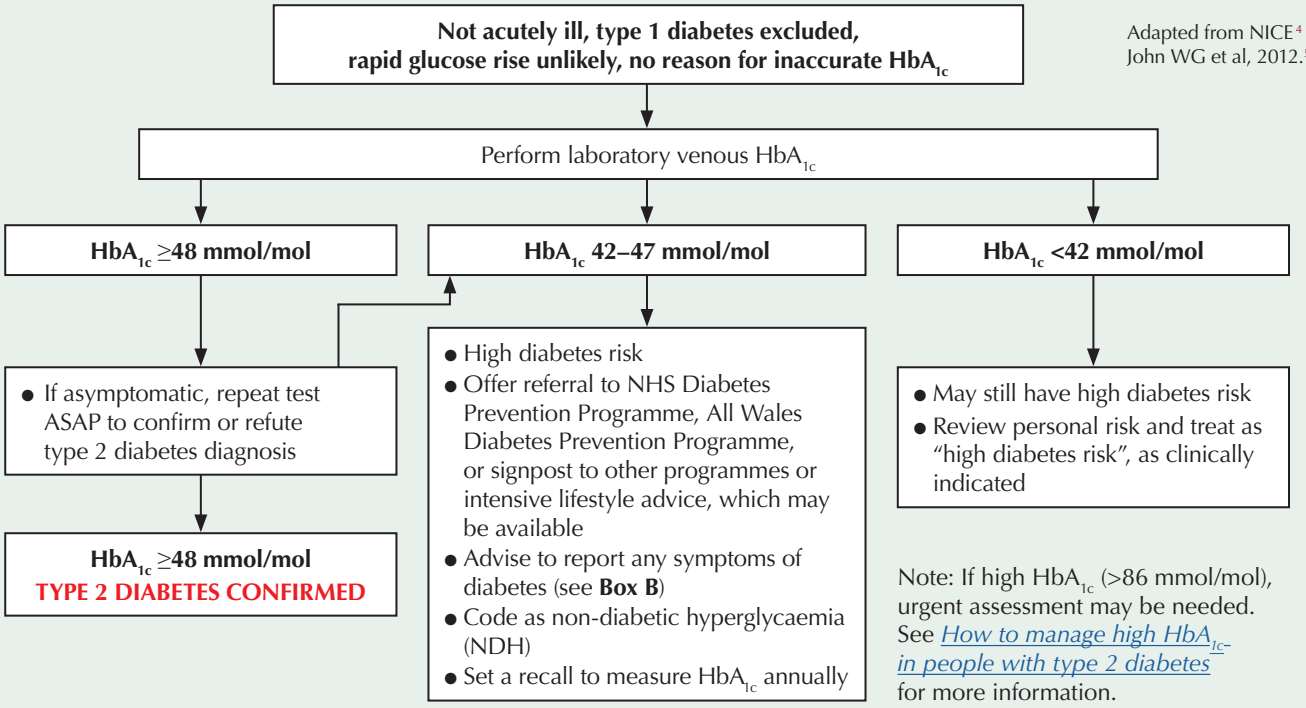
What and why

- An estimated 4.9 million people in the UK have diabetes – 3.9 million diagnosed and approximately 1 million undiagnosed.[1]
- In the first year of the COVID-19 pandemic, new type 2 diabetes diagnoses dropped by two thirds compared to previous years.[2]
- Type 1 and type 2 are the most common forms of diabetes, but there are a number of other types that can present in slightly different ways and require different management strategies.
- Ensuring the correct diagnosis is essential to offering the correct advice and treatment.
- A diagnosis of diabetes has important legal and medical implications for the patient, so a secure diagnosis is essential.

Using HbA_{1c} to diagnose diabetes

In 2011, the WHO concluded that HbA_{1c} can be used as a diagnostic test for diabetes, provided stringent quality assurance tests are in place and assays are standardised to criteria aligned to the international reference values, and there are no conditions present which preclude its accuracy (see **Box A**).[3]

An HbA_{1c} of ≥48 mmol/mol is diagnostic of diabetes. However, a value <48 mmol/mol does not exclude diabetes diagnosed using glucose tests (such as fasting glucose or OGTT). Individuals with an HbA_{1c} <48 mmol/mol may be at risk of developing diabetes and should be monitored according to the recommendations shown below.



Adapted from NICE[4] and John WG et al, 2012.[5]

Note: If high HbA_{1c} (>86 mmol/mol), urgent assessment may be needed. See *How to manage high HbA_{1c} in people with type 2 diabetes* for more information.

