Management of Type 2 diabetes: Treating targets and strategies

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Abstract

Guidelines for care and treatment goals as recommended by the International Diabetes Federation and the American Diabetes Association (ADA) are presented, together with the recent consensus document from the ADA and the European Association for the Study of Diabetes. Targets for control are presented as therapeutic targets to be obtained.

The current approaches to therapy include lifestyle modifications, diet, oral agents and insulin therapy. An algorithm is presented as a practical approach to manage Type 2 diabetes. Some newer agents that will become available in the near future in our country are mentioned. This article outlines the pathophysiology of Type 2 diabetes, emphasising the roles of insulin resistance and insulin deficiency in its aetiopathogenesis. The liver, peripheral tissues and the pancreas are the three important role players in this condition.

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Introduction

Type 2 diabetes is a chronic disease characterised by hyperglycaemia, which is a consequence of insulin resistance and impaired insulin secretion. The longterm complications of diabetic microvascular disease lead to significant morbidity in the form of blindness, end-stage renal disease and limb amputations; diabetic macrovascular disease is characterised by accelerated atherosclerosis, which leads to peripheral gangrene, strokes and premature cardiovascular disease.[1]

It is vitally important to understand the pathophysiology of Type 2 diabetes in order to treat it optimally. The pathophysiologic hallmark of the disease is insulin resistance, which has both genetic and acquired components,[2] and is present in over 90% of patients. Glucose intolerance and hyperglycaemia supervene only when the pancreatic ß-cells are unable to maintain compensatory hyperinsulinaemia to overcome tissue resistance to insulin action, primarily in the liver and in the periphery (at the skeletal muscles and adipose tissues).[3]

In addition to having hyperglycaemia and insulin resistance, over 80% of diabetics are obese and have a host of metabolic abnormalities, including dyslipidaemia, (characterised by increased small dense LDL cholesterol, decreased HDL cholesterol, and increased triglyceride levels), and hypertension. These contribute to the higher incidence of cardiovascular morbidity and mortality.[4]

The development of diabetic complications is no longer inevitable. Good glycaemic control together with management of the major risk factors may prevent or minimise the macro- and microvascular problems. Recent insights into the pathophysiology of diabetes and its complications make it possible not only to effectively manage diabetic complications, but also possibly to postpone or even prevent them.[5]

Thus, in summary:

- Three principal organs are mainly involved in Type 2 diabetes: the pancreas, the liver and the peripheral tissues (muscle and adipose tissues).
- The two initiating pathophysiological defects are firstly, tissue resistance to insulin action (at the liver and peripheral tissues), and secondly islet cell dysfunction (α- and ß-cells).

Screening for Type 2 diabetes, its methods of prevention, and its diagnostic criteria were discussed in our previous article.[9]

In Table I the treatment goals for Type 2 diabetes as recommended by the International Diabetes Federation (IDF) and American Diabetes Association (ADA) are presented. Some important issues in managing Type 2 diabetes include:

- It is a chronic disease, and many patients, after an initial expression of willingness to 'do the right things', start defaulting in their commitments to implementing lifestyle interventions. Regular re-education is needed.
- Type 2 diabetes is largely asymptomatic: Symptoms initially draw attention to the disease, but once therapy is commenced, even if it is not meeting treatment goals, patients often remain asymptomatic usually until the development of a complication. By then, the metaphoric 'horse has bolted'.
- Because of lack of symptoms, patients often have a false sense of confidence that all is well. 'After all, all the initial symptoms are gone!' Regular selfmonitoring becomes important in assessing the glycaemic control. Fasting/pre-meal values reflect hepatic glucose production; high 2-hr postprandial values reflect either insulin resistance or insulin deficiency.
- Patients have to be educated that diabetes is not treated for its symptoms, but in order to prevent complications.

The 2006 consensus statement from the ADA and the European Association for the Study of Diabetes (EASD) emphasised the importance of getting to and maintaining normal glycaemic goals.[12] It emphasised that an HbA_{1C} of > 7% indicated a need to initiate or intensify therapy, whilst trying to normalise the HbA_{1C} level or, at least, decreasing it to < 7%.

