EFLM Paper

Etienne Cavalier*, Konstantinos Makris, Oytun Portakal, Ana Nikler, Pradip Datta, Tomas Zima and Pierre Delanaye for the EFLM Task Group on CKD

Assessing the status of European laboratories in evaluating biomarkers for chronic kidney diseases (CKD) and recommendations for improvement: insights from the 2022 EFLM Task Group on CKD survey

https://doi.org/10.1515/cclm-2023-0987
Received September 6, 2023; accepted September 12, 2023; published online October 2, 2023

Abstract

Objectives: Chronic kidney disease (CKD) is a global health issue, ranking as the third leading cause of death worldwide. CKD diagnosis and management depend on clinical laboratory tests, necessitating consistency for precise patient care. Global harmonization of CKD testing through clinical practice guidelines (CPGs) is recommended. Prior to CPG development, assessing the current CKD testing landscape is crucial. In 2022, the European Federation of Laboratory Medicine (EFLM) conducted an online survey among European laboratories associated with EFLM, evaluating CKD testing practices, including new glomerular filtration rate (GFR) estimation methods. This report summarizes the 2022 survey findings and offers recommendations for improving CKD test standardization.

Methods: An online survey was conducted in November 2022 using a questionnaire hosted on LimeSurvey sent to European laboratories affiliated with the EFLM. The survey results were recorded in Excel files and analysed.

Results: The results highlight significant discrepancies among countries in unit expression, methods, cystatin C use, and GFR calculation equations. Additionally, limited attention to pediatric renal biology specifics, varied proteinuria and albuminuria result expressions, and limited awareness of GFR measurement methods through iohexol clearance are noted.

Conclusions: In an effort to enhance the standardization of crucial biomarkers utilized in nephrology for evaluating renal function and diagnosing kidney injuries, the EFLM Task Group on CKD suggests nine practical recommendations tailored for European laboratories. The group is confident that implementing these measures will minimize result expression discrepancies, ultimately leading to enhanced patient care.

Keywords: creatinine; cystatin C; glomerular filtration rate; recommendations; equations; survey

Task Group on Chronic Kidney Disease (TG-CKD): Board members: Nataša Bogavac Stanojević (RS), Isabel Cachapuz-Guerra (PT), Laurence Chardon (FR), Pradip Datta (US), Pierre Delanaye (BE) Konstantinos Makris (GR), Ana Nikler (HR), Oytun Portakal (TR), Elke Schäffner (DE), Tomas Zima (CZ) and Etienne Cavalier (BE). National Societies' Representatives: Maria Averina (NO), Sanja Stankovic (RS), Janez Klavž (SL) and Nayra Rico Santana (SP).

***Corresponding author: Professor Etienne Cavalier**, Department of Clinical Chemistry, University of Liege, CIRM, CHU de Liège, Domaine du Sart-Tilman, 4000 Liège, Belgium, Phone: +32 4 323 8822; Fax: +32 4 323 8823, E-mail: Etienne.cavalier@chuliege.be. https://orcid.org/0000-0003-0947-2226

Konstantinos Makris, Department of Clinical Biochemistry, KAT General Hospital, Athens, Greece

Oytun Portakal, Department of Biochemistry, Hacettepe University Medical School, Ankara, Türkiye

Ana Nikler, Department of Medical Laboratory Diagnostics, University Hospital "Sveti Duh", Zagreb, Croatia

Pradip Datta, Siemens Healthineers Diagnostics, Newark, DE, USA

Tomas Zima, Institute of Medical Chemistry and Laboratory Medicine, 1st Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic

Pierre Delanaye, Department of Nephrology, Dialysis and Hypertension, CHU de Liège, Liège, Belgium. https://orcid.org/0000-0002-1480-5761

Introduction

Chronic kidney disease (CKD) is a significant health condition characterized by long-term abnormalities in kidney structure or function. In 2019, CKD was responsible for 41.5 million disability-adjusted life years (DALYs) and resulted in

697 million deaths globally. CKD has risen to become the third leading cause of death worldwide and the 11th in the global rankings [1].

Given that CKD often progresses silently, clinicians heavily rely on clinical laboratory results to diagnose, classify, treat, and monitor patients. The Kidney Disease: Improving Global Outcomes (KDIGO) Guidelines play a crucial role in categorizing CKD patients into six stages based on the estimated glomerular filtration rate (eGFR), which is derived from the serum concentration of creatinine [2]. The guidelines also define three levels of kidney damage based on albuminuria. These factors, along with the underlying cause of the disease, form the foundation for assessing the severity and risk associated with CKD. Hence, achieving a high level of harmonization and common practices in these tests globally, or at least within regional contexts, is essential to ensure consistent and accurate results across clinical laboratories, thus avoiding confusion and enabling optimal patient care.

