Online Supplemental Material

Title: Can clinical features be used to differentiate Type 1 from Type 2 diabetes? A systematic review of the literature.

Supplemental Methods

Quality Assessment

Quality assessment was based on QUADAS-2, the recommended approach for diagnostic accuracy studies, which considers risk of bias (internal validity) and applicability (external validity) in 4 domains: Patient Selection, Index Tests, Reference Standard and Patient Flow and Timing. Due to potential variations in the measurement of the Reference Standard, this was considered in more detail separately.

Risk of bias:
Risk of bias in terms of the way the study was conducted, was assessed by examining patient recruitment, the measurements of the clinical predictors, and recording any exclusions made. Timing of the predictors in relation to the C-peptide measurement was also assessed. Of particular interest was how the clinical criteria were derived.

Applicability
When determining external validity, the main point of interest was the inclusion/exclusion criteria, to assess whether the study in question matched our protocol and which subgroups of diabetes patients the study was applicable to. We also aimed to determine whether the clinical predictors (index tests) were applicable to our research question, particularly whether they could be replicated in clinical practice. The timing of these measurements and the reference standard was also of interest, as criteria at diagnosis is likely to differ to criteria measured later on in the course of a patient's diabetes.

Reference standard
When assessing the reference standard for insulin deficiency, details such as the sample taken, meal stimulus, and assay used for measurement were examined. C-peptide results were all converted to nmol/l (=0.333*ng/ml) and fasting serum equivalent[1] where necessary, to enable direct comparison. The justification for the cutoff for insulin deficiency was assessed.

Supplemental Results

Screening and full text review – further details
Of 194 potential references, 59 studies were conference abstracts only and 5 were found to be further duplicates. Full texts were retrieved on 129 references. The remaining reference was unretrievable[2]. A further 29 references were identified from follow-up of conference abstracts, 6 of which had been published since the initial screening had been carried out, and full texts were retrieved on these. 11 studies were not in English. These were initially translated using google translate to gauge likely eligibility and in 10 cases it was clear the references were not appropriate. Full translation was required in only one case which appeared to have a table of relevance.

Full text review - exclusions
Of the 179 excluded studies at full text review stage, 146 were not diagnostic accuracy studies. 23 were excluded as the reference standard was incorrect (either not C-peptide or other features were incorporated into the reference standard along with C-peptide). 10 were excluded as the index test is not routinely measured (islet antibodies or HLA-alleles).

Supplemental Table 1 – Summary data extracted from the 10 included papers.

Author Year	Country	Year of study	Race of population	Sample size	Inclusion (I)/ Exclusion (E)	Treatments	Age group of pop'n	% Male	Prop'n with BMI below cutoff used	Prop'n 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	40%
Benhamou 1992	France	1989-1990	Not specified	88	I: End stage renal disease	All treatments	Not specified	?	Unable to extract	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	7%
Ekpebegh 2013	South Africa	2010-2012	Black African	71	I: Diagnosis of DKA	All treatments	Mean 34.7+/-15.3	54%	65% BMI<30	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	67%
Nielsen 1986	Denmark	1979-1980	Not specified	215	I: Insulin treated only	Insulin treated Only	Not specified	52%	-	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]	61%
Service 1997	USA (Rochester)	1986	Not specified	346	No specific exclusion criteria	All treatments	Not specified	?	Unable to extract	30%
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	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]	24%
Welborn 1983	Australia	1983	All Caucasian	121	No exclusions for food, glucose or renal status	Unclear – assume all	Adults	?	Not specified	21%

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

Supplemental Table 2 - Quality Assessment of internal validity (risk of bias) and external validity (applicability of study) for included studies in terms of a) patient selection, b) the index tests and c) patient flow and timing. ✓ = low risk of bias/valid study, ? = risk of bias/validity unclear, ✗= high risk of bias/problems with validity

