# Assessment of Practical Classification Guidelines for Diabetes in insulin-treated patients

Authors- *Suzy Hope[1], *Sophie Wienand-Barnett[1], Maggie Shepherd[1], Sophie King[1], Charles Fox[2], Kamlesh Khunti[3], Richard Oram[1], Bea Knight[1], Andrew Hattersley[1], Angus Jones[1], **Beverley Shields[1]

*Joint first authors
** Corresponding author

1. University of Exeter Medical School & Royal Devon & Exeter NHS Foundation Trust, Exeter NIHR Clinical Research Facility, Barrack Road, Exeter, EX2 5DW, UK
2. Northampton General Hospital, R&D Unit, Cliftonville, Northampton, NN1 5BD, UK
3. Diabetes Research Centre, College of Medicine, Biological Sciences & Psychology, University of Leicester & The Leicester Diabetes Centre (Air Wing), Leicester General Hospital, Gwendolen Road, Leicester, LE5 4PW, UK

Corresponding author information:

Dr Beverley Shields,
University of Exeter Medical School & Royal Devon & Exeter NHS Foundation Trust,
Exeter NIHR Clinical Research Facility,
RILD Room 03.11,
Barrack Road,
Exeter,
EX2 5DW
Email: B.Shields@exeter.ac.uk
Telephone: 01392 408203

**How this fits in** *(max 4 short sentences – what was prev known, what this adds, esp focusing on relevance to clinicians)*

Correct classification as Type 1 or Type 2 diabetes is fundamental to appropriate diabetes management.

The UK Practical Classification Guidelines for diabetes published by the Royal College of General Practitioners are pragmatically based on age at diagnosis and time from diagnosis to commencing insulin treatment.

This the first study testing the UK classification guidelines in a large cohort of insulin-treated patients against a gold standard classification of diabetes subtype based on presence or absence of retained endogenous insulin secretion (measured using C-peptide) ≥5 years post-diagnosis.

The UK classification criteria correctly classified 86% of patients, with age at diagnosis and time to insulin being the best clinical predictors of long-term endogenous insulin production.

# Assessment of Practical Classification Guidelines for Diabetes in insulin-treated patients


## Abstract

### Background
Differentiating between Type 1(T1D) and Type 2 diabetes(T2D) is fundamental for appropriate treatment and management of patients, but can be challenging, especially when patients are insulin-treated. UK Practical Classification Guidelines (using age at diagnosis and time to insulin treatment) were developed, but their accuracy has not been assessed.

### Aim
To assess the diagnostic accuracy of the UK guidelines against "gold-standard" definitions of T1D and T2D based on measured C-peptide levels.

### Design & Setting
601 adults with insulin-treated diabetes and diabetes duration ≥5years were recruited in Exeter, Northampton & Leicestershire.

### Method
Baseline information and a home urine sample for urinary C-peptide creatinine ratio (UCPCR, a measure of endogenous insulin production) were collected. "Gold-standard" T1D was defined as continuous insulin treatment within 3 years of diagnosis and absolute insulin deficiency (UCPCR<0.2nmol/mmol ≥5years post-diagnosis); all other patients classed as T2D. Diagnostic performance of the clinical criteria assessed and other criteria explored using ROC curves.

### Results
UK guidelines correctly classified 86% of participants.

Most misclassifications occurred in patients classed as T1D who had significant endogenous insulin levels(57/601;9%); the majority in those diagnosed ≥35y and treated with insulin from diagnosis(37/66;56% misclassified).

Time to insulin and age at diagnosis performed best in predicting long-term endogenous insulin production(ROC AUC=0.904 and 0.871); BMI at diagnosis was a less strong predictor of diabetes type (AUC=0.824).

### Conclusion
Current UK guidelines provide a pragmatic clinical approach to classification that reflects long-term endogenous insulin production; caution is needed in older patients commencing insulin from diagnosis, where misclassification rates are increased.

## Introduction

Correctly classifying patients with diabetes with Type 1 or 2 is fundamental to ensuring they receive correct management(1-3). In clinical practice this can be challenging, with 7-15% patients misclassified, and large variations in practice(4-7).

Historical lack of clear clinical guidelines for diabetes classification is likely to have contributed to this variation. International guidelines from WHO(8) and ADA(9) base classification on underlying aetiology, with Type 1 described as a destruction of beta cells leading to absolute insulin deficiency. However these guidelines do not provide clear criteria or classification pathways for clinical use(8, 9).

