Institution: University of Exeter		
Unit of Assessment: UoA 1 Clinical Medicine		
Title of case study: C-peptide testing improves the diagnosis and treatment of people with insulin-treated diabetes.		
Period when the underpinning research was undertaken: 2010-2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Dr Tim McDonald	NIHR Clinical Scientist (Associate Professor) and Consultant Clinical Scientist	2009 to date
Dr Angus Jones	NIHR Clinician Scientist (Associate Professor) and Consultant Physician	2011 to date
Professor Andrew Hattersley	Professor of Molecular Medicine & Consultant Physician	1995 to date
Period when the claimed impact occurred: 1 August 2013 – 31 July 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Exeter researchers have developed, refined and validated simple, non-invasive, reproducible and robust clinical laboratory measures of the amount of insulin made naturally by patients and determined their clinical utility. Prior to this research insulin secretion was rarely measured as part of clinical care of patients with diabetes. These inexpensive (~£10) C-peptide tests are now **offered by seven NHS specialist clinical laboratories across the UK** with over 8,000 tests in 2019 in the Exeter lab alone. **National and International guidelines,** recommend the Exeter developed C-peptide test. NHS Scotland have adopted the measures under a centrally funded national testing policy and routinely test every person diagnosed with type 1 diabetes (>30,000 people). This has led to 6-12% of people with insulin treated diabetes being reclassified, with many being able to **change treatment and stop insulin injections**, by showing that a previous diagnosis of type 1 diabetes was incorrect. Correct diagnosis leads to improvements in glucose control, which is associated with significant reductions in diabetes related complications.

2. Underpinning research

The research led by Dr McDonald and Dr Jones has pioneered national efforts to define the best way to measure insulin secretion in routine diabetes care. With funding from NIHR, Diabetes UK, JDRF and the Health Innovation Challenge fund (>£2.5m), the group has published 36 papers on this subject since 2010 and contributed to international clinical guidelines for use of this test in diabetes classification and treatment.

The amount of insulin that a person with diabetes produces indicates the type of diabetes they have and defines treatment requirements. Patients with type 1 diabetes develop severe insulin deficiency, whereas those with type 2 or genetic types of diabetes do not. When insulin is produced from the proinsulin molecule an equal amount of byproduct called C-peptide is secreted. C-peptide can therefore be used to measure how much insulin a person makes, even if they are treated with insulin injections. Prior to this research, biochemical testing of C-peptide required the patient to fast overnight, omit short acting insulin (frequently resulting in severe post-test hyperglycaemia), attend a clinic for a specific meal followed by giving a blood sample and careful sample storage and handling (including transport on ice), making uptake of the test limited.

2.1. Defining how to measure endogenous insulin for routine clinical care
Exeter researchers have shown that C-peptide can be reliably measured in urine and that it correlates well with blood measures **[3.1, 3.2]**. The team further identified that the widely available preservative boric acid stabilised the test to enable measurement of C-peptide from a posted urine sample, opening up this test to be used by general physicians remote from specialist laboratories **[3.1]**.

They have also shown that by using ethylene diamine tetra acetic acid (EDTA – routinely used for many common blood tests), contrary to received wisdom, blood C-peptide is stable for more than 24 hours making blood C-peptide accessible to primary care and outpatient clinics.

The Exeter team have generated the evidence that a simple non-fasting blood or urine sample is as diagnostically robust as a formal 'mixed meal tolerance test' at identifying clinically important levels of endogenous insulin secretion. This finding removes the need for an expensive and time consuming (more than 3 hours) formal stimulation test. They have also shown that a patient's short acting insulin does not need to be omitted to perform a C-peptide test, making it more convenient for the patient and clinician.

This evidence together removed crucial barriers to implementation that had previously blocked widespread adoption of this test in routine clinical care.

2.2. Using C-peptide to determine the optimum treatment for a person with diabetes
Type 1 and type 2 diabetes have completely different treatment guidelines. These differences relate almost entirely to differences in endogenous insulin secretion: those with Type 1 develop severe insulin deficiency, whereas those with type 2 diabetes maintain substantial insulin secretion. Insulin secretion is also maintained in most monogenic types of diabetes which have very specific treatment. Misdiagnosis is common: 6-12% of people with insulin treated diabetes are misclassified, and most people with monogenic types of diabetes are misdiagnosed as type 1 diabetes. In the past, insulin secretion has not been measured to confirm diagnosis and appropriate treatment.

The Exeter team have shown how urine and blood C-peptide can be used to robustly identify the correct diabetes type and so the optimal treatment, monitoring and follow-up care, as well as risk to family members. They have shown that C-peptide can be used as a cheap (~£10) and convenient test to identify children and young adults who will benefit from a genetic test (~£650) to confirm a diagnosis of monogenetic diabetes **[3.3]**. This strategy reduces inappropriate genetic testing, improves diagnosis and reduces NHS costs. This has been assessed prospectively in the whole of the South West of England as part of the UNITED project **[3.4]**. They have shown widespread misdiagnosis of type 1 and type 2 diabetes, particularly in older adults, and that measuring endogenous insulin secretion using C-peptide in longstanding diabetes is the definitive test of diabetes type **[3.5, 3.6]**.

