

# Standard 19

*Those with uncommon causes of diabetes (eg, cystic fibrosis, monogenic, post-pancreatectomy) should have access to specialist expertise with experience in these conditions.*

## Key practice points

- Diabetes due to uncommon cause is an infrequently encountered, complex condition.
- Correct diagnosis allows for specific and appropriate treatment.
- Most health professionals encounter type 2 diabetes frequently, and have limited experience in managing diabetes with uncommon causes.
- Current guidelines available in New Zealand are based on type 2 diabetes and do not meet the specific needs of people with diabetes from uncommon causes.
- Specialist expertise is required due to the specificity of the condition and unique treatment requirements.

Read this standard in conjunction with the equality and diversity section in the introduction to the Toolkit.

## What the quality statement means for each audience

**Service providers** ensure people with uncommon causes of diabetes have access to specialists with expertise and experience in these conditions.

**Health care professionals** ensure they have the competence and expertise to provide specialist support for people with uncommon causes of diabetes or make appropriate referrals.

**Planners and funders** ensure services are commissioned that provide specialist expertise and experience for people with uncommon causes of diabetes.

**People with uncommon causes of diabetes** receive relevant and experienced specialist diabetes care.

## Definitions

**Uncommon causes of diabetes** are described by the American Diabetes Association (2010) in summary as follows:

- **Monogenetic defects in beta cell function** are characterised by onset at an early age and impaired insulin secretion with minimal or no defects in insulin action. They include different subtypes of gene disorders including neonatal diabetes mellitus, monogenic diabetes of infancy, maturity-onset diabetes of the young (MODY) and other rarer diabetes-associated syndromic diseases.
- **Disease of the exocrine pancreas:** Any process that injures the pancreas may cause diabetes including pancreatitis, pancreatectomy, pancreatic carcinoma, trauma and infection. Cystic fibrosis and haemochromatosis damage beta cells and impair insulin secretion.

- **Endocrinopathies:** Several hormones antagonise insulin action; therefore an excess of these hormones may induce diabetes. Somatostatinoma and aldosteronoma-induced hypokalaemia can cause diabetes in part by inhibiting insulin secretion, but may resolve after removal of the tumour.
- **Drug or chemical induced diabetes:** Many drugs, including thiazides, glucocorticoids, dilantin and more, may impair insulin secretion or action and may precipitate diabetes in those with existing insulin resistance. Certain toxins may permanently destroy beta cells.
- **Infections:** Certain viruses are associated with beta cell destruction, for example congenital rubella, coxsackievirus B, cytomegalovirus, adenovirus and mumps.
- **Uncommon forms of immune-mediated diabetes** may occur in people with a number of autoimmune related conditions, for example stiff-man syndrome where patients usually have high concentrations of GAD autoantibodies of which one-third of the patients will develop diabetes, or anti-insulin receptor antibodies.
- **Other genetic syndromes sometimes associated with diabetes** include Down syndrome, Klinefelter syndrome and Turner syndrome. Wolfram's syndrome is characterised by insulin deficiency and the absence of beta cells at autopsy.

A full list of etiologic classification of diabetes mellitus by the American Diabetes Association (ADA 2010) can be found here:

[http://care.diabetesjournals.org/content/33/Supplement\\_1/S62.full.pdf+html](http://care.diabetesjournals.org/content/33/Supplement_1/S62.full.pdf+html).

Forms of **drug induced diabetes** are described by Comi (2004) as follows:

- **Corticosteroids** may cause hyperglycaemia, which may return to normal after the steroid treatment is stopped. However, particularly if corticosteroids are taken over longer periods of time, steroid treatment can sometimes lead to the development of type 2 diabetes permanently. Whilst on steroid medication, insulin may be required; however, once steroids are discontinued, anti-diabetic medication may be reduced or stopped.
- **Beta-blockers** inhibit insulin secretion by the pancreatic islets in response to glucagon, glucose or arginine.
- **Thiazide diuretics** may increase blood glucose levels. These may, but not always, return to normal if treatment with thiazide diuretics is stopped. They act to reduce insulin secretion and increase insulin sensitivity.
- **Antipsychotics** may cause weight gain and hyperglycaemia. Blood glucose levels may return to normal if medication is stopped. However, if significant weight has been gained over the course of the treatment, insulin resistance and type 2 diabetes may be permanent. The weight gain leading to increased insulin resistance is the most likely mechanism for inducing diabetes; however, inhibition of insulin secretion is likely to be occurring in some people.
- **Statins** in high doses have demonstrated a link to a higher risk of type 2 diabetes, likely due to a decrease in pancreatic beta cell function and decreasing peripheral insulin sensitivity.



