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Real world evidence supports waking salivary cortisone as a screening test for adrenal insufficiency

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Abstract

Objective: Worldwide, adults and children are at risk of adrenal insufficiency largely due to infectious diseases and adrenal suppression from use of anti-inflammatory glucocorticoids. Home waking salivary cortisone is an accurate screening test for adrenal insufficiency, it has potential to reduce costs, and patients prefer it to the adrenocorticotropin (ACTH) (synacthen) stimulation test. We carried out a service evaluation of home waking salivary cortisone in clinical care to identify implementation barriers.

Design, Patients and Measurements: Service evaluation in a centre where 212 patients referred for adrenal insufficiency had a waking salivary cortisone. Problems encountered during testing were recorded and patient feedback, via focus groups, collected.

Results: From all patients providing a waking salivary cortisone 55% had a normal test, 23% adrenal suppression, and 22% an equivocal result requiring a clinical centre ACTH stimulation test. The median (interquartile range [IQR]) for the time of the saliva sample was 07:40 (07:00–08:40). The median (IQR) days between collection and (i) delivery to local laboratory was 1 (0.25–2) day; (ii) reporting by local laboratory was 13 (11–18) days. Patients considered the test is “easy to do” and preferred it to the inpatient ACTH stimulation test. The principal challenge to clinical implementation was results reporting to clinicians due to delays at the local laboratory.

Conclusions: This service evaluation provides real-world evidence that home waking salivary cortisone is an effective, practical screening test for adrenal insufficiency. It identified key barriers to testing implementation that need to be addressed when introducing the test to a health service.

KEYWORDS

ACTH stimulation test, adrenal insufficiency, focus group, salivary cortisone, screening

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1 | INTRODUCTION

Adrenal insufficiency, or cortisol deficiency, is a life-threatening condition which can be primary (adrenal), secondary (pituitary) and tertiary (mainly adrenal suppression secondary to glucocorticoids or opioids). Prevalence is rising due to the increased prescription of glucocorticoid and opioid therapies that suppress adrenal function.¹⁻⁴ The standard tests for adrenal insufficiency are a morning serum cortisol and/or the Adrenocorticotropic (ACTH) stimulation test (AST), also called the short synacthen test.^{5,6} It is estimated that 90,000 ASTs are performed a year in the United Kingdom. The AST and serum cortisol require patients to attend a clinical centre and undergo venesection and the administration of synacthen (cosyntropin). The AST is classed as an inpatient admission with an associated inpatient tariff and waiting times associated with scheduling the AST can result in delayed diagnosis.⁷ It has recently been shown in a diagnostic accuracy study that home waking salivary cortisone is an accurate screening test for adrenal insufficiency.⁸ The test is simple to perform and, as salivary cortisone is stable at room temperature, it may be carried out at home and then sent by post to the laboratory, making testing easier for the patient, and reducing health care costs.^{7,9} The diagnostic accuracy study showed that home waking salivary cortisone predicted the serum cortisol response to synacthen in the AST and if home waking salivary cortisone were used to screen patients, it would have obviated the need for an AST in 70% of patients.⁸

Bridging the gap between research and the clinic is important but not simple and it may take years to convince stakeholders and clinicians to change their clinical practise.¹⁰ A new test should be introduced with robust supporting evidence, and barriers to implementation need to be sought and addressed. Multifaceted interventions targeting change in behaviour or single interventions such as audit and feedback are effective in helping change clinical practice.¹¹ A suitable approach is to evaluate research results locally and then use and action these in everyday clinical management.^{12,13} We have introduced home waking salivary cortisone into our clinical practice and have undertaken a service evaluation to confirm the results of our diagnostic accuracy study and to identify barriers to implementation of home waking salivary cortisone across a health service.