Box A. Situations where HbA_{1c} is not appropriate for diagnosing diabetes[6]

- ALL children and young people
- People of any age suspected of having type 1 diabetes
- People at high diabetes risk who are acutely ill (e.g. those requiring hospital admission), post severe trauma or CVD event
- People taking medication that may cause rapid glucose rise (e.g. steroids, antipsychotics)
- People with acute pancreatic damage, including pancreatic surgery
- In pregnancy
- In those with end-stage renal disease
- People being treated for HIV infection with antivirals
- Interpret HbA_{1c} with caution if abnormal red blood cell lifespan (see **Box C**)
- Note: Be aware that severe hyperglycaemia in people with acute infection, trauma, circulatory or other stress may be transitory and is not diagnostic of diabetes[7]

Box B. Signs and symptoms of diabetes

- Thirsty
- Passing more urine and more frequently (including nocturia)
- Weight loss
- Infections (thrush, abscesses)
- Poor wound healing
- Blurred vision
- Tiredness and lethargy

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Since 2011, diabetes has been diagnosed on the basis of these WHO criteria

Symptoms present (e.g. polyuria, thirst, unexplained weight loss)
A single fasting plasma glucose ≥7.0 mmol/L
OR
A single random plasma glucose ≥11.1 mmol/L
OR
An HbA_{1c} ≥48 mmol/mol (6.5%)

No symptoms
A fasting plasma glucose ≥7.0 mmol/L on two separate occasions
OR
A random plasma glucose ≥11.1 mmol/L on two separate occasions
OR
An HbA_{1c} ≥48 mmol/mol (6.5%) on two separate occasions
OR
An HbA_{1c} ≥48 mmol/mol AND a single elevated plasma glucose (fasting ≥7.0 mmol/L or random ≥11.1 mmol/L)

In the absence of symptoms, two abnormal results are required to make a diagnosis of type 2 diabetes. Ideally, use the same test and repeat it straight away.[7] Even where an HbA_{1c} test is used, **do not wait 3 months to repeat the test** – it should be repeated straight away to confirm the diagnosis of type 2 diabetes.

A random glucose test is not recommended for diagnosing type 2 diabetes. However, a random glucose measurement of 7–11 mmol/L should be followed by fasting blood glucose. If the result of the second test is not diagnostic, an oral glucose tolerance test (OGTT) should be performed.

Note: Lucozade is no longer suitable for use in OGTTs owing to changes in glucose content.

Box C. When to interpret HbA_{1c} with caution[8]

Gives false high ▲	Gives false low ▼
Conditions that **prolong** RBC life, or associated with **decreased** RBC turnover.	Conditions that **reduce** RBC life, or associated with **increased** RBC turnover.
▲ Anaemias associated with decreased RBC turnover ▲ Asplenia ▲ Uraemia ▲ Severe hypertriglyceridaemia ▲ Severe hyperbilirubinaemia ▲ Chronic ingestion of alcohol, salicylate, opioids ▲ Lead poisoning ▲ RBC transfusion*	▲ Anaemia from acute or chronic blood loss ▲ Splenomegaly ▲ Pregnancy** ▲ Vitamin E ingestion ▲ Ribavirin and interferon-alpha ▲ RBC transfusion*

*Typically falsely elevates, but may also falsely decrease.
**False low through 2nd trimester; may rise during 3rd trimester.

Other types of impaired glucose regulation

There are three biochemical categories at high risk of developing type 2 diabetes:

Impaired glucose tolerance
Fasting plasma glucose <7.0 mmol/L
AND
2-hour, 75-g OGTT 7.8–11.0 mmol/L

Impaired fasting glucose
Fasting plasma glucose 5.5–6.9 mmol/L

Impaired glucose regulation
HbA_{1c} 42–47 mmol/mol

Previous **gestational diabetes** (GDM), another biochemical anomaly, carries a high lifetime risk of progression to type 2 diabetes. NICE provides recommendations for testing for GDM.[10]

Other tests to support the diagnosis

A diagnosis should never be made on the basis of glycosuria or finger-prick blood glucose alone, and should be confirmed by a venous sample.

Other tests can be useful to help differentiate between different types of diabetes (see table on final page). These may have to be requested by specialist colleagues where there is clinical uncertainty regarding the type of diabetes.

C-peptide[9]

- C-peptide is a marker of endogenous insulin secretion from pancreatic beta-cells. It may be useful in cases where differentiating between type 1 and type 2 diabetes is not clear.
- In established type 1, endogenous insulin secretion will be either very low or zero, with correspondingly low C-peptide levels.
- There may be some utility for plasma or urine C-peptide measurement in diagnosing monogenic diabetes.

