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A pathway to national guidelines for laboratory diagnostics of chronic kidney disease – examples from diverse European countries

Vanja Radišić Biljak¹, Kristin Moberg Aakre², Dogan Yucel³, Anne-Sophie Bargnoux⁴, Jean-Paul Cristol⁴, Laurence Piéroni⁴

¹ Department of Medical Biochemistry and Laboratory Medicine, Merkur University Hospital, Zagreb, Croatia, on behalf of the Croatian Society of Medical Biochemistry and Laboratory Medicine (CSMBLM)

² Laboratory of Clinical Biochemistry, Haukeland University Hospital, Bergen, Norway

³ Department of Medical Biochemistry, Ankara Training and Research Hospital, University of Health Sciences, Altindag, Ankara and Turkish Biochemical Society

⁴ Laboratoire de Biochimie, CHRU de Montpellier, PhyMedExp, University of Montpellier, France, on behalf of the Société Française de Biologie Clinique (SFBC)

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Corresponding author:

Vanja Radišić Biljak
Department of Medical Biochemistry
and Laboratory Medicine
Merkur University Hospital
Zajčeva 19
10000-Zagreb
Croatia
Phone: +385917967867
E-mail: vanja.radisic@gmail.com

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ABSTRACT

The principal benefit of guidelines is to improve the quality of care received by patients. In the 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (KDIGO) was released and it is designed to provide information and assist decision making. This review gives a brief overview of a various national CKD guidelines that rely on the newly released KDIGO guidelines. All of the included countries (France, Turkey, Norway and Croatia) are non-English speaking countries and they differ in population and socio economic aspects. Examples shown in this review may provide valuable experience for countries that are in process of creating their national CKD guidelines.

INTRODUCTION

For patients (and almost everyone else in health care), the greatest benefit that could be achieved by guidelines is to improve health outcomes (1). In the 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (2) was released by the The Kidney Disease: Improving Global Outcomes (KDIGO). This guideline serves to update the 2002 KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification following a decade of focused research and clinical practice in CKD. Although it is designed to provide information and assist decision making, it is not intended to define a standard of care, and should not be construed as one, nor should it be interpreted as prescribing an exclusive course of management (2).

As a comparison to worldwide recognized British (3), Australian (4, 5) and American CKD guidelines (2), this article gives a brief overview of various national CKD guidelines from diverse European countries: France, Turkey, Norway and Croatia. All of the included countries are non-English speaking countries and they differ in population and socio economic aspects. Through these examples variations in practice will be shown when the needs of individual patients, available resources, and limitations unique to a specific country, were taken into account.

FRENCH GUIDELINES FOR ESTIMATION OF GLOMERULAR FILTRATION RATE (EGFR) – PAST, PRESENT AND THE FUTURE

1) Analytical evaluation and improvement of creatinine measurement: involvement of the scientific societies

As early as 2002, the “Société Française de Biologie Clinique” (SFBC) recognized the glomerular filtration rate (GFR) estimation as a major health problem (6) and created the “Creatinine” Working Group. This laboratory working group

initiated a multicentric study to evaluate inter-assay variation and accuracy of 17 creatinine assays of which 14 were commercially available automated assays (4 enzyme assays, 1 compensated Jaffe assay, and 9 non-compensated Jaffe assays) (7). Using 30 frozen human samples, they demonstrated that a very high inter-assay variation persisted since the median inter-assay coefficient of variation (CV) was 14.2% for 20 low samples (45–150 μM) and 7.7% for 10 high samples (250–350 mM). In addition, the inaccuracy, assessed with three certified reference materials, appears to be relatively high, especially for the lowest concentration with biases ranging from -2.9% to $+57.5\%$ for the low level (68.7 μM) (8).

