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Diagnosing & Monitoring Diabetes: pitfalls and alternatives

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Points of Discussion

Review criteria for diagnosing diabetes

Understand limitations of HbA1c for diagnosing and monitoring diabetes

Discuss alternative options

Common questions

- What's the best test for diagnosing diabetes?
- There's a haemoglobin variant, can I still use HbA1c for diagnosis?
- Can't use HbA1c, can I use fructosamine?

Diagnosis of diabetes

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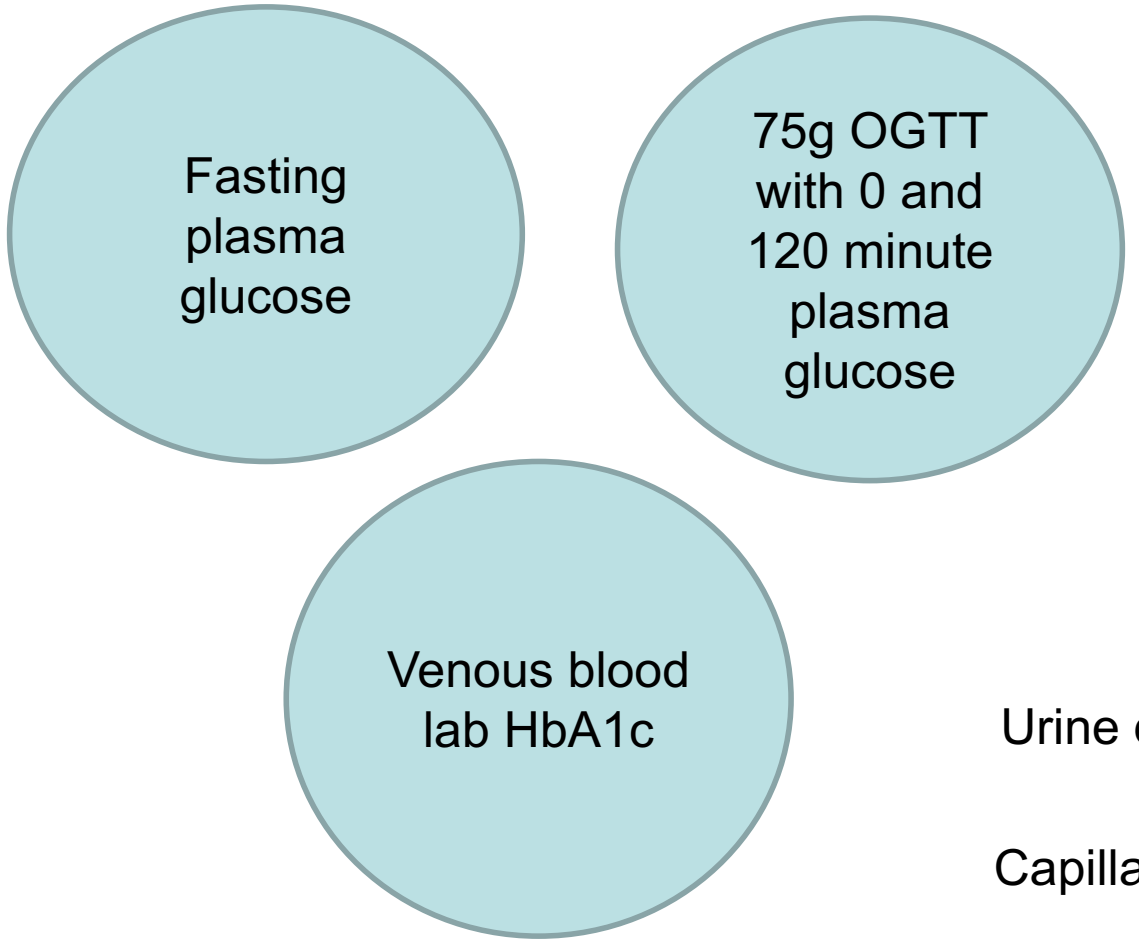

Urine dipstick ✗

Capillary BG ✗

Considerations

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- Biological variability
- Sample stability
- Cost
- Convenience
- Preparation
- Potential interferents
- Type of diabetes
- Age of patient

2011 WHO guidance

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HbA1c can be used for diagnosis of type 2 diabetes

Advantages:

- No specific preparation
- Low biological variability

Disadvantages:

- More expensive than glucose
- Surrogate marker and susceptible to interferences

Mixing testing modalities

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Glucose and HbA1c measure different things

Fasting glucose: level of glucose after an overnight fast

1) Exercise
2) Pre-analytical handling
3) Meal type

HbA1c:

1) glucose exposure
2) red cell turnover

It’s not surprising that there can be discordance
Best not to mix modalities

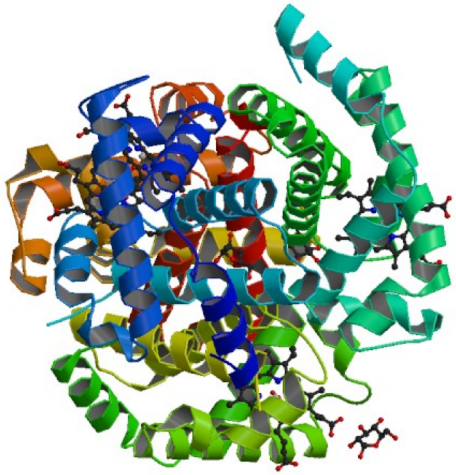
Which is the best test?