2 | METHODS

2.1 | Study design and procedures

This was a service evaluation to assess the use of waking salivary cortisone as a screening test for adrenal insufficiency at the Endocrine Unit and was approved and registered by The Sheffield Teaching Hospitals National Health Service (NHS) Foundation Trust, United Kingdom, as an Institutional Case Notes review (Registration Number 10195). The study evaluated data collected over 6 weeks between the 1 September 2022 and the 20 October 2022. All

patients referred to be assessed for the presence of any type of adrenal insufficiency were sent a Sarstedt Salivette by post immediately on referral, together with a self-addressed stamped envelope and instructions on how to carry out the test. All patients were adults ≥ 16 years old. Patients on exogenous glucocorticoids were asked to omit glucocorticoids the evening before and on the day of the test until after the saliva test was collected. Patients on oral glucocorticoids were only assessed for adrenal insufficiency if on physiological doses of hydrocortisone (≤ 25 mg/day) or prednisolone (≤ 5 mg/day) and patients on higher doses were not considered for testing. Waking was defined as the moment one gets out of bed to commence the day before cleaning teeth and having anything to eat or drink. Patients recorded the time and date the salivary sample was taken. Any patients needing an urgent result within a week, in view of reporting delays, had an AST.

Patients providing inadequate samples (needs at least 50 μ L for assay and not blood stained) or samples arriving more than 3 days after collection (delayed) were invited for AST. Patients not sending the samples were then followed up and invited for AST. For those who sent contaminated samples, identified when salivary cortisol was higher than salivary cortisone usually secondary to hydrocortisone residue or blood, it was left to the clinician's discretion whether to accept the waking salivary cortisone result (when not reflecting cortisone levels influenced by hydrocortisone administration), repeat the sample or carry out an AST. The samples were sent to the local laboratory at Sheffield Teaching Hospitals where they were recorded and were then sent via courier to the central laboratory, Wythenshawe Hospital, Manchester, where they were analysed and then reported to Sheffield where they were reported to the clinician on the electronic system in Sheffield. The time taken from collection to delivery at the local laboratory and to the reporting of the results after analysis at the central laboratory was also recorded. Cortisone levels in saliva were measured by liquid chromatography with tandem mass spectrometry (LC-MS/MS).⁸

Any difficulties encountered with the collection of samples, their analysis, the interpretation of data, and reporting of results were recorded.

To make a comparison with current standard management of referrals, for assessment of adrenal status, we carried out a case review measuring the time between new referral to date of nonurgent AST report between 1 September 2019 and 20 October 2019. This period was chosen to reflect the same time period as the service evaluation but before the COVID pandemic to mitigate any pandemic-related effects on the endocrine or laboratory services.

2.2 | Patients and focus groups

Patients attending the Endocrine Unit were invited to participate in a focus group discussion that was approved by the South Yorkshire and Humber Research Ethics Committee (Reference 19/YH/0333). Potential participants from a range of backgrounds (e.g., age, sex, and ethnicity) tested for adrenal insufficiency using waking salivary

cortisone were approached. Potential participants were contacted by telephone by a member of the clinical team, who explained why they had been contacted and gave a brief description of the purpose of the focus group. Participants who expressed an interest in taking part were then emailed the focus group patient information sheet (PIS) and asked to confirm by return email participation after reading the PIS. A Microsoft Teams joining link was then sent to them via email. The meeting was recorded, and a transcript generated using the option available in Microsoft Teams, and summative notes were taken throughout. This was made clear to the participants at the start of the focus group.

The aims were to discuss:

- Patient acceptability of testing at home versus in hospital.
- The ease of the salivary test compared with the AST.
- Recommendations on how the salivary test could be rolled out into routine practice (including views on how results of the salivary test could be reported to patients).
- Recommendations and guidance for the introduction of the salivary test into routine practice.
- The degree to which adoption of the technology and its clinical findings reflected those of the diagnostic accuracy study.