A pragmatic classification algorithm was thus developed in 2010 by key diabetes stakeholders in the UK, and published by the Royal College of General Practitioners (RCGP) and NHS Diabetes in their Coding, Classification and Diagnosis of Diabetes document(4), Figure 1. This uses age at diagnosis and time to commencing insulin treatment from diagnosis as its diagnostic criteria. The efficacy of this algorithm has not yet been tested on a large cohort of patients with diabetes.

The fundamental difference between Type 1 and Type 2 diabetes is the rapid development of absolute insulin deficiency in Type 1, forming the basis of their different treatment and management. Patients with Type 1 require accurate insulin dose replacement(10, 11); patients with Type 2 continue to produce substantial amounts of their own insulin, responding to non-insulin therapy, or if insulin is needed good control can be achieved with non-physiological insulin regimes(12, 13). Measuring endogenous insulin secretion (using C-peptide, a component of the insulin pro-hormone secreted in equimolar amounts to insulin) in longstanding diabetes may be a useful "gold standard" marker of endogenous insulin production, confirming a diagnosis of Type 1 versus Type 2 diabetes. Development of the spot urine test urinary C-peptide creatinine ratio (UCPCR)(14-17) has enabled practical testing in a community setting. UCPCR is well-correlated with mixed meal tolerance test measures(16, 17), and a UCPCR cut-off of 0.2nmol/mmol gives a sensitivity and specificity of 100% and >95% for detecting severe insulin deficiency(16, 17) as defined by the gold-standard mixed meal test 90-minute C-peptide level of 200pmol/L(18).

We thus aimed to determine the reliability of the 2010 UK Practical Classification Guidelines(4) to correctly classify diabetes in a large cohort of insulin-treated participants against "gold-standard" classification based on measurement of C-peptide, in those with diabetes of $\geq$5 years' duration. Although UCPCR can be used at any stage in diabetes to confirm endogenous insulin levels, in the current study we chose $\geq$5 years' duration in order to avoid misclassifying people with early Type 1 who may have been still producing their own insulin.

## Methods

*Subjects*
Adults with insulin-treated diabetes in 3 UK centres (Exeter, Northampton & Leicestershire) were invited to participate when attending for routine diabetes appointments (in primary and secondary care). 601 white Caucasian and 30 Asian patients with a duration of diabetes ≥5years provided data on age at diagnosis, weight at diagnosis, current age, weight and height, treatment, and time to insulin from diagnosis. BMI at diagnosis and recruitment were calculated where possible; weight at diagnosis for those diagnosed as children converted to the adult equivalent using the UK Child Growth Reference Standards(19).

Participants were asked to collect a urine sample for UCPCR(14) two hours after their largest meal of a day, and return by post for analysis in the Exeter Biochemistry laboratory.

*Classification of Diabetes*
Participants were classified as having Type 1 or Type 2 diabetes using the UK guidelines(4), Figure 1. We developed "gold-standard" criteria:

- 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)(16)
- Type 2 diabetes: if Type 1 diabetes criteria were not met

*Statistical analysis*
Proportions of patients correctly classified by the UK guidelines according to the "gold standard" C-peptide-based definition were calculated, and differences in clinical characteristics between those correctly and incorrectly categorised were explored using the Mann-Whitney test.

Diagnostic performance of continuous variables (age at diagnosis, time to insulin, BMI at diagnosis and recruitment) was assessed using receiver operating characteristic (ROC) curves. Optimal cut-offs for these variables (with maximum specificity and sensitivity for discrimination) were calculated, and we explored whether use of these optimal cut-offs led to improvements in classification over and above the RCGP algorithm using net reclassification improvement(20).

Detailed subgroup analysis could not be carried out on the Asian patients due to small numbers.

Analysis was carried out on Stata version 13.1 and R version 3.1.2.

## Results

We compared the UK clinical classification criteria with "gold-standard" C-peptide-based criteria for defining Type 1 and Type 2 diabetes in this cohort of 601 patients (Figures 2&3). Table 1 shows participant characteristics.

### UK guidelines correctly classify 86% of insulin-treated patients ≥5 years post-diagnosis

514/601 (86%, 95% confidence interval, CI, 83-88%) of patients overall were correctly classified by the UK guidelines when compared with our "gold-standard" criteria: 163/193 (84%, 95% CI 79-89%) with Type 1, and 351/408 (86%, 95% CI 82-89%) with Type 2 (Figure 2). In the Asian group the criteria (taking note of the age cut-off of 30 years for high risk racial groups) performed less well classifying only 21/30(70%) correctly (p=0.02 for comparison with white Caucasians).

