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ORIGINAL ARTICLE

How do laboratory specialists advise clinicians concerning the use and interpretation of renal tests?

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Abstract

Background. The aim of this study was to elucidate how laboratory specialists advise clinicians concerning renal parameters and to compare their advice with guideline recommendations. ***Methods.*** A questionnaire was distributed to laboratory specialists in Norway and The Netherlands together with two case histories from a primary health-care setting and one from a hospital setting, simulating questions from clinicians. The investigations that laboratory specialists suggested were compared to a test panel that was predefined based on clinical practice guideline recommendations (the 'recommended test panel'). The critical differences between two test results (creatinine, estimated glomerular filtration rate [eGFR] and albumin/creatinine ratio [ACR]) and the anticipated precision of the MDRD equation were evaluated. ***Results.*** Fifty-two of the 100 laboratory specialists responded, and most of these were regularly contacted by clinicians to discuss laboratory results. Less than 30% would suggest using the recommended test panel to evaluate renal function in the two primary-care patients. For creatinine and eGFR, median changes stated to signal improvement or deterioration in renal function (creatinine: –14% and +14%, respectively; eGFR: + 18% and –13%, respectively) were similar to what could be calculated using information on analytical and within-subject variation from the literature. There were variable critical differences for the ACR results (median values of –50% for improvement and + 67% for deterioration). Only 23% of the participants would recommend a gold standard clearance examination for a patient who was to undergo nephrotoxic chemotherapy. ***Conclusion.*** Questions from GPs about renal parameters are answered differently by laboratory specialists, and adherences to guideline recommendations are low on some issues.

Key Words: *Albuminuria, clinical chemistry, chronic kidney disease, creatinine, glomerular filtration rate, questionnaire*

Introduction

Chronic kidney disease (CKD) is an important risk factor for cardiovascular and end-stage renal disease [1,2], and recent population-based studies have shown that 10% of the population may be affected [3,4]. Renal disease is often not recognized by physicians [5], leading to delayed treatment of CKD and late referral to nephrology care, conditions shown to increase mortality in CKD patients [6–8]. New renal parameters have been suggested for facilitating earlier diagnosis. The tests that are promoted most often are the albumin/creatinine ratio (ACR) and the Modification of Diet in Renal Disease (MDRD)-based estimated glomerular filtration rate (eGFR) [9–17]. The effect on patient outcomes may be affected by general practitioners requesting different test procedures and interpreting renal test results in various ways. Earlier studies have demonstrated a need for increased information on use and interpretation of renal parameters in primary care [5,18–20]. Specialists in laboratory medicine working in clinical chemistry laboratories are involved in implementing new test procedures and, according to the International Standard for the accreditation of medical laboratories (ISO 15189), may be expected to advise clinicians on the interpretation of test results. Interpretive commenting of new or complicated tests may be valuable [21,22] and is highly appreciated by clinicians [23]. However, studies have revealed a variable quality of commenting of laboratory results

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by laboratory professionals [24–26], also for common laboratory tests such as renal parameters [27].

The aim of this study was to determine whether laboratory specialists give advice to clinicians in accordance with current guideline recommendations for a laboratory evaluation of renal function in primary care. The changes in creatinine, eGFR and ACR results that were considered to be clinically significant were assessed, together with the accuracy of MDRD-based eGFR results in individual patients.

Materials and methods

A questionnaire was developed by three laboratory specialists (from Norway and The Netherlands; see the Appendix) based on scenarios the laboratory specialists had experienced in their daily work. The questionnaire included three case histories and mimicked a situation in which a clinician contacted the laboratory to discuss the results from renal tests in these patients. Two case histories came from a primary-care setting: case 1 was a male patient with hypertension, a creatinine value of 119 μmol/l (reference interval 60–105 μmol/L) and an eGFR of 54 ml/min/1.73 m^2, while case 2 was a male patient with diabetes and an ACR result of 15 mg/mmol (reference interval <2.5 mg/mmol). After the case histories, questions asked by the clinician regarding what further examinations were needed included whether the first results could be used for diagnosing renal disease and what changes in serial results would signal clinically significant changes. The last case history (case 3) represented a typical hospital situation of a 57-year-old female patient with a normal body mass index and borderline reduced renal function (84 μmol/L creatinine and a reported eGFR value of ≥ 60 ml/min/1.73 m^2) who was due to start treatment with a nephrotoxic cytotoxic agent. Questions from the clinicians were related to how her renal function should be monitored before and during treatment. The last part of the questionnaire collected information about the education of the laboratory specialist, years of experience in the laboratory, how often they discussed laboratory tests with clinicians, and whether the case histories were relevant to the problems they usually encountered during their normal working activities.