a) Patient Selection				
Author Year	**Internal Validity** **Risk of bias in patient selection?**		**External Validity** **Does the study match our question?**	
Balasubramanyam 2006	✓	Low. Consecutive recruitment. By choosing only those who have presented with DKA, possible bias toward those with lower C-peptides.	✓	Applicable only for those who have presented with DKA.
Benhamou 1992	✓	Low. Random recruitment. Excluded secondary diabetes and missing data	✓	Applicable for ESRD patients only. Very few details of population
Boyle 1999	✓	Low. New patients enrolled (random) – not all at diagnosis. Excluded renal disease and missing data	✓	Applicable for African American non renal disease group only
Ekpebegh 2013	?	Unclear – cross sectional but few details on recruitment. By choosing only those who have presented with DKA, possible bias toward those with lower C-peptides.	✓	Applicable only for those who have presented with DKA and Black African racial group.
Laakso 1986	✓	Low. Random recruitment – 78% recruitment rate.	✓	Applicable for insulin treated patients only. Older patients
Nielsen 1986	✓	Low. Consecutive recruitment.	✓	Applicable for insulin treated patients only.
Prior 1991	?	Unclear. 582/3711 with C-peptide measurements available. Possible selection bias as those with C-pep measured different from rest (diagnosed older, less likely to be insulin treated and slimmer)	✓	Applicable for patients with retinopathy only. 95% White.
Service 1997	✓	Low. Cross-sectional survey. Representative of all diabetes 10-70 in Rochester area	✓	Applicable to Rochester population aged 10-70
Shields 2010	✓	Low. Recruited through retinal screening. Excluded non-insulin treated and short duration and long time to insulin.	✓	Applicable for insulin treated adults only. >5y duration; insulin treated within 2y of diagnosis
Welborn 1981	?	Unclear, likely random recruitment. Excluded renal failure	✓	Applicable for all except renal failure which was excluded in hospital clinic patients.
Welborn 1983	?	Unclear. Possibly some of same patients as other Welborn paper	?	Unclear

b) Index Test (Clinical Predictors)				
Author	**Internal Validity** **Is there a risk of bias in the way the index tests were measured/cutoffs derived?**		**External Validity** **Are the measurements applicable for our question?**	
Balasubramanyam 2006	✓	Low. Prespecified – objective measures	✓	BMI applicable – assume taken close to DKA episode.

Benhamou 1992	×	High. Regression equation internally derived. Mix of self report/questionnaire – possible recall bias. Unclear how BMI measured	×	Maximum BMI difficult to replicate as dependent on how many and when repeat measurements are taken.
Boyle 1999	✓	Low. Systematic assessment – height and weight measured (ref 21). Clinical rules CRI and CRII prespecified. Others not defined but split validation used.	✓	Yes – BMI cutoff results applicable to African American population.
Ekpebegh 2013	?	Unclear for age at diagnosis. Low for BMI - Systematic assessment and cutoffs defined in advance.	✓	Yes.
Laakso 1986	?	Unclear. Assumed taken off register so unlikely recall bias. Unclear when BMI measured. Lack of detail	✓	Yes.
Nielsen 1986	?	Unclear. Little detail on how cutoffs derived.	✓	Yes.
Prior 1991	✓	Low. Clinical rules pre-specified	✓	Yes
Service 1997	✓	Low. Algorithm pre-specified based on NDDG guidelines.	?	
Shields 2010	×	High – cutoffs internally derived. Age at diagnosis, BMI and time to insulin all self reported – possible recall bias	?	Unclear. BMI taken at time of study so may not be valid at other time points
Welborn 1981	?	Unclear how criteria chosen. Height and weight measured, but no details on how age at diagnosis and treatment were recorded – potential recall bias if patient reported.	✓	Yes.
Welborn 1983	?	Unclear. No details of how key criteria obtained.	✓	Unclear. Very little detail, but similar study to Welborn 1981; possible overlap.

c) Patient Flow and Timing				
Author	**Internal Validity** **Could exclusions have introduced bias?**		**External Validity** **Are the timings in the study applicable to our question?**	
Balasubramanyam 2006	?	Unclear. Doesn't state numbers due to missing data	✓	Applicable to first 12 months following DKA episode (not necessarily at diagnosis of diabetes).
Benhamou 1992	✓	Low. C-peptide measured on random selection of patients	?	Unclear. Cross sectional. Duration of diabetes not reported.
Boyle 1999	✓	Low. Measures taken at time of enrolment.	?	Median diabetes duration 1y but variability around that.
Ekpebegh 2013	✓	Unclear . No exclusions reported.	✓	Applicable to cases presenting with DKA, first manifestation of diabetes.
Laakso 1986	?	Unclear. No exclusions reported.	?	Cross-sectional. Unclear when measured in relation to C-peptide.
Nielsen 1986	?	Unclear. Small subset with C-peptide	?	Cross-sectional. Don't know when baseline visit is in relation to diabetes duration.
Prior 1991	?	Unclear. 346/381 with C-peptide measured. Not clear why	?	Cross sectional. Don't know when visit is in terms

		some missing, but low numbers.		of duration of disease
Service 1997	✓	Low. 11 deaths and 1 refusal – potentially lost those with lower C-peptide but small numbers.	✓	Yes. Some data split by duration.
Shields 2010	✓	Low. C-peptide measures were not included for 46 patients in analysis as either <3h post-food or abnormal renal function. Better for reference standard; timing of sample unlikely to be a bias of people entering the study.	?	Unclear. Duration of diabetes not reported so cannot determine when results would be applicable in time course of diabetes.
Welborn 1981	?	Unclear. Likely similar to above, as same authors and similar study.	?	Unclear