### Most misclassifications were in patients classified as having Type 1 diabetes according the UK guidelines

Of patients misclassified by the UK guidelines' clinical criteria in comparison to our C-peptide derived "gold-standard" criteria, the majority, 57/87(66%) were misclassified as having Type 1 diabetes but were still producing substantial endogenous insulin ≥5 years post-diagnosis. 30/87(34%) were misclassified as having Type 2 (but were severely insulin-deficient and had started insulin treatment within 3 years of diagnosis). The majority of misclassifications (8/9) in the Asian group were also cases where the UK guidelines' criteria suggested Type 1 (NB UK guidelines age cut-off 30) but the patients were still producing their own insulin.

### The majority of misclassified patients with Type 1 diabetes were diagnosed aged ≥35 years, and went immediately onto insulin

By UK guidelines these 66 patients had Type 1 diabetes, but 37/66(56%) had a UCPCR >0.2nmol/mmol, and thus by "gold-standard" criteria had Type 2 diabetes.

### Those misclassified as having Type 1 had clinical characteristics consistent with Type 2; those misclassified as having Type 2 had clinical characteristics more consistent with Type 1

Those misclassified as having Type 1 diabetes were older than those correctly classified (median age (IQR) 44 (30-59) vs 20 (11-30), p<0.001), and had a higher BMI at diagnosis (26.4kg/$m^2$ (23-30.3) vs 21.8(18.9-25.4), p=0.002).

In contrast, those who were insulin deficient but were incorrectly classified by the UK guidelines as having Type 2 diabetes, went onto insulin more quickly than those correctly classified as having Type 2 (time to insulin from diagnosis 12 months(2-18) vs 84 months(42-138), p<0.001), had lower BMI (22.5kg/$m^2$

(21.1-26.3) vs 28.1(25.4-33.3), p<0.001), and were younger at diagnosis (44y(35-56) vs 51(43-59), p=0.014).

## Assessment of optimal clinical criteria for differentiating Type 1 and Type 2 diabetes

We used ROC curves (Figure 4) to examine the discriminative ability of key clinical criteria (time to insulin, age at diagnosis, BMI at diagnosis, and BMI at recruitment) and to identify the best cut-offs for classification based on the "gold-standard" criteria. An area under the curve (AUC) equal to 1 represents the perfect discrimination between types of diabetes, and an AUC>0.8 is generally deemed clinically useful.

The most discriminatory individual characteristic (Figure 4) was months from diagnosis to insulin treatment (AUC 0.904, 95% CI 0.88-0.93), with the optimal cut-off at 12 months, classifying 91.5% patients correctly as having Type 1 and 82.1% correctly as Type 2.

Age at diagnosis was also a useful discriminator between Type 1 and Type 2 diabetes (AUC 0.871, 95% CI 0.84-0.9), with the optimal cut-off being ≤39y for Type 1. This correctly classified 81.9% of patients with Type 1 and 84.3% of those with Type 2 diabetes.

BMI at diagnosis gave an AUC of 0.824 (95% CI 0.77-0.87; data available in 359/601(59.7%) patients), with the optimal cut-off being $\leq$23.1kg/m$^2$. However, although this correctly classified 89.4% of those with Type 2 diabetes, it only classified 65.7% patients with Type 1 correctly. BMI at recruitment was less discriminatory again, giving an AUC of 0.715(95% CI 0.67-0.76) and an optimal cut-off of 28.0kg/m$^{2.}$ This correctly classified just 66.8% people with Type 2 diabetes, and 61.8% people with Type 1.

## Modifying the UK guidelines' clinical criteria only results in marginal improvements in accuracy

The UK guidelines use age at diagnosis and time to insulin as the classification criteria for differentiating between Type 1 and 2 diabetes, with 84.5% correctly classified with Type 1, and 86% as Type 2, compared to the gold-standard. On the basis of the ROC curve data, we incorporated the optimal cut-offs for time to insulin (12 months), age at diagnosis (39), BMI at diagnosis (23.1kg/m$^2$) and recruitment (28.0kg/m$^2$) into modified criteria in various combinations, to see if these improved diagnostic accuracy. Aiming for a sensitivity and specificity of >80% (equivalent to an ROC AUC of >0.8), none were superior to the UK guidelines, as improvements in sensitivity led to greater decreases in specificity and vice versa. The best performing alternative was the combination of age cut-off of 39 and time to insulin of 12 months; this improved correct classification of those with Type 2 diabetes to 94%, but reduced to 78.3% those correctly classified with Type 1 diabetes. In general, adding BMI at diagnosis/recruitment improved the proportion of those with Type 2 correctly classified, but markedly reduced the proportion correctly classified with Type 1 diabetes.

