A practical guide to management of youth-onset type 2 diabetes

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Type 2 diabetes is increasingly being diagnosed in the paediatric population. Making the diagnosis of type 2 diabetes in children and young people can be challenging. The majority of patients should be managed with diet modification and metformin, although insulin is sometimes required. There is limited evidence or experience for other treatments (e.g. glucagon-like peptide-1 receptor agonists) in adolescence, although, drawing on positive experiences in adults with type 2 diabetes, these drugs may prove useful in the future. Type 2 diabetes has an aggressive clinical course in childhood, with a more rapid progression to diabetes-related complications compared to children with type 1 diabetes. Engaging young people with type 2 diabetes within a diabetes service is critical for positive outcomes, and this represents a challenge for all professionals working in the field.

Type 2 diabetes accounts for 90% of diabetes cases globally (Zimmer et al, 2001) and the prevalence of type 2 diabetes in adults is increasing (Sharma et al, 2016). Historically the domain of adult diabetes practice, type 2 diabetes is becoming more prevalent in children. The highest rates of type 2 diabetes in children and adolescents are reported in studies from the US (Mayer-Davis et al, 2017). Recently, the 2015–16 UK incidence of type 2 diabetes in children (<17 years of age) was reported as 0.72 per 100,000 per year, with significant increases over a decade in South Asians and in girls (Candler et al, 2018a). In the UK, type 2 diabetes is less common in young people than type 1 diabetes, accounting for only 2.5% of the total cases reported by the 2016–17 National Paediatric Diabetes Audit (NPDA; Royal College of Paediatrics and Child Health [RCPCH], 2018).

Risk factors for developing youth-onset type 2 diabetes are similar to those for the adult variety (Wilmot et al, 2010), with non-white ethnicity, female gender, family history and obesity strongly associated with the condition (D’Adamo and Caprio, 2011).

Type 2 diabetes has an aggressive disease course. Young people may present with diabetes-related complications and are more likely to develop microvascular complications compared to young people with type 1 diabetes (Wilmot et al, 2010). The long-term risk of cardiovascular disease in young people with type 2 diabetes is worse than in those who are diagnosed as adults (Pinhas-Hamiel and Zeitler, 2007). There is a higher risk of developing nephropathy, retinopathy and peripheral neuropathy in young people with type 2 diabetes compared to those with type 1 diabetes (Dabelea et al, 2017). The rapid development of diabetes-related complications in this population is worrying for the decades ahead, and the key to management lies in early detection, meticulous screening for complications and instigating effective treatment strategies.

Much of the evidence and clinical expertise in managing type 2 diabetes has come from adults,
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Page points

1. Type 2 diabetes in children and young people is diagnosed according to plasma glucose levels; HbA1c is not considered sufficiently accurate for diagnosis in this age group.

2. Approximately two thirds of young people with type 2 diabetes have symptoms of diabetes at diagnosis, most commonly osmotic symptoms followed by recurrent infections.

3. Children who are obese and have additional risk factors, such as non-Caucasian ethnicity and family history of type 2 diabetes, should be screened for the condition.

Box 1. Common characteristics of youth-onset type 2 diabetes.

- Adolescent age (type 2 diabetes is rare before puberty).
- Non-Caucasian ethnicity.
- Female gender.
- Low socioeconomic group.
- Positive family history of type 2 diabetes.
- Overweight or obese.
- Signs of insulin resistance (e.g. acanthosis nigricans, skin tags).
- Recurrent infections (especially in genitalia).
- Low or no insulin requirement.
- Persistently elevated or normal C-peptide >1 year after diagnosis.
- Negative autoantibodies associated with type 1 diabetes.

with drug usage in children often stalled by licensing restrictions and limited evidence. Whilst childhood cases of type 1 diabetes are evenly distributed across socioeconomic groups, this is not the case with youth-onset type 2 diabetes; in the US and Europe, cases come from predominantly lower socioeconomic and educational backgrounds (Copeland et al, 2011). Treatment adherence and lack of engagement with diabetes services are key barriers to effective care; in one Japanese study, over 50% of young people with type 2 diabetes did not attend clinics (Kawahara et al, 1994).