- There isn’t a best test
- They identify different subsets of people with diabetes at different time points

Glycated Haemoglobin

- Hb A (2α & 2β) 97%
- Hb F (2α & 2γ)
- Hb A2 (2α & 2δ)

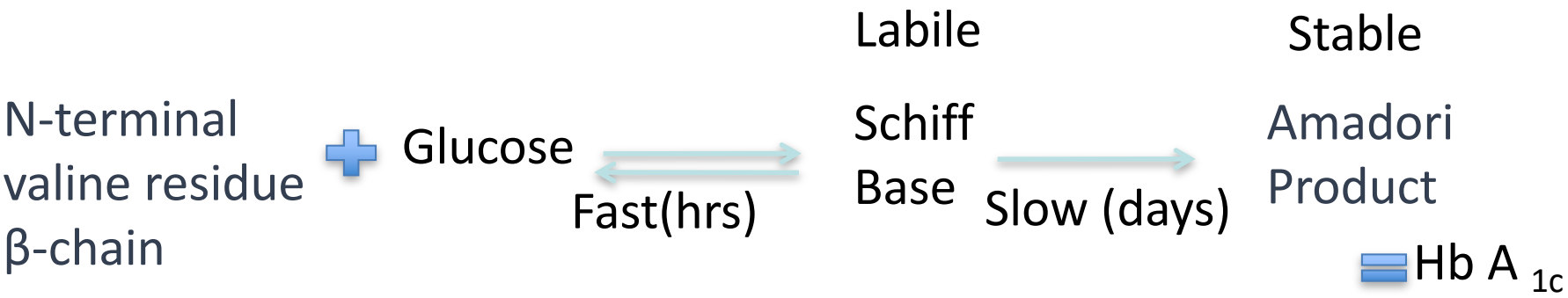
Allen 1958 / McDonald 1978	Hb A_{1a1}	Fructose 1,6 diphosphate	~0.2%
	Hb A_{1a2}	Glucose - 6 – phosphate	~0.2%
	Hb A_{1b}	Pyruvic acid	~0.4%
	Hb A_{1c}	Glucose	~ 5%



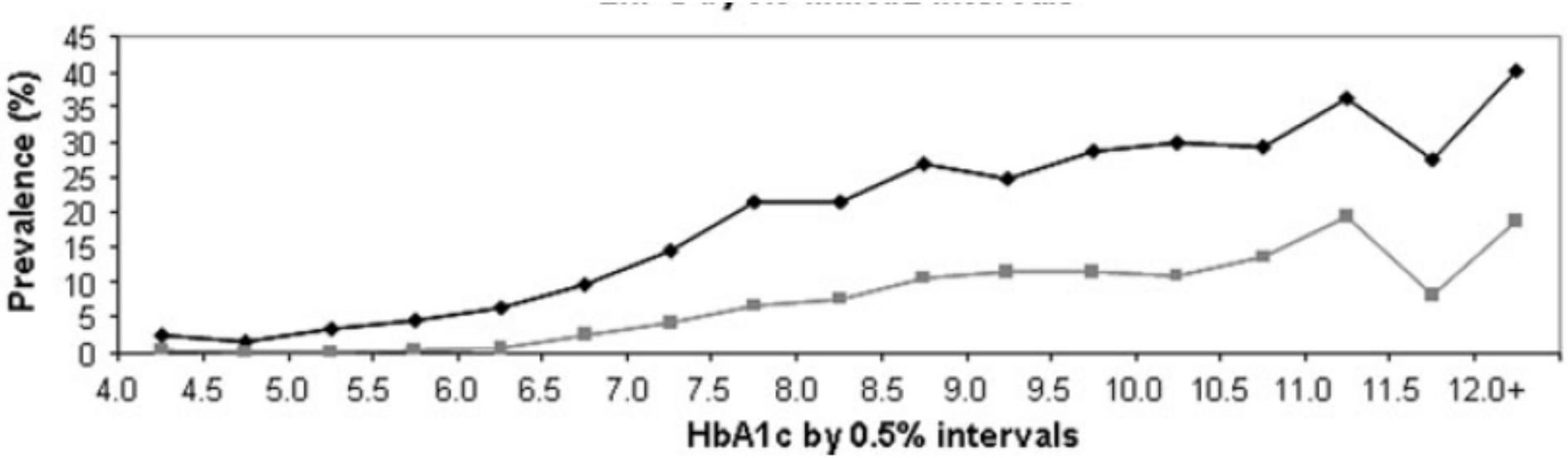
HbA_{1c}

- Reflect last 3 months of glycaemia
- Biased to the 30 days preceding measurement

- Glycated NOT glycosylated (enzymatic)
- Therefore linear relationship
- Irreversible reaction



DETECT-2 Study



The role of HbA1c

Monitoring of any type of diabetes	Every 3 months
Diagnosis of type 2 diabetes	≥48 mmol/mol + symptoms or ≥48 mmol/mol on 2 occasions
Identification of non-diabetic hyperglycaemia	42-47 mmol/mol

Changing role of HbA1c

Biomarker

↓

'Trend'

↓

In context of clinical picture
Interpretation
Alert to discrepancy

Diagnostic Test

↓

'Cut-offs'

↓

Absolute value
One-off
Discrepancy not always apparent

What interferes with HbA1c?