Supplemental Table 3. Reference standard C-peptide cutoffs for insulin deficiency. Cutoffs ordered from lowest to highest. Data presented for each study: cutoff as originally described, cutoff converted to nmol/l, fasting serum equivalent[a] to allow direct comparison across studies, assessment of the justification of the cutoff for insulin deficiency, and its applicability. For studies that reported two cutoffs, the most discriminatory is presented.

Author of study	Cutoff for insulin deficiency in original units; sample type; stimulus used	Cutoff converted to nmol/l, fasting serum[a]	How was cutoff chosen?	Cutoff applicable?
Prior 1993	80 pmol/l; plasma; post-sustacal	0.03 nmol/l	Unclear. ?chosen to maximise clinical diffs.	Yes, but likely to be internally derived. Very few patients between 0.04 and 0.32 nmol/l so any cutoff in this range would have led to similar results.
Welborn 1983	0.16 nmol/l; blood (plasma?); random	0.06 nmol/l	References Welborn 1981	Yes, although cutoff described based on fasting samples, whereas in this study samples were taken without reference to food ingestion.
Ekpebegh 2013	0.5 ng/mL; serum; stimulated	0.07 nmol/l	Not specified.	Unclear - consistent with other studies, but patients recruited close to diagnosis so C-peptide may be affected by "honeymoon" period.
Shields 2010	0.2 nmol/mmol; urine C-peptide creatinine ratio; post-meal	0.08 nmol/l	As reported by Besser et al[3]. to discriminate Type 1 diabetes from MODY.	Yes.
Service 1997	0.17 pmol/ml; blood (plasma?); fasting (and post-glucagon increment <0.07[b])	0.17 nmol/l	"Arbitrarily segregated" … "using previously published criteria for the characterization of IDDM and NIDDM". No reference provided	Unclear from paper but consistent with Welborn 1981. Results at different cutoffs for fasting and increment are also presented.
Welborn 1981	0.16 nmol/l; serum; fasting	0.16 nmol/l	<0.16 well outside 2SDs of mean and exclusively identifies those on insulin therapy.	Yes, but internally derived - insulin use possibly used to determine the reference standard.
Benhamou 1992	0.6 ng/ml; plasma; fasting	0.2 nmol/l	DCCT[4] – No IDDM patients had fasting C-peptide >0.6ng/ml 5 years after diagnosis	Yes.
Nielsen 1986	0.20 pmol/ml; plasma; fasting	0.2 nmol/l	Reference Madsbad et al[5]. from discriminating insulin from non-insulin treated patients	Yes.
Laakso 1987	0.60 nmol/l; blood; post-glucagon	0.2 nmol/l	Not specified.	Unclear, but consistent with other studies.
Balasumbryaman 2006	1 ng/ml; serum; fasting OR 1.5 ng/ml; serum; post-glucagon	0.3 nmol/l OR 0.2 nmol/l	Referenced Maldonado et al[6]. where cutoff obtained from ROC analysis in a "relevant population"	Yes.
Boyle 1999	0.9 ng/ml; not specified (likely plasma); fasting	0.3 nmol/l	Shows histogram and references 6 papers (although 0.9 ng/ml not used as a cutoff in these papers)	Unclear but consistent with other cutoffs reported.

[a]All converted to nmol/l (=0.333*ng/ml); urine to serum, and stimulated to fasting C-peptide (fasting=stimulated/2.5 formula unpublished but derived from MMTT data[7 8]; 0.2nmol/mmol UCPCR=0.2nmol/l stimulated serum C-peptide as described in the review by Jones et al[1]). [b]More than one cutoff reported in the paper.

Supplemental Tables 4. Two-by-two tables of clinical criteria cutoffs against reference standard C-peptide cutoffs for insulin deficency. Data extracted either directly as reported in the paper, or indirectly using reported estimates of sensitivity/specificity or positive/negative predictive value, and sample size and proportion of C-peptide negative/positive. C-peptide negative and C-peptide positive are determined as values below or above the cutoff for insulin deficiency reported in the paper.