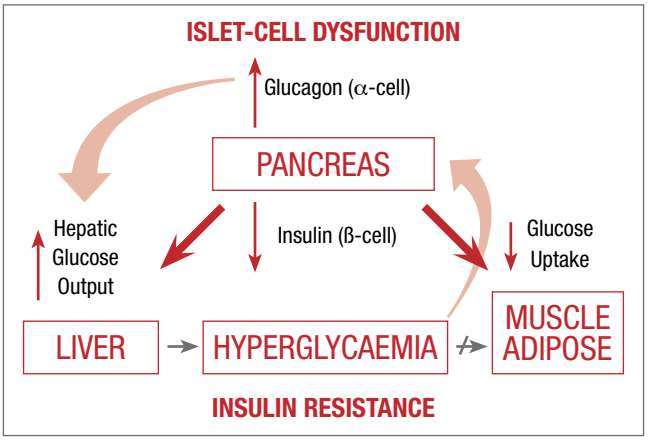

Figure 1: Major pathophysiologic defects in Type 2 diabetes

- This figure depicts the impact of Type 2 diabetes on the feedback loop that regulates glucose homeostasis.[6] In Type 2 diabetes, insulin resistance is increased and insulin secretion impaired.[7] Most patients with Type 2 diabetes have insulin resistance. Normally, pancreatic ß-cells increase insulin secretion to compensate for insulin resistance.

However, when ß-cell function is impaired, hyperglycaemia develops.[7]

- By the time diabetes is diagnosed, ß-cell function has already decreased substantially and continues to decline over time.[7] Once insulin secretion is impaired, an imbalance between insulin and glucagon can develop. Elevated glucagon levels lead to an increase in hepatic glucose production, which leads to an increase in blood glucose.[7] Likewise, with decreased secretion of insulin, less glucose is taken up by the muscle and adipose tissue.[8]

Table I: IDF and ADA GUIDELINES [10, 11]

Treatment goals for HbA_{1C}, FPG, and PPG

Parameter	Normal Level	IDF Goal	ADA Goal
FPG (mmol/l)	< 6.1	< 5.5	5.0 – 7.2
PPG (mmol/l)	< 7.8	< 7.8	< 10.0
HbA_{1C}	4.0% – 6.0%	< 6.5%	< 7.0%

FPG = Fasting plasma glucose PPG = Post-prandial glucose

If glycaemic targets are not attained early, the hyperglycaemia produces 'glucotoxicity' which suppresses ß-cell function leading to reduced insulin release and worsening hyperglycaemia. An aggressive approach is advocated since better controlled patients have a reduced risk of complications, as shown in United Kingdom Prospective Diabetes Study, UKPDS, in which newly diagnosed diabetics were randomised to a conventional group and an intensively treated group. In the observational analysis of the UKPDS cohort, every 1% reduction in HbA_{1C} was associated with highly significant results ($p < 0.0001$) – in the following observations: a mean risk reduction of

- 21% in diabetes-related death
- 37% in microvascular complications
- 43% in peripheral vascular disease
- 14% in myocardial infarction[14]

A combination of patient and doctor apathy characterises current practice, which is a slow (and often ineffective) treatment action. A study examining national data from the 3rd National Health and Nutrition Examination Survey (NHANES III) (1988–1994) and NHANES 1999–2000 in a US population showed that 44.3% and 37.0% of diabetic adults respectively were at a target HbA_{1C} goal of <7%.[13] Where access to therapy is a problem for the large numbers of South Africans in rural and peri-urban areas, our figures would expectedly be far worse!

Management of Type 2 diabetes

A newly diagnosed diabetic must be educated about the disease, which will be a life-long 'partner'. It is also useful to teach them about the genetic nature of the disease, and that others in the family may be potential targets. The family members of a diabetic represent a high-risk group, and screening would be useful – as was discussed in our previous article.[9]

The treatment of Type 2 diabetes can be looked at in terms of:

- Lifestyle modifications
- Diet
- Oral agents
- Insulin therapy
- Newer agents

Lifestyle modifications

The mainstay of treatment of Type 2 diabetes is diet and other lifestyle modifications, such as increasing physical activity and cessation of smoking. Since over 80% of diabetics are obese, the importance of weight reduction cannot be understated. Exercise increases insulin sensitivity, lowers glycaemia and reduces cardiovascular risk factors such as dyslipidaemia and hypertension. On the contrary, bed rest exacerbates the insulin resistance of the obese with pre-existing impaired glucose tolerance.[16]