## Introduction

Those with uncommon causes of diabetes need access to specialist expertise with experience in these conditions due to the specificity of the condition and differing treatment requirements. While there are many uncommon causes of diabetes, examples used for the purpose of this Quality Standard are **monogenic, cystic fibrosis, thalassaemia** and **pancreatectomy**.

Knowing and understanding monogenic diabetes including the differing forms of MODY means that the affected person can be treated in the most appropriate way possible. Advice can also be provided about how the disease will progress and what complications can be expected, and family/whānau members advised about the risks of inheriting the disease (New Zealand Society for the Study of Diabetes [NZSSD] 2012). The study advises consultant diabetes or endocrinology review for all molecular genetic testing of suspected cases due to the expense and the possible need for cascade testing of relatives.

Diabetes mellitus is a well-recognised complication of cystic fibrosis and, as survival in cystic fibrosis improves, so too does the prevalence of cystic fibrosis-related diabetes (The UK Cystic Fibrosis Trust Diabetes Working Group 2004). It is now a common and expected complication of cystic fibrosis as 10–30% of 15- to 25-year-olds with cystic fibrosis will develop diabetes (International Society for Pediatric and Adolescent Diabetes 2000). As people with cystic fibrosis-related diabetes (CFRD) survive longer, they are also at risk of developing diabetes-related complications, and their diabetes management becomes much more complex as the nature of the cystic fibrosis changes (The UK Cystic Fibrosis Trust Diabetes Working Group 2004). Management of diabetes in people with cystic fibrosis presents a different set of challenges to people with type 1 or type 2 diabetes and people with CFRD should be referred to a consultant with a specialty in managing patients with CFRD (The UK Cystic Fibrosis Trust Diabetes Working Group 2004).

Thalassaemia can lead to iron overload affecting beta-cell function and the decreasing insulin sensitivity of puberty contributes to the risk of diabetes. If iron levels remain high, treatment with high doses of insulin may be required (International Society for Pediatric and Adolescent Diabetes 2000). It is suggested that a long period of insulin resistance and hyperinsulinaemia might lead also to secondary beta cell failure (Li et al 2014). Impaired glucose tolerance in these people is common (up to 27%), and patients and health professionals should be aware of the high incidence. It is likely that the fatty replacement of the pancreas cells is irreversible, representing end stage pancreatic disease (Li et al 2014).

Pancreatitis, cancer and trauma can all harm the pancreatic beta cells or impair insulin production, thus causing diabetes. If the damaged pancreas is removed, diabetes will occur due to the loss of the beta cells. People who have had a pancreatectomy will not be able to produce any of their own insulin and will therefore need to take regular insulin injections in a similar way to people with type 1 diabetes. In the past, total pancreatectomy has been avoided due to the risks associated with post-operative brittle insulin dependent diabetes associated with hypoglycaemia, and malabsorption problems. However, with the advent of high quality enzyme formulations and advances in diabetes specialist care there has been a resurgence of interest in total pancreatectomy as a treatment as pancreatic insufficiency can now be managed safely (Crippa et al 2011).



## Guidelines

### Monogenic diabetes

In the European report on treatment and care of diabetes in children by the SWEET group, it is suggested that while in the past many patients with monogenic forms of diabetes have been diagnosed incorrectly as either type 1 diabetes (T1DM) or type 2 diabetes (T2DM) dependent on the age of hyperglycaemia detection, current diagnostic availability should allow specific diagnosis (SWEET 2010).

Genetic testing should be available in all centres either locally or nationally, allowing for specific treatment depending on the genetic defect. Treatment may be as simple as annual follow-up without diet or medication, to intensive diet and/or sulphonylurea or insulin (SWEET 2010). There may be progressive beta-cell deficiency in some children with transcription factor mutations therefore creating the need for oral hypoglycaemic agents. HNF-1 $\alpha$  variants may exhibit sensitivity to small doses of sulphonylureas (with the risk of hypoglycaemia) and may require insulin treatment managed by a specialist team but this is usually in adulthood (International Society for Pediatric and Adolescent Diabetes 2000).

Genetic testing for monogenic diabetes is recommended under the care of an expert diabetologist or endocrinologist (New Zealand Society for the Study of Diabetes 2012).

