Type 1, 2 or something else? Getting the diagnosis (and treatment) right

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Declarations/conflicts of interest

- I have an honorary contract with Royal Devon and Exeter Hospital which provides NHS C-peptide and islet antibody testing
- I have no other conflict of interest

Edith

New diabetes diagnosed aged 65

- BMI 23
- Thirst, polyuria, weight loss,
- Capillary ketones 1.1 (slightly raised)

- Glucose 24, HbA1c 90mmol/mol

- Type 1 or 2 diabetes?

Definitions of diabetes subtypes are (mainly) based on aetiology

Type 1

- Autoimmune beta cell destruction usually leading to severe insulin deficiency
- Idiopathic severe insulin deficiency

Other

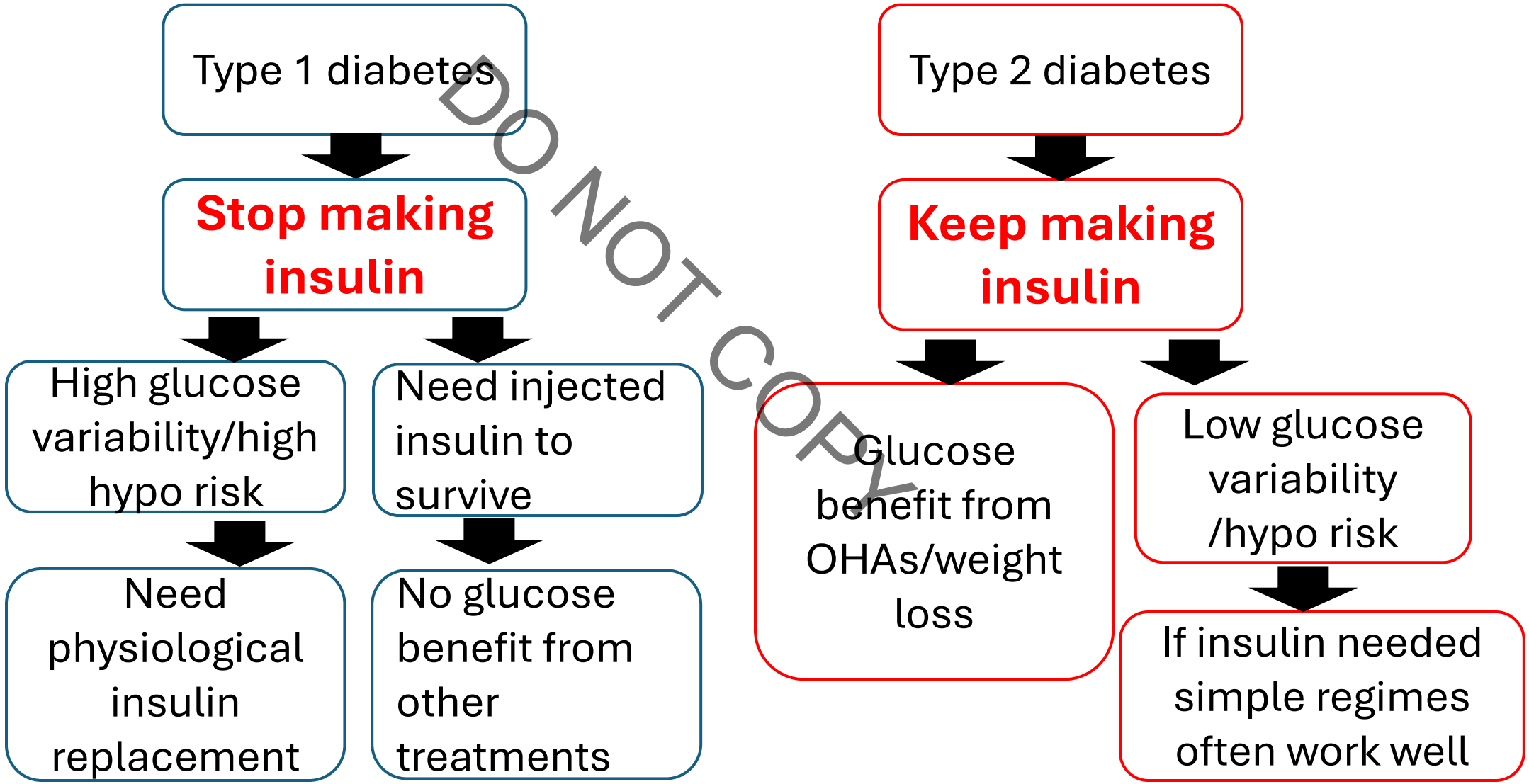
- Other specific non-autoimmune cause
  - E.g. MODY (genetic), Type 3c (pancreatic damage)

Type 2

Make insulin, but not enough

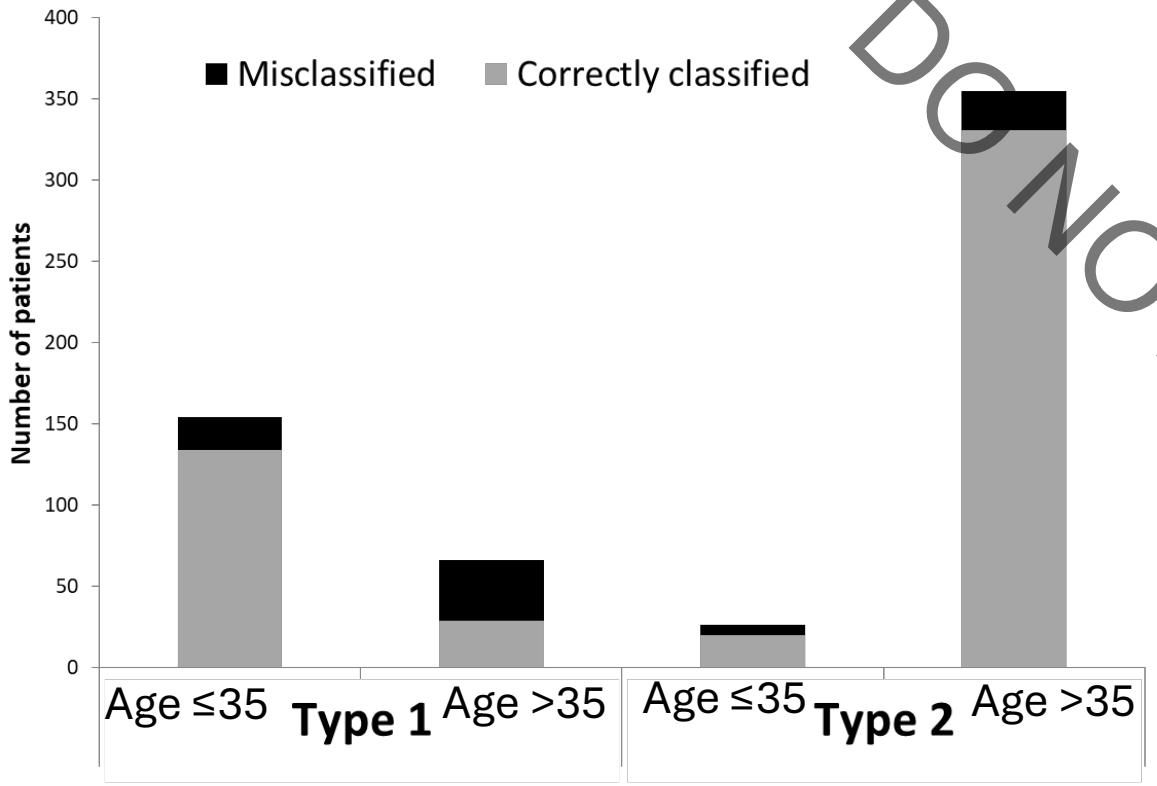
Varying degrees of insulin resistance

Differences in treatment requirements are mainly due to differences in insulin secretion