In 2008 the newly formed working Group «Biologie des fonctions rénales et de l'insuffisance rénale» involving Nephrologists and medical Biologists was supported by both the SFBC and the “Société de Néphrologie”. This group decided to perform a new study after the publication of the “Laboratory Working Group of the National Kidney Disease Education Program” recommendations (NKDEP) for in-vitro diagnostic (IVD) manufacturers (9), highlighting the need for developing methods for creatinine measurement that are reproducible and traceable to isotope dilution mass spectrometry (IDMS). Our evaluation involved 25 clinical laboratories, 12 enzymatic and 4 compensated Jaffe creatinine automated assays. Creatinine was measured in serum pools ranging from 35.9 ± 0.9 $\mu\text{mol/L}$ to 174.5 ± 3.1 $\mu\text{mol/L}$ (IDMS determination). This study demonstrates substantial improvements in the calibration, traceability and precision of the enzymatic methods, reaching the total analytical error of 8% for the majority of enzymatic methods (10). Moreover, most of these assays allowed accurate creatinine measurements for creatinine levels lower than 40 $\mu\text{mol/L}$. By contrast, this requirement was never obtained for the compensated Jaffe methods at the critical level of 74.4 ± 1.4 $\mu\text{mol/L}$ (11).

II) Time to recommendations: a step by step improvement

Based on the international recommendations and our own French studies, we were able to publish some French recommendations. The first recommendation (12), published in 2002 by the «Agence National d'Accréditation et d'Evaluation en Santé» (ANAES, former name of Haute Autorité de Santé, HAS) recommended that laboratory analysts should provide an estimation of GFR value using the Cockcroft-Gault formula for every request for serum creatinine, but no analytical guidelines for creatinine measurement were suggested.

However, as soon as the Kidney Disease Outcome Quality Initiative (K/DOQI) classification was proposed (6) following a position statement from Kidney Disease: Improving Global Outcomes (KDIGO) (13), an update of the French position statement about estimation of GFR and proteinuria has been developed by the «Société de Néphrologie» in 2009.

For renal function measurement, it is recommended to estimate GFR from serum creatinine using IDMS traceable simplified modification of diet in renal disease (MDRD) equation.

These recommendations were published in the French journal of the Société Française de Néphrologie: Néphrologie Therapeutique (14).

This guidelines was further supported by the report of «Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS)» in 2010 recommend an IDMS traceable creatinine assay. They advised the use of enzymatic assays in specific populations like in pediatric patients or in specific situations where Jaffe assays are known to be subject of interferences (15).

Through their collaborative works, the SFBC working group published its own recommendations in the French journal of the SFBC: “Les

Annales de Biologie Clinique”, highlighting the use of IDMS-traceable creatinine assay and the use of CKD-EPI equation (16). Finally, the «Haute Autorité de Santé», driven by the French Ministry of Health, meet an expert panel involving clinical biologists, nephrologists, and geriatricians.

These guidelines, available on the Web site of the HAS in 2011-2012, recommend an IDMS traceable enzymatic creatinine assay in all clinical situations because of better analytical specificity, sensitivity and performances of enzymatic assays compared to Jaffe assays (17).

Further to the publication of KDIGO 2012 clinical practice (2), the HAS recommend that French clinical laboratories report eGFR in adults using the 2009 CKD-EPI creatinine equation which gives the best performance in terms of accuracy. Pending the full adoption of the CKD-EPI equation by health professionals, the 175 MDRD formula may be used in the meantime but Cockcroft and Gault formula should be omitted. It should be noted that the ethnic adjustment factor into the equation does not apply in France due to the non-validation of this correction in non-American black people and to the French law for preventing any ethnic discrimination.

Since it has been demonstrated that mild to moderate CKD is associated with adverse clinical outcomes, the KDIGO working group decided not to combine stage 1–2 CKD.

A precise eGFR above 60 mL/min/1.73 m² is thus valuable. Results of the SFBC study support the use of CKD-EPI equation rather than MDRD and found that accurate enzymatic assays allow estimation of eGFR until 90 mL/min/1.73 m² with MDRD and 120 mL/min/1.73 m² with CKD-EPI equation.

In all cases, compensated Jaffe creatinine assays lead to important errors in eGFR and should be avoided (18).

III) Results and limitations after more than 10 years of scientific communication

Data from the French biochemistry external quality assessment scheme «ProBioQual» (Centre lyonnais d'études pour la PROMotion de la BIOlogie et du contrôle de QUALité, LYON - FRANCE) underline the emergence of standardized Jaffe assays in 2008, and a gradual implementation of enzymatic assays in French laboratories since the creation of these guidelines (Figures 1 and 2).