The NZSSD Monogenic Guidelines can be found here:

[www.nzssd.org.nz/education/2013%20Monogenic\\_diabetes\\_card\\_with\\_forms\\_18%20Dec%20copy.pdf](http://www.nzssd.org.nz/education/2013%20Monogenic_diabetes_card_with_forms_18%20Dec%20copy.pdf)

### Cystic fibrosis

The Standards of Care for Cystic Fibrosis (CF) in New Zealand by the Cystic Fibrosis Association of New Zealand (2011) suggest the following:

- The primary place of CF care should be at a hospital with a CF clinic closest to where the person with cystic fibrosis lives.
- People with cystic fibrosis should be seen at least four times a year in a dedicated CF clinic.
- If attending a smaller local clinic, the makeup of the health professional team may vary; therefore, there needs to be a well-defined relationship with a Regional CF Centre.
- A regional multidisciplinary team should review all people with cystic fibrosis at least annually or more frequently as dictated by individual needs:
  - patients may travel to regional cystic fibrosis centres, or
  - combined clinics may be held locally.
- Core members of the regional centre multidisciplinary team are involved.
- Core members of the regional centre multidisciplinary team at a minimum should include:
  - CF clinician
  - nurse specialist
  - specialist physiotherapist
  - dietitian.

- Between visits regional CF centre support can be augmented through the use of the TelePaediatrics service video link system.
- The extent of regional clinic contact is determined by an individual's need rather than geography.
- All people with cystic fibrosis have an annual review – usually regional CF centre involvement occurs then.
- It is impractical to expect all specialist services can be provided outside regional CF centres:
  - access to specialist services must be available to all patients depending on need and regardless of location
  - the requirement of a regional CF centre is extensive and includes onsite availability from sub-specialists experienced in CF complications including endocrinology
  - people with cystic fibrosis-related diabetes should have access to, and an established working relationship with, an endocrinologist and diabetes service with knowledge and expertise in the management of CFRD.

The UK Cystic Fibrosis Trust recommends the following for people with cystic fibrosis-related diabetes:

‘Ideally the CF Clinician and Diabetologist should carry out a combined general and CFRD Annual Review. In practice, it is usually more convenient for the CFRD Annual Review to be carried out at a different appointment to the general CF Annual Review. The aim of the CFRD Annual Review is to screen for, and if necessary; treat early complications, check that diabetic treatment is adequate and appropriate, to assess nutritional management and to address adherence issues, diabetic education and psychosocial issues’ (The UK Cystic Fibrosis Trust Diabetes Working Group 2004, p 32).

Insulin treatment will improve hyperglycaemia and help to prevent catabolic weight loss in CF particularly during intercurrent infections. High dietary energy intake is recommended including high fat and high complex carbohydrates (International Society for Pediatric and Adolescent Diabetes 2000). The American Diabetes Association recommends as part of their Clinical Care Guideline for Cystic Fibrosis-related Diabetes Management that ‘patients with CFRD should be managed by a multidisciplinary team of health professionals with expertise in CF and diabetes. The diabetes team should be intimately familiar with CFRD, recognising differences between this and type 1 and type 2 diabetes pathophysiology and treatment. Good communication between diabetes and CF care providers is essential. Poor team communication and inadequate or conflicting information from health care providers have been identified as significant sources of stress for patients with CFRD’ (Moran et al 2010, pp 2702–3).

## **Thalassaemia**

The Northern California Comprehensive Thalassemia Center Standard of Care Guidelines can be found here: <http://thalassemia.com/soc/treatment-guidelines-9.aspx>

These guidelines recommend a fasting glucose semi-annually, and if it is greater than 6.1 mmol/L, an oral glucose tolerance test is indicated. In addition a two-hour oral glucose tolerance test should be performed at 10, 12, 14, and 16 years of age and annually thereafter. Further recommendations include that the patient should be referred to endocrinology for management of diabetes mellitus or glucose intolerance and patients diagnosed with glucose intolerance should have their chelation therapy reviewed and intensified (Northern California Comprehensive Thalassemia Center 2012).

The Academy of Medicine of Malaysia has clinical practice guidelines that suggest the early and adequate use of iron chelation can prevent DM, and both DM and impaired glucose tolerance may improve in a third of patients after intensive combined chelation treatment. Use of insulin in a thalassaemia patient with DM is normally required but metabolic control may be difficult to achieve due to variable pancreatic beta cell function. The use of oral anti-diabetic agents is undetermined (Academy of Medicine Malaysia 2009).