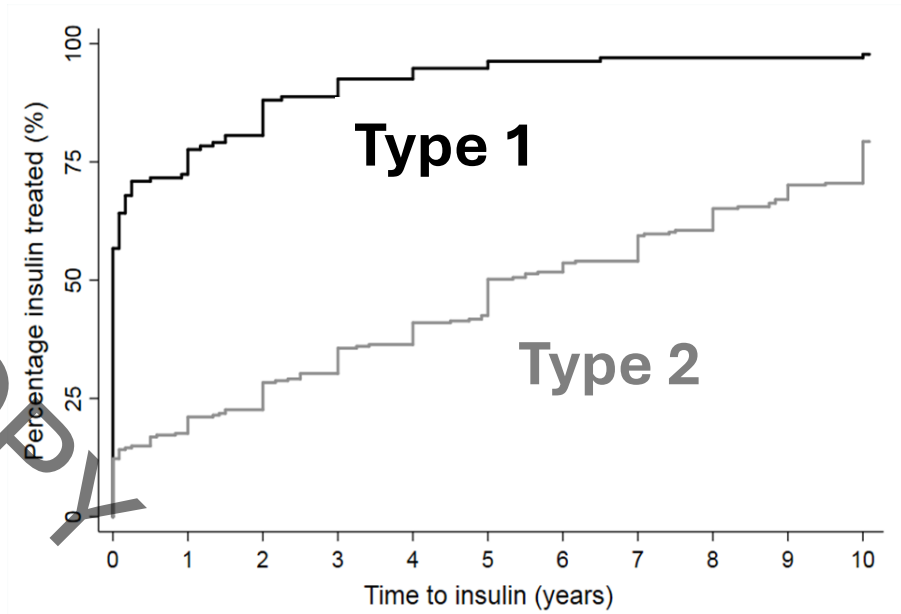


Misclassification of diabetes is common

Those diagnosed and treated as T1D often do not have this condition



40% of those with definite type 1 diabetes after age 30 are initially diagnosed and treated as type 2



Hope et al
BJGP 2015
PMID 27080317

Thomas et al
Diabetologia 2019
PMID 30969375

What happens if we get the diagnosis wrong?

Type 1 misdiagnosed as type 2

- **Risk of DKA**
- Rapid progression
  - Often rapid succession of unsuccessful OHAs
- Poor control
  - Ongoing weight loss/symptoms
- If insulin treated wrong type and education
  - No/late Carb Counting/CGM (e.g. Libre)/Pumps/basal bolus

Type 2 misdiagnosed as Type 1

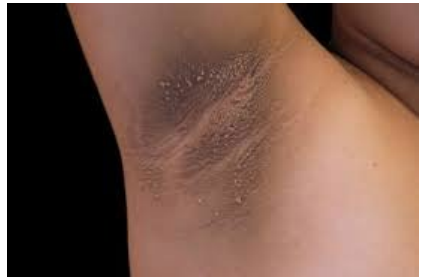
- Unnecessary insulin
  - Injections/weight gain/cost
- Unnecessary monitoring
- Unnecessary/inappropriate education (DAPHNE etc)
- Miss out on other effective therapies

Other subtypes missed

Miss specific treatment, family screening (Monogenic), monitoring

Clinical features and diabetes classification

Characteristic	Type 1	Type 2
Age of onset	Children and young adults?	Later life (but can occur from puberty)
Obesity	Population frequency	Increased frequency
Clinical presentation	Often acute, rapid	Variable; from slow, mild (often insidious) to severe
Ketosis	Common	Uncommon?
Acanthosis nigricans	No association	Increased frequency
Autoimmunity	Increased frequency	Population frequency
Parent with diabetes	2–4%	80% if young onset
Race	Highest prevalence White Northern Europeans	Highest Prevalence non white



Acanthosis

Adapted from Craig 2009 (ISPAD consensus guidelines)

What feature is most helpful in differentiating Type 1 and Type 2 diabetes?

A. Age of diagnosis
B. BMI
C. Severity of symptoms
D. Presence/absence of Ketones

Which clinical feature is the best predictor of diabetes subtype?

At diagnosis	Age	Best in 7/9 studies
	BMI	Best in 1/8 studies
	Ketones	Not discriminatory (2 studies)
	Onset	Not discriminatory (1 study)
After diagnosis	Early insulin requirement	Best in 2/7 studies

Age of diagnosis is the strongest clinical indicator of subtype of diabetes

Systematic review of utility of clinical features in diagnosis of diabetes subtype (*Shields et al 2015 BMJ Open*)

The utility of clinical features for identifying adult-onset type 1 diabetes at diagnosis: evidence from the STARTRIGHT Study

Feature (cut off for sens/spec)	AUC ROC	Sensitivity (T1D)	Specificity (T1D)
BMI (<25 kg/m^2) (waist circumference similar)	0.82	47%	93%
Unintentional weight loss	0.78	80%	75%
Presentation HbA1c (>115mmol/mol) (glucose similar)	0.74	36%	87%
Osmotic symptoms	0.64	93%	34%
Absence of hypertension	0.63	90%	35%
Presentation DKA	0.61	30%	93%
Parental Autoimmune disease	0.55	30%	79%
Other autoimmune disease	0.53	17%	90%
Absence of parental T2D	0.52	86%	31%

T1D= C-peptide <600pmol/L after >3 years, or ≥2 positive autoantibodies (n=566)
T2D= C-peptide ≥ 600pmol/L or no insulin after >3 years, negative autoantibodies (n=699)

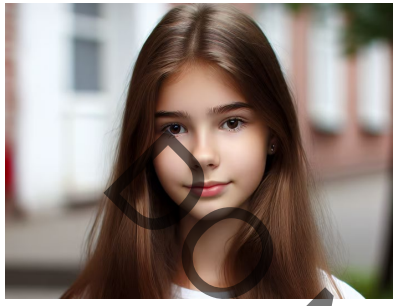
Jones et al, StartRight Study Group (Unpublished)

Diagnosing type 1 diabetes in older adults is very challenging

StartRight

Onset age 15 (~95% T1D)

T1D very likely with any associated feature (predictive value all >96%)



Onset age 65 (~1% T1D)

No single feature makes T1D likely (predictive value all <7%)

Feature (cut off, sensitivity/speceficity)	Predictive value for T1D onset age 15 (95% T1D)	Predictive value for T1D onset age 65 (1% T1D)
BMI (<25 kg/m^2, 47%/93%)	>99%	6%
Unintentional weight loss (80%/75%)	>99%	3%
Presentation HbA1c (>115mmol/mol,36%/87%)	99%	3%
Osmotic symptoms (93%/34%)	96%	1.4%
Absence of hypertension (90%/35%)	96%	1.3%
Presentation DKA (30%/93%)	>99%	5%
Other autoimmune disease (17%/90%)	97%	2%
Absence of parental T2D (86%/31%)	96%	1.2%

Jones et al, StartRight Study Group (Unpublished) *Prevalence at diagnosis derived from Scottish Diabetes Survey incidence data*

Summary: clinical features and diagnosing adult-onset type 1 diabetes

- Age of diagnosis and BMI are by far the most discriminative features

- Weight loss and high presentation glycaemia most discriminative after age of diagnosis and BMI

- In adults no single feature confirms type 1 diabetes, and diagnosis is often very challenging when features of both type 1 and 2 diabetes are present
  - many patients will need careful monitoring and/or futher investigation

Edith

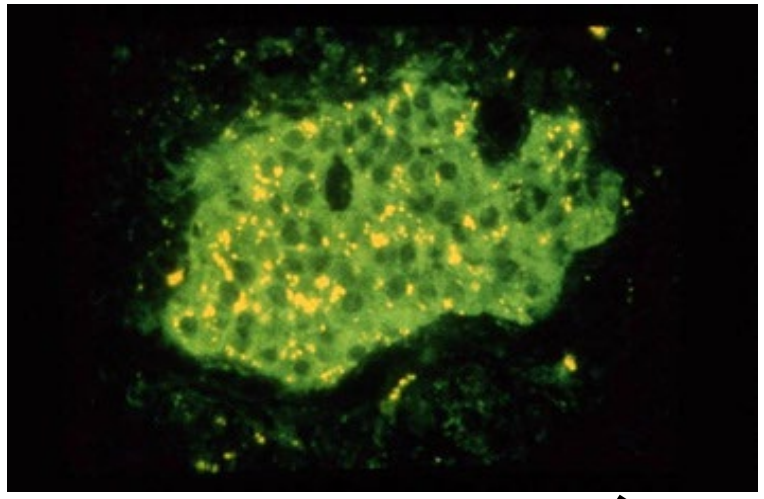
New diabetes diagnosed aged 65

- BMI 23
- Thirst, polyuria, weight loss,
- Capillary ketones 1.1
- Glucose 24, HbA1c 90mmol/mol