- Anything that affects red cell turnover

1. Erythropoiesis Increased HbA1c: iron, vitamin B12 deficiency, decreased erythropoiesis. Decreased HbA1c: administration of erythropoietin, iron, vitamin B12, reticulocytosis, chronic liver disease.
2. Altered Haemoglobin Genetic or chemical alterations in haemoglobin: haemoglobinopathies, HbF, methaemoglobin, may increase or decrease HbA1c.
3. Glycation Increased HbA1c: alcoholism, chronic renal failure, decreased intra-erythrocyte pH. Decreased HbA1c: aspirin, vitamin C and E, certain haemoglobinopathies, increased intra-erythrocyte pH. Variable HbA1c: genetic determinants.
4. Erythrocyte destruction Increased HbA1c: increased erythrocyte life span: Splenectomy. Decreased A1c: decreased erythrocyte life span: haemoglobinopathies, splenomegaly, rheumatoid arthritis or drugs such as antiretrovirals, ribavirin and dapsone.

WHO HbA1c, 2011

Interferences

- *In vivo*
  - The HbA1c level is affected **in the body**, leading to a higher or lower level that does not accurately reflect true glycaemia

- *In vitro*
  - The HbA1c level is affected **during the measurement process**, which leads to a higher or lower level that does not accurately reflect true glycaemia

Hb Variants

- >1200 haemoglobin variants
- Frequency
  - Common
    - HbS, HbC, HbD
  - Rare
    - Hb Camperdown, Hb Woolwich, Hb Sherwood Forest etc.
- Affect red cell turnover
  - Some affect
    - HbS or Hb C etc
  - Silent
    - No **known** affect on red cell turnover
    - (Most not studied)

Type of variants

- Hb XX or Hb XZ:
  - homozygote of compound heterozygote
  - No HbA present
- HbAX
  - Heterozygous
  - HbA present + HbX
- HbA + other problem

- The patient does not make HbA

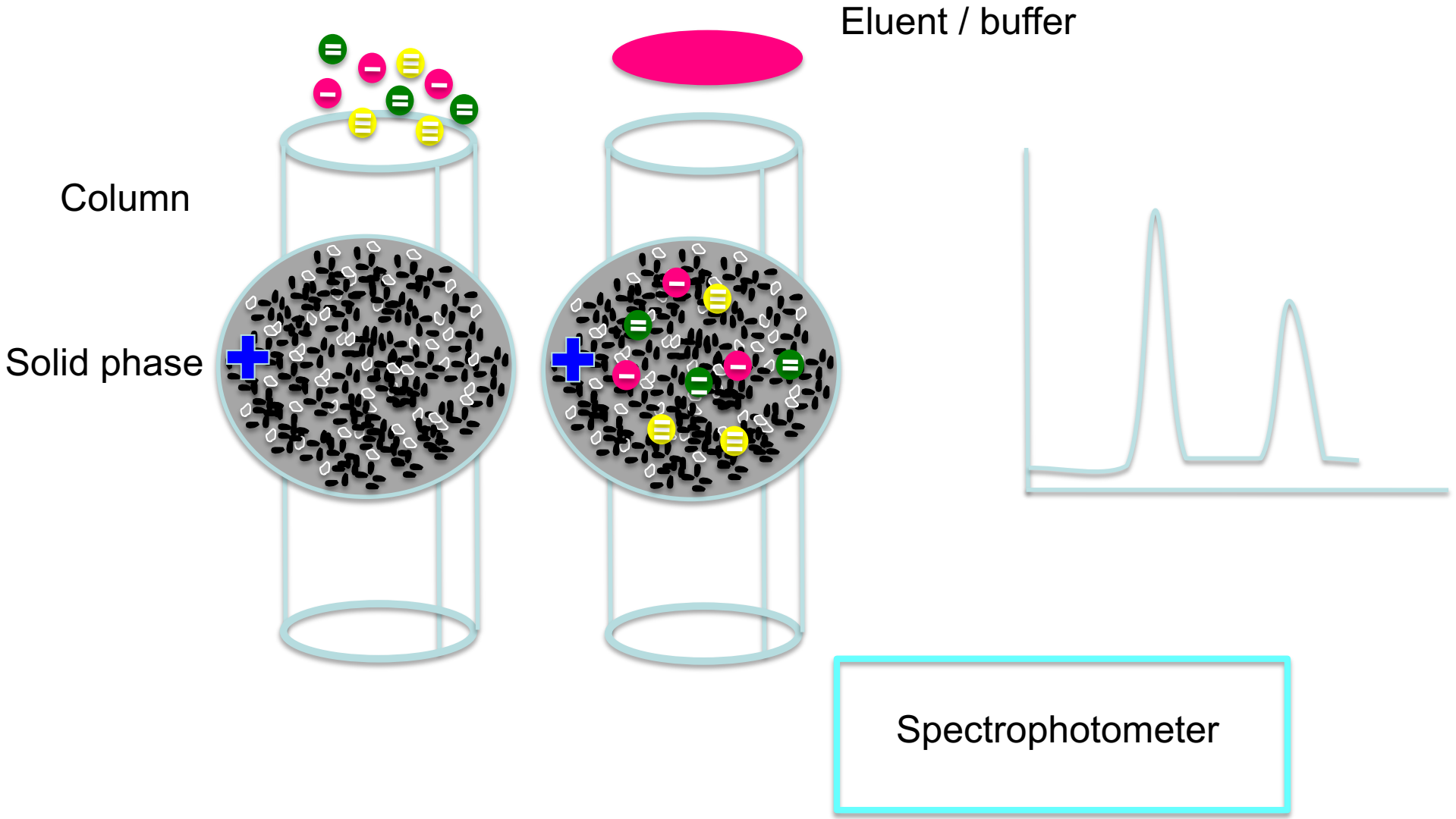
- If a person is a homozygote for a particular Hb variant e.g. Hb SS
  - They will not make HbA1c
  - They will theoretically make HbS1c
- If a person is a compound heterozygote for a particular Hb variant e.g. Hb SC
  - They will not make HbA1c
  - They will theoretically make HbS1c and HbC1c