To facilitate this harmonization, the development or proposal of clinical practice guidelines (CPGs) specific to CKD on a global scale is highly recommended [3]. However, before proceeding with such guidelines, it is crucial to gain a comprehensive overview of the current state of CKD testing in national or supranational environments. In 2019, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Committee on Kidney Disease (IFCC C-KD) designed a questionnaire [4] that was subsequently transformed into an internet survey, enabling clinical laboratories to provide a snapshot of the CKD testing landscape. Building upon this initiative, the European Federation of Laboratory Medicine (EFLM) Task-Group on Chronic Kidney Diseases (EFLM TG-CKD) took the opportunity to administer the questionnaire to European clinical laboratories in 2022. This allowed for a new assessment of the evolution of CKD testing, particularly in light of important developments, such as the emergence of new equations for estimating glomerular filtration rate (GFR).

In this report, we will summarize the findings of the 2022 survey. Additionally, we will propose simple recommendations aimed at enhancing the harmonization of commonly used tests in the field of CKD.

Methods

The questionnaire, together with all the translations in eight languages, can be found elsewhere [4]. For the purpose of the survey, the English version was transformed into a LimeSurvey (https://limesurvey.org) online survey tool under the supervision of the EFLM Communication Committee chaired by Dr. Daniel Rajdl. The 2022 version of the questionnaire was slightly modified and adapted to the changes that occurred since 2019, notably the introduction of the 2021 “race-free” CKD-EPI and 2019 EKFC equations [5, 6]. The survey was sent in November 2022 to National societies affiliated with the EFLM only since it was an initiative of the EFLM TG-CKD limited to European laboratories. A reminder was sent to increase the number of participants and the survey was closed after about 2 months. The results of the survey were extracted on an Excel files that was analysed by one of the authors (EC). For the representativeness of the participation by country, the results were normalized by million of habitants per country. We used Adobe PDF X-Change Editor (Adobe Systems Incorporated, San Jose, CA) to graphically represent the results on European maps that were imported from d-maps website (https://d-maps.com). For the sake of space and clarity, we used the ISO 3166-1 alpha-2 codes to designate the participating countries.

Results

Thirty-five countries, member of the EFLM, have participated to this survey. These countries were Albania (AL), Bosnia and Herzegovina (BA), Belgium (BE), Bulgaria (BG), Switzerland (CH), Cyprus (CY), Czechia (CZ), Germany (DE), Denmark (DK), Estonia (EE), Finland (FI), France (FR), Greece (GR), Croatia (HR), Hungary (HU), Ireland (IE), Italy (IT), Lithuania (LT), Latvia (LV), Montenegro (ME), Portugal (PT), North Makedonia (MK), Norway (NO), Poland (PL), Romania (RO), Russian Federation (RU), Serbia (RS), Slovenia (SI), Slovakia (SK), Spain (SP), Sweden (SE), The Netherlands (NL), United Kingdom (UK) and Turkey (TR). We did not receive any results from Austria, Island, Luxemburg and Ukraine. For technical reasons, it was not possible to receive results from Israel and Georgia.

Six hundred and seventy-five participants have attempted to connect to the questionnaire. Among these, 568 have declared measuring creatinine: 19.4 % from primary care facilities and private laboratories, 47.2 % from general hospitals and 42.6 % from academic ones. The participation varied from country to country. Figure 1 proposes the normalization of the participation country by country per million of habitants.

The methods used to measure creatinine were uncompensated Jaffe (11.3 %), compensated Jaffe (46.1 %), enzymatic (39.1 %) and dry chemistry (0.9 %). Twenty-four facilities (4.2 %) used a point of care to measure creatinine on whole blood. Figure 2 presents the type of method predominantly used for creatinine measurement by country.

Regarding the units to express creatinine, 47.1 % of the participants used ponderal ones (mg/dL) with either zero or one digit (10.4 %) or two digits (36.7 %) whereas international units (µg/L) were used by 51.8 % of the participants (42.8 % without any digit and 9.0 % with one digit). Both ponderal