Data collection

In Norway, only medical doctors are able to specialize in clinical chemistry, and consequently nearly all laboratory specialists are physicians. All registered laboratory specialists or people under specialist education were eligible for the survey, but registered professionals who were retired or known by the authors to work in other specialities were excluded. In 2009, the questionnaire was distributed by mail to 76 physicians working in Norwegian laboratories. Two reminders were sent after 3 and 6 weeks. In The Netherlands, most laboratory specialists have a scientific background, with only a minority having medical training. The questionnaire was sent to 24 laboratory specialists as part of a regular external quality-assessment program covering the interpretation of laboratory results.

Statistics, calculations and interpretation

Differences between professions were evaluated using the chi-square test for categorical data and Student's *t*-test for continuous variables. Tests suggested by the laboratory specialists were classified by the authors as either 'useful' or 'unnecessary', based on recommendations in international guidelines [9–12,14–16]. The number of laboratory specialists who, based on the same guidelines, suggested a 'recommended test panel' for the primary-care patients was noted. For case 1, the recommended test panel included repeating eGFR measurement and testing for albuminuria (i.e. defined as urine dip stick and/or urine albumin or protein measurements). Screening for haematuria (dip stick or sediment) was regarded to be correct but not obligatory. For case 2, repeated urine albumin testing and eGFR measurement were regarded to be the recommended test panel, whilst for case 3, gold standard clearances testing [10] (e.g. iohexol, iothalamate or chromium-labelled ethylenediaminetetraacetic acid [Cr-EDTA] but not creatinine clearance), eGFR and testing for albuminuria (urine dip stick and/or urine albumin or protein measurements) were considered useful.

Clinically important changes in creatinine, eGFR and ACR results were evaluated using the concept of critical difference (CD). The CD is defined as the minimal difference needed between two consecutive results to be certain (with a specified level of confidence) that the results are truly different, and that the difference is not due only to analytical imprecision (analytical coefficient of variation [CVa]) or intra-individual biological variation (individual coefficient of variation [CVi]) [28]:

$$\mathrm{CD} = \mathrm{bias} + \mathrm{z\ value} \times \sqrt{2} \times \sqrt{\left(\mathrm{CVa}^2 + \mathrm{CVi}^2\right)}$$

A CD value of 13% was calculated for creatinine using a typical CVa of 2% (the CVa was obtained at the Laboratory of Clinical Biochemistry, Haukeland University Hospital, Bergen, Norway), a CVi of 5.3% [29] and a z value of 1.64, reflecting 95% confidence for a one-sided test. It was assumed that there was no bias in the analytical method between the two measurements. CD values for creatinine ($\pm 13\%$) were used in the isotope dilution mass spectrometry traceable MDRD formula [30] to calculate a CD

value for an eGFR of 13% for deteriorating and 17% for improved renal function, respectively:

$$\text{eGFR} = 175 \times (S_{cr}/88.4)^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female})$$

For ACR, CVa and CVi values of 5% and 34% [31–34] were used, respectively, giving (with a z value of 1.64) a CD value of 80%. The participants' answers were compared to the calculated CD values and guideline recommendations regarding clinically important changes [10,35].

Multiple linear or logistic regressions were used to evaluate whether the participants' reported profession, years of working experience in the laboratory, prevalence of contact with clinicians or relevance of the case history (dependent variables) predicted the use of an adequate test panel or the magnitude of suggested values for critical differences.