- What should we do?
  - Initial management
  - Investigations

Common tests to assist diabetes classification

Islet autoantibodies

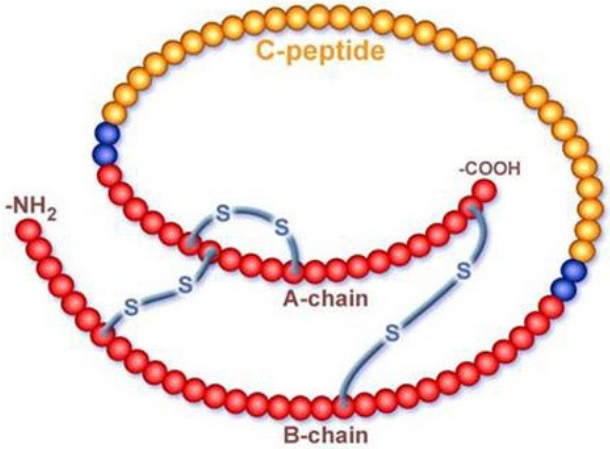


Cost ~£27

GAD65	IA-2	ZnT8	Insulin

- Marker that the immune system is attacking the cells that make insulin

C-peptide



Cost ~£10

- Marker of insulin secretion
- Produced in equal amounts to insulin
- Allows measurement of insulin secretion in those injecting insulin

The different clinical roles of islet autoantibodies and C-peptide

Islet autoantibodies

- Most helpful at/close to diagnosis (<3yr)
- Good predictor of the future (will this patient become severely insulin deficient and need treatment as type 1 diabetes?)
- Not usually helpful in longstanding diabetes (over ~3 years)
  - In longstanding diabetes antibody testing does not tell us what treatment is needed
  - Exception = looking for rare genetic diabetes (MODY)

C-peptide

- Most helpful in longstanding diabetes (>3yr)
- Poor predictor of the future
  - Only helpful at diagnosis if diagnosis is not clear after antibody testing, and C-peptide is low.
- Clinical use is identifying current treatment requirements
  - People who loose/keep their C-peptide have the treatment needs of type 1/2 diabetes

Misra Practical Diabetes 2017
Jones Hattersley Diabetic Medicine 2013 PMID 23413806

Edith

‘Type 1’ diabetes diagnosed aged 65

- BMI 23
- Thirst, polyuria, weight loss,
- 2+ ketones, not acidotic
- Glucose 24, HbA1c 90mmol/mol
- Started on insulin
- GAD positive
- IA2/ZNT8 negative

- Type 1 or 2 diabetes?
- Does the number or titre of antibodies matter?
- Management?

Edith

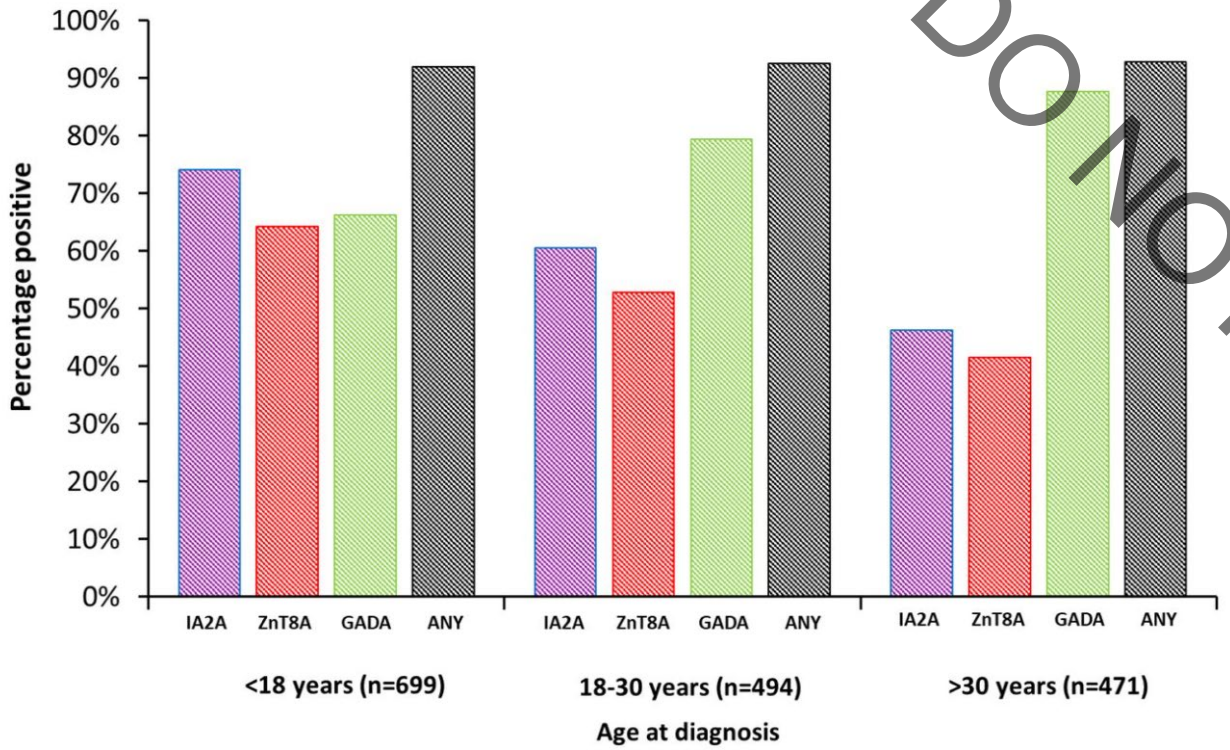
‘Type 1’ diabetes diagnosed aged 65

- BMI 23
- Thirst, polyuria, weight loss,
- 1+ ketones,
- Glucose 24, HbA1c 90mmol/mol
- Started on insulin
- GAD, IA2 and ZNt8 negative

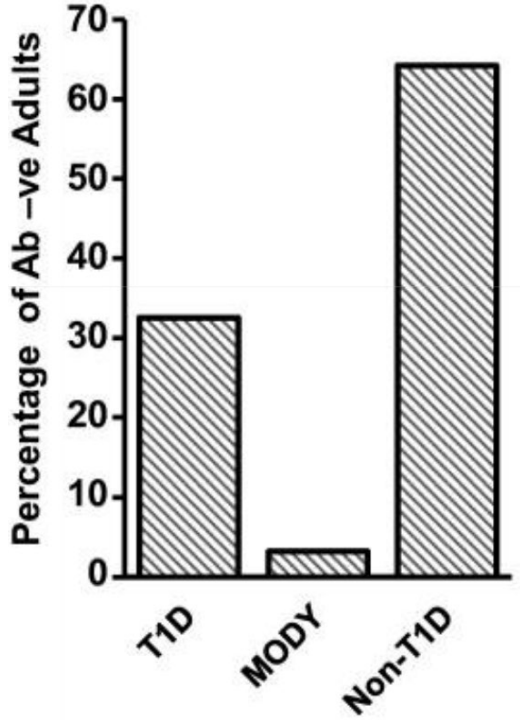
- Type 1 or 2 diabetes?
- What do we do now?