Single criteria:

Balasumbryaman 2006

	C-peptide negative	**C-peptide positive**	
BMI <28kg/m^1	142	42	184
BMI>=28kg/m^2	23	86	109
	165	128	293*

*1 result missing

Boyle 1999

	C-peptide negative	**C-peptide positive**	
Age at diagnosis <20y	50	88	138
Age at diagnosis >=20y	195	3280	3475
	245	3368	3613

	C-peptide negative	**C-peptide positive**	
Age at diagnosis <45y	160	1455	1615
Age at diagnosis >=45y	85	1913	1998
	245	3368	3613

	C-peptide negative	**C-peptide positive**	
BMI <20 kg/m^2	25	51	76
BMI>=20 kg/m^2	220	3317	3537
	245	3368	3613

	C-peptide negative	**C-peptide positive**	
BMI<25 kg/m^2	100	462	562
BMI>=25 kg/m^2	145	2906	3051
	245	3368	3613

	C-peptide negative	**C-peptide positive**	
BMI <29 kg/m^2	175	1463	1638
BMI>=30 kg/m^2	70	1905	1975
	245	3368	3613

Ekpebegh 2013

	C-peptide negative	**C-peptide positive**	
Age at diagnosis <30y	20	10	30
Age at diagnosis >=30y	15	26	41
	35	36	71

	C-peptide negative	**C-peptide positive**	
BMI<30kg/m^2	27	19	46
BMI>=30kg/m^2	8	17	25
	35	36	71

Laakso 198
using postglucagon male and female combined as the most discriminative

	C-peptide negative	C-peptide positive	
Age at diagnosis <=40y	70	12	82
Age at diagnosis >40y	45	44	89
	115	56	171

	C-peptide negative	C-peptide positive	
Time to insulin <=2y	80	8	88
Time to insulin >2y	35	48	83
	115	56	171

	C-peptide negative	C-peptide positive	
BMI<=27kg/m^2	87	19	106
BMI >27kg/m^2	28	37	65
	115	56	171

Nielsen 1986

	C-peptide negative	C-peptide positive	
Age at diagnosis <=30y	95	8	103
Age at diagnosis >30y	53	59	112
	148	67	215

Prior 1991

	C-peptide negative	C-peptide positive	
Age at diagnosis <=30y	295	40	335
Age at diagnosis >30y	56	184	240
	351	224	575

	C-peptide negative	C-peptide positive	
Age at diagnosis <=40y	340	91	431
Age at diagnosis >40y	11	133	144
	351	224	575

	C-peptide negative	C-peptide positive	
PDW<100%	118	17	135
PDW>=100%	233	207	440
	351	224	575

	C-peptide negative	C-peptide positive	
PDW<120%	306	83	389
PDW>120%	45	141	186
	351	224	575

	C-peptide negative	C-peptide positive	
On insulin	349	168	517
Off insulin	2	56	58
	351	224	575

	C-peptide negative	C-peptide positive	
Time to insulin <1y	322	56	378
Time to insulin >=1y	29	168	197
	351	224	575

Shields 2010

	C-peptide negative	C-peptide positive	
Age at diagnosis <39y	27	1	28
Age at diagnosis >=39y	13	31	44
	40	32	72

	C-peptide negative	C-peptide positive	
BMI <29kg/m^2	31	14	45
BMI>=29kg/m^2	9	18	27
	40	32	72

	C-peptide negative	C-peptide positive	
Time to insulin <=1.5m	32	14	46
Time to insulin >1.5m	8	18	26
	40	32	72

Welborn 1983

	C-peptide negative	C-peptide positive	

Age at diagnosis <=40y	21	14	35
Age at diagnosis >40y	4	82	86
	25	96	121

	C-peptide negative	**C-peptide positive**	
PDW<=120%	20	32	52
PDW>120%	5	64	69
	25	96	121

	C-peptide negative	**C-peptide positive**	
Time to insulin <2y	25	17	42
Time to insulin >2y + not on insulin	0	79	79
	25	96	121

Welborn 1981

	C-peptide negative	**C-peptide positive**	
Age at diagnosis <=40y	35	29	64
Age at diagnosis >40	11	126	139
	46*	155	203

	C-peptide negative	**C-peptide positive**	
On insulin	48	47	95
Off insulin	0	108	108
	48	155	203

Combined criteria

Boyle 1999

	C-peptide negative	C-peptide positive	
Age diag <30 and insulin treated	33	104	137
Other	74	1596	1670
	107	1700	1807

	C-peptide negative	C-peptide positive	
Age diag <30 insulin treated and BMI <26	16	27	43
Other	91	1673	1764
	107	1700	1807