Results

Characterization of the participants

In Norway, all of the 33 laboratory specialists who responded (43%) were physicians, whilst 18 of the 19 the Dutch respondents (79%) were clinical chemists and only one was a physician. The overall response rate was 52%. The average time the respondents had worked in the laboratory was 13 years (with 10th and 90th percentiles of 1 and 30 years, respectively), and the relevance of the case histories compared to questions they usually received during a work day, rated on a scale from 1 (totally irrelevant) to 10 (very similar), was 4.6 (with 10th and 90th percentiles of 1.6 and 8.0, respectively). With regard to contact with clinicians, 58% of the respondents were contacted by clinicians every day or 1–4 times per week, 15% were contacted 1–2 times per month and 19% were contacted only a few times per year or never. These parameters were similar between clinical chemists and physicians.

Case 1

Based on the first case history (see Appendix), 4% of the respondents stated that the patient did not have CKD, whilst 25% believed that the patient did have CKD, and 71% stated they could not tell and suggested further testing. The tests recommended to diagnose CKD are listed in Table I. Between them, the 52 respondents suggested a total of 87 tests, 21 (24%) of which were considered unnecessary to answer the question as to whether or not the patient had CKD (according to current guideline recommendations). Seventy-one percent of the respondents did not suggest the recommended test panel, including repeated eGFR and albuminuria testing for the patient (see Materials and methods). The CD values (percentages) are shown in Figure 1, and cumulative percentages of absolute changes signalling a clinically significant change for creatinine and eGFR values of 119 μmol/L and 54 ml/min/1.73 m^2, respectively, are shown in Figure 2.

Table I. Percentage of respondents ($N = 52$) recommending different tests in response to a low eGFR result (case 1), a positive ACR result (case 2) and for monitoring renal function in a patient with cancer treated with a nephrotoxic cytotoxic agent (case 3). The grey area indicates the unnecessary tests recommended. A few of the participants suggested that multiple similar tests (e.g. that albumin/creatinine ratio and urinary albumin or protein/creatinine ratio and urinary protein should be assessed to investigate albuminuria in cases 1 and 2). The total percentage of respondents suggesting albuminuria testing is therefore lower than what may be found when adding the different investigations suggested.

	Case 1	Case 2	Case 3
Creatinine/eGFR	52	40	83
ACR	21	56	17
Urinary albumin	19	19	4
Protein/creatinine ratio	2	4	2
Urinary protein	12	6	2
Urine dip stick	15	4	6
Sediment	10	0	4
Cystatin C	6	6	12
Urea	8	4	14
Creatinine clearance	4	2	6
Other clearance tests	8	4	23
Other blood tests	15	6	7

Case 2

In total, 10% of the respondents felt that one positive ACR result was sufficient to diagnose renal disease in a diabetic patient; the different tests suggested for further evaluating the patient are listed in Table I. A follow-up ACR or urine albumin measurement was recommended by 69% of the participants. Thus, the 52 respondents recommended a total of 73 tests to be conducted, 12 of which (17%) were considered unnecessary. Only 25% suggested the recommended test panel including at least one repeated urine albumin test in combination with eGFR. The CD values stated for an ACR value of 15 mg/mmol are shown in Figure 1 (percentages), and cumulative percentages for absolute changes are shown in Figure 2.

Case 3

The tests suggested for evaluating the patient's renal function are listed in Table I; 23% recommended a gold standard clearance procedure (e.g. iohexol, iothalamate or Cr-EDTA). In total, 94 tests were suggested by the 52 respondents, of which 23 (26%) were found to be unnecessary in relation to the questions regarding the case history (see Materials and methods). In total, 23% would recommend testing for albuminuria, while only 12% would request a combination gold standard clearance measurement and albuminuria evaluation. Most of the respondents