Negative islet autoantibodies do not exclude type 1 diabetes, but may make it unlikely in older adults

~2/3 adults newly diagnosed as type 1 who are antibody negative are misclassified



ADDRESS 2
Supporting TYPE 1 Diabetes Research



Thomas, Patel, ADRESS 2 Consortium Diabetologia 2022

Thomas et al, Patel Diabetologia 2022 PMID: 36355183
Eason et al Diabetes Care 2022 PMID: 36205650

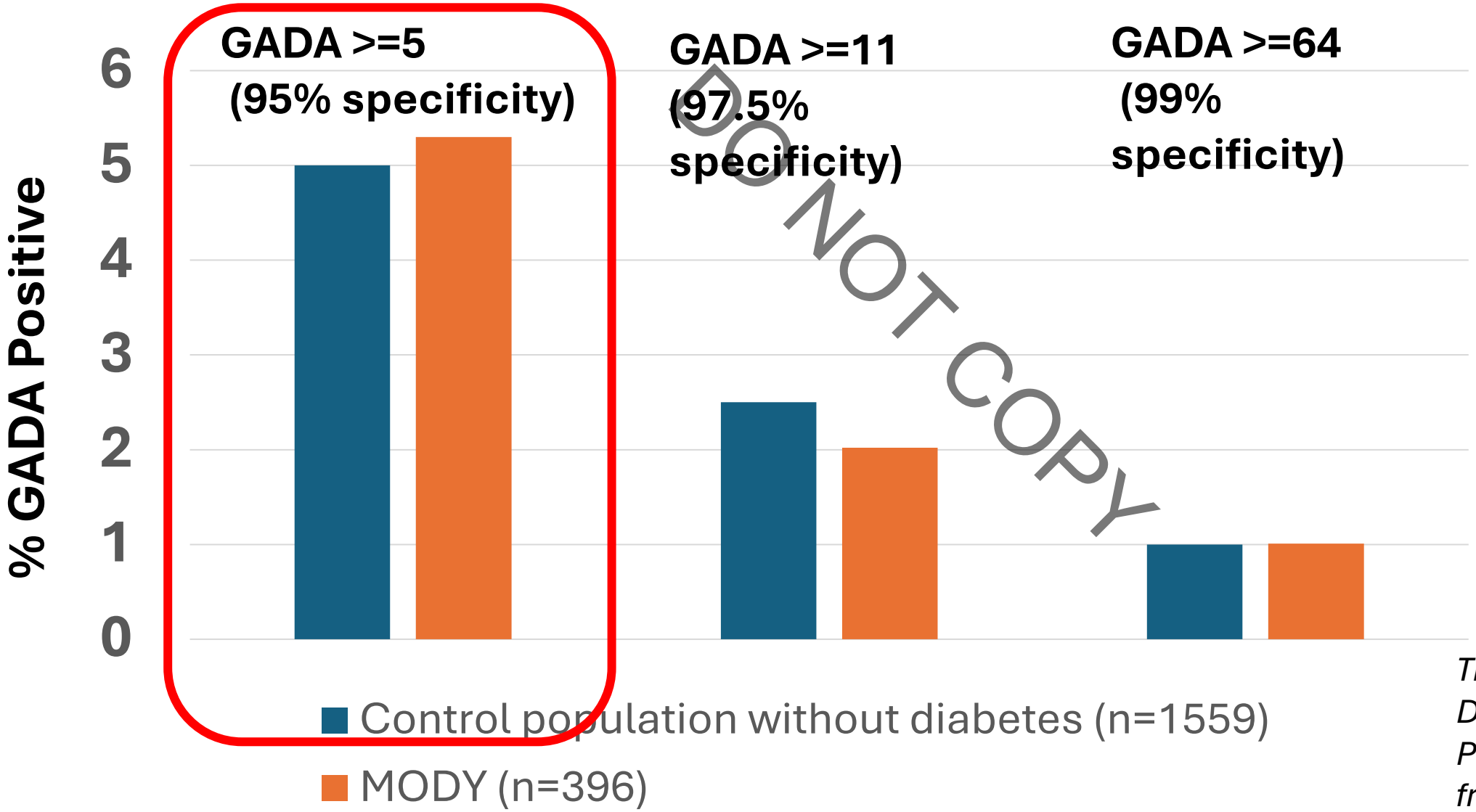
John

- 65 year old
- New diabetes
- BMI 28, mild symptoms,
- HbA1c 80mmol/mol
- GAD positive, titre 50 units (threshold 10 units)
- IA2/ZNT8 negative

- Is this autoimmune/type 1 diabetes?

Having one antibody does not necessarily mean you have autoimmune/type 1 diabetes – false positive results can occur

Manufacturer recommended threshold

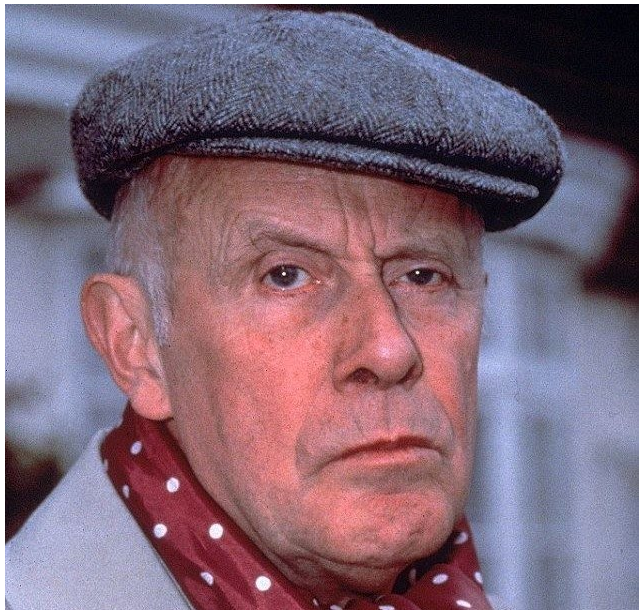


Two or more positive antibodies almost always confirm T1D (specificity >99.9%)

Thomas Jones Diabetologia 2023 PMID 37728732, Data from Tim McDonald

Interpreting a test depends on how likely it is that the person tested has the condition of interest

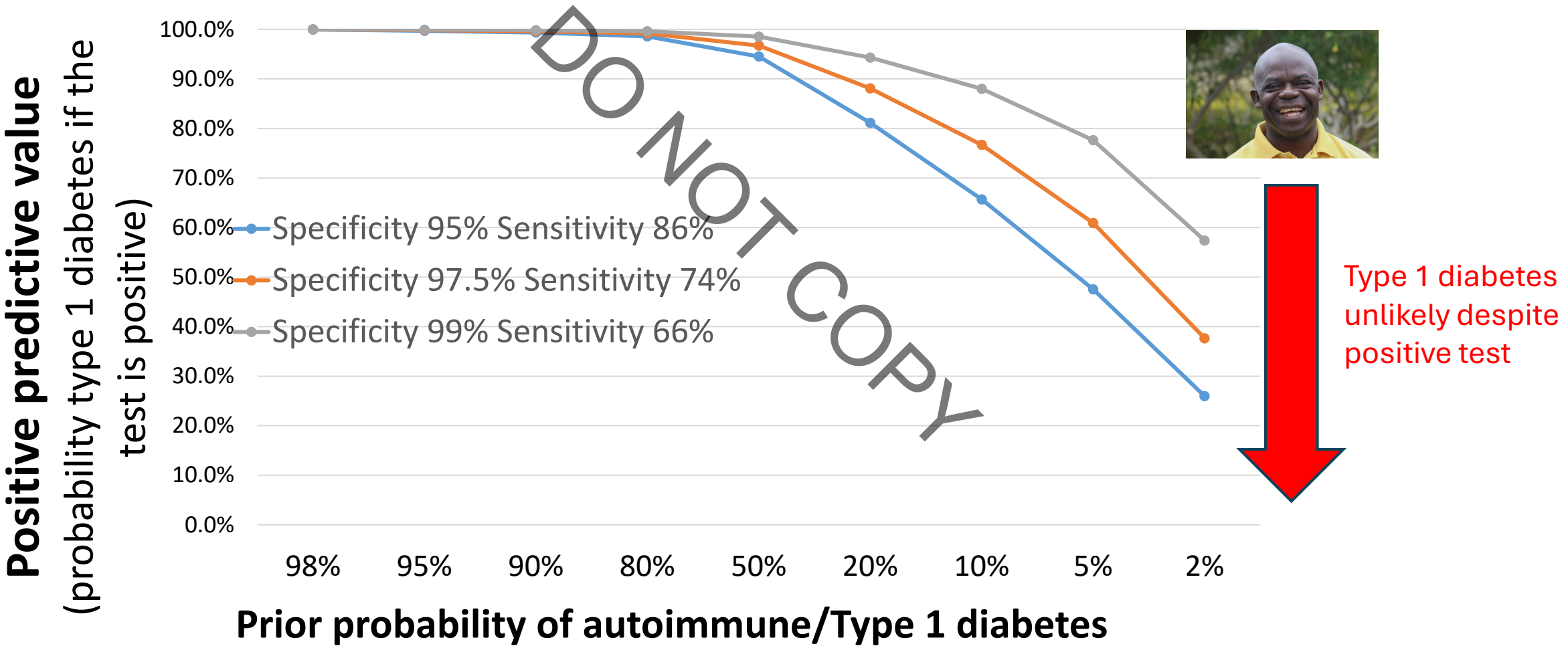
Pregnancy test:
99% specificity
99% sensitivity