The purpose of this review is to present a practical guide to diagnosis, management and follow-up of children and young people with type 2 diabetes.

Making the diagnosis of type 2 diabetes in children and adolescents

Type 2 diabetes is characterised by insulin resistance combined with diminishing insulin production (due to glucose toxicity-related beta-cell destruction) that results in failure to maintain euglycaemia. The degree of reduction in insulin secretion will depend on the stage of the condition (Druet et al, 2006), with 85% of adolescents reported to have some degree of insulin deficiency at diagnosis (Gungor et al, 2005). Diabetes is diagnosed according to American Diabetes Association (2000) criteria: fasting glucose ≥7 mmol/L; a random glucose level of ≥11.1 mmol/L with diabetes symptoms; or a 2-hour glucose level of ≥11.1 mmol/L in a standard oral glucose tolerance test. The HbA1c cut-off of ≥48 mmol/mol (6.5%) used for adults is currently not considered sufficiently accurate in children to make a diagnosis (Nowicka et al, 2011).

A summary of the features of youth-onset type 2 diabetes is shown in Box 1. A recent study of young people with type 2 diabetes in the UK found that a third were asymptomatic at diagnosis (identified during screening for obesity complications; Candler et al, 2018a). Half had osmotic symptoms (e.g. polydipsia, polyuria and weight loss), while recurrent infections, especially those affecting the genitalia, were the next most common presentation.

Obesity is strongly associated with type 2 diabetes (Copeland et al, 2011; Candler et al, 2018a), although the strength of association between BMI and type 2 diabetes is not universal across all ethnicities. A significantly lower BMI at presentation is seen in South Asian children compared with Caucasian children (Candler et al, 2018a), which reflects the tendency of South Asian populations to accrue central (visceral) fat, which causes more insulin resistance than subcutaneous fat (Ramachandran et al, 1997), and 10–15% of Japanese children with type 2 diabetes have what is considered a normal weight (Urakami, 2018).

Children with obesity (≥98th percentile) and two additional risk factors, such as family history of type 2 diabetes, non-Caucasian ethnicity, clinical signs or biochemical evidence suggestive of insulin resistance or polycystic ovary syndrome, should be screened for type 2 diabetes with an oral glucose tolerance test (Viner et al, 2012). Non-Caucasian ethnicity has been described as a risk factor for type 2 diabetes in Europe and North America (Hamman et al, 2014; Candler et al, 2018a), as has female gender (Wilmot and Idris, 2014; Candler et al, 2018a), with an approximate 2:1 female-to-male ratio reported in the latest NPDA (RCPCH, 2018). Family history is common in those with type 2 diabetes and should be explored fully as part of any assessment.

Typically, those with type 2 diabetes are thought to test negative for autoantibodies associated with type 1 diabetes. The NICE (2015) NG18 guideline does not recommend routine measurement of autoantibodies, although measuring autoantibodies can certainly help to support a diagnosis of type 2 diabetes if the test is negative. However, studies do
report positive antibodies in this population, with 10% of those with a diagnosis of type 2 diabetes in the TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) study being excluded due to positive antibodies (Copeland et al, 2011). Some studies report a more dramatic beta-cell loss in those with positive antibodies compared to those with negative antibodies (Tfayli et al, 2009), although a recent study has reported similar clinical outcomes between the two groups (Rivera-Vega et al, 2015). There remains controversy as to whether these patients with positive antibodies represent a "forme fruste" of type 1 diabetes.

Insulin resistance is a hallmark feature of type 2 diabetes and may be evidenced clinically by acanthosis nigricans (Stuart et al, 1998). Those with no or low insulin requirements (less than 0.5 units/kg/day) should raise the suspicion of type 2 diabetes (NICE, 2015). At diagnosis there is limited utility of C-peptide in distinguishing between type 2 and type 1 diabetes, although with time (e.g. after 12 months) it becomes a more sensitive test (Borg et al, 2003; NICE, 2015). Cut-off points for a C-peptide or insulin level suggestive of type 2 diabetes are controversial; some researchers have used the presence of raised insulin levels (>132 pmol/L) or raised C-peptide levels (>0.6 nmol/L) as signs of biochemical insulin resistance (Williams et al, 2002; Jones and Hattersley, 2013), and International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines state that a C-peptide level above the normal range 12–14 months after diagnosis is unlikely in type 1 diabetes (Zeitler et al, 2018).