2.3 | Outcome measures

As part of the evaluation, we recorded patient demographic data, the outcomes of waking saliva cortisone interpretation, the number of samples that were inadequate, not returned, or delayed return, or contaminated. The timings between collection of samples and: (i) arrival at Sheffield Teaching Hospitals local laboratory; (ii) reporting of result on electronic system after analysed by central laboratory in Manchester were reported. The samples were evaluated by consultant endocrinologists using the following predefined protocol:

- Patients with waking saliva cortisone <7 nmol/L were diagnosed as having adrenal insufficiency.
- Patients with levels ≥ 17 nmol/L were diagnosed as not having adrenal insufficiency.
- Patients with levels between 7 and 16.9 nmol/L, were considered equivocal and were invited for an AST.
- An AST 30-min cortisol of >430 nmol/L on Roche Elecsys Cortisol II assay was considered a normal test.⁸

M. D. provided support with any difficulties encountered by nonexperienced consultants when interpreting the results.

2.4 | Statistical methods

The baseline demographic and clinic characteristics of the participants were collected. For the noncontinuous variables median and interquartile range (IQR) are presented. For the categorical variables,

the number and percentage of participants in each of the categories and the total number of observations are presented.

3 | RESULTS

3.1 | Demographic data

Over 6 weeks 265 patients were referred to be assessed for the presence of adrenal insufficiency by eight endocrinology consultants and 212 patients were assessed using a waking salivary cortisone as a first-line screening test (Figure 1). Seventy-three were men and median (IQR) age was 52 (39–67) years. Thirty-six percent of patients were assessed for steroid-induced adrenal insufficiency. Reasons for the assessment can be found in Table 1.

3.2 | Waking saliva cortisone outcomes

Out of 212 patients, 45 (21%) had an equivocal result. Forty-seven (22%) patients were diagnosed with new onset or persistent adrenal insufficiency and 112 (53%) patients were diagnosed as not suffering from adrenal insufficiency (Figure 2). Eight patients (4%) had inadequate or delayed samples. The median (IQR) was 1.8 nmol/L (0.5–5.2), 12.1 nmol/L (8.9–14.6) and 28.6 nmol/L (22.7–36.7) for the adrenal insufficiency, equivocal and normal groups, respectively. From the 45 patients with an equivocal result 38 had an AST and 50% passed the test.

Based on the results of the waking salivary cortisone collected over 6 weeks, 22/77 patients being assessed for steroid-induced adrenal suppression were given a regime to wean off steroids completely with advice to continue following steroid sick day rules for 6–12 months. For 37/77 patients no change was necessary, and 13/77 patients were advised to wean down to a lower dose of steroids. Four patients on intermittent steroids had a normal test and one patient not on oral steroids was started on hydrocortisone. From the postadrenalectomy patients, 2/6 patients were weaned off hydrocortisone completely and 3/6 had their dose reduced. None of these patients suffered an adrenal crisis following cessation of steroids. Patients were followed up for at least 6 months after the service evaluation.

3.3 | Sample processing

The median (IQR) time of sample on waking was 07:40 (07:00–08:40). The median (IQR) time between waking saliva collection and: (i) samples delivered at Sheffield Teaching Hospitals laboratory was 1 day (0.25–2); (ii) for reporting by the local laboratory after analysis at the Central Laboratory in Manchester was 13 days (11–18).

Twenty-one patients had contaminated samples, 15 of which were with hydrocortisone; these were then followed by an AST or repeat sample in 15 patients while in six patients the saliva cortisone could be interpreted.