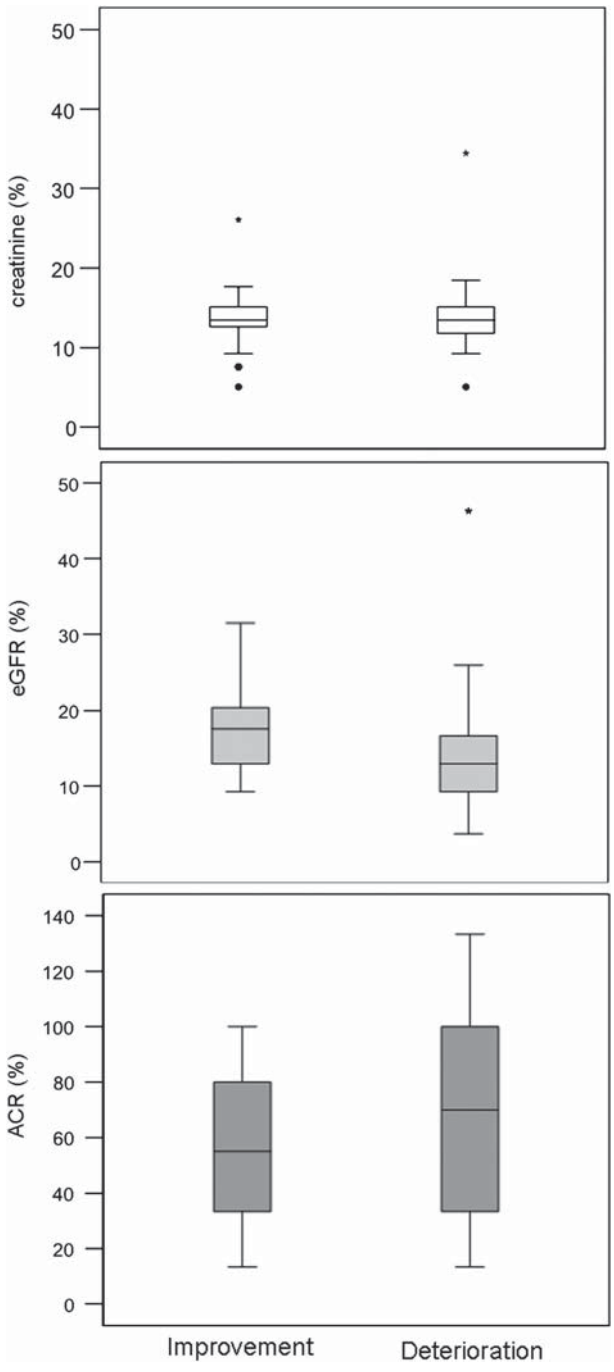

Figure 1. CD values (%) denoted to signal changes in the renal status of patients. The start values for creatinine, eGFR and ACR were 119 μmol/L, 54 ml/min/1.73 m^2 and 15 mg/mmol, respectively. The horizontal line denotes the median value and the boxes represent the interquartile range. Outliers (defined as cases with values between 1.5 and 3 box lengths from the upper or lower edge of the box) are shown as black dots, and the asterisks denote extreme values more than 3 box lengths from the upper edge of the box.

