National Institute for Health and Care Excellence

Final

Type 1 diabetes in adults: diagnosis and management

[C] Evidence reviews for diagnosis of diabetes

NICE guideline NG17

Evidence reviews underpinning recommendations 1.1.1 to 1.1.9 and recommendations for research 1 and 2 in the NICE guideline

March 2022

Final

These evidence reviews were developed by the Guideline Development Team

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1.1 Review question

In adults with diabetes, what are the best clinical predictors or biomarker tests (alone or in combination) to distinguish between diagnosis of type 1 diabetes, type 2 diabetes, and other forms of diabetes?

1.1.1 Introduction

It is estimated that more than one in 16 people in the UK has diabetes (diagnosed or undiagnosed) representing a significant cost to the healthcare system. Whilst a specific diagnosis of diabetes type is vital to ensure correct treatment, it is misclassified in 7-15 percent of cases. The potential harms of receiving incorrect treatment with or without insulin is high, so it is vital to ensure that as many initial diagnoses are as correct as possible.

Whilst clinical characteristics (e.g., age at presentation, BMI, and time to insulin treatment from presentation) have often been used for diagnosis, the age and BMI of people living with type 1 and type 2 diabetes now overlap to a greater degree. There is also the potential to use a combination of clinical characteristics as well as biomarkers (c-peptide and antibody markers) to perform a more specific classification of diabetes type at diagnosis. For a healthcare professional to make a decision on what type of diabetes an individual has, they have to examine the results of clinical characteristics and biomarker tests together, as well as considering at what stage they are at in their diabetes diagnosis. There are other subtypes of diabetes with different patient profiles, such as ketosis-prone diabetes (KPD) and latent autoimmune diabetes in adults (LADA) that require different combinations of characteristics and biomarkers at different thresholds to diagnose.

Although a combination of clinical predictors and biomarker tests are now used to classify diabetes in clinical practice, more information is needed on what timepoints and which order these tests/ predictors are best used. There is also the possibility that age at diagnosis and BMI thresholds for distinguishing type of diabetes have changed, as BMI in people with type 1 diabetes is increasing, whilst the age at which people are being diagnosed with type 2 diabetes is decreasing.

This review will assess the diagnostic accuracy of classifying diabetes by type using clinical characteristics and biomarkers, or a combination of both, at varying thresholds and in varying patient populations.

1.1.2 Summary of the protocol

Table 1 PICO table

Population	Adults with type 1, type 2, or other types of diabetes
Index tests	Clinical predictors (alone or in combination) including: • BMI (<25) • age at diagnosis • presence of ketones • diabetic ketoacidosis • family history • presence of auto immune conditions • ethnicity

	• time to commencing insulin treatment from diagnosis • weight loss C-peptide (alongside glucose levels) • plasma C-peptide (stimulated) • urinary C-peptide • urinary C-peptide/creatinine ratio C-peptide (alongside glucose levels) with antibody tests: • insulin autoantibodies (IAA) • anti-glutamic acid decarboxylase 65 antibody or anti-glutamic acid decarboxylase antibody (GADA) • insulinoma-associated (IA-2/ICA512) autoantibody • zinc transporter 8 (ZnT8) • islet-specific glucose-6-phosphatase catalytic subunit (IGRP)
Reference standard	• Any clinical predictors or biomarker tests listed above
Outcomes	Probability of diagnosing diabetes type measured by: • Likelihood Ratios • Sensitivity • Specificity • PPV • NPV • AUC • Correlation coefficient

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods in Appendix B.

The review question was interpreted as “do these people have type x diabetes”, not “do these people have type x or type y diabetes, with type X being positive and type Y being negative” as these do not mean the same thing.

GRADE was not used for most of the included primary studies in this review because the studies did not report likelihood ratios with confidence intervals or because the studies did not report data that could be transformed into a 2 x 2 table and used to calculate likelihood ratios with confidence intervals. Therefore, imprecision could not be evaluated on these studies which is part of the GRADE framework. Instead risk of bias was used to appraise study quality, and quality was assessed by risk of bias and a committee discussion of study directness and usefulness.

Declarations of interest were recorded according to NICE’s conflicts of interest policy.

1.1.4 Diagnostic evidence

1.1.4.1 Included studies

A systematic literature search was conducted for this review on the diagnostic accuracy of clinical predictors or biomarker tests (alone or in combination). This returned 12,849

references (see Appendix C for the literature search strategy). Based on title and abstract screening against the review protocol, 12,698 references were excluded, and 151 references were ordered for screening based on their full texts.

Of the 151 references screened as full texts, 13 references met the inclusion criteria specified in the review protocol for this question (Appendix A). Of these 11 were primary studies and 2 were systematic reviews (Lutgens 2008, Shields 2015). Lutgens 2008 was investigated as a source of references, of which one was included (Fourlanos, 2006) and one excluded (Monge 2004). Shields 2015 was included in this evidence review in full as the majority of included studies met the inclusion criteria and the committee deemed it would be potentially useful evidence for decision making. Studies were checked to avoid double counting as outlined in Appendix B. The clinical evidence study selection is presented as a diagram in Appendix D.

1.1.4.2 Excluded studies

See Appendix G for a list of references for excluded studies, with reasons for exclusion.

1.1.5 Summary of studies included in the diagnostic evidence

The included evidence consists of one systematic review of diagnostic studies (Shields 2015) and 11 primary studies (Balasubramanyam 2006, Covic 2000, Fourlanos 2006, Garnier 2018, Hope 2016, Jones 2011, Koskinen 1986, Sia 2020, Tanaka 2004, Thunander 2012, Wang 2019).

A summary of the included systematic review (Shields 2015) is included in Table 2.

Of the primary studies, 4 studies looked at only newly diagnosed adults with diabetes (Fourlanos 2006, Sia 2020, Tanaka 2004, Thunander 2012), 1 study looked at both people with newly diagnosed diabetes and people with longer term diabetes (Garnier 2018), whilst the other 6 studies examined people with longer term diabetes only. One study looked at people with KPD (Balasubramanyam 2006), 1 study looked at distinguishing people with fulminant diabetes subtypes (Tanaka 2004), 1 study looked at distinguishing people with LADA from people with type 2 diabetes (Fourlanos 2006), and 1 study distinguished between people who were GADA+ and people with type 2 diabetes (Sia 2020). The rest of the studies looked at distinguishing people with type 1 diabetes from people with type 2 diabetes, which was sometimes defined as “autoimmune and non-autoimmune diabetes”. Characteristics of included studies are presented in Table 3.

Table 2: Summary of systematic review characteristics

Author (year)	Inclusion criteria	Exclusion criteria	Index tests	Number of primary studies included
Shields (2015)	Diagnostic accuracy studies of clinical predictors of insulin deficiency, with the reference standard of insulin deficiency being defined by cut-offs of C-peptide results. All measurements of C-peptide and all cut-offs for insulin deficiency were included. Clinical predictors were defined as any routinely measured clinical feature and studies were eligible if there was a cut-off for that clinical predictor assessed against the measure of insulin deficiency.	Studies where patients had known causes of diabetes, for example, monogenic, secondary or syndromic diabetes, were excluded.	• Age at diagnosis • Time to insulin • BMI	11

*Balasubramanyam 2006 is also an include in the systematic review

Table 3: Summary of included studies characteristics

Author (year)	Design	Country	Sample size	Type of diabetes	Years with diabetes	Index test	Reference standard	Risk of bias (directness)
Balasubramanyam (2006)	Cross-sectional study	USA	294	• Ketosis prone diabetes	4.1 (7.3) [a]	• Beta-cell function (Alpha/Beta classification) • BMI-based • ADA • Modified ADA	C-peptide level	Low (Directly applicable)
Covic (2000)	Cross-sectional study	USA	127	• Type 2 • Other types	20.6 (9.4) [a]	• Accepted clinical c-pep criteria • Revised clinical c-pep criteria • Pre-HD [CP] .0.50 nmol/L (no age of DM onset criteria is used) strict clinical criteria • Pre-HD [CP] .0.50 nmol/L (no age of DM onset criteria is used) revised clinical criteria • New algorithm to identify ESRD patients as type 2 diabetes	Standard clinical criteria	Moderate (Directly applicable)
Fourlanos (2006)	Cross-sectional study	Australia	130	• LADA • Type 2	Newly diagnosed (<2 months)	• LADA clinical risk score factors: ○ Age of diabetes onset >50, ○ Acute symptoms of polydipsia/polyuria, and/or unintentional weight loss before diagnosis ○ BMI <25 ○ Genetic risk of autoimmune disease	GADA antibody presence	Moderate (Directly applicable)

Author (year)	Design	Country	Sample size	Type of diabetes	Years with diabetes	Index test	Reference standard	Risk of bias (directness)
						• LADA clinical risk score ≥2 factors • LADA clinical risk score ≤1 factors		
Garnier (2018)	Retrospective cohort study	France	109	• Type 1 • Type 2 • Other	< 6 months from onset (25) >= 6 months from onset (84)	• GADA • GADA + ZNT8A • ZNT8A • ZNt8A + IA-2 • IA2 • GADA + ZNT8A +IA-2	Clinical diagnosis	High (Indirectly applicable)
Hope (2016)	Cross-sectional study	UK	631	• Type 1 • Type 2	≥5 years with diabetes	• T1: Diagnosed <35 years (30 in high-risk ethnicities) AND continual insulin treatment within 6 months of diagnosis OR Diagnosis >= 35 years AND continual insulin treatment from diagnosis	continuous insulin treatment within the first 3 years of diagnosis and absolute insulin deficiency (UCPCR <0.2 nmol/ mmol ≥5 years post-diagnosis)	Moderate (Directly applicable)
Jones (2011)	Cross-sectional study	UK	51	• Type 1 • Type 2	14 (9 to 20) [b]	• Urine c-peptide:creatinine ratio	C-peptide level	Low (Directly applicable)
Koskinen (1986)	Prospective cohort study	Finland	61	• Insulin requiring • Non-insulin requiring	• Insulin requiring (13 [0 to 39]) [c]	• Glucagon stimulated plasma c-peptide (nmol/l) • Basal plasma c-peptide (nmol/l)	Tendency to ketoacidosis verified with blood gas	Low (Directly applicable)

Author (year)	Design	Country	Sample size	Type of diabetes	Years with diabetes	Index test	Reference standard	Risk of bias (directness)
					• Non-insulin requiring (6 [0 to 12]) [c]	• Basal plasma c-peptide (nmol/l)/fasting blood glucose (mmol/l) • Glucagon-stimulated plasma c-peptide (nmol/l) x creatinine clearance (ml/min) • Basal plasma c-peptide (nmol/l) x creatinine clearance (ml/min) • 2h postprandial urinary c-peptide (nmol) • 2h postprandial urinary c-peptide concentration (nmol/l) • 2h postprandial urinary c-peptide (nmol)/creatinine (mmol) • 4h postprandial urinary c-peptide (nmol) • 4h postprandial urinary c-peptide concentration (nmol/l) • 4h postprandial urinary c-peptide (nmol)/creatinine (mmol)	analysis (base excess below -4 mmol/l)	
Sia (2020)	Case-control study	Taiwan	510	• GADA+ diabetes • Type 2	Newly diagnosed (< 6 months)	• Linear discriminant functions constructed from five major variables (Age at onset, BMI, Triglycerides, HbA1c, HDL-C)	GADA antibody positive test	High (Partially applicable)

Author (year)	Design	Country	Sample size	Type of diabetes	Years with diabetes	Index test	Reference standard	Risk of bias (directness)
Tanaka (2004)	Prospective cohort study	Japan	125	• Fulminant type 1 • Acute onset type 1	Newly diagnosed (<= 90 days)	• Sum c-peptide ≤0.540 nmol/l • Fasting serum c-peptide ≤0.033 nmol/l • Age at onset >20 years • BMI >19.1 kg/m^2 • Duration hyperglycaemic symptoms ≤8 days • Glucose >33.6 mmol/l • HbA1c ≤8.0% • Arterial pH ≤7.21 • Amylase >345 IU/l • Lipase >173 U/l • Elastase one >231 ng/dl	Autoantibody negativity (ICA, IAA, IA-A2, GADA) and normal or near-normal HbA1c	Low (Partially applicable)
Thunander (2012)	Prospective cohort study	Sweden	1180	• Autoimmune • Non-autoimmune	Newly diagnosed (<= 90 days)	• Fasting c-peptide 0.5 nmol/l • Fasting c-peptide 0.6 nmol/l • Fasting c-peptide 0.7 nmol/l • Fasting c-peptide 0.8 nmol/l • Fasting c-peptide 0.9 nmol/l • Fasting c-peptide 1 nmol/l • Age at diagnosis 40 years • Age at diagnosis 50 years • Age at diagnosis 55 years • BMI 23 kg/m2 • BMI 24kg/m2 • BMI 25kg/m2	GADA+	Low (Directly applicable)
Wang (2019)	Cross-sectional study	China	192	• Type 1 • Type 2	• Type 1 (6.5 [1.5 to 13]) [c]	• UCPCR ≥0 21 nmol/mmol	C-peptide, ketosis, and insulin treatment	Moderate (Partially applicable)

Author (year)	Design	Country	Sample size	Type of diabetes	Years with diabetes	Index test	Reference standard	Risk of bias (directness)
					• Type 2 8 [2.3 to 14]) [c]		6 months from onset	

(a) mean (standard deviation)
(b) median (interquartile range)
(c) mean [range]

See appendix E for full evidence tables.

1.1.6 Summary of the diagnostic evidence

Only 2 studies (Fourlanos 2006, Sia 2020) provided enough information for a full GRADE analysis to be performed, and are presented in Table 4.

The rest of the primary studies are presented in study order, detailing population, reference standard and index test. Quality was assessed by risk of bias and a committee discussion of study directness and usefulness.

A summary of GRADE results from the Shields 2015 systematic review are presented in Table 5. Risk of bias scores were adapted from the risk of bias analysis conducted in the systematic review. Studies that could not be analysed using GRADE have their results presented in Table 6.

GRADE Analysis with Likelihood ratios

For Fourlanos (2006), a positive result on LADA clinical risk score (2 factors or more) would lead to a moderate increase in the probability of recipient having LADA compared to before the test result was known. Whereas a negative result on LADA clinical risk score (1 factor or less) showed a large decrease in probability of LADA compared to before the test result was known.

- Age of diabetes onset >50,
- acute symptoms of polydipsia/polyuria, and/or unintentional weight loss before diagnosis
- BMI <25
- Genetic risk of autoimmune disease (type 1)

For Sia (2020), which used a similar method of a pooled set of risk factors, found a very large increase in the probability of having GADA+ diabetes (which encompasses Type 1 and LADA) compared to before the test result was known. Whereas a negative result of the pooled set of risk factors resulted in a moderate decrease in the probability of having GADA+ diabetes.

From the perspective of GADA+ discrimination, these were:

- Age of onset <30
- BMI <23
- Triglycerides >= 98 mg/dL
- HbA1c >= 8.6%
- HDL-C >= 46 mg/dL

Table 4: Summary of GRADE tables

No. studies (sample size)	Study design	Diagnostic accuracy			Quality	Interpretation of effect
		Sensitivity	Specificity	Likelihood ratios		
Diabetes diagnosis: LADA vs Type 2 Index test: LADA clinical risk score >= 2 factors Reference standard: GADA antibody positivity						
1 (Fourlanos 2006) (n=130)	Cross-sectional	90.0 (53.3, 98.6)	71.7 (63.0, 79.0)	LR+ 3.17 (2.23, 4.51)	Moderate	Moderate increase in probability of LADA
				LR- 0.14 (0.02, 0.89)	Low	Large decrease in probability of LADA
Diabetes diagnosis: GADA+ diabetes vs Type 2 diabetes Index test: Linear discriminant functions constructed from five major variables Reference standard: GADA antibody positive test						
1 (Sia 2020) (n=510)	Case-control	75.3 (68.3, 81.2)	92.9 (89.7, 95.2)	LR+ 10.66 (7.18, 15.83)	Very low	Very large increase in probability of GADA+ diabetes
				LR- 0.26 (0.20, 0.34)	Very low	Moderate decrease in probability of GADA+ diabetes

Systematic reviews

Shields 2015

The Shields (2015) systematic review examined an array of characteristics, all to diagnose insulin deficiency vs no insulin deficiency.

Table 5: Summary of GRADE tables from Shields review: Single characteristics as above for distinguishing types of diabetes (all looking at diagnosing insulin deficiency (suggesting type 1) vs no insulin deficiency (suggesting type 2))

No. studies (sample size)	Study design	Diagnostic accuracy			Quality	Interpretation of effect
		Sensitivity	Specificity	Likelihood ratios		
Index test: Age at diagnosis (threshold <20 years) Reference standard: C-peptide 0.3 nmol/l						
1 (Boyle 1999)	Cross-sectional	20.4 (15.8, 25.9)	97.4 (96.8, 97.9)	LR+ 7.81 (5.66, 10.77)	High	Large increase in probability of type 1 diabetes
				LR- 0.81 (0.76, 0.87)	High	Slight decrease in probability of type 1 diabetes
Index test: Age at diagnosis (threshold ≤30 years) Reference standard: C-peptide 0.03 nmol/l						
1 (Prior 1991)	Cross-sectional	84.0 (79.8, 87.5)	82.1 (76.6, 86.6)	LR+ 4.70 (3.54, 6.25)	Low	Moderate increase in probability of type 1 diabetes
				LR- 0.19 (0.15, 0.24)	Low	Large decrease in probability of type 1 diabetes
Index test: Age at diagnosis (threshold ≤30 years) Reference standard: C-peptide 0.2 nmol/l						
1 (Nielsen 1986)	Cross-sectional	64.2 (56,2, 71.5)	88.1 (77.9, 93.9)	LR+ 5.37 (2.77, 10.41)	Moderate	Large increase in probability of type 1 diabetes

No. studies (sample size)	Study design	Diagnostic accuracy			Quality	Interpretation of effect
		Sensitivity	Specificity	Likelihood ratios		
				LR- 0.40 (0.32, 0.51)	Low	Moderate decrease in probability of type 1 diabetes
Index test: Age at diagnosis (threshold <30 years) Reference standard: C-peptide 0.07 nmol/l						
1 (Ekpehbegh 2013)	Cross-sectional	57.1 (40.6, 72.3)	72.2 (55.6, 84.4)	LR+ 2.05 (1.12, 3.74)	Moderate	Moderate increase in probability of type 1 diabetes
				LR- 0.59 (0.38, 0.91)	Moderate	Slight decrease in probability of type 1 diabetes
Index test: Age at diagnosis (threshold <39 years) Reference standard: C-peptide 0.08 nmol/l						
1 (Shields 2010)	Cross-sectional	67.5 (51.7, 80.1)	96.9 (80.9, 99.6)	LR+ 21.60 (3.10, 150.46)	Low	Very large increase in probability of type 1 diabetes
				LR- 0.33 (0.21, 0.52)	Very low	Moderate decrease in probability of type 1 diabetes
Index test: Age at diagnosis (threshold ≤40 years) Reference standard: C-peptide 0.03 nmol/l						
1 (Prior 1991)	Cross-sectional	96.9 (94.4, 98.3)	59.4 (52.8, 65.6)	LR+ 2.38 (2.03, 2.79)	Low	Moderate increase in probability of type 1 diabetes
				LR- 0.05 (0.02, 0.09)	Low	Very large decrease in probability of type 1 diabetes
Index test: Age at diagnosis (threshold ≤40 years) Reference standard: C-peptide 0.06 nmol/l						

No. studies (sample size)	Study design	Diagnostic accuracy			Quality	Interpretation of effect
		Sensitivity	Specificity	Likelihood ratios		
1 (Welborn 1983)	Cross-sectional	84.0 (64.3, 93.9)	85.4 (76.9, 91.2)	LR+ 5.76 (3.44, 9.62)	Low	Large increase in probability of type 1 diabetes
				LR- 0.18 (0.07, 0.46)	Low	Large decrease in probability of type 1 diabetes
Index test: Age at diagnosis (threshold ≤40 years) Reference standard: C-peptide 0.16 nmol/l						
1 (Welborn 1981)	Cross-sectional	76.1 (61.8, 86.2)	81.3 (74.4, 86.7)	LR+ 4.06 (2.82, 5.86)	Low	Moderate increase in probability of type 1 diabetes
				LR- 0.29 (0.17, 0.49)	Low	Moderate decrease in probability of type 1 diabetes
Index test: Age at diagnosis (threshold ≤40 years) Reference standard: C-peptide 0.2 nmol/l						
1 (Laakso 1987)	Cross-sectional	60.9 (51.7, 69.3)	78.6 (65.9, 87.4)	LR+ 2.84 (1.68, 4.79)	Low	Moderate increase in probability of type 1 diabetes
				LR- 0.49 (0.38, 0.65)	Low	Moderate decrease in probability of type 1 diabetes
Index test: Age at diagnosis (threshold <45 years) Reference standard: C-peptide 0.3 nmol/l						
1 (Boyle 1999)	Cross-sectional	65.3 (59.1, 71.0)	56.8 (55.1, 58.5)	LR+ 1.51 (1.36, 1.66)	High	Slight increase in probability of type 1 diabetes
				LR- 0.61 (0.51, 0.72)	High	Slight decrease in probability of type 1 diabetes

No. studies (sample size)	Study design	Diagnostic accuracy			Quality	Interpretation of effect
		Sensitivity	Specificity	Likelihood ratios		
Index test: On insulin – Yes Reference standard: C-peptide 0.03 nmol/l						
1 (Prior 1991)	Cross-sectional	99.4 (97.8, 99.9)	25.0 (19.8, 31.1)	LR+ 1.32 (1.22, 1.43)	Low	Slight increase in probability of type 1 diabetes
				LR- 0.02 (0.00, 0.09)	Low	Very large decrease in probability of type 1 diabetes
Index test: On insulin – Yes Reference standard: C-peptide 0.16 nmol/l						
1 (Welborn 1981)	Cross-sectional	99.0 (85.7, 99.9)	69.6 (61.9, 76.3)	LR+ 3.25 (2.56, 4.12)	Low	Moderate increase in probability of type 1 diabetes
				LR- 0.01 (0.00, 0.23)	Low	Very large decrease in probability of type 1 diabetes
Index test: Time to insulin (threshold ≤1.5 m) Reference standard: C-peptide 0.08 nmol/l						
1 (Shields 2010)	Cross-sectional	80.0 (64.8, 89.7)	56.3 (39.0, 72.1)	LR+ 1.82 (1.19, 2.78)	Very low	Slight increase in probability of type 1 diabetes
				LR- 0.35 (0.17, 0.71)	Very low	Moderate decrease in probability of type 1 diabetes
Index test: Time to insulin (threshold <1 year) Reference standard: C-peptide 0.03 nmol/l						
1 (Prior 1991)	Cross-sectional	91.7 (88.4, 94.2)	75.0 (68.9, 80.2)	LR+ 3.67 (2.91, 4.61)	Low	Moderate increase in probability of type 1 diabetes

No. studies (sample size)	Study design	Diagnostic accuracy			Quality	Interpretation of effect
		Sensitivity	Specificity	Likelihood ratios		
				LR- 0.11 (0.07, 0.15)	Low	Large decrease in probability of type 1 diabetes
Index test: Time to insulin (threshold <2 years) Reference standard: C-peptide 0.06 nmol/l						
1 (Welborn 1983)	Cross-sectional	98.1 (75.6, 99.9)	82.0 (73.0, 88.4)	LR+ 5.43 (3.54, 8.33)	Low	Large increase in probability of type 1 diabetes
				LR- 0.02 (0.00, 0.36)	Low	Very large decrease in probability of type 1 diabetes
Index test: Time to insulin (threshold ≤2 years) Reference standard: C-peptide 0.2 nmol/l						
1 (Laakso 1987)	Cross-sectional	69.6 (60.6, 77.3)	85.7 (73.9, 92.7)	LR+ 4.87 (2.53, 9.35)	Moderate	Moderate increase in probability of type 1 diabetes
				LR- 0.35 (0.26, 0.47)	Moderate	Moderate decrease in probability of type 1 diabetes
Index test: BMI (threshold ≤20 kg/m^2) Reference standard: C-peptide 0.3 nmol/l						
1 (Boyle 1999)	Cross-sectional	10.2 (7.0, 14.7)	98.5 (98.0, 98.8)	LR+ 6.73 (4.25, 10.68)	High	Large increase in probability of type 1 diabetes
				LR- 0.91 (0.87, 0.95)	High	Slight decrease in probability of type 1 diabetes
Index test: PDW (threshold <100%) Reference standard: C-peptide 0.03 nmol/l						

No. studies (sample size)	Study design	Diagnostic accuracy			Quality	Interpretation of effect
		Sensitivity	Specificity	Likelihood ratios		
1 (Prior 1991)	Cross-sectional	33.6 (28.9, 38.7)	92.4 (88.1, 95.2)	LR+ 4.43 (2.74, 7.15)	Low	Moderate increase in probability of type 1 diabetes
				LR- 0.71 (0.66, 0.78)	Low	Slight decrease in probability of type 1 diabetes
Index test: BMI (threshold <25 kg/m^2) Reference standard: C-peptide 0.3 nmol/l						
1 (Boyle 1999)	Cross-sectional	40.8 (34.8, 47.1)	86.3 (85.1, 87.4)	LR+ 2.97 (2.50, 3.53)	High	Moderate increase in probability of type 1 diabetes
				LR- 0.68 (0.61, 0.76)	High	Slight decrease in probability of type 1 diabetes
Index test: PDW (threshold <120%) Reference standard: C-peptide 0.03 nmol/l						
1 (Prior 1991)	Cross-sectional	87.2 (83.3, 90.3)	62.9 (56.4, 69.0)	LR+ 2.35 (1.97, 2.80)	Very low	Moderate increase in probability of type 1 diabetes
				LR- 0.20 (0.15, 0.27)	Low	Large decrease in probability of type 1 diabetes
Index test: PDW (threshold ≤120%) Reference standard: C-peptide 0.06 nmol/l						
1 (Welborn 1983)	Cross-sectional	80.0 (60.0, 91.4)	66.7 (56.7, 75.4)	LR+ 2.40 (1.70, 3.38)	Very low	Moderate increase in probability of type 1 diabetes
				LR- 0.30 (0.13, 0.66)	Very low	Moderate decrease in probability of type 1 diabetes

No. studies (sample size)	Study design	Diagnostic accuracy			Quality	Interpretation of effect
		Sensitivity	Specificity	Likelihood ratios		
Index test: BMI (threshold ≤27 kg/m^2) Reference standard: C-peptide 0.2 nmol/l						
1 (Laakso 1987)	Cross-sectional	75.7 (67.0, 82.6)	66.1 (52.8, 77.2)	LR+ 2.23 (1.52, 3.26)	Low	Moderate increase in probability of type 1 diabetes
				LR- 0.36 (0.25, 0.53)	Low	Moderate decrease in probability of type 1 diabetes
Index test: BMI (threshold <28 kg/m-1) Reference standard: C-peptide 0.3 or 0.2 nmol/l						
1 (Balasubramanyam 2006)	Cross-sectional	86.1 (79.9, 90.6)	67.2 (58.6, 74.8)	LR+ 2.62 (2.03, 3.38)	High	Moderate increase in probability of type 1 diabetes
				LR- 0.20 (0.13, 0.30)	High	Large decrease in probability of type 1 diabetes
Index test: BMI (threshold <29 kg/m^2) Reference standard: C-peptide 0.3 nmol/l						
1 (Boyle 1999)	Cross-sectional	71.4 (65.5, 76.7)	56.6 (54.9, 58.2)	LR+ 1.64 (1.50, 1.79)	High	Slight increase in probability of type 1 diabetes
				LR- 0.50 (0.41, 0.61)	Moderate	Moderate decrease in probability of type 1 diabetes
Index test: BMI (threshold <29 kg/m^2) Reference standard: C-peptide 0.08 nmol/l						
1 (Shields 2010)	Cross-sectional	77.5 (62,1, 87.9)	56.3 (39.0, 72.1)	LR+ 1.77 (1.15, 2.71)	Very low	Slight increase in probability of type 1 diabetes

No. studies (sample size)	Study design	Diagnostic accuracy			Quality	Interpretation of effect
		Sensitivity	Specificity	Likelihood ratios		
				LR- 0.40 (0.20, 0.76)	Very low	Moderate decrease in probability of type 1 diabetes
Index test: BMI (threshold <30 kg/m^2) Reference standard: C-peptide 0.07 nmol/l						
1 (Ekpehbegh 2013)	Cross-sectional	77.1 (60.5, 88.1)	47.2 (31.7, 63.3)	LR+ 1.46 (1.02, 2.09)	Moderate	Slight increase in probability of type 1 diabetes
				LR- 0.48 (0.24, 0.97)	Moderate	Moderate decrease in probability of type 1 diabetes

Table 6: Diagnostic evidence where GRADE analysis not possible

Index test	Sample size	Likelihood ratio +/-	AUC	Sens	Spec	PPV/NPV	Risk of bias
Balasubramanyam 2006 – Distinguishing preserved b-cell function (type 1b diabetes) from lost b-cell function (type 1a diabetes) 12 months after DKA in adults with ketosis-prone diabetes presenting with DKA Reference standard: C-peptide level (peak plasma C-peptide response to glucagon >=1.5 ng/ml or fasting serum C-peptide level was >=1 ng/ml)							
Beta-cell function (αβ classification)	294	24.55/0.01	0.972	99.4	95.9	97.1/99.2	Low
Modified ADA	294	38.99/0.69	0.703	31.6	99.2	98.2/51.1	Low
BMI-based	294	4.75/0.38	0.766	67.3	85.8	78.6/77.2	Low
ADA	294	8.34/0.54	0.707	48.8	94.2	71.9/28.1	Low
Balasubramanyam 2006 – Distinguishing preserved b-cell function (type 1b diabetes) from lost b-cell function (type 1a diabetes) 12 months after DKA in adults with newly diagnosed ketosis-prone diabetes presenting with DKA Reference standard: C-peptide level (peak plasma C-peptide response to glucagon >=1.5 ng/ml or fasting serum C-peptide level was >=1 ng/ml)							
Beta-cell function *(αβ classification)*	138	21.79/0.01	0.969	99.1	95.5	99.1/95.5	Low
Modified ADA	138	Inf/0.66	0.672	34.5	100	100/22.5	Low

Index test	Sample size	Likelihood ratio +/-	AUC	Sens	Spec	PPV/NPV	Risk of bias
BMI-based	138	3.03/0.37	0.742	72.2	76.2	94.3/33.3	Low
ADA	138	1.16/0.45	0.562	89.7	22.7	85.9/29,4	Low
Covic 2000 – Distinguishing type 2 from type 1 diabetes in diabetic end stage renal disease patients Reference standard: C-peptide >0.5nmol/L							
Accepted clinical c-pep criteria *(age of diabetes onset <25 years, treatment only with insulin and/or history of DKA)*	127	NR	NR	100	5.1	70.4/100	Moderate
Revised clinical c-pep criteria *(see description under index tests in evidence table)*	127	NR	NR	100	6.3	76/100	Moderate
Covic 2000 – Distinguishing type 2 from type 1 diabetes in diabetic end stage renal disease patients Reference standard: pre-haemodialysis c-peptide >0.5 nmol/L (no age of onset criteria used)							
accepted clinical c-pep criteria *(age of diabetes onset <25 years, treatment only with insulin and/or history of DKA)*	127	NR	NR	97.7	7.7	70.5/60	Moderate
revised clinical c-pep criteria *(see description under index tests in evidence table)*	127	NR	NR	97.8	9.4	76.2/60	Moderate
New algorithm to identify ESRD patients as type 2 DM: pre-HD [CP] >0.50 nmol/L and age of DM onset >=38 years *(see flow diagram in evidence table)*	127	NR	NR	87.2	95.1	97.4/78.8	Moderate
Garnier 2018 – distinguishing LADA from type 2 in adult diabetes patients Reference standard: "clinical diagnosis"							
GADA	109	NR	NR	31	NR	NR	High
GADA + ZNT8A	109	NR	NR	12	NR	NR	High
ZNT8A	109	NR	NR	10	NR	NR	High

Index test	Sample size	Likelihood ratio +/-	AUC	Sens	Spec	PPV/NPV	Risk of bias
ZNt8A + IA-2	109	NR	NR	3	NR	NR	High
IA2	109	NR	NR	6	NR	NR	High
GADA + ZNT8A +IA-2	109	NR	NR	10	NR	NR	High
Garnier 2018 – distinguishing LADA from type 2 in adult diabetes patients – subgroup: Adults with diabetes onset < 6 months **Reference standard: "clinical diagnosis"**							
ZNT8A	25	NR	NR	52		NR	High
Garnier 2018 – distinguishing LADA from type 2 in adult diabetes patients – subgroup: Adults with diabetes onset >= 6 months **Reference standard: "clinical diagnosis"**							
ZNT8A	84	NR	NR	29	NR	NR	High
Hope 2016 – distinguishing type 1 from type 2 in adult diabetes patients **Reference standard: Urinary c-peptide: creatinine ratio <=0.2 nmol/mmol and continual insulin treatment within 3 years of diagnosis**							
Time to insulin from diagnosis 12 months	601	NR	0.904 (0.88-0.93)	91.5	82.1	NR	Moderate
Age at diagnosis <= 39 years	601	NR	0.871 (0.84 – 0.90)	81.9	84.3	NR	Moderate
BMI at diagnosis <= 23.1kg/m^2	359	NR	0.824 (0.77, 0.87)	65.7	89.4	NR	Moderate
BMI at recruitment <= 28 kg/m^2	601	NR	0.72 (0.67, 0.76)	61.8	66.8	NR	Moderate
Jones 2011 – distinguishing patients with/without clinically significant endogenous insulin secretion in adults **Reference standard: mixed meal tolerance test stimulated c-peptide < 0.2 nmol/l**							
fasting urine c-peptide creatinine ratio < 0.1	51	NR	0.99	100	97.7	NR	Low
urine c-peptide creatinine ratio after mixed-meal tolerance test < 0.3	51	NR	1	100	100	NR	Low

Index test	Sample size	Likelihood ratio +/-	AUC	Sens	Spec	PPV/NPV	Risk of bias
home urine c-peptide creatinine ratio after standard breakfast < 0.1	51	NR	1	100	100	NR	Low
home urine c-peptide creatinine ratio after largest meal < 0.3	51	NR	0.99	100	95.3	NR	Low
Jones 2011 – distinguishing patients with/without clinically significant endogenous insulin secretion in adults Reference standard: stimulated c-peptide < 0.6 nmol/l							
fasting urine c-peptide creatinine ratio < 0.4	51	NR	0.95	92.3	81	NR	Low
urine c-peptide creatinine ratio after mixed-meal tolerance test < 1.3	51	NR	0.96	92.3	94.6	NR	Low
home urine c-peptide creatinine ratio after standard breakfast < 0.4	51	NR	0.95	84.6	92.1	NR	Low
home urine c-peptide creatinine ratio after largest meal < 0.6	52	NR	0.96	92.3	91.9	NR	Low
Koskinen 1986 – distinguishing insulin requirement from non-insulin requirement with diabetes Reference standard: "evidence of tendency to ketoacidosis"							
glucagon stimulated plasma c-peptide (nmol/l) <0.6	61	NR	NR	100	94	NR	Low
basal plasma c-peptide (nmol/l) < 0.4	61	NR	NR	100	71	NR	Low
basal plasma c-peptide (nmol/l)/ fasting blood glucose (mmol/l) <0.04	61	NR	NR	100	71	NR	Low