- Requesting an HbA1c in a homozygote or compound heterozygote at NWLP:
  - would not be able to provide a result, as no HbA1c is generated
  - There is no value in measuring the glycated variant
  - But, if you've worked somewhere else you may have received a result in the past
    - Why the discrepancy?
    - Who is right?

Our method

- Tosoh G8
- Anion exchange HPLC
- Very specifically only identifies HbA1c

Anion exchange chromotography



Other methods

- Some methods
  - Don’t identify the presence of Hb variants
  - Don’t specifically measure HbA1c, but instead identify any Hb with glucose attached (glycohaemoglobin)
  - Marketed as *‘not susceptible to interference from Hb variants’*

Which is better?

- Our expert opinion
  - It's better to know about potential Hb variants that can affect red cell turnover than to fly blind
  - We **do not** advocate measuring glycohaemoglobin in these situations as the result is meaningless
    - **It is unknown if glycated variants have the same relationship with microvascular complications**
    - **A falsely high or low result may result in erroneous management decisions**

- Patient is a heterozygote for a particular Hb variant:

Key question

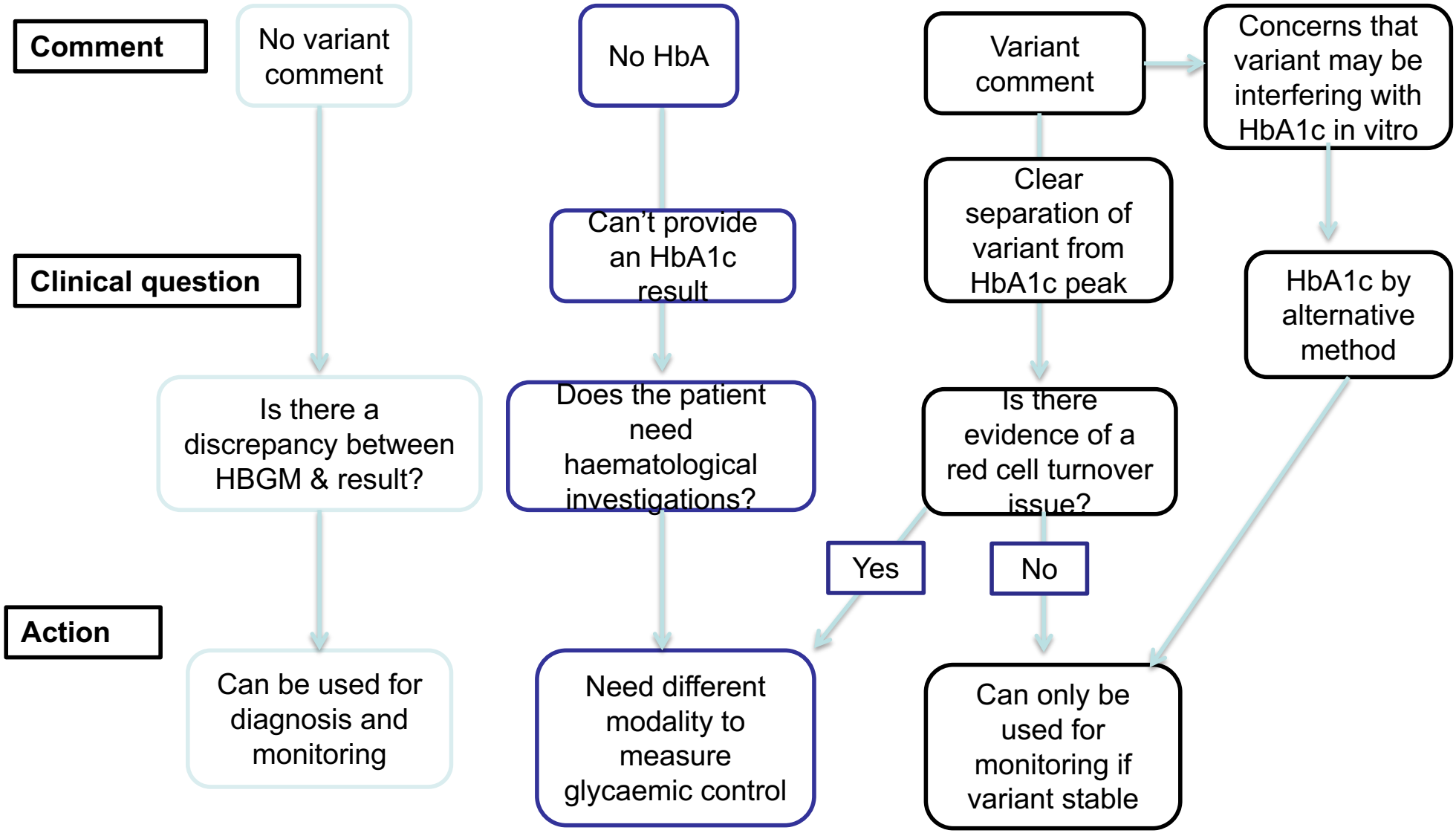
- In most cases of heterozygotes for a particular variant, we can issue an HbA1c result.