## Discussion

### Summary

### The UK guidelines are an accurate method of predicting long-term endogenous insulin production.

Our results show the UK guidelines perform well in correctly classifying those with insulin-treated diabetes based on the development of absolute insulin deficiency, with 86% agreeing with a "gold-standard" based on endogenous insulin levels and time to insulin from diagnosis. This supports their use as a useful pragmatic way of classifying patients. When all patients with diabetes are considered, the performance of the UK guidelines will be even better as the vast majority of patients who are not insulin-treated will be correctly classified as having Type 2 diabetes.

### Patients diagnosed at an older age (≥35 years) with insulin treatment commenced at diagnosis are at the highest risk of being misclassified when using the UK guidelines.

The majority of classification errors occur when using the UK criteria to define Type 1 diabetes in participants diagnosed ≥35 years and on insulin treatment from diagnosis. Clinically, where the subtype of diabetes is unclear, giving insulin from diagnosis is a rational decision to avoid the potential consequences of untreated Type 1 diabetes such as ketoacidosis. This study demonstrates that the majority of these patients are likely to have Type 2 (and therefore may potentially not require insulin), so revisiting the diagnosis following an acute presentation may be worthwhile.

### Time to insulin from diagnosis, and age at diagnosis are the best predictors of long-term endogenous insulin production

In clinical practice, emphasis is often placed on BMI to help in differentiating between Type 1 and Type 2 diabetes. Our data suggests that amongst insulin-treated patients, time to insulin and age at diagnosis are better predictors of diabetes subtype than BMI, with ROC AUCs of 0.904 and 0.871 respectively, and 0.824 for BMI at diagnosis. Median BMI at diagnosis of those with Type 1 by our "gold-standard" criteria was lower than those with Type 2 diabetes - 21.8kg/$m^2$ vs 28.1kg/$m^2$ ($p<0.001$), but the interquartile ranges overlapped (19.8-26.3 and 25.4-32.9kg/$m^2$). By time of recruitment (ie ≥5 years from diagnosis), the difference in BMI between those with Type 1 and 2 was smaller: 26.5kg/$m^2$ (23.1-29.3) vs 29.7 (26.6-34.5), although still significant ($p<0.001$), and the ROC AUC was low (0.715), highlighting the reduced discriminative ability of this as a clinical marker to differentiate between Type 1 and 2 diabetes once on insulin.

### Strengths and limitations

These are the only pragmatic clinical guidelines produced by clinical bodies for the classification of T1D and T2D, and to our knowledge this is the first

assessment of them in comparison to a C-peptide based gold-standard, rather than coding errors (4, 6, 21, 22). We studied insulin-treated patients with a duration of ≥5 years. If considering all patients with diabetes the misclassification rate of 14% is likely to be significantly lower: patients tablet or diet-treated ≥5y from diagnosis are likely to have been correctly diagnosed with Type 2 diabetes. In patients with a diabetes duration of <5y, a few patients with Type 1 may be still producing insulin (the "honeymoon period") and not yet insulin-treated; however it is rare for patients with Type 1 diabetes to be off insulin for prolonged periods.

Due to recruitment locations and difficulty in recruiting Asian patients (23), the majority of our recruited patients were white Caucasian, with only 30 Asian patients studied. We thus cannot comment on these criteria for high prevalence populations and further work is needed in these groups.

We had limited data on BMI at diagnosis (available for 60% participants), which could be improved in future prospective study. Age and gender could be considered in more detail in any future (larger) classification studies. It would be interesting to follow up those identified as misclassified, and those diagnosed with Type 2 and still producing insulin beyond 5 years, to find out if some might be able to withdraw successfully from insulin.