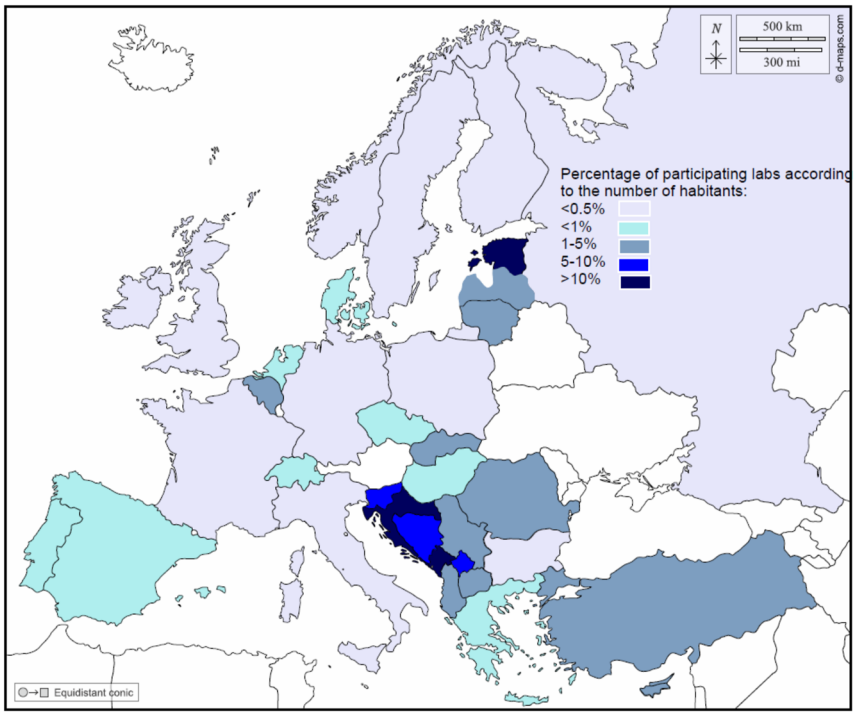

Figure 1: Percentage of laboratories who have participated to the 2022 EFLM survey normalized by million of inhabitants.

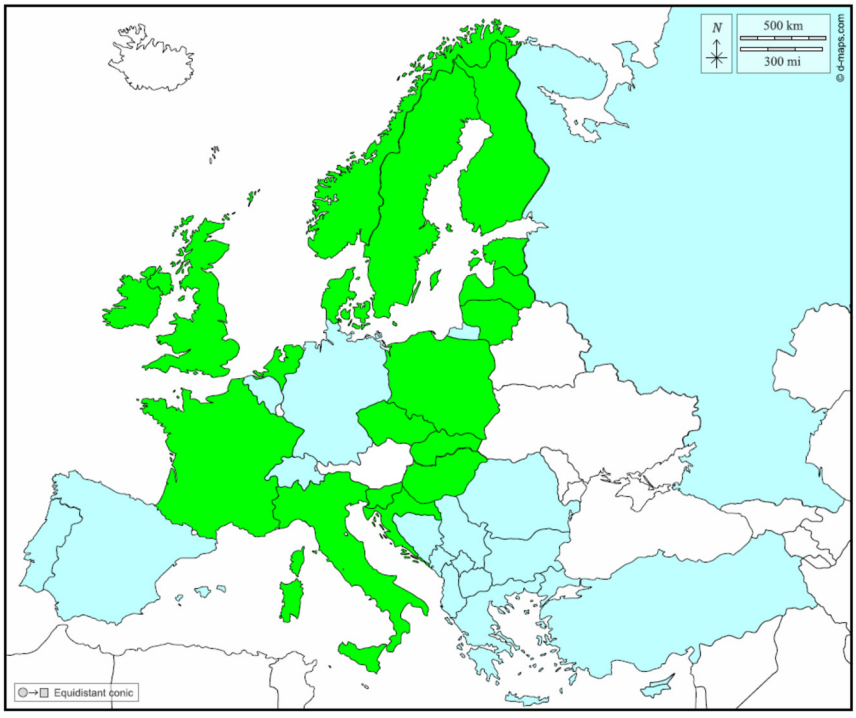

Figure 2: Distribution of the most widely used method for measuring serum creatinine per country: enzymatic (light green) or Jaffé (light blue).

and international units were proposed by 1.4 % of the participants. The unit chosen varied according to the country and was very different from country to country. However, inside the same country, the choice of the unit (ponderal vs. international) was very homogenous. Figure 3 presents the unit predominantly used in each country.