	C-peptide negative	C-peptide positive	
Age diag <28.9 insulin treated and BMI <31.7	26	49	75
Other	81	1651	1732
	107	1700	1807

Laakso 1987

	C-peptide negative	C-peptide positive	
Age at diagnosis <=40 and time to insulin <=2y	51	2	53
Opposite	64	54	118
	115	56	171

	C-peptide negative	C-peptide positive	
Age at diagnosis <=40 and BMI <=27	53	5	58
Opposite	62	51	113
	115	56	171

	C-peptide negative	C-peptide positive	
Time to insulin <=2y and and BMI <=27	63	4	67
Opposite	52	52	104
	115	56	171

	C-peptide negative	C-peptide positive	
Age at diagnosis <=40 , time to insulin <=2y and and BMI <=27	40	1	41
Opposite	75	55	130
	115	56	171

Prior 1991

	C-peptide negative	C-peptide positive	
Age at diagnosis <=30, time to insulin <=1y and PDW<120%	248	11	259
Opposite	103	213	316
	351	224	575

	C-peptide negative	C-peptide positive	
Age at diagnosis <=30, time to insulin <=1y OR ad<40, tti<1y PDW<120%	309	22	331
Opposite	42	202	244
	351	224	575

	C-peptide negative	C-peptide positive	
Age at diagnosis <20, time to insulin immediately	238	16	254
Other	113	208	321
	351	224	575

	C-peptide negative	C-peptide positive	
Age at diagnosis <20, time to insulin immediately OR Age at diagnosis >=20, time to insulin immediately PDW<=120%	328	61	389
Other	23	163	186
	351	224	575

	C-peptide negative	C-peptide positive	
Age diag <30 tti <1y	277	15	292
Other	74	209	283
	351	224	575

	C-peptide negative	C-peptide positive	
Age diag <40 tti <1y	313	28	341
Other	38	196	234
	351	224	575

Welborn 1983

	C-peptide negative	C-peptide positive	
Age diag <40 and tti<=2y	21	4	25
Other	4	92	96
	25	96	121

	C-peptide negative	C-peptide positive	
Age diag <=40y tti<2y OR age diag>40y tti<2y and PDW<120%	23	6	29
Other	2	90	92

	25	96	121

Welborn 1981

	C-peptide negative	C-peptide positive	
Age diag<=4-y and on insulin	35	12	47
Other	13	143	156
	48	155	203

Equations or algorithms

Service 1997

Algorithm:
Type 1=insulin treated+ketosis+slim OR insulin treated, no ketosis, diagnosed <=21y and acute onset

	C-peptide negative	C-peptide positive	
Type 1 acc to algorithm	74	25	99
Other	10	237	247
	84	262	346

Benhamou 1992

Regression equation = T=(0.01166*time to insulin)+(0.01324*age diagnosis)+(0.01188*BMI max)-0.22834.

	C-peptide negative	C-peptide positive	
T<=0.5	14	3	17
T>0.5	0	71	71
	14	74	88

Boyle 1999

Regression equation =
Log OR=1.09+(2.19if ins treated)-(0.031*age diag)-(0.127*BMI)

	C-peptide negative	C-peptide positive	
T1 prob>0.2	55	153	208
T1 prob<=0.2	52	1547	1599
	107	1700	1807

Supplemental Table 5 Criteria for predicting insulin deficiency – combined criteria

Age at diagnosis (a/d) and BMI	Author	Sensitivity	Specificity	% correctly classified	PPV	NPV	% C-pep negative
a/d<=40 BMI<=27	Laakso 1987	46	91	61	91	45	67

Time to insulin (tti) and BMI	Author	Sensitivity	Specificity	% correctly classified	PPV	NPV	% C-pep negative
tti<=2 BMI<=27	Laakso 1987	55	93	67	94	50	67

Age at diagnosis and time to insulin	Author	Sensitivity	Specificity	% correctly classified	PPV	NPV	% C-pep negative
a/d<=20 tti immed	**Prior 1991**	**68**	**93**	**78**	**94**	**65**	**61**
a/d<30 tti<1y	**Prior 1991**	**79**	**93**	**85**	**95**	**74**	**61**
ad<30 on insulin	Boyle 1999	31	94	90	76	96	7
ad <=40 on insulin	**Welborn 1981**	**73**	**92**	**88**	**74**	**92**	**24**
a/d<40 tti<1y	**Prior 1991**	**89**	**88**	**89**	**92**	**84**	**61**
ad<=40 tti<=2	**Welborn 1983**	**84**	**96**	**93**	**84**	**96**	**21**
a/d<=40 tti<=2	Laakso 1987	44	96	61	96	46	67