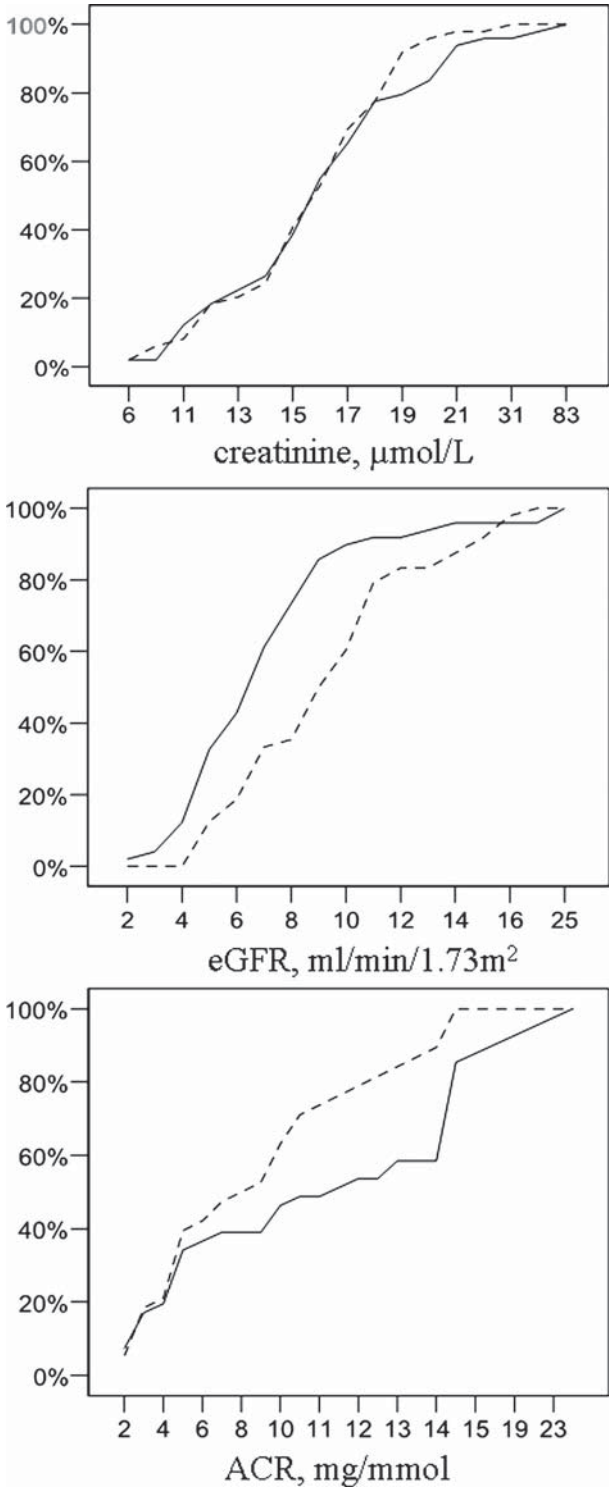

Figure 2. Cumulative percentages of absolute values denoted for CD by participants: -----improvement; —— deterioration.

(62%) gave a similar response to question 3A and 3B (see Appendix) implying that they would recommend that the tests used by the clinician at the follow-up should be the same as those applied initially (Table I, question 3A) A gold standard clearance measurement before every treatment was recommended by 8%.

Relationship between the findings and the participants' background data

There was a positive correlation between CD values given for improvement in creatinine levels and number of years the participant had worked in the laboratory, but otherwise there were no significant correlations between profession, number of years

that the participants had worked in the laboratory, how often they were contacted by clinicians or how relevant they found the case histories and the test panel used or CD values given. There were no differences between the Dutch and Norwegian laboratory specialists.

Discussion

The most important finding in this study was that few laboratory specialists would suggest the test combinations recommended by the current guidelines for diagnosing renal disease in primary-care patients with hypertension or diabetes. Based on analytical and intra-individual biological variation, laboratory specialists gave adequate advice regarding significant changes in test results, whilst the imprecision/uncertainty of MDRD-based eGFR results [36] was not recognized.

According to the Kidney Disease Quality Outcome Initiative classification, CKD should be diagnosed based on two eGFR measurements made more than 3 months apart [15]. Most laboratory specialists did suggest that the patient had CKD or required further testing, but only half suggested retesting of the eGFR. Temporary reductions in eGFR can be encountered (e.g. in acute illness), and retesting is probably included in the definition of CKD to avoid a false-positive diagnosis. However, since patient 1 was in a stable situation, laboratory specialists may have considered retesting to be of lesser value, given the low within-subject biological variation of creatinine [29]. Urine investigations are important in patients at risk for CKD [37–39], and the consequence of a positive result is to initiate treatment with angiotensin converting enzyme inhibitors or angiotensin receptor blockers, which have been shown to improve the renal prognosis in albuminuric patients with diabetes or hypertension [10,11,40–42]. A survey from general practice showed that the importance of urine investigations should be conveyed to GPs; e.g. 42% of patients with CKD stage 3 had a specific urine albumin test and overall only 2/3 had any urine protein investigation [20]. In the current study, urine testing for albumin or protein in a hypertensive patient with one low eGFR result (case 1) was recommended by 38% of the respondents. Since laboratories often give recommendations regarding indications for testing, communicating the importance of these analyses to laboratory specialists could benefit patient care.