We have concentrated on the two main types of diabetes, but recognise there are alternative subgroups such as genetic forms of diabetes (e.g. MODY). These are rare but also part of the UK guidelines(4), and have their own criteria for diagnosis(24). It is important the clinician takes into account other factors that may indicate these. The term latent autoimmune diabetes in adults (LADA) is sometimes proposed for adults with islet autoantibodies who eventually (up to 12 years) become severely insulin-deficient, but do not require insulin for at least the first 6 months (25-28). However LADA is not included in international guidelines for classification or treatment, and given endogenous insulin status determines treatment requirements, we feel it appropriate to classify according to UCPCR status as per our "gold-standard" criteria.

Our gold-standard criteria used a UCPCR cut-off of 0.2nmol/mmol, which has a sensitivity and specificity of 100% and >95% to detect absolute insulin deficiency (16, 29). It is the best "gold-standard" we have in this context, being practical for use in large numbers of community-dwelling adults. Insulin treatment has the potential to suppress endogenous insulin (30-32), but we have shown this rarely affects diabetes classification (32) – and the small possibility of an over-diagnosis of Type 1 diabetes is a safer direction of error than the opposite.

**Comparisons with existing literature**

Previous reports on "misclassification" of diabetes(4, 6, 21, 22) were mainly based on contraindications in coding rather than on gold standard definitions of insulin deficiency(18, 33, 34).

A recently published systematic review systematically identified diagnostic accuracy studies in the literature which compared clinical criteria with C-peptide cut-offs(7). Age at diagnosis, time to insulin, and BMI are the clinical characteristics most frequently used to classify Type 1 and 2 diabetes, but few studies have addressed clearly which are most strongly associated with long-term C-peptide secretion(7). Where strength of association has been measured, time to insulin and age at diagnosis appear stronger than BMI. Combinations of the former two improve diagnostic accuracy, with BMI adding little(7).

**Implications for clinical practice**

Correct classification of Type 1 or Type 2 diabetes is important so the appropriate treatment and management guidelines are followed(3, 35), to include treatment, education (eg DAFNE for those with Type 1), and monitoring of complications – all of which are based on the presence or absence of endogenous insulin.

The clinical problem facing GPs and other healthcare professionals is that classification can be tricky at diagnosis – and all guidelines, including these UK classification guidelines, rely on information available further down the line (eg time to insulin). The gold-standard classification using UCPCR at/beyond 5 years from diagnosis by definition cannot completely solve this conundrum: UCPCR>0.2nmol/mol <5 years from diagnosis may represent someone with Type 1 diabetes still in the "honeymoon" phase, or someone with Type 2 diabetes. UCPCR <0.2nmol/mmol within 5 years of diagnosis can diagnose Type 1 diabetes however. Studies designed to improve classification at diagnosis, eg by using islet antibodies, are needed to address this problem.

We have shown that the UK guidelines based on time to insulin and age at diagnosis are accurate and pragmatic for classifying patients with diabetes. "Time to insulin" is subject to many influences - physician or patient factors, or guidelines for treatment in a particular area/patient population – but the high rate of correlation of diagnosis with the gold-standard suggests overall timing of insulin initiation may be reasonably consistent. However it is important to revisit the diabetes diagnosis particularly in those diagnosed >35 years of age, given the high rates of misclassification seen in this category of patients. We suggest if there is diagnostic uncertainty, a review of diagnosis is made, specialist advice sought and further investigations (eg C-peptide and islet autoantibodies) be considered.

We did not find that modification of the criteria used or the cut-offs proposed would improve their diagnostic performance. Our study, like others (7), suggest age of diagnosis is a better clinical predictor of Type 1 diabetes than BMI which is often used clinically to determine diabetes subtype in intermediate patients - supporting that more emphasis should be placed on age of diagnosis in uncertain cases. This is perhaps particularly relevant in a time when the average population BMI is ever increasing.

## Conclusion

Our study demonstrates that the UK Practical Classification Guidelines for Diabetes are an accurate means for determining diabetes subtype, with time to insulin and age at diagnosis being the most discriminatory clinical characteristics. Older patients treated with insulin from diagnosis had the highest rate of misclassification (56% classed incorrectly as having Type 1), and further investigation should be considered in this subgroup.

## Funding

This study was funded by NHS Diabetes, with direct funding from the Department of Health, and the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) programme (PB-PG-0711-25111).

ATH is an NIHR and a Wellcome Trust senior investigator. BMS, SVH, ATH, BAK, MS & SK are supported by the NIHR Exeter Clinical Research Facility. NIHR have supported SVH and AGJ through academic clinical fellowships, and AGJ through a doctoral research fellowship and clinical lectureship. RO was supported by Diabetes UK through a doctoral research fellowship.

