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Rapid Evidence Synthesis: Healthy.io

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Rapid Evidence Synthesis:

Rapid Evidence Syntheses (RES) are produced by the National Institute for Health and Care Research (NIHR) Applied Research Collaboration Greater Manchester (ARC-GM). The methods used are based on a framework set out in Norman et al. 2022 and previously registered on the Open Science Framework (OSF).[a,b]

RES use evidence synthesis approaches and draw on the GRADE Evidence to Decision framework[3] to provide rapid assessments of the existing evidence and its relevance to specific decision problems. In the first instance they focus on evidence from guidance and existing evidence syntheses. They are undertaken in a real-time context of decision-making around adoption of innovative health technologies and are designed to provide a "good-enough" answer to inform decision problems in a short timescale. RES methods are flexible and adaptive. They have evolved in response to user feedback and differ depending on the nature of the assessment undertaken.

RES are not intended to serve as a substitute for a systematic review or rapid review of evidence.

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We welcome feedback and are particularly interested to hear how you have used this Rapid Evidence Synthesis.

Please send any queries or comments to:

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This work was undertaken by the National Institute for Health Research (NIHR) Applied Research Collaboration Greater Manchester (ARC-GM). The views expressed are those of the author and not necessarily those of the NIHR or the Department of Health and Social Care.

[a] Norman, G. Rapid evidence synthesis to support health system decision making. *OSF registration*. 2020 [cited 2023]; Available from: osf.io/hsxk5

[b] Norman, G., et al., Rapid Evidence Synthesis To Enable Innovation And Adoption in Health and Social Care. *Systematic Reviews*, 2022. 11: p. 250. https://doi.org/10.1186/s13643-022-02106-z

[3] Alonso-Coello, P., et al., GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ,* 2016. 353: p. i2016.

1. Summary

There is directly relevant evidence from uncontrolled studies in people with diabetes without an up-to-date test showing variable uptake and completion and high acceptability of Healthy.io among people who complete screening.

There were high rates of non-participation due to digital exclusion. Evidence on the impact on health outcomes and clear data on test accuracy are lacking and lack of a control group limits the conclusions that can be drawn.

There is some indirectly relevant randomised evidence that a different smartphone-based home testing intervention may increase screening uptake in unselected people with hypertension.

1.1 Nice MedTech briefing

A NICE MedTech briefing on Healthy.io is based on an uncontrolled study in people with diabetes. An additional uncontrolled study was subsequently undertaken. NICE concluded that Healthy.io can help improve compliance with ACR testing and that most people prefer home testing. Key uncertainties were lack of long-term follow-up data evaluating its effect on kidney and cardiovascular outcomes. NICE also identified concerns around access for people who experience digital exclusion and people with some disabilities.

1.2 Sensitivity and specificity

The sensitivity and specificity of Healthy.io were not reported. Data supplied to the United States FDA indicated that the test showed substantial equivalence to standard semiquantitative ACR testing. The economic model used data for sensitivity (87%) and specificity (88%) taken from a reliable but non-recent (2014) systematic review of semiquantitative ACR tests in people with diabetes. Another reliable 2014 systematic review of point-of-care semiquantitative ACR testing in relevant primary care or outpatient populations found mean sensitivity of 76% and specificity of 93% but very high variation between tests, especially for sensitivity, and recommended that semiquantitative point-of-care testing not be used to rule out albuminuria.

1.3 Effects of using Healthy.io

There are no randomised or nonrandomised controlled studies of Healthy.io. Two uncontrolled studies reported data on adherence and acceptability. Neither study reported data on clinical outcomes for participants and it is not possible to draw conclusions about impact on these. The proportion of people contacted who completed screening was 23% in the published study. The most common reason given for declining participation was not having a smartphone. 90% responding reported finding the test easy to use. Because there is no control group the impact of the intervention on testing adherence is uncertain

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There is no evidence for the impact relative to alternative and, in particular non-digital, interventions. Both studies were undertaken in Northern England and are directly relevant to people with diabetes and no up-to-date test in Greater Manchester, but participants were younger than the eligible population and participation may be lower among people from areas of higher deprivation.

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An economic model was developed and is clearly described. Data on health outcomes, including end stage renal disease which drives the model, are taken from the published literature not the studies of Healthy.io. The findings of lifetime cost savings (-£2,008) are partially driven by the younger age of participants and are reduced when population mean ages are used. The assumption that people not receiving the Healthy.io intervention would continue to have zero screening uptake was not supported by study data.