Index test	Sample size	Likelihood ratio +/-	AUC	Sens	Spec	PPV/NPV	Risk of bias
glucagon -stimulated plasma c-peptide (nmol/l) x creatinine clearance (ml/min) <45	61	NR	NR	97	94	NR	Low
basal plasma c-peptide (nmol/l) x creatinine clearance (ml/min) <26	61	NR	NR	93	94	NR	Low
2h postprandial urinary c-peptide (nmol) <1.5	61	NR	NR	97	82	NR	Low
2h postprandial urinary c-peptide concentration (nmol/l) <5	61	NR	NR	86	88	NR	Low
2h postprandial urinary c-peptide (nmol)/creatinine (mmol) <1	61	NR	NR	86	94	NR	Low
4h postprandial urinary c-peptide (nmol) <3	61	NR	NR	97	82	NR	Low
4h postprandial urinary c-peptide concentration (nmol/l) <5	61	NR	NR	86	94	NR	Low
4h postprandial urinary c-peptide (nmol)/creatinine (mmol) <1	61	NR	NR	72	94	NR	Low
Tanaka 2004 – Distinguishing fulminant diabetes from acute onset type 1 in newly diagnosed adults							

Index test	Sample size	Likelihood ratio +/-	AUC	Sens	Spec	PPV/NPV	Risk of bias
Reference standard: Autoantibody negativity (ICA, IAA, IA-A2, GADA) and HbA1c levels							
sum c-peptide <= 0.540 nmol/l	125	NR	0.974 +/- 0.013	96.0 (79.7–99.9)	94.0 (87.4–97.8)	80.0 (61.4–92.3)/ 98.9 (94.3–100.0)	Low
fasting serum c-peptide <= 0.033 nmol/l	125	NR	0.974 +/- 0.013	96.0 (79.7–99.9)	94.0 (87.4–97.8)	80.0 (61.4–92.3)/ 98.9 (94.3–100.0)	Low
Age at onset >20 years	125	NR	0.555 +/- 0.066	100.0 (86.2–100.0)	20.0 (12.7–29.2)	23.8 (16.0–33.1) / 100.0 (83.2–100.0)	Low
BMI > 19.1 kg/m2	125	NR	0.715 +/- 0.062	76.0 (54.9–90.6)	64.0 (53.8–73.4)	34.5 (22.2–48.6) / 91.4 (82.3–96.8)	Low
Duration hyperglycaemic symptoms <= 8 days	125	NR	0.944 +/- 0.020	96.0 (79.7–99.9)	88.0 (80.0–93.6)	66.7 (49.0–81.4) / 98.9 (93.9–100.0)	Low
glucose >33.6 mmol/l	125	NR	0.827 +/- 0.053	76.0 (54.9–90.6)	81.0 (71.9–88.2)	50.0 (33.9–66.6) / 93.1 (85.6–97.4)	Low
HbA1c <= 8.0%	125	NR	0.969 +/- 0.014	96.0 (79.7–99.9)	89.0 (81.2–94.4)	68.6 (50.7–83.2) / 98.9 (94.0–100.0)	Low

Index test	Sample size	Likelihood ratio +/-	AUC	Sens	Spec	PPV/NPV	Risk of bias
Arterial pH <= 7.21	125	NR	0.841 +/- 0.037	84.0 (63.9–95.4)	74.0 (64.3–82.3)	44.7 (30.2–59.9) / 94.9 (87.4–98.6)	Low
Amylase >345 IU/l	125	NR	0.877 +/- 0.046	68.0 (46.5–85.1)	92.0 (84.8–96.5)	68.0 (46.5–85.1) / 92.0 (84.8–96.5)	Low
Lipase >173 U/l	125	NR	0.797 +/- 0.056	64.0 (42.5–82.0)	92.0 (84.8–96.5)	66.7 (44.7–84.4) / 91.1 (83.8–95.8)	Low
Elastase one >231 ng/dl	125	NR	0.918 +/- 0.039	80.0 (59.3–93.2)	91.0 (83.6–95.8)	69.0 (49.2–84.7) / 94.8 (88.3–98.3)	Low
Thunander 2012 – distinguishing autoimmune (type 1) from non-auto-immune diabetes (type 2) in newly diagnosed adults Reference standard: GADA Ab positivity							
Fasting C-peptide 0.5 nmol/l	1180	NR	0.78 +/- 0.04	96	40	NR	Low
Fasting C-peptide 0.6 nmol/l	1180	NR	0.78 +/- 0.04	94	51	NR	Low
Fasting C-peptide 0.7 nmol/l	1180	NR	0.78 +/- 0.04	89	66	NR	Low
Fasting C-peptide 0.8 nmol/l	1180	NR	0.78 +/- 0.04	83	61	NR	Low
Fasting C-peptide 0.9 nmol/l	1180	NR	0.78 +/- 0.04	76	65	NR	Low
Fasting C-peptide 1 nmol/l	1180	NR	0.78 +/- 0.04	66	71	NR	Low

Index test	Sample size	Likelihood ratio +/-	AUC	Sens	Spec	PPV/NPV	Risk of bias
Age at diagnosis 40 years	1180	NR	0.68 +/- 0.04	97	18	NR	Low
Age at diagnosis 50 years	1180	NR	0.68 +/- 0.04	87	34	NR	Low
Age at diagnosis 55 years	1180	NR	0.68 +/- 0.04	77	53	NR	Low
BMI 23 kg/m2	1180	NR	0.66 +/- 0.04	87	27	NR	Low
BMI 24kg/m2	1180	NR	0.66 +/- 0.04	81	44	NR	Low
BMI 25kg/m2	1180	NR	0.66 +/- 0.04	74	47	NR	Low
Wang 2019 – Distinguishing T1 from non T1 in adults with diabetes **Reference standard: fasting serum c-peptide level <0.2 nmol/L, ketosis onset, insulin treatment 6 months from onset, autoantibody positivity, and insulin dependent insulin treatment**							
UCPCR ≥ 0 21 nmol/mmol	172	NR	0.949	87	93	NR	Moderate
Wang 2019 – Distinguishing T1 from T2 in adults with diabetes **Reference standard: fasting serum c-peptide level <0.2 nmol/L, ketosis onset, insulin treatment 6 months from onset, autoantibody positivity, and insulin dependent insulin treatment**							
UCPCR ≥ 0 21 nmol/mmol	172	NR	0.932	82	93	NR	Moderate

1.1.7 Economic evidence

1.1.7.1 Included studies

A systematic search was performed to identify economic evidence for the review question, with 3,160 papers identified. Following the initial review of titles and abstracts, no papers were selected for screening on full text as none of the papers reported a cost-utility analysis performed to identify the cost-effectiveness of methods to distinguish between type 1 and type 2 diabetes or other forms of diabetes. The study selection is shown in appendix J.

1.1.7.2 Excluded studies

All papers identified were excluded in the initial review of titles and abstracts. Hence no studies were selected for screening on full text.

1.1.7.3 Unit costs

As the recommendations made are likely to imply an increase in the use of autoantibody testing at the time of diagnosis for people with type 1 diabetes, the committee considered the unit costs of the tests, in order to understand the potential resource impact that would cause. A cost of £29.04 (Exeter clinical laboratory) was identified relating to the tests of interest (this is the cost for measuring multiple antibodies, and therefore matches what was recommended). The committee agreed that, whilst in practice this may be a slight overestimate as discounts might be obtained for bulk testing, it was nevertheless a reasonable value to use. The committee's discussions on this figure and its implications are captured in the discussion on cost effective and resource use below (section 1.1.8.4).

1.1.7.4 Economic model

No economic modelling was done for this review question.

1.1.8 The committee's discussion and interpretation of the evidence

1.1.8.1 The outcomes that matter most

The committee noted that the way it interpreted the review question was important. In the results found, the research question is often "do these people have type x diabetes", not "do these people have type x or type y diabetes" as these do not mean the same thing. Thus they referred to which type of diabetes was being diagnosed, as opposed to "positive, or "negative" results.

The committee highlighted the importance of distinguishing between people with type 1 and type 2 diabetes (and other types) at primary care stage due to the differing treatment pathways that follow, particularly insulin treatment. The committee noted that misdiagnosis is common and stated the most common misdiagnosis is people with type 1 diabetes diagnosed as having type 2 diabetes (a "false negative" in the context of type 1 diabetes) which could lead to the person not receiving insulin treatment and their health deteriorating. People with type 2 being diagnosed as type 1 also has repercussions as they receive unnecessary insulin treatment, and conditions such as LADA can mask what is thought to be a simple type 2 diagnosis. The committee acknowledged it is less harmful to be diagnosed with type 1 diabetes when the person actually has type 2 diabetes. However, there are still harms, including the long-term effects and costs of unnecessary insulin therapy, the missed opportunity for oral diabetes therapies and the psychological impact of misdiagnosis. Revising the diagnosis has its own ramifications regarding a person being on unnecessary

treatment long term and the costs of tests and unnecessary treatment as well as the stress to the person of changing the diagnosis.

The committee prioritised likelihood ratios for decision making as they can be used to interpret the likelihood of a diagnosis at an individual level. This indicates how a test result would change a person's diagnosis as well as those of their healthcare professional. This is preferable to population level characteristics of sensitivity and specificity.

1.1.8.2 The quality of the evidence

Despite the inclusion of more diagnostic test accuracy review evidence than in the previous guideline, the committee agreed that overall this data from individual studies was of poor quality, heterogenous, and often did not directly compare the diagnostic accuracy of characteristics/antibodies/C-peptide tests in distinguishing between people with type 1 and people with other types of diabetes. The committee therefore agreed that the evidence reviewed did not give a clear indicator as to which test was the most effective at distinguishing between people with type 1 diabetes and people with type 2 diabetes, and it had to rely on their own clinical experience in making many of the recommendations.

This general lack of evidence was supported by the Shields 2015 systematic review, which also commented on the surprising lack of useful evidence in this area in their 2015 searches: "There were only 11 appropriate studies identified by Shields (2015) that examined which clinical characteristics could discriminate between T1 and T2D, using the reference standard of insulin deficiency. This is a remarkably low number of studies, and the same number identified in this review, considering the vast majority of the >200 million worldwide patients with diabetes who will be classified into type 1 or type 2 on the basis of clinical features alone and an incorrect classification will result in inappropriate treatment". The committee noted that diabetes has become more prevalent and yet the issue of no comparative diagnostic evidence remains the same. The committee were also aware of an ongoing research project, ADDRESS-2, which is investigating the characteristics of people newly diagnosed with type 1 diabetes in the UK. These findings should help improve our understanding of type 1 diabetes diagnosis and could feed into future updates of this guideline. As a result of this lack of high-quality evidence to inform the diagnosis of diabetes, the committee made a research recommendation outlining the need for further research on the best clinical feature or combination of features for distinguishing between type 1 diabetes and other forms of diabetes.

The committee pointed out several shortcomings in the papers identified:

Regarding disease types in the included studies, the committee agreed that neither the fulminant diabetes study (Tanaka 2004), the KPD study (Balasubramanyam 2006), nor the LADA vs type 2 studies (Fourlanos 2006) and Garnier 2018 (on the screening of ZnT8 autoantibodies) were helpful in answering this review question. The committee agreed none of these studies helped understand how clinical predictors or biomarkers could help distinguish people with type 1 diabetes from other types of diabetes. Regarding recommendations on other forms of diabetes (such as LADA, KPD) the committee also agreed that the evidence presented was too low quality to make other diabetes sub-type specific recommendations.

Regarding the quality of the evidence within the studies, only two primary papers presented enough diagnostic data to produce 2x2 tables and thus calculate likelihood ratios (Fourlanos 2007 and Sia 2020). Fourlanos 2007 was not looking at type 1 vs type 2 whilst Sia (2020) had the highest risk of bias of all included studies due to its case control study design. Sia (2020) also distinguished GADA+ (which can be type 1 OR LADA) from type 2. This means a meta-analysis of diagnostic evidence could not be conducted. These studies also presented

pooled risk data including characteristics not in the protocol (HbA1c, triglycerides, HDL-C) and the nature of their analysis meant these factors could not be interrogated individually.

Studies such as Hope (2016) presented their arm data in a way that meant negative patient numbers could not be calculated, whereas studies like Jones (2011), Thunander (2012) and Wang (2019) did not present confidence intervals with their data, meaning patient numbers could not be back calculated. This collection of reporting errors meant GRADE quality of outcome analysis could not be conducted for the majority of the studies in this review. This led to risk of bias being the only assessable measure of outcome quality for this data, meaning issues with imprecision and indirectness had to be discussed in a consensus fashion with the committee.

Whilst there were different lengths of “time with diabetes” in the studies, with some newly diagnosed and some with more established cases, the studies were too heterogenous in terms of methods of diagnosis. Due to this lack of analysis, recommendations around the usefulness of different diagnostic tests at different timepoints were made by committee consensus using their clinical experience.

The committee queried the directness of Covic (2000) in particular, as it included haemodialysis patients only. They also highlighted that the type 2 definition used in the study was no longer relevant, as the presence of DKA can occur in people with type 2 diabetes as well.

The Shields (2015) systematic review provided 2x2 data. The committee highlighted issues with the Shields (2015) systematic review, noting that one study did not meet the inclusion criteria for this evidence review (Benhamou 1992 is a validation study). There was also significant heterogeneity in ethnicity in the remaining studies, with studies such as Boyle (1999) and Ekpebegh (2013) including a majority of Black or African American patients, whilst studies such as Prior (1991), Laakso (1986), Nielsen (1986) and Welborn (1983) included a majority of white patients. The issue with this heterogeneity is discussed in the benefits and harms section. The committee noted that the age of some of these papers (prior to 1999) also meant that the thresholds of these populations for age at diagnosis and weight-based measurements were no longer applicable to modern populations. This is due to large demographic shifts in age/weight and diabetes type as discussed in other sections of this review (a similar observation was made with Koskinen (1986) outside of this systematic review). The papers in Shields (2015) also suffered similar risk of bias issues to the primary studies included in the NICE evidence review, with unclear patient flow and timings and a variation in reference standard cut-offs (although these were more similar than the primary studies, as Shields 2015 only included studies with a C-peptide reference standard). Based on the poor quality of these studies and the inherent mechanism of action of C-peptide that means it will not function well as a predictor at time of diabetes presentation, the committee decided this systematic review could not inform decision making. As a result of this lack of high-quality evidence on the effectiveness of c-peptide, the committee made a research recommendation outling the need for further research on the effectiveness of c-peptide at correcting misclassification of diabetes diagnosis and what is the optimal timing in distinguishing subtypes of diabetes.

The committee agreed that C-peptide along with blood glucose levels was the best reference standard available, but this was only true for a longer time after an initial presentation of diabetes. Regarding earlier presentation of diabetes, they stated that quantitative autoantibody tests would have been a preferable reference standard.

1.1.8.3 Benefits and harms

The committee noted that the previous guideline did not contain any DTA evidence, and wished to raise this justification for many of the large changes made to recommendations in this update.

Clinical characteristics

The committee agreed that there was not enough high-quality evidence to justify a change in any of the characteristics currently used to help diagnose type 1 diabetes. Nor was there enough evidence to justify a change in the current thresholds.

The committee agreed there was evidence of shifting diabetes demographics outside of this evidence review that could potentially justify reducing the age of onset threshold to 40 years, as this would mean previous recommendations and the evidence they were made upon would be out of date with current diabetes populations, and risk increasing already large percentage of misdiagnosed cases mentioned in papers such as Foteinopoulou 2020. The committee thought this risked the recommendations ruling out type 2 diabetes occurring in these “middle-aged” patients, which the committee said in their experience is still the majority of cases. The committee noted that BMI in people with type 1 diabetes is increasing, and age at diagnosis in people with type 2 diabetes is decreasing. This means the ability of these characteristics alone to discriminate between these types of diabetes is becoming less useful. It was further noted that whilst there is a growing crossover regarding people’s age and BMI between type 1 and type 2 diabetes, these characteristics are still useful for a large percentage of patient diagnoses. They stated that the percentage increase in BMI in people with type 1 diabetes is partly due to an overall increase in obesity rates, and the observed shift in people with type 1 diabetes being younger and people type 2 patients was not robust enough to justify changing the recommendations at this time.

The committee noted the misconception that type 1 diabetes only occurs in non-overweight young people and that the recommendations should not perpetuate this. BMI and age assumptions regarding diabetes type could lead to more misdiagnosis than other factors such as ketosis/ rapid weight loss/ personal and/or family history of autoimmune disease.

The committee noted that ethnicity is currently not mentioned in the recommendations, despite the possibility of adjusting BMI and age thresholds based upon this factor. However, it was agreed that ethnicity alone couldn’t be used to classify diabetes type, and reference was made in discussions to ADDRESS-2, which is a published observational study investigating variations in diabetes clinical presentation between children, adults, and different ethnicities.

The committee agreed that unlike in type 2 diabetes, where using BMI based on a white population may lead healthcare professionals to underdiagnose type 2 diabetes in other populations, in type 1 diabetes the threshold will raise suspicion in non-white populations, which was noted to be positive to identify those cases.

To address the issues noted above with regard to age, BMI and the misconceptions related to diagnosing diabetes type solely on these characteristics the committee agreed to make a recommendation stating that neither characteristic should be used alone to determine diabetes type. The committee acknowledged that no individual criteria should take priority, and in practice they are rarely considered in isolation. Individual characteristics can be helpful for practitioners to combine with their own clinical knowledge to decide rather than

assumptions being made based purely on age and BMI. The committee hoped that the recommendation would make it clear that if the “whole picture” doesn’t fit then further investigations are needed to determine a diagnosis.

Autoantibody testing

As already mentioned, the committee agreed that based on their experience age and BMI alone were no longer effective in classifying diabetes type, as some people do not present classic type 1 symptoms, and cited examples of clinical practice where autoantibody testing is occurring more routinely at diagnosis. This practice helps avoid unnecessarily prescribing insulin for people where this is not required. The committee also noticed that there is a huge quality of life consideration for people with diabetes and the need for a definitive diagnosis. This can also reduce the fear of hypoglycaemia. The committee considered that autoantibody testing was now standard practice.

Misclassification of type 2 diabetes as type 1 diabetes is high risk for DKA and can be fatal, so the committee agreed approaching the risk from this perspective would reduce the risk of severe effects such as DKA.

The committee noted that people with diabetes may feel that autoantibody testing gives them a much better understanding and clearer diagnosis of the condition, as opposed to characteristic classification, as autoantibody testing is a biological marker.

The committee also commented that antibody testing can help avoid assumptions about links between ethnicity and diabetes type (e.g., the assumption people from black and Asian minority ethnic backgrounds are more likely to be type 2), as it means healthcare professionals do not have to rely on characteristics alone at point of diabetes presentation.

The committee therefore agreed that it was important not to discourage the use of autoantibody testing as a “one-off” at diagnosis to avoid the misclassification of diabetes type. A recommendation was therefore made based on their experience to ensure that autoantibody testing is appropriate in people where a diagnosis of type 1 diabetes is suspected. The committee also noted that autoantibody testing is much more useful in earlier presentation of diabetes as autoantibody levels decline at a greater rate the longer a person has had diabetes due to the destruction of b-cells. They also clarified that doing multiple parallel autoantibody tests using different autoantibodies is preferable to reduce the false negative rate. This is based on the committee’s expert knowledge in the field and published literature showing that the prevalence of these antibodies is higher in people with Type 1 and LADA at diagnosis. This is because a positive antibody test indicates beta-cell deficiency and thus insulin requirement. They also highlighted the importance of autoantibody testing in some diabetes types such as ketosis-prone diabetes (KPD), where access to testing can be poor. KPD also occurs at a higher rate in ethnic minority populations.

The committee agreed the wording of this recommendation covered suspected monogenic diabetes. The committee explained that based on their clinical experience this should be a consideration at this point in the diagnostic process. They considered not mentioning it in the recommendations could lead to cases being missed or misdiagnosed and agreed that people with suspected monogenetic diabetes would be referred to secondary care for autoantibody testing as part of standard care.

The committee did not consider additional evidence for this topic was likely to change the recommendations.

C-peptide testing

Due to a lack of clinical evidence the committee agreed that they were unable to recommend routine non-fasting c-peptide testing. This test has a significant cost in clinical practice however despite this the committee noted that it would be an appropriate test in cases where autoantibody test results and characteristics are inconsistent making an appropriate diagnosis decision difficult (for example a negative autoantibody result but characteristics that suggest type 1 diabetes. This was based on the test being used this way in established practice and wider literature.

The committee highlighted that non-fasting c-peptide testing should always be performed in parallel with blood glucose testing, otherwise the results cannot be interpreted, C-peptide indicates the degree of endogenous insulin production in the pancreas, and this should be broadly proportional to blood glucose levels, as the body is supposed to produce insulin in response to blood glucose level increases. They also noted that C-peptide testing needs to involve a specialist team either locally or hospital based.

The committee made a recommendation based on their experience to highlight that c-peptide is more appropriate for revisiting a diagnosis due to its improvement in discriminating value the longer after an initial diagnosis it is done, unlike autoantibody testing. They noted that there can still be an overlap up to approximately 3 years after diagnosis. This time component was not covered in the evidence found and was thus decided by committee consensus, as if it is not addressed it could incur more misdiagnoses and associated costs.

The committee noted that serum C-peptide is more appropriate in individual clinical diagnosis settings as it can be paired with blood glucose, while urine C-peptide is mainly used in epidemiological studies, and thus serum c-peptide was used in the recommendation wording.

1.1.8.4 Cost effectiveness and resource use

The health economic searches found no relevant papers in the UK or other similar countries on the diagnostic tests to distinguish between type 1 diabetes, type 2 diabetes and other forms of diabetes. The committee agreed that the lack of evidence was unsurprising, as most previous cost-effectiveness work had focused on population screening type interventions to identify people with diabetes, rather than differential diagnosis of different diabetes subtypes.

The committee noted that because the recommendations for who to suspect type 1 diabetes in were broadly similar to the previous version of the guidance, these should not result in any substantial changes in practice. However, they noted that there will be an increase in the costs of diagnostic tests given that more antibody tests at the time of diagnosis are now recommended. Specifically, the new recommendations are to measure autoantibodies in all people with an initial clinical diagnosis of type 1 diabetes, rather than only in people where the clinician feels uncertain about the diagnosis. The recommendations on the use of C-peptide tests have also changed, but these were not expected to result in a substantial increase in costs. Specifically, although the recommendation to use C-peptide is stronger now than in the previous version of the guideline, this is offset by the fact the new guideline recommends only measuring C-peptides in people where the diagnosis cannot be resolved with autoantibody test results, rather than conducting simultaneous measurement of autoantibodies and c-peptide, as stated in the previous recommendations. This would also lead to a more effective use of c-peptide tests as those tests are least accurate if conducted at the time of diagnosis.

To estimate the overall cost impact of increased use of antibody tests, we used an estimate of £29.04 for the cost of autoantibody testing, from a reference provided by the committee. The committee agreed that, whilst in practice this may be a slight overestimate as discounts might be obtained for bulk testing, it was nevertheless a reasonable value to use. According to the National Diabetes Audit 2019-20, there are an estimated 7,325 adults in the UK diagnosed with type 1 diabetes each year (taking those with a duration of diabetes less than 1 year). Thus, assuming all of these people are given autoantibody tests, the total cost would be around £212,718. This is likely to be an overestimate of the likely cost impact of the change, as although there may be a small number of extra people not included in this figure who are tested (people suspected of having type 1 diabetes but ultimately diagnosed with another diabetes type), a significant proportion of these people will already be having autoantibodies measured under the previous recommendations and the changes in practice towards antibody testing that have already taken place.

While there was no cost-effectiveness study evaluating antibody tests in the differentiation of types of diabetes, the committee thought that measuring autoantibodies in people with suspected type 1 diabetes would be a cost-effective use of resources, due to the high risk of people with diabetes being misclassified and receiving incorrect treatment. This can result in both additional costs from the use of ineffective treatments and clinical harm, either with a delay to insulin prescription in people with type 1 diabetes, or unnecessary use of insulin in people with type 2 diabetes. In real clinical practice, misdiagnosis is common without antibody testing and patients being offered the wrong treatments might develop diabetic ketoacidosis (DKA) or other fatal complications at a later point, in addition to simply having poorly controlled diabetes due to being given the wrong treatment. According to a cost analysis conducted using individual patient data from the 2014 national survey, the average cost of an episode of DKA was £2,064 per patient in the UK, including physician and nursing time, laboratory and diagnostic assessment, intravenous insulin and ward per diem.[a] Therefore, even excluding the clinical and psychological harm done by misdiagnosis, the large downstream cost of treating these complications can be much higher than the cost of offering antibody testing, and only a small number of these expensive adverse consequences are necessary to outweigh the low cost of autoantibody tests. Further, the committee noted that since antibody tests are more accurate when conducted at the time of initial diagnosis, they would also be more cost-effective to conduct at that time rather than later, since the cost will be the same but more information will be obtained from the test at the time of diagnosis.

1.1.8.5 Other factors the committee took into account

The committee noted alternative diagnoses should also be considered, particularly pancreatic cancer, due to its similar symptoms and potential severity. The main characteristics to consider in pancreatic cancer included over 60s and significant weight loss. In such cases an urgent CT scan would be needed. A cross reference to recommendation 1.2.5 in the NICE Suspected cancer: recognition and referral guideline has been made.

1.1.9 Recommendations supported by this evidence review

This evidence review supports recommendations 1.1.1 – 1.1.9 and research recommendations 1 and 2 in the NG17 guideline.

[a] Dhatariya KK, Skedgel C, Fordham R. The cost of treating diabetic ketoacidosis in the UK: a national survey of hospital resource use. Diabetic Medicine. 2017;34(10):1361-6.

Appendices

Appendix A – Review protocols

Review protocol for body imaging for re-staging

ID	Field	Content	Developer comments *(delete before publication)*
0.	PROSPERO registration number	CRD42021236303	
1.	Review title	In adults with diabetes, what is the best clinical predictors or biomarker test (alone or in combination) to distinguish between diagnosis of type 1 diabetes, type 2 diabetes, and other forms of diabetes.	Original question: In adults with diabetes, what is the best marker (C-peptide plus or minus antibodies) to distinguish between a diagnosis of type 1 diabetes, type 2 diabetes and other forms of diabetes? Scope question: 1. In adults with diabetes, what is the best combination of clinical characteristics to distinguish between a diagnosis of type 1 diabetes, type 2 diabetes and other forms of diabetes? 2. In adults with diabetes, what is the best marker (c-peptides plus or minus antibodies) to distinguish between a diagnosis of type 1 diabetes, type 2 diabetes and other forms of diabetes?

			NOTE: During framework meeting (18/2/2020) two separate questions were developed. The committee stated that for most patients, decision making at diagnosis would be based on the clinical characteristics alone. The committee also stated that the current list of clinical characteristics needs updating.
2.	Review question	In adults with diabetes, what is the best combination of clinical characteristics to distinguish between a diagnosis of type 1 diabetes, type 2 diabetes and other forms of diabetes? In adults with diabetes, what is the best marker (c-peptides plus or minus antibodies) to distinguish between a diagnosis of type 1 diabetes (caused by an absolute insulin deficiency usually resulting from autoimmune destruction of the insulin-producing beta cells in the pancreas), type 2 diabetes (insulin resistance and a relative insulin deficiency resulting in persistent hyperglycaemia) and other forms of diabetes?	NOTE: The 2015 update did not review clinical characteristics but recommendation 1.1.1 and 1.1.2 were developed as part of the update. The committee discussion section highlights that the GDG recognised that in most people presenting with a new diagnosis of diabetes, clinical features are utilised (ketosis at diagnosis, rapidity of symptom onset, age at presentation, body mass index and a family history of autoimmune disease). The GDG also states that differentiation of diabetes types might become increasingly difficult with increases in body mass index in the population in general.

3.	Objective	To determine the best individual/combination of clinical characteristics, as well as the best individual/combination of biomarkers, for distinguishing between a diagnosis of type 1 diabetes, type 2 diabetes, or other forms of diabetes	1/11/2020: Committee highlighted that diabetes has been reported to be misclassified in 7-15% cases which can lead to the wrong treatment. In clinical practice, the type of diabetes may not be clear not diagnosis (not uncommon experience) and only revealed some time later (weeks or months after diagnosis). This question is very important in clinical practice both in primary and secondary care.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • MEDLINE In-Process • Database of Abstracts of Reviews of Effect (DARE) • APA PsychINFO • EconLit • NHS-EED • INAHTA	Searches currently still with David and IS team awaiting confirmation of scope. Preliminary results suggest >17,000 includes.

		Clinical searches will be restricted by: • English language • Human studies • Publication type • McMaster Diagnostic filter • NICE Observational studies filter or health-evidence.ca systematic review filter Economics searches will be restricted by: • English language • Human studies • Publication type • McMaster Diagnostic filter • NICE Economics evaluation filter (adapted from CRD) or NICE quality of life filter (adapted from ScHARR) The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.	
5.	Condition or domain being studied	Type 1 diabetes, Type 2 diabetes, other types of diabetes (e.g. LDA, Double diabetes).	

6.	Population	Inclusion: Adults with type 1, type 2, or other types of diabetes (e.g. LADA, double diabetes, Ketosis Prone Diabetes [Flatbush diabetes], type 4 diabetes) Exclusion: Children with diabetes, Young adults with diabetes (<18 years old), Adults with Monogenetic diabetes, gestational diabetes or pre-diabetes.	If mixed population paper possesses an adult subgroup it is included. We have excluded mixed populations as the original guideline did, children out of scope. LADA, double, Ketosis Prone [Flatbush] and Type 4 diabetes identified by committee members as rare but distinct forms as opposed to the general wording of "other types of diabetes". Gestational diabetes excluded as it is covered by NG3.
7.	Intervention/Exposure/Test	Clinical predictors (alone or in combination) including: • BMI (<25) • age at diagnosis • presence of ketones • diabetic ketoacidosis • family history • presence of auto immune conditions • ethnicity • time to commencing insulin treatment from diagnosis • weight loss C-peptide (alongside glucose levels) • plasma C-peptide (stimulated) • urinary C-peptide • urinary C-peptide/creatinine ratio	Surveillance report highlighted that new evidence was identified that suggested that people with late-onset type 1 diabetes may be at risk of misclassification and that clinical characteristics like BMI may not be as accurate as C-peptide tests when distinguishing between diabetes types in people aged over 35 years. ***Clinical predictors:***

		C-peptide (alongside glucose levels) with antibody tests: • insulin autoantibodies (IAA) • anti-glutamic acid decarboxylase 65 antibody or anti-glutamic acid decarboxylase antibody (GADA) • insulinoma-associated (IA-2/ICA512) autoantibody • zinc transporter 8 (ZnT8) • islet-specific glucose-6-phosphatase catalytic subunit (IGRP)	Committee members highlighted that newly diagnosed people with diabetes have c-peptide/ antibody testing routinely regardless of age and BMI as specified in the current guideline. 11/ 01/ 21 – following discussion with RQ clinical leads Whilst its agreed type-1 diabetes can be present at any age (with a significant number diagnosed under the age of 30), age does have a role in diagnosis of type 1, but this role is less important than that of BMI. There is also increasing overlap in the age of type 1 and type 2 patients (people with T2D are trending younger). Whilst it is agreed the age threshold of >50 in the 2015 guideline may be too high, there is no agreement on what an accurate age threshold would be, and so this must be investigated in the evidence. It should be clarified in the final recommendations that age is only one criterion of many to help distinguish whether a person has type 1 diabetes.

			Large overlap in 18-30 age group. A BMI threshold of less than 25 means type 1 diabetes is more likely, whilst a BMI >25 does not necessarily distinguish between the two. The mean BMI of a person with T1D is now around 27 and has been trending higher, causing more overlap between T1D and T2D. BMI threshold can be ethnicity dependent (for example, people from South Asian or Chinese ethnicities would be classed as being overweight with a BMI of >23) so this should be considered in any papers looking at these populations. Clinical predictors (BMI, age at diagnosis, presence of ketones, family history, presence of autoimmune conditions and ethnicity) carried forward from scoping framework. Committee also noted that time to insulin has been shown to improve predictability of diabetes types (Shields 2015)

			Committee highlighted that diabetic ketoacidosis may also point towards type 1 diabetes. Some clinical predictors are more valuable e.g., DKA. BMI and ethnicity are graded lower on the list. ***Biomarker testing:*** Biomarkers carried forward from framework. Committee members highlighted that the guideline for type 1 diabetes reflects current practice, but the clinical practice may have changes in relation to c-peptide testing and antibody screening. 11/ 01/ 21 – following discussion with RQ clinical leads There are many factors that complicate looking for results of c-peptide DTAs *Timing of c-peptide test:*

			• there are advantages to doing a stimulated c-peptide test at diagnosis, B-cell function and thus as c-peptide levels are far higher in T2 patients at this stage, and you would be less likely to misdiagnose T2 as T1, and thus T2 patients are not put on unnecessary costly insulin therapy/monitoring with related side effects. It can be harder to distinguish c-peptide the later into a patient's diabetes you test. • However, there is a risk of misdiagnosing T1 patients as T2, which has the potential consequences of causing severe

			consequences such as ketoacidosis. There are concerns c-peptide results will be misinterpreted if done at diagnosis *Stimulated/fasting/urinary c-peptide* • Data should be collected looking at whether C-peptide measure was stimulated/fasting or urinary. Stimulated glucose should be used as this type of measure gives you informative c-peptide AND glucose relationship. • Some studies may conduct random c-peptide tests in which random samples are taken at any time during the day. Would need to look at

			methods highlighted in the paper. • *"Honeymooning"* • When people with T1D begin insulin therapy it can be relatively well controlled due to them still producing a small amount of insulin themselves, this in known as the "honeymoon" period and if the only results are during this period it can lead to misinterpretation of measurements It is vital when we reach the stage of recommendation writing that the guidance is clear in how to interpret c-peptide results, and that this should NEVER be done without the relevant blood glucose levels. We should also keep

			an eye out for this in the evidence base. There are concerns around differential interpretation of c-peptide results in different settings depending on their experience with c-peptide testing. **Antibodies:** All antibodies but IGRP are used commonly in clinical practice. GADA/GAD65 being a key test. Multiple committee members raised concerns about ICA being an “out of date” test. It was explained that it is an immunofluorescence test providing a qualitative result, as opposed to all the other antibody tests which give you a numeric result and a normal range. Based on this information it has been removed from the protocol. ZnT8 is a highly specific antibody and may be used in a proportion of patients where GAD returns a negative result.

			No committee members objected to the idea of IGRP being used in clinical practice so we feel we did not have enough information to exclude it form the protocol.
8.	Comparator/Reference standard/Confounding factors	Any predictors or biomarker tests listed as clinical characteristics.	Committee were consulted about appropriate reference standards. The committee highlighted that there is no single gold standard/ reference standard. Should be noted that C-peptide was used as preference standard in Shields 2015 SR.
9.	Types of study to be included	Diagnostic accuracy studies	QA team queried if association review would be conducted for the clinical predictors. Development team highlighted that there is a substantial evidence base for DTA evidence for clinical features (Shields 2015). The committee also stated that looking at the evidence for association alone was not a priority.
10.	Other exclusion criteria	• Validation studies • detecting markers in relatives of people with diabetes • examining risk calculators only	Lynam 2019 paper validated multivariable clinical diagnostic models to assist distinguishing between type1 and type 2 diabetes.