- Is she pregnant?

- Is he pregnant?

Do not test islet antibodies in people who do not have clinical features suggestive of type 1 diabetes – misleading results may be common



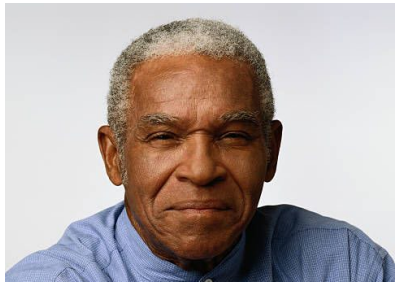
Jones et al Diabetes Care 2021 PMID 34016607

John

- 65 year old
- New diabetes
- BMI 28, mild symptoms,
- HbA1c 80mmol/mol
- GAD positive, titre 50 units (threshold 10 units)
- IA2/ZNT8 negative

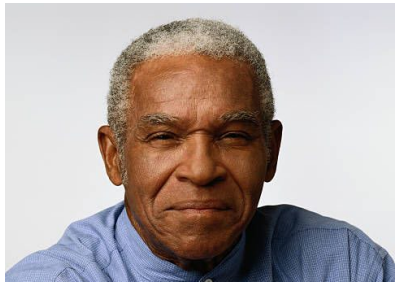
- What do we do? (and would you diagnose ‘LADA’?)

Barry



- 65 year old
- New diabetes
- BMI 28, mild symptoms,
- HbA1c 80mmol/mol
- Diagnosed as type 2, initial treatment with metformin and lifestyle
- Rapid progression, 3 agents, glucose 20, HbA1c 110mmol/mol after 18 months

Barry

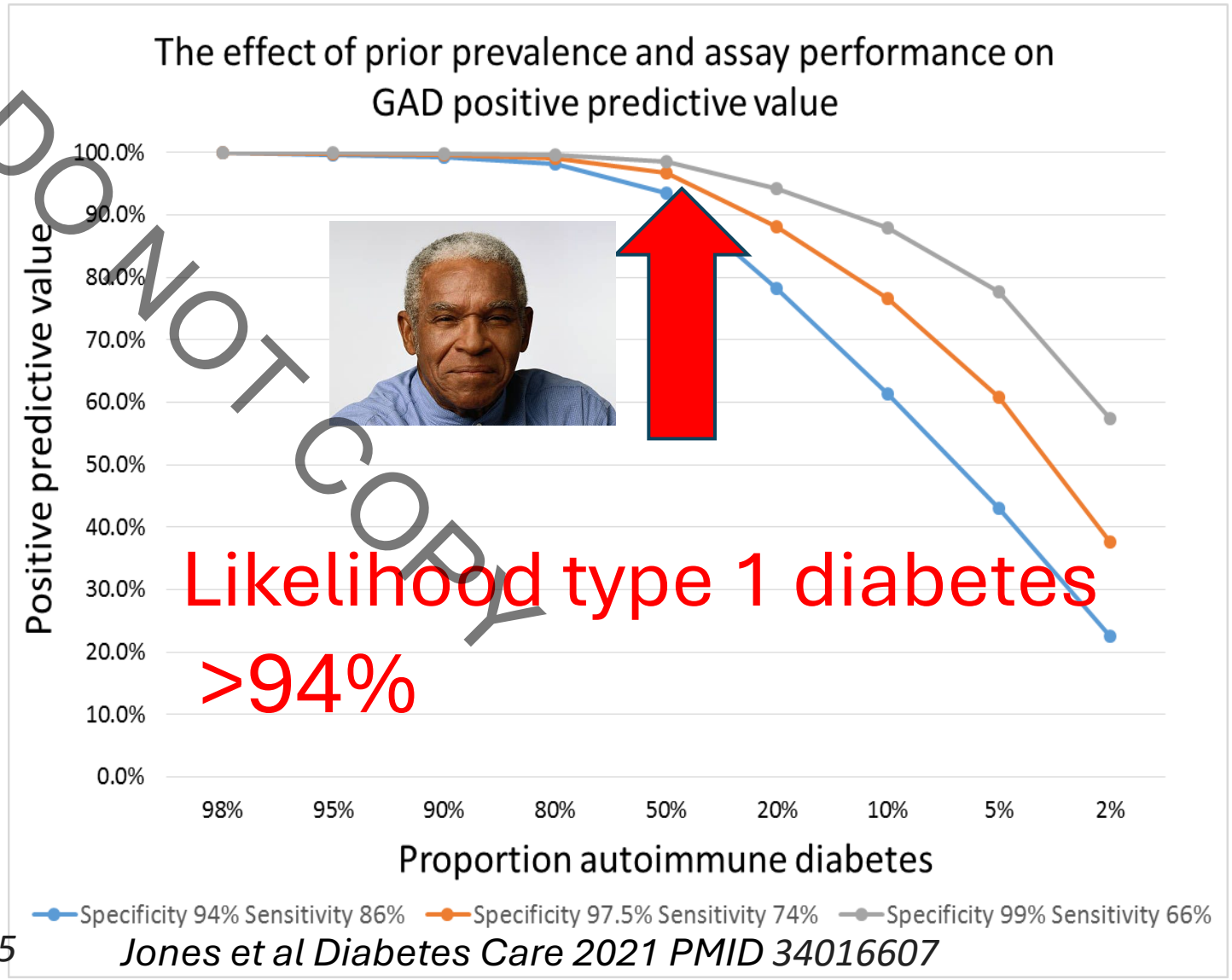


- 65 year old
- New diabetes
- BMI 28, mild symptoms,
- HbA1c 80mmol/mol
- Initial treatment with metformin and lifestyle
- Rapid progression, 3 agents, glucose 20, HbA1c 110mmol/mol after 18 months
- GAD positive, IA2/Znt8 negative
- Does Barry have type 1 diabetes?

Test antibodies in all ‘Type 2’ who rapidly progress to insulin (<3 years): one or more positive usually confirms type 1 diabetes

Positive predictive value of progression to insulin < 3 years:

47%



Likelihood type 1 diabetes >94%

Thomas et al Diabetologia 2019 PMID 30969375

Jones et al Diabetes Care 2021 PMID 34016607

Summary: Autoantibodies in diabetes classification

- Test at diagnosis in all suspected Type 1 diabetes
  - EASD/ADA & NICE guidelines advise routine testing at diagnosis in all adult onset suspected T1D (including rapid insulin progression in apparent T2D)

- A positive islet antibody in the setting of suspected Type 1 diabetes (or 'T2D' and rapid progression) will usually confirm T1D.
  - 2+ antibodies confirms T1D regardless of the clinical setting

- While negative islet autoantibodies do not exclude Type 1 diabetes, other diagnoses should be strongly considered
  - Especially in older adults

Note: there is almost never any point repeating antibodies!