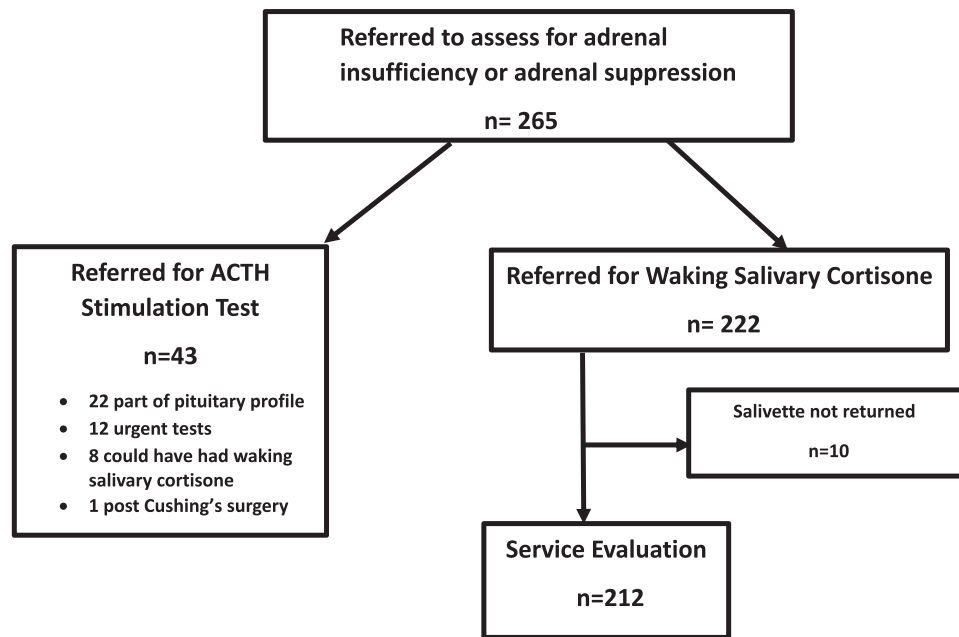


FIGURE 1 Consort flow chart indicating the total number of patients referred to the Endocrine Unit between 1 September 2022 to 20 October 2022 to confirm or exclude adrenal suppression.

TABLE 1 Baseline demographics of patients referred to the Endocrine Unit between 1 September 2022 and 20 October 2022 who provided a waking salivary cortisone to diagnose/confirm or exclude adrenal suppression.

Variable	Value
<i>n</i>	212
Age (years; median [IQR])	52 (39–67)
Sex	139F; 73M
Testing reason	
– Steroid-induced adrenal insufficiency	77 (36%)
– Symptoms (not on steroids)	54 (25%)
– Pituitary (tumours/radiotherapy)	65 (31%)
– Opioids	2 (0.9%)
– Postadrenalectomy	6 (2.8%)
– Immunotherapy	5 (2.4%)
– No cause	3 (1.4%)
Time of sample (median; IQR)	07:40 (07:00–08:40)
Days between collection and reporting from local lab (median; IQR)	13 (11–18)
Days between collection and delivery to local lab (median; IQR)	1 (0.25–2)

Abbreviation: IQR, interquartile range.

Three samples were delayed and had to be discarded. Five samples were inadequate. Ten salivary samples were not returned and only one patient responded to follow up. One patient needing an urgent AST did not respond and two patients with equivocal waking

saliva cortisone did not respond to an invitation for AST testing. No kits were lost in the post.

For time comparison from referral to test reporting we looked at a time period before the pandemic and before we introduced salivary testing. The median (range) time between referral and reporting of the AST from 1 September 2019 to 20 October 2019 was 21 (9–76) days; *n* = 13.

3.4 | Clinical barrier

One out of eight endocrinologists initially found difficulty with results interpretation and the use of recommended cut-offs. Towards the end of the 6-week evaluation no other queries were raised.

3.5 | Patient focus groups

The focus group was conducted with nine patients who had done the waking saliva test and an AST test and lasted 1 h 47 min. Six participants identified as female and three as male, and they ranged in age from 42 to 67 years. Seven of these individuals were White British, 1 was Black African-Caribbean, and 1 was from another White background.

3.5.1 | Positive findings

Participants found the waking salivary test to be easy to perform at home. The written instructions were useful and easy to follow, even for nonnative English speakers. They believed the test saved the NHS