		• non-English language studies • conference abstracts	Committee highlighted that clinical calculators are not used to determine the probability of type 1 diabetes vs type 2 diabetes in routine clinical practice but is used in research. Calculators are commonly used to determine the probability of monogenic diabetes, but this is out of scope of this update.
11.	Context	This review is part of an update of the NICE guideline "Type 1 diabetes in adults: diagnosis and management (NG17)"	
12.	Primary outcomes (critical outcomes)	• Likelihood Ratios • Sensitivity • Specificity • PPV • NPV • AUC • Correlation coefficient	2015 update did not include diagnostic accuracy measures but included outcomes such as presence of marker, concentration/titre of marker, change in marker over time and change in concentration/titre of marker over time. Committee agreed that DTA measures should be looked at as part of this question. Likelihood ratios added by internal GUT QA, not likely to find in search but will be our main method of outcome presentation.

13.	Secondary outcomes (important outcomes)	NA	
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Data will be extracted from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control conditions; study methodology; recruitment and study completion rates; outcomes and times of measurement and information for assessment of the risk of bias. Study investigators may be contacted for missing data where time and resources allow. This review will make use of the priority screening functionality within the EPPI-reviewer software.	
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.	
16.	Strategy for data synthesis	Where possible, the data will be separated out based on time of diagnosis. Studies including newly	11/ 01/ 21 – following discussion

		diagnosed patients (diagnosis made up to 1 year before the study) will be analysed separately to studies using a population with established diabetes. Diagnostic test accuracy (DTA) data will be used to generate a 2x2 classification of true positives and false negatives (in people who, according to the reference standard, truly have the condition) and false positives and true negatives (in people who, according to the reference standard, do not). Meta-analyses of outcome data will be conducted for all comparators that are reported by more than one study, with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011). Fixed- and random-effects models (der Simonian and Laird) will be fitted for all comparators, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model is clearly not met, even after appropriate pre-specified subgroup analyses is conducted, random-effects results are presented. Fixed-effects models are deemed to be inappropriate if one or both of the following conditions was met: • Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis.	with RQ clinical leads There is a debate as to when c-peptide testing should be conducted. There are advantages to doing a stimulated c-peptide test at diagnosis, but some people with T1D may still produce c-peptide leading to misdiagnosis. Where possible, studies will be separated out based on time of diagnosis. This criteria was carried forward from 2015 guideline. Where possible we will separate out studies that have explicitly conducted glucose testing alongside c-peptide testing as this is key to contextualise c-peptide levels.

		• The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$. • Meta-analyses will be performed in Cochrane Review Manager V5.3	
17.	Analysis of sub-groups	• People with chronic kidney disease	Committee also highlighted that literature on mental illness has shown that there is a higher chance of misdiagnosis in this group.
18.	Type and method of review	☐ Intervention ☒ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☒ Service Delivery ☐ Other (please specify)	
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	[For the purposes of PROSPERO, the date of commencement for the systematic review can be defined as any point after completion of a protocol but before formal screening of the identified studies against the eligibility criteria begins. A protocol can be deemed complete after sign-off by the NICE team with responsibility for quality assurance.]	

<table>
<tr><td>22.</td><td>Anticipated completion date</td><td colspan="3">[Give the date by which the guideline is expected to be published. This field may be edited at any time. All edits will appear in the record audit trail. A brief explanation of the reason for changes should be given in the Revision Notes facility.]</td><td></td></tr>
<tr><td>23.</td><td>Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td><td></td></tr>
<tr><td></td><td></td><td>Preliminary searches</td><td>☑</td><td>☐</td><td></td></tr>
<tr><td></td><td></td><td>Piloting of the study selection process</td><td>☐</td><td>☐</td><td></td></tr>
<tr><td></td><td></td><td>Formal screening of search results against eligibility criteria</td><td>☐</td><td>☐</td><td></td></tr>
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<tr><td></td><td></td><td>Data analysis</td><td>☐</td><td>☐</td><td></td></tr>
<tr><td>24.</td><td>Named contact</td><td colspan="3">a. Named contact
Guideline Updates Team

b Named contact e-mail
Diabetesupdate@nice.org.uk</td><td></td></tr>
</table>

		c Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and NICE Guideline Updates	
25.	Review team members	From the Guideline Updates Team: • Caroline Mulvihill • Joseph Crutwell • Shreya Shukla • Joshua Pink • David Nicholls	
26.	Funding sources/sponsor	This systematic review is being completed by the Centre for Guidelines which receives funding from NICE.	
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10158	

29.	Other registration details	None	
30.	Reference/URL for published protocol	None	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Diagnosis, clinical characteristics, biomarker test, type 1 diabetes, type 2 diabetes, adults	
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued	
35..	Additional information		
36.	Details of final publication	www.nice.org.uk	

Appendix B – Methods

Remit

The aim of this review is to determine what is the best clinical predictors or biomarker test (alone or in combination) to distinguish between diagnosis of type 1 diabetes, type 2 diabetes, and other forms of diabetes.

This guideline was developed using the methods described in the 2018 NICE guidelines manual. Declarations of interest were recorded according to the NICE conflicts of interest policy.

Developing the review questions and outcomes

The review questions developed for this guideline were based on the key areas identified in the guideline scope. They were drafted by the NICE guideline updates team and refined and validated by the guideline committee.
The review questions were based on the following frameworks:

- Population, index test(s), reference standard and outcome for reviews of diagnostic and predictive accuracy

Full literature searches, critical appraisals and evidence reviews were completed for all review questions.

Reviewing research evidence

Review protocols

Review protocols were developed with the guideline committee to outline the inclusion and exclusion criteria used to select studies for each evidence review. Where possible, review protocols were prospectively registered in the PROSPERO register of systematic reviews.

Searching for evidence

Evidence was searched for each review question using the methods specified in the 2018 NICE guidelines manual.

Selecting studies for inclusion

All references identified by the literature searches and from other sources (for example, previous versions of the guideline or studies identified by committee members) were uploaded into EPPI reviewer software (version 5) and de-duplicated. Titles and abstracts were assessed for possible inclusion using the criteria specified in the review protocol. 10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

The following evidence reviews made use of the priority screening functionality within the EPPI-reviewer software: [insert links to evidence reviews that used the priority screening functionality in EPPI]. This functionality uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being ‘includes’ or ‘excludes’

during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened. Research is currently ongoing as to what are the appropriate thresholds where reviewing of abstracts can be stopped, assuming a defined threshold for the proportion of relevant papers it is acceptable to miss on primary screening. As a conservative approach until that research has been completed, the following rules were adopted during the production of this guideline:

- In every review, at least 50% of the identified abstracts (or 1,000 records, if that is a greater number) were always screened.
- After this point, screening was only terminated if a pre-specified threshold was met for a number of abstracts being screened without a single new include being identified. This threshold was set according to the expected proportion of includes in the review (with reviews with a lower proportion of includes needing a higher number of papers without an identified study to justify termination) and was always a minimum of 250.

As an additional check to ensure this approach did not miss relevant studies, systematic reviews (or qualitative evidence syntheses in the case of reviews of qualitative studies) were included in the review protocol and search strategy for all review questions. Relevant systematic reviews or qualitative evidence syntheses were used to identify any papers not found through the primary search. Committee members were also consulted to identify studies that were missed. If additional studies were found that were erroneously excluded during the priority screening process, the full database was subsequently screened.
The decision whether or not to use priority screening was taken by the reviewing team depending on the perceived likelihood that stopping criteria would be met, based on the size of the database, heterogeneity of studies included in the review and predicted number of includes. If it was thought that stopping criteria were unlikely to be met, priority screening was not used, and the full database was screened.
The full text of potentially eligible studies was retrieved and assessed according to the criteria specified in the review protocol. A standardised form was used to extract data from included studies. Study investigators were contacted for missing data when time and resources allowed (when this occurred, this was noted in the evidence review and relevant data was included).

Incorporating published evidence syntheses

For all review questions where a literature search was undertaken looking for a particular study design, published evidence syntheses (quantitative systematic reviews or qualitative evidence syntheses) containing studies of that design were also included. All included studies from those syntheses were screened to identify any additional relevant primary studies not found as part of the initial search. Evidence syntheses that were used solely as a source of primary studies were not formally included in the evidence review (as they did not provide additional data) and were not quality assessed.

If published evidence syntheses were identified sufficiently early in the review process (for example, from the surveillance review or early in the database search), they were considered for use as the primary source of data, rather than extracting

information from primary studies. Syntheses considered for inclusion in this way were quality assessed to assess their suitability using the appropriate checklist, as outlined in **Table 7**. Note that this quality assessment was solely used to assess the quality of the synthesis in order to decide whether it could be used as a source of data, as outlined in **Table 8**, not the quality of evidence contained within it, which was assessed in the usual way as outlined in the section on 'Appraising the quality of evidence'.

Table 7: Checklists for published evidence syntheses

Type of synthesis	Checklist for quality appraisal
Systematic review of quantitative evidence	ROBIS
Network meta-analysis	Modified version of the PRISMA NMA tool (see appendix K of 'Developing NICE guidelines, the manual')
Qualitative evidence synthesis	ENTREQ reporting standard for published evidence synthesis (https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-12-181) is the generic reporting standard for QES, however specific reporting standards exist for meta-ethnography (eMERGe [https://emergeproject.org/]) and for realist synthesis (RAMESES II [https://www.ramesesproject.org/]). If these reporting standards are not appropriate to the QES then an adapted PRISMA framework is used (see Flemming K, Booth A, Hannes K, Cargo M, Noyes J. Cochrane Qualitative and Implementation Methods Group guidance series-paper 6: reporting guidelines for qualitative, implementation, and process evaluation evidence syntheses. Journal of Clinical Epidemiology 2018; 97: 79-85).
Individual patient data meta-analysis	Checklist based on Tierney, Jayne F., et al. "Individual participant data (IPD) meta-analyses of randomised controlled trials: guidance on their use." PLoS Med 12.7 (2015): e1001855.

Each published evidence synthesis was classified into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.
- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.
- Low quality – It is possible that relevant and important studies have been missed by the review.

Each published evidence synthesis was also classified into one of three groups for its directness as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

- Fully applicable – The identified review fully covers the review protocol in the guideline.
- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline (for example, some of the factors in the protocol only).

- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

The way that a published evidence synthesis was used in the evidence review depended on its quality and applicability, as defined in **Table 8**. When published evidence syntheses were used as a source of primary data, data from these evidence syntheses were quality assessed and presented in GRADE/CERQual tables in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these were checked to ensure none of the data had been double counted through this process.

Table 8: Criteria for using published evidence syntheses as a source of data

Quality	Applicability	Use of published evidence synthesis
High	Fully applicable	Data from the published evidence synthesis were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review. If the review was considered up to date (following discussion with the guideline committee and NICE lead for quality assurance), no additional search was conducted.
High	Partially applicable	Data from the published evidence synthesis were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. If the review was considered up to date (following discussion with the guideline committee and NICE lead for quality assurance), no additional search was conducted. For other sections not covered by the evidence synthesis, searches were undertaken as normal.
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full-text papers of included studies were still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the evidence synthesis, searches were undertaken as normal.

Appraising the quality of evidence

Diagnostic accuracy studies

Individual diagnostic accuracy studies were quality assessed using the QUADAS-2 tool. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.

- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, index features and/or reference standard in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, index feature and/or reference standard.
- Partially indirect – Important deviations from the protocol in one of the population, index feature and/or reference standard.
- Indirect – Important deviations from the protocol in at least two of the population, index feature and/or reference standard.

GRADE for diagnostic accuracy evidence

Evidence from diagnostic accuracy studies was initially rated as high-quality, and then downgraded according to the standard GRADE criteria (risk of bias, inconsistency, imprecision and indirectness) as detailed in **Table 10** below. The choice of primary outcome for decision making was determined by the committee and GRADE assessments were undertaken based on these outcomes. In all cases, the downstream effects of diagnostic accuracy on patient- important outcomes were considered. This was done explicitly during committee deliberations and reported as part of the discussion section of the review detailing the likely consequences of true positive, true negative, false positive and false negative test results. In reviews where a decision model is being carried (for example, as part of an economic analysis), these consequences were incorporated here in addition.

Using likelihood ratios as the primary outcomes

The following schema (**Table 9**), adapted from the suggestions of Jaeschke et al. (1994), was used to interpret the likelihood ratio findings from diagnostic test accuracy reviews.

Table 9 Interpretation of likelihood ratios

Value of likelihood ratio	Interpretation
LR ≤ 0.1	**Very large** decrease in probability of disease
0.1 < LR ≤ 0.2	**Large** decrease in probability of disease
0.2 < LR ≤ 0.5	**Moderate** decrease in probability of disease
0.5 < LR ≤ 1.0	**Slight** decrease in probability of disease
1.0 < LR < 2.0	**Slight** increase in probability of disease
2.0 ≤ LR < 5.0	**Moderate** increase in probability of disease
5.0 ≤ LR < 10.0	**Large** increase in probability of disease
LR ≥ 10.0	**Very large** increase in probability of disease

The schema above has the effect of setting a clinical decision threshold for positive likelihoods ratio at 2, and a corresponding clinical decision threshold for negative likelihood ratios at 0.5. Likelihood ratios (whether positive or negative) falling

between these thresholds were judged to indicate no meaningful change in the probability of disease.

GRADE assessments were only undertaken for positive and negative likelihood ratios but results for sensitivity and specificity are also presented alongside those data.

The committee were consulted to set 2 clinical decision thresholds for each measure: the likelihood ratio above (or below for negative likelihood ratios) which a test would be recommended, and a second below (or above for negative likelihood ratios) which a test would be considered of no clinical use. These were used to judge imprecision (see below). If the committee were unsure which values to pick, then the default values of 2 for LR+ and 0.5 for LR- were used based on **Table 9**, with the line of no effect as the second clinical decision line in both cases.

Table 10: Rationale for downgrading quality of evidence for diagnostic accuracy data

If studies could not be pooled in a meta-analysis, GRADE assessments were undertaken for each study individually and reported as separate lines in the GRADE profile.

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels.
Imprecision	If the 95% confidence interval for the outcome crossed one of the clinical decision thresholds, the outcome was downgraded one level. If the 95% confidence interval spanned both thresholds, the outcome was downgraded twice.

GRADE criteria	Reasons for downgrading quality
	See the sections on 'Using likelihood ratios as the primary outcome'
Publication bias	If the review team became aware of evidence of publication bias (for example, evidence of unpublished trials where there was evidence that the effect estimate differed in published and unpublished data), the outcome was downgraded once. If no evidence of publication bias was found for any outcomes in a review (as was often the case), this domain was excluded from GRADE profiles to improve readability.

Appendix C – Literature search strategies

Name: Dave Nicholls	QA/reviewed by: Sarah Glover (translations checked by Jenny Craven)

Topic/question details:

In adults with diabetes, what is the best combination of clinical characteristics to distinguish between a diagnosis of type 1 diabetes, type 2 diabetes and other forms of diabetes?

In adults with diabetes, what is the best marker (c-peptides plus or minus antibodies) to distinguish between a diagnosis of type 1 diabetes (caused by an absolute insulin deficiency usually resulting from autoimmune destruction of the insulin-producing beta cells in the pancreas), type 2 diabetes (insulin resistance and a relative insulin deficiency resulting in persistent hyperglycaemia) and other forms of diabetes

Databases	Date searched	Version/files	No. retrieved	EPPI data
Cochrane Central Register of Controlled Trials (CENTRAL)	22/01/2021	Issue 1 of 12, January 2021	1916	15104-17019
Cochrane Database of Systematic Reviews (CDSR)	22/01/2021	Issue 1 of 12, January 2021	10	15094-15103
Database of Abstracts of Reviews of Effect (DARE)	24/01/2021	n/a	178	17020-17197
Embase (Ovid)	22/01/2021	1974 to 2021 January 20	7593	7334-14296
MEDLINE (Ovid)	22/01/2021	1946 to January 20, 2021 (during annual reload – backdate update search to 01 December 2020)	6829	1-6829
MEDLINE In-Process (Ovid)	22/01/2021	1946 to January 20, 2021 (during annual reload – backdate update search to 01 December 2020)	429	6830-7258
MEDLINE Epub Ahead of Print	22/01/2021	January 20, 2021 (during annual reload – backdate update search to 01 December 2020)	75	7259-7333
APA PsycINFO (Ovid)	25/01/2021	1806 to January Week 3 2021	167	14297-15093

Search strategies

Database: Medline
Database: Ovid MEDLINE(R) <1946 to January 20, 2021> Search Strategy: --- 1 exp Diabetes Mellitus/ (435104) 2 diabet*.ti,ab. (560314) 3 (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).ti,ab. (1707) 4 lada.ti,ab. (548) 5 (dm1 or iddm or t1d* or dka).ti,ab. (19864) 6 (dm2 or t2d* or mody or niddm).ti,ab. (33965) 7 (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).ti,ab. (320) 8 (DM adj4 onset* adj4 (maturit* or adult* or slow*)).ti,ab. (62) 9 (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).ti,ab. (93) 10 (DM adj4 (earl* or sudden onset or juvenile or child*)).ti,ab. (868) 11 (DM adj4 (keto* or acidi* or gastropare*)).ti,ab. (77) 12 (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).ti,ab. (4388) 13 (DM adj4 ("type 4" or type4 or "type iv" or "type four" or T4 or T-4 or TIV or T-IV)).ti,ab. (26) 14 or/1-13 (625888) 15 *Diabetes, Gestational/ (9473) 16 (gestation* or pregnan*).ti. (240132) 17 15 or 16 (241299) 18 14 not 17 (606366) 19 C-Peptide/ (8480) 20 ("c peptide*" or c-peptide or Cpeptide or ((connect* or gamma*) adj4 peptide)).ti,ab. (14059) 21 (creatinine* adj4 (ratio* or quota* or proportion*)).ti. (958) 22 Autoantibodies/ (68445) 23 (antibod* or anti bod*or autoantibod* or auto-antibod* or auto-anti-bod* or autoantigen* or auto-antigen* or auto-anti-gen*).ti,ab. (809480) 24 22 or 23 (836306) 25 (islet cell or beta cell or decarboxylase or glutamic or insulin*).ti,ab. (391050) 26 "Islets of Langerhans"/ (36377) 27 glutamate decarboxylase/ (8348) 28 (glutam* adj4 (decarbox* or carbox*)).ti,ab. (9735) 29 insulinoma/ (4596) 30 glucose-6-phosphatase/ (5007) 31 (glucose 6 phosphatase or glucosephosphatase).ti,ab. (4516) 32 Zinc Transporter 8/ (358) 33 zinc transporter 8.ti,ab. (214) 34 (islet adj4 (phosphatase or catalytic or subunit* or sub-unit*)).ti,ab. (193) 35 (igrp* or iaa* or ica* or ia-2* or ia2* or znt8* or gad* or CA512).ti,ab. (88151) 36 or/25-35 (491823) 37 24 and 36 (26275) 38 or/19-21,37 (42152) 39 Body Mass Index/ (130391) 40 ((body mass or quetelet*) adj2 index).ti,ab. (161895)

41 BMI.ti,ab. (124677)
42 "Age of Onset"/ (38449)
43 ((age* adj2 onset*) or age-of-onset or age-at-onset).ti,ab. (32173)
44 Ketones/ (15644)
45 ketone*.ti,ab. (22996)
46 Diabetic Ketoacidosis/ (6557)
47 (diabetic adj4 (ketoacidos* or acidos*)).ti,ab. (5276)
48 DKA.ti,ab. (1610)
49 Family Health/ (23544)
50 Genetic Predisposition to Disease/ (140910)
51 ((famil* or household* or forebear* or parent* or relativ*) adj4 health*).ti,ab. (51727)
52 (genetic* adj4 (predispos* or suscept*)).ti,ab. (36134)
53 addison disease/ (4603)
54 ((Addison* adj4 diseas*) or ((primar* adj4 (adren* adj4 insuff*)) or hypoadren*)).ti,ab. (4671)
55 anemia, hemolytic, autoimmune/ (5877)
56 ((H?emolyt adj4 An?emi*) or (cold adj4 (agglutin* or antibod*) adj4 diseas*)).ti,ab. (423)
57 anti-glomerular basement membrane disease/ (2034)
58 (((((Anti Glomerul* or Antiglomerul*) adj4 Basement* adj4 Membran*) or anti gbm) adj4 Diseas*) or (goodpasture* adj4 syndrom*) or (lung adj4 purpura adj4 nephrit*)).ti,ab. (1662)
59 anti-neutrophil cytoplasmic antibody-associated vasculitis/ (1866)
60 (((Anti Neutrophil adj4 Cytoplasm* adj4 Antibod*) or ANCA or pauci immune) adj4 Vasculit*).ti,ab. (3177)
61 antiphospholipid syndrome/ (8278)
62 ((anti phospholipid* or antiphospholipid* or hughes*) adj4 syndrom*).ti,ab. (8792)
63 arthritis, juvenile/ (10552)
64 arthritis, rheumatoid/ (100516)
65 ((Juvenil* or Rheumat*) adj4 (Arthrit* or oligoarthrit* or still or still*)).ti,ab. (103667)
66 "autoimmune diseases of the nervous system"/ (1245)
67 ((autoimmun* or immun*) adj4 (diseas* or disorder*) adj4 (nervous or neurologic*)).ti,ab. (3297)
68 autoimmune hypophysitis/ (121)
69 (((autoimmun* or idiopath* or lymphoid* or lymphocyt* or igg4*) adj4 (hypophys* or adenohypophys* or infundibuloneurohypophys*)) or (anti pit 1 adj4 antibod* adj4 syndrom*)).ti,ab. (708)
70 autoimmune lymphoproliferative syndrome/ (210)
71 (((autoimmun* adj4 lymphoproliferat*) or canale smith or caspase*) adj4 (syndrom* or deficien*)).ti,ab. (1324)
72 autoimmune pancreatitis/ (56)
73 (((autoimmun* or idiopath* or igg4*) adj4 pancreatit*) or type 1 aip or type 2 aip).ti,ab. (2689)
74 birdshot chorioretinopathy/ (105)
75 (birdshot adj4 (chorioretin* or retinochoroid*)).ti,ab. (320)
76 dermatitis herpetiformis/ (2711)
77 ((dermatit* adj4 herpetiform*) or (duhring* adj4 diseas*)).ti,ab. (2197)
78 glomerulonephritis, iga/ (6220)
79 (((IGA or immunoglob*) adj4 (glomerulonephrit* or nephr*)) or (berger* adj4 diseas*)).ti,ab. (7767)
80 glomerulonephritis, membranous/ (3253)
81 (((membran* or extramembran*) adj4 (glomeruloneph* or neuropath*)) or ((heymann or (idiopath* adj4 membran*)) adj4 nephrit*)).ti,ab. (4839)
82 graves disease/ (15216)
83 (((graves* or basedow*) adj4 diseas*) or (exophthal* adj4 goiter*)).ti,ab. (12330)

84 hepatitis, autoimmune/ (3663)
85 (autoimmun* adj4 hepatit*).ti,ab. (5702)
86 immunoglobulin g4-related disease/ (485)
87 (((Immunoglob* adj4 (G4-Related or G4related or "G4 Related")) or IGG4*) adj4 (Diseas* or RD)).ti,ab. (2496)
88 linear iga bullous dermatosis/ (163)
89 (Linear* adj4 (Bullous* or IGA) adj4 Dermatos*).ti,ab. (535)
90 lupus erythematosus, systemic/ (55215)
91 ((Lupus* adj4 Erythemat*) or libman sacks).ti,ab. (54765)
92 ophthalmia, sympathetic/ (722)
93 (sympathetic* adj4 (ophthal* or uveit*)).ti,ab. (780)
94 pemphigoid, bullous/ (3769)
95 pemphigus/ (8304)
96 pemphig*.ti,ab. (13113)
97 polyendocrinopathies, autoimmune/ (1260)
98 ((autoimmun* adj4 (polyendocrin* or polygland*)) or apeced or ((aire or multiple endocrin*) adj4 deficien*) or aps type 1 or (schmidt* adj4 syndrom*)).ti,ab. (1584)
99 purpura, thrombocytopenic, idiopathic/ (6473)
100 (((autoimmune* or idiopath* or immun*) adj4 thrombocytopen) or (werlhof* adj4 diseas*)).ti,ab. (263)
101 thyroiditis, autoimmune/ (7095)
102 ((autoimmun* or lympho*) adj4 thyroidit*).ti,ab. (4534)
103 undifferentiated connective tissue diseases/ (106)
104 (Undifferent* adj4 Connect* adj4 Tissue* adj4 Diseas*).ti,ab. (347)
105 Celiac Disease/ (20209)
106 ((c?eliac* or nontropic* or non-tropic*) adj4 (diseas* or sprue*)).ti,ab. (16804)
107 (gluten* adj4 enteropath*).ti,ab. (956)
108 exp Hypothyroidism/ (32985)
109 hypothyroid*.ti,ab. (31537)
110 ((tsh or thyroid stimulat* hormone*) adj4 deficienc*).ti,ab. (435)
111 exp Hyperthyroidism/ (43541)
112 hyperthyroid*.ti,ab. (21545)
113 Gastritis, Atrophic/ (2659)
114 (atrophic* adj4 gastrit*).ti,ab. (3909)
115 Population Characteristics/ (11414)
116 (populat* adj4 (character* or heterogen* or statistic*)).ti,ab. (43708)
117 (ethnic* or nationalit*).ti,ab. (130158)
118 Weight Loss/ (37326)
119 (weigh* adj4 (loss* or reduc*)).ti,ab. (112549)
120 Time-to-Treatment/ (7646)
121 ("time to treatment*" or "door to treatment*" or (delay* adj4 (treatment* or therap*))).ti,ab. (40610)
122 or/39-121 (1229839)
123 38 or 122 (1264950)
124 18 and 123 (120102)
125 (sensitiv: or predictive value:).mp. or accurac:.tw. (1926164)
126 124 and 125 (14119)
127 animals / not humans/ (4745641)
128 126 not 127 (13366)
129 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. (2099477)

130	128 not 129 (13263)
131	limit 130 to english language (12626)
132	Observational Studies as Topic/ (5806)
133	Observational Study/ (91437)
134	Epidemiologic Studies/ (8529)
135	exp Case-Control Studies/ (1135871)
136	exp Cohort Studies/ (2080075)
137	Cross-Sectional Studies/ (350630)
138	Controlled Before-After Studies/ (582)
139	Historically Controlled Study/ (193)
140	Interrupted Time Series Analysis/ (1098)
141	Comparative Study.pt. (1880501)
142	case control$.tw. (115696)
143	case series.tw. (62223)
144	(cohort adj (study or studies)).tw. (182466)
145	cohort analy$.tw. (7186)
146	(follow up adj (study or studies)).tw. (46004)
147	(observational adj (study or studies)).tw. (91867)
148	longitudinal.tw. (213112)
149	prospective.tw. (512067)
150	retrospective.tw. (465040)
151	cross sectional.tw. (301103)
152	or/132-151 (4479989)
153	(MEDLINE or pubmed).tw. (175472)
154	systematic review.tw. (132179)
155	systematic review.pt. (141793)
156	meta-analysis.pt. (125173)
157	intervention$.ti. (129795)
158	or/153-157 (403334)
159	152 or 158 (4771063)
160	131 and 159 (6829)

Notes

See QA record

Database: MIP

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to January 20, 2021>
Search Strategy:

1	exp Diabetes Mellitus/ (0)
2	diabet*.ti,ab. (81951)
3	(DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).ti,ab. (336)
4	lada.ti,ab. (83)
5	(dm1 or iddm or t1d* or dka).ti,ab. (3178)
6	(dm2 or t2d* or mody or niddm).ti,ab. (8592)

7 (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).ti,ab. (62)
8 (DM adj4 onset* adj4 (maturit* or adult* or slow*)).ti,ab. (7)
9 (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).ti,ab. (12)
10 (DM adj4 (earl* or sudden onset or juvenile or child*)).ti,ab. (144)
11 (DM adj4 (keto* or acidi* or gastropare*)).ti,ab. (13)
12 (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).ti,ab. (1109)
13 (DM adj4 ("type 4" or type4 or "type iv" or "type four" or T4 or T-4 or TIV or T-IV)).ti,ab. (6)
14 or/1-13 (82650)
15 *Diabetes, Gestational/ (0)
16 (gestation* or pregnan*).ti. (23293)
17 15 or 16 (23293)
18 14 not 17 (80140)
19 C-Peptide/ (0)
20 ("c peptide*" or c-peptide or Cpeptide or ((connect* or gamma*) adj4 peptide)).ti,ab. (1281)
21 (creatinine* adj4 (ratio* or quota* or proportion*)).ti. (139)
22 Autoantibodies/ (0)
23 (antibod* or anti bod*or autoantibod* or auto-antibod* or auto-anti-bod* or autoantigen* or auto-antigen* or auto-anti-gen*).ti,ab. (58522)
24 22 or 23 (58522)
25 (islet cell or beta cell or decarboxylase or glutamic or insulin*).ti,ab. (37171)
26 "Islets of Langerhans"/ (0)
27 glutamate decarboxylase/ (0)
28 (glutam* adj4 (decarbox* or carbox*)).ti,ab. (749)
29 insulinoma/ (0)
30 glucose-6-phosphatase/ (0)
31 (glucose 6 phosphatase or glucosephosphatase).ti,ab. (282)
32 Zinc Transporter 8/ (0)
33 zinc transporter 8.ti,ab. (49)
34 (islet adj4 (phosphatase or catalytic or subunit* or sub-unit*)).ti,ab. (3)
35 (igrp* or iaa* or ica* or ia-2* or ia2* or znt8* or gad* or CA512).ti,ab. (12772)
36 or/25-35 (49581)
37 24 and 36 (1382)
38 or/19-21,37 (2702)
39 Body Mass Index/ (0)
40 ((body mass or quetelet*) adj2 index).ti,ab. (26392)
41 BMI.ti,ab. (22914)
42 "Age of Onset"/ (0)
43 ((age* adj2 onset*) or age-of-onset or age-at-onset).ti,ab. (3451)
44 Ketones/ (0)
45 ketone*.ti,ab. (9867)
46 Diabetic Ketoacidosis/ (0)
47 (diabetic adj4 (ketoacidos* or acidos*)).ti,ab. (1002)
48 DKA.ti,ab. (434)
49 Family Health/ (0)
50 Genetic Predisposition to Disease/ (0)
51 ((famil* or household* or forebear* or parent* or relativ*) adj4 health*).ti,ab. (8289)
52 (genetic* adj4 (predispos* or suscept*)).ti,ab. (4350)
53 addison disease/ (0)
54 ((Addison* adj4 diseas*) or ((primar* adj4 (adren* adj4 insuff*)) or hypoadren*)).ti,ab. (539)
55 anemia, hemolytic, autoimmune/ (0)

56 ((H?emolyt adj4 An?emi*) or (cold adj4 (agglutin* or antibod*) adj4 diseas*)).ti,ab. (57)
57 anti-glomerular basement membrane disease/ (0)
58 (((((Anti Glomerul* or Antiglomerul*) adj4 Basement* adj4 Membran*) or anti gbm) adj4 Diseas*) or (goodpasture* adj4 syndrom*) or (lung adj4 purpura adj4 nephrit*)).ti,ab. (146)
59 anti-neutrophil cytoplasmic antibody-associated vasculitis/ (0)
60 (((Anti Neutrophil adj4 Cytoplasm* adj4 Antibod*) or ANCA or pauci immune) adj4 Vasculit*).ti,ab. (585)
61 antiphospholipid syndrome/ (0)
62 ((anti phospholipid* or antiphospholipid* or hughes*) adj4 syndrom*).ti,ab. (950)
63 arthritis, juvenile/ (0)
64 arthritis, rheumatoid/ (0)
65 ((Juvenil* or Rheumat*) adj4 (Arthrit* or oligoarthrit* or still or still*)).ti,ab. (11090)
66 "autoimmune diseases of the nervous system"/ (0)
67 ((autoimmun* or immun*) adj4 (diseas* or disorder*) adj4 (nervous or neurologic*)).ti,ab. (636)
68 autoimmune hypophysitis/ (0)
69 (((autoimmun* or idiopath* or lymphoid* or lymphocyt* or igg4*) adj4 (hypophys* or adenohypophys* or infundibuloneurohypophys*)) or (anti pit 1 adj4 antibod* adj4 syndrom*)).ti,ab. (91)
70 autoimmune lymphoproliferative syndrome/ (0)
71 (((autoimmun* adj4 lymphoproliferat*) or canale smith or caspase*) adj4 (syndrom* or deficien*)).ti,ab. (110)
72 autoimmune pancreatitis/ (0)
73 (((autoimmun* or idiopath* or igg4*) adj4 pancreatit*) or type 1 aip or type 2 aip).ti,ab. (458)
74 birdshot chorioretinopathy/ (0)
75 (birdshot adj4 (chorioretin* or retinochoroid*)).ti,ab. (39)
76 dermatitis herpetiformis/ (0)
77 ((dermatit* adj4 herpetiform*) or (duhring* adj4 diseas*)).ti,ab. (137)
78 glomerulonephritis, iga/ (0)
79 (((IGA or immunoglob*) adj4 (glomerulonephrit* or nephr*)) or (berger* adj4 diseas*)).ti,ab. (820)
80 glomerulonephritis, membranous/ (0)
81 (((membran* or extramembran*) adj4 (glomeruloneph* or neuropath*)) or ((heymann or (idiopath* adj4 membran*)) adj4 nephrit*)).ti,ab. (378)
82 graves disease/ (0)
83 (((graves* or basedow*) adj4 diseas*) or (exophthal* adj4 goiter*)).ti,ab. (1422)
84 hepatitis, autoimmune/ (0)
85 (autoimmun* adj4 hepatit*).ti,ab. (933)
86 immunoglobulin g4-related disease/ (0)
87 (((Immunoglob* adj4 (G4-Related or G4related or "G4 Related")) or IGG4*) adj4 (Diseas* or RD)).ti,ab. (678)
88 linear iga bullous dermatosis/ (0)
89 (Linear* adj4 (Bullous* or IGA) adj4 Dermatos*).ti,ab. (52)
90 lupus erythematosus, systemic/ (0)
91 ((Lupus* adj4 Erythemat*) or libman sacks).ti,ab. (5167)
92 ophthalmia, sympathetic/ (0)
93 (sympathetic* adj4 (ophthal* or uveit*)).ti,ab. (117)
94 pemphigoid, bullous/ (0)
95 pemphigus/ (0)
96 pemphig*.ti,ab. (1338)
97 polyendocrinopathies, autoimmune/ (0)

98 ((autoimmun* adj4 (polyendocrin* or polygland*)) or apeced or ((aire or multiple endocrin*) adj4 deficien*) or aps type 1 or (schmidt* adj4 syndrom*)).ti,ab. (193)
99 purpura, thrombocytopenic, idiopathic/ (0)
100 (((autoimmune* or idiopath* or immun*) adj4 thrombocytopen) or (werlhof* adj4 diseas*)).ti,ab. (0)
101 thyroiditis, autoimmune/ (0)
102 ((autoimmun* or lympho*) adj4 thyroidit*).ti,ab. (481)
103 undifferentiated connective tissue diseases/ (0)
104 (Undifferent* adj4 Connect* adj4 Tissue* adj4 Diseas*).ti,ab. (41)
105 Celiac Disease/ (0)
106 ((c?eliac* or nontropic* or non-tropic*) adj4 (diseas* or sprue*)).ti,ab. (1917)
107 (gluten* adj4 enteropath*).ti,ab. (54)
108 exp Hypothyroidism/ (0)
109 hypothyroid*.ti,ab. (3753)
110 ((tsh or thyroid stimulat* hormone*) adj4 deficienc*).ti,ab. (42)
111 exp Hyperthyroidism/ (0)
112 hyperthyroid*.ti,ab. (1869)
113 Gastritis, Atrophic/ (0)
114 (atrophic* adj4 gastrit*).ti,ab. (369)
115 Population Characteristics/ (0)
116 (populat* adj4 (character* or heterogen* or statistic*)).ti,ab. (6799)
117 (ethnic* or nationalit*).ti,ab. (18337)
118 Weight Loss/ (0)
119 (weigh* adj4 (loss* or reduc*)).ti,ab. (18662)
120 Time-to-Treatment/ (0)
121 ("time to treatment*" or "door to treatment*" or (delay* adj4 (treatment* or therap*))).ti,ab. (6454)
122 or/39-121 (135489)
123 38 or 122 (137543)
124 18 and 123 (14932)
125 (sensitiv: or predictive value:).mp. or accurac:.tw. (266441)
126 124 and 125 (1311)
127 animals/ not humans/ (1)
128 126 not 127 (1311)
129 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. (149359)
130 128 not 129 (1309)
131 limit 130 to english language (1307)
132 Observational Studies as Topic/ (0)
133 Observational Study/ (94)
134 Epidemiologic Studies/ (0)
135 exp Case-Control Studies/ (1)
136 exp Cohort Studies/ (1)
137 Cross-Sectional Studies/ (0)
138 Controlled Before-After Studies/ (0)
139 Historically Controlled Study/ (0)
140 Interrupted Time Series Analysis/ (0)
141 Comparative Study.pt. (47)
142 case control$.tw. (16177)
143 case series.tw. (15004)
144 (cohort adj (study or studies)).tw. (33923)

