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A summary of worldwide national activities in Chronic Kidney Disease (CKD) testing

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ABSTRACT

Chronic kidney disease (CKD) is a major public health issue worldwide and is associated with adverse health outcomes, especially in low- and middle-income countries. In a cash limited healthcare system, guidelines that improve the efficiency of health care free up resources needed for other healthcare services. This short review presents some examples from national acitivities in CKD testing, including countries throughout the globe: Mexico in North America, Uruguay in South America, Italy in Europe, Nigeria in Africa and India in Asia. Considering the fact that treatment of CKD is cost-effective and improves outcomes, this observation argue in favor of including CKD in national guidelines and noncommunicable chronic disease (NCD) programs. This diverse example of national activities fullfil the very first step in achieving this goal.

INTRODUCTION

Chronic kidney disease (CKD) is a major public health issue worldwide and is associated with adverse health outcomes, especially in low- and middle-income countries (1-4). Considering the fact that CKD is associated with high health-care costs, CKD is readily identifiable, treatment of CKD is cost-effective and improves outcomes (5), many countries are developing or refining national strategies for CKD (6). Howevever, despite two decades of widely accepted CKD clinical practice guidelines, such as the Kidney Disease Outcomes Quality Initiative (KDOQI) and recently The Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (7) and continuing medical education for physicians, recent reports from many developed countries indicate that CKD care remains suboptimal (8).

In a cash limited healthcare system, guidelines that improve the efficiency of health care free up recources needed for other healthcare services (9). Perhaps the intial step to create a guideline is to explore the current status of CKD testing in a national enviroment. Therefore, the aim of this article was to present a summary of worldwide national activities in CKD testing in various countries without already developed national CKD guidelines.

NORTH AMERICA

Creatinine standardization Mexican Pilot Study to determine accuracy and trueness

In Mexico, a national end-stage renal disease registry has not been developed. However, data from single state registries (10) and from the US Renal Data System (11) indicate that some Mexican states have an unusually high incidence and prevalence of CKD. Early recognition of CKD in the Mexican population will provide opportunities for slowing and in some cases preventing the natural progression of this disease to end-stage and the need for dialysis.

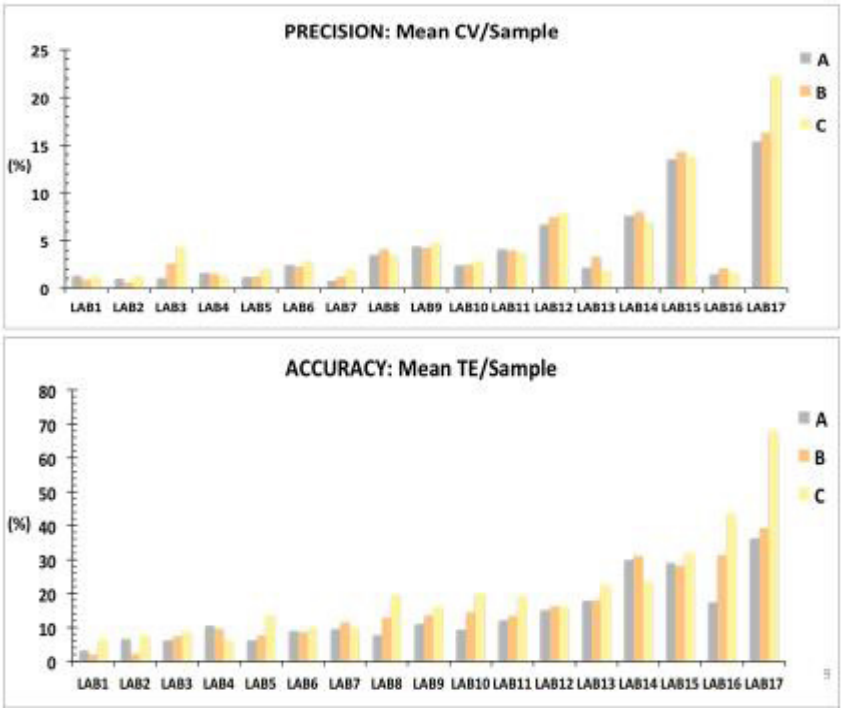
The early recognition of CKD may be achieved through an estimation of glomerular filtration rate (eGFR) – a well-recognized index of renal function. The calculation of eGFR for a given patient is based upon their age, gender and serum Creatinine (Cr) test result. The accurate measurement of creatinine is therefore an essential requirement for the accurate assessment of renal function. Significant differences exist between clinical laboratories (CL) for the measurement of creatinine. Standardizing the measurement and reporting of this analyte by CLs is an essential pre-requisite for the accurate diagnosis and management of CKD. In this short report, we examined the accuracy of creatinine measurements from some CLs in Mexico.