## Implementation advice

Correct diagnosis of a possible uncommon cause of diabetes allows for individualised and appropriate treatment resulting in reduced complications and more effective response to treatment (Juszczak et al 2014).

Joint clinics are one of the most effective settings for clinicians to look after people with dual conditions where members of both the specialist diabetes team and condition specialist work together to look after the individual. This enables the health professionals to manage the complex needs of both conditions and allows all to learn from each other and provide a consistent approach (Tzoulis et al 2014).

People with diabetes receiving corticosteroid treatment or those who develop diabetes as a result of corticosteroids can be particularly difficult to manage due to the fluctuations in therapy requirements and circadian glycaemic pattern (Burt et al 2011). Prescribers of corticosteroids should work in partnership with diabetes expert teams at the commencement of treatment to enable early, appropriate and frequent anti-diabetes medication changes as needed for the individual (Stevens et al 2011). This includes all those prescribing corticosteroids across the disciplines including, but not limited to, neurological, respiratory, haematology, oncology and palliative care.

In remote locations, care is likely to be provided by a locally based physician and these practitioners should have ready access to the facilities and advice provided by specialist diabetes teams. For complex individuals, annual reviews should take place with the specialist team (International Society for Pediatric and Adolescent Diabetes 2000). This model of shared care should strengthen rather than weaken the relationship between the person with diabetes and their local provider (Cystic Fibrosis Association of New Zealand 2011).

Specialist teams from district or regional centres might organise outreach clinics where people with diabetes have difficulty travelling. The specific role of this diabetes team is to provide specialised hospital medical care, expert comprehensive ambulatory care of diabetes and associated conditions, expert advice on issues related to diabetes (exercise, travel and sickness), and screening for complications (International Society for Pediatric and Adolescent Diabetes 2000).

Telemedicine consultations with diabetes specialist services should be considered as they can remove barriers associated with location to accessing these services (Levin et al 2013). Ideally, there should also be specialist telephone support available 24 hours a day (International Society for Pediatric and Adolescent Diabetes 2000).



## Implementation examples / innovations



### A joint thalassaemia and diabetes clinic

A joint thalassaemia and diabetes clinic was established at the Department of Diabetes, Whittington Health, London in 2005. Patients were reviewed by a multidisciplinary team including a consultant diabetologist and haematologist. A four-year study showed improvement in glycaemic control with fructosamine reduction and improved lipids. When patients attending the clinic were compared to a national diabetes audit, the number achieving goals for glycaemic, blood pressure and cholesterol control were significantly higher. A fifth of the patients had macrovascular complications while a significant number had endocrinopathies and the combined clinic was able to effectively manage these complex patients (Tzoulis et al 2014).



### Pennsylvania telemedicine consultation service

To address the problem rural communities face in accessing specialist diabetes care, a telemedicine consultation service was trialled in rural Pennsylvania. Twenty-five patients with diabetes participated via a 45-minute videoconferencing consultation with an endocrinologist at an urban centre and a locally based diabetes nurse. Patients and providers uniformly reported high levels of satisfaction and acceptability. Mean HbA1c decreased from 9.6% (~80 mmol/mol) to 8.5% (69 mmol/mol) ( $p < 0.001$ ) (Toledo et al 2012).



## Assessment tools

### Process

The proportion of people with uncommon causes of diabetes who have access to specialists with expertise and experience in these conditions.

Numerator	The number of people in the denominator accessing specialists with expertise and experience in their condition
Denominator	The number of people with uncommon causes of diabetes



## Resources

New Zealand Society for the Study of Diabetes (NZSSD) website, health professionals' section provides a monogenic screening card: [www.nzssd.org.nz/professionals.html](http://www.nzssd.org.nz/professionals.html)

### Consumer tools

Global Genes provides consumers with advice in regards to genetic testing:  
<https://globalgenes.org/toolkits/genetic-testing-is-this-my-path-to-a-diagnosis-3/introduction/>

The same website in the future will also have toolkits available that some may find helpful for 'Transitioning to adulthood as a rare disease patient' and 'Caring for yourself as a caregiver' found at: <https://globalgenes.org/toolkits/>

**Cystic Fibrosis Foundation.** 2011. *Managing Cystic Fibrosis Related Diabetes CFRD: Instruction guide for patients and families* (5th edition). USA: Cystic Fibrosis Foundation.

**The National Diabetes Information Clearinghouse** provides information for the consumer on monogenic forms of diabetes:  
<http://diabetes.niddk.nih.gov/dm/pubs/mody/index.aspx>.



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