Approaching the diagnosis by assessing the individual and taking all these factors into consideration is key. With an increasingly overweight paediatric population, those with type 1 diabetes may also be overweight at presentation; therefore, a thorough assessment is required.

Management options
The evidence for treatment of type 2 diabetes in young people is limited and, therefore, much of the management options are extrapolated from adult experience. The target HbA1c is ≤48 mmol/mol (6.5%) but individual short-term goals should be set for each patient (NICE, 2015). Weight loss should be the central tenet to any treatment regimen, as excess weight is the major driver of disease development.

Pharmacological treatment
The vast majority of young people with type 2 diabetes are treated with diet/lifestyle and any agents other than metformin (Hamilton-Shield et al, 2009; Candler et al, 2018b). Metformin should be offered from diagnosis (NICE, 2015; Zeitler et al, 2018) once the young person is metabolically stable and not acidic. A randomised, double-blind, placebo-controlled trial of metformin demonstrated improved glycaemic control in children with type 2 diabetes (Jones et al, 2002). A starting dose of 500 mg once daily was used for 1–2 weeks and then increased gradually over a 3–4-week period to a target dose of 1000–2000 mg daily. This gradual escalation in dose, as well as taking the medication with food, should help avoid the gastrointestinal side effects associated with the drug. Over 90% of participants in the TODAY study were successfully managed on metformin monotherapy in the short term (Laffel et al, 2012).

Insulin is indicated initially if the young person is metabolically unstable, has elevated HbA1c (>70 mmol/mol [8.6%] at diagnosis; Zeitler et al, 2018) or if the diagnosis is unclear (e.g. between type 1 diabetes and type 2 diabetes). Insulin should be weaned over the following 2–6 weeks if possible. Insulin should be considered if not achieving target HbA1c after 4 months of metformin monotherapy (Zeitler et al, 2018), and should comprise either once-daily basal insulin or, if required, a basal–bolus regimen. There is a concern that the anabolic effects of insulin will lead to weight gain; therefore, it should be started with dietary advice to minimise the associated weight gain. If weight gain is a particular concern or consequence of insulin therapy, the team will need to consider other agents such as glucagon-like peptide-1 (GLP-1) receptor agonists. There is an argument that early insulin treatment allows “beta-cell rest” and protects beta-cells from further glucotoxicity (Weng et al, 2008). We believe that weight loss is paramount to early metabolic control and hence preservation of beta-cells. Although insulin has a role in some patients with type 2 diabetes, weight loss must remain the central tenet of treatment.

Page points
1. With increasing rates of paediatric obesity, thorough assessment may be required to differentiate type 2 from type 1 diabetes, including autoantibody and C-peptide tests.
2. The majority of young people with type 2 diabetes are treated with diet/lifestyle and metformin. Metformin should be offered from diagnosis, and the dose should be titrated up to help avoid gastrointestinal side effects.
3. Insulin, either once daily or a basal–bolus regimen may be required for those with high HbA1c and those who fail to achieve target glycaemic control after 4 months on metformin, as well as those in whom the type 2 diagnosis is uncertain.
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GLP-1 agonists are increasingly used in the paediatric population, with 4% of young people with type 2 diabetes from the UK reportedly on these drugs at 1 year post-diagnosis (Candler et al, 2018b). In adults, GLP-1 agonists (e.g. liraglutide) have been shown to be efficacious and safe in reducing HbA1c, with fewer episodes of hypoglycaemia compared with sulfonylureas (e.g. glibenpiride; Nauck et al, 2009). In children, the experience of using GLP-1 agonists is limited; however, studies have shown liraglutide to be safe and effective compared with placebo in a paediatric population (Klein et al, 2014).

Sulfonylureas are not often used in paediatric practice and may not be licensed in children in some countries. However, a study of glibenpiride versus metformin as monotherapy showed similar efficacy in terms of glycaemic parameters, albeit with greater weight gain seen in the glibenpiride group (Gottschalk et al, 2007).