To avoid a false-positive diagnosis of albuminuria, the guidelines recommend two positive tests to be obtained before treatment is commenced [9,11]. Compared to studies in general practice, a larger percentage of the respondents (69%) advised confirmation of a positive ACR result in a diabetic patient (case 2) [19], probably reflecting knowledge of the high within-subject biological variability [31]. About 40% suggested, as recommended, eGFR monitoring in the diabetic patient [9,11]. If the patient in case 2 had a reduced eGFR, lack of testing could lead to delayed recognition and treatment of characteristic CKD complications (e.g. anaemia and bone disease) [11]. A baseline eGFR measurement is also useful to better detect a rapid decline in glomerular filtration rate (GFR), which should lead to referral to a nephrology service [10].

In case 3, the purpose of the question was to evaluate whether eGFR measurements are considered to be sufficiently accurate for clinical decisions in a situation where overlooking reduced renal function could cause harm to the patient (e.g. overdosing of toxic drugs and irreversible renal damage). The low percentage of the respondents recommending gold-standard clearance measurements indicate that laboratory specialists are not aware of the imprecision/uncertainty of the MDRD formula (i.e. that the percentages of eGFR results within $\pm$ 30% of the measured GFR value is approximately 80%) [36]. This means that for patient 3 (at an eGFR value of 61 ml/min/1.73 m^2), there is an 80% probability that the measured GFR value would range from 43–79 ml/min/1.73 m^2. It is unlikely that laboratory specialists would accept such a level of uncertainty given the scenario described for case 3, and this is seemingly also the reason for guidelines to recommend more accurate clearance procedures (e.g. iohexol, iothalamate or Cr-EDTA) [10].

Quite a high proportion of the respondents suggested performing unnecessary tests. The creatinine clearance test is known to be cumbersome and no more accurate than eGFR measurements [43–45], and should therefore usually be avoided. Gold-standard GFR measurements are recommended only for certain populations with specific characteristics (e.g. case 3) [10,12], but were suggested by some respondents for evaluating renal function in common primary-care CKD patients (cases 1 and 2). Urea is influenced by multiple factors and is usually used for evaluating post-renal uraemia or the need for dialysis [46]. Cystatin C has not yet been proven superior to creatinine-based eGFR measurements and could be biased in malignant disease (e.g. case 3) [44,47]. The use of unnecessary tests is inconvenient for both patient and physician, and is not cost effective.

For creatinine, CD values were similar for the improvement and the deterioration of renal function, had a low variation between the participants and were close to what could be expected after calculating the CD with a CVi of 5.3% [29]. For eGFR, larger values were given for improvement than for deterioration, and these were similar to what could be calculated after inserting a $\pm$ 13% change in creatinine values in the logarithmic MDRD formula. The values were larger than the 4–5 ml/min/1.73m^2 currently suggested by the few guidelines that consider

clinical meaningful changes in eGFR [10,35]. The heterogeneity in replies is less compared to that usually seen in primary care [18,20] probably indicating that values are calculated. Calculation of CD values is a topic relevant to all laboratory tests and has been discussed within the field of clinical chemistry for decades [28,48]. Much larger variations were found in CD values given for ACR, probably reflecting the diversity of data found when reviewing the literature regarding this topic [31].

The validity of a home-made questionnaire may be argued. Case-history-based questionnaires are considered a robust method [49], and the present response rate was adequate compared to what is usually obtained in questionnaire-based surveys amongst physicians [50]. However, it should be remembered that questionnaires are usually answered by those who have the most knowledge about the issue being evaluated, so our findings should be interpreted as best-practice data. No large differences were seen between the responses from the laboratory physicians and clinical chemists. However, the number of participants was relatively low and the survey may therefore be under-powered for exploring this topic.