- However, is this HbA1c an accurate measure of glycaemia?
  - Is there abnormal red cell turnover?
  - Is there a discrepancy between HbA1c and blood glucose monitoring?

- There may be inaccuracies in HbA1c levels in the presence of a variant
  - Therefore NOT to be used for diagnosis as cannot be confident of absolute values
  - Assuming variant stable, can be used for monitoring of diabetes

- Hb A + Other

- High HbF
  - may signify abnormal red cell turnover
  - we flag and do not report HbA1c in these situations
- Other abnormal peaks detected
  - we may corroborate the result using an alternative method


Comment
Clinical question
Action
No variant comment
Is there a discrepancy between HBGM & result?
Can be used for diagnosis and monitoring
No HbA
Can't provide an HbA1c result
Does the patient need haematological investigations?
Need different modality to measure glycaemic control
Variant comment
Concerns that variant may be interfering with HbA1c in vitro
Clear separation of variant from HbA1c peak
HbA1c by alternative method
Is there evidence of a red cell turnover issue?
Yes
No
Can only be used for monitoring if variant stable

Alternatives to HbA1c

- Monitoring
  - Home blood glucose monitoring
    - 7-point profile gives a good indication of control in most individuals
  - Continuous glucose monitoring
    - in more complex cases, e.g. insulin treated, referral to a Diabetologist for CGM may be warranted (ICHNT team happy to receive referrals)

- We do not advocate measurement of fructosamine
  - it is not validated as a measure of glycaemia i.e. we do not know what the target should be
  - it is affected by CKD and proteinuria
  - assays are imprecise

Alternatives to HbA1c

- Diagnosis
  - 2 hour- OGTT
  - fasting glucose
- Monitoring
  - 7 point home blood glucose monitoring
  - Some specialists might consider CGM