The Diabetes Prevention Study from the US showed that 30-min/day of moderate aerobic physical activity (150-min per week), coupled with a 5–10% reduction in body weight, produced a 58% reduction in diabetes, whilst pharmacological intervention using metformin produced a 31% reduction in these high-risk patients, as compared to the standard group. The secondary objectives of the study assessed differences between the 3 groups in the development of cardiovascular disease and its risk factors. Intensive lifestyle modification resulted in a decrease in cardiovascular risk factors.[18]

The current recommendations for Type 2 diabetes patients are a minimum of 30–45 min of moderate physical activity 3–5 days per week, or 150-min/week. This can be split into 10-min 3 times daily, or 15-min twice daily if this is more convenient. One should use the stairs rather than lifts. It is not essential to join a gymnasium – but physical movement is important.

Exercise usually does not cause hypoglycaemia in Type 2 diabetes (in contrast to type 1 diabetes), and therefore extra carbohydrates are generally not necessary.[15] It is recommended that diabetics initiating exercises for the first time be assessed to rule out overt or covert coronary artery disease. It is well known that diabetics may have asymptomatic ischaemic heart disease, or have atypical symptoms. This may be related to diabetic cardiac dysautonomia.

The ADA exercise guidelines[23] outline certain patients who may be at a high risk of further injury if they exercise, and are advised to do so under doctors' supervision.

They are:

1. Those with Type 2 diabetes of more than 10 years duration
2. Those with Type 1 diabetes of more than 15 years duration
3. Those with other risk factors for coronary artery disease
4. Those with documented proliferative retinopathy
5. Those with nephropathy, even microalbuminuria
6. Those with peripheral vascular disease

Diet

The ADA or American Association of Clinical Endocrinologists (AACE) endorses no specific diets for diabetes. Although multiple studies have attempted to identify the optimal macronutrient mix for the diabetic diet, none has been identified. The current article will deal only with essential principles. Distributing pre-printed diet sheets cannot be considered to be adequate. We live in a multicultural society with wide variations in eating patterns. Furthermore, individuals have different eating habits both in terms of timing and content.

We recommend that diet plans should be individualised. Enquire what their general eating patterns and preferences are, and then advise what is acceptable, and what needs changing. If they eat thrice daily, do not suggest six meals a day, because the meal portions may not change despite the increase in its frequency – a formula for further weight gain!

Generally, the emphasis should be on a low fat (avoid fried foods) and a more complex high-fibre carbohydrate diet, particularly foods with soluble fibre such as leafy vegetables, fruits, cereals, roots and pulses. Brown bread or whole wheat bread, pasta, basmati rice, chapattis or potatoes should be the main part of meals, avoiding the use of spreads. Saturated fats should be restricted and monosaturated fats (such as olive oil) should be the replacement. 'Diabetic foods' containing sorbitol or fructose are best avoided or limited – they are expensive, and may contain many calories though not in the form of sugar. If taken, they should replace the usual snack. Salt intake should be limited (< 6 gm/day) and less if hypertension is present. Carbohydrates should be 55–60%, fats < 30% (and lower if hyperlipidaemia is present), and proteins 10–15% of the daily intake.[15]

The safe recommended limit for alcohol consumption per week is 14 units for a female and 21 units for a male. Units of alcohol relate to specific drinks, e.g. a glass of wine and one half pint (250 mls) of beer equates to one unit. Therefore a pint of laager (3.5% alcohol by volume) would be 2 units. However, strong alcoholic drinks (e.g. 8% ABV laager) would equate to 4 units or more per pint. This is important to convey as individuals may greatly underestimate their true alcohol consumption. It is also important for individuals as part of their hypocaloric diets to appreciate the calorific values of alcoholic drinks. A glass of wine for instance is 85 kcal, a shot of spirits (vodka, brandy) about 50 kcal and beer is 90 kcal per half pint (250ml).[16]

Though weight-reducing drugs are effective in providing weight loss,[15] they are expensive. Furthermore, just as in the drug treatment for hypertension, hyperlipidaemia and diabetes, we believe therapy will have to be life-long. Stopping therapy results in a reversion towards the pre-treatment status. At the current time lifestyle modification should be the principal target. We aim to reduce weight by between 5–10%, which is associated with significant improvement in glycaemic control. There is no need (nor success) in getting people to ideal body weight.