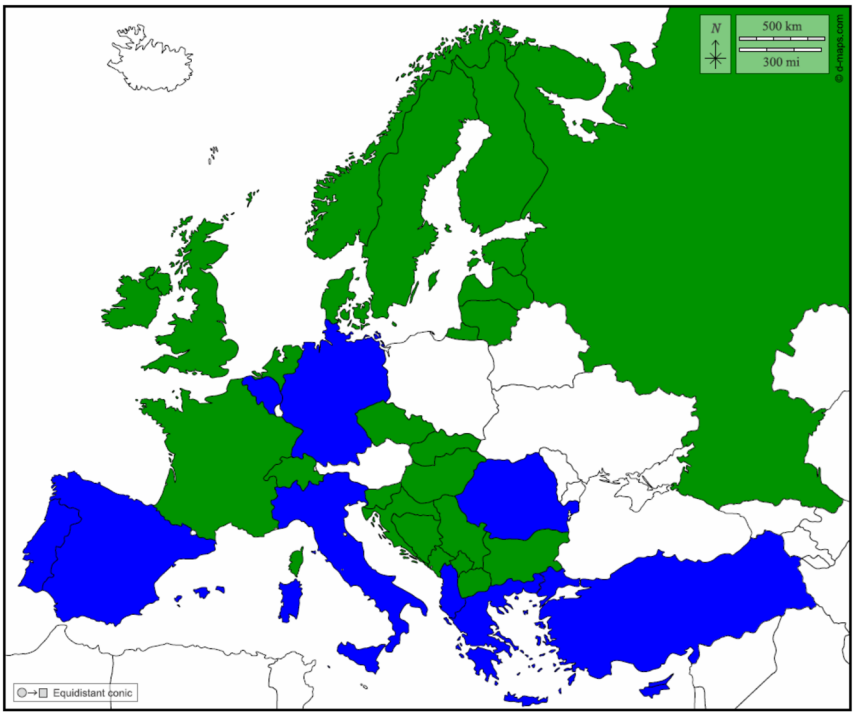

Figure 3: Distribution of the most widely used units for the expression of serum creatinine results per country: molar (dark green) or ponderal (dark blue).

The majority of the participants (69.9 %) automatically reported an estimation of the GFR in adults with a formula when creatinine determination was prescribed, whereas 14.5 % reported an eGFR only when requested by the clinician. Of note, 15.7 % of the participants did not report any eGFR. Figure 4 represents the habits on reporting GFR for each country.

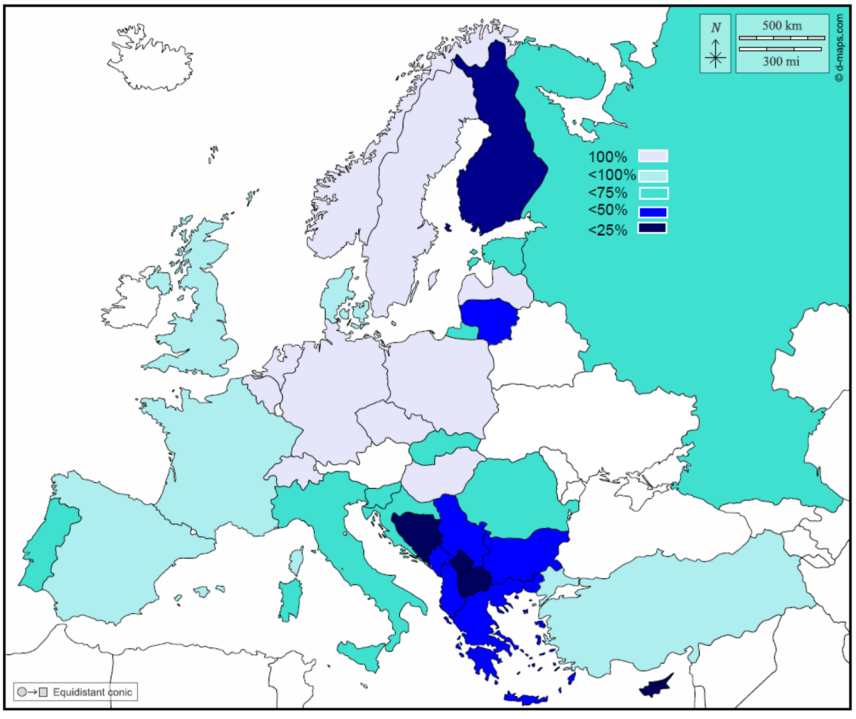

Figure 4: Percentage of automatic reporting of GFR when serum creatinine is requested per country.

Among the formulas used to report eGFR, the CKD-EPI 2009 equation [7] was the most largely used (53.4 %). The second most frequently used equation was the 2021 "race free" version of the CKD-EPI equation [8] which is now proposed by 20.1 % of the participants, followed by the MDRD formula [9] (17.1 %). Twenty-eight (6.6 %) laboratories also mentioned using the Cockcroft-Gault equation [10], six laboratories the revised Lund-Malmö one [11]. Three laboratories were using the FAS equation [12] and three other the new EKFC one [6].

The "race" factor for the CKD-EPI 2009 equation was not used by the majority of the laboratories (75.0 %). The laboratories provided a calculation with a race factor when the clinician or the patient provided the information in 17.2 % of the cases, mentioned a comment proposing the adaptation for black race in 7.8 % of them or systematically provided both results in 6.9 % of the situation.

Ten laboratories (1 in BE, SI, NO; 2 in FR and 5 in SE) measured the GFR by iohexol clearance by LCMS/MS or HPLC/UV. Two laboratories in SP mentioned their will to set-up iohexol clearance for measuring GFR.