In 2017, about 65% of French laboratories use enzymatic creatinine assays. In addition, all laboratories give the creatinine result with an estimation of GFR. Some of them add the staging of CKD according to the KDIGO from stage I to V. As a limitation, these recommendations are clearly designed for adult population, no French recommendations are edited for children.

Reliable estimates of high eGFR are important for drug dosing, nevertheless, the HAS draws attention to the difficulties of drug dosage adjustments. For example, there are currently conflicting recommendations between the current CKD guidelines (19) and the «Groupe Français d'Etude sur l'Hémostase et la Thrombose (GEHT)» regarding the use of direct oral anticoagulants for the prevention and treatment of thromboembolic disease in patients with reduced renal function.

Clinicians are reluctant to use the MDRD or CKD-EPI formula reported by the lab since the estimation of renal function with the Cockcroft and Gault formula is used for the pharmacokinetics studies and the development of drug dosing guidelines. In addition, the values obtained with the Cockcroft formula in patients >75 years are systematically lower than the values obtained with the MDRD formula. This should allow a safe use of prescription of direct oral anticoagulants.

Figure 1 Creatinine assays before French recommendations

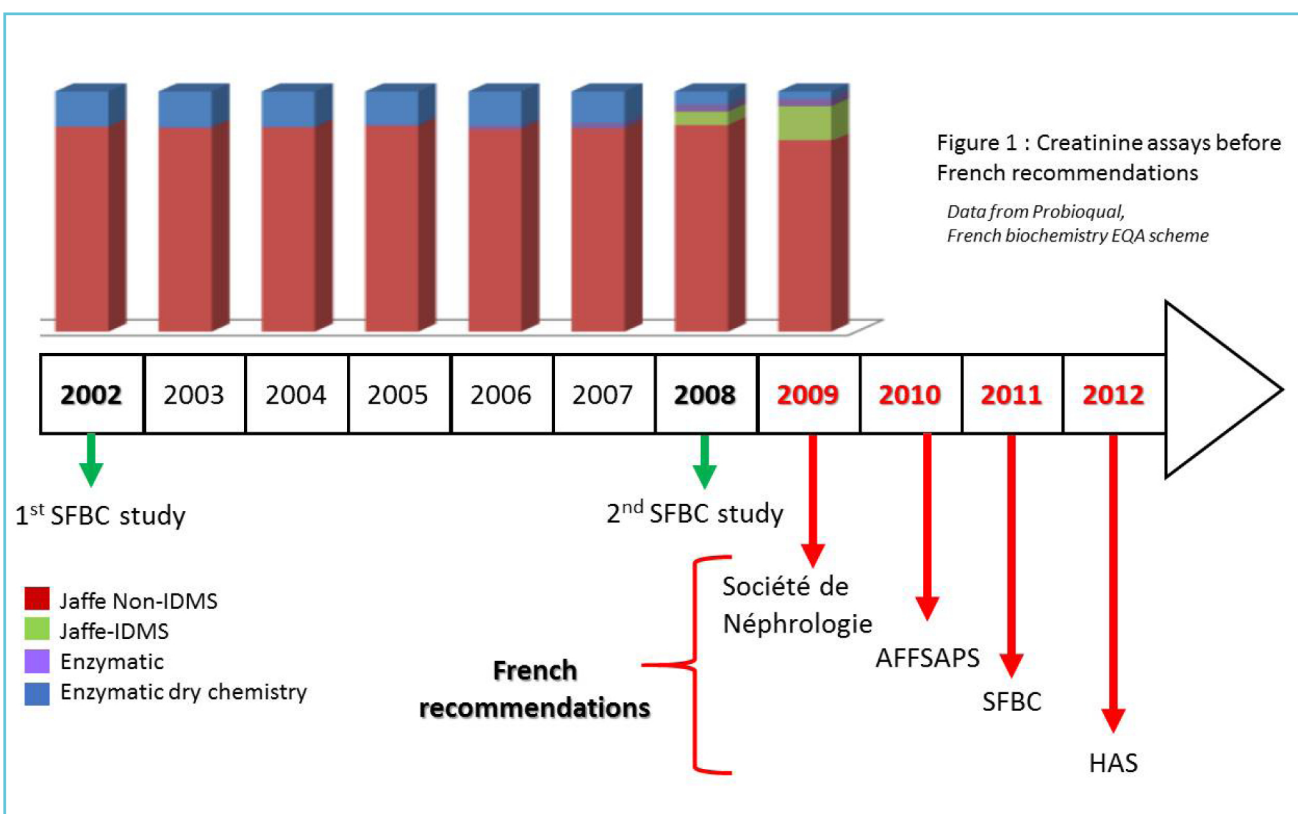
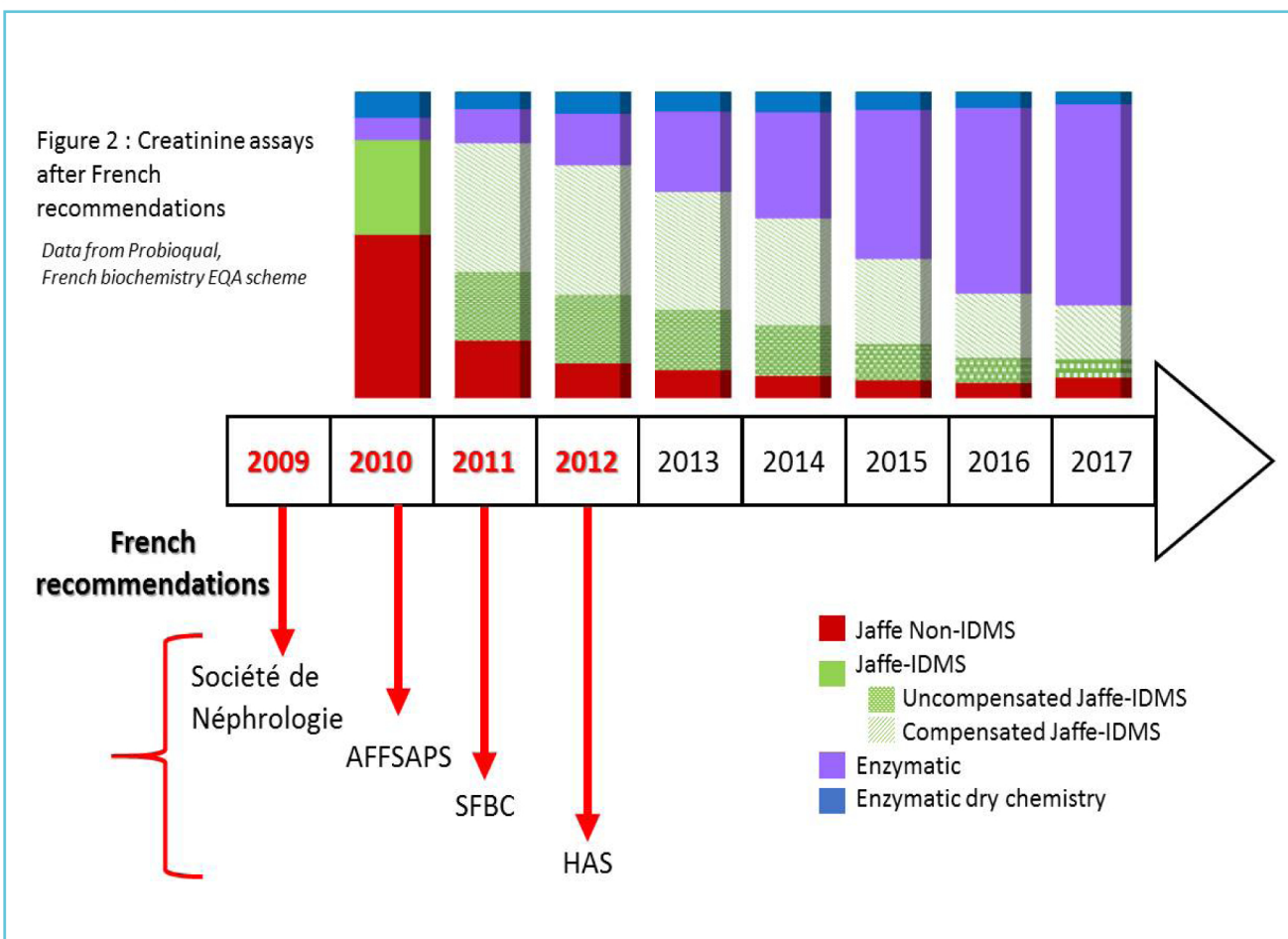