KK is an NIHR Senior Investigator, and acknowledges support of the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care (CLAHRC) East Midlands. KK is an advisor to the Department of Health National Health Service (NHS) Health Checks Programme.

The views given in this paper do not necessarily represent those of NIHR, the NHS or the Department of Health.

## Competing interests

KK (Chair) and ATH were members of the Department of Health - RCGP – Coding Classification and Diagnosis of Diabetes Steering Group, which produced the RCGP guidelines assessed in this article.

## Acknowledgements

We thank all the study volunteers, staff recruiting patients for this study in Northampton, Leicester and Exeter, the retinal screening teams and local general practitioner practices involved, and all staff at the NIHR Exeter Clinical Research Facility.

## Ethical Approval

This study was approved by the Devon and Torbay research ethics committee, all participants gave written informed consent.

**Figures**

**Figure 1:** UK Practical Classification Guidelines for Diabetes (extract showing classification guidelines for Type 1 and Type 2 diabetes)

**Table 1:** Participant characteristics: median (interquartile range)

**Figure 2:** Classification of type of diabetes according to UK guidelines' clinical criteria compared to "gold-standard" C-peptide-based criteria

**Figure 3:** Proportion of patients classified as Type 1 or Type 2 diabetes according to the UK guidelines (Figures 1 & 2).

Grey bars: proportion whose classification is correct according to the C-peptide–derived "gold standard" definition; black bars: proportion misclassified.
Age diag - age at diagnosis, TTI - time to insulin treatment from diagnosis

**Figure 4:** ROC curve for discriminating between Type 1 and Type 2 diabetes based on the gold standard definition.

Red: time to insulin from diagnosis (AUC=0.904); black: age at diagnosis (AUC=0.871); blue: BMI at diagnosis (AUC=0.824); green: BMI at recruitment (AUC=0.715)

**REFERENCES**


1. NICE. Diabetes in adults (QS6). http://guidance.nice.org.uk/QS62011.
2. NICE. Type 1 diabetes: Diagnosis and management of type 1 diabetes in children, young people and adults. 2004.
3. NICE. Type 2 diabetes: The management of type 2 diabetes. 2009.
4. RCGP. Coding, Classification and Diagnosis of Diabetes. A review of the coding, classification and diagnosis of diabetes in primary care in England with recommendations for improvement. NHS England, 2011.
5. Farmer A, Fox R. Diagnosis, classification, and treatment of diabetes. BMJ. 2011;342:d3319.
6. Stone MA, Camosso-Stefinovic J, Wilkinson J, de Lusignan S, Hattersley AT, Khunti K. Incorrect and incomplete coding and classification of diabetes: a systematic review. Diabet Med. 2010;27(5):491-7.
7. Shields BM, Peters JL, Cooper C, Lowe J, Knight BA, Powell RJ, et al. Can clinical features be used to differentiate type 1 from type 2 diabetes? A systematic review of the literature. BMJ Open. 2015;5(11).
8. IDF W. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. 2006.
9. American Diabetes A. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2008;31 Suppl 1:S55-60.
10. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. JAMA. 2003;289(17):2254-64.
11. American Diabetes A. Standards of medical care in diabetes--2013. Diabetes Care. 2013;36 Suppl 1:S11-66.
12. Yki-Jarvinen H. Combination therapies with insulin in type 2 diabetes. Diabetes Care. 2001;24(4):758-67.
13. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012;35(6):1364-79.
14. McDonald T, Knight B, Shields B, Bowman P, Salzmann M, Hattersley A. Stability and reproducibility of a single-sample urinary C-Peptide/Creatinine ratio and its correlation with 24-h Urinary C-Peptide. Clin Chem. 2009;55(11):2035 - 9.
15. Bowman P, McDonald TJ, Shields BM, Knight BA, Hattersley AT. Validation of a single-sample urinary C-peptide creatinine ratio as a reproducible alternative to serum C-peptide in patients with Type 2 diabetes. Diabet Med. 2012;29(1):90-3.
16. Besser R, Ludvigsson J, Jones A, McDonald T, Shields B, Knight B, et al. 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. 2011;34(3):607 - 9.
17. Jones A, Besser R, McDonald T, Shields B, Hope S, Bowman P, et al. Urine C-peptide creatinine ratio (UCPCR) is an alternative to stimulated serum C-peptide measurement in late onset insulin treated diabetes. Diabet Med. 2011;28(9):1034 - 8.