Low HbA1c

- HbA1c <20 mmol/mol

- Almost certainly indicates abnormal red cell turnover

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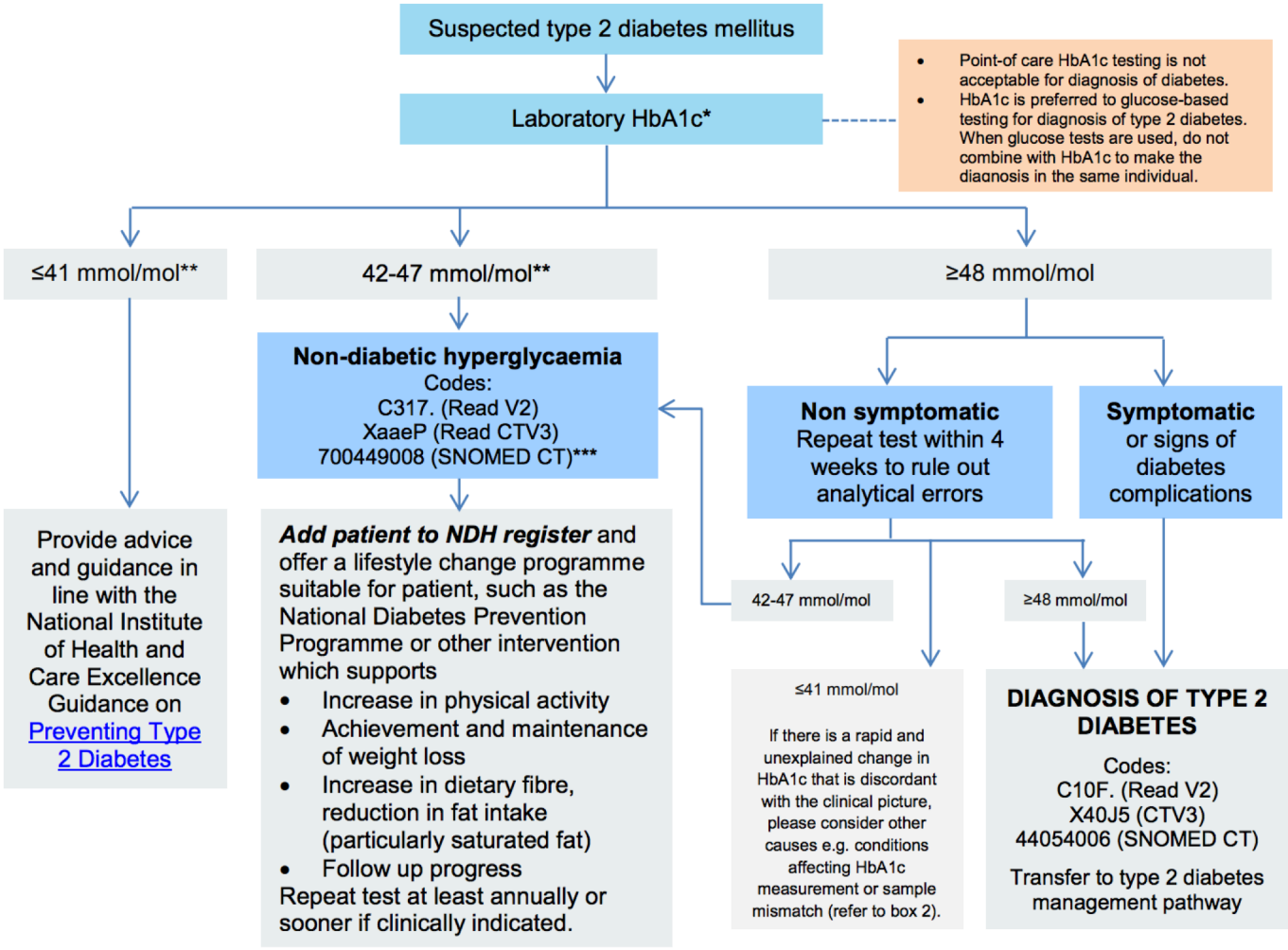