Figure 2 Creatinine assays after French recommendations



IV) Lessons and perspectives

The strong involvement of the French scientific societies, mainly the “Société de néphrologie” and the SFBC leading to the constitution of joint working group associating clinicians and medical biologists, allows the creation of the French recommendations for GFR estimation. In addition, these collaborative groups allow the initiation and realization of multicentric studies. Similarly to the creatinine study, the SFBC group conducted a multicentric evaluation of automated cystatin C assays before (2008) and after (2015) standardization using the certified reference material ERM-DA 471. In the latter study, we showed that bias remains the major component of the combined uncertainty because of possible

problems associated with the implementation of traceability (20). Although some manufacturers have clearly improved their calibration protocols relative to ERM-DA471, most of them failed to meet the criteria for acceptable cystatin C measurements. As a result, no recommendations are currently available in France for cystatin C.

To date, the SFBC and Société de Néphrologie have initiated two working groups, one about the biomarkers of Chronic Kidney Disease – Bone and Mineral disorders and one about urinary markers of renal dysfunctions. These groups produced reviews for the journal of the SFBC (“Les Annales de Biologie Clinique”) and organized multicentric evaluations of albuminuria and urinary calcium and phosphate determinations.

INCREASING AWARENESS ABOUT CHRONIC KIDNEY DISEASE AND IMPLEMENTATION OF A NEW PRACTICE GUIDELINE IN TURKEY

CKD is an important and growing public health problem in Turkey like in all over the World. For the year 2015, general incidence and general prevalence of end stage renal disease in Turkey were 147.3 and 935.4 per million population. But the prevalence of CKD is very high, 15.7% in Turkey. Currently, there are about 100 000 patients undergoing hemodialysis or peritoneal dialysis in our country. Hence, the awareness level should be increased. Currently, awareness level is <10% in the World and not more than 2% in Turkey.

Although the laboratory examinations are sine quo non for screening, diagnosis, evaluation, staging and monitoring of CKD, these examinations are mostly analysed by using different analytical methods and techniques and therefore different results can be obtained and reported with different units. For this reason, a uniform and standard approach is required for laboratory practice. From this point of view, the Turkish Biochemical Society (TBS) planned a strategy through implementation of a series of steps. These steps are presented as follows.

The working group

TBS organized a working group on CKD (WG-CKD) in 2014. The WG-CKD was essentially consisted of laboratory specialists from different level hospital laboratories and the representatives of main diagnostic companies.

The survey

The WG-CKD at first coordinated a questionnaire for Turkish laboratories. The survey included questions addressing the assessment of awareness about the CKD and especially on creatinine and urinary albumin measurements

such as instrument use, creatinine and urine albumin methods and their traceability, calibration and control procedures, external quality assessment scheme, reporting of eGFR, reporting of creatinine and albumin results. There were similar questions also relating to serum cystatin C and urine total protein in the survey.

About 100 specialists from different hospital laboratories, a total of 94 labs, participated in the survey. The major analytical systems and reagents for creatinine were of Roche Diagnostics (29.4%), Abbott Diagnostics (28.24%), Beckman-Coulter Inc. (27.06%), Siemens Healthcare (5.88%), and Mindray (1.18%). More than 90% of the laboratories were using the Jaffe method and only 8% were using the enzymatic creatinine method. The methods were traceable to SRM 967 (50.79%), SRM 914 (33.33%) and SRM 909 (11.11%), essentially. Creatinine results were mostly reported with conventional units (mg/dL, 95.18%).