2.3. Predicting treatment response and hypoglycemia
Clinical studies carried out by the Exeter team have shown that C-peptide is an important predictor of how well an individual patient responds to specific diabetes drugs. For example, the C-peptide test can identify individuals who would not benefit from treatment with an expensive therapeutic known as a glucagon-like peptide-1 receptor agonist (GLP-1RA) **[3.5]**.

Similarly, they have demonstrated that low C-peptide measured on a pragmatic random sample is associated with markedly increased glucose variability and hypoglycaemia in patients with insulin-treated type 2 diabetes and represents a practical, stable and inexpensive biomarker for assessment of hypoglycaemia risk **[3.6]**.

3. References to the research

3.1. McDonald, T.J., Knight, B.A., Shields, B.M., Bowman, P., Salzmann, M.B. & **Hattersley, A.T**. (2009) Stability and reproducibility of a single-sample urinary C-peptide/creatinine ratio and its correlation with 24-h urinary C-peptide. *Clinical Chemistry* 55(11), 2035-9. DOI: 10.1373/clinchem.2009.129312

3.2. Besser, R.E., Ludvigsson, J., **Jones, A.G.**, **McDonald, T.J.**, Shields, B.M., Knight, B.A. **& Hattersley, A.T.** (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. DOI: 10.2337/dc10-2114

3.3. Besser, R.E., Shepherd, M.H., **McDonald, T.J.**, Shields, B.M., Knight, B.A., Ellard, S. & **Hattersley, A.T.** (2011) Urinary C-peptide creatinine ratio is a practical outpatient tool for identifying hepatocyte nuclear factor 1-{alpha}/hepatocyte nuclear factor 4-{alpha} maturity-onset diabetes of the young from long-duration type 1 diabetes. *Diabetes Care* 34(2), 286-91. DOI: 10.2337/dc10-1293

3.4. Shields, B.M., Shepherd, M., Hudson, M., **McDonald, T.J.**, Colclough, K., Peters, J., Knight, B.A., Hyde, C.J., Ellard, S., Pearson, E.R., **Hattersley, A.T.** & UNITED study team (2017) Population-Based Assessment of a Biomarker-Based Screening Pathway to Aid Diagnosis of Monogenic Diabetes in Young-Onset Patients. *Diabetes Care* 40(8), 1017-25. DOI: 10.2337/dc17-0224

3.5. Jones, A.G., **McDonald, T.J.**, Shields, B.M., Hill, A.V., Hyde, C.J., Knight, B.A., **Hattersley, A.T.** & PRIBA Study Group (2016) Markers of beta-Cell Failure Predict Poor Glycemic Response to GLP-1 Receptor Agonist Therapy in Type 2 Diabetes. *Diabetes Care* 39(2), 250-7. DOI: 10.2337/dc15-0258

3.6. Hope, S.V., Knight, B.A., Shields, B.M., Hill, A.V., Choudhary, P., Strain, W.D., **McDonald, T.J.** & **Jones, A.G**. (2018) Random non-fasting C-peptide testing can identify patients with insulin-treated type 2 diabetes at high risk of hypoglycaemia. *Diabetologia* 61(1), 66-74. DOI: 10.1007/s00125-017-4449-2

4. Details of the impact

4.1. A new diagnostic technology has been adopted in the UK to measure how much insulin patients are making themselves

Prior to the research outlined above, C-peptide was rarely measured as part of the clinical care of patients with diabetes, with use confined to investigation of unexplained hypoglycaemia (low blood glucose) in patients without diabetes. The Exeter team's research has changed this completely. Most diabetes teams in the UK now use this test to help classification and treatment of patients, and many perform the test in all patients with insulin-treated diabetes.

The novel urine c-peptide creatinine ratio (UCPCR) test is now widely available and testing services are offered by seven NHS specialist clinical laboratories across the UK **[5.1]**. The Blood Sciences laboratory at the Royal Devon and Exeter NHS Foundation Trust alone received over 8,000 NHS referrals for this test in 2019 and has received samples from over 120 hospitals and laboratories in the UK and Ireland. Many other hospital laboratories also use the UCPCR test, including the University of Rochester Medical Centre in New York **[5.2]**. The test is also now used as a practical measure of insulin secretion in research outside Exeter, with at least 18 papers reporting its use in the past 6 years **[5.3]**.

4.2. Changed national and international diabetes policy and guidelines

National and international guidelines now advocate C-peptide testing as a result of the research from the Exeter group; including from the UK National Institute for Health and Care Excellence (NICE) **[5.4]**; the Association of British Clinical Diabetologists **[5.5]**; and the International Society of Pediatric and Adolescent Diabetes **[5.6]**. NHS National Services

Scotland has recently commissioned routine C-peptide testing of everyone diagnosed with type 1 diabetes in Scotland, representing more than 30,000 patients, commencing in February 2021 **[5.7]**.
Professor Strachan, who led the application for national commissioning of C-peptide testing in Scotland, said **[5.7]:** "*It is in no way an exaggeration to say that the Exeter research completely informed the design of our C-peptide testing program in Edinburgh and that it would have been impossible for us to introduce such a program and the forthcoming national program in Scotland without the Exeter data*."