A vast majority (71.5 %) of the participants do not measure cystatin C (CysC). The use of CysC is however rather country dependent (Figure 5). Regarding the measuring technology, turbidimetry is more often used than nephelometry (65.0 vs. 28.5 %, respectively). Among the labs who measure CysC, 43.9 % of do not provide systematic eGFR. The equations which were mostly used to report CysC eGFR in adults were the 2012 CKD-EPI ones [13], either using CysC alone (25.2 %) or/and both creatinine and CysC (8.4 %). The 2021 creatinine and CysC-based equation to estimate eGFR without race [5] has been implemented in 15 (14 %) of the laboratories. CAPA equation [14] was used in 5 laboratories (all in SE), Larsson [15], FAS and Hoek [16] equations in one laboratory each.

The majority of the participants (72.2 %) measuring CysC used the mg/L as unit, either with one digit (47.2 %) or two digits (25.0 %). The 27.8 % remaining used the mg/dL unit, either with two digits (18.5 %), one digit (7.4 %) or even no digit (n=2; 1.9 %).

Approximately the same percentage of participants (61.6 %) have provided a response for the question on eGFR based on creatinine for children. The original [17] and revised [18] Schwartz formulas were the mostly used (by 19.0 and 20.5 % of the participants), followed by the EKFC equation (11 participants; 3.2 %), the FAS equation (n=5), and the Lund-Malmö one (n=3).

Sixty-eight percent of the CysC users also measure it in children (n=73) but the majority of them (53.4 %) did not provide any CysC-based eGFR. The 2012 CKiD [19] was the mostly used equation (n=18; 24.7 %). The other equations used to estimate eGFR in kids was the 2021 creatinine and CysC-based equation to estimate eGFR without race (n=6; 8.2 %), the CAPA equation (n=5; 6.8 %), the FAS equation (n=3), the Larson and the Filler equation (n=1 each).

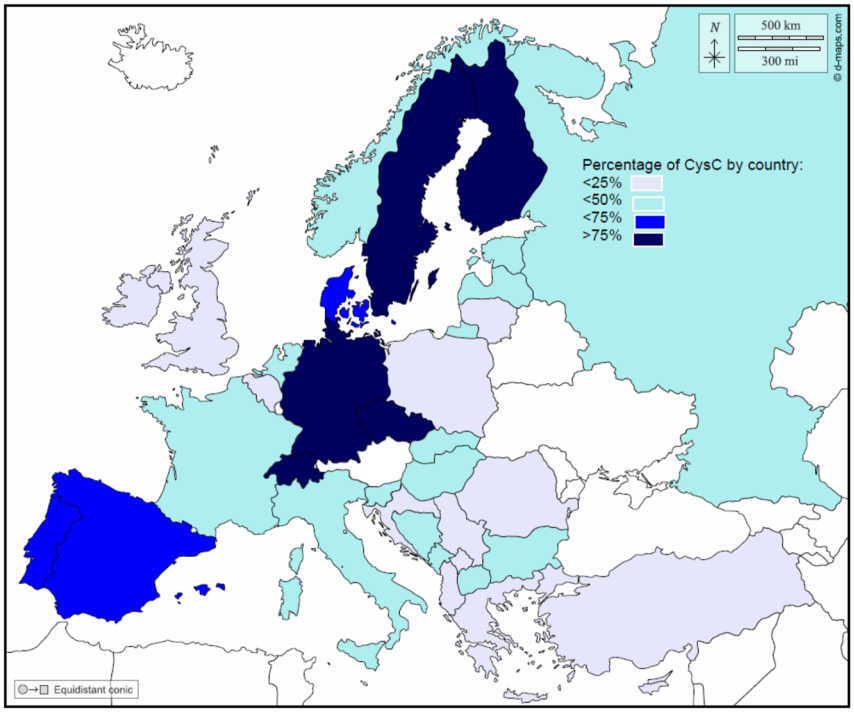

Figure 5: Percentage of the use of cystatin C per country.

Proteinuria and albuminuria were measured by 346 and 273 participants, respectively. Strips aiming at a qualitative estimation of urine proteins or the albumin to creatinine ratio were used by 198 and 51 participants, respectively. Urine proteins were quantified by turbidimetry (50.3 %), colorimetry (38.4 %) and nephelometry (9.5 %) whereas albuminuria remained mainly quantified by turbidimetry (90.8 %) compared to nephelometry (9.2 %).

Albuminuria results were provided to clinicians in different forms and units. The cut-offs varied according to the expression of the results (i.e. <20 mg/L, <30 mg/g creatinine, <30 mg/24 h, spot sample, <2 mg/dL, <2.5 (or <3.0) mg/mmol creatinine, <20 µg/min).

Discussion

The results of this survey reflect the behaviour of different European laboratories regarding the most important biomarkers used in nephrology to assess renal function and diagnose kidney injury.