In the TODAY study, rosiglitazone (a thiazolidinedione) combined with metformin demonstrated greater efficacy than metformin alone in maintaining an adequate HbA1c (Zeitler et al, 2012). However, due to concerns of increased cardiovascular risk in adults (Nissen and Wolski, 2007), this agent is not currently licensed for use in the UK in children.

There is no evidence for the use of dipeptidyl peptidase-4 inhibitors in youth-onset type 2 diabetes, although these drugs are making their way in to paediatric practice (Candler et al, 2018b). Equally, no studies have reported outcomes for the use of sodium–glucose cotransporter 2 inhibitors in paediatric practice, although the pharmacokinetics of these drugs in children appear similar to those in adults according to a recent study (Tamborlane et al, 2018).

Diet and lifestyle interventions

Structured education should be given to children and young people and their families about the condition. An emphasis should be made on lifestyle change and weight loss. The TODAY study developed a structured education package for young people with type 2 diabetes, and nearly 80% successfully completed the programme (Grey et al, 2009). Young people with type 2 diabetes have a more sedentary lifestyle, are less physically active and display a worse cardiovascular profile compared with overweight/obese controls (Shaibi et al, 2008; Kriska et al, 2013). Television and computer use in young people with type 2 diabetes is associated with an increased HbA1c over time and, therefore, should be actively discouraged (Li, 2015). Conversely, increased regular physical activity is associated with a lower HbA1c in young people (Herbst et al, 2014).

Dietary advice and support to make healthier food choices and lose weight should be available from a specialist dietitian (NICE, 2015). Compared to their peers with type 1 diabetes, young people with type 2 diabetes consume twice the amount of sugar-sweetened beverages, a greater proportion of energy from saturated fat and fewer micronutrients, and they often report consuming “more than they would like” (Mayer-Davis et al, 2006). Dietary advice may include avoiding high-fat, high-calorie-density food and drink; increasing fruit and vegetable intake to >5 per day; and consuming foods with a lower glycaemic index (NICE, 2015; Zeitler et al, 2018). Taking a whole-family approach to changing eating habits is important (Zeitler et al, 2018).

In the TODAY study, a greater reduction in BMI and improved body composition were seen in those treated with lifestyle/dietary interventions and metformin compared to metformin alone 6 months after treatment, although the difference was not sustained at 24 months (TODAY Study Group, 2013a). In the UK, a reduction in BMI was significantly associated with lower HbA1c 1 year after diagnosis in young people with type 2 diabetes (Candler et al, 2018b).

One small study of 20 young people with type 2 diabetes admitted for a very-low-calorie diet (680–800 kcal/day) demonstrated a significant reduction in BMI, insulin dose and HbA1c at the end of the diet, with a sustained reduction in BMI even at 2 years compared with diabetes treatment in the clinic alone (Willi et al, 2004). Although a small study, this suggests that rapid weight loss after diagnosis offers the best therapeutic option, especially given recent findings in adults with newly diagnosed type 2 diabetes (Lean et al, 2018).

A less utilised option for treatment of obesity and type 2 diabetes in children is bariatric surgery. The results are striking, with 95–100% rates of diabetes remission reported following surgery (Stefater et al, 2018).
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and Inge, 2017). However, surgical treatment is not without its risks, including postoperative complications, micronutrient deficiencies and impaired bone mineral density.

Overall, there is little evidence that lifestyle interventions alone are adequate to treat type 2 diabetes in young people (McGavock et al., 2015), and UK national recommendations support this (NICE, 2015).

Taking a holistic approach
A holistic, multidisciplinary approach is needed to care for young people with type 2 diabetes. These patients report a lower quality of life compared to those with type 1 diabetes (Naughton et al., 2008). One study has reported a prevalence of neuropsychiatric disorders of nearly 20% in those with paediatric type 2 diabetes, with two thirds of these on psychotropic medication (Levit Katz et al., 2005). Screening for mood disturbances and the subsequent input of a psychologist and/or child and adolescent mental health teams is crucial.