Kate

- New diagnosis type 2 diabetes age 30, BMI 30
- Insulin treated from diagnosis (high glucose/ketones)

7 years post diagnosis:

HbA1c 66mmol/mol (8.2%) on twice daily mixed insulin

Struggling with weight, hypos

Investigations?

Insulin treated patients with low C-peptide have the treatment requirements of type 1 diabetes

- Can not withdraw insulin
  - Low success rates c-peptide <~600pmol/L
- High DKA risk
  - <~200pmol/L 'absolute insulin requirement'
- Have very high glucose variability and hypoglycaemia risk
  - Physiological insulin regimes/carb counting/'diabetes tech' needed
- Have poor response to most adjuvent therapies
  - Even if very obese/insulin resistant

Reviewed in Jones Hattersley 2013 Diabetic Medicine

Insulin treated patients who retain high C-peptide have the treatment requirements of type 2 diabetes

- Can often safely withdraw insulin
  - Even after DKA (if >600pmol/L)
- Have very low DKA risk
  - >200pmol/l significant protection
- Have low glucose variability and hypoglycaemia risk
  - If insulin needed non-physiological regimes + continued orals/GLP1-RA effective
- Have good glycaemic benefit from adjuvent therapies
  - Largely regardless of insulin resistance/adiposity

Reviewed in Jones Hattersley 2013 Diabetic Medicine

What does the test result mean?
Clinical thresholds in insulin treated diabetes

Stimulated C-peptide level (Post meal blood, post MMTT)	Interpretation
<200pmol/L	Severe/'absolute' insulin deficiency, treat as T1D regardless of aetiology, MODY unlikely.
>600pmol/L	Substantial endogenous insulin secretion: If duration >3 years T1D unlikely. May achieve glycaemic control without insulin.
200-600pmol/L	Some insulin secretion. Likely T1D/insulin requirement but can be seen in thin/longstanding T2D. Consider MODY if antibody negative.

For fasting blood samples divide above by 2.5 (600pmol/L = 250pmol/L 200pmol/L = 80pmol/L)

1 nmol/l = 1000 pmol/l = 3 ng/ml

Caution around thresholds:

- Biological & assay variation

Review - Jones Hattersley Diabetic Medicine 2013

Kate

- New diagnosis type 2 diabetes age 30
- BMI 30
- Insulin treated from diagnosis (high glucose/ketones)

7 years post diagnosis:

HbA1c 66mmol/mol (8.2%) on twice daily mixed insulin

Struggling with weight, hypos

C-peptide result 50pmol/L (random non fasting)

- Treat as Type 1 diabetes

Kate

- New diagnosis type 2 diabetes age 30
- BMI 30
- Insulin treated from diagnosis (high glucose/ketones)

7 years post diagnosis:

HbA1c 66mmol/mol (8.2%) on twice daily mixed insulin

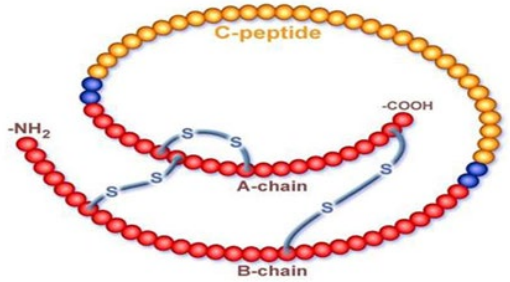
Struggling with weight, hypos

C-peptide result 1900pmol/L (random non fasting)

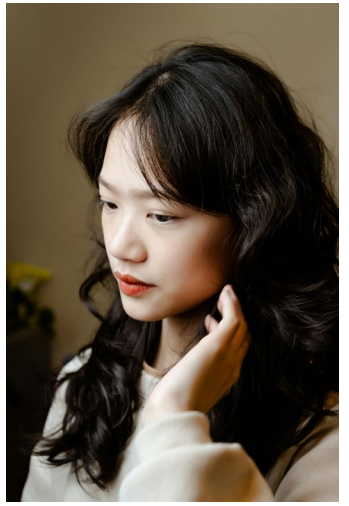
Add non-insulin glucose lowering therapy

Consider insulin withdrawal if good response

Summary: C-peptide



- Inexpensive, easy to measure and widely available
- Preferred test in longstanding (>3 years) insulin treated diabetes where diabetes subtype is uncertain
  - Consider in all 'T2D' where insulin was started within 3 years of diagnosis, & 'T1D' if islet antibodies at diagnosis were negative (or not tested)
  - Consider in insulin treated patients close to diagnosis where type of diabetes uncertain and antibodies are negative
  - DO NOT TEST C-PEPTIDE IF THE PATIENT IS NOT ON INSULIN
- Those who retain high C-peptide, or loose it, usually have the treatment requirements of type 2 and type 1 diabetes respectively



Jane

Diabetes diagnosed aged 25 , tired otherwise well

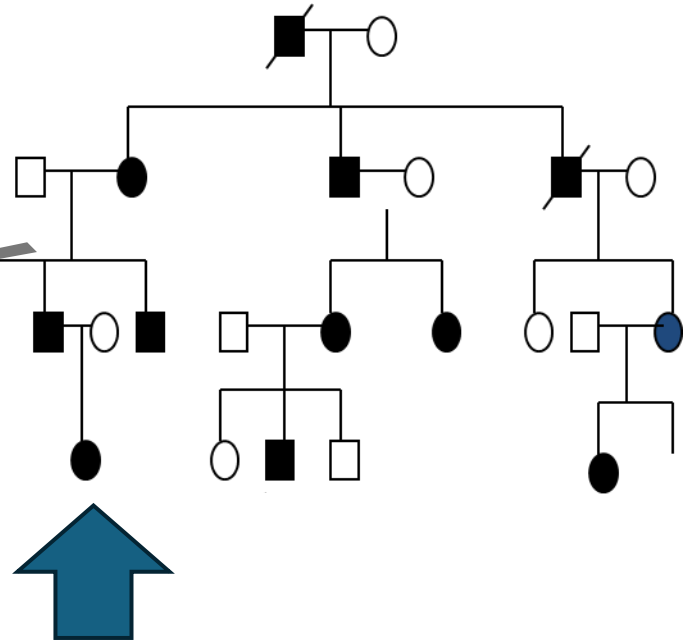
BMI 23

HbA1c 50mmol/mol no treatment

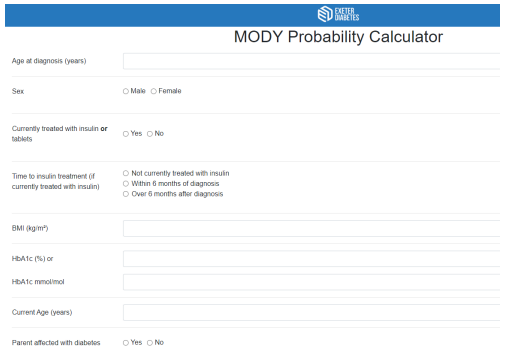
Strong family history of diabetes

Differential diagnosis?

Investigations?



Diagnosing MODY



- Use the MODY calculator to assess clinical likelihood
  - http://www.diabetesgenes.org/content/mody-probability-calculator

- NHS funding for genetic testing if:
  - Young onset diabetes: <35 white European, <30 high T2D prevalence ethnic groups

  And

  - MODY calculator >10% **OR** diagnosis HbA1c <7.5% and age ≤18

  OR BMI<30 and parent affected

  And

  - Where insulin treated positive C-peptide (>200pmol/L) and ≥2 negative islet autoantibodies

All info needed to arrange testing is on the Exeter "Diabetesgenes" website

Other unusual types/causes of diabetes

- Neonatal
  - ‘Type 1’ under 6m usually genetic and best treated with tablets
- Genetic insulin resistance/lipodystrophy
- Mitochondrial
  - Family history early diabetes and deafness
- Haemochromatosis
- Cushings
- Inherited syndromes
- Exocrine pancreatic disease (Type 3c - pancreatitis, pancreatic cancer)
- Iatrogenic – corticosteroids, immune checkpoint inhibitors
- Outside some exceptions (monogenic neonatal diabetes) glycaemic treatment largely depends on preservation/loss of endogenous insulin secretion

Are there really 5 subtypes of type 2 diabetes?