Oral agents

The authors of the new evidence-based ADA and EASD consensus algorithm continue to endorse the major features of the algorithm. This newer algorithm proposes implementation of lifestyle interventions and treatment with metformin at the time of diagnosis, the rapid additions of medications and change to new regimens, and the early addition of insulin when target HbA_{1C} is not met.[17]

We recommend that all diabetics have the following blood tests done to establish a baseline: Full blood count; urea, electrolytes and creatinine; liver function tests, TSH, urine microalbumin, fasting lipogram and HbA_{1C}. Any dyslipidaemia or systemic hypertension (BP > 140/90 mmHg) needs to be treated appropriately with lifestyle and dietary changes, and pharmacotherapy as required. It is not within the scope of the present article to discuss this in any further detail.

Self-monitoring of blood glucose

We recommend that all Type 2 diabetics perform regular self-monitoring of blood glucose (SMBG). This is based on the motivation that:

- Diabetes is a largely asymptomatic disease, even if it is uncontrolled.
- Regular self-monitoring done at specified times provides much information about the patient's glycaemic trend, particularly if used with a downloadable computer program.
- High fasting values reflect excessive hepatic glucose production due to hepatic insensitivity to insulin. High 2-hr postprandial reflect either insulin resistance or insulin deficiency. This knowledge allows the doctor to make appropriate drug choices.
- SMBG complements HbA_{1C} measures – it is well known that the latter represents a mean over a three-month period, whereas the former identifies mean fasting and postprandial values.

Wide excursions in blood glucose would provide a normal mean value of the HbA_{1C}, whereas actual blood glucose readings would reflect the correct state of glycaemic control and their excursion patterns

- It provides an assessment of glucose excursions due to medications and lifestyle changes (changes due to different foods)
- It provides information on hypoglycaemia to patient and doctor
- It empowers patients and makes them 'part of the team'

SMBG is of little value in the context of unmotivated patients who are not interested in self-monitoring, and also where the doctors are not interested in checking the results 'because they have no time'. Although there has been much debate on whether type 2 diabetics not taking insulin should do SMBG, there are two recent meta-analyses of randomised clinical trials have examined the effects of SBGM in people with Type 2 diabetes not treated with insulin.[19,20] Both showed that SMBG achieved a statistically significant reduction of 0.4% in HbA_{1C}.

We recommend that all diabetics be started on SMBG. Initially the patients are advised to test at regular intervals, the frequency of which varies from patient to patient. Usually they are advised to test once daily, but at different times of the day (fasting, 2-hr post breakfast, post lunch or post supper). Once stabilised, they are advised to do alternate day testing but still in the above format. Additional testing is done if hypoglycaemia is suspected, or different meal types are ingested.

HbA_{1C} should be tested 2–4 times per year depending on whether control is still being established, or has been established.

IDF guidelines[22]

The 2005 global guidelines from the IDF call for glycaemic control to normal or near-normal values where practicable. This advice incorporates a general target of HbA_{1C} < 6.5%, although still lower values of glycaemia should be attained if possible. Roughly equivalent targets for plasma glucose are provided for use between HbA_{1C} measurements (fasting capillary glucose levels < 6.0 mmol/L and 1–2 hour postprandial capillary glucose < 8.0 mmol/l).

The IDF glycaemic targets are flexible: Higher levels of glycaemia (unspecified) can be accepted where there is a risk of therapy-induced hypoglycaemia in patients with issues, such as patients with physical or mental handicaps. Patients should be told that any improvement in control could reduce risk of diabetic complications.

ADA guidelines[23]

The ADA follows a similar trend with somewhat different targets. A goal of HbA_{1C} < 7.0 is specified, but with the added instruction that a normal HbA_{1C} should be strived for (HbA_{1C} <6.0%) for individual patients where possible but without unacceptable frequency of hypoglycaemic episodes. The following targets are recommended on SMBG: fasting capillary glucose levels 5.0–7.2 mmol/L and peak postprandial capillary glucose < 10.0 mmol/l. ADA guidelines have traditionally focussed on measurement of fasting plasma glucose (FPG). The ADA supports SMBG.