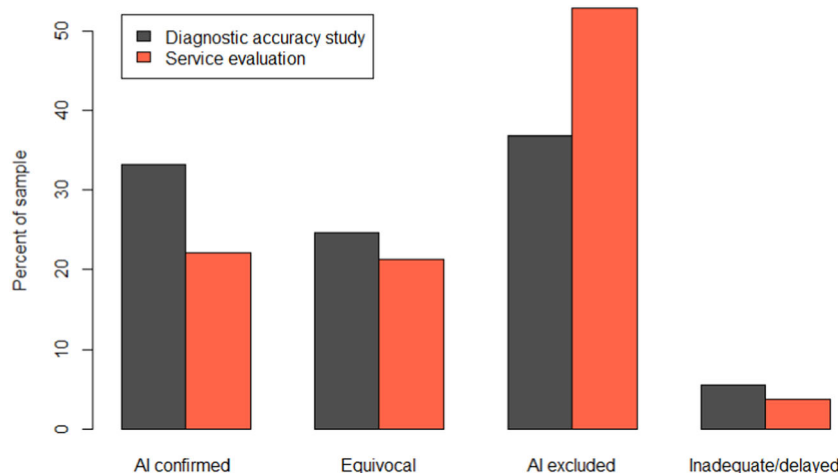


FIGURE 2 Bar chart comparing the prevalence of adrenal suppression using waking salivary cortisone in the diagnostic accuracy study and the service evaluation. The bars show the prevalence of adrenal insufficiency (waking salivary cortisone <7 nmol/L), equivocal tests (waking salivary cortisone between 7 and 16.9 nmol/L) and patients with adrenal insufficiency excluded (waking salivary cortisone ≥ 17 nmol/L), comparing the diagnostic accuracy study and the service evaluation [χ^2 testing ($\chi^2(2) = 11.39$, $p = .003$)]. In the service evaluation, all patients referred with a potential diagnosis of adrenal insufficiency were assessed, whereas in the diagnostic accuracy study, only patients with a high risk for adrenal suppression were assessed. The number of inadequate or delayed samples in both studies are also shown to be very similar. [Color figure can be viewed at wileyonlinelibrary.com]

time and money, reduced travel and, therefore, has environmental and financial benefits and reduces stress due to not having to have any needles. The reduced number of tests conducted in hospital would free up appointment slots reducing waiting times for patients and allow health care professionals to deliver other areas of specialist care.

3.5.2 | Negative findings

The cotton swab was large, which made it uncomfortable and unpleasant to chew. Some people may find it difficult to produce enough saliva for the test, for example, those with conditions that result in dry membranes. They raised concern that by staying at home patients would not develop a relationship with the endocrine clinical team; regular users of the Endocrine Unit enjoy the experience of attending the unit and having contact with professionals.

3.5.3 | Suggestions

The focus group patients suggested that one should attempt to improve the taste of the plain cotton swab by making it peppermint flavour to aid palatability. They believed a link to a video with instructions might be useful for people who have difficulty reading English or more visual learners; this could be part of a 'testing kit' including the salivette, written instructions and a video link demonstrating how to carry out the test and steroid sick day rule advise for those diagnosed with adrenal suppression. The patients suggested a range of methods for receiving the home testing kit

including by post, collection from the Endocrine Unit (or other relevant department) at the hospital, their GP, or local pharmacy if the test was available on prescription. All participants agreed that posting their samples in a return envelope is easy to do, dropping them off at their local GP surgery was an alternative suggestion. The participants agreed that a quick phone call with the results would be ideal, but that they were also happy to receive emails. They did however note that not everyone has access to a smartphone or computer, in which case a letter sent by traditional mail would be suitable.

4 | DISCUSSION

We have performed a service evaluation of home waking salivary cortisone following its introduction as a screening test for adrenal insufficiency in clinical care. In a diagnostic accuracy study, we had shown that waking salivary cortisone is an accurate predictor of the 30-min cortisol post-ACTH stimulation and established that a cut-off value of ≥ 17 nmol/L excluded adrenal insufficiency with a sensitivity of 97% and a value <7 nmol/L confirmed adrenal insufficiency with a specificity of 97%. By using these criteria, one obviated the need for an ACTH stimulation test in 70% of patients.⁸ In this service evaluation the results replicated the diagnostic accuracy study with 75% of patients not requiring an ACTH stimulation test (Figure 2).

The time from referral to adrenal function testing is significantly reduced using waking salivary cortisone as the test kit can be sent out immediately and only took 1 day for the sample to be delivered to the local laboratory after collection. This is faster compared to the time from referral to carry out a nonurgent AST in a clinical centre of

around 21 days, increasing to 76 days during busy periods. Delayed diagnosis of adrenal insufficiency is frequent, with some patients diagnosed only at an acute hospital admission and, therefore, at risk of adrenal crisis.¹⁴ The home saliva test, therefore, potentially reduces this risk if analysed and reported in a timely manner after sample delivery.