145 cohort analy$.tw. (1161)
146 (follow up adj (study or studies)).tw. (3863)
147 (observational adj (study or studies)).tw. (20391)
148 longitudinal.tw. (39212)
149 prospective.tw. (71505)
150 retrospective.tw. (85137)
151 cross sectional.tw. (68604)
152 or/132-151 (285453)
153 (MEDLINE or pubmed).tw. (42167)
154 systematic review.tw. (35269)
155 systematic review.pt. (1725)
156 meta-analysis.pt. (60)
157 intervention$.ti. (24552)
158 or/153-157 (80100)
159 152 or 158 (351432)
160 131 and 159 (429)

Database: Medline epubs

Database: Ovid MEDLINE(R) Epub Ahead of Print <January 20, 2021>
Search Strategy:
---
1 exp Diabetes Mellitus/ (0)
2 diabet*.ti,ab. (11238)
3 (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).ti,ab. (29)
4 lada.ti,ab. (17)
5 (dm1 or iddm or t1d* or dka).ti,ab. (536)
6 (dm2 or t2d* or mody or niddm).ti,ab. (1195)
7 (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).ti,ab. (7)
8 (DM adj4 onset* adj4 (maturit* or adult* or slow*)).ti,ab. (1)
9 (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).ti,ab. (2)
10 (DM adj4 (earl* or sudden onset or juvenile or child*)).ti,ab. (21)
11 (DM adj4 (keto* or acidi* or gastropare*)).ti,ab. (0)
12 (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).ti,ab. (88)
13 (DM adj4 ("type 4" or type4 or "type iv" or "type four" or T4 or T-4 or TIV or T-IV)).ti,ab. (0)
14 or/1-13 (11337)
15 *Diabetes, Gestational/ (0)
16 (gestation* or pregnan*).ti. (3457)
17 15 or 16 (3457)
18 14 not 17 (10863)
19 C-Peptide/ (0)
20 ("c peptide*" or c-peptide or Cpeptide or ((connect* or gamma*) adj4 peptide)).ti,ab. (172)
21 (creatinine* adj4 (ratio* or quota* or proportion*)).ti. (17)
22 Autoantibodies/ (0)
23 (antibod* or anti bod*or autoantibod* or auto-antibod* or auto-anti-bod* or autoantigen* or auto-antigen* or auto-anti-gen*).ti,ab. (7009)
24 22 or 23 (7009)
25 (islet cell or beta cell or decarboxylase or glutamic or insulin*).ti,ab. (4228)

26 "Islets of Langerhans"/ (0)
27 glutamate decarboxylase/ (0)
28 (glutam* adj4 (decarbox* or carbox*)).ti,ab. (74)
29 insulinoma/ (0)
30 glucose-6-phosphatase/ (0)
31 (glucose 6 phosphatase or glucosephosphatase).ti,ab. (37)
32 Zinc Transporter 8/ (0)
33 zinc transporter 8.ti,ab. (7)
34 (islet adj4 (phosphatase or catalytic or subunit* or sub-unit*)).ti,ab. (3)
35 (igrp* or iaa* or ica* or ia-2* or ia2* or znt8* or gad* or CA512).ti,ab. (1701)
36 or/25-35 (5899)
37 24 and 36 (195)
38 or/19-21,37 (370)
39 Body Mass Index/ (0)
40 ((body mass or quetelet*) adj2 index).ti,ab. (4377)
41 BMI.ti,ab. (4075)
42 "Age of Onset"/ (0)
43 ((age* adj2 onset*) or age-of-onset or age-at-onset).ti,ab. (648)
44 Ketones/ (0)
45 ketone*.ti,ab. (342)
46 Diabetic Ketoacidosis/ (0)
47 (diabetic adj4 (ketoacidos* or acidos*)).ti,ab. (163)
48 DKA.ti,ab. (78)
49 Family Health/ (0)
50 Genetic Predisposition to Disease/ (0)
51 ((famil* or household* or forebear* or parent* or relativ*) adj4 health*).ti,ab. (1583)
52 (genetic* adj4 (predispos* or suscept*)).ti,ab. (532)
53 addison disease/ (0)
54 ((Addison* adj4 diseas*) or ((primar* adj4 (adren* adj4 insuff*)) or hypoadren*)).ti,ab. (55)
55 anemia, hemolytic, autoimmune/ (0)
56 ((H?emolyt adj4 An?emi*) or (cold adj4 (agglutin* or antibod*) adj4 diseas*)).ti,ab. (7)
57 anti-glomerular basement membrane disease/ (0)
58 (((((Anti Glomerul* or Antiglomerul*) adj4 Basement* adj4 Membran*) or anti gbm) adj4 Diseas*) or (goodpasture* adj4 syndrom*) or (lung adj4 purpura adj4 nephrit*)).ti,ab. (13)
59 anti-neutrophil cytoplasmic antibody-associated vasculitis/ (0)
60 (((Anti Neutrophil adj4 Cytoplasm* adj4 Antibod*) or ANCA or pauci immune) adj4 Vasculit*).ti,ab. (109)
61 antiphospholipid syndrome/ (0)
62 ((anti phospholipid* or antiphospholipid* or hughes*) adj4 syndrom*).ti,ab. (143)
63 arthritis, juvenile/ (0)
64 arthritis, rheumatoid/ (0)
65 ((Juvenil* or Rheumat*) adj4 (Arthrit* or oligoarthrit* or still or still*)).ti,ab. (1743)
66 "autoimmune diseases of the nervous system"/ (0)
67 ((autoimmun* or immun*) adj4 (diseas* or disorder*) adj4 (nervous or neurologic*)).ti,ab. (107)
68 autoimmune hypophysitis/ (0)
69 (((autoimmun* or idiopath* or lymphoid* or lymphocyt* or igg4*) adj4 (hypophys* or adenohypophys* or infundibuloneurohypophys*)) or (anti pit 1 adj4 antibod* adj4 syndrom*)).ti,ab. (13)
70 autoimmune lymphoproliferative syndrome/ (0)
71 (((autoimmun* adj4 lymphoproliferat*) or canale smith or caspase*) adj4 (syndrom* or deficien*)).ti,ab. (16)

72 autoimmune pancreatitis/ (0)
73 (((autoimmun* or idiopath* or igg4*) adj4 pancreatit*) or type 1 aip or type 2 aip).ti,ab. (41)
74 birdshot chorioretinopathy/ (0)
75 (birdshot adj4 (chorioretin* or retinochoroid*)).ti,ab. (12)
76 dermatitis herpetiformis/ (0)
77 ((dermatit* adj4 herpetiform*) or (duhring* adj4 diseas*)).ti,ab. (21)
78 glomerulonephritis, iga/ (0)
79 (((IGA or immunoglob*) adj4 (glomerulonephrit* or nephr*)) or (berger* adj4 diseas*)).ti,ab. (91)
80 glomerulonephritis, membranous/ (0)
81 (((membran* or extramembran*) adj4 (glomeruloneph* or neuropath*)) or ((heymann or (idiopath* adj4 membran*)) adj4 nephrit*)).ti,ab. (31)
82 graves disease/ (0)
83 (((graves* or basedow*) adj4 diseas*) or (exophthal* adj4 goiter*)).ti,ab. (148)
84 hepatitis, autoimmune/ (0)
85 (autoimmun* adj4 hepatit*).ti,ab. (90)
86 immunoglobulin g4-related disease/ (0)
87 (((Immunoglob* adj4 (G4-Related or G4related or "G4 Related")) or IGG4*) adj4 (Diseas* or RD)).ti,ab. (118)
88 linear iga bullous dermatosis/ (0)
89 (Linear* adj4 (Bullous* or IGA) adj4 Dermatos*).ti,ab. (6)
90 lupus erythematosus, systemic/ (0)
91 ((Lupus* adj4 Erythemat*) or libman sacks).ti,ab. (824)
92 ophthalmia, sympathetic/ (0)
93 (sympathetic* adj4 (ophthal* or uveit*)).ti,ab. (10)
94 pemphigoid, bullous/ (0)
95 pemphigus/ (0)
96 pemphig*.ti,ab. (202)
97 polyendocrinopathies, autoimmune/ (0)
98 ((autoimmun* adj4 (polyendocrin* or polygland*)) or apeced or ((aire or multiple endocrin*) adj4 deficien*) or aps type 1 or (schmidt* adj4 syndrom*)).ti,ab. (27)
99 purpura, thrombocytopenic, idiopathic/ (0)
100 (((autoimmune* or idiopath* or immun*) adj4 thrombocytopen) or (werlhof* adj4 diseas*)).ti,ab. (0)
101 thyroiditis, autoimmune/ (0)
102 ((autoimmun* or lympho*) adj4 thyroidit*).ti,ab. (54)
103 undifferentiated connective tissue diseases/ (0)
104 (Undifferent* adj4 Connect* adj4 Tissue* adj4 Diseas*).ti,ab. (6)
105 Celiac Disease/ (0)
106 ((c?eliac* or nontropic* or non-tropic*) adj4 (diseas* or sprue*)).ti,ab. (214)
107 (gluten* adj4 enteropath*).ti,ab. (5)
108 exp Hypothyroidism/ (0)
109 hypothyroid*.ti,ab. (481)
110 ((tsh or thyroid stimulat* hormone*) adj4 deficienc*).ti,ab. (6)
111 exp Hyperthyroidism/ (0)
112 hyperthyroid*.ti,ab. (231)
113 Gastritis, Atrophic/ (0)
114 (atrophic* adj4 gastrit*).ti,ab. (35)
115 Population Characteristics/ (0)
116 (populat* adj4 (character* or heterogen* or statistic*)).ti,ab. (866)
117 (ethnic* or nationalit*).ti,ab. (3899)

118 Weight Loss/ (0)
119 (weigh* adj4 (loss* or reduc*)).ti,ab. (2271)
120 Time-to-Treatment/ (0)
121 ("time to treatment*" or "door to treatment*" or (delay* adj4 (treatment* or therap*))).ti,ab. (1001)
122 or/39-121 (20611)
123 38 or 122 (20889)
124 18 and 123 (2179)
125 (sensitiv: or predictive value:).mp. or accurac:.tw. (27139)
126 124 and 125 (193)
127 animals/ not humans/ (0)
128 126 not 127 (193)
129 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. (17105)
130 128 not 129 (193)
131 limit 130 to english language (192)
132 Observational Studies as Topic/ (0)
133 Observational Study/ (4)
134 Epidemiologic Studies/ (0)
135 exp Case-Control Studies/ (0)
136 exp Cohort Studies/ (0)
137 Cross-Sectional Studies/ (0)
138 Controlled Before-After Studies/ (0)
139 Historically Controlled Study/ (0)
140 Interrupted Time Series Analysis/ (0)
141 Comparative Study.pt. (0)
142 case control$.tw. (2791)
143 case series.tw. (2878)
144 (cohort adj (study or studies)).tw. (9465)
145 cohort analy$.tw. (386)
146 (follow up adj (study or studies)).tw. (636)
147 (observational adj (study or studies)).tw. (4468)
148 longitudinal.tw. (7292)
149 prospective.tw. (13896)
150 retrospective.tw. (19724)
151 cross sectional.tw. (11167)
152 or/132-151 (55531)
153 (MEDLINE or pubmed).tw. (9332)
154 systematic review.tw. (9035)
155 systematic review.pt. (64)
156 meta-analysis.pt. (73)
157 intervention$.ti. (4246)
158 or/153-157 (16854)
159 152 or 158 (68913)
160 131 and 159 (75)

Database: EMBASE

Database: Embase <1974 to 2021 January 20>

Search Strategy:

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1 exp diabetes mellitus/ (994822)
2 diabet*.ti,ab. (973464)
3 (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).ti,ab. (4152)
4 lada.ti,ab. (1034)
5 (dm1 or iddm or t1d* or dka).ti,ab. (41689)
6 (dm2 or t2d* or mody or niddm).ti,ab. (75154)
7 (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).ti,ab. (744)
8 (DM adj4 onset* adj4 (maturit* or adult* or slow*)).ti,ab. (111)
9 (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).ti,ab. (171)
10 (DM adj4 (earl* or sudden onset or juvenile or child*)).ti,ab. (1923)
11 (DM adj4 (keto* or acidi* or gastropare*)).ti,ab. (199)
12 (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).ti,ab. (10964)
13 (DM adj4 ("type 4" or type4 or "type iv" or "type four" or T4 or T-4 or TIV or T-IV)).ti,ab. (39)
14 or/1-13 (1182931)
15 *pregnancy diabetes mellitus/ (18049)
16 (gestation* or pregnan*).ti. (301314)
17 15 or 16 (303168)
18 14 not 17 (1148214)
19 C peptide/ (22392)
20 ("c peptide*" or c-peptide or Cpeptide or ((connect* or gamma*) adj4 peptide)).ti,ab. (22988)
21 (creatinine* adj4 (ratio* or quota* or proportion*)).ti. (1600)
22 autoantibody/ (73200)
23 (antibod* or anti bod*or autoantibod* or auto-antibod* or auto-anti-bod* or autoantigen* or auto-antigen* or auto-anti-gen*).ti,ab. (1111177)
24 22 or 23 (1143778)
25 (islet cell or beta cell or decarboxylase or glutamic or insulin*).ti,ab. (560679)
26 pancreas islet/ (22229)
27 glutamate decarboxylase/ (8380)
28 (glutam* adj4 (decarbox* or carbox*)).ti,ab. (12368)
29 insulinoma/ (8676)
30 insulinoma cell line/ (214)
31 glucose 6 phosphatase/ (6105)
32 (glucose 6 phosphatase or glucosephosphatase).ti,ab. (5157)
33 zinc transporter 8.ti,ab. (391)
34 (islet adj4 (phosphatase or catalytic or subunit* or sub-unit*)).ti,ab. (239)
35 (igrp* or iaa* or ica* or ia-2* or ia2* or znt8* or gad* or CA512).ti,ab. (148858)
36 or/25-35 (715983)
37 24 and 36 (37907)
38 or/19-21,37 (65182)
39 body mass/ (466995)
40 ((body mass or quetelet*) adj2 index).ti,ab. (280830)
41 BMI.ti,ab. (324022)
42 onset age/ (84857)
43 ((age* adj2 onset*) or age-of-onset or age-at-onset).ti,ab. (58219)
44 ketone/ (20442)
45 ketone*.ti,ab. (46017)
46 diabetic ketoacidosis/ (12897)
47 (diabetic adj4 (ketoacidos* or acidos*)).ti,ab. (9695)

48 DKA.ti,ab. (4789)
49 family health/ (10652)
50 genetic predisposition/ (59146)
51 ((famil* or household* or forebear* or parent* or relativ*) adj4 health*).ti,ab. (78648)
52 (genetic* adj4 (predispos* or suscept*)).ti,ab. (55719)
53 Addison disease/ (4971)
54 ((Addison* adj4 diseas*) or ((primar* adj4 (adren* adj4 insuff*)) or hypoadren*)).ti,ab. (5322)
55 autoimmune hemolytic anemia/ (8941)
56 ((H?emolyt adj4 An?emi*) or (cold adj4 (agglutin* or antibod*) adj4 diseas*)).ti,ab. (649)
57 glomerulonephritis/ (30648)
58 (((((Anti Glomerul* or Antiglomerul*) adj4 Basement* adj4 Membran*) or anti gbm) adj4 Diseas*) or (goodpasture* adj4 syndrom*) or (lung adj4 purpura adj4 nephrit*)).ti,ab. (2321)
59 ANCA associated vasculitis/ (6739)
60 (((Anti Neutrophil adj4 Cytoplasm* adj4 Antibod*) or ANCA or pauci immune) adj4 Vasculit*).ti,ab. (7580)
61 antiphospholipid syndrome/ (17398)
62 ((anti phospholipid* or antiphospholipid* or hughes*) adj4 syndrom*).ti,ab. (15339)
63 juvenile rheumatoid arthritis/ (20656)
64 rheumatoid arthritis/ (184783)
65 ((Juvenil* or Rheumat*) adj4 (Arthrit* or oligoarthrit* or still or still*)).ti,ab. (175106)
66 neurologic disease/ (131813)
67 ((autoimmun* or immun*) adj4 (diseas* or disorder*) adj4 (nervous or neurologic*)).ti,ab. (5940)
68 autoimmune hypophysitis/ (196)
69 (((autoimmun* or idiopath* or lymphoid* or lymphocyt* or igg4*) adj4 (hypophys* or adenohypophys* or infundibuloneurohypophys*)) or (anti pit 1 adj4 antibod* adj4 syndrom*)).ti,ab. (1120)
70 autoimmune lymphoproliferative syndrome/ (848)
71 (((autoimmun* adj4 lymphoproliferat*) or canale smith or caspase*) adj4 (syndrom* or deficien*)).ti,ab. (2024)
72 autoimmune pancreatitis/ (3838)
73 (((autoimmun* or idiopath* or igg4*) adj4 pancreatit*) or type 1 aip or type 2 aip).ti,ab. (5306)
74 birdshot chorioretinopathy/ (117)
75 (birdshot adj4 (chorioretin* or retinochoroid*)).ti,ab. (503)
76 dermatitis herpetiformis/ (3309)
77 ((dermatit* adj4 herpetiform*) or (duhring* adj4 diseas*)).ti,ab. (2385)
78 immunoglobulin A nephropathy/ (12463)
79 (((IGA or immunoglob*) adj4 (glomerulonephrit* or nephr*)) or (berger* adj4 diseas*)).ti,ab. (12086)
80 membranous glomerulonephritis/ (7950)
81 (((membran* or extramembran*) adj4 (glomeruloneph* or nephropath*)) or ((heymann or (idiopath* adj4 membran*)) adj4 nephrit*)).ti,ab. (11482)
82 Graves disease/ (21439)
83 (((graves* or basedow*) adj4 diseas*) or (exophthal* adj4 goiter*)).ti,ab. (17285)
84 autoimmune hepatitis/ (12914)
85 (autoimmun* adj4 hepatit*).ti,ab. (11819)
86 immunoglobulin G4 related disease/ (3416)
87 (((Immunoglob* adj4 (G4-Related or G4related or "G4 Related")) or IGG4*) adj4 (Diseas* or RD)).ti,ab. (5090)
88 linear iga bullous dermatosis/ (353)
89 (Linear* adj4 (Bullous* or IGA) adj4 Dermatos*).ti,ab. (817)

90 systemic lupus erythematosus/ (93032)
91 ((Lupus* adj4 Erythemat*) or libman sacks).ti,ab. (81279)
92 sympathetic ophthalmia/ (845)
93 (sympathetic* adj4 (ophthal* or uveit*)).ti,ab. (748)
94 bullous pemphigoid/ (4223)
95 pemphigus/ (4496)
96 pemphig*.ti,ab. (16690)
97 polyendocrinopathy/ (530)
98 ((autoimmun* adj4 (polyendocrin* or polygland*)) or apeced or ((aire or multiple endocrin*) adj4 deficien*) or aps type 1 or (schmidt* adj4 syndrom*)).ti,ab. (2491)
99 idiopathic thrombocytopenic purpura/ (15244)
100 (((autoimmune* or idiopath* or immun*) adj4 thrombocytopen) or (werlhof* adj4 diseas*)).ti,ab. (91)
101 autoimmune thyroiditis/ (6974)
102 ((autoimmun* or lympho*) adj4 thyroidit*).ti,ab. (7161)
103 connective tissue disease/ (18873)
104 (Undifferent* adj4 Connect* adj4 Tissue* adj4 Diseas*).ti,ab. (775)
105 celiac disease/ (31436)
106 ((c?eliac* or nontropic* or non-tropic*) adj4 (diseas* or sprue*)).ti,ab. (27250)
107 (gluten* adj4 enteropath*).ti,ab. (1365)
108 exp hypothyroidism/ (69226)
109 hypothyroid*.ti,ab. (51283)
110 ((tsh or thyroid stimulat* hormone*) adj4 deficienc*).ti,ab. (731)
111 exp hyperthyroidism/ (60327)
112 hyperthyroid*.ti,ab. (28265)
113 atrophic gastritis/ (6546)
114 (atrophic* adj4 gastrit*).ti,ab. (6447)
115 "population and population related phenomena"/ (14962)
116 (populat* adj4 (character* or heterogen* or statistic*)).ti,ab. (70787)
117 (ethnic* or nationalit*).ti,ab. (212604)
118 Weight Loss/ (30191)
119 (weigh* adj4 (loss* or reduc*)).ti,ab. (204756)
120 time to treatment/ (18427)
121 ("time to treatment*" or "door to treatment*" or (delay* adj4 (treatment* or therap*))).ti,ab. (76339)
122 or/39-121 (2154033)
123 38 or 122 (2204218)
124 18 and 123 (281606)
125 (sensitiv: or predictive value:).mp. or accurac:.tw. (2676835)
126 124 and 125 (32351)
127 nonhuman/ not human/ (4747383)
128 126 not 127 (30932)
129 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. (6648193)
130 128 not 129 (20588)
131 limit 130 to english language (19642)
132 Clinical study/ (156531)
133 Case control study/ (167033)
134 Family study/ (26143)
135 Longitudinal study/ (150141)
136 Retrospective study/ (1020726)

137 comparative study/ (884025)
138 Prospective study/ (657033)
139 Randomized controlled trials/ (194838)
140 138 not 139 (649838)
141 Cohort analysis/ (661490)
142 cohort analy$.tw. (13998)
143 (Cohort adj (study or studies)).tw. (327016)
144 (Case control$ adj (study or studies)).tw. (143568)
145 (follow up adj (study or studies)).tw. (65219)
146 (observational adj (study or studies)).tw. (181854)
147 (epidemiologic$ adj (study or studies)).tw. (109552)
148 (cross sectional adj (study or studies)).tw. (239624)
149 case series.tw. (111471)
150 prospective.tw. (901983)
151 retrospective.tw. (944940)
152 or/132-137,140-151 (4267192)
153 (MEDLINE or pubmed).tw. (284599)
154 exp systematic review/ or systematic review.tw. (335131)
155 meta-analysis/ (206382)
156 intervention$.ti. (211642)
157 or/153-156 (710136)
158 152 or 157 (4820622)
159 131 and 158 (7593)

Database: Psychinfo

Database: APA PsycInfo <1806 to January Week 3 2021>
Search Strategy:
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1 exp Diabetes Mellitus/ (8726)
2 diabet*.ti,ab. (31935)
3 (DM adj4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)).ti,ab. (91)
4 lada.ti,ab. (6)
5 (dm1 or iddm or t1d* or dka).ti,ab. (1117)
6 (dm2 or t2d* or mody or niddm).ti,ab. (1803)
7 (DM adj4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)).ti,ab. (12)
8 (DM adj4 onset* adj4 (maturit* or adult* or slow*)).ti,ab. (4)
9 (DM adj4 depend* adj4 (non-insulin* or non insulin* or noninsulin*)).ti,ab. (4)
10 (DM adj4 (earl* or sudden onset or juvenile or child*)).ti,ab. (51)
11 (DM adj4 (keto* or acidi* or gastropare*)).ti,ab. (7)
12 (DM adj4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)).ti,ab. (238)
13 (DM adj4 ("type 4" or type4 or "type iv" or "type four" or T4 or T-4 or TIV or T-IV)).ti,ab. (0)
14 or/1-13 (32834)
15 exp Gestational Diabetes/ (210)
16 (gestation* or pregnan*).ti. (17251)
17 15 or 16 (17262)
18 14 not 17 (32259)

19 ("c peptide*" or c-peptide or Cpeptide or ((connect* or gamma*) adj4 peptide)).ti,ab. (190)
20 (creatinine* adj4 (ratio* or quota* or proportion*)).ti. (4)
21 (antibod* or anti bod*or autoantibod* or auto-antibod* or auto-anti-bod* or autoantigen* or auto-antigen* or auto-anti-gen*).ti,ab. (14049)
22 (islet cell or beta cell or decarboxylase or glutamic or insulin*).ti,ab. (13568)
23 (glutam* adj4 (decarbox* or carbox*)).ti,ab. (1247)
24 zinc transporter 8.ti,ab. (0)
25 (islet adj4 (phosphatase or catalytic or subunit* or sub-unit*)).ti,ab. (0)
26 (igrp* or iaa* or ica* or ia-2* or ia2* or znt8* or gad* or CA512).ti,ab. (10786)
27 or/22-26 (23530)
28 21 and 27 (530)
29 or/19-20,28 (721)
30 exp Body Mass Index/ (6153)
31 ((body mass or quetelet*) adj2 index).ti,ab. (20239)
32 BMI.ti,ab. (18241)
33 exp "Onset (Disorders)"/ (13649)
34 ((age* adj2 onset*) or age-of-onset or age-at-onset).ti,ab. (12221)
35 ketone*.ti,ab. (397)
36 (diabetic adj4 (ketoacidos* or acidos*)).ti,ab. (156)
37 DKA.ti,ab. (63)
38 exp Family History/ (2984)
39 exp Genetics/ and exp Predisposition/ (788)
40 ((famil* or household* or forebear* or parent* or relativ*) adj4 health*).ti,ab. (30853)
41 (genetic* adj4 (predispos* or suscept*)).ti,ab. (4445)
42 exp Addisons Disease/ (41)
43 ((Addison* adj4 diseas*) or ((primar* adj4 (adren* adj4 insuff*)) or hypoadren*)).ti,ab. (125)
44 exp Immunologic Disorders/ (48234)
45 ((H?emolyt adj4 An?emi*) or (cold adj4 (agglutin* or antibod*) adj4 diseas*)).ti,ab. (2)
46 (((((Anti Glomerul* or Antiglomerul*) adj4 Basement* adj4 Membran*) or anti gbm) adj4 Diseas*) or (goodpasture* adj4 syndrom*) or (lung adj4 purpura adj4 nephrit*)).ti,ab. (5)
47 (((Anti Neutrophil adj4 Cytoplasm* adj4 Antibod*) or ANCA or pauci immune) adj4 Vasculit*).ti,ab. (11)
48 ((anti phospholipid* or antiphospholipid* or hughes*) adj4 syndrom*).ti,ab. (121)
49 exp Rheumatoid Arthritis/ (1938)
50 ((Juvenil* or Rheumat*) adj4 (Arthrit* or oligoarthrit* or still or still*)).ti,ab. (2958)
51 ((autoimmun* or immun*) adj4 (diseas* or disorder*) adj4 (nervous or neurologic*)).ti,ab. (565)
52 (((autoimmun* or idiopath* or lymphoid* or lymphocyt* or igg4*) adj4 (hypophys* or adenohypophys* or infundibuloneurohypophys*)) or (anti pit 1 adj4 antibod* adj4 syndrom*)).ti,ab. (5)
53 (((autoimmun* adj4 lymphoproliferat*) or canale smith or caspase*) adj4 (syndrom* or deficien*)).ti,ab. (16)
54 (((autoimmun* or idiopath* or igg4*) adj4 pancreatit*) or type 1 aip or type 2 aip).ti,ab. (5)
55 (birdshot adj4 (chorioretin* or retinochoroid*)).ti,ab. (0)
56 ((dermatit* adj4 herpetiform*) or (duhring* adj4 diseas*)).ti,ab. (7)
57 (((IGA or immunoglob*) adj4 (glomerulonephrit* or nephr*)) or (berger* adj4 diseas*)).ti,ab. (11)
58 (((membran* or extramembran*) adj4 (glomeruloneph* or neuropath*)) or ((heymann or (idiopath* adj4 membran*)) adj4 nephrit*)).ti,ab. (12)
59 (((graves* or basedow*) adj4 diseas*) or (exophthal* adj4 goiter*)).ti,ab. (226)
60 (autoimmun* adj4 hepatit*).ti,ab. (31)

61 (((Immunoglob* adj4 (G4-Related or G4related or "G4 Related")) or IGG4*) adj4 (Diseas* or RD)).ti,ab. (24)
62 ((Lupus* adj4 Erythemat*) or libman sacks).ti,ab. (1036)
63 (sympathetic* adj4 (ophthal* or uveit*)).ti,ab. (5)
64 pemphig*.ti,ab. (40)
65 ((autoimmun* adj4 (polyendocrin* or polygland*)) or apeced or ((aire or multiple endocrin*) adj4 deficien*) or aps type 1 or (schmidt* adj4 syndrom*)).ti,ab. (11)
66 (((autoimmune* or idiopath* or immun*) adj4 thrombocytopen) or (werlhof* adj4 diseas*)).ti,ab. (0)
67 ((autoimmun* or lympho*) adj4 thyroidit*).ti,ab. (96)
68 (Undifferent* adj4 Connect* adj4 Tissue* adj4 Diseas*).ti,ab. (0)
69 exp Celiac Disease/ (233)
70 ((c?eliac* or nontropic* or non-tropic*) adj4 (diseas* or sprue*)).ti,ab. (378)
71 (gluten* adj4 enteropath*).ti,ab. (10)
72 exp Hypothyroidism/ (701)
73 hypothyroid*.ti,ab. (1605)
74 ((tsh or thyroid stimulat* hormone*) adj4 deficienc*).ti,ab. (4)
75 exp Hyperthyroidism/ (275)
76 hyperthyroid*.ti,ab. (692)
77 (atrophic* adj4 gastrit*).ti,ab. (18)
78 exp Demographic Characteristics/ (179585)
79 (populat* adj4 (character* or heterogen* or statistic*)).ti,ab. (8254)
80 (ethnic* or nationalit*).ti,ab. (95305)
81 exp Weight Loss/ (3905)
82 (weigh* adj4 (loss* or reduc*)).ti,ab. (15527)
83 ("time to treatment*" or "door to treatment*" or (delay* adj4 (treatment* or therap*))).ti,ab. (5603)
84 or/30-83 (417720)
85 29 or 84 (418284)
86 18 and 85 (8779)
87 (sensitiv: or predictive value:).mp. or accurac:.tw. (268271)
88 86 and 87 (584)
89 animals/ not humans/ (7274)
90 88 not 89 (584)
91 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. (3284)
92 90 not 91 (584)
93 limit 92 to english language (574)
94 case control$.tw. (11621)
95 case series.tw. (4160)
96 (cohort adj (study or studies)).tw. (22853)
97 cohort analy$.tw. (948)
98 (follow up adj (study or studies)).tw. (13197)
99 (observational adj (study or studies)).tw. (10988)
100 longitudinal.tw. (121575)
101 prospective.tw. (62186)
102 retrospective.tw. (37049)
103 cross sectional.tw. (82877)
104 or/94-103 (308269)
105 (MEDLINE or pubmed).tw. (24754)
106 systematic review.tw. (30607)

107 or/105-106 (44275)
108 104 or 107 (345895)
109 93 and 108 (167)

Database: Cochrane (CDSR/CENTRAL)

Search Name: GU - Diabetes guidelines update_diagnosis
Date Run: 22/01/2021 23:38:37
Comment: DN 22 01 2021

ID	Search	Hits
#1	MeSH descriptor: [Diabetes Mellitus] explode all trees	31624
#2	diabet*:ti,ab	89857
#3	(DM near/4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)):ti,ab	252
#4	lada:ti,ab	68
#5	(dm1 or iddm or t1d* or dka):ti,ab	3477
#6	(dm2 or t2d* or mody or niddm):ti,ab	10814
#7	(DM near/4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)):ti,ab	226
#8	(DM near/4 onset* near/4 (maturit* or adult* or slow*)):ti,ab	0
#9	(DM near/4 depend* near/4 (non-insulin* or non insulin* or noninsulin*)):ti,ab	20
#10	(DM near/4 (earl* or sudden onset or juvenile or child*)):ti,ab	124
#11	(DM near/4 (keto* or acidi* or gastropare*)):ti,ab	7
#12	(DM near/4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)):ti,ab	1249
#13	(DM near/4 ("type 4" or type4 or "type iv" or "type four" or T4 or T-4 or TIV or T-IV)):ti,ab	2
#14	{OR #1-#13}	93095
#15	MeSH descriptor: [Diabetes, Gestational] this term only	910
#16	(gestation* or pregnan*):ti	18064
#17	{OR #15-#16}	18155
#18	#14 NOT #17	90314
#19	MeSH descriptor: [C-Peptide] this term only	1247
#20	(c peptide* or c-peptide or Cpeptide or ((connect* or gamma*) near/4 peptide)):ti,ab	6076
#21	(creatinine* near/4 (ratio* or quota* or proportion*)):ti	64
#22	MeSH descriptor: [Autoantibodies] this term only	681
#23	(antibod* or anti bod*or autoantibod* or auto-antibod* or auto-anti-bod* or autoantigen* or auto-antigen* or auto-anti-gen*):ti,ab	33631
#24	{OR #22-#23}	33845
#25	(islet cell or beta cell or decarboxylase or glutamic or insulin*):ti,ab	50728
#26	MeSH descriptor: [Islets of Langerhans] this term only	285
#27	MeSH descriptor: [Glutamate Decarboxylase] this term only	72
#28	(glutam* near/4 (decarbox* or carbox*)):ti,ab	177
#29	MeSH descriptor: [Insulinoma] this term only	12
#30	MeSH descriptor: [Glucose-6-Phosphatase] this term only	2
#31	(glucose 6 phosphatase or glucosephosphatase):ti,ab	229
#32	MeSH descriptor: [Zinc Transporter 8] this term only	5
#33	zinc transporter 8:ti,ab	33