Antidiabetic therapy algorithm: ADA/EASD Consensus Statement[28]

A Consensus Statement issued jointly by the ADA and the European Association for the Study of Diabetes (EASD) represents an important break with earlier thinking in regard to the initiation of oral antidiabetic therapy. They noted the high failure rate of lifestyle interventions by themselves to control glycaemia and agreed that, for the majority, a trial of lifestyle intervention alone before the addition of oral antidiabetic therapy allowed a needless period of hyperglycaemia.

The statement firmly supports the prescription of metformin at the time of diabetes diagnosis for patients without contraindications to it. The approach to treatment thereafter is flexible, with other treatments added to metformin as appropriate. These recommendations also differ from those of the IDF in that, in general, triple oral therapy is not supported, and early use of insulin is encouraged. However, it is recognised that lifestyle intervention and this therapy should be maintained throughout the course of the disease.

We recommend that the patient be started on metformin 500 mg bd with or after meals. The patient's glycaemic control is assessed (using SMBG) over a month, and should the control be sub-optimal, the metformin dose may be increased to 850 mg bd. It is not our practice to commence dual drug therapy immediately even if the HbA_{1C} levels are very high since it is frequently observed that once newly diagnosed diabetics commence the correct diet and metformin, HbA_{1C} levels normalise within 3 months.

If the glycaemia remains uncontrolled, the ADA/EASD consensus suggests three options for addition to the current therapy:

- Basal insulin – considered the most effective option
- Sulphonylureas – considered the lowest cost option
- Thiazolidinediones (TZD) – has the lowest risk of hypoglycaemia

One should optimise the selected option and titrate to achieve glycaemic control.

If control is not attained, one should intensify the selected option, or add insulin, or sulphonylurea, or thiazolidinediones.

Should the objective still not be attained, one should eventually end up with an intensified insulin regimen with/without metformin, and with/without a thiazolidinedione. Lifestyle changes and metformin should be maintained throughout the treatment period.

The individual drugs noted above are not discussed in any detail as it is beyond the scope of the current article. They will be discussed in a future article. The effects of each and newer treatment options are presented below. Insulin therapy regimens for Type 2 diabetes, too, will be discussed in a future volume of this Journal.

Table II summarises glucose-lowering interventions as monotherapy, with their expected effects on HbA_{1C}, their advantages and disadvantages.

Our current management practice in newly diagnosed type 2 diabetics is to initiate management with training on lifestyle intervention skills and correct dietary practice. Our therapy is based on pathophysiological considerations. We commence therapy with metformin at a lower dose of 500 mg nocte or bd, and, depending on the response, we intensify therapy increasing the dose to 850mg to 1gm bd. This addresses the problem of insulin resistance. The metformin has a greater effect on reversing hepatic insulin resistance than on peripheral resistance.

TABLE II: Summary of glucose-lowering interventions as monotherapy [18]

Interventions	Expected decrease in HbA1C (%)	Advantages	Disadvantages
Step 1: Initial			
Lifestyle to decrease weight and increase activity	1 – 2	Low cost, many benefits	Fails for most in first year
Metformin	1 – 2	Weight neutral, inexpensive	GI side effects, rare lactic acidosis
Step 2: Additional Therapy			
Insulin	1.5 – 3.5	No dose limit, inexpensive, improved lipid profile	Injections, monitoring, hypoglycaemia, weight gain
Sulphonylureas	1 – 2	Inexpensive	Weight gain, hypoglycaemia*
Thiazolidinediones (glitazones)	0.5 – 1.4	Improved lipid profile# Potential decreased risk of MI#	Fluid retention, twofold increased risk of CHF, potential increased risk of MI**, atherogenic lipid profile, weight gain, expensive
Other Drugs			
□-Glucosidase inhibitors	0.5 – 0.8	Weight neutral	Frequent GI side effects, tds dosing, expensive
Exenatide	0.5 – 1.0	Weight loss	Injections, frequent GI side effects, expensive, little experience
Glinides	1.0 – 1.5##	Short duration	Tds dosing, expensive, hypoglycaemia,
Pramlintide	0.5 – 1.0	Weight loss	Injections, tds dosing, frequent GI side effects, expensive, little experiences
Sitagliptin	0.5 – 0.8	Weight neutral	Little experience, expensive