There were more patients diagnosed with adrenal insufficiency in the diagnostic accuracy study compared to the service evaluation, 33% versus 22% (Figure 2).⁸ The reason for this is that the population in the service evaluation included all patients referred with potential adrenal insufficiency as opposed to only high-risk patients included in the diagnostic accuracy study. The number of inadequate samples in this service evaluation was similar to that in the diagnostic accuracy study with more contaminated samples. The patients in clinical care included in the service evaluation had no video link to instructions on how to do the test and written recommendations were less detailed and this could explain the more contaminated samples but in general problems related to testing were similar. This suggests that as the clinical protocol was like the study protocol, the latter can be implemented in clinical care. Focus group feedback was positive with patients preferring home waking salivary cortisone to the AST. Patients believed the test reduces health care costs and enhances patient benefit by reducing travel to clinical centres, the stress of attending a hospital and reduces the environmental burden.

One of the major inconveniences we faced was the time between sample collection and result reporting by the local laboratory after analysis at a central laboratory. At our Clinical Chemistry department, we do not have the facility to measure saliva cortisone and cortisol by LC-MS/MS and therefore samples were sent to an external laboratory to be analysed. Analysis and reporting by the central laboratory were not the cause for delay, but rather that the local laboratory required the sample to be sent to them for registration rather than straight to the central laboratory and then sent by courier on a once weekly basis. This needs to be addressed as it results in delay in diagnosis as well as additional cost of transferring to the central laboratory. This is an issue in the health service that needs to be resolved as point of care and home testing becomes more available with central laboratories. The turnaround to receive a result from when the sample is received in the central laboratory was only 48 h. The central laboratory used by our centre at Wythenshawe Hospital, University Hospital of South Manchester is well placed to deal with samples from external sources. The laboratory acts as a reference site for over 100 hospitals in the United Kingdom and 10 hospitals in the Republic of Ireland. Thus, if samples were sent directly from the patient to the central laboratory and reported direct to clinicians, time from referral to results could be 3 days. There are six labs in total in the sample exchange scheme of UKNEQAS measuring cortisol/cortisone and another 20 labs capable of measuring salivary cortisone in the United Kingdom. There are another 36 labs measuring steroids in northern Europe/Scandinavia using LC-MS/MS, four of these are already measuring salivary cortisone.

Low- and middle-income countries (LMIC) with areas distant to central laboratories may also benefit from being able to send the salivary samples by post. The need for noninvasive, simple-to-use

diagnostics is particularly pertinent in the developing world, where many diseases remain poorly defined and may receive insufficient treatment. Basic diagnostic tests like serum cortisol, ACTH and AST are not available in some LMIC.¹⁵ Often, little information about the burden of disease is available to guide government/population health decisions and in this respect waking salivary cortisone may have the greatest impact in communities that presently do not receive adequate laboratory or other health services. The use of LC-MS/MS to measure saliva cortisol and cortisone eliminates problems due to cross-reactivity and allows the separate reporting of both salivary cortisol and cortisone and also identifies when the patient's sample is contaminated by hydrocortisone.^{16–18} LC-MS/MS is not currently used to measure steroids in most LMIC; however, with the increased access to and adoption of remote and tele-health systems post-Covid then the waking salivary cortisone offers a viable alternative to the AST in LMIC as the salivary sample can be sent to a central laboratory by routine post in these countries. Salivary cortisone is stable in room temperature for at least 72 h and at 4°C for a week and withstands repeated freeze-thaw cycles.⁹ In clinical centres where salivettes are not available passive drool can be used as there is no difference in glucocorticoids measured.⁹