Reference ranges recommended by diagnostic companies were used (about 80%) and age - and/or sex-related reference ranges were reported (89.73%) by a majority of the labs. Only 49.30% and 18.31% of the laboratories were reporting eGFR for adult and pediatric population, respectively. Mostly CKD-EPI formula was used (44.74%) for eGFR, and cystatin C use was only 10.53%). Cystatin C was measured by nephelometric and turbidimetric methods and only 5.2% of the labs were participate in an EQAS. Urine albumin was measured by turbidimetric (86.00%) and nephelometric (12%) methods and all specimen types, 24-h urine, random, first morning and second morning, were accepted. The majority of the laboratories (88.37%) did not use decision limits for urine albumin.

The guideline

The WG-CKD decided to prepare a short guideline based on KDIGO 2012 clinical practice guideline for the evaluation and management of CKD for laboratory specialists. The guideline was completed and published in 2015 and included the following key recommendations (21).

1. Creatinine assays should be traceable to a reference material which creatinine concentration assigned by GC-IDMS technique.
2. When reporting the creatinine result, eGFR should also be reported in adult (>18 years) population. A warning expression should be included in the report form if eGFR result is <60 mL/min/1.73 m².
3. eGFR values should be expressed quantitatively up to 90 mL/min/1.73 m² by CKD-EPI equation. Above 90 mL/min/1.73 m², eGFR values can be expressed quantitatively or >90 mL/min/1.73 m².
4. eGFR equations of the adult population should not be used for pediatric population. Different equations utilizing also patient height should be used. The enzymatic creatinine assay should be preferred. eGFR based on cystatin C can be used for confirmation in the pediatric population.
5. Cystatin C measurements, at least when eGFR based on creatinine is not reliable and for confirmation should be encouraged.
6. Proteinuria or albuminuria values should be reported in proportion to creatinine.

Implementation of the guideline

The guideline was accepted by the Ministry of Health and it was circulated by Department of Elderly Health and Disables, Public Health Institution of Turkey, under the Turkey's Prevention and Control Program of Kidney Diseases (2014 – 2017) in December 2015. The guideline was also announced from the website

of the Department of Laboratory Services, Ministry of Health (<http://dosyamerkez.saglik.gov.tr/Eklenti/2621,kbh1pdf.pdf?>).

Currently, the guideline is implemented by all public and private medical laboratories at all levels, primary, secondary, and tertiary health institutions across Turkey. In this connection, eGFR is reported with CKD-EPI formula through serum creatinine in adult population and with Schwartz formula in the pediatric population; proteinuria and albuminuria are also interpreted and reported according to the guideline.

We hope, the implementation of the guideline by all medical laboratories, will have important consequences on standardisation and harmonisation of laboratory tests relating to CKD and of course on patient safety.

NORWEGIAN RECOMMENDATIONS FOR DIAGNOSING CKD

In Norway, two recommendations regarding diagnosing CKD have been published within the last years. One is the recommendation from the Norwegian Society of Medical Biochemistry (NSMB) regarding estimation of GFR based on creatinine measurements (22), and the other is the Diabetes Guideline (23) from the Norwegian Directorate of Health that includes a chapter on diagnosis and follow-up on diabetes nephropathy. Amongst other things this guideline describes how urinary albumin testing should be undertaken.

NSMBs recommendations for estimating GFR

The recommendation was worked through by a working group consisting of five specialists in laboratory medicine and one laboratory technician, and was published in 2016. The group got feedback from local nephrologists during their work.

The main messages in the recommendations

- Creatinine should be measured using an enzymatic assay
- eGFR should be calculated using the CKD-EPI formula
- eGFR results should be multiplied by 1.15 if the patient is Afro-American
- Renal disease should be classified according to the guideline from KDIGO (2)

Implementation of the recommendation

In 2017 most Norwegian laboratories use an enzymatic assay. The last numbers from the Norwegian EQA scheme (NOKLUS) shows that 57 laboratories use enzymatic assays and only two uses the Jaffe method. This is an improvement from before the recommendations were produced, when 8 laboratories used the Jaffe method. NSMB has not yet evaluated if Norwegian laboratories have changed formula for eGFR calculations from the MDRD formula to the CKD-EPI formula, but oral communications with the main laboratories in Norway indicate that this change has been undertaken.