1.4 Similar interventions

There is a well-conducted randomised controlled trial of a similar intervention Dip.io undertaken in a population of 500 unselected people with hypertension in the U.S. This found that the intervention combined with reminders and options for centre-based testing increased the proportion of people completing screening (29% compared with 18% in the control group) but the impact on cases detected was less clear. Patient satisfaction and expressed preference for the intervention were high. The study did not report clinical outcomes for participants. This is low certainty evidence because of imprecision and because it is indirectly relevant; it evaluates a different intervention and trial participants may differ in age, diagnostic criteria, baseline likelihood of completing screening, and deprivation indices, compared with people with hypertension in the UK.

1.5 Care and management of people identified as having CKD

There are clear recommendations from NICE for the care and management of people identified as having CKD.

2. Methods

2.1 Description of the intervention

The intervention consists of a urine analysis kit for semiquantitative albumin-creatinine ratio (ACR) testing which is sent to a person's home address and a smart-phone app *healthy.io* which is used to complete the test. Test results are then available to healthcare providers. The intervention is intended to be used in Greater Manchester for people considered at risk of developing chronic kidney disease (CKD) who are invited to annual health checks which include urine analysis for CKD, but who do not have a completed urine analysis within the previous 12 months. In the first instance it will be used for people with diabetes and hypertension in this group. Annual urine analysis using ACR testing is recommended by NICE in these populations.(1) People who are identified as "positive" by the test are invited for repeat testing using quantitative methods; if the finding is confirmed they may receive appropriate treatment and advice.

2.2 Search

We searched Medline OVID and the Cochrane Library (including CENTRAL and the Cochrane Database of Systematic Reviews. We used searches based on the following facets: point-of-care testing or home testing; kidney or renal disease or function; albuminuria or proteinuria or albumin or creatinine or ACR. We did not use terms related to diabetes or hypertension as we wished to identify evidence relating to all populations eligible for screening in the UK. We also searched the NICE website and the website of the sponsor. Searches were conducted in March 2023. We used citation checking and forward citation searching from identified studies and documents. We drew on published and unpublished studies provided by the sponsor.

2.3 Key Questions

Question 1. What is the evidence for the sensitivity and specificity of the Healthy.io home urine ACR analysis in identifying people who have clinical CKD in a population considered high risk for developing CKD? The "gold standard" was standard practice-based urine analysis.

Question 2. What is the evidence for the effect of testing using Healthy.io home urine ACR analysis on health outcomes for people considered high risk for developing CKD? There is currently no core outcome set for CKD which does not require transplant so we included clinical outcomes reported by study authors. Laboratory outcomes and proportion of target population screened were secondary outcomes.

Question 3. What is the evidence on the sensitivity and specificity of using any home urine analysis kit for people at risk of CKD? This included any tests used to identify potential CKD. The "gold standard" was standard practice-based urine analysis.

Question 4. What is the evidence for the effect of testing using any home urine analysis kit on health outcomes for people considered high risk for developing CKD? We included clinical outcomes reported by study authors. Laboratory outcomes and proportion of target population screened were secondary outcomes.

Question 5. What is the evidence for the effectiveness and safety of treatment for people identified through urine analysis as having CKD?

2.4 Inclusion criteria

2.4.1 Population

People considered to be at high risk of developing CKD because they have diabetes or hypertension (we planned that we might also consider evidence for people considered at high risk for other reasons).

2.4.2 Intervention

Ffor Q1 and Q2 the intervention is the healthy.io app used to analyse urine for ACR. For Q3 the intervention is any home urine analysis kit used to identify potential CKD. For Q4 we considered any home based urine testing for identification of CKD. For Q5 we considered any interventions.

2.4.3 Comparator

The relevant comparator is care as usual or no intervention. We would also consider comparisons with other interventions to increase screening uptake.

2.4.4 Outcomes

For Q1 and Q3 outcomes are measures of diagnostic accuracy: sensitivity and specificity; diagnostic odds ratio and 2x2 data which enables the calculation of these. For Q2, Q4 and Q5 we accepted all clinical outcomes reported and considered laboratory outcomes and screening uptake measures as secondary outcomes. We also reported patient acceptability data.

2.2.5. Study designs

We considered the most robust evidence appropriate to each question. In the first instance we looked for existing evidence syntheses. Where necessary we considered primary studies with the most rigorous designs for the questions addressed. For Q1 and Q3 the most robust designs for primary studies would have been diagnostic accuracy studies. For Q2 and Q4 these would have been randomised controlled trials (RCTs) of “test and treat approaches” and for Q5 RCTs of interventions. Where necessary we considered relevant studies with less rigorous designs.