Treatment adherence has been shown to predict HbA1c 1 year after diagnosis (Candler et al., 2018b). Unfortunately, engaging this population in the diabetes service can be challenging. The work of the paediatric diabetes specialist nurse (PDSN) is key to engaging these patients and helping them take ownership of the management. The barriers to self-management are multifaceted (Mulvaney et al., 2008). Improving engagement may involve bringing in other workers or agencies (e.g. youth workers, school nurses) to help support the young person.

Checking with the GP as to prescription collection may help understand adherence to medication. In the UK and Europe, type 2 diabetes in children is much more prevalent in those from lower socioeconomic groups (McGavock et al., 2017), and this combined with psychological difficulties may prompt the need for close liaison with social care teams. Positive experiences have been reported in having a social worker as part of the team working with young people with type 2 diabetes (Ciporen, 2012). It is a safeguarding concern if the child is repeatedly not brought to appointments, and this should be escalated accordingly.

Much of the expertise among PDSN teams will be in managing type 1 diabetes; therefore, a way forward might be to identify a dedicated PDSN to take on all cases of type 2 diabetes in each centre and thus concentrate expertise.

Screening for complications
Youth-onset type 2 diabetes is often associated with complications at diagnosis (Copeland et al., 2011), and complications become more prevalent as the condition develops (Pinhas-Hamiel and Zeitler, 2007; Nadeau et al., 2016). Higher rates of nephropathy, hypertension, retinopathy and peripheral neuropathy have been reported in adolescents with type 2 diabetes compared to those with type 1 diabetes despite a shorter duration of disease (Eppens et al., 2006; Dabelea et al., 2017).

Microalbuminuria is of particular concern in young people with type 2 diabetes, with 6.3% of the TODAY study cohort displaying microalbuminuria at baseline (median diabetes duration of 7 months), and 16.6% at 36 months’ follow-up (TODAY Study Group, 2013b). Worryingly, in the UK, over a quarter of newly diagnosed young people with type 2 diabetes did not have their urinary albumin:creatinine ratio measured in the first year following diagnosis (Candler et al., 2018b). Screening for dyslipidaemia is recommended for those with type 2 diabetes, although experience of prescribing statins is limited among paediatric diabetes professionals, with only 14% reporting having prescribed the drug in the last 5 years (Candler et al., 2017).

Non-alcoholic fatty liver disease has been reported to occur in up to half of young people with type 2 diabetes (Bloomgarden, 2007), and polycystic ovary syndrome has been reported in 15% of girls with type 2 diabetes (Candler et al., 2018b). In our centre, we measure liver function tests yearly in our type 2 diabetes cases. While there are limited data in young people, obstructive sleep apnoea has been reported in 70–90% of adults with type 2 diabetes (Rice et al., 2012). Therefore, ISPAD has recommended additional screening for these conditions in its guidelines (Zeitler et al., 2018), though these are not included in the NICE (2015) guideline.

Both NICE (2015) and ISPAD (Zeitler et al., 2018) have produced guidance on screening for the above complications in young people with diabetes. A summary of the recommendations is shown in Table 1.
### Table 1. Complications of youth-onset type 2 diabetes – summary of screening recommendations and actions from NICE (2015) and ISPAD (Zeitler et al, 2018).