The guideline for diagnosing and follow up of Diabetes Nephropathy

This guideline is part of the official Norwegian Diabetes Guideline. It was produced by a working group established by the Norwegian Directorate of Health and gives recommendations regarding the diagnosis and follow-up of renal disease in diabetes patients. The group members were endocrinologists, nephrologists, general practitioners and a specialist in laboratory medicine. Recommendations related to diagnosing renal disease focused on eGFR and measurement of urinary albumin. The group recommended that these tests were conducted on a yearly basis and more often if positive results or progressive disease were detected.

The laboratory specialist was also a member of the eGFR working group described above, so recommendations related to eGFR were harmonized between the two groups and are identically to those described above.

Some information was available regarding followed up and diagnosis of albuminuria in diabetes patients in Norway when the work started. This task is primarily done in primary care, and > 95% of general practitioners screen diabetes patients for albuminuria (24). General practitioners commonly use high quality quantitative point of care instruments that measure albumin/creatinine ratio in morning or spot samples (25).

The main recommendations related to urine albumin measurements

- Urine albumin should be measured as albumin/creatinine ratio.
- A morning sample or a random spot sample should be used.
- Two positive samples are necessary to diagnose albuminuria. The second sample should be taken within 3 months from the first sample.
- Albuminuria should be classified as recommended by KDIGO (2).
- Physical activity, acute inflammatory response and urinary tract infection may lead to false positive results and should therefore be avoided during testing.
- Biological variation is high and reference change values of 100-200% may be expected.

Implementation of the guideline

The implementation of this guideline has not yet been evaluated by the Norwegian health care authorities.

ADVANTAGES AND OBSTACLES IN CREATING NATIONAL CHRONIC KIDNEY DISEASE LABORATORY RECOMMENDATIONS IN CROATIA

In 2013, the Joint Croatian Working Group (JCWG) for laboratory diagnostic of CKD on the behalf of Croatian society of medical biochemistry and laboratory medicine (CSMBLM) and Croatian chamber of medical biochemists (CCMB) conducted a survey across Croatian medical-biochemistry laboratories to assess the current practice in this area of laboratory medicine. The results from the survey were published in the presented article in the first issue of national *Biochemia Medica* Journal in 2015 (26).

The results of the survey showed that there is a large heterogeneity among Croatian laboratories regarding measuring methods, reporting units and reference intervals (cut-off values), both for creatinine and urine albumin or protein. The two key prerequisites for CKD screening, automatic reporting of eGFR and albuminuria or proteinuria assessment, are not implemented nationwide. There is a need for harmonization in laboratory diagnostics of CKD in Croatia (26). There is still a substantial number of laboratories that use the non-standardized uncompensated Jaffe method, almost one quarter of all Croatian medical-biochemistry labs. Only about 11% of laboratories use enzymatic method. The rest of laboratories measure creatinine with compensated Jaffe method traceable to IDMS method and Standard Reference Material 967.

The majority of laboratories that participated in the survey generally do not report results for eGFR (75%). Among laboratories that report eGFR, there is a statistically significant difference in distribution by type of institution ($P < 0.001$), with the lowest number of laboratories from primary health care institutions.

The most prevalent equation for calculating eGFR, at the time point when the survey was conducted, was MDRD equation for standardized creatinine, which was in accordance with the recommendations of Croatian Chamber at that time. However, there were some answers indicating using the MDRD equation for standardized creatinine with the results of serum creatinine measured with non-standardized uncompensated Jaffé method, and reporting of results for eGFR calculated with MDRD equation as an exact number regardless of eGFR value.

Majority of laboratories that participated in the survey do not measure urine albumin or protein (75%), predominantly in primary health care laboratories. There is a large heterogeneity among type of sample recommended for measuring urine albumin or protein and reporting units, consequently. The results indicate that assessment of albuminuria and proteinuria in a large number of laboratories is still performed in 24-hour urine samples.