CLs nationwide were invited to participate, and a questionnaire was distributed. The CLs that voluntarily accepted to participate received 3 sets of human serum samples (3 samples/set) with differing concentrations of creatinine provided by CEQAL. The creatinine reference values in these samples had been assigned by the ID/MS reference method for the measurement of creatinine (12).

Each CLs recorded the measurement of Cr in each set of samples (one sample set analyzed on each of three separate days), the methodology, and the manufacturer´s information were also provided. Intra and inter-run coefficient of variation (CV) as well as total error percentage (TE %) were calculated and used for comparison.

A total of 17 CLs, 5 from public and 12 from private sector participated voluntarily. The mean CV% was 4.56 (1 to 18.04 %) and mean TE% was 16.6 (3.9 to 47.9%). When grouped, public CLs had a mean CV% of 3.93 and a mean TE% of 19.0, and private CLs of 4.82% and 15.7%, respectively.

Figure 1 Precision and accuracy of 17 Mexican clinical laboratories measuring creatinine using different methods and instruments

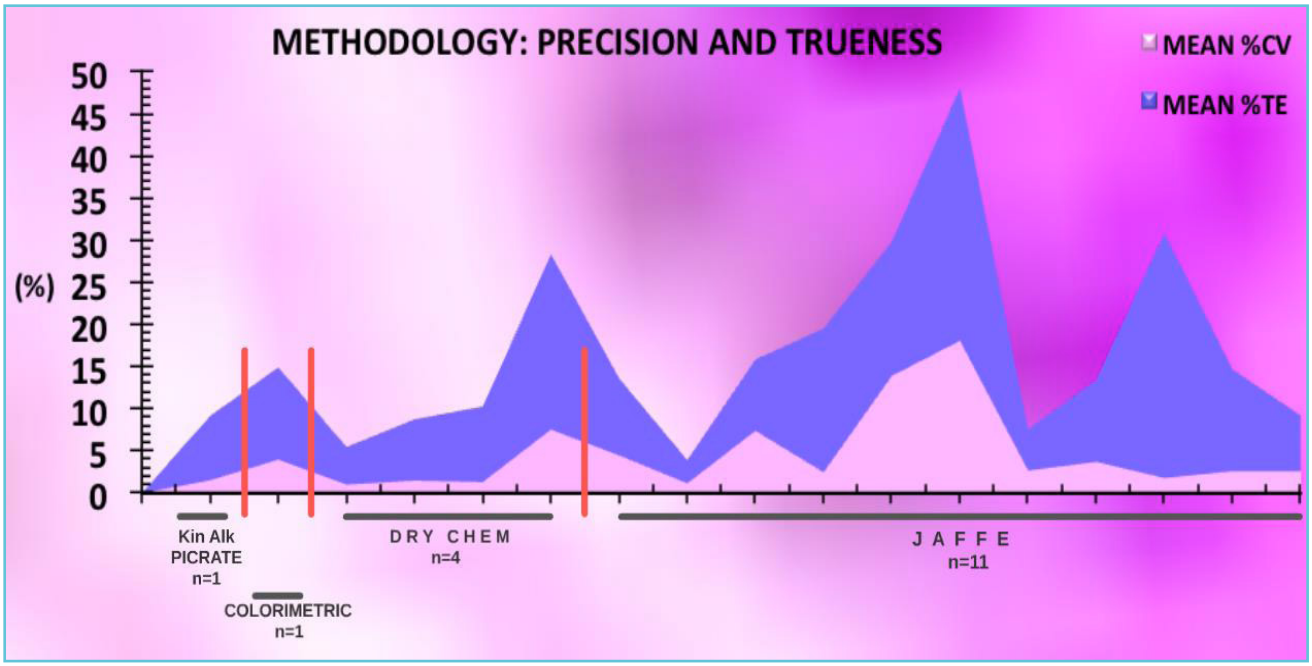


When compared individually to international standards, 4 CLs had a "minimum acceptable performance" (≤11.4 TE %), 3 a "desirable performance" (≤7.6 TE %), and 10 an "undesirable performance" (between 13.41 and 47.93 TE %). None had an "optimum performance" (≤3.8 TE %) (see Figure 1).

Most of the participating laboratories were operating Jaffe methods (see Figure 2). The bimodal nature of the Jaffe results may reflect differences between Jaffe and Jaffe compensated methods. This level of detail was not captured in this study. Some of the observed between method differences may have been due in part to the non-specificity of the Jaffe method. The between method precision data show that better precision can be achieved with a closed system (dry chemistry) as opposed to an open system (Jaffe). These data serve to highlight the methodological differences (in addition to calibration issues) that can exist between laboratories and the significant impact that they can have on reported test results.

The performance data from this accuracy based assessment pilot study serve to highlight the inaccuracy and variability of creatinine test results from a small sampling of Mexican laboratories. A desirable and/or minimum level of performance was achieved by 41% of the laboratories whereas an unacceptable level of performance was recorded for 59% of the participating laboratories. The methods used were alkaline picrate (n=1), colorimetric (n=1), dry chemistry (n=4) and Jaffe (n=11). These data demonstrate that there is an urgent need for a nationwide creatinine standardization program in Mexico that is directed towards improving the accuracy and reporting of creatinine test