Jaffe or enzymatic methods to measure serum creatinine (sCr) are rather equivalently used by European laboratories. However, the repartition is very country-related since some countries have clearly totally abandoned the Jaffe methods for the enzymatic ones whereas, in some other European countries, Jaffe methods are still massively used. If we can argue on the interest of the enzymatic technique in adults, especially in CKD patients, **there is no doubt that enzymatic methods should be the only ones to be used in children due to their better accuracy in the lower concentration ranges** [20, 21]. Regarding the units used to express sCr concentration, a similar repartition was observed between molar and ponderal units. Even if the "µmol/L" unit is recommended from a metrological perspective, it is more important that the same unit is used in the same region. The results from the survey show that, **within the same country, the same unit is used**, which is reassuring. Regarding the number of digits, we observed some disparity of the responders, which should be improved. To avoid such disparities, **we recommend rounding to the nearest whole number when sCr results are expressed in µmoL/L (i.e.: 87.6 µmol/L → 88 µmoL/L) and, for ponderal units (mg/dL), to round to the nearest 100th of a whole number (i.e.: 1.21 mg/dL, NOT 1.2 mg/dL or 1.213 mg/dL)**.

The KDIGO guidelines recommend the automatic estimation of GFR when serum creatinine is available. However, in 2022, 30 % of laboratories were still not adhering to this recommendation, indicating a need for improvement. This situation appears to be more prevalent in certain countries such as BA, GR, KS, RO, and RS. Therefore, these countries will require a concerted effort to ensure compliance with the KDIGO recommendation.

In terms of equations used to estimate GFR, the 2009 CKD-EPI equation was employed by just over half of the European laboratories. Interestingly, the newer "race-free" CKD-EPI equation emerged as the second most commonly utilized equation in Europe, with approximately 20 % of laboratories reporting its use. The transition from the 2009 equation to the 2021 equation appears to be a logical progression, particularly for laboratories that were already employing the 2009 CKD-EPI equation. However, two European Scientific Societies, EFLM [22] and ERA [23] (European Renal Association) have written position papers against the use of this equation in Europe, but these papers have been published during the second half of 2022. Also, the EFLM has favoured the EKFC equation, established and validated in European populations, but this new formula has also been recently published (2021) and European laboratories might not be aware of it. **As a European Society, we favour the use of European equations, either EKFC or Lund Malmö ones since they have been established and validated in a European population. The most important remains however to avoid too much disparity at the regional level. Laboratories should also avoid using more than one equation to estimate sCr based eGFR**.

Approximately 70 % of European laboratories do not measure CysC. The cost of the test, as well as potential national policies that do not provide reimbursement, are likely reasons why CysC is not widely used in some countries, such as the UK, while virtually all labs in other countries, like SE, utilize it. This discrepancy could also be attributed to the influence of national opinion leaders and/or guidelines. The survey reveals that approximately half of the laboratories that measure CysC do not provide a cystatin C-based eGFR, even though they do so when creatinine is requested. Among those that do provide eGFR, some laboratories use an equation that only considers CysC, while others utilize equations that incorporate both CysC and creatinine. It is not the purpose of this paper to determine whether CysC should be measured in addition to or instead of SCr, but **we believe it is important for laboratories to provide an eGFR when CysC is requested. When both SCr and CysC are requested, an equation that calculates the eGFR based on both biomarkers should be provided. As for the equations to be used, we prefer European ones such as CAPA, Larsson, or EKFC, which was published in the New England Journal of Medicine a few months after the survey's**

completion. However, regional harmonization should also be pursued in this regard.

There seems to be some disparity regarding the units used to express CysC, even in the same country, which is an issue. **We recommend that serum cystatin C concentration are expressed in mg/L and rounded to the nearest 100th of a whole number (i.e. 1.21 mg/L, NOT 1.2 mg/L or 1.213 mg/L)**.

This survey reveals that an important work should be done to improve the reporting of results for children and adolescents. Indeed, among the 60 % of the overall participants that provided a response to the question of the eGFR based on creatinine for children, around three quarters of them (74.7 %) did not provide any creatinine-based eGFR for children or adolescents, either with creatinine or CysC. This situation calls for immediate improvement. **We strongly recommend using an eGFR equation in children and adolescents. In this regard, we advocate for the utilization of European equations such as the CAPA or the EKFC equations. The EKFC equation is particularly noteworthy as it allows for a seamless transition from paediatric to adult equations without any artificial "jump," making it suitable for use across a wide age range starting from 2 years old and extending into adulthood**.