<table>
<thead>
<tr>
<th>Complication</th>
<th>Guideline</th>
<th>Recommended routine screening</th>
<th>Cut-off</th>
<th>Further action</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>NICE</td>
<td>At diagnosis and then annual BP measurement</td>
<td>&gt;95th centile for height, age and sex</td>
<td>Repeated resting BP tests; if still elevated, proceed to 24-hour ambulatory BP measurement</td>
<td>No specific recommendations</td>
</tr>
<tr>
<td></td>
<td>ISPAD</td>
<td>BP measurement at diagnosis and then at every visit</td>
<td>&gt;95th centile for height, age and sex</td>
<td>Confirm elevated BP on two additional days</td>
<td>If elevated BP, instigate lifestyle advice If still elevated after 6 months, commence antihypertensive treatment (angiotensin-converting enzyme inhibitor as first line)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>NICE</td>
<td>Lipid profile (total cholesterol, HDL-C, non-HDL-C and triglycerides) at diagnosis and then annually</td>
<td>None specified</td>
<td>Repeat further sample (fasting or non-fasting) before considering further management</td>
<td>No specific recommendations</td>
</tr>
<tr>
<td></td>
<td>ISPAD</td>
<td>Lipid profile (as for NICE) after 3 months of treatment/when glycaemic control achieved, then annually</td>
<td>Targets: LDL-C &lt;2.6 mmol/L HDL-C &gt;0.9 mmol/L Triglycerides &lt;1.7 mmol/L</td>
<td>If LDL-C &gt;2.6 mmol/L, instigate lifestyle advice and repeat fasting lipid profile in 6 months If triglycerides &gt;1.6 mmol/L fasting or &gt;11.3 mmol/L non-fasting, begin medication (fibric acid as first line)</td>
<td>If LDL-C still elevated on repeat sample: • LDL-C 2.6–3.3 mmol/L: maximise non-pharmacological treatment • LDL-C &gt;3.4 mmol/L: begin medication (statin as first line)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>NICE</td>
<td>Annual retinal screening from 12 years (younger if blood glucose suboptimal)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ISPAD</td>
<td>Annual screening from diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephropathy</td>
<td>NICE</td>
<td>At diagnosis and thereafter annual screening with first morning urine for ACR</td>
<td>Microalbuminuria: 3–30 mg/mmol</td>
<td>If between 3–30 mg/mmol, repeat with two further first morning urine tests before further investigation or referral</td>
<td>If repeatedly between 3–30 mg/mmol or &gt;30 mg/mmol, perform further investigations</td>
</tr>
<tr>
<td></td>
<td>ISPAD</td>
<td>At diagnosis and then annually with a spot urine ACR</td>
<td>Microalbuminuria: ACR 3.4–33.8 mg/mmol in a spot urine sample (preferred) Timed overnight or 24-hour collections with albumin excretion rate of 20–199 µg/min</td>
<td>Elevated ACR should be confirmed on two of three samples with first morning urine</td>
<td>If elevated ACR is confirmed, an angiotensin-converting enzyme inhibitor should be started and BP optimised</td>
</tr>
<tr>
<td>NAFLD</td>
<td>ISPAD*</td>
<td>Assessment of liver enzymes at diagnosis then annually</td>
<td>Alanine aminotransferase as sex-specific upper limits of normal (ULN) in children (22 IU/L for girls and 26 IU/L for boys)</td>
<td>If elevated, encourage weight loss and optimise glycaemic control If more than three-times ULN, consider cause</td>
<td>If persistently elevated liver enzymes (more than three-times ULN), refer to hepatologist/gastroenterologist</td>
</tr>
<tr>
<td>PCOS</td>
<td>ISPAD*</td>
<td>Patients should be screened for menstrual irregularities at diagnosis and at each visit</td>
<td></td>
<td>If amenorrhoea, hirsuitism or acne, consider work-up for PCOS</td>
<td></td>
</tr>
<tr>
<td>OSA</td>
<td>ISPAD*</td>
<td>Enquire about symptoms of OSA (e.g. snoring, morning headaches, daytime sleepiness from diagnosis)</td>
<td></td>
<td>Consider sleep study and referral to respiratory team</td>
<td></td>
</tr>
</tbody>
</table>

*No specific NICE guidance for screening. ACR=albumin:creatinine ratio; BP=blood pressure; HDL-C=high-density lipoprotein cholesterol; ISPAD=International Society for Pediatric and Adolescent Diabetes; LDL-C=low-density lipoprotein cholesterol; NAFLD=non-alcoholic fatty liver disease; NICE=National Institute for Health and Care Excellence; OSA=obstructive sleep apnoea; PCOS=polycystic ovary syndrome.
Conclusion
Type 2 diabetes is becoming more prevalent in the pediatric population, especially among adolescent girls and those of non-Caucasian ethnicity. Paediatric diabetes professionals may not be experienced in managing children with type 2 diabetes and, therefore, clear guidance and recommendations are needed. Research should explore ways to optimise care in this little-studied population of people with type 2 diabetes to prevent serious complications in the future.

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