3. Results

3.1 Evidence directly relevant to Healthy.io (questions 1 & 2)

NICE published a MedTech innovation briefing on the Healthy.io test in August 2020.(2) This considered the available evidence including any ongoing studies and was based on a systematic literature search and a submission from the sponsor. The briefing included the evidence from the Modality study (see below).(3) Their searches also identified an abstract reporting feasibility and acceptability of use of Healthy.io in pregnant women, which they did not consider to be a directly relevant population,(4) and an RCT of a different smartphone app for urine analysis.(5) They identified two ongoing studies at the time of their assessment, one in Barking in London and one in Breda in the Netherlands. The references for these are those used by NICE.(6, 7)

NICE considered the equality implications of the technology and stated that:

"The ACR product is only available to people who have access to and can use a smartphone device. The company states that the app is compatible with a wide range of smartphones. The ACR product may be unsuitable for people with visual or cognitive impairment, problems with manual dexterity or learning disabilities. The company states that the app uses a combination of spoken word, text, and video set at a reading age of 9 years."

NICE considered the level of innovation, the potential patient impact and the potential system impact by consulting with experts. While they considered that there were potential benefits to both patients and the healthcare system, they expressed concerns around the accessibility of the technology, the cost of the technology, and, in particular, the lack of evidence around diagnostic accuracy for the technology. The concerns around accessibility and costs were also expressed by patient organisations as were the potential benefits in terms of increased options for some groups of patients.

Based on the evidence considered NICE concluded that Healthy.io can help improve compliance with ACR testing and that most people prefer home testing. They identified key uncertainties as the lack of long-term follow-up data evaluating its effect on kidney and cardiovascular outcomes.

3.1.1 Sensitivity and specificity of Healthy.io (question 1)

We did not identify diagnostic accuracy studies relating to Healthy.io. NICE found no published evidence on the sensitivity and specificity of the test.(2) However the company supplied evidence to the American FDA which was collected during regulatory approval which showed substantial equivalence to standard semiquantitative testing.(8)

The model developed using the data from the Modality study took estimates from the published literature on semiquantitative testing, rather than from data relating specifically to the Healthy.io test. This was based on a sensitivity of 87% and specificity of 88% identified in a 2014 meta-analysis of 12 studies,(9) and the equivalence of healthy.io to standard semiquantitative testing.(8) The model assumed that a positive (abnormal) result on the Healthy.io test would lead to patients receiving a quantitative test, for which the sensitivity and specificity were 96% and 98%.

The economic models based on the studies below used data on the % of positive tests predicted or found, together with the estimated sensitivity and specificity from the literature. The Modality study used a figure of 20% based on prevalence data and assumed sensitivity and specificity data.

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3.1.2 Evidence for effects of testing using Healthy.io (question 2)

The evidence discussed here was supplied by the sponsor; one study is a published peer reviewed paper(3) and the other is in a report prepared by an independent consultancy.(10) Both are evaluations based on a single group without a control or comparator group and both were undertaken in the last five years in Northern England. There are no outcome data beyond the proportion of people who returned a test result. Clinical outcome data in these studies are extrapolated from other data sources. We did not identify any additional studies of the intervention. One of these studies was included in the NICE briefing,(3) one has been conducted subsequently.(10)

text relating to the report from the independent consultancy has been removed because it contains confidential information we do not have permission to publish

Modality evaluation (Hull and Airedale) and model development:
A single arm clinical evaluation (Modality evaluation) of the intervention was conducted in Hull and Airedale in Northern England, in people who had not undergone screening in previous 18 months.(3) This was the evidence base for the NICE MedTech briefing.(2) Population demographics were not reported but in Hull 16.1% of residents identified as Black, Asian or Minority Ethnic (BAME) group, which includes white, but non-British, residents. This compares to 26.5% of people nationally.(11) Hull was the fourth most deprived local authority out of 317 in 2019.(12)

2,196 people were contacted, of whom 695 (32%) people agreed to be tested and 499 (23% of the total contacted) completed and retuned the test.(3) While 72% of those who agreed to be tested completed testing these comprise only 23% of those initially contacted, due to the high rate of non-response or declining of invitation for screening. The main reason given for declining screening was not owning a smartphone. The percentage of people agreeing to screening is substantially lower than seen in an RCT of a similar intervention, where 71% agreed to participate (see below Q4).(5) Of those who completed screening 92% found the test easy to use and "a majority" preferred it to testing at a GP surgery.