Figure 2 Precision and trueness data sorted according to creatinine method used



results throughout the country. Standardized measurements of creatinine in Mexico will identify opportunities for preventing CKD while at the same time making sure that "most at risk" Mexicans are accurately identified, diagnosed and managed appropriately.

Recommendations for improving serum Cr measurement (13) as well as IFCC/WASPaLM TF-CKD survey results guided us to initiate this pilot study.

SOUTH AMERICA

Standardization of creatinine in Uruguay

CKD in Uruguay has a prevalence of 7%.

Interaction between laboratories and clinicians has taken place in a unique way through the External Evaluation Program conducted by the Committee for Standardization and Quality Control (CECC).

The Integrated Health System (SIS) in Uruguay has a National Fund of Resources (FNR), whose mission is to provide financing for highly specialized medical services, allowing them to be available with equity for the entire population.

Our country has a Renal Health Program (PSR), dependent on the FNR and the Ministry of Public Health (MSP), executed by the Honorary Committee on Renal Health (CHSR). The main purpose of PSR is to prevent CKD and improve the quality of life of the patients who carry it, seeking their integration into the SIS.

In view of the enormous economic losses the country was suffering, the CHSR contacted the CECC, looking for our help , with the hypothesis that the diagnosis of CKD could be improved as the quality of the creatinine result improved. Creatinine is the main tool for diagnosis of CKD throughout the glomerular filtration rate calculation. It was through the CECC that they could integrate all the laboratories in the country to standardize creatinine.

This Project was declared of National Interest by the Government, and CECC obtained a grant from the National Innovation Research Agency (ANII).

Given the need to have a Reference Laboratory to obtain target values of creatinine with traceability to reference methods and advice for the design of standardization procedures, the CECC incorporated into the national project the Reference Laboratory of the Argentine Biochemical Foundation (LARESBIC), which was formalized by an agreement that was signed in 2010.

The standardization was done using a reference method calibrated with certified materials by NIST and DGKL, with traceable values to the primary method of Isotopic Dilution and Mass Spectrometry.

The preparation, packaging and distribution in dry ice of the material used (native serum), was in charge of the CECC. An aliquot of vials was sent to LARESBIC Argentina under the same conditions, for the assignment of reference values (creatininase/sarcosine oxidase).