We have compared the advice of laboratory specialists for renal laboratory investigations in hypertensive and diabetic patients with the current guideline recommendations (i.e. two positive eGFR or urine albumin measurements are necessary; patients should have urine albumin/protein and eGFR measurements). Such an approach is possible since a broad consensus is found amongst guidelines on these subjects. The assumption that various responses were caused by lack of familiarity with guideline recommendations is strengthened by the finding that homogeneous responses were seen on issues that are usually insufficiently presented in guidelines, but considered well known to laboratory specialists (i.e. CD values). On the other hand, some laboratory specialists might have had sufficient knowledge of the guideline recommendations but may disagree with the current advice. The study did not examine either the evidence base of the current guidelines or the clinical consequences of the advice offered.

An important matter in the field of clinical chemistry is how to improve the quality of post-analytical laboratory activities, and others have shown that commenting on renal parameters is useful [21] and may in general reduce test requisition errors [23]. The present study shows that laboratory specialists may adequately advise clinicians about how to interpret changes in test results, but might give different and sometimes misleading information related to indications for and interpretation of common renal laboratory tests [27]. The use of similar queries might help to reduce the variance of post-analytical laboratory practice in the future, especially if feedback reports are distributed to the participants [51,52]. Establishing an external quality assessment for post-analytical laboratory activities should be considered.

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Appendix

The questionnaire

Patient 1

A GP calls the laboratory and asks for your advice regarding a 60 year old man who has visited for a routine check of hypertension. The patients blood pressure was 155/94 mmHg, and he had no other chronic diseases. His GP has obtained the following results from the laboratory; s-creatinine 119 µmol/L (60-105 µmol/L), estimated GFR 54 mL/min/1.73m^2.

The GP asks you:

1A. Based on this laboratory result, does the patient have chronic kidney disease?

Yes☐ No☐

Maybe,☐ and further testing would be necessary; please specify what laboratory test(s) you would recommend to further evaluate if the patient has chronic kidney disease?

_____

1B. The GP tells you that s-creatinine/eGFR will be repeated in 4 months and asks; how large difference do you think is necessary between the first and second results to denote (95%CI);

- a deterioration in renal function;
  s-creatinine should increase to _____µmol/L
  eGFR should decrease to _____ ml/min/1,73m^2

- an improved renal function;
  s-creatinine should decrease to _____µmol/L
  eGFR should increase to _____ ml/min/1,73m^2
  (Note! Exact values above 60 mL/min/1.73m^2 may also be denoted)

Patient 2

A GP calls you and asks how to evaluate if a 57 year old male, who was diagnosed with type 2 diabetes 2 years ago, has developed diabetes associated renal disease. He has not been tested yet, except with an ordinary urine dipstick test, which was negative. You recommend that the patients should provide a morning urine to be analyzed as an albumin/creatinine ratio (ACR) analysis. The GP is not very familiar with this test and its interpretation.

He asks you:

2A. If one positive test result is obtained, is that sufficient to diagnose renal disease?

Yes☐ (please proceed to question 2C) No (please answer question 2B)☐

2B. If no, what test(s) would you recommend to confirm or exclude renal disease?

Specify_____

Imagine the case that the patient has an ACR analysis and that a result of 15 mg/mmol creatinine is achieved. A new test is obtained one year thereafter;

2C. How large difference do you think is necessary between these two ACR results to denote a significant (95%CI):

- deterioration in the patients renal function:
  ACR should increase to _____ mg/mmol creatinine
- improvement in the patients renal function:
  ACR should decrease to _____mg/mmol creatinine

Patient 3

A colleague in the oncology department calls you and asks about a 57 year old female patient with a malignant disease. Her BMI is normal; 22 kg/m^2. s-creatinine is 84 µmol/L (45-90 µmol/L) and eGFR >60 mL/min/1,73m^2. She will receive treatment with a highly nephrotoxic cytostatica and it is recommended to monitor her renal function during the whole treatment.

The Oncologist asks by which test(s) he should monitor her renal function?

3A. What test(s) would you recommend?

_____

3B. When should the test(s) be repeated for monitoring her renal function during the treatment with cytostatica? (please specify for each test if more than one);

Before every cycle (specify the test(s))_____☐
Before every second cycle (specify the test(s))_____☐
Before every third cycle (specify the test(s))_____☐
Testing should be performed at other time interval, pleace specify;_____☐