A cost effectiveness analysis was carried out using data from this evaluation and reported in the same publication.(3) The economic evaluation was carried out by an independent consultancy but was funded by Health.io who produce the app used in the testing. This economic evaluation used data from various sources (Diabetes UK, Health Survey for England 2009/2010, and a long-term study of diabetes complications epidemiology(13)) to populate the model with numbers of people at each point. Costs for administration and treatments were also derived from the published literature (references are given in the paper) and adjusted to 2017/2018 prices. NICE noted that the cost of the testing was £11.00 in this study which was less than the cost of £12.10 at the time of their assessment in 2020 (the cost of standard testing was £6 at this time).(2) The authors document the

sources of the assumptions and inputs to the model appropriately and these appear to be based on reasonable sources in most cases.

The authors conducted a number of sensitivity analyses to test the impact of their assumptions and inputted values, including the sensitivity and specificity of the test itself. The primary outcome was incidence of end stage renal disease (ESRD), and cost savings are driven by cases of this assumed to be avoided by earlier diagnosis. All outcome data were modelled based on evidence from other sources. The results of any follow-up begun as a result of positive tests were not reported and were not used to inform the model. One year, five year, ten year and lifetime horizons were used. The base case model found an incremental cost saving of -£2,008 per patient over a lifetime.

Model assumptions included 0% compliance with testing in a usual care arm (compared to 72% in the intervention arm) which would appear to be non-conservative: lack of a test in the previous 18 months will not necessarily or even usually mean lack of a test *ever*. Furthermore the authors themselves note data which suggests that this may not be a reliable assumption with 11% of people approached by this study declining participation *because they had already booked a test* and evidence of increased compliance with standard care in the control arm of an RCT of a related intervention.(5) Sensitivity analyses based on this did not change the direction of model results but it did substantially reduce the cost savings over a lifetime horizon this from -£2,008 to -£655. The model also appears to assume that adherence in the first year is replicated in subsequent years, which may not be conservative.

The authors noted that the age of people using the intervention was a key driver of their finding of cost-effectiveness. Younger people have a greater potential benefit of being diagnosed with CKD and accessing treatment because they have more remaining life years on average and thus a greater potential gain in QALY. The average starting age of people entering the model was 54. Since the prevalence of diabetes increases with age – it is 9.0% for people aged 45 to 54 but rises to 23.8% for people aged 75 or older.(14) This would suggest that the people included in the Modality evaluation – and hence in the economic model – may be disproportionately young relative to the age profile of people with diabetes eligible for screening. The mean age of unscreened patients nationally is noted as 61 years. This means that the incremental cost saving would be reduced if participation were more representative of the eligible population.

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Note on demographics

Data on participation demographics and reasons for declining suggest that these evaluations could usefully have also considered alternative approaches to increasing screening in people without a recent test, such as practice-based outreach, given the low rates of acceptance in the Modality study and the high numbers declining due to digital exclusion in both evaluations. The authors of the Leeds study note that the proportion of people being tested has declined since the removal in 2014 of the test from the Quality Outcomes Framework, which incentivised practices to undertake testing; data reported by Diabetes UK in 2018 indicated a decline from over 75% of people with type 2 diabetes to 65% in 2018; figures for people with Type 1 diabetes fell from over 56% to 50%.(16)

There is evidence that groups who already experience disadvantage and poorer health outcomes also experience digital exclusion; this impacts older people, those living in rural areas and those living in areas of high deprivation. (17) There may be potential implications for equity of access to care in

directing resources to interventions such as Healthy.io if resources are not also directed to approaches to increasing screening uptake which are not subject to the same barriers to access. As NICE noted there may also be access implications for people with some forms of disability.(2)

The cost savings of using Healthy.io may depend substantially on its uptake being disproportionately concentrated among younger people in the eligible populations. The model developed here relates to people with diabetes. It is therefore directly only relevant to this group of people and will be indirectly relevant to people eligible for CKD screening due to other health conditions.

3.2 Evidence indirectly relevant to Healthy.io (questions 3 & 4)

3.2.1 Sensitivity and specificity of home urine analysis kits (question 3)

We did not identify evidence from systematic reviews relating to the diagnostic accuracy of home urine analysis for ACR testing.

A 2014 systematic review (search date 2012) included 12 diagnostic accuracy studies of ACR for random urine samples from patients with diabetes.(9) The pooled estimates from this review are the source of the sensitivity (87%) and specificity (88%) estimates used in the models in the healthy.io studies above. This assessed ACR testing in general rather than home testing or point-of-care testing. The search was not extensive in terms of databases included but review methods, where reported, were rigorous and included appropriate assessment of study quality which was assessed as satisfactory overall. The results of this review are probably reliable although it is now over ten years since the search was conducted. It may be indirectly relevant to point-of-care testing.