#34 (islet near/4 (phosphatase or catalytic or subunit* or sub-unit*)):ti,ab 6
#35 (igrp* or iaa* or ica* or ia-2* or ia2* or znt8* or gad* or CA512):ti,ab 7898
#36 {OR #25-#35} 58199
#37 #24 AND #36 1542
#38 #19 OR #20 OR #21 OR #37 7707
#39 MeSH descriptor: [Body Mass Index] this term only 10153
#40 ((body mass or quetelet*) near/2 index):ti,ab 33728
#41 BMI:ti,ab 40337
#42 MeSH descriptor: [Age of Onset] this term only 606
#43 ((age* near/2 onset*) or age-of-onset or age-at-onset):ti,ab 1227
#44 MeSH descriptor: [Ketones] this term only 191
#45 ketone*:ti,ab 983
#46 MeSH descriptor: [Diabetic Ketoacidosis] this term only 136
#47 (diabetic near/4 (ketoacidos* or acidos*)):ti,ab 473
#48 DKA:ti,ab 275
#49 MeSH descriptor: [Family Health] this term only 427
#50 MeSH descriptor: [Genetic Predisposition to Disease] this term only 1022
#51 ((famil* or household* or forebear* or parent* or relativ*) near/4 health*):ti,ab 5756
#52 (genetic* near/4 (predispos* or suscept*)):ti,ab 690
#53 MeSH descriptor: [Addison Disease] this term only 55
#54 ((Addison* near/4 diseas*) or ((primar* near/4 (adren* near/4 insuff*)) or hypoadren*)):ti,ab 148
#55 MeSH descriptor: [Anemia, Hemolytic, Autoimmune] this term only 18
#56 ((H*molyt near/4 An*emi*) or (cold near/4 (agglutin* or antibod*) near/4 diseas*)):ti,ab 22
#57 MeSH descriptor: [Anti-Glomerular Basement Membrane Disease] this term only 4
#58 (((((Anti Glomerul* or Antiglomerul*) near/4 Basement* near/4 Membran*) or anti gbm) near/4 Diseas*) or (goodpasture* near/4 syndrom*) or (lung near/4 purpura near/4 nephrit*)):ti,ab 1462
#59 MeSH descriptor: [Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis] this term only 72
#60 (((Anti Neutrophil near/4 Cytoplasm* near/4 Antibod*) or ANCA or pauci immune) near/4 Vasculit*):ti,ab 440
#61 MeSH descriptor: [Antiphospholipid Syndrome] this term only 91
#62 ((anti phospholipid* or antiphospholipid* or hughes*) near/4 syndrom*):ti,ab 367
#63 MeSH descriptor: [Arthritis, Juvenile] this term only 299
#64 MeSH descriptor: [Arthritis, Rheumatoid] this term only 5846
#65 ((Juvenil* or Rheumat*) near/4 (Arthrit* or oligoarthrit* or still or still*)):ti,ab 15248
#66 MeSH descriptor: [Autoimmune Diseases of the Nervous System] this term only 5
#67 ((autoimmun* or immun*) near/4 (diseas* or disorder*) near/4 (nervous or neurologic*)):ti,ab 156
#68 MeSH descriptor: [Autoimmune Hypophysitis] this term only 0
#69 (((autoimmun* or idiopath* or lymphoid* or lymphocyt* or igg4*) near/4 (hypophys* or adenohypophys* or infundibuloneurohypophys*)) or (anti pit 1 near/4 antibod* near/4 syndrom*)):ti,ab 2
#70 MeSH descriptor: [Autoimmune Lymphoproliferative Syndrome] this term only 1
#71 (((autoimmun* near/4 lymphoproliferat*) or canale smith or caspase*) near/4 (syndrom* or deficien*)):ti,ab 24
#72 MeSH descriptor: [Autoimmune Pancreatitis] this term only 0
#73 (((autoimmun* or idiopath* or igg4*) near/4 pancreatit*) or type 1 aip or type 2 aip):ti,ab 100
#74 MeSH descriptor: [Birdshot Chorioretinopathy] this term only 0

#75 (birdshot near/4 (chorioretin* or retinochoroid*)):ti,ab 7
#76 MeSH descriptor: [Dermatitis Herpetiformis] this term only 12
#77 ((dermatit* near/4 herpetiform*) or (duhring* near/4 diseas*)):ti,ab 26
#78 MeSH descriptor: [Glomerulonephritis, IGA] this term only 243
#79 (((IGA or immunoglob*) near/4 (glomerulonephrit* or nephr*)) or (berger* near/4 diseas*)):ti,ab 617
#80 MeSH descriptor: [Glomerulonephritis, Membranous] this term only 115
#81 (((membran* or extramembran*) near/4 (glomeruloneph* or neuropath*)) or ((heymann or (idiopath* near/4 membran*)) near/4 nephrit*)):ti,ab 80
#82 MeSH descriptor: [Graves Disease] this term only 340
#83 (((graves* or basedow*) near/4 diseas*) or (exophthal* near/4 goiter*)):ti,ab 493
#84 MeSH descriptor: [Hepatitis, Autoimmune] this term only 30
#85 (autoimmun* near/4 hepatit*):ti,ab 235
#86 MeSH descriptor: [Immunoglobulin G4-Related Disease] this term only 6
#87 ((Immunoglob* near/4 (G4related or G4 Related) or IGG4*) near/4 (Diseas* or RD)):ti,ab 36
#88 MeSH descriptor: [Linear IgA Bullous Dermatosis] this term only 0
#89 (Linear* near/4 (Bullous* or IGA) near/4 Dermatos*):ti,ab 0
#90 MeSH descriptor: [Lupus Erythematosus, Systemic] this term only 818
#91 ((Lupus* near/4 Erythemat*) or libman sacks):ti,ab 2028
#92 MeSH descriptor: [Ophthalmia, Sympathetic] this term only 0
#93 (sympathetic* near/4 (ophthal* or uveit*)):ti,ab 16
#94 MeSH descriptor: [Pemphigoid, Bullous] this term only 45
#95 MeSH descriptor: [Pemphigus] this term only 76
#96 pemphig*:ti,ab 305
#97 MeSH descriptor: [Polyendocrinopathies, Autoimmune] this term only 1
#98 ((autoimmun* near/4 (polyendocrin* or polygland*)) or apeced or ((aire or multiple endocrin*) near/4 deficien*) or aps type 1 or (schmidt* near/4 syndrom*)):ti,ab 248
#99 MeSH descriptor: [Purpura, Thrombocytopenic, Idiopathic] this term only 283
#100 (((autoimmune* or idiopath* or immun*) near/4 thrombocytopen) or (werlhof* near/4 diseas*)):ti,ab 0
#101 MeSH descriptor: [Thyroiditis, Autoimmune] this term only 80
#102 ((autoimmun* or lympho*) near/4 thyroidit*):ti,ab 159
#103 MeSH descriptor: [Undifferentiated Connective Tissue Diseases] this term only 5
#104 (Undifferent* near/4 Connect* near/4 Tissue* near/4 Diseas*):ti,ab 9
#105 MeSH descriptor: [Celiac Disease] this term only 354
#106 ((c*liac* or nontropic* or non-tropic*) near/4 (diseas* or sprue*)):ti,ab 717
#107 (gluten* near/4 enteropath*):ti,ab 5
#108 MeSH descriptor: [Hypothyroidism] explode all trees 447
#109 hypothyroid*:ti,ab 1858
#110 ((tsh or thyroid stimulat* hormone*) near/4 deficienc*):ti,ab 737
#111 MeSH descriptor: [Hyperthyroidism] explode all trees 701
#112 hyperthyroid*:ti,ab 1070
#113 MeSH descriptor: [Gastritis, Atrophic] this term only 105
#114 (atrophic* near/4 gastrit*):ti,ab 354
#115 MeSH descriptor: [Population Characteristics] this term only 1
#116 (populat* near/4 (character* or heterogen* or statistic*)):ti,ab 2887
#117 (ethnic* or nationalit*):ti,ab 9380
#118 MeSH descriptor: [Weight Loss] this term only 6130
#119 (weigh* near/4 (loss* or reduc*)):ti,ab 23435
#120 MeSH descriptor: [Time-to-Treatment] this term only 363

#121	("time to treatment*" or "door to treatment*" or (delay* near/4 (treatment* or therap*))):ti,ab 6470
#122	{OR #39-#121} 128683
#123	#38 or #122 134215
#124	#18 AND #123 23555
#125	(sensitiv* or predictive value* or accurac*):ti,ab,kw 98749
#126	#124 and #125 3396
#127	"conference":pt or (clinicaltrials or trialsearch):so 524840
#128	#126 NOT #127 1927
#129	"www.who.int":so 148857
#130	#128 NOT #129 1927

Line 87 – G4-related didn't work, so taken out

Database: CRD

1	MeSH DESCRIPTOR Diabetes Mellitus EXPLODE ALL TREES	2444
2	(diabet*)	4478
3	((DM near4 ("type 1" or type1 or "type I" or "type one" or T1 or T-1 or TI or T-I)))	2
4	(lada)	1
5	((dm1 or iddm or t1d* or dka))	53
6	((dm2 or t2d* or mody or niddm))	83
7	((DM near4 (autoimmun* or auto immun* or brittle or labile or insulin depend* or insulin deficien*)))	0
8	((DM near4 onset* near4 (maturit* or adult* or slow*)))	0
9	((DM near4 depend* near4 (non-insulin* or non insulin* or noninsulin*)))	0
10	((DM near4 (earl* or sudden onset or juvenile or child*)))	1
11	((DM near4 (keto* or acidi* or gastropare*)))	0
12	((DM near4 ("type 2" or type2 or "type ii" or "type two" or T2 or T-2 or TII or T-II)))	4
13	((DM near4 ("type 4" or type4 or "type iv" or "type four" or T4 or T-4 or TIV or T-IV)))	0
14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	4525
15	MeSH DESCRIPTOR Diabetes, Gestational	83
16	((gestation* or pregnan*)):TI	1095
17	#15 OR #16	1101
18	#14 NOT #17	4377

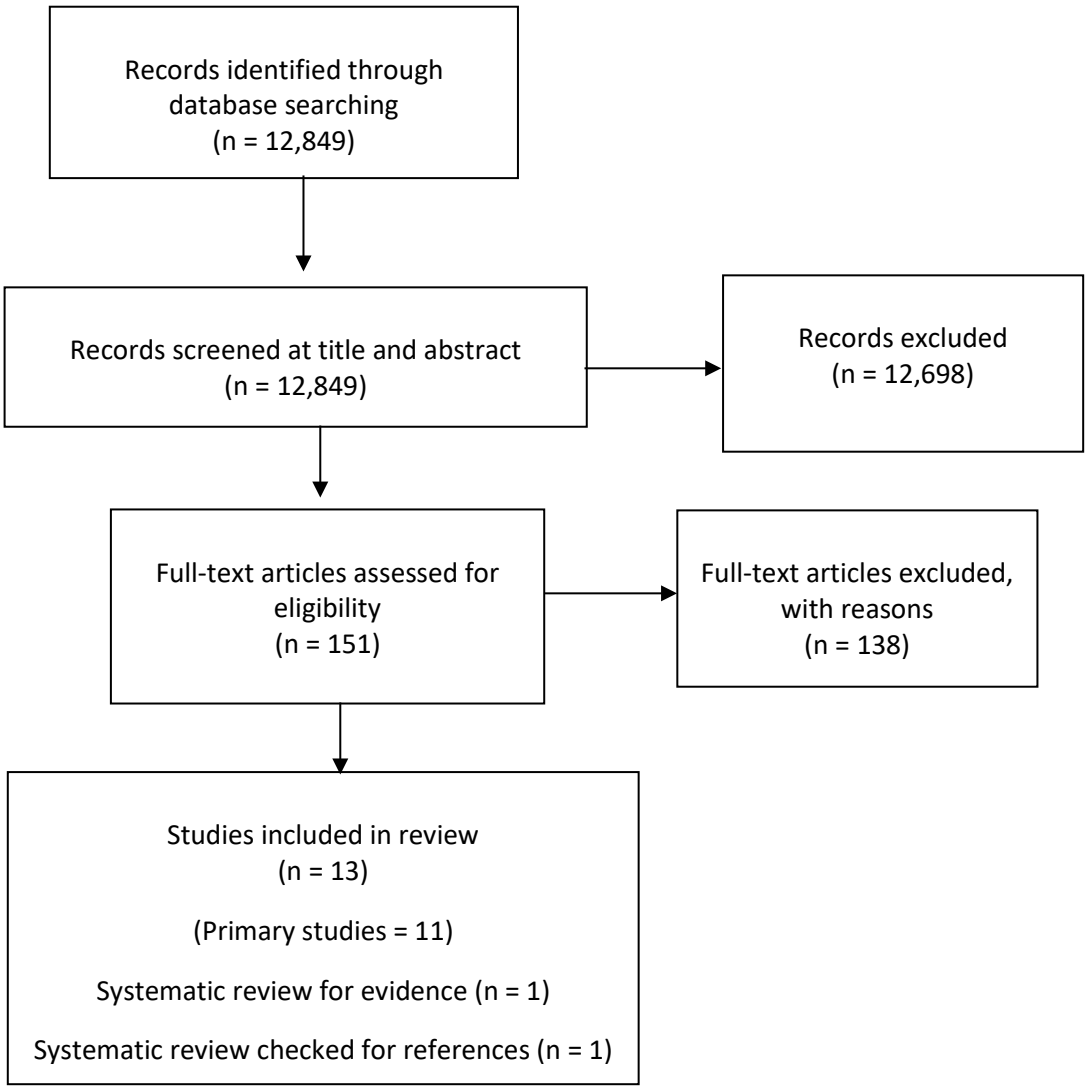
19	MeSH DESCRIPTOR C-Peptide	4
20	(("c peptide*" or c-peptide or Cpeptide or ((connect* or gamma*) near4 peptide)))	25
21	((creatinine* near4 (ratio* or quota* or proportion*))):TI	8
22	MeSH DESCRIPTOR Autoantibodies	46
23	((antibod* or anti bod*or autoantibod* or auto-antibod* or auto-anti-bod* or autoantigen* or auto-antigen* or auto-anti-gen*))	2286
24	#22 OR #23	2300
25	((islet cell or beta cell or decarboxylase or glutamic or insulin*))	1106
26	MeSH DESCRIPTOR Islets of Langerhans	7
27	MeSH DESCRIPTOR glutamate decarboxylase	0
28	((glutam* near4 (decarbox* or carbox*)))	1
29	MeSH DESCRIPTOR insulinoma	4
30	MeSH DESCRIPTOR glucose-6-phosphatase	1
31	((glucose 6 phosphatase or glucosephosphatase))	1
32	MeSH DESCRIPTOR Zinc Transporter 8 EXPLODE ALL TREES	0
33	(zinc transporter 8)	0
34	((islet near4 (phosphatase or catalytic or subunit* or sub-unit*)))	0
35	((igrp* or iaa* or ica* or ia-2* or ia2* or znt8* or gad* or CA512))	197
36	#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35	1305
37	#24 AND #36	17
38	#19 OR #20 OR #21 OR #37	49
39	MeSH DESCRIPTOR Body Mass Index	363
40	(((body mass or quetelet*) near2 index))	1100
41	(BMI)	444
42	MeSH DESCRIPTOR Age of Onset	31
43	(((age* near2 onset*) or age-of-onset or age-at-onset))	102
44	MeSH DESCRIPTOR Ketones	14
45	(ketone*)	18
46	MeSH DESCRIPTOR Diabetic Ketoacidosis	12
47	((diabetic near4 (ketoacidos* or acidos*)))	25
48	(DKA)	3

49	MeSH DESCRIPTOR Family Health	39
50	MeSH DESCRIPTOR Genetic Predisposition to Disease	767
51	(((famil* or household* or forebear* or parent* or relativ*) near4 health*))	426
52	((genetic* near4 (predispos* or suscept*)))	817
53	MeSH DESCRIPTOR addison disease	0
54	(((Addison* near4 diseas*) or ((primar* near4 (adren* near4 insuff*)) or hypoadren*)))	3
55	MeSH DESCRIPTOR anemia, hemolytic, autoimmune	0
56	(((H*emolyt near4 An*emi*) or (cold near4 (agglutin* or antibod*) near4 diseas*)))	0
57	MeSH DESCRIPTOR anti-glomerular basement membrane disease	0
58	((((((Anti Glomerul* or Antiglomerul*) near4 Basement* near4 Membran*) or anti gbm) near4 Diseas*) or (goodpasture* near4 syndrom*) or (lung near4 purpura near4 nephrit*)))	0
59	MeSH DESCRIPTOR anti-neutrophil cytoplasmic antibody-associated vasculitis	5
60	((((Anti Neutrophil near4 Cytoplasm* near4 Antibod*) or ANCA or pauci immune) near4 Vasculit*))	10
61	MeSH DESCRIPTOR antiphospholipid syndrome	13
62	(((anti phospholipid* or antiphospholipid* or hughes*) near4 syndrom*))	17
63	MeSH DESCRIPTOR arthritis, juvenile	26
64	MeSH DESCRIPTOR arthritis, rheumatoid	537
65	(((Juvenil* or Rheumat*) near4 (Arthrit* or oligoarthrit* or still or still*)))	906
66	MeSH DESCRIPTOR autoimmune diseases of the nervous system	3
67	(((autoimmun* or immun*) near4 (diseas* or disorder*) near4 (nervous or neurologic*)))	7
68	MeSH DESCRIPTOR autoimmune hypophysitis	0
69	((((autoimmun* or idiopath* or lymphoid* or lymphocyt* or igg4*) near4 (hypophys* or adenohypophys* or infundibuloneurohypophys*)) or (anti pit 1 near4 antibod* near4 syndrom*)))	0
70	MeSH DESCRIPTOR autoimmune lymphoproliferative syndrome	0
71	((((autoimmun* near4 lymphoproliferat*) or canale smith or caspase*) near4 (syndrom* or deficien*)))	0
72	MeSH DESCRIPTOR autoimmune pancreatitis EXPLODE ALL TREES	0
73	((((autoimmun* or idiopath* or igg4*) near4 pancreatit*) or type 1 aip or type 2 aip))	6
74	MeSH DESCRIPTOR birdshot chorioretinopathy	0
75	((birdshot near4 (chorioretin* or retinochoroid*)))	0
76	MeSH DESCRIPTOR dermatitis herpetiformis	2

77	(((dermatit* near4 herpetiform*) or (duhring* near4 diseas*)))	3
78	MeSH DESCRIPTOR glomerulonephritis, iga	22
79	((((IGA or immunoglob*) near4 (glomerulonephrit* or nephr*)) or (berger* near4 diseas*)))	26
80	MeSH DESCRIPTOR glomerulonephritis, membranous	13
81	((((membran* or extramembran*) near4 (glomeruloneph* or neuropath*)) or ((heymann or (idiopath* near4 membran*)) near4 nephrit*)))	2
82	MeSH DESCRIPTOR graves disease	19
83	((((graves* or basedow*) near4 diseas*) or (exophthal* near4 goiter*)))	30
84	MeSH DESCRIPTOR hepatitis, autoimmune	3
85	((autoimmun* near4 hepatit*))	7
86	MeSH DESCRIPTOR immunoglobulin g4-related disease	0
87	(((((Immunoglob* near4 (G4-Related or G4related or "G4 Related")) or IGG4*) near4 (Diseas* or RD)))	0
88	MeSH DESCRIPTOR linear iga bullous dermatosis	0
89	((Linear* near4 (Bullous* or IGA) near4 Dermatos*))	0
90	MeSH DESCRIPTOR lupus erythematosus, systemic	55
91	(((Lupus* near4 Erythemat*) or libman sacks))	95
92	MeSH DESCRIPTOR ophthalmia, sympathetic	0
93	((sympathetic* near4 (ophthal* or uveit*)))	0
94	MeSH DESCRIPTOR pemphigoid, bullous	2
95	MeSH DESCRIPTOR pemphigus	4
96	(pemphig*)	13
97	MeSH DESCRIPTOR polyendocrinopathies, autoimmune	0
98	(((autoimmun* near4 (polyendocrin* or polygland*)) or apeced or ((aire or multiple endocrin*) near4 deficien*) or aps type 1 or (schmidt* near4 syndrom*)))	0
99	MeSH DESCRIPTOR purpura, thrombocytopenic, idiopathic	36
100	((((autoimmune* or idiopath* or immun*) near4 thrombocytopen) or (werlhof* near4 diseas*)))	0
101	MeSH DESCRIPTOR thyroiditis, autoimmune	2
102	(((autoimmun* or lympho*) near4 thyroidit*))	1
103	MeSH DESCRIPTOR undifferentiated connective tissue diseases	0
104	((Undifferent* near4 Connect* near4 Tissue* near4 Diseas*))	1
105	MeSH DESCRIPTOR Celiac Disease	35

106	(((c*eliac* or nontropic* or non-tropic*) near4 (diseas* or sprue*)))	50
107	((gluten* near4 enteropath*))	2
108	MeSH DESCRIPTOR Hypothyroidism EXPLODE ALL TREES	37
109	(hypothyroid*)	87
110	(((tsh or thyroid stimulat* hormone*) near4 deficienc*))	0
111	MeSH DESCRIPTOR Hyperthyroidism EXPLODE ALL TREES	43
112	(hyperthyroid*)	53
113	MeSH DESCRIPTOR Gastritis, Atrophic	7
114	((atrophic* near4 gastrit*))	11
115	MeSH DESCRIPTOR Population Characteristics	1
116	((populat* near4 (character* or heterogen* or statistic*)))	559
117	((ethnic* or nationalit*))	822
118	MeSH DESCRIPTOR Weight Loss	464
119	((weigh* near4 (loss* or reduc*)))	1090
120	MeSH DESCRIPTOR Time-to-Treatment	19
121	(("time to treatment*" or "door to treatment*" or (delay* near4 (treatment* or therap*))))	298
122	#39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119 OR #120 OR #121	5943
123	#38 OR #122	5980
124	#18 AND #123	908
125	((sensitiv* or predictive value* or accurac*))	17726
126	(#124 AND #125) IN DARE	178

Appendix D – Diagnostic evidence study selection



Appendix E – Diagnostic evidence tables

Systematic reviews

Shields, 2015

Bibliographic Reference	Shields, Beverley M; Peters, Jaime L; Cooper, Chris; Lowe, Jenny; Knight, Bridget A; Powell, Roy J; Jones, Angus; Hyde, Christopher J; Hattersley, Andrew T; Can clinical features be used to differentiate type 1 from type 2 diabetes? A systematic review of the literature.; BMJ open; 2015; vol. 5 (no. 11); e009088

Study Characteristics

Study design	Systematic review Systematic review of all diagnostic accuracy Studies published since 1979 using clinical criteria to predict insulin deficiency (measured by C-peptide).
Study details	Dates searched 1979 to 2015 Databases searched MEDLINE, MEDLINE in Process, EMBASE, PsycINFO, Social Policy and Practice, AMED, British Nursing Index, CINAHL, HMIC, Sociological Abstracts, ASSIA, Cochrane, Web of Science, Centre for Reviews and Dissemination). Sources of funding

	This study was funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) programme (PB-PG-0711-25111) and supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South West Peninsula at the Royal Devon and Exeter NHS Foundation Trust. ATH and BMS are core members of the NIHR Exeter Clinical Research Facility
Inclusion criteria	Included studies comprised diagnostic accuracy studies of clinical predictors of insulin deficiency, with the reference standard of insulin deficiency being defined by cut-offs of C-peptide results. All measurements of C-peptide and all cut-offs for insulin deficiency were included. Clinical predictors were defined as any routinely measured clinical feature and studies were eligible if there was a cut-off for that clinical predictor assessed against the measure of insulin deficiency. There were no restrictions on race, age or country of origin.
Exclusion criteria	Studies where patients had known causes of diabetes, for example, monogenic, secondary or syndromic diabetes, were excluded. Studies examining islet autoantibodies only were excluded as they are not routinely measured.
Number of studies included in the systematic review	Studies examining islet autoantibodies only were excluded as they are not routinely measured.
Studies from the systematic review that are not relevant for use in the current review	Prior 1991 Welborn 1983 Laakso 1987 Benhamou 1992 Shields 2010 Service 1997 Boyle 1999 Welborn 1981 Nielsen 1986 Ekpebegh 2013

	Balasubramanyam 2006

Section	Question	Answer
Study eligibility criteria	Did the review adhere to pre-defined objectives and eligibility criteria?	Yes
	Were the eligibility criteria appropriate for the review question?	Yes
	Were eligibility criteria unambiguous?	Yes
	Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Yes
	Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Yes
	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Yes
	Were methods additional to database searching used to identify relevant reports?	Yes
	Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Probably yes

Section	Question	Answer
	Were restrictions based on date, publication format, or language appropriate?	Yes
	Were efforts made to minimise error in selection of studies?	Yes
	Concerns regarding methods used to identify and/or select studies	Low
Data collection and study appraisal	Were efforts made to minimise error in data collection?	Yes
	Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes
	Were all relevant study results collected for use in the synthesis?	Yes
	Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes
	Were efforts made to minimise error in risk of bias assessment?	Yes
	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Did the synthesis include all studies that it should?	Yes
	Were all pre-defined analyses reported or departures explained?	Yes
	Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Yes
	Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Yes

Section	Question	Answer
	Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	No information
	Were biases in primary studies minimal or addressed in the synthesis?	Yes *(Highlighted in the discussion but as meta-analysis was not conducted which meant that sensitivity analysis was not possible)*
	Concerns regarding the synthesis and findings	No
Overall study ratings	Overall risk of bias	Low
	Applicability as a source of data	Fully applicable

Study characteristics – Shields 2015 review

Author/Year	Country	Year of study	Race of population	Sample size	Inclusion or Exclusion criteria	Treatments	Age group of population	% Male	Proportion with BMI below cutoff used	Proportion C-peptide negative
Balasubramanyam 2006	USA (Texas)	1999-2003	44.8% African American; 43.5% Hispanic; 10.8% Caucasian; <1% Asian	294	I: Presented with DKA	Unclear – assume all treatments		60%	Cutoff of 28kg/m^2 = 44th centile	0.4
Benhamou 1992	France	1989-1990	Not specified	88	I: End stage renal disease	All treatments	Not specified	?	Unable to extract	0.16
Boyle 1999	USA (Georgia)	1991-1996	All African American	3613 (1807 for testing)	E: Serum creatinine >2mg/dl E: Missing data	All treatments	Split by category – table 1	37%	45% patients BMI<29	0.07

Ekpebegh 2013	South Africa	2010-2012	Black African	71	I: Diagnosis of DKA	All treatments	Mean 34.7+/-15.3	54%	65% BMI<30	0.49
Laakso 1987	Finland	1987	Not specified	171	I: Insulin treated only I: aged 45-64 living in region of Kuopio central Hospital	Insulin treated only	Range 45-64	47%	49% of patients BMI<27	0.67
Nielsen 1986	Denmark	1979-1980	Not specified	215	I: Insulin treated only	Insulin treated Only	Not specified	52%	-	0.69
Prior 1991	USA (Baltimore)	1980-1985	96.5% White	575	I: Mild-severe non-proliferative or early proliferative diabetic retinopathy; I: Aged 18-70	All treatments	Range 18-70	?	68% PDW<120%[a]	0.61
Service 1997	USA (Rochester)	1986	Not specified	346	No specific exclusion criteria	All treatments	Not specified	?	Unable to extract	0.3
Shields 2010	UK	2010	Not specified	72	I: Insulin treated only E: <5y duration and on insulin <2y of diagnosis	Insulin treated only	Adults	?	63% BMI<29	0.56
Welborn 1981	Australia	1981	Not specified	201	E: Known renal failure	All treatments	Mean 53 +/-17 for hosp; 55 +/-16 for country	53%	43% of cohort PDW<120%^{a}	0.24
Welborn 1983	Australia	1983	All Caucasian	121	No exclusions for food, glucose or renal status	Unclear – assume all	Adults	?	Not specified	0.21

a: 120% PDW (percentage desirable weight) equates to BMI<27.2 for men, <26.9 for women.

Primary studies

Balasubramanyam 2006

Balasubramanyam, 2006

Bibliographic Reference	Balasubramanyam, Ashok; Garza, Gilberto; Rodriguez, Lucille; Hampe, Christiane S; Gaur, Lakshmi; Lernmark, Ake; Maldonado, Mario R; Accuracy and predictive value of classification schemes for ketosis-prone diabetes.; Diabetes care; 2006; vol. 29 (no. 12); 2575-9

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Houston, Texas, USA Setting General hospital Study dates June 1999 - December 2003 Sources of funding NR Types of diabetes examined Ketosis-prone diabetes
Inclusion criteria	Disease at entry Diabetic ketoacidosis Data required BMI, Beta-cell autoantibodies, Beta-cell function within 2 weeks of resolution of resolution of index DKA episode and 6-12 months later, regular follow-up [at least 2 visits per year], dose and frequency of insulin treatment after DKA episode

Exclusion criteria	Criteria 1 NR
Number of participants	294
Length of follow-up	Mean duration of 31 months (range 12-60 months)
Loss to follow-up	**NR**
Index test(s)	BMI Multiple ADA Modified ADA BMI-classification Alpha/Beta GAD65 GAD65/67
Reference standard (s)	C-peptide level "Preserved Beta-cell function" as defined by fasting serum C-peptide level was ≥1 ng/ml or the maximum glucagon- stimulated serum C-peptide level was ≥1.5 ng/ml

	Absent Beta-cell function as defined by C-peptide level was <1 ng/ml or the maximum glucagon-stimulated serum C-peptide level was <1.5 ng/ml These cut-off levels and the correlations between the fasting C-peptide cut-off and the peak glucagon-stimulated C-peptide cut-off have been validated by previously published receiver operator characteristic (ROC) analyses (3,10,11).
Diagnostic data format	Sensitivity/Specificity/PPV/NPA/LR/ROC AUC table

Study arms

ADA (N = 294) Type 1a: KPD patients with low β-cell function, autoimmune markers, and clinical characteristics of type 1 diabetes. Type 1b: KPD patients with some preservation of β-cell function and clinical characteristics of type 2 diabetes.
Modified ADA (N = 294) Type 1a: Patients with autoantibodies against islet cell or -cell antigens Those who lack autoantibodies are subdivided into two groups: “KPD–insulin dependent” (KPD-ID) and “KPD–noninsulin dependent” (KPD-NID), based on long-term requirement for exogenous insulin.
BMI classification (N = 294) Differentiates KPD patients into “lean” (defined by these investigators as BMI <28 kg/m2) and “obese” (BMI >28 kg/ m2) subtypes
AB (N = 294)

Based on the presence or absence of markers of beta-cell autoimmunity (autoantibodies) together with presence or absence of -cell function. KPD patients are differentiated into four categories:

Alpha+ Beta - those with autoimmunity and absent Beta-cell function;

Alpha plus Beta plus, those with autoimmunity but preserved -cell function;

Alpha minus Beta minus those without autoimmunity but absent -cell function; and

Alpha minus Beta plus, those without autoimmunity and preserved -cell function.

Population characteristics

Study-level characteristics

	Study (N = 294)
Sample size	
Age at presentation	
Mean/SD	38 (11)
Age at diagnosis of diabetes	
Mean/SD	33 (14)
Years with diabetes	
Range	0 to 45
Mean/SD	4.1 (7.3)
Male	

	Study (N = 294)
Nominal	175
Ethnicity	
Nominal	294
African-American	
Nominal	132
Hispanic	
Nominal	128
Caucasian	
Nominal	32
Asian	
Nominal	2
Precipitating factor	
Acute illness	54
Non-compliance	105
New-onset diabetes	135

	Study (N = 294)
unprovoked DKA	
BMI	
Range	16.9 to 63.9
Mean/SD	29.4 (8.7)
Baseline A1c	
Mean/SD	13.4 (2.5)
Distribution of BMI	
Lean (BMI < 25kg/m2)	
Nominal	112
Overweight (BMI 25-29.9 kg/m2)	
Nominal	69
Obese (BMI >= 30 kg/m2)	
Nominal	109

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Yes *(294 consecutive patients who presented with DKA to the Ben Taub General Hospital, Houston, Texas between June 1999 and December 2003.)*
	Was a case-control design avoided?	Yes
	Did the study avoid inappropriate exclusions?	Unclear *(Exclusion criteria not specified.)*
	Could the selection of patients have introduced bias?	Unclear *(Exclusion criteria not reported.)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
	If a threshold was used, was it pre-specified?	Yes
	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Unclear if index test was results were interpreted without knowledge of reference standard.)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Yes

Section	Question	Answer
	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(Unclear if reference standard was results were interpreted without knowledge of index test.)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Yes
	Did all patients receive a reference standard?	Yes
	Did patients receive the same reference standard?	Yes
	Were all patients included in the analysis?	Yes
	Could the patient flow have introduced bias?	Low
Overall risk of bias and directness	Risk of Bias	Low *(It was unclear if reference standard was results were interpreted without knowledge of index test but as the tests were objective (c-peptide and serological markers) study was not downgraded.)*
	Directness	Directly applicable

Covic 2000

Covic, 2000

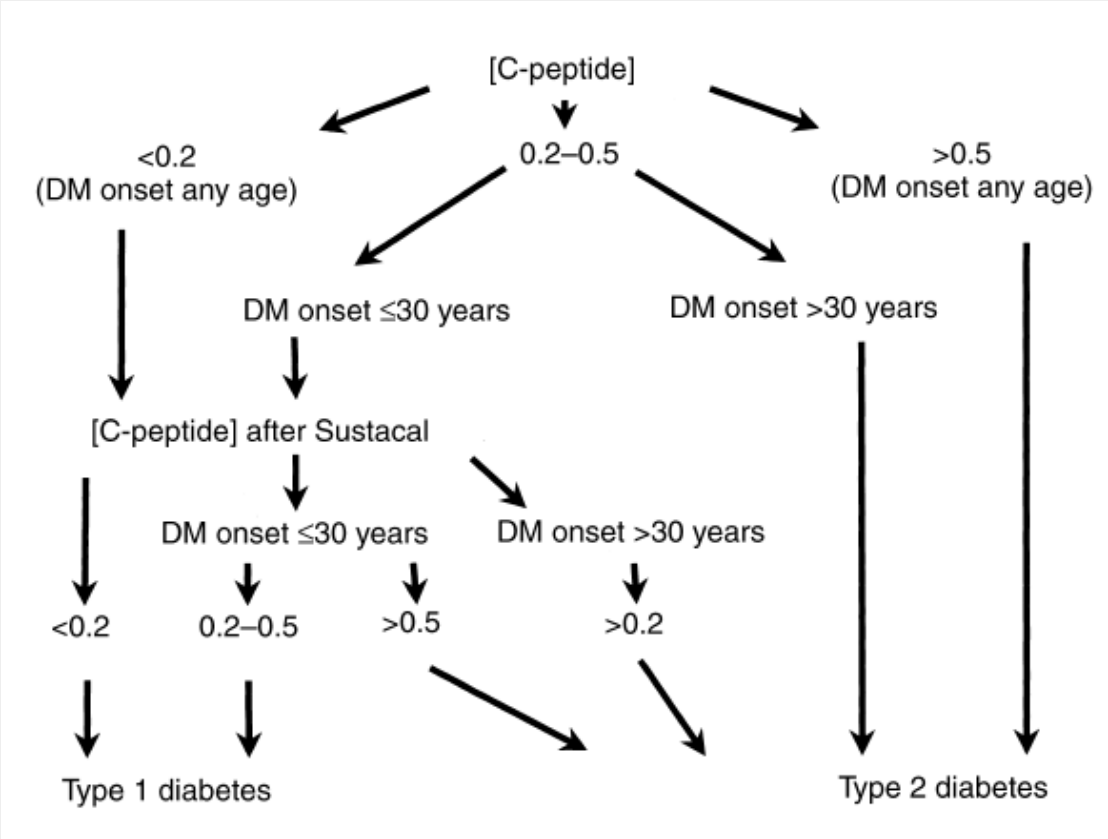
Bibliographic Reference	Covic, A.M.C.; Schelling, J.R.; Constantiner, M.; Iyengar, S.K.; Sedor, J.R.; Serum C-peptide concentrations poorly phenotype type 2 diabetic end-stage renal disease patients; Kidney International; 2000; vol. 58 (no. 4); 1742-1750

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Cleveland, Ohio, USA Setting 8 haemodialysis units Sources of funding National institutes of health grants RO1 DK38558, RO1 DK02281, P50 DK54644, RO1 DK 54178, and MO1RR00080. Additional support was obtained from the American heart association northeast Ohio affiliate, Baxter extramural grant program, central Ohio diabetes association, juvenile diabetes foundation, kidney foundation of Ohio, and Leonard C. Rosenburg renal foundation. Types of diabetes examined Type 2 vs other types
Inclusion criteria	Family history of diabetes And at least 1 diabetic sibling
Number of participants	127

Length of follow-up	NA
Loss to follow-up	NA
Index test(s)	Multiple T1: Age of onset <25 years and one of the following criteria- a) history of DKA b) treatment with insulin only and/or insulin therapy initiated less than one year after diabetes diagnosis c) weight at diagnosis and/or maximal body weight <105% of the ideal bodyweight T2: 1. Onset of diabetes after 40 years of age, no history of DKA, and one of the following criteria: a, weight at diagnosis and/or maximum weight >115% of ideal body weight b. no consistent insulin therapy during the first two years after diabetes diagnosis 2. both 1a and 1b if diabetes onset occurred between 30 and 40 years Unclassified: not categorised by above Age at diagnosis
Reference standard (s)	Multiple standard clinical criteria (age of diabetes onset ,25 years, treatment only with insulin and/or history of DKA) modified DCCT criteria: If Pre-HD c-peptide >0.5 nmol/L: These diabetic ESRD patients were classified as T2 diabetes without a sustacal-stimulation test since in the DCCT study, only type 2 diabetics had basal or stimulated c-peptide concentration >0.50 nmol/L

	If Pre-HD C-peptide value between 0.20 nmol/L and 0.50 nmol/L: Using DCCTG criteria, a sustacal stimulation test was performed if diabetes onset occurred before the age of 30. ESRD patients with sustacal stimulated c-peptide concentrations >0.50 nmol/L were classified as type 2 diabetics. Patients with stimulated c-peptide concentrations <0.50 nmol/l were classified as type 1 diabetics. If diabetes onset was after 30 years of age, patients were categorized as type 2 diabetics without performing a sustacal stimulation test. Pre-HD C-peptide value <0.20 nmol/L. Sustacal-stimulation tests were performed in all patients with pre-HD c-peptide concentrations <0.20 nmol/L (0.6 ng/L). If stimulated C-peptide concentrations remained <0.20 nmol/L, subjects were considered type 1 diabetic regardless of age of diabetes onset. Patients were classified as type 2 diabetics if the age of diabetes onset was after the patient was 30 years of age, and the stimulated c-peptide concentrations were >0.20 nmol/L. If diabetes onset appeared when patients were less than 30 years of age, they were classified as type 1 diabetics if stimulated C-peptide concentrations were >=20 nmol/L but >=0.50 nmol/L, and patients were classified as type 2 diabetics if the stimulated c-peptide levels were >0.50 nmol/L.