4.3. Quality of life for people with diabetes has been enhanced through improved diabetes classification and treatment

Between 6-12% of people with insulin-treated diabetes are reclassified following a C-peptide test, and most of them subsequently receive a different treatment. In those previously thought to have type 1 diabetes, a high C-peptide after 3 years duration will confirm either type 2 diabetes (if over 35 years old) or, in younger patients, mean a high likelihood of monogenic diabetes.

In type 2 diabetes adding oral agents to insulin greatly improves glucose control in comparison to insulin alone (reducing risk of diabetes complications), and many patients can stop insulin which has substantial quality of life and cost benefits. Most patients with adolescent or adult onset monogenic diabetes (called MODY) can replace insulin with specific inexpensive tablet therapy and substantially improve glucose levels with large cost savings to the NHS: universal C-peptide testing as part of a strategy to identify MODY has been shown to be cost effective **[5.8]**.

The experience of Edinburgh Royal Infirmary demonstrates the impact of C-peptide testing on patients, as described in the statement from a Consultant Diabetologist **[5.7].** By offering testing to all those diagnosed with type 1 diabetes in a single clinic, 58 people previously diagnosed and treated as having type 1 diabetes were reclassified: 14 of these patients actually had monogenic diabetes, and 44 had type 2 diabetes. Thirteen of these patients, who were previously thought to have a lifelong requirement for insulin injections, were able to discontinue insulin and the associated glucose monitoring, and instead use inexpensive tablet therapies. This included young patients who were receiving pump therapy, at a cost of over £3000 per year; and a patient receiving continuous glucose monitoring, which cost about £2000 per year. The money saved by switching the treatment of just one of these patients has covered the entire cost of the C-peptide screening program at the infirmary.

Other patients who added tablets to their insulin therapy as a result of reclassification markedly improved their glucose control, measured by HbA1c, which reduced by 15mmol/mol. Improved glucose control is associated with substantial reductions in diabetes related complications, for example in the UKPDS study (Stratton et.al. BMJ 2000) an 11mmol/mol lower HbA1c was associated with reductions of 37%, 14% and 21% in microvascular complications, myocardial infarction and diabetes related death respectively. Other hospitals have reported similar outcomes, for example selective UCPCR testing in 80 patients at the Surrey and Sussex Healthcare Trust led to 42 patients being reclassified, with 31 changing treatment **[5.9].**

5. Sources to corroborate the impact

5.1. AssayFinder is a free service for laboratories registering as assay providers, and for anyone trying to find an assay. Many laboratories registered with AssayFinder offer this test in the UK using blood or urine (UCPCR) samples. Available at https://bit.ly/39f6zZX.

5.2. Examples of hospitals using the Exeter developed Urine C-peptide Creatinine Ratio (UCPCR) protocol:

- University of Rochester Medical Centre, New York https://bit.ly/3d9H0Lf
- North Bristol NHS Trust https://bit.ly/3tTmJA4
- Gloucestershire Hospitals NHS Trust https://bit.ly/3tThfW5
- Royal Cornwall Hospitals Trust https://bit.ly/3vZ2Nxt
- University Hospitals Birmingham https://bit.ly/3f9zORT
- Royal Berkshire NHS Trust https://bit.ly/3rtv4Jr
- Leeds Teaching Hospitals NHS Trust https://bit.ly/3slbvnv

5.3. Examples of research articles by non-Exeter research teams that use the Urine C-peptide Creatinine Ratio (UCPCR) protocol.

5.4 NICE guidelines. Diabetes (type 1 and type 2) in children and young people: diagnosis and management (2015). Available at https://web.archive.org/web/20201217122119/https://www.nice.org.uk/guidance/ng18

5.5. Association of British Clinical Diabetologists. Standards of Care for Type 1 Diabetes (2020) Available at https://web.archive.org/web/20201217122256/https://abcd.care/resource/standards-care-management-adults-type-1-diabetes-2020

5.6. International Society of Paediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines 2018: The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatric Diabetes* 19 (Suppl. 27), 47–63. DOI:10.1111/pedi.12772

5.7. Letter of testimony from Consultant Diabetologist, Edinburgh Royal Infirmary.

5.8. Peters, J.L., Anderson, R., Shields, B., King, S., Hudson, M., Shepherd, M., McDonald, T.J., Pearson, E., Hattersley, A. & Hyde, A. (2020) Strategies to identify individuals with monogenic diabetes: results of an economic evaluation. *BMJ Open* 10, e034716. DOI: 10.1136/bmjopen-2019-034716

5.9. Outcomes of UCPCR testing in the Surrey and Sussex Healthcare NHS Trust diabetes service (conference abstract and presentation). Available at https://www.easd.org/virtualmeeting/home.html#!resources/the-diagnostic-utility-of-urinary-c-peptide-creatinine-ratio-ucpcr-insights-from-a-review-of-the-local-use-of-ucpcr-in-the-diabetes-clinic