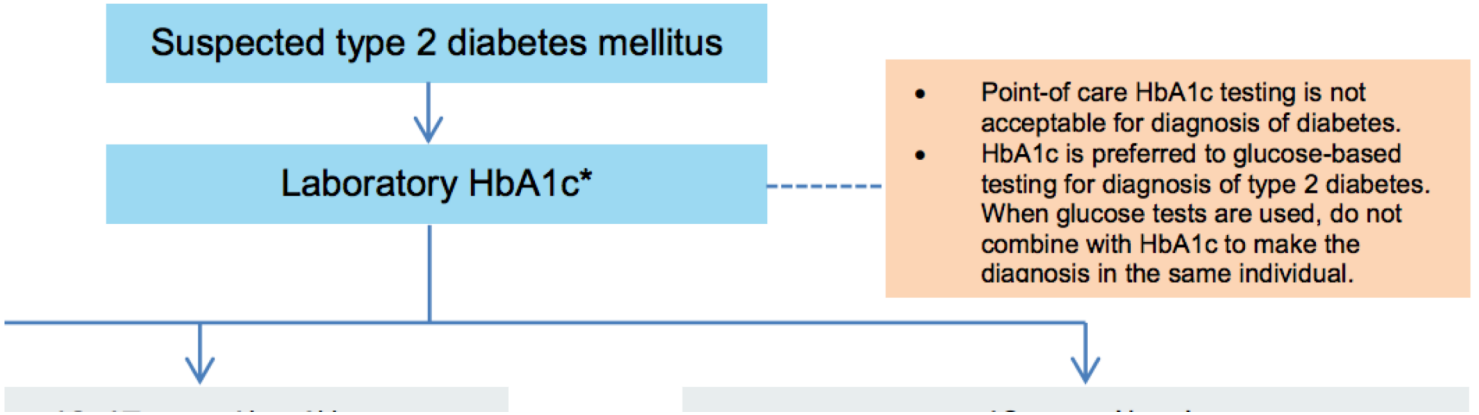
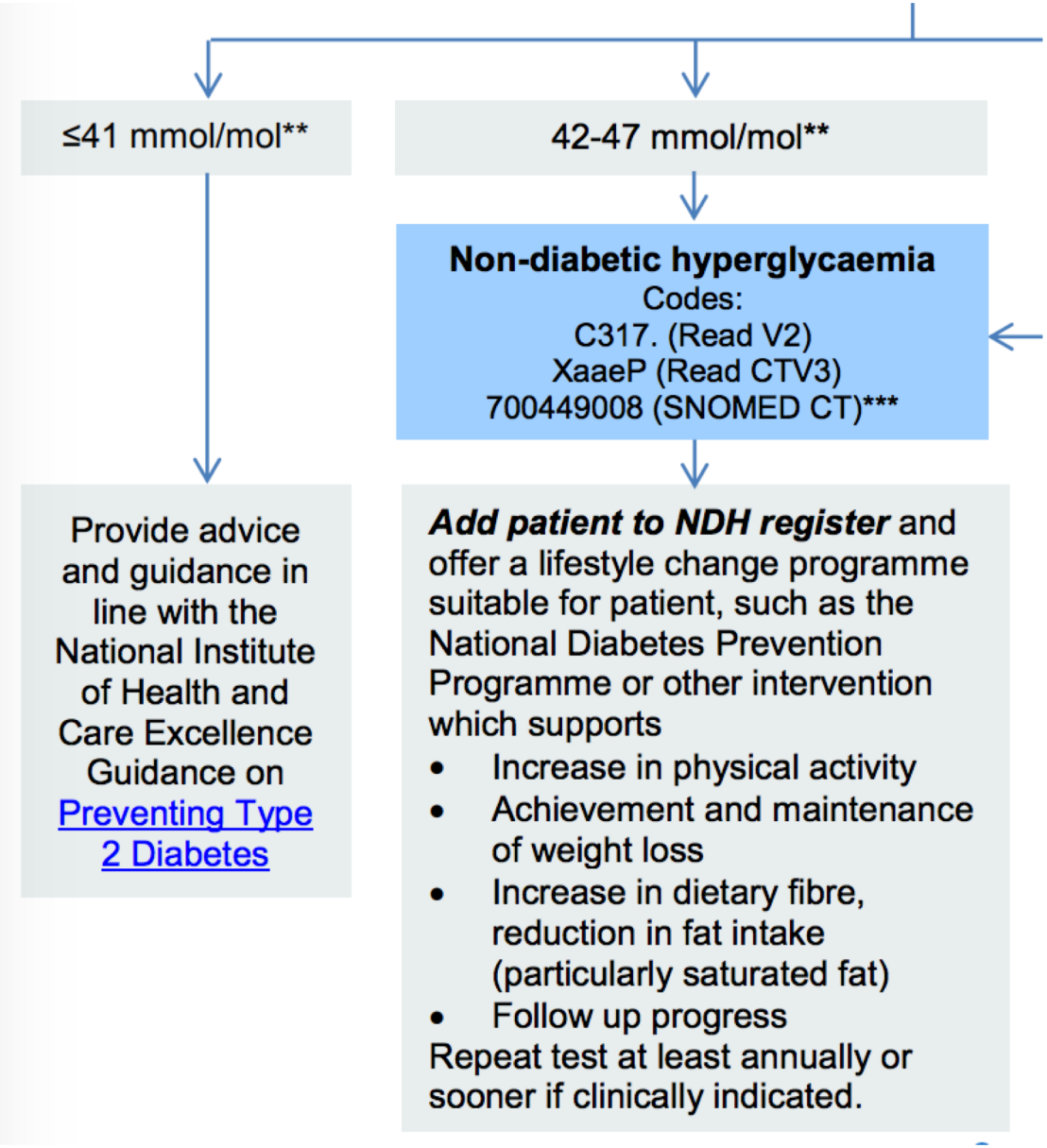
Flowchart - Recommended cut off points for diagnosis of type 2 diabetes mellitus using HbA1c and interventions[1,2,4,10,13]