Age at diagnosis, tti and BMI	Author	Sensitivity	Specificity	% correctly classified	PPV	NPV	% C-pep negative
a/d<20 tti immed OR a/d>=20 ins immed PDW<=120	**Prior 1991**	**93**	**73**	**85**	**84**	**88**	**61**
ad<28.9 on ins bmi<31.7	Boyle 1999	24	97	93	35	95	7
a/d<30 tti<1y PDW<120%	**Prior 1991**	**71**	**95**	**80**	**96**	**67**	**61**
a/d<30 tti<1 OR a/d<40 tti<1 PDW<120%	**Prior 1991**	**88**	**90**	**91**	**93**	**83**	**61**
ad<30 on ins BMI<26	Boyle 1999	15	98	93	37	95	7
a/d<=40 tti<=2 BMI<=27	Laakso 1987	35	98	56	98	42	67
ad<=40 tti<2 OR ad>40 tti<2 PDW<120%	**Welborn 1983**	**92**	**94**	**93**	**79**	**98**	**21**

Equations or algorithms	Author	Sensitivity	Specificity	% correctly classified	PPV	NPV	% C-pep negative
Algorithm: Ins treated & ketosis & ≤120%PDW OR	**Service 1997**	**75**	**96**	**90**	**88**	**90**	**24**

Ins treated & no ketosis & age diag<21y & acute onset							
Regression equation (T1 if >0.5): (0.0116*tti)+(0.01324*age diag)+(0.01188*BMI)	**Benhamou 1992**	**100**	**96**	**97**	**82**	**100**	**16**
Regression equation (T1=prob>0.2) Log OR=1.09+(2.19if ins treated)-(0.031*age diag)-(0.127*BMI)	Boyle 1999	51	91	89	26	97	7
Classification tree: Insulin treated, diagnosed<28.9 and BMI<31.7	Boyle 1999	24	97	93	35	95	7
Classification tree including age diag, tti and BMI: *Details not reported*	Shields 2010			82			

Supplemental Search Annex

Database	Hits
1. MEDLINE	5804
2. MEDLINE in Process	205
3. EMBASE	8566
4. PsycINFO	23
5. Social Policy and Practice	0
6. AMED	11
7. British Nursing Index (BNI)	11
8. CINAHL	24
9. HMIC	5
10. Sociological Abstracts	3
11. ASSIA	2
12. Cochrane (all)	1611 (1613 2 from methods)
13. Web of Science (Conference Proceedings Citation Index)	4792
14. Centre for Reviews and Dissemination	3
Total	21060
Duplicates Removed	-10143
Unique Records	10917

1.
Database: MEDLINE
Host: OVID
Data Parameters: 1946 to October Week 2 2012
Date Searched: Tuesday, 23rd October 2012
Hits: 5804
Strategy:

#	Searches	Results
1	exp Diabetes Mellitus, Type 1/	57591
2	((typ$ 1 or typ$ I or type 1) adj3 diabet$).ti,ab.	29301
3	(T1DM or dm1).ti,ab.	2338
4	diabet$.ti,ab.	348751
5	1 or 2 or 3 or 4	355909
6	C-Peptide/	6951
7	(c-peptide$ or c peptide$).ti,ab.	8707
8	"Connecting Peptide$".ti,ab.	292
9	6 or 7 or 8	11014
10	5 and 9	6230
11	exp animals/ not humans.sh.	3795620
12	10 not 11	5897

13	limit 12 to yr="1979 -Current"	5804

Limits: Search limited to human only populations and by date
Notes: N/A
File Name: Medline Endnote RIS n=5804.txt

2.
Database: Medline in Process
Host: OVID
Data Parameters: October 22nd , 2012
Date Searched: Tuesday, 23rd October 2012
Hits: 205
Strategy:

Search Strategy:

#	Searches	Results
1	exp Diabetes Mellitus, Type 1/	0
2	((typ$ 1 or typ$ I or type 1) adj3 diabet$).ti,ab.	1502
3	(T1DM or dm1).ti,ab.	222
4	diabet$.ti,ab.	17913
5	1 or 2 or 3 or 4	17961
6	C-Peptide/	0
7	(c-peptide$ or c peptide$).ti,ab.	285
8	"Connecting Peptide$".ti,ab.	8
9	6 or 7 or 8	291
10	5 and 9	205
11	exp animals/ not humans.sh.	3
12	10 not 11	205
13	limit 12 to yr="1979 -Current"	205