Autoantibodies[9]

- Can help to distinguish between autoimmune type 1 diabetes and other forms of diabetes.
- Islet cell cytoplasmic antibodies (ICA) are present in 70–80% of type 1 diabetes cases.
- Glutamic acid decarboxylase (GAD) antibodies are present in 70–80% of type 1 diabetes cases.
- Insulinoma-associated 2 antibodies are present in 60% of type 1 diabetes cases.
- If antibodies are present in a person with signs and symptoms of diabetes, this is diagnostic of type 1 diabetes.
- NICE recommends measuring anti-GAD and anti-ICA antibodies in the diagnosis of type 1 diabetes or LADA. Both tests have close to 100% specificity for autoimmune diabetes, but GAD has far higher sensitivity (96% vs 37.5%) and the antibodies also persist for much longer. Indeed, there is evidence that testing for GAD antibodies alone may be just as clinically useful and more cost effective than measuring both antibodies.

Arrange urgent upper abdominal imaging if aged ≥60 years with weight loss and any gastrointestinal symptoms, back pain or new-onset diabetes (see Recognition and management of pancreatogenic (type 3c) diabetes).

Always consider the possibility of type 1 diabetes

Type 1 diabetes is the commonest cause of diabetes in children and young adults. However, type 1 diabetes can develop at any age. Consider diagnosis of type 1 diabetes in adults who have any of the following:

- Ketosis
- Rapid weight loss
- Age of onset <50 years
- BMI <25 kg/m^2
- Personal and/or family history of autoimmune disease

Do not discount a diagnosis of type 1 diabetes if an adult presents with a BMI of ≥25 kg/m^2 or is aged ≥50 years.

Always assume type 1 until proven otherwise! Perform finger-prick tests for blood glucose and ketones.

Children usually present with severe symptoms, and diagnosis should then be based on a single raised blood glucose result, as above. About 40% of children present with DKA as the first presentation of diabetes[11] and 6% of DKA in adults occurs in people with new-onset diabetes[12]. Hospital admission should be immediate. Diabetes UK's 4Ts campaign seeks to educate people on the symptoms of diabetes in children.

Signs of diabetic ketoacidosis

- Excessive thirst
- Polyuria
- Dehydration
- Shortness of breath and laboured breathing
- Abdominal pain
- Leg cramps
- Nausea and vomiting
- Mental confusion and drowsiness
- Ketones can be detected on the person's breath (pear-drop smell) or in the blood or urine

Interpreting blood ketone readings:

Below 0.6 mmol/L
This is a normal reading

0.6–1.5 mmol/L
Slightly increased risk of DKA
Test again in 2 hours

1.6–2.9 mmol/L
Increased risk of DKA
Contact diabetes team/GP as soon as possible

3 mmol/L or over
Very high risk of DKA
Seek medical help immediately

Key points about DKA

- DKA is an extreme consequence of insulin deficiency, and can result in severe dehydration and electrolyte imbalance.
- Symptoms develop rapidly, over a few hours or days.
- **If you suspect DKA, perform a finger-prick glucose test and check finger-prick blood for ketones.**
- Glucose ≥11.1 mmol/L, with ketonuria ≥++ (or blood ketones >3 mmol/L) is highly suggestive.
- **Immediate admission for hospital assessment is indicated.**

A diagnosis of diabetes is a life-changing event and responses vary considerably. How the diagnosis is communicated to a person can have a significant impact on how they relate to their condition. For further support, see How to help people come to terms with a diabetes diagnosis.

Diagnosis and classification of diabetes for primary care

- The diagnosis and classification of diabetes in primary care is increasingly challenging. *GPnotebook* has created a downloadable table to help you to establish the right diagnosis as accurately as possible and ultimately to avoid any harm: https://bit.ly/3G2aJ6M.
- Diabetes Genes provides information on genetic types of diabetes. This includes information to aid differential diagnosis of diabetes to ensure correct diagnosis and treatment of genetic subtypes.