The most important issue that occurred is the fact that laboratories still use non-standardized methods for creatinine results and do not report eGFR values. Also, the majority of laboratories do not measure urine albumin, especially in primary care health setting. These facts set the background for the process of standardization and harmonization in this area of laboratory medicine which resulted in issuing first national recommendations for laboratory diagnostics of chronic kidney disease in Croatia (27). These national recommendations, based on the relevant 2012 KDIGO Guideline, represent the first step in accomplishing the goal of standardization and harmonization in this area of laboratory medicine. The recommendations were published on English language, however Croatian translation was printed in a form of a booklet and distributed to every medical-biochemistry laboratory in Croatia (Figure 3).

Figure 3**The main page of a Croatian national recommendations for laboratory diagnostics of chronic kidney disease (booklet)**

The national recommendations are mainly based on the KDIGO 2012 guidelines, however, novel literature findings are also incorporated. Considering the results obtained via conducted survey, our main goal was to provide recommendations that can be easily applied in every medical biochemistry laboratory in Croatia. We, as a WG and authors of recommendations, decided to start at the basic laboratory tests used in laboratory diagnostics of CKD: creatinine, eGFR, urine albumin-to-creatinine ratio (ACR)

and urine protein-to-creatinine ratio (PCR). The text of the national recommendations is organized to identify critical points in four major laboratory tests used in basic laboratory diagnostics of CKD. The draft of the recommendations was sent to numerous national and international experts for their comments. The manuscript was also made available for public consultation. All comments were carefully considered and incorporated into the final version of the recommendations.

It is rather difficult to give unique and uniform recommendations, regarding a large heterogeneity amongst methods and populations. Our intention was to point out to some weak points in pre-, post- and analytical phase, as well as some basic pediatric considerations, but every laboratory must set their own specifications for method performance and handling the specimens, according to their possibilities and conditions.

The main messages in the recommendations are as follows:

- Creatinine should be measured using an enzymatic assay
 - eGFR should be calculated using the CKD-EPI formula
 - Urine albumin should be measured as albumin/creatinine ratio.
 - A morning sample or a random spot sample should be used.
1. Creatinine assays should be traceable to a reference material which creatinine concentration assigned by GC-IDMS technique.
 2. When reporting the creatinine result, eGFR should also be reported in adult (>18 years) population. A warning expression should be included in the report form if eGFR result is <60 mL/min/1.73 m².
 3. eGFR values should be expressed quantitatively up to 90 mL/min/1.73 m² by CKD-EPI equation. Above 90 mL/min/1.73 m², eGFR values can be expressed quantitatively or >90 mL/min/1.73 m².
 4. eGFR equations of the adult population should not be used for pediatric population. Different equations utilizing also patient height should be used. The enzymatic creatinine assay should be preferred. eGFR based on cystatin C can be used for confirmation in the pediatric population.

So, our final goal for 2017, as a Joint Working Group, will be a complete implementation of national guidelines.

Every member of the WG participates in the implementation process. We intend to provide relevant information to every medical biochemist in our geographically diverse country. To facilitate implementation of national guidelines the members of a national WG gave a series of lectures entitled: „The role of laboratory testing in detection and classification of chronic kidney disease: national recommendations”.

To assess the national recommendations implementation process, our subsequent actions include repeating a slightly modified survey by the end of 2017. The biggest challenge remains introduction of albuminuria measurement in primary health care laboratories. This is a regulatory issue that requires the involvement of the State and our health care system to finance the introduction of the new tests in primary health care labs that represent about 70% of medical-biochemistry labs in Croatia. This problem is already presented twice to responsible regulatory bodies, however no agreement was made so far.

Future plans also include cooperation with Croatian Society for Nephrology, Dialysis and Transplantation of Croatian Medical Association – initial contact has already been established and there is good will to continue with this project in the future.

CONCLUSION

Guidelines call attention to increasing awareness to CKD and implementation of a new guideline for medical laboratories (Turkey), clinical services, and preventive interventions (France, Norway).

As seen in Croatian example, services that were not previously offered to patients may be available as a response to newly released guidelines.

Explicit guidelines improve clinical practice; however clinical guidelines will achieve the full potential only if appropriate strategies are selected at each stage of the implementation (28). Examples shown in this review may provide valuable experience for countries that are in process of creating their national CKD guidelines.

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