C-peptide: DCCT criteria
C-peptide concentrations were assayed in a serum sample obtained at the initiation of dialysis, and diabetes was classified as type 1 or type 2. C-peptide concentrations are expressed as nmol/L. Prior to classification, serum C-peptide levels were repeated after overnight fasting and Sustacal stimulation in study participants, who had random C-peptide concentrations ,0.5 nmol/L and diabetes onset prior to an age of 30, or in subjects of any age with C-peptide concentrations ,0.2 nmol/L. No additional tests were obtained in study participants, who had serum C-peptide concentrations .0.5 nmol/L or in subjects with C-peptide concentrations from 0.2 to 0.5 nmol/L but in whom diabetes onset occurred after 30 years of age.

	Obtained predialysis blood samples (at 7am for first shift, 12pm for second shift, and 4pm for third shift subjects) for serum glucose and c-peptide concentrations. Diabetic ESRD patients were classified as T1 or T2 according to their c-peptide concentrations using the DCCT algorithm with the modifications outlined under index test.
Diagnostic data format	se sp ppv npv for correct diagnosis of type 2 vs other types
Additional comments	

Population characteristics

Study-level characteristics

	Study (N = 127)
Sample size	
Nominal	127
Age	
Mean/SD	61.9 (10.1)
Age at diabetes onset	
Mean/SD	41.3 (12.7)
Diabetes duration	
Mean/SD	20.6 (9.4)

	Study (N = 127)
Pre-haemodialysis c-peptide concentration *(nmol/L)*	
Mean/SD	3.22 (1.85)

Section	**Question**	**Answer**
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Yes
	Was a case-control design avoided?	Yes
	Did the study avoid inappropriate exclusions?	Unclear *(Exclusion criteria not specified.)*
	Could the selection of patients have introduced bias?	Unclear *(Exclusion criteria not specified.)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear *(Unclear if index test results were interpreted without knowledge of the results of the reference standard.)*
	If a threshold was used, was it pre-specified?	Yes

Section	Question	Answer
	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear *(Unclear what reference standard was used when examining the diagnostic test accuracy of the new algorithm to identify ESRD patients as type 2 DM.)*
	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear *(Unclear if reference standard results were interpreted without knowledge of the results of the index test.)*
	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(Unclear what reference standard was used when examining the diagnostic test accuracy of the new algorithm to identify ESRD patients as type 2 DM.)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Unclear
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Yes
	Did all patients receive a reference standard?	Yes
	Did patients receive the same reference standard?	Yes
	Were all patients included in the analysis?	Yes
	Could the patient flow have introduced bias?	Low

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Moderate *(Unclear what reference standard was used when examining the diagnostic test accuracy of the new algorithm to identify ESRD patients as type 2 DM.)*
	Directness	Directly applicable

Fourlanos 2006

Fourlanos, 2006

Bibliographic Reference	Fourlanos, Spiros; Perry, Christine; Stein, Mark S; Stankovich, Jim; Harrison, Leonard C; Colman, Peter G; A clinical screening tool identifies autoimmune diabetes in adults.; Diabetes care; 2006; vol. 29 (no. 5); 970-5

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Australia Setting national diabetes register, the National Diabetes Services Scheme

	Study dates NR Sources of funding This study was supported by a Juvenile Diabetes Research Center Program Grant (to L.C.H.). S.F. is a Postgraduate Scholar of the National Health and Medical Research Council of Australia. Types of diabetes examined LADA vs T2
Inclusion criteria	Age 30-75 Disease at entry Non-insulin requiring diabetes Length of time with diabetes <2 months since diagnosis
Number of participants	130
Length of follow-up	NA
Loss to follow-up	NA
Index test(s)	Multiple "LADA clinical risk score" as designed in retrospective study Five distinguishing clinical features were significantly more frequent in subjects with LADA than in subjects with type 2 diabetes at diagnosis (Fig. 1). These were 1) age of diabetes onset <=50 years, 2) acute symptoms of polydipsia and/or polyuria and/or unintentional weight loss before m2, diagnosis, 3) BMI 25 kg/ 4) a personal history of DR3- and/or DR4-related autoimmune disease, and 5) a family history of DR3- and/or DR4-related autoimmune disease.

Reference standard (s)	GADA GADA antibody presence
Diagnostic data format	AUC and sensitivity/specificity from ROC curve analysis
Additional comments	Full clinical characteristics for retrospective study only.

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Yes
	Was a case-control design avoided?	Yes
	Did the study avoid inappropriate exclusions?	Unclear *(Exclusion criteria not specified.)*
	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear *(Unclear if the index test results were interpreted without knowledge of the results of the reference standard.)*

Section	Question	Answer
	If a threshold was used, was it pre-specified?	No
	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(All subjects were interviewed to gather data on clinical features. Unclear if there was missing data.)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Yes
	Did all patients receive a reference standard?	Yes
	Did patients receive the same reference standard?	Yes
	Were all patients included in the analysis?	Yes
	Could the patient flow have introduced bias?	Low

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Moderate *(All subjects were interviewed to gather data on clinical features. Unclear if there was missing data.)*
	Directness	Directly applicable

Garnier 2018

Garnier, 2018

Bibliographic Reference	Garnier, Lorna; Marchand, Lucien; Benoit, Marine; Nicolino, Marc; Bendelac, Nathalie; Wright, Catherine; Moulin, Philippe; Lombard, Christine; Thivolet, Charles; Fabien, Nicole; Screening of ZnT8 autoantibodies in the diagnosis of autoimmune diabetes in a large French cohort.; Clinica chimica acta; international journal of clinical chemistry; 2018; vol. 478; 162-165

Study Characteristics

Study type	Retrospective cohort study
Study details	Study location Lyon, France Setting Immunology dept blood test patients at hospital Study dates 2012 - 2013

	Sources of funding NR Types of diabetes examined T1, T2, Other
Inclusion criteria	Data required Patients who have had blood tests
Exclusion criteria	Criteria 1 NR
Number of participants	109
Length of follow-up	NA
Loss to follow-up	NA
Index test(s)	GAD65 GADA+ (5AU/mL) IA-2A 7AU/mL ZnT8 15AU/mL
Reference standard (s)	Multiple "Clinical diagnosis" unclear what this is

Diagnostic data format	Sensitivity only.
Additional comments	

Study-level characteristics

	Study (N = 109)
Sample size	
Male	
Nominal	64
Mean age (SD)	
Custom value	41.3 years [range 18-83]
Duration of diabetes time between sera analysis and T1D diagnosis	
Onset < 6 months	
Nominal	25
Onset >= 6 months	
Nominal	84

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Yes
	Was a case-control design avoided?	Yes
	Did the study avoid inappropriate exclusions?	Unclear *(Exclusion criteria not specified.)*
	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(Population included children.)*
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear *(Unclear if index test results were interpreted without knowledge of the results of the reference standard.)*
	If a threshold was used, was it pre-specified?	Yes *(The cut-off for positivity was chosen according to the manufacturer's recommendation for the ELISA and immunoassay.)*
	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low

Section	Question	Answer
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear *(Reference standard not clearly defined. Study onl)*
	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear *(Unclear if reference standard results were interpreted without knowledge of the results of the index test.)*
	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(Reference standard not clearly defined. Unclear if reference standard results were interpreted without knowledge of the results of the index test.)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Unclear *(Reference standard not clearly defined.)*
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear *(Interval between index test and reference standard not specified.)*
	Did all patients receive a reference standard?	Yes
	Did patients receive the same reference standard?	Yes
	Were all patients included in the analysis?	Yes
	Could the patient flow have introduced bias?	Unclear *(Interval between index test and reference standard not specified.)*
Overall risk of bias and directness	Risk of Bias	High *(Reference standard not clearly defined.)*
	Directness	Indirectly applicable *(Population included children.)*

Hope 2016

Hope, 2016

Bibliographic Reference	Hope, Suzy V; Wienand-Barnett, Sophie; Shepherd, Maggie; King, Sophie M; Fox, Charles; Khunti, Kamlesh; Oram, Richard A; Knight, Bea A; Hattersley, Andrew T; Jones, Angus G; Shields, Beverley M; Practical Classification Guidelines for Diabetes in patients treated with insulin: a cross-sectional study of the accuracy of diabetes diagnosis.; The British journal of general practice : the journal of the Royal College of General Practitioners; 2016; vol. 66 (no. 646); e315-22

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Three UK centres (Exeter, Northampton and Leicester) Setting in primary care, both urban and rural, and secondary care Study dates NR Sources of funding NHS Diabetes, with direct funding from the Department of Health (DoH), and the National Institute for Health Research (NIHR) under its Research for Patient Benefit programme Types of diabetes examined

	Type 1, Type 2
Inclusion criteria	Age Adults Disease at entry "insulin treated diabetes" Length of time with diabetes ≥5 years
Exclusion criteria	Criteria 1 NR
Number of participants	601 ("European") 30 ("Asian")
Length of follow-up	NR
Loss to follow-up	NR
Index test(s)	Multiple UK Practical classification guidelines for diabetes Type 1: Diagnosed <35 years (30 in high-risk ethnicities) AND continual insulin treatment within 6 months of diagnosis OR Diagnosis >= 35 years AND continual insulin treatment from diagnosis Type 2: Diagnosis <35 years AND not on continual insulin treatment within 6 months of diagnosis OR Diagnosis <= 35 years AND not on continual insulin treatment from diagnosis
Reference standard (s)	Multiple

	Type 1 diabetes: continuous insulin treatment within the first 3 years of diagnosis and absolute insulin deficiency (UCPCR <0.2 nmol/mmol ≥5 years post-diagnosis) Type 2 diabetes: UCPCR >0.2 nmol/mmol, or UCPCR <0.2 nmol/mmol but not treated with insulin for first 3 years after diagnosis. UCPCR = urine test urinary C-peptide creatinine ratio
Diagnostic data format	ROC curves with AOC and optimal cut-offs -> sensitivity/specificity measures Data for a 2x2 table
Additional comments	

Population characteristics

Arm-level characteristics

	Type 1 Gold standard (N = 0)	**Type 2 Gold standard (N = 0)**	**Type 1 UK guideline (N = 0)**	**Type 2 UK guideline (N = 0)**	**Overall (N = 601)**
Sample size					
Nominal	193	408	220	381	601
Age At recruitment					
MedianIQR	54 (41 to 64)	68 (60 to 74)	53 (41 to 64)	68 (61 to 75)	64 (53 to 73)
Sex (male) %					

	Type 1 Gold standard (N = 0)	Type 2 Gold standard (N = 0)	Type 1 UK guideline (N = 0)	Type 2 UK guideline (N = 0)	Overall (N = 601)
Nominal	48.7	62.8	52.7	61.4	58.2
BMI at recruitment					
MedianIQR	26.5 (23.1 to 29.3)	29.7 (26.6 to 34.5)	26.8 (23.8 to 29.7)	30 (26.6 to 34.5)	28.7 (25.3 to 33.3)
Age at diagnosis					
MedianIQR	24 (12 to 36)	50 (42 to 59)	25 (13 to 39)	50 (43 to 58)	45 (30 to 56)
BMI at diagnosis					
MedianIQR	21.8 (19.8 to 26.3)	28.4 (25.4 to 32.9)	22.9 (20 to 27.6)	28.3 (25.2 to 33.6)	27 (23.9 to 32)
HbA1c (%) latest					
MedianIQR	8.1 (7.4 to 8.9)	7.9 (7.2 to 8.8)	8 (7.3 to 8.9)	7.9 (7.3 to 8.8)	8 (7.3 to 8.8)
Insulin IU/kg/24 hours					
MedianIQR	0.61 (0.5 to 0.84)	0.65 (0.42 to 0.93)	0.61 (0.49 to 0.88)	0.64 (0.43 to 0.92)	0.64 (0.44 to 0.9)
UCPCR nmmol/mmol					
MedianIQR	0.019 (0.019 to 0.03)	1.19 (0.59 to 2.25)	0.019 (0.019 to 0.22)	1.1 (0.4 to 1.1)	0.6 (0.03 to 1.6)

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Yes
	Was a case-control design avoided?	Yes
	Did the study avoid inappropriate exclusions?	Unclear *(Exclusion criteria not specified.)*
	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear *(Unclear if index test results were interpreted without knowledge of the results of the reference standard.)*
	If a threshold was used, was it pre-specified?	Yes
	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Clinical characteristics were provided by participants. Unclear if there was missing data.)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low

Section	Question	Answer
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear *(Unclear if the reference standard results were interpreted without knowledge of the results of the index test.)*
	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(Unclear if the reference standard results were interpreted without knowledge of the results of the index test.)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Yes
	Did all patients receive a reference standard?	Yes
	Did patients receive the same reference standard?	Yes
	Were all patients included in the analysis?	Yes
	Could the patient flow have introduced bias?	Low
Overall risk of bias and directness	Risk of Bias	Moderate *(Clinical characteristics were provided by participants. Unclear if there was missing data.)*
	Directness	Directly applicable

Jones 2011

Jones, 2011

Bibliographic Reference	Jones, A G; Besser, R E J; McDonald, T J; Shields, B M; Hope, S V; Bowman, P; Oram, R A; Knight, B A; Hattersley, A T; Urine C-peptide creatinine ratio is an alternative to stimulated serum C-peptide measurement in late-onset, insulin-treated diabetes.; Diabetic medicine : a journal of the British Diabetic Association; 2011; vol. 28 (no. 9); 1034-8

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Exeter, UK Setting Clinical research facility Study dates NR Sources of funding This project was supported by the Peninsula NIHR Clinical Research Facility and the Peninsula Collaboration for Leadership in Applied Health Research and Care (PenCLAHRC). ATH, BAK and BMS are supported by the Peninsula NIHR Clinical Research Facility. NIHR have supported AGJ, SVH, RAO and PB through academic clinical fellowships and AGJ through a doctoral research fellowship. REJB is supported by a Diabetes UK clinical training fellowship. Types of diabetes examined T1, T2
Inclusion criteria	Disease at entry

	insulin-treated diabetes Length of time with diabetes diagnosed after age 30
Number of participants	51
Length of follow-up	NA
Loss to follow-up	NA
Index test(s)	Urine C-peptide:Creatinine ratio
Reference standard (s)	C-peptide level serum C-peptide measurement 90 min after a standardized mixed-meal tolerance test (as a measure of insulin secretion capacity)
Diagnostic data format	AUC, optimal cut-off, sensitivity/specificity
Additional comments	

Population characteristics

Study-level characteristics

	Study (N = 51)
Sample size	
Nominal	51

	Study (N = 51)
T1 diagnosis	
Nominal	9
T2 diagnosis	
Nominal	42
Male	
Nominal	36
Age	
MedianIQR	66 (61 to 74)
Duration of diabetes	
MedianIQR	14 (9 to 20)
BMI *(kg/m2)*	
MedianIQR	29 (26 to 33)
HbA1c *(%)*	
MedianIQR	8 (7.6 to 8.5)

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Yes
	Was a case-control design avoided?	Yes
	Did the study avoid inappropriate exclusions?	Unclear *(Exclusion criteria not specified.)*
	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear *(Unclear if the index test results were interpreted without knowledge of the results of the reference standard.)*
	If a threshold was used, was it pre-specified?	No
	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Unclear if the index test results were interpreted without knowledge of the results of the reference standard.)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Yes

Section	Question	Answer
	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear *(Unclear if results from the reference standard were interpreted without knowledge of the results of the index test.)*
	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(Unclear if results from the reference standard were interpreted without knowledge of the results of the index test.)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Yes
	Did all patients receive a reference standard?	Yes
	Did patients receive the same reference standard?	Yes
	Were all patients included in the analysis?	Yes
	Could the patient flow have introduced bias?	Low
Overall risk of bias and directness	Risk of Bias	Low *(It was unclear if the index test results were interpreted without knowledge of the results of the reference standard, but as tests were objective, study was not downgraded.)*
	Directness	Directly applicable

Koskinen 1986

Koskinen, 1986

Bibliographic Reference	Koskinen, P; Viikari, J; Irjala, K; Kaihola, H L; Seppala, P; Plasma and urinary C-peptide in the classification of adult diabetics.; Scandinavian journal of clinical and laboratory investigation; 1986; vol. 46 (no. 7); 655-63

Study Characteristics

Study type	Prospective cohort study
Study details	Study location Finland Setting University hospital Study dates NR Sources of funding NR Types of diabetes examined "insulin requiring" "non-insulin requiring" diabetes
Inclusion criteria	Age Adults Disease at entry

	diabetes
Exclusion criteria	Criteria 1 NR
Number of participants	61
Loss to follow-up	
Index test(s)	C-peptide level Basal c-peptide Stimulated c-peptide Basal c-peptide/fasting glucose Glucagon stimulated c-peptide x creatinine clearance Basal c-peptide x creatinine clearance 2-h/4h postprandial urinary c-peptide 2-h/4h postprandial urinary c-peptide concentration 2h/4h pp urinary c-peptide/creatinine
Reference standard (s)	DKA Requirement of insulin therapy was judged during this period using the following criteria: insulin treatment was considered necessary if there was evidence of tendency to ketoacidosis verified with blood gas analysis (base excess below -4 mmol/l) provided no transitory

	deteriorating factors (e.g. an acute infection) could be demonstrated. Insulin therapy was chosen if fasting blood glucose was constantly ≥13 mmol/l provided neither obesity nor dietary errors were causing ineffectiveness of oral antidiabetic.
Additional comments	all biochemical measures +/- 2SD

Study arms

insulin requiring (N = 36)
non-insulin requiring (N = 25)

Population characteristics

Arm-level characteristics

	insulin requiring (N = 36)	**non-insulin requiring (N = 25)**
Age		
Custom value	Mean 38 (16-75)	Mean 62 (23-88)
Duration of diabetes		
Custom value	Mean 13 (range 0-39)	Mean 6 (range 0-12)
Glucagon-stimulated plasma C-peptide (nmol/l) *(+/- 2SD)*		
Custom value	0.24 (0.04-0.72)	1.5 (0.32-4.9)
Basal plasma Cpeptide (nmoVl)		

	insulin requiring (N = 36)	non-insulin requiring (N = 25)
Custom value	0.19 (0.05 - 0.50)	1.1 (0.21 - 3.6)
Basal plasma C-peptide (nmoV1)l fasting blood glucose (mmoV1)		
Custom value	0.019 (0.004- 0.053)	0.11 (0.015-0.38)
Glucagon-stimulated plasma C-peptide (nmolll) x creatinine clearance (mllmin)		
Custom value	20 (3.3-66)	101 (25 - 292)
Basal plasma C-peptide (nmol/l) x creatinine clearance (mumin)		
Custom value	16 (3.5 - 48)	69 (18 - 191)
2-h postprandial urinary Cpeptide (nmol)		
Custom value	0.29 (0.003-5.3)	2.4 (0.2 - 12)
2-h postprandial urinary Cpeptide concentration (nmoVl)		
Custom value	2.1 (0.003-3.1)	20 (2-96)
2-h postprandial urinary Cpeptide (nmol)/creatinine (mmol)		
Custom value	0.28 (0.004-5.1)	3.2 (0.8-9.3)
4-h postprandial urinary Cpeptide (nmol)		
Custom value	0.75 (0.001-10.8)	5.6 (1.1-18)

	insulin requiring (N = 36)	non-insulin requiring (N = 25)
4-h postprandial urinary Cpeptide concentration (nmolll)		
Custom value	2.1 (0.04 - 26)	20 (3-87)
4-h postprandial urinary Cpeptide (nmol)/creatinine (mmol		
Custom value	0.39 (0.007 - 5.4)	3.7 (0.9 - 11)

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Yes
	Was a case-control design avoided?	Yes
	Did the study avoid inappropriate exclusions?	Unclear *(Exclusion criteria not specified.)*
	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low

Section	Question	Answer
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear *(Unclear if index test results were interpreted without knowledge of the results of the reference standard.)*
	If a threshold was used, was it pre-specified?	Yes
	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear *(Unclear if results from the reference standard were interpreted without knowledge of the results of the index test.)*
	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear
	Did all patients receive a reference standard?	Yes

Section	Question	Answer
	Did patients receive the same reference standard?	Yes
	Were all patients included in the analysis?	Yes
	Could the patient flow have introduced bias?	Low
Overall risk of bias and directness	Risk of Bias	Low *(It was unclear if results of the index test were interpreted without the knowledge of the results of the reference standard, however as tests were objective, study was not downgraded.)*
	Directness	Directly applicable

Sia 2020

Sia, 2020

Bibliographic Reference	Sia, H.-K.; Tu, S.-T.; Liao, P.-Y.; Lin, K.-H.; Kor, C.-T.; Yeh, L.-L.; A convenient diagnostic tool for discriminating adult-onset glutamic acid decarboxylase antibody-positive autoimmune diabetes from type 2 diabetes: A retrospective study; PeerJ; 2020; vol. 2020 (no. 2); e8610

Study Characteristics

Study type	Case-control study
Study details	Study location Taiwan

	Setting Study dates Jan 2009 - Dec 2018 Sources of funding None. Types of diabetes examined GADA+ diabetes vs T2DM
Inclusion criteria	Disease at entry Diabetes
Exclusion criteria	Criteria 1 GADA <1.0U/mL Criteria 2 incomplete lipid A1c data Criteria 3 diabetes not diagnosed within the previous six months, Criteria 4 age at onset <20 years excessive alcohol consumption
Number of participants	Case group: 152 Reference group: T2DM: 358
Length of follow-up	NA
Loss to follow-up	NA

Index test(s)	Multiple Linear discriminant functions constructed from five major variables for discriminating GADA+ from T2DM patients. BMI <23kg/m2, age at onset <30 years, triglycerides, HDL-C >= 46 mg/dL, HbA1c >= 8%
Reference standard (s)	GADA GADA positivity
Diagnostic data format	2x2 table
Additional comments	2x2 table for GADA+ vs linear discriminants

Study arms

GADA (+) (N = 152)
Reference group: T2DM (N = 358)

Population characteristics

Arm-level characteristics

	GADA (+) (N = 152)	**Reference group: T2DM (N = 358)**
Male		
Nominal	74	202

	GADA (+) (N = 152)	Reference group: T2DM (N = 358)
Age at onset		
Mean/SD	37.6 (12.6)	50.4 (11.7)
BMI		
Mean/SD	21.7 (3.8)	26.8 (4.5)
Lipid Profile		
Total cholesterol		
Mean/SD	184 (46.9)	194.4 (41.9)
TG		
Mean/SD	82.9 (65.2)	162.2 (119.9)
HDL-C		
Mean/SD	58 (18.7)	42.7 (10.5)
HbA1c		
Mean/SD	10.5 (3.2)	8.2 (2.3)
GPT		
Mean/SD	25.1 (18.7)	35.2 (29.2)

	GADA (+) (N = 152)	Reference group: T2DM (N = 358)
Creatinine		
Mean/SD	0.8 (0.2)	0.8 (0.2)
Smoking		
Nominal	33	64
Use of statins		
Nominal	5	6
USe of fibrates		
Nominal	1	5

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Yes
	Was a case-control design avoided?	No *(Study included patients who received GADA test and those who did not)*

Section	Question	Answer
	Did the study avoid inappropriate exclusions?	Yes
	Could the selection of patients have introduced bias?	High *(Case-control design used. Patients who tested GADA positive were included and those who were newly diagnosed with T2DM were included as a reference group.)* Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	No
	If a threshold was used, was it pre-specified?	Yes
	Could the conduct or interpretation of the index test have introduced bias?	High *(Index test interpreted with knowledge of the results of the reference standard.)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High *(Index test includes 5 discriminant factors of which 3 were not applicable to the review question (TG, HDL-C and HbA1c))*
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Yes

Section	Question	Answer
	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear
	Did all patients receive a reference standard?	Yes
	Did patients receive the same reference standard?	No
	Were all patients included in the analysis?	Yes
	Could the patient flow have introduced bias?	High *(GADA test was only in the 636 patients. The reference group were deemed to have T2DM based on age of onset and GADA was not a routine test in this group.)*
Overall risk of bias and directness	Risk of Bias	High *(Case-control design utilised.)*
	Directness	Partially applicable *(Index test includes 5 discriminant factors of which 3 were not applicable to the review question (TG, HDL-C and HbA1c).)*

Tanaka 2004

Tanaka, 2004

Bibliographic Reference	Tanaka, Shoichiro; Endo, Toyoshi; Aida, Kaoru; Shimura, Hiroki; Yokomori, Norihiko; Kaneshige, Masahiro; Furuya, Fumihiko; Amemiya, Shin; Mochizuki, Mie; Nakanishi, Koji; Kobayashi, Tetsuro; Distinct diagnostic criteria of fulminant type 1 diabetes based on serum C-peptide response and HbA1c levels at onset.; Diabetes care; 2004; vol. 27 (no. 8); 1936-41

Study Characteristics

Study type	Prospective cohort study
Study details	Study location Japan Setting Toranomon hospital Study dates 1980 to 2001 Sources of funding This study was partly supported by grants from the Ministry of Education, Science, Sports and Culture, Japan, and the Japan Diabetes Foundation. Types of diabetes examined "Fulminant T1 vs Acute onset T1"
Inclusion criteria	Disease at entry ADA criteria type 1 diabetes
Exclusion criteria	Criteria 1

	presence of mtDNA mutation (1 excluded)
Number of participants	124
Length of follow-up	2 years
Loss to follow-up	0
Index test(s)	C-peptide level change in C-peptide <=0.540 nmol/l Fasting serum C-peptide <=0.033 nmol/l BMI >19.1 kg/m2 Age at onset >20 years Duration <= 8 days Other non-characteristics of interest Glucose >33.6 mmol/l, HbA1c <= 8%, Arterial pH <= 7.21, Amylase >345 IU/l Lipase >173 U/l Elastase one >231 ng/dl
Reference standard (s)	Multiple Fulminant: negative for autoantibodies against pancreatic antigens (including ICA, GADAb, IA-2Ab, and IAA) and had normal or near-normal HbA1c levels (<=8.3%) at onset of diabetes

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Yes
	Was a case-control design avoided?	Yes
	Did the study avoid inappropriate exclusions?	Yes
	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
	If a threshold was used, was it pre-specified?	No
	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Unclear if index test results were interpreted without knowledge of the results of the reference standard.)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Yes

Section	Question	Answer
	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(Unclear if reference standard results were interpreted without knowledge of the results of the index test.)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Yes
	Did all patients receive a reference standard?	Yes
	Did patients receive the same reference standard?	Yes
	Were all patients included in the analysis?	Yes
	Could the patient flow have introduced bias?	Low
Overall risk of bias and directness	Risk of Bias	Low *(It was unclear if results of the index test were interpreted without knowledge of the results of the reference standard, but as tests were objective, the study was not downgraded.)*
	Directness	Partially applicable *(Fulminant diabetes not specified in review protocol.)*

Thunander 2012

Thunander, 2012

Bibliographic Reference	Thunander, Maria; Torn, Carina; Petersson, Christer; Ossiansson, Birger; Fornander, Jan; Landin-Olsson, Mona; Levels of C-peptide, body mass index and age, and their usefulness in classification of diabetes in relation to autoimmunity, in adults with newly diagnosed diabetes in Kronoberg, Sweden.; European journal of endocrinology; 2012; vol. 166 (no. 6); 1021-9

Study Characteristics

Study type	Prospective cohort study
Study details	Study location Kronoberg, Sweden Setting 25 healthcare centres and two hospitals Study dates 1998-2001 Sources of funding The work was financed by the Health Care Regions of Skane and Kronoberg, Southern Sweden; Lund University funding of Clinical research (ALF) and the Swedish Council of Medical Research, grant no K97-19X12242. Types of diabetes examined Autoimmune vs non autoimmune diabetes
Inclusion criteria	Age >= 20 years

	Disease at entry Diabetes Length of time with diabetes Newly diagnosed
Exclusion criteria	Criteria 1 Data collected at ≥91 day intervals or data incomplete Criteria 2 secondary or gestational diabetes
Number of participants	NA
Length of follow-up	NA
Loss to follow-up	
Index test(s)	C-peptide level Fasting c-peptide 0.5 to 1.00 in 0.1 increments BMI 23, 24, 25 Age Age at onset 40, 50 and 55
Reference standard (s)	Multiple GADA radioimmunoprecipitation; ICA
Diagnostic data format	ROC curve and sensitivity/specificity for different thresholds

Population characteristics

Study-level characteristics

	Study (N = 1180)
Age	
Mean/SD	65.5 (14.3)
Male	
Nominal	598

Arm-level characteristics

	Autoimmune	**Non-autoimmune**
Mean Fasting c-peptide		
Mean/SD	0.73 (0.5)	1.42 (0.9)
BMI		
Mean/SD	26 (4.8)	28.9 (5.3)

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Yes
	Was a case-control design avoided?	Yes
	Did the study avoid inappropriate exclusions?	Yes
	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
	If a threshold was used, was it pre-specified?	Yes
	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Unclear if index test was interpreted without knowledge of the results of the reference standard.)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	No
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Yes
	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear *(Unclear if the reference standard results were interpreted without knowledge of the results of the index test.)*

Section	Question	Answer
	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear *(Unclear if the reference standard results were interpreted without knowledge of the results of the index test.)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Yes
	Did all patients receive a reference standard?	Yes
	Did patients receive the same reference standard?	Yes
	Were all patients included in the analysis?	Yes
	Could the patient flow have introduced bias?	Low
Overall risk of bias and directness	Risk of Bias	Low *(It was unclear if index test was interpreted without knowledge of the results of the reference standard, but as tests were objective, the study was not downgraded.)*
	Directness	Directly applicable

Wang 2019

Wang, 2019

Bibliographic Reference	Wang, Yanai; Gao, Ying; Cai, Xiaoling; Chen, Ling; Zhou, Lingli; Ma, Yumin; Gong, Siqian; Han, Xueyao; Ji, Linong; Clinical Implications of Urinary C-Peptide Creatinine Ratio in Patients with Different Types of Diabetes.; Journal of diabetes research; 2019; vol. 2019; 1747684

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Beijing, China Setting Hospital Study dates NR Sources of funding This research was supported by the Beijing Municipal Commission of Science and Technology funds (Nos. Z141100007414002 and D131100005313008) and the National Key Research and Development Program (No. 2016YFC1304901). Types of diabetes examined T1 and non-T1
Inclusion criteria	Disease at entry Diabetes (WHO 1999 criteria)
Exclusion criteria	Criteria 1 NR

Number of participants	T1: 56 T2: 136
Length of follow-up	NA
Loss to follow-up	NA
Index test(s)	Urine C-peptide:Creatinine ratio
Reference standard (s)	Multiple T1: Fasting serum c-peptide <0.2 nmol/L, ketosis onset and insulin-dependent treatment within 6 months from onset or adult onset, positive islet autoantibodies, and insulin-dependent insulin treatment. T2: adult nonketosis onset diabetes with negative islet autoantibodies (GADA, IA 2 ICA)
Diagnostic data format	AUC sensitivity and specificity for T1 vs T3 UCPCR discriminating both

Study arms

T1DM (N = 56)
T2DM (N = 136)

Population characteristics

Arm-level characteristics

	T1DM (N = 56)	T2DM (N = 136)
Male		
Nominal	28	87
Diagnosis age		
MedianIQR	32 (23.3 to 46)	42 (32 to 49)
Age		
MedianIQR	46 (26.5 to 59.5)	53 (42 to 60)
Diabetes duration		
MedianIQR	6.5 (1.5 to 13)	8 (2.3 to 14)
BMI		
MedianIQR	22.3 (19.1 to 24.5)	24.9 (22.8 to 27.7)
PArent affected		
Nominal	16	72
Triglyceride		
MedianIQR	0.98 (0.66 to 1.46)	1.47 (1.18 to 2.38)
Total cholesterol		

	T1DM (N = 56)	T2DM (N = 136)
MedianIQR	4.63 (3.71 to 5.63)	4.49 (3.68 to 5.2)
HDL-C		
Male		
MedianIQR	1.29 (1.04 to 1.55)	0.97 (0.85 to 1.16)
Female		
MedianIQR	1.45 (1.23 to 1.67)	0.98 (0.8 to 1.15)
LDL-c		
MedianIQR	2.42 (1.69 to 3.47)	2.52 (1.97 to 3.23)
UA		
MedianIQR	280 (231 to 327)	357 (292 to 425)
FBG		
MedianIQR	9.8 (6.5 to 14.6)	7.2 (5.6 to 9.4)
A1C		
MedianIQR	9.2 (7.8 to 11.3)	9.1 (7.5 to 11)
FCP		

	T1DM (N = 56)	T2DM (N = 136)
MedianIQR	0.02 (0.01 to 0.1)	0.61 (0.41 to 0.91)
popst-prandial c-peptide		
MedianIQR	0.05 (0.01 to 0.15)	0.61 (0.41 to 0.91)
Creatinine		
MedianIQR	58.5 (47 to 68.8)	63 (52.3 to 72)
UCPCR		
MedianIQR	0 (0.01 to 0.1)	0.47 (0.23 to 1.01)
Treatment		
Without insulin		
Nominal	0	79