Only a small number of laboratories currently use the reference method (iohexol clearance) for measuring GFR. In the majority of countries, this technique is not available, whereas in countries like SE, it is commonly practiced. We have identified only a few countries (BE, DE, FR, IT, NL, NO, SE, SI, TR and UK) where at least one laboratory offers the measurement of iohexol using HPLC/UV or LCMS/MS. With the discontinuation of inulin and the nuclear medicine technique ^{51}Cr-EDTA clearance, and also the emergence of new, commercially available methods to measure iohexol, there is an opportunity for clinical laboratories to fill this gap. **We recommend that at least one laboratory in each European country is capable of measuring iohexol to measure GFR**. Interestingly, many survey participants reported that they do not receive requests for measuring GFR. However, it is intriguing to note that a significant number of participants mistakenly consider creatinine clearance based on 24-h urine collection as a reference method for measuring GFR, which is entirely incorrect.

Interpreting the results of the survey about proteinuria and albuminuria is more challenging. These tests were performed by most of the participants, who unfortunately provide results in different units. Also, the cut-offs used for albuminuria varied according to the expression of the results (i.e. <20 mg/L, <30 mg/g creatinine, <30 mg/24 h, spot sample, <2 mg/dL, <2.5 (or <3.0) mg/mmol creatinine, <20 µg/min). The responders of the survey also disagree on the best sample needed to measure albuminuria. Accordingly, a real confusion exists for this highly relevant biomarker of renal damage, which is totally unfortunate. **We recommend using the normalisation of albuminuria by urine creatinine (ACR) and to express the results either in mg/g or mg/mmol. There again, a regional harmonization is of greatest importance. Cut-offs should thus be <30 mg/g or <3 mg/mmol. The recommended sample should be first urine sample collected during mid-stream voiding in the morning. The term "microalbuminuria" should be abandoned and replaced with the term "albuminuria"**.

In conclusion, the EFLM TG-CKD conducted a survey on the practices of European clinical laboratories in managing biochemical tests related to CKD. While the participation was significant, it should be noted that these results only offer a partial reflection of the actual situation. Some countries were underrepresented, while others were overrepresented due to the extensive participation of their laboratories. The findings emphasize crucial areas for improvement, for which we have proposed recommendations.

Specifically, there is a need to harmonize the reporting of significant figures for serum creatinine and cystatin C. Additionally, the equations used for eGFR based on serum creatinine should be standardized, and the 2021 CKD-EPI equation should not be used in Europe. Instead, European equations should be favoured. Furthermore, the utilization of cystatin C is expected to increase in the coming years, warranting improvements. Laboratories measuring cystatin C should provide cystatin C-based equations, both independently and in combination with serum creatinine, again prioritizing European equations.

The results also shed light on the inadequate service provided by clinical laboratories for children, and we have put forth recommendations to address this issue. Furthermore, the prominence of measured glomerular filtration rate (mGFR) is expected to grow in the future, but currently, only a few laboratories/countries can offer this service. Efforts should be made to improve this situation, particularly through the development of commercially available solutions.

Lastly, the survey highlighted the challenges associated with measuring albumin in urine. To benefit clinicians and ultimately improve patient care, we have provided recommendations to address these issues and establish a standardized approach. These recommandations are summarized in Table 1.

Table 1: Summary of the recommendations of the EFLM Task Group on Chronic Kidney Diseases to improve harmonization of the practices of the European clinical laboratories for biomarkers of kidney function.

Biomarker	Aspect	Recommendation
Serum creatinine	Analytical determination in children	Enzymatic methods should be the only ones to be used in children due to their better accuracy in the lower concentration ranges
Serum creatinine	Units	Even if molar units are recommended from a metrological perspective, it is more important that the same unit is used in the same region/country
Serum creatinine	Number of digits	We recommend rounding to the nearest whole number when sCr results are expressed in µmoL/L and, for ponderal units (mg/dL), to round to the nearest 100th of a whole number
Creatinine-based eGFR equations	Equation	As a European Society, we favour the use of European equations, either EKFC or Lund Malmö ones since they have been established and validated in a European population. The most important remains however to avoid too much disparity at the regional level. Laboratories should also avoid using more than one equation to estimate sCr based eGFR
Cystatin C-based equations	Equation	It is important for laboratories to provide an eGFR when CysC is requested. When both SCr and CysC are requested, an equation that calculates the eGFR based on both biomarkers should be provided. As for the equations to be used, we prefer European ones such as CAPA, Larsson, or EKFC. However, regional harmonization should also be pursued in this regard
Cystatin C	Units and number of digits	We recommend that serum cystatin C concentration are expressed in mg/L and rounded to the nearest 100th of a whole number
eGFR equations in children	Equation	We strongly recommend using an eGFR equation in children and adolescents. In this regard, we advocate for the utilization of European equations such as the CAPA or the EKFC equations. The EKFC equation is particularly noteworthy as it allows for a seamless transition from paediatric to adult equations without any artificial "jump," making it suitable for use across a wide age range starting from 2 years old and extending into adulthood
Measured GFR	Availability of iohexol clearance	We recommend that at least one laboratory in each European country is capable of measuring iohexol clearance to measure GFR
Albuminuria	Normalization of the results	We recommend using the normalisation of albuminuria by urine creatinine (ACR) and to express the results either in mg/g or mg/mmol. There again, a regional harmonization is of greatest importance.
	Units	
	Best sample	Cut-offs should thus be <30 mg/g or <3 mg/mmol.
	Correct spelling	The recommended sample should be first urine sample collected during mid-stream voiding in the morning.
		The term "microalbuminuria" should be abandoned and replaced with the term "albuminuria".