Limits: Search limited to human only populations and by date
Notes: N/A
File Name: Medline in Process RIS n=205.txt

3.
Database: Embase
Host: OVID
Data Parameters: Embase 1980 to 2012 Week 42, Embase 1974 to 1979
Date Searched: Tuesday, 23rd October 2012
Hits: 8566
Strategy:

Search Strategy:

#	Searches	Results

1	insulin dependent diabetes mellitus/	70536
2	((typ$ 1 or typ$ I or type 1) adj3 diabet$).ti,ab.	41404
3	(T1DM or dm1).ti,ab.	4248
4	diabet$.ti,ab.	495933
5	1 or 2 or 3 or 4	507285
6	C peptide/	11467
7	(c-peptide$ or c peptide$).ti,ab.	11576
8	"Connecting Peptide$".ti,ab.	307
9	6 or 7 or 8	14807
10	5 and 9	8775
11	exp animal/ not human/	1352023
12	10 not 11	8718
13	limit 12 to yr="1979 -Current"	8566

Limits: The search is limited to human only populations and by date to 1979-Current.
Notes: N/A
File Name: Embase Endnote RIS n=8566.txt

4.
Database: PsycINFO
Host: OVID
Data Parameters: 1806 to October Week 3 2012
Date Searched: Tuesday, 23rd October 2012
Hits: 23
Strategy:

#	Searches	Results
1	exp Diabetes Mellitus, Type 1/	0
2	((typ$ 1 or typ$ I or type 1) adj3 diabet$).ti,ab.	1197
3	(T1DM or dm1).ti,ab.	178
4	diabet$.ti,ab.	16010
5	1 or 2 or 3 or 4	16087
6	C-Peptide/	0
7	(c-peptide$ or c peptide$).ti,ab.	70
8	"Connecting Peptide$".ti,ab.	1
9	6 or 7 or 8	71
10	5 and 9	25
11	exp animals/ not humans.sh.	250508
12	10 not 11	23

13	limit 12 to yr="1979 -Current"	23

Limits: Search limited to human only populations and by date
Notes: N/A
File Name: PsycINFO Endnote RIS n=23.txt

5.
Database: Social Policy and Practice (SPP)
Host: OVID
Data Parameters: 201207
Date Searched: Tuesday, 23rd October 2012
Hits: 0
Strategy:

#	Searches	Results
1	exp Diabetes Mellitus, Type 1/	0
2	((typ$ 1 or typ$ I or type 1) adj3 diabet$).ti,ab.	59
3	(T1DM or dm1).ti,ab.	0
4	diabet$.ti,ab.	839
5	1 or 2 or 3 or 4	839
6	C-Peptide/	0
7	(c-peptide$ or c peptide$).ti,ab.	0
8	"Connecting Peptide$".ti,ab.	0
9	6 or 7 or 8	0
10	5 and 9	0
11	exp animals/ not humans.sh.	0
12	10 not 11	0
13	limit 12 to yr="1979 -Current"	0

Limits: N/A
Notes: N/A
File Name: No File Recorded

6.
Database: AMED
Host: Ebsco Host
Data Parameters: 1995-Current
Date Searched: Tuesday, 23rd October 2012
Hits: 11
Strategy:

TI diabet* OR AB diabet*
TI (((c-peptide*) or (c peptide*))) OR AB (((c-peptide*) or (c peptide*)))
TI "Connecting Peptide*" OR AB "Connecting Peptide*"
S2 or S3
(S2 or S3) AND (S1 and S4)

Limits: None Used

Notes: N/A
File Name: Amed Endnote RIS n=11.txt

7.
Database: British Nursing Index (BNI)
Host: ProQuest
Data Parameters: 1994-Current
Date Searched: Monday, October 22nd 2012
Hits: 11
Strategy:

1. ti((diabet*)) OR ab((diabet*))
2. ti(((''c peptide*'') or (c-peptide*) or (connecting peptide*))) OR ab(((''c peptide*'') or (c-peptide*) or (connecting peptide*)))
3. 1 AND 2

Limits: None Used
Notes: N/A
File Name: BNI Endnote RIS n=11

8.
Database: Cinahl
Host: Ebsco Host
Data Parameters: 1981-Current
Date Searched: Tuesday, 23rd October 2012
Hits: 24
Strategy:

TI diabet* OR AB diabet*
Search modes - Boolean/Phrase

TI ((("c peptide*") or (c-peptide*) or (connecting peptide*))) OR AB ((("c peptide*") or (c-peptide*) or (connecting peptide*)))
Search modes - Boolean/Phrase