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Yes

Section	Question	Answer
	Was a case-control design avoided?	Yes
	Did the study avoid inappropriate exclusions?	Unclear *(Exclusion criteria not specified.)*
	Could the selection of patients have introduced bias?	Unclear *(Exclusion criteria not specified.)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(Population is partially applicable as it includes patients with monogenic diabetes.)*
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
	If a threshold was used, was it pre-specified?	Yes
	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Unclear if index test was interpreted without knowledge of the reference standard.)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Yes *(Diabetes was diagnosed in accordance with the 1999 WHO criteria.)*
	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear

Section	Question	Answer
	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear
	Did all patients receive a reference standard?	Yes
	Did patients receive the same reference standard?	Yes
	Were all patients included in the analysis?	Yes
	Could the patient flow have introduced bias?	Unclear *(Unclear interval between index and reference test.)*
Overall risk of bias and directness	Risk of Bias	Moderate *(Unclear interval between index and reference test.)*
	Directness	Partially applicable *(Study compared T1DM with non-T1DM. Non-T1DM population included patients with monogenic diabetes which is not included in the protocol.)*

Appendix F – GRADE tables

Table 11: Fourlanos 2006

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Index test: LADA clinical risk score Reference standard: GADA antibody positivity										
Fourlanos 2006	Cross-sectional	130	90.0 (53.3, 98.6)	71.7 (63.0, 79.0)	LR+ 3.17 (2.23, 4.51)	Serious[1]	Not serious	N/A	Not serious	Moderate
					LR- 0.14 (0.02, 0.89)	Serious[1]	Not serious	N/A	Serious[2]	Low

1. All subjects were interviewed to gather data on clinical features. Unclear if there was missing data
2. 95% confidence interval for likelihood ratio crosses 1 clinical decision threshold (LR+ = 2, LR- = 0.5)

Table 12: Sia 2020

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Index test: Linear discriminant functions constructed from five major variables Reference standard: GADA Ab positive test										
Sia 2020	Cross-sectional	510	75.3 (68.3, 81.2)	92.9 (89.7, 95.2)	LR+ 10.66 (7.18, 15.83)	Very serious[1]	Serious[2]	N/A	Not serious	Very low
					LR- 0.26 (0.20, 0.34)	Very serious[1]	Serious[2]	N/A	Not serious	Very low

1. Case-control design utilised
2. Index test includes 5 discriminant factors of which 3 were not applicable to the review question (TG, HDL-C and HbA1c)

Table 13: Shields review

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Index test: Age at diagnosis (threshold <20 years) Reference standard: C-peptide 0.3 nmol/l[1]										
1 (Boyle 1999)	Cross-sectional	3613	20.4 (15.8, 25.9)	97.4 (96.8, 97.9)	LR+ 7.81 (5.66, 10.77)	Not serious	Not serious	N/A	Not serious	High
					LR- 0.81 (0.76, 0.87)	Not serious	Not serious	N/A	Not serious	High
Index test: Age at diagnosis (threshold ≤30 years) Reference standard: C-peptide 0.03 nmol/l[1]										
1 (Prior 1991)	Cross-sectional	575	84.0 (79.8, 87.5)	82.1 (76.6, 86.6)	LR+ 4.70 (3.54, 6.25)	Very serious[2]	Not serious	N/A	Not serious	Low
					LR- 0.19 (0.15, 0.24)	Very serious[2]	Not serious	N/A	Not serious	Low
Index test: Age at diagnosis (threshold ≤30 years) Reference standard: C-peptide 0.2 nmol/l[1]										
1 (Nielsen 1986)	Cross-sectional	215	64.2 (56,2, 71.5)	88.1 (77.9, 93.9)	LR+ 5.37 (2.77, 10.41)	Serious[3]	Not serious	N/A	Not serious	Moderate
					LR- 0.40 (0.32, 0.51)	Serious[3]	Not serious	N/A	Serious[4]	Low
Index test: Age at diagnosis (threshold <30 years) Reference standard: C-peptide 0.07 nmol/l[1]										
1 (Ekpehbegh 2013)	Cross-sectional	71	57.1 (40.6, 72.3)	72.2 (55.6, 84.4)	LR+ 2.05 (1.12, 3.74)	Not serious	Not serious	N/A	Serious[4]	Moderate
					LR- 0.59 (0.38, 0.91)	Not serious	Not serious	N/A	Serious[4]	Moderate
Index test: Age at diagnosis (threshold <39 years) Reference standard: C-peptide 0.08 nmol/l[1]										

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Shields 2010)	Cross-sectional	72	67.5 (51.7, 80.1)	96.9 (80.9, 99.6)	LR+ 21.60 (3.10, 150.46)	Very serious[5]	Not serious	N/A	Not serious	Low
					LR- 0.33 (0.21, 0.52)	Very serious[5]	Not serious	N/A	Serious[4]	Very low
Index test: Age at diagnosis (threshold ≤40 years) Reference standard: C-peptide 0.03 nmol/l[1]										
1 (Prior 1991)	Cross-sectional	575	96.9 (94.4, 98.3)	59.4 (52.8, 65.6)	LR+ 2.38 (2.03, 2.79)	Very serious[2]	Not serious	N/A	Not serious	Low
					LR- 0.05 (0.02, 0.09)	Very serious[2]	Not serious	N/A	Not serious	Low
Index test: Age at diagnosis (threshold ≤40 years) Reference standard: C-peptide 0.06 nmol/l[1]										
1 (Welborn 1983)	Cross-sectional	121	84.0 (64.3, 93.9)	85.4 (76.9, 91.2)	LR+ 5.76 (3.44, 9.62)	Very serious[6]	Not serious	N/A	Not serious	Low
					LR- 0.18 (0.07, 0.46)	Very serious[6]	Not serious	N/A	Not serious	Low
Index test: Age at diagnosis (threshold ≤40 years) Reference standard: C-peptide 0.16 nmol/l[1]										
1 (Welborn 1981)	Cross-sectional	201	76.1 (61.8, 86.2)	81.3 (74.4, 86.7)	LR+ 4.06 (2.82, 5.86)	Very serious[7]	Not serious	N/A	Not serious	Low
					LR- 0.29 (0.17, 0.49)	Very serious[7]	Not serious	N/A	Not serious	Low
Index test: Age at diagnosis (threshold ≤40 years) Reference standard: C-peptide 0.2 nmol/l[1]										
	Cross-sectional	171	60.9 (51.7, 69.3)	78.6 (65.9, 87.4)	LR+ 2.84 (1.68, 4.79)	Serious[8]	Not serious	N/A	Serious[4]	Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Laakso 1987)					LR- 0.49 (0.38, 0.65)	Serious[8]	Not serious	N/A	Serious[4]	Low
Index test: Age at diagnosis (threshold <45 years) Reference standard: C-peptide 0.3 nmol/l[1]										
1 (Boyle 1999)	Cross-sectional	3613	65.3 (59.1, 71.0)	56.8 (55.1, 58.5)	LR+ 1.51 (1.36, 1.66)	Not serious	Not serious	N/A	Not serious	High
					LR- 0.61 (0.51, 0.72)	Not serious	Not serious	N/A	Not serious	High
Index test: On insulin – Yes Reference standard: C-peptide 0.03 nmol/l[1]										
1 (Prior 1991)	Cross-sectional	575	99.4 (97.8, 99.9)	25.0 (19.8, 31.1)	LR+ 1.32 (1.22, 1.43)	Very serious[2]	Not serious	N/A	Not serious	Low
					LR- 0.02 (0.00, 0.09)	Very serious[2]	Not serious	N/A	Not serious	Low
Index test: On insulin – Yes Reference standard: C-peptide 0.16 nmol/l[1]										
1 (Welborn 1981)	Cross-sectional	203	99.0 (85.7, 99.9)	69.6 (61.9, 76.3)	LR+ 3.25 (2.56, 4.12)	Very serious[7]	Not serious	N/A	Not serious	Low
					LR- 0.01 (0.00, 0.23)	Very serious[7]	Not serious	N/A	Not serious	Low
Index test: Time to insulin (threshold ≤1.5 m) Reference standard: C-peptide 0.08 nmol/l[1]										
1 (Shields 2010)	Cross-sectional	72	80.0 (64.8, 89.7)	56.3 (39.0, 72.1)	LR+ 1.82 (1.19, 2.78)	Very serious[5]	Not serious	N/A	Serious[4]	Very low
					LR- 0.35 (0.17, 0.71)	Very serious[5]	Not serious	N/A	Serious[4]	Very low
Index test: Time to insulin (threshold <1 year)										

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Reference standard: C-peptide 0.03 nmol/l[1]										
1 (Prior 1991)	Cross-sectional	575	91.7 (88.4, 94.2)	75.0 (68.9, 80.2)	LR+ 3.67 (2.91, 4.61)	Very serious[2]	Not serious	N/A	Not serious	Low
					LR- 0.11 (0.07, 0.15)	Very serious[2]	Not serious	N/A	Not serious	Low
Index test: Time to insulin (threshold <2 years) **Reference standard: C-peptide 0.06 nmol/l[1]**										
1 (Welborn 1983)	Cross-sectional	121	98.1 (75.6, 99.9)	82.0 (73.0, 88.4)	LR+ 5.43 (3.54, 8.33)	Very serious[6]	Not serious	N/A	Not serious	Low
					LR- 0.02 (0.00, 0.36)	Very serious[6]	Not serious	N/A	Not serious	Low
Index test: Time to insulin (threshold ≤2 years) **Reference standard: C-peptide 0.2 nmol/l[1]**										
1 (Laakso 1987)	Cross-sectional	171	69.6 (60.6, 77.3)	85.7 (73.9, 92.7)	LR+ 4.87 (2.53, 9.35)	Serious[8]	Not serious	N/A	Not serious	Moderate
					LR- 0.35 (0.26, 0.47)	Serious[8]	Not serious	N/A	Not serious	Moderate
Index test: BMI (threshold <20 kg/m^2) **Reference standard: C-peptide 0.3 nmol/l[1]**										
1 (Boyle 1999)	Cross-sectional	3613	10.2 (7.0, 14.7)	98.5 (98.0, 98.8)	LR+ 6.73 (4.25, 10.68)	Not serious	Not serious	N/A	Not serious	High
					LR- 0.91 (0.87, 0.95)	Not serious	Not serious	N/A	Not serious	High
Index test: PDW (threshold <100%) **Reference standard: C-peptide 0.03 nmol/l[1]**										
1 (Prior 1991)	Cross-sectional	575	33.6 (28.9, 38.7)	92.4 (88.1, 95.2)	LR+ 4.43 (2.74, 7.15)	Very serious[2]	Not serious	N/A	Not serious	Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
					LR- 0.71 (0.66, 0.78)	Very serious[2]	Not serious	N/A	Not serious	Low
Index test: BMI (threshold <25 kg/m^2) Reference standard: C-peptide 0.3 nmol/l[1]										
1 (Boyle 1999)	Cross-sectional	3613	40.8 (34.8, 47.1)	86.3 (85.1, 87.4)	LR+ 2.97 (2.50, 3.53)	Not serious	Not serious	N/A	Not serious	High
					LR- 0.68 (0.61, 0.76)	Not serious	Not serious	N/A	Not serious	High
Index test: PDW (threshold <120%) Reference standard: C-peptide 0.03 nmol/l[1]										
1 (Prior 1991)	Cross-sectional	575	87.2 (83.3, 90.3)	62.9 (56.4, 69.0)	LR+ 2.35 (1.97, 2.80)	Very serious[2]	Not serious	N/A	Serious[4]	Very low
					LR- 0.20 (0.15, 0.27)	Very serious[2]	Not serious	N/A	Not serious	Low
Index test: PDW (threshold ≤120%) Reference standard: C-peptide 0.06 nmol/l[1]										
1 (Welborn 1983)	Cross-sectional	121	80.0 (60.0, 91.4)	66.7 (56.7, 75.4)	LR+ 2.40 (1.70, 3.38)	Very serious[6]	Not serious	N/A	Serious[4]	Very low
					LR- 0.30 (0.13, 0.66)	Very serious[6]	Not serious	N/A	Serious[4]	Very low
Index test: BMI (threshold ≤27 kg/m^2) Reference standard: C-peptide 0.2 nmol/l[1]										
1 (Laakso 1987)	Cross-sectional	171	75.7 (67.0, 82.6)	66.1 (52.8, 77.2)	LR+ 2.23 (1.52, 3.26)	Serious[8]	Not serious	N/A	Serious[4]	Low
					LR- 0.36 (0.25, 0.53)	Serious[8]	Not serious	N/A	Serious[4]	Low
Index test: BMI (threshold <28 kg/m-1) Reference standard: C-peptide 0.3 or 0.2 nmol/l[1]										

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Balasubramanyam 2006)	Cross-sectional	293	86.1 (79.9, 90.6)	67.2 (58.6, 74.8)	LR+ 2.62 (2.03, 3.38)	Not serious	Not serious	N/A	Not serious	High
					LR- 0.20 (0.13, 0.30)	Not serious	Not serious	N/A	Not serious	High
Index test: BMI (threshold <29 kg/m^2) Reference standard: C-peptide 0.3 nmol/l[1]										
1 (Boyle 1999)	Cross-sectional	3613	71.4 (65.5, 76.7)	56.6 (54.9, 58.2)	LR+ 1.64 (1.50, 1.79)	Not serious	Not serious	N/A	Not serious	High
					LR- 0.50 (0.41, 0.61)	Not serious	Not serious	N/A	Serious[4]	Moderate
Index test: BMI (threshold <29 kg/m^2) Reference standard: C-peptide 0.08 nmol/l[1]										
1 (Shields 2010)	Cross-sectional	72	77.5 (62,1, 87.9)	56.3 (39.0, 72.1)	LR+ 1.77 (1.15, 2.71)	Very serious[5]	Not serious	N/A	Serious[4]	Very low
					LR- 0.40 (0.20, 0.76)	Very serious[5]	Not serious	N/A	Serious[4]	Very low
Index test: BMI (threshold <30 kg/m^2) Reference standard: C-peptide 0.07 nmol/l[1]										
1 (Ekpehbegh 2013)	Cross-sectional	71	77.1 (60.5, 88.1)	47.2 (31.7, 63.3)	LR+ 1.46 (1.02, 2.09)	Not serious	Not serious	N/A	Serious[4]	Moderate
					LR- 0.48 (0.24, 0.97)	Not serious	Not serious	N/A	Serious[4]	Moderate

1. Cut-off converted to nmol/l; fasting serum equivalent (=0.333*ng/ml); urine to serum, and stimulated to fasting C-peptide (fasting=stimulated/2.5 formula unpublished but derived from mixed-meal tolerance test data [Besser 2011; Jones 2011]; 0.2nmol/mmol Urine C-Peptide:Creatinine Ratio [UCPCR]=0.2nmol/l stimulated serum C-peptide [Jones 2013]).
2. Significant missing patient data
3. Lack of detail on index tests cut-off and patient flow
4. 95% confidence interval for likelihood ratio crosses 1 clinical decision threshold
5. Cut-offs internally derived: Age at diagnosis, BMI and time to insulin; all self-reported: possible recall bias

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

6. Almost no data reported
7. Almost no data on risk of bias criteria reported
8. Lack of detail on index tests and patient flow

Appendix G – Excluded studies

Study	Code [Reason]
Almajwal, Ali M, Al-Baghli, Nadira A, Batterham, Marijka J et al. (2009) Performance of body mass index in predicting diabetes and hypertension in the Eastern Province of Saudi Arabia. Annals of Saudi medicine 29(6): 437-45	- Incorrect study type *Detecting diabetes but does not distinguish by type. The main results in table 2 look at the diagnostic performance of BMI in detecting diabetes and/or hypertension using BMI cut-off values.*
Alperet, Derrick Johnston, Lim, Wei-Yen, Mok-Kwee Heng, Derrick et al. (2016) Optimal anthropometric measures and thresholds to identify undiagnosed type 2 diabetes in three major Asian ethnic groups. Obesity (Silver Spring, Md.) 24(10): 2185-93	- Incorrect study type *Again identifying undiagnosed diabetes only, paper does not look at distinguishing between the different types of diabetes.*
Anderson, Ariana E, Kerr, Wesley T, Thames, April et al. (2016) Electronic health record phenotyping improves detection and screening of type 2 diabetes in the general United States population: A cross-sectional, unselected, retrospective study. Journal of biomedical informatics 60: 162-8	- Assessment tool do not match that specified in the protocol *EHR records is a blended measure that does not fit our criteria, and comparator is a blended measure of which some predictors do not match protocol. We wouldn't be able to pull out specific diagnostic data for relevant predictors from this paper.*
Aviles-Santa, M Larissa, Schneiderman, Neil, Savage, Peter J et al. (2016) IDENTIFYING PROBABLE DIABETES MELLITUS AMONG HISPANICS/LATINOS FROM FOUR U.S. CITIES: FINDINGS FROM THE	- Assessment tool do not match that specified in the protocol

Study	Code [Reason]
HISPANIC COMMUNITY HEALTH STUDY/STUDY OF LATINOS. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 22(10): 1151-1160	*OGTT Gold standard to fasting plasma glucose and HbA1c, none of which are the predictors/biomarkers we are interested in.*
Bagheri, A., Sadek, A., Chan, T. et al. (2009) Using surrogate markers in primary electronic patient record systems to confirm or refute the diagnosis of diabetes. Informatics in primary care 17(2): 121-129	- Review article but not a systematic review *Not a systematic review*
Bao, Wei, Hu, Frank B, Rong, Shuang et al. (2013) Predicting risk of type 2 diabetes mellitus with genetic risk models on the basis of established genome-wide association markers: a systematic review. American journal of epidemiology 178(8): 1197-207	- Not looking at relevant predictors or biomarkers *Uses combined risk scores and genetic risk scores which do not stratify out desired predictors or biomarkers.*
Bennet, L, Groop, L, Lindblad, U et al. (2014) Ethnicity is an independent risk indicator when estimating diabetes risk with FINDRISC scores: a cross sectional study comparing immigrants from the Middle East and native Swedes. Primary care diabetes 8(3): 231-8	- Not looking at relevant predictors or biomarkers *Findrisc score not individual biomarkers*
Bermudez, Valmore, Salazar, Juan, Rojas, Joselyn et al. (2016) Diabetes and Impaired Fasting Glucose Prediction Using Anthropometric Indices in Adults from Maracaibo City, Venezuela. Journal of community health 41(6): 1223-1233	- Not looking at relevant predictors or biomarkers *Contains BMI but reference standard not mentioned and does not compare against another BMI threshold.*
Betterle, C, Presotto, F, Pedini, B et al. (1987) Islet cell and insulin autoantibodies in organ-specific autoimmune patients. Their behaviour and predictive value for the development of type 1 (insulin-dependent) diabetes mellitus. A 10-year follow-up study. Diabetologia 30(5): 292-7	- Reference standard in study does not match that specified in protocol *Only IAA and ICA so no relevant comparison*

Study	Code [Reason]
Bindraban, Navin R, van Valkengoed, Irene G M, Mairuhu, Gideon et al. (2008) Prevalence of diabetes mellitus and the performance of a risk score among Hindustani Surinamese, African Surinamese and ethnic Dutch: a cross-sectional population-based study. BMC public health 8: 271	- Incorrect study type *Has sens/ spec data for age and BMI but unclear whether this is distinguishing between t1 and T2 and also ref standard unclear Table 2 just states determinants of diabetes, which isn't useful for review question*
Biradar, S.B., Kallaganad, G.S., Rangappa, M. et al. (2011) Correlation of spot urine protein-creatinine ratio with 24-hour urinary protein in type 2 diabetes mellitus patients: A cross sectional study. Journal of Research in Medical Sciences 16(5)	- No outcome of interest *looking at proteinuria not differentiating diabetes type*
Bosi, E P, Garancini, M P, Poggiali, F et al. (1999) Low prevalence of islet autoimmunity in adult diabetes and low predictive value of islet autoantibodies in the general adult population of northern Italy. Diabetologia 42(7): 840-4	- No outcome of interest *Looking at Ab concentrations only.*
Buijsse B, Simmons RK, Griffin SJ, Schulze MB (2011) Risk assessment tools for identifying individuals at risk of developing type 2 diabetes. Epidemiologic Reviews 33(1): 46-62	- Not looking at relevant predictors or biomarkers *looking at combined risk scores*
Bullard, Kai McKeever, Ali, Mohammed K, Imperatore, Giuseppina et al. (2015) Receipt of Glucose Testing and Performance of Two US Diabetes Screening Guidelines, 2007-2012. PloS one 10(4): e0125249	- Not a relevant population *Looking at dysglycaemia prior to diabetes diagnosis for screening, not diabetes diagnosis itself.*
Cameron, A.J., Zimmet, P.Z., Soderberg, S. et al. (2007) The metabolic syndrome as a predictor of incident diabetes mellitus in Mauritius. Diabetic Medicine 24(12): 1460-1469	- Not looking at relevant predictors or biomarkers

Study	Code [Reason]
Cejkova, P, Novota, P, Cerna, M et al. (2007) KCNJ11 E23K polymorphism and diabetes mellitus with adult onset in Czech patients. Folia biologica 53(5): 173-5	- Not looking at relevant predictors or biomarkers *genetic testing only*
Chen, Yin-Chun, Huang, Yu-Yao, Li, Hung-Yuan et al. (2015) Professional continuous glucose monitoring for the identification of type 1 diabetes mellitus among subjects with insulin therapy. Medicine 94(3): e421	- Not looking at relevant predictors or biomarkers *glucose monitoring only*
Choi, K M, Lee, J, Kim, D R et al. (2002) Comparison of ADA and WHO criteria for the diagnosis of diabetes in elderly Koreans. Diabetic medicine: a journal of the British Diabetic Association 19(10): 853-7	- Not looking at relevant predictors or biomarkers *Focused on CV risk factors not diabetes diagnosis criteria*
Chu, F.-L.; Hsu, C.-H.; Jeng, C. (2015) Lowered cutoff points of obesity indicators are better predictors of hypertension and diabetes mellitus in premenopausal Taiwanese women. Obesity Research and Clinical Practice 9(4): 328-335	- Not looking at relevant predictors or biomarkers *Only predicting general diabetes*
Chume, Fernando Chimela, Kieling, Mayana Hernandez, Correa Freitas, Priscila Aparecida et al. (2019) Glycated albumin as a diagnostic tool in diabetes: An alternative or an additional test?. PloS one 14(12): e0227065	- Not looking at relevant predictors or biomarkers *Glycated albumin not a biomarker of interest*
Cosson, E, Nguyen, M T, Hamo-Tchatchouang, E et al. (2011) What would be the outcome if the American Diabetes Association recommendations of 2010 had been followed in our practice in 1998-2006?. Diabetic medicine: a journal of the British Diabetic Association 28(5): 567-74	- Not looking at relevant predictors or biomarkers *HbA1c/OGTT only no relevant predictors/biomarkers. Not comparing 2 diabetes types.*
Dario, T., Riccardo, G., Silvia, P. et al. (2020) The utility of assessing C-peptide in patients with insulin-treated type 2 diabetes: a cross-sectional study. Acta Diabetologica	- Not a relevant population *Type 2 only, looking at comparison between two type 2 regimens.*

Study	Code [Reason]
de Graaff, L C G; Smit, J W A; Radder, J K (2007) Prevalence and clinical significance of organ-specific autoantibodies in type 1 diabetes mellitus. The Netherlands journal of medicine 65(7): 235-47	- Not a relevant population *Looking at AB prevalence in Type 1 specifically, not diagnostic.* - No outcome of interest
Decochez, K, De Leeuw, I H, Keymeulen, B et al. (2002) IA-2 autoantibodies predict impending type I diabetes in siblings of patients. Diabetologia 45(12): 1658-66	- Not a relevant population *biomarkers in relatives of diabetes patients*
Di Bonito, P, De Bellis, A, Capaldo, B et al. (1996) Soluble CD8 antigen, stimulated C-peptide and islet cell antibodies are predictors of insulin requirement in newly diagnosed patients with unclassifiable diabetes. Acta diabetologica 33(3): 220-4	- Reference standard in study does not match that specified in protocol *Reference standard is treatment with insulin and no detail provided on how reference standard was measured.*
Diaz, V A, Mainous, A G 3rd, Baker, R et al. (2007) How does ethnicity affect the association between obesity and diabetes?. Diabetic medicine : a journal of the British Diabetic Association 24(11): 1199-204	- Not a relevant population *the paper does not distinguish between type of diabetes*
Djekic, K.; Mouzeyan, A.; Ipp, E. (2012) Latent autoimmune diabetes of adults is phenotypically similar to type 1 diabetes in a minority population. Journal of Clinical Endocrinology and Metabolism 97(3): e409-e413	- Incorrect study type *Not a diagnostic accuracy study*
Doi, Yasufumi, Kubo, Michiaki, Yonemoto, Koji et al. (2008) Fasting plasma glucose cutoff for diagnosis of diabetes in a Japanese population. The Journal of clinical endocrinology and metabolism 93(9): 3425-9	- Not looking at relevant predictors or biomarkers *Fasting plasma glucose cut offs only.*

Study	Code [Reason]
Dong, X L, Liu, Y, Sun, Y et al. (2011) Comparison of HbA1c and OGTT criteria to diagnose diabetes among Chinese. Experimental and clinical endocrinology & diabetes: official journal, German Society of Endocrinology [and] German Diabetes Association 119(6): 366-9	- Not looking at relevant predictors or biomarkers *HBA1C compared to OGTT, compares other factors but no DAT on those.*
Drzewoski, J and Czupryniak, L (2001) Concordance between fasting and 2-h post-glucose challenge criteria for the diagnosis of diabetes mellitus and glucose intolerance in high risk individuals. Diabetic medicine : a journal of the British Diabetic Association 18(1): 29-31	- Not looking at relevant predictors or biomarkers *Comparing two different OGTT criteria.*
Duggan, S.N., O'Connor, D.B., Antanaitis, A. et al. (2020) Metabolic dysfunction and diabetes mellitus during long-term follow-up of severe acute pancreatitis: A case-matched study. Pancreatology 20(5): 813-821	- Assessment tool do not match that specified in the protocol *Not a diagnostic study.*
Dunseath, Gareth, Ananieva-Jordanova, Rossitza, Coles, Rebecca et al. (2015) Bridging-type enzyme-linked immunoassay for zinc transporter 8 autoantibody measurements in adult patients with diabetes mellitus. Clinica chimica acta; international journal of clinical chemistry 447: 90-5	- Study does not contain any relevant index tests *Validation of an ELISA test.*
El Fakiri, F; Bruijnzeels, MA; Hoes, AW (2007) No evidence for marked ethnic differences in accuracy of self-reported diabetes, hypertension, and hypercholesterolemia. Journal of clinical epidemiology 60(12): 1271-1279	- No outcome of interest *Association study looking at self-report vs GP report of diabetes based on CV risk factors.*
Eriksson, J, Forsen, B, Haggblom, M et al. (1992) Clinical and metabolic characteristics of type 1 and type 2 diabetes: an epidemiological study from the Narpes community in western Finland. Diabetic medicine : a journal of the British Diabetic Association 9(7): 654-60	- Reference standard in study does not match that specified in protocol *No reference standard to compare index to that is in protocol*

Study	Code [Reason]
Falorni, A, Gambelunghe, G, Forini, F et al. (2000) Autoantibody recognition of COOH-terminal epitopes of GAD65 marks the risk for insulin requirement in adult-onset diabetes mellitus. The Journal of clinical endocrinology and metabolism 85(1): 309-16	- Reference standard in study does not match that specified in protocol *Reference standard is treatment with insulin and no detail provided on how reference standard was measured.*
Fatima, Aziz, Khawaja, Khadija Irfan, Burney, Saira et al. (2013) Type 1 and type 2 diabetes mellitus: are they mutually exclusive? Singapore medical journal 54(7): 396-400	- Incorrect study type *only DTA outcomes are assay sens/spec as opposed to sens/spec from diagnostic test*
Forst, T, Standl, E, Hohberg, C et al. (2004) IRIS II study: the IRIS II score--assessment of a new clinical algorithm for the classification of insulin resistance in patients with Type 2 diabetes. Diabetic medicine : a journal of the British Diabetic Association 21(10): 1149-53	- validation study
Funakoshi, S., Fujimoto, S., Hamasaki, A. et al. (2011) Utility of indices using C-peptide levels for indication of insulin therapy to achieve good glycemic control in Japanese patients with type 2 diabetes. Journal of Diabetes Investigation 2(4): 297-303	- Not a relevant population *Examining disease progression within T2 patients not distinguishing between types of diabetes*
Garg, Divya, Naugler, Christopher, Bhella, Vishal et al. (2018) Chronic kidney disease in type 2 diabetes: Does an abnormal urine albumin-to-creatinine ratio need to be retested?. Canadian family physician Medecin de famille canadien 64(10): e446-e452	- Not a relevant population *Not looking at differentiation diabetes but diagnosing microalbuminuria*
Guerrero, F, Ortego, J, Cordoba, J A et al. (2000) Clinical parameters (body mass index and age) are the best predictors for the need of insulin therapy during the first 18 months of diabetes mellitus in young adult patients. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme 32(5): 185-9	- Reference standard in study does not match that specified in protocol *Reference standard is treatment with insulin and no detail provided on how reference standard was measured.*

Study	Code [Reason]
Hadaegh, F, Zabetian, A, Harati, H et al. (2006) Waist/height ratio as a better predictor of type 2 diabetes compared to body mass index in Tehranian adult men--a 3.6-year prospective study. Experimental and clinical endocrinology & diabetes: official journal, German Society of Endocrinology [and] German Diabetes Association 114(6): 310-5	- No outcome of interest *prediction of outcomes*
Hadaegh, Farzad; Shafiee, Gita; Azizi, Fereidoun (2009) Anthropometric predictors of incident type 2 diabetes mellitus in Iranian women. Annals of Saudi medicine 29(3): 194-200	- association study
Hamilton, E.J., Davis, W.A., Makepeace, A. et al. (2016) Prevalence and prognosis of a low serum testosterone in men with type 2 diabetes: the Fremantle Diabetes Study Phase II. Clinical Endocrinology 85(3): 444-452	- No outcome of interest *Looking at testosterone levels and associations with that onle*
Harano, Y, Kosugi, K, Hyosu, T et al. (1984) Ketone bodies as markers for type 1 (insulin-dependent) diabetes and their value in the monitoring of diabetic control. Diabetologia 26(5): 343-8	- No outcome of interest *No relevant diagnostic outcomes*
Hawa, M.I., Buchan, A.P., Ola, T. et al. (2014) LADA and CARDS: A prospective study of clinical outcome in established adult-onset autoimmune diabetes. Diabetes Care 37(6): 1643-1649	- Incorrect study type *Not a DAT, simply looking at levels of Ab in LADA and didn't have any sens/spec data*
Heianza, Yoriko, Arase, Yasuji, Saito, Kazumi et al. (2013) Development of a screening score for undiagnosed diabetes and its application in estimating absolute risk of future type 2 diabetes in Japan: Toranomon Hospital Health Management Center Study 10 (TOPICS 10). The Journal of clinical endocrinology and metabolism 98(3): 1051-60	- Not a relevant population *Looking at identifying undiagnosed diabetes as opposed to distinguishing between types*

Study	Code [Reason]
Heneberg, P., Simcikova, D., Cechakova, M. et al. (2019) Autoantibodies against ZnT8 are rare in Central-European LADA patients and absent in MODY patients, including those positive for other autoantibodies. Journal of Diabetes and its Complications 33(1): 46-52	- Not a relevant population *Only comparing LADa with MODY at ROC*
Hohendorff, J., Zapala, B., Ludwig-Slomczynska, A.H. et al. (2019) The utility of MODY Probability Calculator in probands of families with early-onset autosomal dominant diabetes from Poland. Minerva Medica 110(6): 499-506	- Not a relevant population *MODY patients*
Hosseini, S.M., Maracy, M.R., Amini, M. et al. (2009) A risk score development for diabetic retinopathy screening in Isfahan-Iran. Journal of Research in Medical Sciences 14(2): 105-110	- No outcome of interest *Looking at diabetic retinopathy sens/spec not distinguishing between t1 and t2*
Hother-Nielsen, O, Faber, O, Sorensen, N S et al. (1988) Classification of newly diagnosed diabetic patients as insulin-requiring or non-insulin-requiring based on clinical and biochemical variables. Diabetes care 11(7): 531-7	- Reference standard in study does not match that specified in protocol *"Requirement of insulin" not an acceptable reference standard*
Hsia, Daniel S, Larrivee, Sandra, Cefalu, William T et al. (2015) Impact of Lowering BMI Cut Points as Recommended in the Revised American Diabetes Association's Standards of Medical Care in Diabetes-2015 on Diabetes Screening in Asian Americans. Diabetes care 38(11): 2166-8	- Incorrect study type *screening for "diabetes" only no clarity on type distinguishing*
Huang, Gan, Mo, Xuxu, Li, Muwen et al. (2012) Autoantibodies to CCL3 are of low sensitivity and specificity for the diagnosis of type 1 diabetes. Acta diabetologica 49(5): 395-9	- Not looking at relevant predictors or biomarkers *ccl3 focused, and looking at ab levels compared to other diseases not same marker levels in T1 and T2*

Study	Code [Reason]
Huang, Gan, Xiang, Yufei, Pan, Lingling et al. (2013) Zinc transporter 8 autoantibody (ZnT8A) could help differentiate latent autoimmune diabetes in adults (LADA) from phenotypic type 2 diabetes mellitus. Diabetes/metabolism research and reviews 29(5): 363-8	- No outcome of interest *prevalence study for ZnT8*
Ingemansson, Sofie, Vaziri-Sani, Fariba, Lindblad, Ulf et al. (2013) Long-term sustained autoimmune response to beta cell specific zinc transporter (ZnT8, W, R, Q) in young adult patients with preserved beta cell function at diagnosis of diabetes. Autoimmunity 46(1): 50-61	- Study does not contain any relevant index tests *Looking at sensitivity only and in validation of assay, more concerned with ab levels*
Ipadeola, Arinola; Adeleye, Jokotade O; Akinlade, Kehinde S (2015) Latent autoimmune diabetes amongst adults with type 2 diabetes in a Nigerian tertiary hospital. Primary care diabetes 9(3): 231-6	- Incorrect study type *Not a diagnostic accuracy study*
Jafari-Koshki, Tohid, Arsang-Jang, Shahram, Aminorroaya, Ashraf et al. (2018) Risk modeling in prospective diabetes studies: Association and predictive value of anthropometrics. Diabetes & metabolic syndrome 12(4): 563-567	- Not looking at relevant predictors or biomarkers *relatives*
Jamar, Giovana, Almeida, Flavio Rossi de, Gagliardi, Antonio et al. (2017) Evaluation of waist-to-height ratio as a predictor of insulin resistance in non-diabetic obese individuals. A cross-sectional study. Sao Paulo medical journal = Revista paulista de medicina 135(5): 462-468	- Reference standard in study does not match that specified in protocol *BMI versus homeostatic model assessment only*
Janghorbani, M. and Amini, M. (2016) The Visceral Adiposity Index in Comparison with Easily Measurable Anthropometric Markers Did Not Improve Prediction of Diabetes. Canadian Journal of Diabetes 40(5): 393-398	- Reference standard in study does not match that specified in protocol *not comparing BMI to a relevant indicator*

