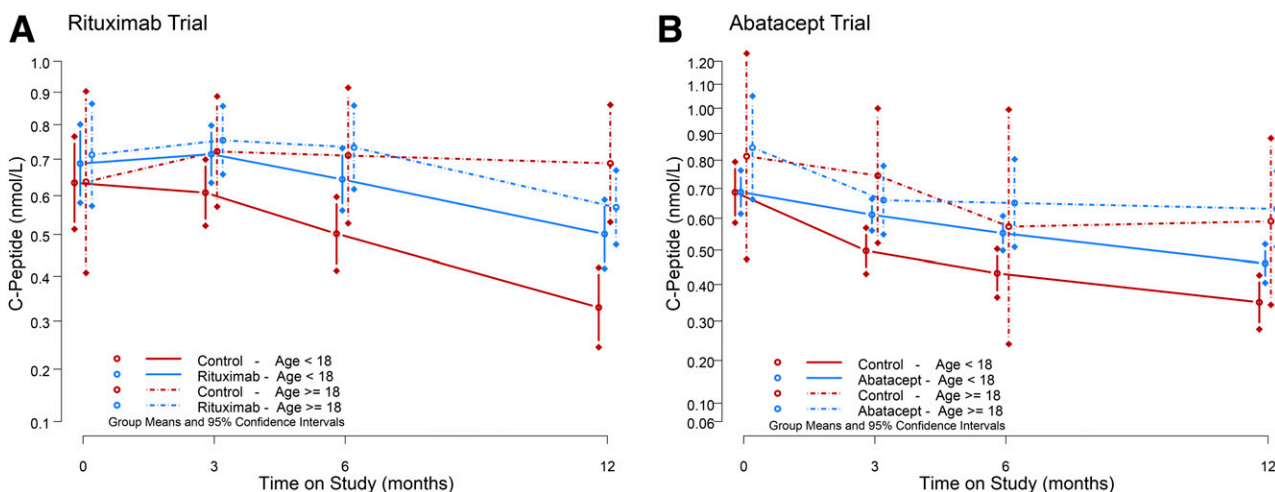
**Orphan Drug Status**

FDA’s Orphan Drug Act grants special status to a drug or biological product (“drug”) to treat a rare (for example, affects <200,000 people in the U.S.) disease or condition (81). Similar statutes exist in the EU (82). There are significant incentives to encourage drug manufacturers to develop therapies for small populations, where the financial rewards would otherwise be nonexistent. The same regulatory requirements for safety and efficacy must be established for orphan drugs as with all therapies.

As there are <200,000 children with type 1 diabetes in the U.S., development of disease-modifying therapies in type 1 diabetes could possibly meet these criteria. In the U.S., but not in the EU, there are several new products for β-cell preservation in new-onset type 1 diabetes designated as orphan drugs.

**ETHICAL ASPECTS**

It is critical to conduct research aimed at improving health care for children with diabetes. At the same time, children are not able to consent for themselves, and it is of paramount importance to protect the children who participate. To achieve this balance, the Institute of Medicine has six requirements for pediatric research (83). The present analysis focuses on the first four of these requirements.



**Figure 4—Impact of age on response to disease-modifying therapy. A:** C-peptide over time in TrialNet participants randomized to treatment with rituximab (blue line) or placebo (red line) who were aged <18 years (solid lines) or aged ≥18 years (dashed lines) at the time of randomization (69). **B:** C-peptide over time in TrialNet participants randomized to treatment with abatacept (blue line) or placebo (red line) who were aged <18 years (solid lines) or aged ≥18 years (dashed lines) at the time of randomization (66).

First, children should be enrolled in research only when it has the potential to collect valuable data. Each intervention included in the study should have sufficient scientific value to justify the risks and burdens it poses to participants.

Second, it is important to ensure that there is a compelling reason to enroll children. If the same data could be obtained by studying adults, then children should not be enrolled. When to initiate trials in children needs to be determined on a case-by-case basis, taking into account the extent to which similar data can be collected in adults, the effectiveness and safety of available treatments for children, and the risks and potential benefits of the interventions under study (84). Typically, it is acceptable to enroll children in research when it offers them a favorable risk-to-benefit ratio or it poses low net risks.

Third, whether research offers a favorable risk-to-benefit ratio depends on two assessments. Is the risk-to-benefit profile of the interventions included in the study favorable for eligible participants and at least as favorable as the available alternatives (85)? If there is compelling evidence that an intervention poses no chance of serious harm to children with type 1 diabetes, then even a theoretical chance of an important benefit could be enough to make an intervention's risk-to-benefit profile favorable. In contrast, if there is reason to believe that an intervention poses some serious risks to children with diabetes, one would need evidence of efficacy to categorize the intervention as offering a favorable risk-to-benefit ratio. The degree of benefit and level of evidence in this case needs to be commensurate with the level of potential harm and the degree of evidence supporting that potential.