The issue of contaminated samples is important. The number of contaminated samples was minimal but one should be vigilant to identify these. In health, the saliva cortisone level is six times higher than saliva cortisol. Higher saliva cortisol than cortisone levels are a sign of a contaminated sample usually with hydrocortisone tablet residues in the mouth if the patient has not omitted the hydrocortisone as recommended on the evening and morning before the test.¹⁶ The advantage is that one can identify patients who have not omitted their tablets; this is also important as saliva cortisone levels will also rise, reflecting higher serum cortisol levels posthydrocortisone administration, and will confound the test result. Blood in the mouth will also result in higher saliva cortisol levels as serum cortisol is around four times higher than serum cortisone.¹⁶ Advice to avoid brushing teeth an hour before sampling is necessary. Contaminated samples should be repeated or followed up with an ACTH stimulation test unless the clinician is confident the salivary cortisone can be interpreted. The number of contaminated samples was higher in the service evaluation than in the study, 10% versus 5%, where patients were well supported. The minimal difference highlights the importance of clear instructions and education when patients are asked to do saliva tests in clinical care.

A problem highlighted during this clinical study was the difficulty for one doctor to interpret the saliva test results as they had no previous experience with the test. This signifies the need for health care worker education on the rationale for the test and provision of instructions on how to perform and interpret the results.

Limitations of the evaluation are that the study was carried out over a short 6-week period mainly to assess the collection, sampling, and reporting process of waking salivary cortisone results and to establish barriers to implementing the test in clinical practise. One salivary sample was measured to assess for adrenal insufficiency.

In a feasibility study moderate reproducibility of a waking salivary cortisone sample (mean coefficient of variation [CV%] 17.1%) was shown but more formal and larger studies are necessary to assess this. The reproducibility was much better than that of salivary cortisol (mean CV% 31.9%).¹⁹ The study was undertaken in the same hospital as the diagnostic accuracy study, and now needs to be extended to assess generalisability; however, the study evaluated all nonurgent patients needing a waking saliva cortisone eliminating any recruitment bias and showed that the study protocol could be adopted in routine clinical practice and was preferred by patients to the AST. Our focus groups do give us important feedback about the use and implementation of this test in clinical care but one must take into consideration that this was a small number of people and it is hard to know to what extent this represents the views of all users.

The results from this study indicate that waking salivary cortisone is a suitable screening test that can be used in clinical care especially if information technology processes are modified to allow direct posting of the sample to a central laboratory with prompt reporting at the local laboratory. The use of the test is supported by world experts in the area.²⁰ Future studies are needed to evaluate the implementation of the test across multiple hospitals, together with an assessment of the costs and effects of this novel diagnostic pathway.

AUTHOR CONTRIBUTIONS

Miguel Debono and Richard Ross analysed the data and conceptualised the analyses. Miguel Debono wrote the first version of the manuscript. Miguel Debono collected the data. Sharon Caunt and Jane Fearnside collected patient feedback from focus groups. Brian Keevil analysed the samples and provided the results. Jen Lewis carried out statistical analysis. Charlotte Elder and Simon Dixon helped with conceptualising the analyses. Miguel Debono, Jen Lewis, Richard Ross and Sharon Caunt have accessed and verified the data and Miguel Debono and Richard Ross were responsible for the decision to submit the manuscript.

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CONFLICT OF INTEREST STATEMENT

R. R. was a director of Diurnal Limited. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The deidentified individual participant data that underlie the results reported in this Article can be obtained from the corresponding author (miguel.debono@nhs.net) upon reasonable request.