Four surveys were made

Level I: 98 Laboratories. 3 creatinine levels/3 samples/3days Date: March 2008

Level II: 73 Laboratories. 3 creatinine levels/3 samples/3days Date: November 2008

Level III: 101 Laboratories. 5 creatinine levels/2 samples/3days Date: September 2009

Level IV: Laboratories. 5 creatinine levels/2 samples/3days Date: March 2011

Imprecision, Systematic Error, Total Error and Regression Parameters were obtained.

Eleven years after the start of these activities, and with four surveys conducted and continuous monitoring through our EQAs, the evolution of the analyte is considered to have been favorable in statistically significant terms.

The analytical quality parameters have improved since the first distribution, but in the last two the situation has been maintained. This positive impact will deepen in the measure that the laboratories can incorporate the corrections that arise from the standardization, for which it will be necessary to lower their intra-laboratorial CVs through the Internal and External Control and using homogenous systems with traceability to the primary reference method.

EUROPE

STATUS OF LABORATORY TESTS FOR CHRONIC KIDNEY DISEASE IN ITALY

1. Educational activities by the Italian Society of Clinical Biochemistry and Laboratory Medicine (SIBioC)

After the issuing of the 2012 Kidney Disease Improving Global Outcomes Initiative (KDIGO) guideline (7), which included specific recommendations for the clinical laboratory, SIBioC has worked to diffuse the guideline content among the professional community in Italy, with the aim to help laboratories to implement the recommendations in their daily practice.

This was obtained through the publication of a number of papers in *Biochimica Clinica*, the SIBioC official journal, and the efforts of SIBioC Working Groups dealing with renal disease, that organized training courses using both traditional meeting and e-learning approaches.

2. Cooperation between SIBioC and clinical organisations

In 2009, a joint SIBioC-Italian Society on Nephrology recommendation was released (14) and, more recently, the Italian Minister of Health has issued a national guideline on identification and prevention of CKD in adults, with the proactive contribution of laboratory experts (15).

3. Laboratory tests

a. Serum creatinine

Two national evaluations have been recently published on the status of creatinine measurement

in Italy, both using commutable control materials with target values assigned by a higher-order reference procedure (16,17). Data seem to indicate that the standardization efforts are still having effects lower than expected. In 2014, only 41% of laboratories showed optimal performance [i.e., a total error (TE)<4.5%], while 16.6% were unable to reach even the minimum quality goal (i.e., TE<13.3%). It should be noted that enzymatic methods, although strongly promoted by SIBioC (18,19), are used in a minority of laboratories (~25%).

Table 1 **Main results of the 2015 national survey on the urine albumin measurement, compared with the results obtained in a similar survey performed in 2007 (Italy)**

	2007	2015
Type of sample		
24-h collection	43%	16%
First morning void	9%	59%
Second morning void	-	6%
Random	30%	19%
Partecipation to an EQAS		
Yes	28%	44%
No	72%	56%
Measurement unit		
mg/mmol creatinine or mg/g creatinine	15%	52%
µg/min	9%	5%
mg/24 h	33%	9%
mg/L	29%	26%

b. eGFR

Data on the use of equations to derive the GFR are still sparse and heterogeneous (17).

In 2013, employed equations were MDRD (69%), CKD-EPI (15%), Cockcroft-Gault (7%) and Schwartz (1%).

More importantly, ~25% of laboratories did not offer any eGFR option.

c. Urine albumin

In 2007 and 2015, SIBioC did two surveys to check the use of this parameter. As reported in the Table 1, results were encouraging in showing the improvement of adherence to the KDIGO recommendations.

EQAS show some variability among different commercial measuring systems, even if the whole performance is not so bad.

In 2014, 3.6% of laboratories were unable to fulfil the minimum quality level, while 88.6% showed good performance (defined as a TE<11%) (17).

4. Final remarks

SIBioC is dedicating many efforts to the standardisation of laboratory procedures for CKD diagnostics, through the action of its Working Groups and the publication of recommendations.