* Severe hypoglycaemia is relatively infrequent with sulphonylurea therapy. The longer-acting agents (e.g. chlorpropamide and glibenclamide are more likely to cause hypoglycaemia than glipizide, glimeparide, or gliclazide. # Pioglitazone ** Rosiglitazone ## Repaglinide is more effective at lowering HbA1C than nateglinide. GI – Gastrointestinal MI – Myocardial infarction

A failure to attain control may be due to inadequately addresses peripheral insulin resistance, and we would, at this stage, add a pioglitazone 15 mg, increasing to 30 mg if necessary. It must be remembered that, due to insulin resistance, there is often secondary hyperinsulinaemia present, and sensitising the peripheral tissues will improve insulin action. The glitazones have a more pronounced effect on the peripheral tissues than the liver, and a combination of metformin and glitazones have a synergistic effect.

Should the response over a further month still be sub-optimal, it could mean that although the tissues have been sensitised, a poor response could mean insulin deficiency. We would consider the addition of a sulphonylurea to augment insulin secretion, starting with a lower dose and titrating upwards. A failure to achieve improved glycaemia on SMBG could mean that the ß-cell secretory capacity is reduced, and we would consider the addition of a basal insulin, or a predinner premixed biphasic insulin. If the response is still unsatisfactory, we would proceed to the use of twice daily premixed biphasic insulin, or use a basal/bolus regimen, depending on the patient's lifestyle and need for flexibility in terms of occupational or other demands.

A number of good quality oral generic medicines in all the drug classes are available in South Africa at the current time, and therefore cost-considerations should not prove to be a funding obstacle when prescribing these products.

The newer exciting products such as the DPP-4 inhibitors (Sitagliptin), the GLP-1 analogs (Exenatide) and pramlintide are currently not available in South Africa. They will be a welcome addition to our current therapeutic armamentarium.

Conclusion

Physicians must be aware that cardiovascular risk is increased even before the diagnosis of diabetes. Cardiovascular causes represent the major reasons for death in Type 2 diabetes. Intensive treatment has a tendency to reduce mortality. The Steno-2 studies have clearly pointed out that a reduction in cardiovascular risk in people with diabetes is feasible when all abnormalities are addressed simultaneously. Indeed, in atrisk patients with Type 2 diabetes, intensive intervention with multiple drug combinations and behaviour modification had sustained beneficial effects with respect to vascular complications and on mortality rates from any cause and from cardiovascular causes.[24]

Post-trial follow-up from the Steno-2 study demonstrated a maintained reduction in mortality following intensive control of multiple cardio-metabolic risk factors in patients with Type 2 diabetes.

In the Steno 2 study Type 2 diabetes patients were randomised to either intensive therapy or conventional therapy for 7.8 years. The intensive treatment included lifestyle education, optimised glycaemic control and treatment of known risk factors (including hypertension and hyperlipidaemia) using a multiple drug regimen. Patients were subsequently followed for 5.5 years post-trial, and the time to death from any cause was analysed. Fewer patients who received intensive treatment died during this 13-year follow up period, compared with those who received conventional treatment, 24 vs 40; hazard ratio, 0.54. Intensive therapy was also associated with a significantly lower risk of death from cardiovascular causes, of cardiovascular events and progression to end-stage renal disease.[24]

However, a number of recently reported large studies (ADVANCE,[25] ACCORD,[26] have shown that glycaemic control at target HbA_{1c} levels significantly reduces the risk of microvascular complications, but there is no convincing evidence that the same applies to macrovascular disease.[25,26] In keeping with ACCORD, ADVANCE, VADT (Intensive glucose control on cardiovascular outcomes in the Veterans Administration Diabetes Trial),[28] and in the Heart 2D Study,[26] glucose lowering is not shown as the major shortterm modulator of cardiovascular disease risk in patients with advanced disease. Use of other CVD-modifying drugs is being considered vital to reducing risk.

At the current time, it is our belief that diabetic control should be established early, and maintained, together with control of other important risk factors such as hypertension and hyperlipidaemia, and the use of prophylactic aspirin. These efforts are more likely to make a significant impact on reducing macrovascular disease. It appears that the impact of these interventions will only become evident after many years of control, and perhaps not just after 5–10 years, as seen in the randomised clinical trials.

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