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REFERENCES

1. Broersen LHA, Pereira AM, Jørgensen JOL, Dekkers OM. Adrenal insufficiency in corticosteroids use: systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2015;100(6):2171-2180. doi:10.1210/jc.2015-1218
2. Chalitsios CV, Shaw DE, McKeever TM. A retrospective database study of oral corticosteroid and bisphosphonate prescribing patterns in England. *NPJ Prim Care Respir Med.* 2020;30(1):5. doi:10.1038/s41533-020-0162-6
3. Li T, Cunningham JL, Gilliam WP, Loukianova L, Donegan DM, Bancos I. Prevalence of opioid-induced adrenal insufficiency in patients taking chronic opioids. *J Clin Endocrinol Metab.* 2020;105(10):e3766-e3775. doi:10.1210/clinem/dgaa499
4. Macfarlane GJ, Beasley M, Jones GT, Stannard C. The epidemiology of regular opioid use and its association with mortality: prospective cohort study of 466 486 UK biobank participants. *EClinicalMedicine.* 2020;21:100321. doi:10.1016/j.eclinm.2020.100321
5. Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. *Lancet Diabetes Endocrinol.* 2015;3(3):216-226. doi:10.1016/S2213-8587(14)70142-1
6. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2016;101(2):364-389. doi:10.1210/jc.2015-1710
7. Nalla AA, Thomsen G, Knudsen GM, Frokjaer VG. The effect of storage conditions on salivary cortisol concentrations using an enzyme immunoassay. *Scand J Clin Lab Invest.* 2015;75(1):92-95. doi:10.3109/00365513.2014.985252
8. Debono M, Elder CJ, Lewis J, et al. Home waking salivary cortisone to screen for adrenal insufficiency. *NEJM Evid.* 2023;2(2):EVI-2):EVIDoA2200182. doi:10.1056/EVIDoA2200182
9. Tonge JJ, Keevil BG, Craig JN, Whitaker MJ, Ross RJ, Elder CJ. Salivary steroid collection in children under conditions replicating home sampling. *J Clin Endocrinol Metab.* 2022;107(11):3128-3136. doi:10.1210/clinem/dgac419
10. Boaz A, Baeza J, Fraser A, European Implementation Score Collaborative Group (EIS). Effective implementation of research into practice: an overview of systematic reviews of the health literature. *BMC Res Notes.* 2011;4:212. doi:10.1186/1756-0500-4-212
11. Squires JE, Sullivan K, Eccles MP, Worswick J, Grimshaw JM. Are multifaceted interventions more effective than single-component interventions in changing health-care professionals' behaviours? an overview of systematic reviews. *Implement Sci.* 2014;9:152. doi:10.1186/s13012-014-0152-6
12. Parker LE, de Pillis E, Altschuler A, Rubenstein LV, Meredith LS. Balancing participation and expertise: a comparison of locally and centrally managed health care quality improvement within primary care practices. *Qual Health Res.* 2007;17(9):1268-1279. doi:10.1177/1049732307307447
13. Kristensen N, Nymann C, Konradsen H. Implementing research results in clinical practice—the experiences of healthcare professionals. *BMC Health Serv Res.* 2016;16:48. doi:10.1186/s12913-016-1292-y
14. Erichsen MM, Løvås K, Skinningsrud B, et al. Clinical, immunological, and genetic features of autoimmune primary adrenal insufficiency:

- observations from a Norwegian registry. *J Clin Endocrinol Metab.* 2009;94(12):4882-4890. doi:10.1210/jc.2009-1368
15. Mofokeng TRP, Beshyah SA, Mahomed F, Ndlovu KCZ, Ross IL. Significant barriers to diagnosis and management of adrenal insufficiency in Africa. *Endocr Connect.* 2020;9(5):445-456. doi:10.1530/EC-20-0129
 16. Debono M, Harrison RF, Whitaker MJ, et al. Salivary cortisone reflects cortisol exposure under physiological conditions and after hydrocortisone. *J Clin Endocrinol Metab.* 2016;101(4):1469-1477. doi:10.1210/jc.2015-3694
 17. Raff H, Phillips JM. Bedtime salivary cortisol and cortisone by LC-MS/MS in healthy adult subjects: evaluation of sampling time. *J Endocr Soc.* 2019;3(8):1631-1640. doi:10.1210/js.2019-00186
 18. Raff H. Measurement of salivary cortisone to assess the adequacy of hydrocortisone replacement. *J Clin Endocrinol Metab.* 2016;101(4):1350-1352. doi:10.1210/jc.2016-1228
 19. Sørensen SO, Pedersen J, Rasmussen MG, Kristensen PL, Grøntved A. Feasibility of home-based sampling of salivary cortisol and cortisone in healthy adults. *BMC Res Notes.* 2021;14(1):406. doi:10.1186/s13104-021-05820-4
 20. Raff H, Zhang CD. A new approach—home waking salivary cortisone to screen for adrenal insufficiency. *NEJM Evid.* 2023;2(2):EVIDe2200306. doi:10.1056/EVIDe2200306

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