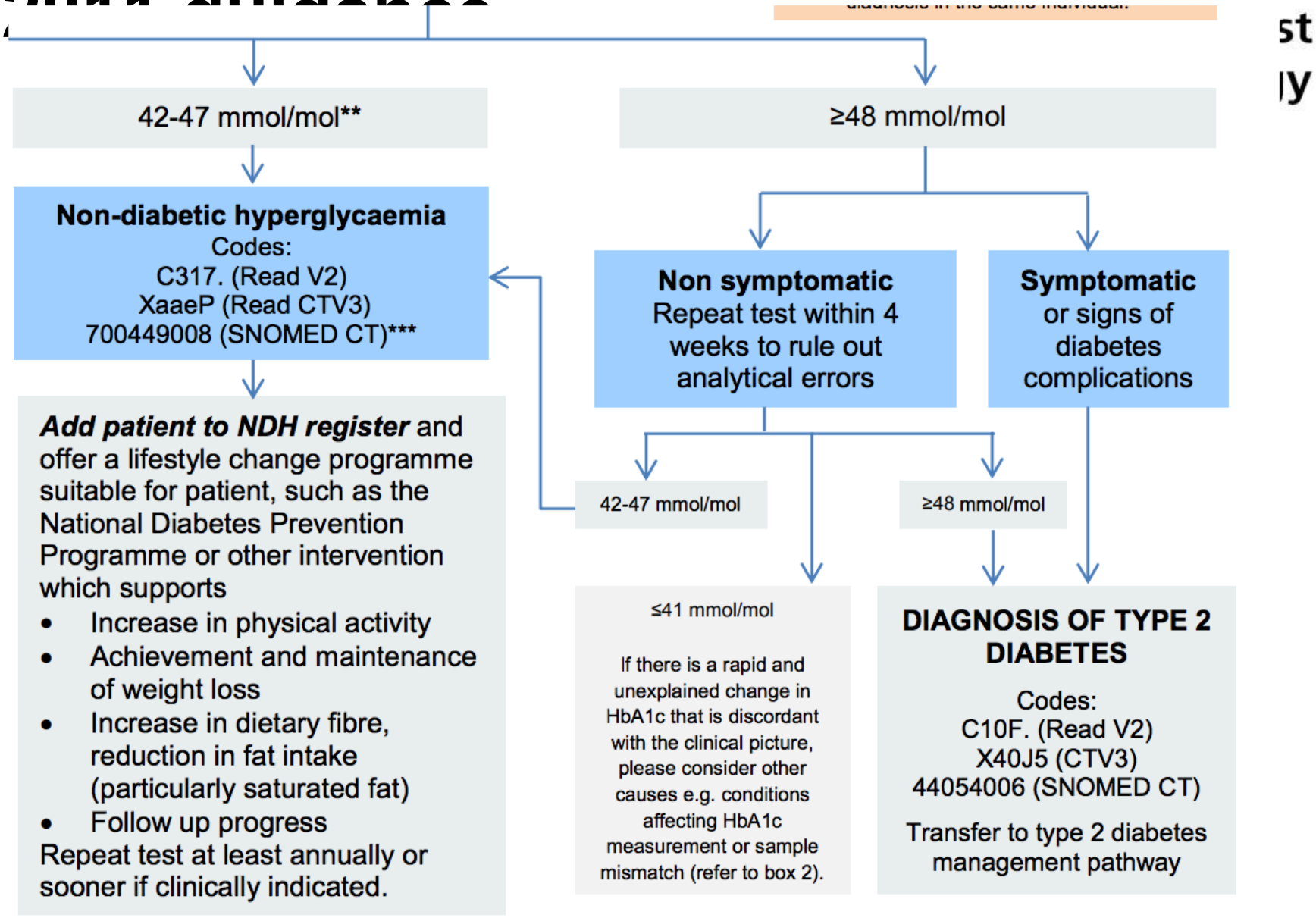


nended cut off points for diagnosis of type 2 diabetes
lc and interventions[1,2,4,10,13]

Clinical Network




≤41 mmol/mol**
42-47 mmol/mol**
Non-diabetic hyperglycaemia
Codes:
C317. (Read V2)
XaaeP (Read CTV3)
700449008 (SNOMED CT)***
Provide advice and guidance in line with the National Institute of Health and Care Excellence Guidance on Preventing Type 2 Diabetes
Add patient to NDH register and offer a lifestyle change programme suitable for patient, such as the National Diabetes Prevention Programme or other intervention which supports
• Increase in physical activity
• Achievement and maintenance of weight loss
• Increase in dietary fibre, reduction in fat intake (particularly saturated fat)
• Follow up progress
Repeat test at least annually or sooner if clinically indicated.


42-47 mmol/mol**
≥48 mmol/mol
Non-diabetic hyperglycaemia
Codes:
C317. (Read V2)
XaaeP (Read CTV3)
700449008 (SNOMED CT)***
Non symptomatic
Repeat test within 4 weeks to rule out analytical errors
Symptomatic
or signs of diabetes complications
Add patient to NDH register and offer a lifestyle change programme suitable for patient, such as the National Diabetes Prevention Programme or other intervention which supports
• Increase in physical activity
• Achievement and maintenance of weight loss
• Increase in dietary fibre, reduction in fat intake (particularly saturated fat)
• Follow up progress
Repeat test at least annually or sooner if clinically indicated.
42-47 mmol/mol
≥48 mmol/mol
≤41 mmol/mol
If there is a rapid and unexplained change in HbA1c that is discordant with the clinical picture, please consider other causes e.g. conditions affecting HbA1c measurement or sample mismatch (refer to box 2).
DIAGNOSIS OF TYPE 2 DIABETES
Codes:
C10F. (Read V2)
X40J5 (CTV3)
44054006 (SNOMED CT)
Transfer to type 2 diabetes management pathway

*BOX 1 & 2: Exclusions to using HbA1c for diagnosis of type 2 diabetes mellitus (glucose based diagnosis required)[1,3,12,14]	
BOX 1 **URGENT BLOOD GLUCOSE BASED TESTING REQUIRED**	• Suspected type 1 diabetes, (all ages) • Short (<2 months)/rapid onset of diabetes symptoms • Patients at high diabetes risk who are acutely ill (e.g. those requiring hospital admission) • Acute pancreatic damage or pancreatic surgery • All children and young people up to the age of 30 years old • Patients taking medication that may cause rapid glucose rise e.g. corticosteroids, antipsychotic drugs (2 months or less)

BOX 2
BLOOD GLUCOSE BASED TESTING REQUIRED
	• Pregnancy (current or recent <2months)
	• Haematological factors
	  ○ Anaemia – haemolytic and iron deficiency
	  ○ Haemoglobinopathies
	• Renal failure (CKD Stage 3b and above)
	• Human Immunodeficiency Virus (HIV) infection
	• Presence of genetic, haematologic and illness-related factors that influence HbA1c and its measurement.
	• Factors affecting the life span of red cells - recent commencement of erythropoietin therapy will result in a decrease in HbA1c as will occur with some haemoglobinopathies, splenomegaly, rheumatoid arthritis or with drugs such as antiretrovirals, ribavirin and dapsone. Increased erythrocyte lifespan e.g. in splenectomy may increase HbA1c levels

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Any questions,
feedback or comments?