Further resources

- *Making the right diagnosis in diabetes* is a free CPD module developed by the PCDS to provide healthcare professionals with an understanding of:
  - The different types of diabetes
  - The different tests available in the diagnosis of diabetes
  - The selection of the most appropriate diagnostic tests
  - How to devise a care plan

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Diagnosis and classification of diabetes for primary care

	Type 1 diabetes	LADA	Type 2 diabetes	Monogenic diabetes	GDM	Type 3c diabetes (pancreatogenic)
Pathophysiology and diagnosis	Autoimmune destruction of pancreatic beta-cells. Clinical diagnosis ± PG and ketone levels. Urgent specialist discussion required. It is increasingly challenging to differentiate T1D from T2D, partly due to the obesity epidemic. Often the safest strategy is to presume T1D until proven otherwise	LADA is essentially "slow-onset" T1D. Gradual autoimmune destruction of pancreatic beta-cells. Diagnosis and management similar to T1D. See: www.diabetes.org.uk/diabetes-the-basics/othertypes-of-diabetes/latentautoimmune-diabetes	IR with relative insulin deficiency. T2D is usually diagnosed when HbA_{1c} ≥48 mmol/mol. If use of HbA_{1c} is inappropriate (e.g. pregnant women, women who are 2 months postpartum, ESRD) then T2D is diagnosed by an FPG ≥7 mmol/L. If asymptomatic, the diagnosis should never be based on a single abnormal HbA_{1c} or PG level; at least 1 additional abnormal test is essential	Genetic mutation leading to diabetes. Most common is MODY. See: www.diabetesgenes.org for diagnosis guidance	Impaired glucose tolerance in pregnancy due to pancreatic beta-cell dysfunction on background of IR. NICE guideline NG3 (last updated December 2020) diagnostic criteria: FPG ≥5.6 mmol/L or 2-hour PG post 75 g OGTT ≥7.8 mmol/L	Diabetes associated with disease, trauma or surgery of the exocrine pancreas. Causes include acute and chronic pancreatitis, pancreatic surgery, cystic fibrosis, haemochromatosis and pancreatic cancer. See: https://pancreaticcanceraction.org/help-and-support/living-with-pancreaticcancer/type-3c-diabetes
Age at diagnosis	Usually <25 years but can occur at any age	Can occur at any adult age. Often initially mistaken for T2D	Both adults and children at any age	MODY onset often during 2nd to 5th decades and usually <45 years	Can occur in any women of child-bearing age. Women with GDM have a nearly 10-fold higher risk of developing T2D. Follow-up after delivery: women require lifelong annual HbA_{1c}	Both adults and children at any age. Exclude pancreatic cancer in those >60 years with new-onset diabetes and weight loss
Weight at diagnosis	Usually thin but can be overweight. Marked weight loss common	Variable	Usually overweight	Variable	RF for GDM include overweight/obesity but baseline weight can be variable	Variable
Family history of diabetes	Infrequent (5–10%)	Variable	Frequent (75–90%)	Multi-generational. MODY is AD. A strong FH of diabetes (any type) involving two or three consecutive generations may point towards a diagnosis of MODY	FH of diabetes is an important RF for GDM	Variable. Haemochromatosis and CF are AR
History of autoimmune disease	Often personal or FH (e.g. thyroid and coeliac disease)	Variable	Variable	Variable	Variable	Variable but often PEI present (e.g. diarrhoea and steatorrhoea, abdominal discomfort, flatulence and bloating). Check stool sample for faecal elastase-1. Low levels suggestive of PEI
Pancreatic autoantibodies	Present	Present	Absent	Absent	Absent	Absent
C-peptide levels	Low/absent	Initially normal then low/absent	Normal to high	Normal	Normal to high	Low
Insulin sensitivity	Normal when treated	Some IR	Reduced	Normal (maybe reduced if obese)	Reduced	Compensatory increase in peripheral insulin sensitivity
Insulin requirements	Immediate; specialist input urgently required	Latent; months to years	Variable	Variable	Variable	Variable. Much more likely to need insulin within 5 years of diagnosis
Risk of DKA	High	Low initially but high once insulin-deficient	Low but euglycaemic DKA is a rare side-effect of SGLT2 inhibitors. See What next after metformin?	Low	Low	Low but hypoglycaemia is common and can be prolonged

AD=autosomal dominant; AR=autosomal recessive; CF=cystic fibrosis; DKA=diabetic ketoacidosis; FH=family history; FPG=fasting plasma glucose; GDM=gestational diabetes mellitus; IR=insulin resistance; LADA=latent autoimmune diabetes in adults; MODY=maturity onset diabetes of the young; OGTT=oral glucose tolerance test; PEI=pancreatic exocrine insufficiency; PG=plasma glucose; RF=risk factor(s); SGLT2=sodium–glucose cotransporter-2; T1D=type 1 diabetes; T2D=type 2 diabetes

Source: **www.gpnotebookeducation.com**