Acknowledgments: We would like to thank Dr. Daniel Rajdl (EFLM Communication Committee) and Mrs Silvia Cattaneo (EFLM Office) for their kind technical support.
Research ethics: Not applicable.
Informed consent: Not applicable.
Author contributions: The authors have accepted responsibility for the entire content of this manuscript and approved its submission. Etienne Cavalier and Pradip Datta are consultant for Nephrolyx.
Competing interests: The authors state no conflict of interest.
Research funding: None declared.
Data availability: Not applicable.

References

1. Rutter H, Horton R, Marteau TM. Global burden of disease 2019: GBD cause and risk summaries chronic kidney disease. Lancet 2020;396:152–3.
2. KDIGO Working Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int 2013;3:1–163.
3. Levin A, Tonelli M, Bonventre J, Coresh J, Donner JA, Fogo AB, et al. Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. Lancet 2017;390:1888–917.
4. Biljak VR, Grubb A, Guerra IC, Cavalier E, Raymondo S, Sierra-Amor R, et al. The first step in creating national Chronic Kidney Disease (CKD) guidelines-a questionnaire. Biochem Med 2019;29:1–30.
5. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. N Engl J Med 2021;385:1737–49.
6. Pottel H, Björk J, Courbebaisse M, Couzi L, Ebert N, Eriksen BO, et al. Development and validation of a modified full age spectrum creatinine-based equation to estimate glomerular filtration rate. Ann Intern Med 2021;174:183–91.
7. Levey AS, Stevens La, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.
8. Levey AS, Tighiouart H, Titan SM, Inker LA. Estimation of glomerular filtration rate with vs without including patient race. JAMA Intern Med 2020;180:793–5.

9. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461–70.
10. Cockcroft D, Gault M. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
11. Nyman U, Grubb A, Larsson A, Hansson LO, Flodin M, Nordin G, et al. The revised Lund-Malmö GFR estimating equation outperforms MDRD and CKD-EPI across GFR, age and BMI intervals in a large Swedish population. Clin Chem Lab Med 2014;52: 815–24.
12. Pottel H, Hoste L, Dubourg L, Ebert N, Schaeffner E, Eriksen BO, et al. An estimated glomerular filtration rate equation for the full age spectrum. Nephrol Dial Transplant 2016;31:798–806.
13. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367:20–9.
14. Grubb A, Horio M, Hansson LO, Björk J, Nyman U, Flodin M, et al. Generation of a new cystatin C-based estimating equation for glomerular filtration rate by use of 7 assays standardized to the international calibrator. Clin Chem 2014;60:974–86.
15. Larsson A, Malm J, Grubb A, Hansson LO. Calculation of glomerular filtration rate expressed in mL/min from plasma cystatin C values in mg/L. Scand J Clin Lab Invest 2004;64:25–30.
16. Hoek FJ, Kemperman FAW, Krediet RT. A comparison between cystatin C, plasma creatinine and the Cockcroft and Gault formula for the estimation of glomerular filtration rate. Nephrol Dial Transplant 2003; 18:2024–31.
17. Schwartz GJ, Haycock GB, Edelmann CM, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 1976;58:259.
18. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009;20:629.
19. Schwartz GJ, Schneider MF, Maier PS, Moxey-Mims M, Dharnidharka VR, Warady BA, et al. Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. Kidney Int 2012;82:445–53.
20. Piéroni L, Delanaye P, Boutten A, Bargnoux AS, Rozet E, Delatour V, et al. A multicentric evaluation of IDMS-traceable creatinine enzymatic assays. Clin Chim Acta 2011;412:2070–5.
21. Cobbaert CM, Baadenhuijsen H, Weykamp CW. Prime time for enzymatic creatinine methods in pediatrics. Clin Chem 2009;55:549–58.
22. Delanaye P, Schaeffner E, Cozzolino M, Langlois M, Plebani M, Ozben T, et al. The new, race-free, chronic kidney disease epidemiology consortium (CKD-EPI) equation to estimate glomerular filtration rate: is it applicable in Europe? A position statement by the European Federation of clinical chemistry and laboratory medicine (EFLM). Clin Chem Lab Med 2022;61:44–7.
23. Gansevoort RT, Anders HJ, Cozzolino M, Fliser D, Fouque D, Ortiz A, et al. What should European nephrology do with the new CKD-EPI equation? Nephrol Dial Transplant 2023;38:1.