S1 and S2
Search modes - Boolean/Phrase

S1 and S2
Limiters - Exclude MEDLINE records
Search modes - Boolean/Phrase

Limits: N/A
Notes: A server-side de-duplication was run to exclude Medline records.
File Name: Cinahl Endnote RIS n=24.txt

9.
Database: HMIC
Host: OVID
Data Parameters: 1979 to September 2012
Date Searched: Tuesday, 23rd October 2012
Hits: 5
Strategy:

#	Searches	Results
1	exp Diabetes Mellitus, Type 1/	0

2	((typ$ 1 or typ$ I or type 1) adj3 diabet$).ti,ab.	132
3	(T1DM or dm1).ti,ab.	3
4	diabet$.ti,ab.	3553
5	1 or 2 or 3 or 4	3553
6	C peptide/	0
7	(c-peptide$ or c peptide$).ti,ab.	10
8	"Connecting Peptide$".ti,ab.	0
9	6 or 7 or 8	10
10	5 and 9	5
11	exp animal/ not human/	0
12	10 not 11	5
13	limit 12 to yr="1979 -Current"	5

Limits: Date limited 1979-Current
Notes: N/A
File Name: HMIC Endnote RIS n=5.txt

10.
Database: Sociological Abstracts
Host: ProQuest
Data Parameters: 1963-Current
Date Searched: Monday, October 22nd 2012
Hits: 3
Strategy:

1. ti((diabet*)) OR ab((diabet*))
2. ti((("c peptide*") or (c-peptide*) or (connecting peptide*))) OR ab((("c peptide*") or (c-peptide*) or (connecting peptide*)))
3. 1 AND 2

Limits: None Used
Notes: N/A
File Name: Soc Abs Endnote RIS n=3

11
Database: ASSIA
Host: ProQuest
Data Parameters: 1987-Current
Date Searched: Monday, October 22nd 2012
Hits: 2
Strategy:

1. ti((diabet*)) OR ab((diabet*))
2. ti((("c peptide*") or (c-peptide*) or (connecting peptide*))) OR ab((("c peptide*") or (c-peptide*) or (connecting peptide*)))
3. 1 AND 2

Limits: None Used
Notes: N/A

File Name: Assia Endnote RIS N=2

12.
Database: Cochrane Library
Host: http://www.thecochranelibrary.com/view/0/index.html
Data Parameters: Issue 10 of 12, Oct 2012
Date Searched: Tuesday, 23rd October 2012
Hits: 1611 (Reviews: 127; DARE: 20; Central 1449; HTA 3; NHS EEDS 12)
Strategy:

#1 MeSH descriptor: [Diabetes Mellitus, Type 1] explode all trees
#2 ((typ* 1 or typ* I or type 1) near/3 diabet*)
#3 (T1DM or dm1)
#4 diabet*
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [C-Peptide] explode all trees
#7 ((c-peptide*) or (c peptide*))
#8 "Connecting Peptide*"
#9 #6 or #7 or #8
#10 #5 and #9

Limits: N/A
Notes: N/A
File Name:

13.
Database: Web of Science
Host: ISI
Data Parameters: 1900-Present. SSCI, 1975-Present
Date Searched: Tuesday, 23rd October 2012
Hits: 4792
Strategy:

Topic=(diabet*) AND Topic=((("c peptide*") or ("c-peptide*") or ("connecting peptide*")))
Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1979-01-01 - 2012-10-23
Lemmatization=Off

Limits: Lemmatization=Off. The search was limited by date 1979-Current
Notes: SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH were all searched
File Name: WOS Endnote RIS n=4792

14.
Database: CRD
Host: http://www.york.ac.uk/inst/crd/index.htm
Data Parameters: 1989-Current
Date Searched: Monday, October 22nd 2012
Hits: 3
Strategy:

(diabet*) AND ((("c peptide*") or (c-peptide*) or (connecting peptide*))) FROM 1979 TO 2012

Limits: Date Limited 1979-2012
Notes: N/A
File Name: CRD endnote RIS n=3.txt

15.
Database: PROSPERO
Host: http://www.york.ac.uk/inst/crd/index.htm

Data Parameters: Feb 2011-Current
Date Searched: Monday, October 22nd 2012
Hits: 1
Strategy:

(C peptide)

Limits: N/A
Notes: N/A
File Name: Prospero

Supplementary References

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5. Madsbad S, Faber OK, Binder C, et al. Prevalence of residual beta-cell function in insulin-dependent diabetics in relation to age at onset and duration of diabetes. Diabetes 1978;**27 Suppl 1**:262-4
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