18. Palmer JP, Fleming GA, Greenbaum CJ, Herold KC, Jansa LD, Kolb H, et al. C-peptide is the appropriate outcome measure for type 1 diabetes clinical trials to preserve beta-cell function: report of an ADA workshop, 21-22 October 2001. Diabetes. 2004;53(1):250-64.
19. Freeman JV, Cole TJ, Chinn S, Jones PR, White EM, Preece MA. Cross sectional stature and weight reference curves for the UK, 1990. Arch Dis Child. 1995;73(1):17-24.
20. Pencina MJ, D' Agostino RB, D' Agostino RB, Vasan RS. Evaluating the added predictive ability of a new marker: From area under the ROC curve to reclassification and beyond. Stat Med. 2008;27(2):157-72.
21. Rhodes ET, Laffel LMB, Gonzalez TV, Ludwig DS. Accuracy of Administrative Coding for Type 2 Diabetes in Children, Adolescents, and Young Adults. Diabetes Care. 2007;30(1):141-3.
22. De Lusignan S, Khunti K, Belsey J, Hattersley A, Van Vlymen J, Gallagher H, et al. A method of identifying and correcting miscoding, misclassification and misdiagnosis in diabetes: a pilot and validation study of routinely collected data. Diabet Med. 2010;27(2):203-9.
23. Khunti K KSBJ. Diabetes UK and South Asian Health Foundation recommendations on diabetes research priorities for British South Asians. 2009.
24. Ellard S, Bellanné-Chantelot C, Hattersley AT. Best practice guidelines for the molecular genetic diagnosis of maturity-onset diabetes of the young. Diabetologia. 2008;51(4):546-53.
25. Tuomi T, Groop LC, Zimmet PZ, Rowley MJ, Knowles W, Mackay IR. Antibodies to glutamic acid decarboxylase reveal latent autoimmune diabetes mellitus in adults with a non-insulin-dependent onset of disease. Diabetes. 1993;42(2):359-62.
26. Zimmet PZ, Tuomi T, Mackay IR, Rowley MJ, Knowles W, Cohen M, et al. Latent autoimmune diabetes mellitus in adults (LADA): the role of antibodies to glutamic acid decarboxylase in diagnosis and prediction of insulin dependency. Diabet Med. 1994;11(3):299-303.
27. Groop LC, Bottazzo GF, Doniach D. Islet Cell Antibodies Identify Latent Type I Diabetes in Patients Aged 35–75 Years at Diagnosis. Diabetes. 1986;35(2):237-41.
28. Stenström G, Gottsäter A, Bakhtadze E, Berger B, Sundkvist G. Latent Autoimmune Diabetes in Adults: Definition, Prevalence, β-Cell Function, and Treatment. Diabetes. 2005;54(suppl 2):S68-S72.
29. Jones AG, Besser RE, McDonald TJ, Shields BM, Hope SV, Bowman P, et al. Urine C-peptide creatinine ratio is an alternative to stimulated serum C-peptide measurement in late-onset, insulin-treated diabetes. Diabet Med. 2011;28(9):1034-8.
30. Lindstrom T, Arnqvist HJ, Ludvigsson J, von Schenck HH. C-peptide profiles in patients with non-insulin-dependent diabetes mellitus before and during insulin treatment. Acta Endocrinol. 1992;126(6):477-83.
31. Albareda M, Rigla M, Rodríguez-Espinosa J, Caballero A, Chico A, Cabezas R, et al. Influence of exogenous insulin on C-peptide levels in subjects with type 2 diabetes. Diabetes Res Clin Pract. 2005;68(3):202-6.
32. Besser REJ, Jones AG, McDonald TJ, Shields BM, Knight BA, Hattersley AT. The impact of insulin administration during the mixed meal tolerance test. Diabet Med. 2012;29(10):1279-84.

33. Service FJ, Rizza RA, Zimmerman BR, Dyck PJ, O'Brien PC, Melton LJ. The Classification of Diabetes by Clinical and C-Peptide Criteria: A prospective population-based study. Diabetes Care. 1997;20(2):198-201.
34. B. Berger GS, G. Sundkvist. Random C-peptide in the classification of diabetes. Scand J Clin Lab Invest. 2000;60(8):687-93.
35. NICE. CG15 Type 1 diabetes in adults: full guideline 2008.