We identified a second 2014 systematic review (search date 2013) which included sixteen diagnostic accuracy studies of semiquantitative or quantitative point-of-care tests using random urine samples collected in primary or outpatient care from patient groups relevant to this RES.(19) Machine-read point-of-care tests were compared to laboratory measurement. The review used methods designed to reduce bias and error at all stages of the review process and the quality assessment of included studies found none to be at high risk of bias. For semiquantitative tests the sensitivity estimate was 76% (95% CI 63% to 86%) and specificity was 93% (95% CI 84% to 97%). There was a high level of variation in results across different semiquantitative tests especially for sensitivity which ranged from 18% to 93%; specificity ranged from 60% to 100%. Quantitative tests had higher sensitivity and specificity at 96% (95% CI 78% to 99%) and 98% (95% CI 93% to 99%) respectively. The authors concluded semiquantitative point-of-care ACR tests should not be used to rule out albuminuria.

We identified three other systematic reviews which focused on point-of-care testing in different settings and populations but none of these included studies of urine ACR testing.(20, 21, 22) Because of the lack of directly relevant up-to-date evidence synthesis we looked for primary studies evaluating the sensitivity and specificity of point-of-care testing. We identified one study which may be particularly relevant.(23) This cross-sectional study evaluated the performance of the Hipee S2 point-of-care test urine dipstick analyser for semiquantitative ACR testing in a population of 1,603 people who were either inpatients, outpatients, or undergoing a health check-up at hospitals in China. This analyser can be connected to smartphones although there is no indication that smartphones were used in this study. The population evaluated is broader than that being considered here, where the incidence of albuminuria may be higher. The test showed sensitivity of

between 87.2% and 90.7% and specificity of between 70.7% and 78.4% when compared to the results of quantitative testing. These figures are broadly comparable to those from other studies published since the identified systematic reviews. (24, 25, 26, 27)

3.2.2 Evidence for effects of testing using home urine analysis kits (question 4)

There is an RCT of a similar intervention (Dip.io) which enrolled 999 people with hypertension in an integrated health system of 55 primary care clinics in a rural area of the US state of Pennsylvania.(5) The evidence from this trial is only directly relevant to people with hypertension and is indirectly relevant to the intervention assessed, as noted in the NICE briefing.(2) Hypertension is an indication for screening in the UK as well as the US. The mean age of the trial participants was 50.5 years and the mean blood pressure measurements were systolic 139.8 and diastolic 86.2 mmHg. This means that only some of the participants would meet the NICE criteria for hypertension of 140/90 mmHg. As the proportion of people with hypertension increases with age, rising to around 75% in people aged over 70), the trial participants may also be younger than the population of people with clinical hypertension in the UK. Enrolment of a population within a US insurance-based system may also mean that the population differs from a UK population when measures of deprivation are considered. This intervention was not targeted; there was no requirement that participants not have an up-to-date test and both those who routinely attended screening and those who did not were eligible.

All participants were sent a postal reminder to complete screening and documentation for the urine test as well as a booklet about the importance of screening. Participants were randomised to no further intervention (care as usual) or to the smartphone-based home testing. The smartphone urine-analysis kit was Dip.io. The trial is evaluating a combined intervention of reminders with options to complete screening at home or at an outpatient lab rather than home screening alone.

Of the 499 people randomised to the intervention, 75 completed screening out an outpatient lab and 97 consented for home testing of which 69 completed the test. 144/499 people in the intervention arm completed screening compared with 90/500 in the control group. The odds ratio (OR) for completing screening was 1.85 (95% CI 1.37-2.49). Detection of albuminuria was comparable between the arms, with four patients in each arm (although more people were tested in the intervention arm), and for those with an exploratory outcome of trace protein was not clearly different (OR 1.52, 95% CI 0.88 to 2.61). Satisfaction was high with 98% rating the intervention as easy to use and 89% preferring home testing. The reporting of trial methods was brief but did not raise concerns about methodology. The trial did not evaluate the health outcomes of people in the trial so does not provide any information about the impact of offering home testing on clinical outcomes.

3.3 Effectiveness and safety of treatment for people identified through urine analysis as having CKD (question 5)

There are clear recommendations from NICE for the care and management of people identified as having CKD.(1) These include recommendations for information and education, risk assessments and referral criteria, pharmaceutical interventions and identifying and managing additional complications of CKD such as anaemia.

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