In practice, one way to determine whether a study offers a favorable risk-to-benefit ratio is to consider, or determine through consultation, the following: Given what is known about the interventions included in the study and what is known about the available alternatives, would an independent and expert clinician regard enrolling children who have diabetes as promoting the children's clinical interests? If so, the study offers a favorable risk-to-benefit ratio. If not, the study involves an unfavorable risk-to-benefit ratio and thereby poses some degree of net risk to participants.

Fourth, when one or more of the interventions included in a study pose net risks, one needs to determine whether the net risks of the intervention and the cumulative net risks of the study are acceptable. Exposing children to research risks and burdens to collect data to benefit future patients raises important ethical issues (86,87). However, outside of the research context, children frequently engage in activities that pose some risks and are designed to benefit others, such as collecting money for a charity. Widespread acceptance of these activities suggests that pediatric research that does not offer a prospect of direct benefit can also be acceptable when it has the potential to gather valuable data and the net risks are low. This view is supported by empirical studies that found that children and their parents are overall equally willing to have the child help others by participating in research or a charitable activity (88,89).

Empirical data suggest that adolescents aged  $\geq 12$ –14 years are able to understand research and make their own decisions whether to enroll (90). This suggests that enrolling adolescents who understand and agree (assent) poses significantly fewer ethical concerns than enrolling younger children who cannot

understand the research in question. For this reason, it may be acceptable to expose adolescents who give their assent to somewhat higher net risks than younger children who cannot understand the research in question.

## SUMMARY

The burden of type 1 diabetes, whether diagnosed in childhood or adulthood, with regard to daily management, glycemic control, and acute and chronic complications, remains despite improvements in treatment regimens. Moreover, the burden of type 1 diabetes on society is likely to increase in the future with the increasing incidence of the disease and longer life expectancy. Importantly, there are unique aspects of disease burden in those diagnosed as children including worse glycemic control during teenage years, emotional distress of parents, and more significant neurocognitive effects in the youngest individuals. Disease-modifying therapy that can delay the onset of clinical disease or preserve endogenous secretion after the diagnosis has the potential to significantly reduce the burden of the disease on society, individuals, and families.

Robust data obtained from observational and clinical trials indicate that the development of the disease and the

**Table 2—Key messages from the conference and open research questions**

### Key messages

1. Differences between childhood- and adult-onset type 1 diabetes should be part of the design of studies of disease-modifying therapies.
2. Studying disease-modifying agents in children should not require efficacy data from adults.
3. Children may benefit more from disease-modifying therapies due to the more rapid loss of insulin secretion before and after their diagnosis, the unique burdens on them and their families, and the greater vulnerability of young children's neurocognitive development.
4. Investigators should work with regulatory agencies early in the study design process and leverage the pediatric expertise of the agencies.
5. A practical approach to assessing risk-to-benefit ratio is to consider the following: Given what is known about the intervention and the limited alternatives, would an independent and expert clinician regard enrolling children with type 1 diabetes as promoting the children's clinical interests?

### Open research questions

1. What is the long-term effect of age at onset and early glycemic control on complication risk both within childhood and adolescence (i.e., pre- vs. peri- or postpuberty) and in comparison with adult-onset type 1 diabetes?
2. What are the biological mechanisms underlying the varying pathways to type 1 diabetes? Which mechanisms are seen in all individuals and which are age dependent?
3. Given the high frequency of residual  $\beta$ -cell function in adults, how should type 1 diabetes in adults be defined? What is the incidence and prevalence of the disease in adults?
4. Are there differences in loss of residual insulin secretion rates in young adults compared with older adults?
5. How is QOL affected by disease-modifying therapies? Do effects differ between adults and children?
6. Are there biomarkers of responses to immune therapies that can discriminate responses in children and adults?



subsequent clinical course are significantly different between adults and children. Children, particularly younger children, may stand to benefit the most from disease-modifying therapy because they are at an increased risk of cognitive dysfunction, progress faster through the stages of the disease, have at the time of diagnosis a lower C-peptide that then declines more quickly over time, and pose the greatest challenges for clinical management. There are also differences in therapeutic response in trials of disease-modifying therapies in adults compared with pediatric participants. Although disease-modifying therapies are important goals for all those with type 1 diabetes, these data emphasize the need to design studies that account for age-related differences and to avoid reliance on efficacy outcomes in adults in order to study children. Important differences in pathophysiology suggest that different therapeutic approaches may be needed.

There is widespread agreement that there needs to be a favorable risk-to-benefit ratio for each therapy being considered for a clinical trial. The challenge is how to understand the level of evidence needed to support potential benefit. Thus, the standard strategy of requiring both safety and efficacy to be demonstrated in adults first has the real possibility to deny or delay the use of a potentially useful therapy to the pediatric population. Risks must be understood in the context of the current clinical burden and QOL experienced by children and their families. Evidence other than proof of efficacy in an adult population should be considered in evaluating potential benefits of therapy. Considering the risks and benefits of each therapy must be a dynamic process; information relevant to the disease burden, disease course, and response to therapy must be examined and reexamined over time (Table 2). As evident from the enthusiasm and passion manifest at the consensus conference, patients, families, industry, academia, advocacy groups, funders, and regulators all have important perspectives to contribute to the discussion; all are interested in improving the lives of those with type 1 diabetes.

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