Study	Code [Reason]
Kasuga, A, Maruyama, T, Nakamoto, S et al. (1999) High-titer autoantibodies against glutamic acid decarboxylase plus autoantibodies against insulin and IA-2 predicts insulin requirement in adult diabetic patients. Journal of autoimmunity 12(2): 131-5	- Reference standard in study does not match that specified in protocol *"insulin requirement" is not a valid reference standard*
Klompas, Michael, Eggleston, Emma, McVetta, Jason et al. (2013) Automated detection and classification of type 1 versus type 2 diabetes using electronic health record data. Diabetes care 36(4): 914-21	- Study does not contain any relevant index tests *Looking at electronic health records not characteristics*
Ko, G T, Chan, J C, Lau, E et al. (1997) Fasting plasma glucose as a screening test for diabetes and its relationship with cardiovascular risk factors in Hong Kong Chinese. Diabetes care 20(2): 170-2	- Not looking at relevant predictors or biomarkers *OGTT and FPG only*
Ko, Gary T C, Chan, Juliana C N, Chow, Chun-Chung et al. (2004) Effects of obesity on the conversion from normal glucose tolerance to diabetes in Hong Kong Chinese. Obesity research 12(6): 889-95	- Incorrect study type *predicting progression to diabetes with OGTT and likelihood ratio based on bmi cutoffs. Study followed participants to examine progression to diabetes.*
Koopman, Anitra D M, Beulens, Joline W, Voerman, Ellis et al. (2019) The association between GAD65 antibody levels and incident Type 2 Diabetes Mellitus in an adult population: A meta-analysis. Metabolism: clinical and experimental 95: 1-7	- association study *Association SLR*
Ku, Grace M V and Kegels, Guy (2013) The performance of the Finnish Diabetes Risk Score, a modified Finnish Diabetes Risk Score and a simplified Finnish Diabetes Risk Score in community-based cross-sectional screening of undiagnosed type 2 diabetes in the Philippines. Primary care diabetes 7(4): 249-59	- Not looking at relevant predictors or biomarkers *No biomarkers and BMI only in 1 arm*

Study	Code [Reason]
Landin-Olsson, M, Nilsson, K O, Lernmark, A et al. (1990) Islet cell antibodies and fasting C-peptide predict insulin requirement at diagnosis of diabetes mellitus. Diabetologia 33(9): 561-8	- Not looking at relevant predictors or biomarkers *ICA only*
Lee, Crystal Man Ying, Woodward, Mark, Pandeya, Nirmala et al. (2017) Comparison of relationships between four common anthropometric measures and incident diabetes. Diabetes research and clinical practice 132: 36-44	- association study
Lee, S C, Ko, G T, Li, J K et al. (2001) Factors predicting the age when type 2 diabetes is diagnosed in Hong Kong Chinese subjects. Diabetes care 24(4): 646-9	- association study
Li, X, Zhou, Z G, Huang, G et al. (2004) Optimal cutoff point of glutamate decarboxylase antibody titers in differentiating two subtypes of adult-onset latent autoimmune diabetes. Annals of the New York Academy of Sciences 1037: 122-6	- Not a relevant population *Looking at subgroups of LADA not diabetes type classification*
Lim, H.M.; Chia, Y.C.; Koay, Z.L. (2020) Performance of the Finnish Diabetes Risk Score (FINDRISC) and Modified Asian FINDRISC (ModAsian FINDRISC) for screening of undiagnosed type 2 diabetes mellitus and dysglycaemia in primary care. Primary Care Diabetes 14(5): 494-500	- Not looking at relevant predictors or biomarkers *FIDNRISC is a risk calculator*
Lin, Jiunn-Diann (2015) Levels of the first-phase insulin secretion deficiency as a predictor for type 2 diabetes onset by using clinical-metabolic models. Annals of Saudi medicine 35(2): 138-45	- Reference standard in study does not match that specified in protocol *Looking at parameters vs first phase insulin secretion which is not a relevant marker.*
Lobner, K, Khoo-Morgenthaler, U Y, Seissler, J et al. (1999) Detection of autoantibodies to the diabetes-associated antigen IA-2 by a sensitive	- validation study

Study	Code [Reason]
enzyme-linked immunosorbent assay. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme 31(12): 686-91	
Longato, E., Acciaroli, G., Facchinetti, A. et al. (2019) Simple Linear Support Vector Machine Classifier Can Distinguish Impaired Glucose Tolerance Versus Type 2 Diabetes Using a Reduced Set of CGM-Based Glycemic Variability Indices. Journal of Diabetes Science and Technology 14(2): 297-302	- Not looking at relevant predictors or biomarkers *Looking at variability of blood glucose concentration*
Lotta, Luca A, Abbasi, Ali, Sharp, Stephen J et al. (2015) Definitions of Metabolic Health and Risk of Future Type 2 Diabetes in BMI Categories: A Systematic Review and Network Meta-analysis. Diabetes care 38(11): 2177-87	- Not looking at relevant predictors or biomarkers *All looking at FG or OGTT for type II diagnosis, no relevant biomarkers. As well as metabolic health*
Lounici Boudiaf, A, Bouziane, D, Smara, M et al. (2018) Could ZnT8 antibodies replace ICA, GAD, IA2 and insulin antibodies in the diagnosis of type 1 diabetes?. Current research in translational medicine 66(1): 1-7	- association study
Magri, Caroline J; Fava, Stephen; Galea, Joseph (2016) Prediction of insulin resistance in type 2 diabetes mellitus using routinely available clinical parameters. Diabetes & metabolic syndrome 10(2suppl1): 96-s101	- Not looking at relevant predictors or biomarkers *BMI only relevant one and not used to distinguish diabetes types*
Marcadenti, Aline, Fuchs, Sandra C, Moreira, Leila B et al. (2011) Accuracy of anthropometric indexes of obesity to predict diabetes mellitus type 2 among men and women with hypertension. American journal of hypertension 24(2): 175-80	- Not looking at relevant predictors or biomarkers *BMI only relevant measure and no ref standard*

Study	Code [Reason]
Mauvais-Jarvis, Franck, Sobngwi, Eugene, Porcher, Raphael et al. (2004) Ketosis-prone type 2 diabetes in patients of sub-Saharan African origin: clinical pathophysiology and natural history of beta-cell dysfunction and insulin resistance. Diabetes 53(3): 645-53	- Incorrect study type *Characterisation of disease study*
Middleton, Rachel J, Foley, Robert N, Hegarty, Janet et al. (2006) The unrecognized prevalence of chronic kidney disease in diabetes. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association 21(1): 88-92	- Not looking at relevant predictors or biomarkers *no biomarkers in protocol are in this study*
Mirzaei, Masoud and Khajeh, Mohammad (2018) Comparison of anthropometric indices (body mass index, waist circumference, waist to hip ratio and waist to height ratio) in predicting risk of type II diabetes in the population of Yazd, Iran. Diabetes & metabolic syndrome 12(5): 677-682	- association study
Mirzaei, Masoud, Khajeh, Mohammad, Askarishahi, Mohsen et al. (2018) Behavioral and familial predictors of diabetes mellitus in adults aged 20-69 in Yazd, Iran during 2014-2015. Diabetes & metabolic syndrome 12(5): 667-671	- Incorrect study type *predicting, not diagnosis, diabetes*
Mitchell, Alex J, Vancampfort, Davy, Manu, Peter et al. (2019) Which clinical and biochemical predictors should be used to screen for diabetes in patients with serious mental illness receiving antipsychotic medication? A large observational study. PloS one 14(9): e0210674	- Reference standard in study does not match that specified in protocol *Diagnostic, but comparing BMI to OGTT/fasting glucose so not a relevant ref standard Also uses risk calculators. Doesn't help distinguish between the types of diabetes. Ref standard is T2 only (OGTT/fasting glucose measures)*
Morgenthaler, N G, Seissler, J, Achenbach, P et al. (1997) Antibodies to the tyrosine phosphatase-like protein IA-2 are highly associated with IDDM, but not with autoimmune endocrine diseases or stiff man syndrome. Autoimmunity 25(4): 203-11	- association study

Study	Code [Reason]
Murata, Takashi, Tsuzaki, Kokoro, Nirengi, Shinsuke et al. (2017) Diagnostic accuracy of the anti-glutamic acid decarboxylase antibody in type 1 diabetes mellitus: Comparison between radioimmunoassay and enzyme-linked immunosorbent assay. Journal of diabetes investigation 8(4): 475-479	- Reference standard in study does not match that specified in protocol *Reference standard is unclear and simply comparing two GADA assays*
Nakanishi, K, Kobayashi, T, Sugimoto, T et al. (1988) Predictive value of insulin autoantibodies for further progression of beta cell dysfunction in non-insulin-dependent diabetics. Diabetes research (Edinburgh, Scotland) 9(3): 105-9	- Article could not be retrieved
Niskanen, L K, Tuomi, T, Karjalainen, J et al. (1995) GAD antibodies in NIDDM. Ten-year follow-up from the diagnosis. Diabetes care 18(12): 1557-65	- Not looking at relevant predictors or biomarkers *Gad vs ICA only*
Nooney, J.G., Kirkman, M.S., Bullard, K.M. et al. (2020) Identifying optimal survey-based algorithms to distinguish diabetes type among adults with diabetes. Journal of Clinical and Translational Endocrinology 21: 100231	- Incorrect study type *Looking at differentiating diabetes based on survey responses not clinical setting.*
O'Brien, Matthew J, Bullard, Kai McKeever, Zhang, Yan et al. (2018) Performance of the 2015 US Preventive Services Task Force Screening Criteria for Prediabetes and Undiagnosed Diabetes. Journal of general internal medicine 33(7): 1100-1108	- Not a relevant population *Looking at prediabetes/undiagnosed diabetes (dysglycaemia)*
Oak, Shilpa, Radtke, Jared, Landin-Olsson, Mona et al. (2009) Comparison of three assays for the detection of GAD65Ab-specific anti-idiotypic antibodies. Journal of immunological methods 351(12): 55-61	- validation study *validation of two new GADA assays.*

Study	Code [Reason]
Okura, T., Nakamura, R., Fujioka, Y. et al. (2018) Body mass index >=23 is a risk factor for insulin resistance and diabetes in Japanese people: A brief report. PLoS ONE 13(7): e0201052	- Incorrect study type *predicting risk not diagnosing type*
Omech, Bernard, Mwita, Julius Chacha, Tshikuka, Jose-Gaby et al. (2016) Validity of the Finnish Diabetes Risk Score for Detecting Undiagnosed Type 2 Diabetes among General Medical Outpatients in Botswana. Journal of diabetes research 2016: 4968350	- Not looking at relevant predictors or biomarkers *FINDRISC is a risk calculator and also seems to be validation study*
Oram, Richard A, Patel, Kashyap, Hill, Anita et al. (2016) A Type 1 Diabetes Genetic Risk Score Can Aid Discrimination Between Type 1 and Type 2 Diabetes in Young Adults. Diabetes care 39(3): 337-44	- Not looking at relevant predictors or biomarkers *Genetic risk scores not a relevant marker*
Ozsu, E., Cizmecioglu, F.M., Yesiltepe Mutlu, G. et al. (2019) Maturity onset diabetes of the Young due to Glucokinase, HNF1-A, HNF1-B, and HNF4-A mutations in a cohort of Turkish children diagnosed as type 1 diabetes mellitus. Hormone Research in Paediatrics 90(4): 257-265	- Not a relevant population *MODY*
Park, K S, Park, Y J, Kim, S W et al. (2000) Comparison of glucose tolerance categories in the Korean population according to World Health Organization and American Diabetes Association diagnostic criteria. The Korean journal of internal medicine 15(1): 37-41	- Not looking at relevant predictors or biomarkers *Not DTA, no relevant biomarkers*
Petruzelkova, L, Ananieva-Jordanova, R, Vcelakova, J et al. (2014) The dynamic changes of zinc transporter 8 autoantibodies in Czech children from the onset of Type 1 diabetes mellitus. Diabetic medicine: a journal of the British Diabetic Association 31(2): 165-71	- Not a relevant population *Children*

Study	Code [Reason]
Pfutzner, A, Harzer, O, Kunt, T et al. (2000) Comparison of immunoassays for the detection of anti-GAD65 autoantibodies in patients with diabetes mellitus. Clinical laboratory 46(56): 275-9	- Not looking at relevant predictors or biomarkers *Focusing on type of assay as opposed to different criteria for distinguishing diabetes type.*
Rama Chandran, S., Bhalshankar, J., Farhad Vasanwala, R. et al. (2018) Traditional clinical criteria outperform high-sensitivity C-reactive protein for the screening of hepatic nuclear factor 1 alpha maturity-onset diabetes of the young among young Asians with diabetes. Therapeutic Advances in Endocrinology and Metabolism 9(9): 271-282	- Not a relevant population *MODY*
Rhee, Mary K, Ho, Yuk-Lam, Raghavan, Sridharan et al. (2019) Random plasma glucose predicts the diagnosis of diabetes. PloS one 14(7): e0219964	- Not looking at relevant predictors or biomarkers *Comparing characteristics with random plasma glucose and general glucose measures only.*
Richard, J-L, Sultan, A, Daures, J-P et al. (2002) Diagnosis of diabetes mellitus and intermediate glucose abnormalities in obese patients based on ADA (1997) and WHO (1985) criteria. Diabetic medicine: a journal of the British Diabetic Association 19(4): 292-9	- Not looking at relevant predictors or biomarkers *BMI only marker of relevance, other markers glucose levels based.*
Sayadi, M.; Zibaeenezhad, M.J.; Ayatollahi, S.M.T. (2017) Simple prediction of type 2 diabetes mellitus via decision tree modeling. International Cardiovascular Research Journal 11(2): 71-76	- Incorrect study type *validating and testing prognostic model.*
Schwarz, Peter E H, Li, Jiang, Reimann, Manja et al. (2009) The Finnish Diabetes Risk Score is associated with insulin resistance and progression towards type 2 diabetes. The Journal of clinical endocrinology and metabolism 94(3): 920-6	- Not looking at relevant predictors or biomarkers *FINDRISC is a risk calculator*

Study	Code [Reason]
Sharma, M., Petersen, I., Nazareth, I. et al. (2016) An algorithm for identification and classification of individuals with type 1 and type 2 diabetes mellitus in a large primary care database. Clinical Epidemiology 8: 373-380	- Incorrect study type *Looking at health records not characteristics specifically.*
Shields, B.M., Peters, J.L., Cooper, C. et al. (2012) Identifying clinical criteria to predict Type 1 diabetes, as defined by absolute insulin deficiency: A systematic review protocol. BMJ Open 2(6): e002309	- Incorrect study type *protocol for shields 2015*
Simony, Rosana Farah, Gimeno, Suely Godoy Agostinho, Ferreira, Sandra Roberta Gouveia et al. (2007) Which body mass index is best associated with risk of diabetes mellitus and hypertension in a Japanese-Brazilian population?. Cadernos de saude publica 23(2): 297-304	- association study
Skogberg, Natalia, Laatikainen, Tiina, Lundqvist, Annamari et al. (2018) Which anthropometric measures best indicate type 2 diabetes among Russian, Somali and Kurdish origin migrants in Finland? A cross-sectional study. BMJ open 8(5): e019166	- Not looking at relevant predictors or biomarkers *BMI only protocol measure.*
Sosenko, Jay M, Skyler, Jay S, DiMeglio, Linda A et al. (2015) A new approach for diagnosing type 1 diabetes in autoantibody-positive individuals based on prediction and natural history. Diabetes care 38(2): 271-6	- Not a relevant population *Relatives of patients with diabetes (Auto-Ab + patients)*
Tanamas, Stephanie K, Magliano, Dianna J, Balkau, Beverley et al. (2015) The performance of diabetes risk prediction models in new populations: the role of ethnicity of the development cohort. Acta diabetologica 52(1): 91-101	- Not looking at relevant predictors or biomarkers *Risk prediction models not diagnostic.*
Tatovic, D, Luzio, S, Dunseath, G et al. (2016) Stimulated urine C-peptide creatinine ratio vs serum C-peptide level for monitoring of beta-cell function in	- Incorrect study type

Study	Code [Reason]
the first year after diagnosis of Type 1 diabetes. Diabetic medicine: a journal of the British Diabetic Association 33(11): 1564-1568	*monitoring with c-peptide, but could contain useful data about how it can measure c-peptide levels.*
Taylor, R. and Zimmet, P. (1981) Limitation of fasting plasma glucose for the diagnosis of diabetes mellitus. Diabetes Care 4(5): 556-558	- Not looking at relevant predictors or biomarkers *OGTT and FPG only*
Tfayli, Hala, Bacha, Fida, Gungor, Neslihan et al. (2010) Islet cell antibody-positive versus -negative phenotypic type 2 diabetes in youth: does the oral glucose tolerance test distinguish between the two?. Diabetes care 33(3): 632-8	- Not a relevant population *paediatric*
Thanabalasingham, G, Shah, N, Vaxillaire, M et al. (2011) A large multi-centre European study validates high-sensitivity C-reactive protein (hsCRP) as a clinical biomarker for the diagnosis of diabetes subtypes. Diabetologia 54(11): 2801-10	- Not a relevant population *MODY monogenic*
Tian, T., Pei, H., Chen, Z. et al. (2020) Comparison of lipid accumulation product and body mass index as indicators of diabetes diagnosis among 215,651 Chinese adults. PeerJ 2020(2): e8483	- Reference standard in study does not match that specified in protocol *BMI not vs a relevant marker (LAP) and not vs itself*
Turner, R, Stratton, I, Horton, V et al. (1997) UKPDS 25: autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. UK Prospective Diabetes Study Group. Lancet (London, England) 350(9087): 1288-93	- Reference standard in study does not match that specified in protocol *investigated whether the presence of antibodies can predict the need for insulin in people with type 2 diabetes, but no valid ref standard to GADA*
Umeno, A., Fukui, T., Hashimoto, Y. et al. (2018) Early diagnosis of type 2 diabetes based on multiple biomarkers and non-invasive indices. Journal of Clinical Biochemistry and Nutrition 62(2): 187-194	- Not looking at relevant predictors or biomarkers *Type 2 glucose and other related biomarkers only*

Study	Code [Reason]
Valdes, Sergio, Botas, Patricia, Delgado, Elias et al. (2008) Does the new American Diabetes Association definition for impaired fasting glucose improve its ability to predict type 2 diabetes mellitus in Spanish persons? The Asturias Study. Metabolism: clinical and experimental 57(3): 399-403	- Not looking at relevant predictors or biomarkers *Impaired fasting glucose and type II only*
Valdez, S N, Sica, M P, Labovsky, V et al. (2001) Combined measurement of diabetes mellitus immunological markers: an assessment of its benefits in adult-onset patients. Autoimmunity 33(4): 227-36	- No outcome of interest *Prevalence of markers as opposed to their usefulness at distinguishing diabetes types, no outcomes of interest*
Vazquez-Benitez, Gabriela (2008) Pre-screening tools for diabetes: An escalating approach in diverse populations. Evidence from CODA project. Dissertation Abstracts International: Section B: The Sciences and Engineering 68(11b): 7290	- Article could not be retrieved
Venkatrao, Murali, Nagarathna, Raghuram, Patil, Suchitra S et al. (2020) A composite of BMI and waist circumference may be a better obesity metric in Indians with high risk for type 2 diabetes: An analysis of NMB-2017, a nationwide cross-sectional study. Diabetes research and clinical practice 161: 108037	- Not looking at relevant predictors or biomarkers *BMI only relevant predictor and it is compared to irrelevant ones.*
Vikram, N K, Misra, A, Pandey, R M et al. (2003) Anthropometry and body composition in northern Asian Indian patients with type 2 diabetes: receiver operating characteristics (ROC) curve analysis of body mass index with percentage body fat as standard. Diabetes, nutrition & metabolism 16(1): 32-40	- Incorrect study type *Has different BMI thresholds but no valid ref standard so not diagnostic.*
Vlad, A, Serban, V, Sima, Alexandra et al. (2004) The value of basal C peptide and its relationship with pancreatic autoantibodies in young adults	- No outcome of interest *No DAT outcomes*

Study	Code [Reason]
with type 2 diabetes mellitus. Romanian journal of internal medicine = Revue roumaine de medecine interne 42(2): 333-41	
Walikonis, J E and Lennon, V A (1998) Radioimmunoassay for glutamic acid decarboxylase (GAD65) autoantibodies as a diagnostic aid for stiff-man syndrome and a correlate of susceptibility to type 1 diabetes mellitus. Mayo Clinic proceedings 73(12): 1161-6	- Incorrect study type *Not DAT Ab detection %s only*
Wannamethee, S G, Papacosta, O, Whincup, P H et al. (2010) Assessing prediction of diabetes in older adults using different adiposity measures: a 7 year prospective study in 6,923 older men and women. Diabetologia 53(5): 890-8	- Not looking at relevant predictors or biomarkers *association study and BMI only relevant marker*
Waugh, N, Royle, P, Craigie, I et al. (2012) Screening for cystic fibrosis-related diabetes: a systematic review. Health technology assessment (Winchester, England) 16(24): iii-179	- Not looking at relevant predictors or biomarkers *Looked at glucose measures only*
Wei, Wen, Xin, Xie, Shao, Bing et al. (2015) The relationship between anthropometric indices and type 2 diabetes mellitus among adults in north-east China. Public health nutrition 18(9): 1675-83	- Not looking at relevant predictors or biomarkers *Pools T2DM with "impaired glucose tolerance" and no valid reference standard.*
White, K., Mondesir, F.L., Bates, L.M. et al. (2014) Diabetes risk, diagnosis, and control: Do psychosocial factors predict hemoglobin A1C defined outcomes or accuracy of self-reports?. Ethnicity and Disease 24(1): 19-27	- Not looking at relevant predictors or biomarkers *Looking at self-reporting of diabetes not type distinguishing*
Wiest-Ladenburger, U, Hartmann, R, Hartmann, U et al. (1997) Combined analysis and single-step detection of GAD65 and IA2 autoantibodies in IDDM can replace the histochemical islet cell antibody test. Diabetes 46(4): 565-71	- Reference standard in study does not match that specified in protocol *- The ref standard is very unclear in the study and appears to be ICA.*

Study	Code [Reason]
Willis, J A, Scott, R S, Brown, L J et al. (1996) Islet cell antibodies and antibodies against glutamic acid decarboxylase in newly diagnosed adult-onset diabetes mellitus. Diabetes research and clinical practice 33(2): 89-97	- Not looking at relevant predictors or biomarkers *GADA compared to ICA only*
Winnock, F, Christie, M R, Batstra, M R et al. (2001) Autoantibodies to a 38-kDa glycosylated islet cell membrane-associated antigen in (pre)type 1 diabetes: association with IA-2 and islet cell autoantibodies. Diabetes care 24(7): 1181-6	- association study *assocqiation study and focused on irrelevant ab (GLIMA)*
Woldegebriel, Ataklti Gebertsadik, Fenta, Kiros Ajemu, Aregay, Asfawosen Berhe et al. (2020) Effectiveness of Anthropometric Measurements for Identifying Diabetes and Prediabetes among Civil Servants in a Regional City of Northern Ethiopia: A Cross-Sectional Study. Journal of nutrition and metabolism 2020: 8425912	- Not looking at relevant predictors or biomarkers *BMI only relevant one and not being compared to other measures.*
Wu, Hon-Yen, Peng, Yu-Sen, Chiang, Chih-Kang et al. (2014) Diagnostic performance of random urine samples using albumin concentration vs ratio of albumin to creatinine for microalbuminuria screening in patients with diabetes mellitus: a systematic review and meta-analysis. JAMA internal medicine 174(7): 1108-15	- Not looking at relevant predictors or biomarkers *urinary albumin only*
Xu, Ping, Beam, Craig A, Cuthbertson, David et al. (2012) Prognostic accuracy of immunologic and metabolic markers for type 1 diabetes in a high-risk population: receiver operating characteristic analysis. Diabetes care 35(10): 1975-80	- Incorrect study type *prediction not diagnosis of diabetes*
Xu, Z, Qi, X, Dahl, A K et al. (2013) Waist-to-height ratio is the best indicator for undiagnosed type 2 diabetes. Diabetic medicine : a journal of the British Diabetic Association 30(6): e201-7	- Not looking at relevant predictors or biomarkers *BMI only relevant measure*

Study	Code [Reason]
Yang, Lin, Luo, Shuoming, Huang, Gan et al. (2010) The diagnostic value of zinc transporter 8 autoantibody (ZnT8A) for type 1 diabetes in Chinese. Diabetes/metabolism research and reviews 26(7): 579-84	- Reference standard in study does not match that specified in protocol *ADA criteria not a valid reference standard for classifying types of diabetes in this case.*
Yoshizawa, S., Kodama, S., Fujihara, K. et al. (2016) Utility of nonblood-based risk assessment for predicting type 2 diabetes mellitus: A meta-analysis. Preventive Medicine 91: 180-187	- Not a relevant population *Used as source of studies but all found to be irrelevant (validation/other exclusion criteria clear form Ab data)*
Yuan, X., Liu, T., Wu, L. et al. (2015) Validity of self-reported diabetes among middle-aged and older Chinese adults: The China Health and Retirement Longitudinal Study. BMJ Open 5(4): e006633	- Not looking at relevant predictors or biomarkers *Self-reported diabetes diagnostic accuracy only concern no type to type distinguishing*
Zafari, Neda, Lotfaliany, Mojtaba, Mansournia, Mohammad Ali et al. (2018) Optimal cut-points of different anthropometric indices and their joint effect in prediction of type 2 diabetes: results of a cohort study. BMC public health 18(1): 691	- Incorrect study type *prediction of type 2 not diagnostic*
Zafra-Tanaka, J.H., Miranda, J.J., Gilman, R.H. et al. (2020) Obesity markers for the prediction of incident type 2 diabetes mellitus in resource-poor settings: The CRONICAS Cohort Study. Diabetes Research and Clinical Practice 170: 108494	- Incorrect study type *prediction of type 2 not diagnostic*
Zhang, Lu, Zhang, Zhenzhen, Zhang, Yurong et al. (2014) Evaluation of Finnish Diabetes Risk Score in screening undiagnosed diabetes and prediabetes among U.S. adults by gender and race: NHANES 1999-2010. PloS one 9(5): e97865	- Not looking at relevant predictors or biomarkers *FINDRISC is a risk calculator*

Study	Code [Reason]
Zhou, Hao, Li, Yuqian, Liu, Xiaotian et al. (2017) Development and evaluation of a risk score for type 2 diabetes mellitus among middle-aged Chinese rural population based on the RuralDiab Study. Scientific reports 7: 42685	- Not looking at relevant predictors or biomarkers *risk calculator, and validation study*

Appendix H – Research recommendations – full details

H.1.1 Research recommendation

1. What is the best clinical feature or combination of features for distinguishing between type 1 diabetes and other forms of diabetes?

2. What is the effectiveness of c-peptide at correcting misclassification of diabetes diagnosis and what is the optimal timing in distinguishing subtypes of diabetes?

H.1.2 Rationale for research recommendation

What is the best clinical feature or combination of features for distinguishing between type 1 diabetes and other forms of diabetes?

Importance to 'patients' or the population	Misdiagnosis of diabetes type has both short term and long-term effects on patients physical and mental health. A correct diagnosis can help patients manage their condition better, feel better and increase their quality of life as they feel they understand their condition.
Relevance to NICE guidance	There is a lack of high-quality diagnostic test accuracy papers looking at individual or combinations of clinical characteristics compared to c-peptide. This meant many recommendations had to be based on committee consensus, despite diabetes being a common condition with a large patient population. The findings from further research can feed into future updates of this guideline.
Relevance to the NHS	Misclassification of type 1 diabetes is still common and has long term effects on patient wellbeing and costs to the NHS, particularly when focusing on clinical criteria.

	Preconceptions about the relationship between these criteria and diabetes still exist and the relationship between some criteria (age and BMI) and diabetes subtype is changing over time. These changes should be captured in quantitative data. This has the potential to reduce costs and complications and have a positive resource impact on the NHS.
National priorities	Diabetes is one of the most common and costly conditions in the UK and any improvement in its correct classification and treatment will have wide reaching benefits across the whole national health service.
Current evidence base	There is a lack of high-quality diagnostic test accuracy papers looking at individual or combinations of clinical characteristics compared to c-peptide. Studies are required that investigate both individual and combinations of clinical characteristics and present 2x2 table data. This will allow for data analysis, subsequent meta-analysis and updated recommendations.
Equality considerations	Ethnicity is often cited as one of the criteria considered when looking at diabetes subtype, so there will be equality considerations when making assumptions about this relationship.

What is the effectiveness of c-peptide at correcting misclassification of diabetes diagnosis and what is the optimal timing in distinguishing subtypes of diabetes?

Importance to 'patients' or the population	Misdiagnosis of diabetes type has both short term and long-term effects on patients physical and mental health. A correct diagnosis can increase patient's quality of life as they feel they

	understand their condition and how to manage it better. C-peptide is a key biochemical test available to help prevent diabetes misdiagnosis.
Relevance to NICE guidance	There is a lack of high-quality diagnostic test accuracy papers looking at the effectiveness of c-peptide at correcting misclassification of diabetes diagnosis and what is the optimal timing. This meant many recommendations had to be based on committee consensus, despite diabetes being a common condition with a large patient population. C-peptide has a greater predictive value the longer after initial diagnosis the test is conducted, which suggests it is ideal for revisiting a diagnosis. However there is currently little evidence on this leading to this updated recommendation also being based on committee consensus. The findings from further research can feed into future updates of this guideline
Relevance to the NHS	Misclassification of type 1 diabetes is still common and has long term effects on patient wellbeing and costs to the NHS, particularly when focusing on clinical criteria. C-peptide has also been used at time of diagnosis despite its potentially poor predictive value. This has the potential to reduce costs and complications and have a positive resource impact on the NHS. Preconceptions about the relationship between these criteria and diabetes as well as c-peptides predictive value at early timepoints still exist and the relationship between some criteria (age and BMI) and diabetes subtype is changing over time. These changes should be captured in quantitative data.

National priorities	Diabetes is one of the most common and costly condition in the UK and any improvement in its correct classification and treatment will have wide reaching benefits across the whole national health service.
Current evidence base	There is a lack of high-quality diagnostic test accuracy papers looking at the effectiveness of c-peptide at correcting misclassification of diabetes diagnosis and what is the optimal timing. Studies are required that present 2x2 table data and allow for data analysis and subsequent meta-analysis and updated recommendations The time point at which patients are at in their diabetes should be considered, as it is thought c-peptide has a better discriminative value the longer after initial diabetes diagnosis.
Equality considerations	Ethnicity is often cited as one of the criteria considered when looking at diabetes subtype, so there will be equality considerations when making assumptions about this relationship.

H.1.3 Modified PICO table

What is the best clinical characteristic or combination of characteristics for distinguishing between type 1 diabetes and other forms of diabetes?

Population	Adults with undiagnosed diabetes
Index test	Clinical predictors (alone or in combination) including: • BMI (<25)

	• age at diagnosis • presence of ketones • diabetic ketoacidosis • family history • presence of auto immune conditions • ethnicity • time to commencing insulin treatment from diagnosis • weight loss
Reference standard	Serum C-peptide (with matching blood glucose)
Outcome	DTA outcomes (sensitivity, specificity, likelihood ratios, predictive values, optimal cut-off value (AUC)
Study design	Diagnostic test accuracy study ideally cross-sectional
Timeframe	DTA timeframe with differing timepoints
Additional information	Isolate characteristics rather than blending into a risk score, explore different thresholds if possible.

What is the effectiveness of c-peptide at correcting misclassification of diabetes diagnosis and what is the optimal timing for the test in distinguishing subtypes of diabetes?

Population	Adults with type 1 or type 2 diabetes having a diagnosis revisited
Index test	Serum C-peptide
Reference standard	Correct diabetes diagnosis

Outcome	DTA outcomes (sensitivity, specificity, likelihood ratios, predictive values, optimal cut-off value (AUC)
Study design	Diagnostic test accuracy study with a series of cross-sectional tests at different length of diabetes timepoints
Timeframe	DTA timeframe with differing timepoints
Additional information	Separate subgroups by length of time of diabetes if possible.

Appendix I – Included studies

Systematic reviews

As a source of primary studies only:

Lutgens, Maurice W M D, Meijer, Melanie, Peeters, Babette et al. (2008) Easily obtainable clinical features increase the diagnostic accuracy for latent autoimmune diabetes in adults: an evidence-based report. Primary care diabetes 2(4): 207-11

As a whole review:

Shields, Beverley M, Peters, Jaime L, Cooper, Chris et al. (2015) Can clinical features be used to differentiate type 1 from type 2 diabetes? A systematic review of the literature. BMJ open 5(11): e009088

Primary studies

Balasubramanyam, Ashok, Garza, Gilberto, Rodriguez, Lucille et al. (2006) Accuracy and predictive value of classification schemes for ketosis-prone diabetes. Diabetes care 29(12): 2575-9

Covic, A.M.C., Schelling, J.R., Constantiner, M. et al. (2000) Serum C-peptide concentrations poorly phenotype type 2 diabetic end-stage renal disease patients. Kidney International 58(4): 1742-1750

Fourlanos, Spiros, Perry, Christine, Stein, Mark S et al. (2006) A clinical screening tool identifies autoimmune diabetes in adults. Diabetes care 29(5): 970-5

Garnier, Lorna, Marchand, Lucien, Benoit, Marine et al. (2018) Screening of ZnT8 autoantibodies in the diagnosis of autoimmune diabetes in a large French cohort. Clinica chimica acta; international journal of clinical chemistry 478: 162-165

Hope, Suzy V, Wienand-Barnett, Sophie, Shepherd, Maggie et al. (2016) Practical Classification Guidelines for Diabetes in patients treated with insulin: a cross-sectional study of the accuracy of diabetes diagnosis. The British journal of general practice : the journal of the Royal College of General Practitioners 66(646): e315-22

Jones, A G, Besser, R E J, McDonald, T J et al. (2011) Urine C-peptide creatinine ratio is an alternative to stimulated serum C-peptide measurement in late-onset, insulin-treated diabetes. Diabetic medicine: a journal of the British Diabetic Association 28(9): 1034-8

Koskinen, P, Viikari, J, Irjala, K et al. (1986) Plasma and urinary C-peptide in the classification of adult diabetics. Scandinavian journal of clinical and laboratory investigation 46(7): 655-63

Sia, H.-K., Tu, S.-T., Liao, P.-Y. et al. (2020) A convenient diagnostic tool for discriminating adult-onset glutamic acid decarboxylase antibody-positive autoimmune diabetes from type 2 diabetes: A retrospective study. PeerJ 2020(2): e8610

Tanaka, Shoichiro, Endo, Toyoshi, Aida, Kaoru et al. (2004) Distinct diagnostic criteria of fulminant type 1 diabetes based on serum C-peptide response and HbA1c levels at onset. Diabetes care 27(8): 1936-41

Thunander, Maria, Torn, Carina, Petersson, Christer et al. (2012) Levels of C-peptide, body mass index and age, and their usefulness in classification of diabetes in relation to autoimmunity, in adults with newly diagnosed diabetes in Kronoberg, Sweden. European journal of endocrinology 166(6): 1021-9

Wang, Yanai, Gao, Ying, Cai, Xiaoling et al. (2019) Clinical Implications of Urinary C-Peptide Creatinine Ratio in Patients with Different Types of Diabetes. Journal of diabetes research 2019: 1747684

Supplementary References from Shields 2015

Besser RE, Ludvigsson J, Jones AG, et al. (2011) Urine C-peptide creatinine ratio is a noninvasive alternative to the mixed-meal tolerance test in children and adults with type 1 diabetes. Diabetes Care; 34(3):607-9.

Jones AG, Besser RE, McDonald TJ, et al. (2011) Urine C-peptide creatinine ratio is an alternative to stimulated serum C-peptide measurement in late-onset, insulin-treated diabetes. Diabet Med;28(9):1034-8.

Jones AG, Hattersley AT. (2013) The clinical utility of C-peptide measurement in the care of patients with diabetes. Diabet Med; 30(7):803-17.

Appendix J – Economic evidence study selection