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Health

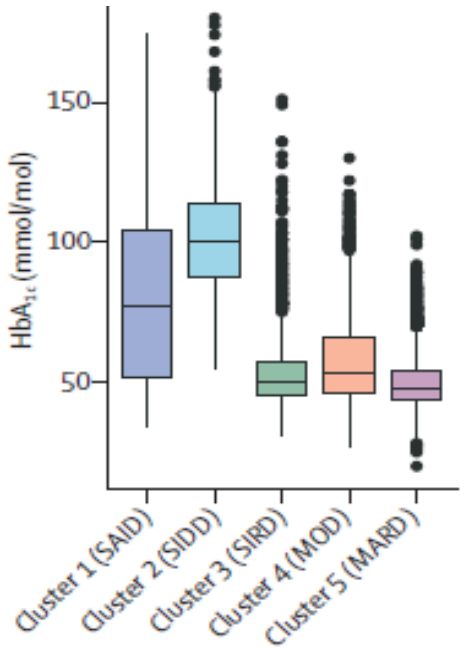
Diabetes is actually five separate diseases, research suggests

By James Gallagher
Health and science correspondent, BBC News

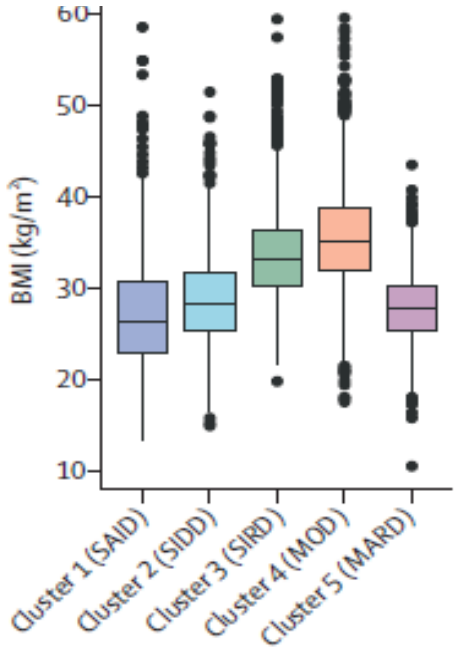
Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables

Emma Ahlqvist, Petter Storm, Annemari Käräjämäki, Mats Martinell*, Mozhgan Dorkhan, Annelie Carlsson, Petter Vikman, Rashmi B Prasad, Dina Mansour Aly, Peter Almgren, Ylva Wessman, Nael Shaat, Peter Spégel, Hindrik Mulder, Eero Lindholm, Olle Melander, Ola Hansson, Ulf Malmqvist, Åke Lernmark, Kaj Lahti, Tom Forsén, Tiinamaija Tuomi, Anders H Rosengren, Leif Groop*

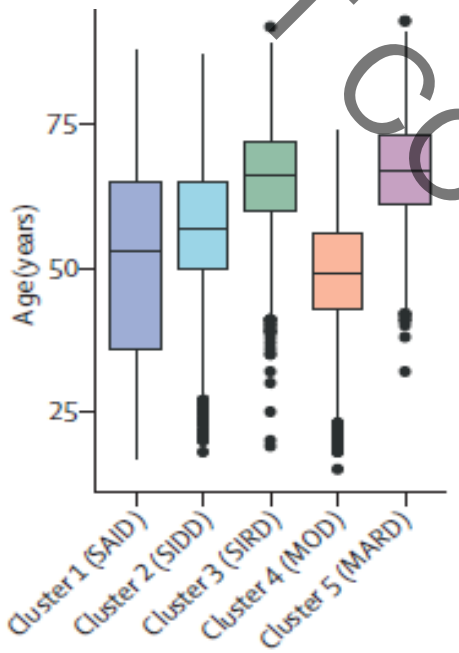
HbA1c



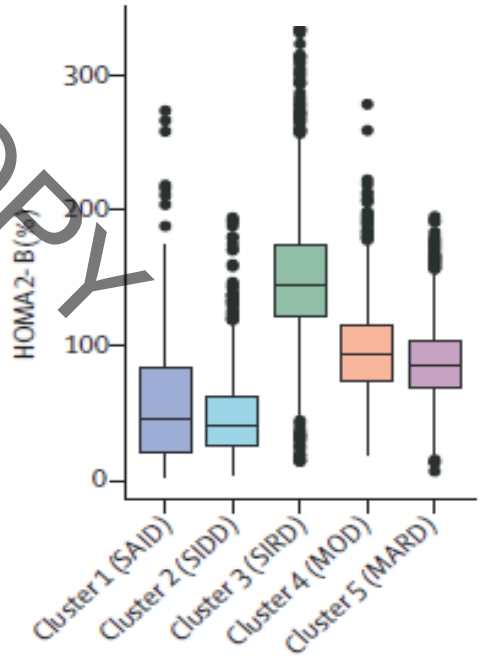
BMI



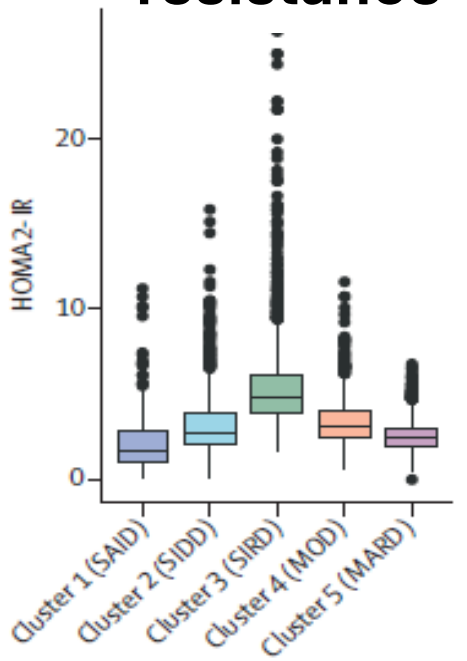
Age



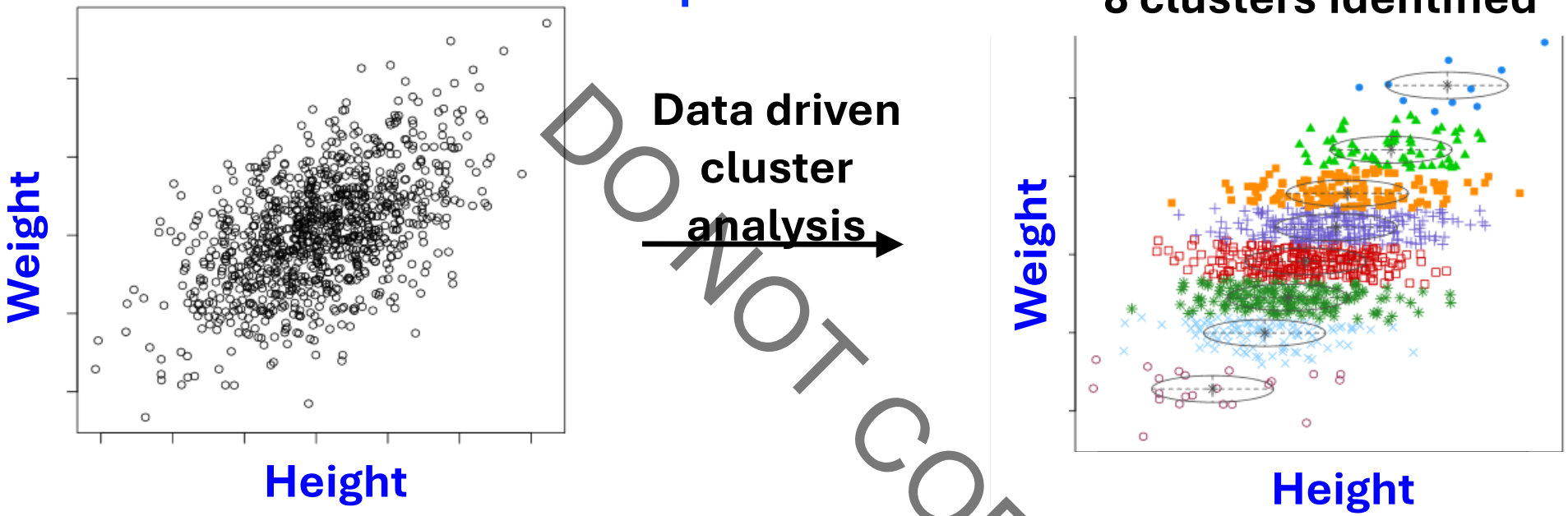
Insulin secretion



Insulin resistance



Cluster analysis to identify similar groups of patients



Darren L Dahly https://darrendahly.github.io/post/cluster

Limitations:

- Data-driven method to find groups in any data, **not biological subtypes**
- **people within a group may have features very different from others**
- We could choose/create any number of groups – no evidence for a particular number
- dependent on features chosen – different features chosen = different groups
- clinical features change over time
- Less utility than simple continuous features (e.g. age at diagnosis/BMI/EGFR) in predicting outcomes *(Dennis et al Lancet Diabetes 2019)*

Conclusions

- Diagnosis diabetes subtype can be challenging, and misclassification is common
- Where classification is unclear careful monitoring and trial of treatment is often appropriate
  - Insulin if unsure and unwell
- Rapid progression (insulin <3 years of diagnosis) strongly suggests missed type 1 diabetes
- Measure islet antibodies at diagnosis where T1D is suspected, and in apparent T2D needing early insulin
- In longstanding diabetes C-peptide is the preferred initial classification test and guides treatment requirements

Victor

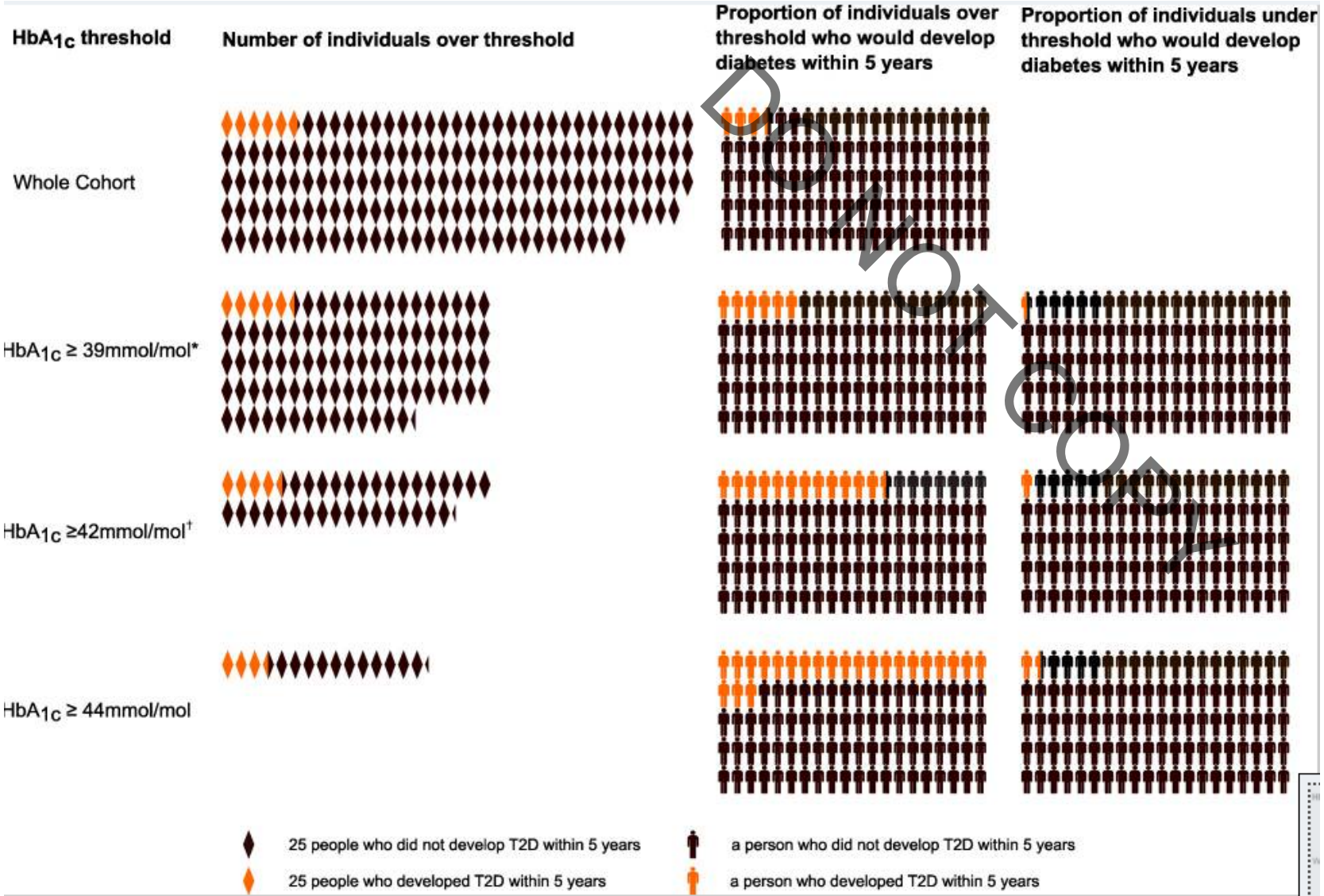
- 75
- PMH IHD, hypertension
- BMI 22
- HbA1c 43mmol/mol

Age and HbA1c

- HbA1c increases with age out of keeping with glucose levels
- A person in their 70's with normal glucose tolerance has HbA1c 3-4mmol higher than a 30 yr old.
- Older people (>65) are more likely to revert to normal glucose than develop diabetes.
- Pre-diabetes is not associated with adverse outcomes in older adults
- Those developing T2D over 80 live longer than those who do not develop T2D!

Dubowitz Diab Med 2014, Masuch BMC Endocrine disorders 2019, Rooney et al Jama int med 2021, Zhang et al 2023 Lancet Regional Health, Sattar et al Ciurculation 2019

People with very mildly raised HBA1c are at very low risk of progression to diabetes



- 22% 5 year risk of T2D in those with HbA21c defined ‘pre-diabetes’ aged >=40
- Those HbA1c 42-43mmol/mol, only have a 7% risk, but comprise 61% of all ‘prediabetes’

Rodgers et al
BMC Medicine 2021

Ali

- 28yr old man
- 2 months after pancreatitis
- Tired
- HbA1c 49mmol/mol
- What else do we want to know?

When is HbA1c not appropriate?

- ALL children and young people
- Patients of any age suspected of having Type 1 diabetes
- Patients at high diabetes risk who are acutely ill (e.g. those requiring hospital admission)
- Patients taking medication that may cause rapid glucose rise e.g. steroids, antipsychotics
- Patients with acute pancreatic damage, including pancreatic surgery
- In pregnancy
- Presence of genetic, haematologic and illness-related factors that influence HbA1c and its measurement

Why may HbA1c be inappropriate?

A1C values influenced by red cell survival.

(1) falsely high values -- low red cell turnover-- disproportionate number of older red cells

ex: iron, vitamin B12, or folate deficiency anemia.

(2) falsely low values -- rapid red cell turnover – greater younger red cells

ex: haemolysis , hemorrhage, treated for iron, vitamin B12, or folate deficiency

Panzer, S, Kronik, G, Lechner, K, et al. Glycosylated hemoglobins (GHb): An index of red cell survival. Blood 1982; 59:1348.

Cautions for HbA1c use

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.
5. Assays Increased HbA1c: hyperbilirubinaemia, carbamylated haemoglobin, alcoholism, large doses of aspirin, chronic opiate use. Variable HbA1c: haemoglobinopathies. Decreased HbA1c: hypertriglyceridaemia.

* Some of the above interfering factors are “invisible” in certain of the available assays