The situation is, however, far from optimal with large room for improvement, as indicated by EQAS and surveys results. In particular, some goals, indicated by Graziani et al. (17) with the corresponding indicators, have been identified for being pursued in a relatively short time.

It is also worthy to note that many of these objectives (availability of eGFR and use of CKD-EPI equation, report of albuminuria in the recommended terminology and unit, use of the recommended sample for urine albumin) can be achieved at no additional costs under the direct control of the clinical laboratory.

AFRICA

NATIONAL ACTIVITIES IN CKD TESTING: THE NIGERIAN CURRENT SITUATION

Prevalence

Various studies with different results possibly because mild-moderate cases excluded; meta-analysis for Saharan Africa gives prevalence as 13.9% (20). Prevalence of CKD in a Nigerian family practice population: 250 consecutive, newly registered patients during 2005-2006; 45% had increased urine albumin on first testing, persistent in 12.4%; 20% had low e-GFR on first testing, persistent in 10% (21).

Causes of CKD in Nigeria

Hypertension 30%; chronic glomerulonephritis 28%; diabetes 3%; obstructive uropathy 5%; others 3.9%; unknown 30% (Arogundade et al 2005); 37% CKD in a population of diabetic subjects (22); 38% CKD in HIV positive population in outpatient clinic (23); 24% CKD (e-GFR MDRD) in a HIV/AIDS population in tertiary referral unit (24,25).

The enormity of CKD in Nigeria

The Situation in a Teaching Hospital in South-East Nigeria showed CKD accounts for 8-10% of hospital admissions; death from end-stage renal disease constituted 22% of medical deaths (26).

Current/existing practices

Since information on activities in CKD testing at national level on how nephrologists/laboratories investigate patients can mainly be provided by national surveys, most of which is questionnaire-based with voluntary participation.

A questionnaire was sent to the membership of Association of Clinical Chemists of Nigeria (ACCN) in different hospitals across Nigeria (representing a complex mixture of private and public clinical laboratories) to seek information

on the current practices. The information obtained was then collated, analysed, and summarized for this submission.

Not surprisingly, there is evidence of differences in practice across laboratories in different parts of Nigeria. These differences are seen in all aspects of CKD testing including methods being used, commercial assay kits, commercial standards, commercial controls (SRMs or CRMs), and even some slight variations exist in creatinine reference interval values across laboratories in different states.

Chronic Kidney Disease testing in Nigeria (Summarized in Table 2)

1. ***Serum creatinine:*** in routine use, mostly commercial enzymatic and kinetic assay kits
2. ***eGFR (Cockcroft-Gault):*** still being used by some (though very few), based on some validation studies done in some population groups
3. ***eGFR (creatinine-based, MDRD):*** widely in routine use
4. ***eGFR (creatinine-based CKD-EPI):*** widely in routine use
5. ***Albumin/creatinine ratio:*** in routine use
6. ***Urine protein*****:** in routine use
7. ***Urinalysis* (*dipstick):*** mainly in routine screening/medical tests
8. ***Conventional 24-hour urine profile*****:** still being used in some institutions
9. ***eGFR (Cystatin C based CKD-EPI):*** currently for research use only, not yet routine
10. ***eGFR (Creatinine with cystatin C-based CKD-EPI):*** currently for research use only, not yet routine
11. ***Kidney injury molecule 1 (KIM 1):*** currently for research use only, not yet routine

Creatinine assay

Most institutions use commercial enzymatic (kinetic) assay kits.

Use of automation in creatinine assay

This is also widely distributed across the country, though less widely than the Roche Reflotron Point-of-Care machine. Automation systems in current use in different parts of the country include: ARCHITECT C4000, ABBOTT LABORATORIES, USA, Miura 200, ISE, Italy and TC-Matrix, Teco Diagnostics, USA etc.

Use of Point-of-Care Testing (POCT) in creatinine assay

Roche Reflotron machine, a point of care clinical chemistry equipment that measures creatinine with the result being made available within 5 minutes is widely distributed and used across the country (available in 196 health institutions across the country). Also, point of care testing equipment for measuring albumin to creatinine ratio is being used in some centers.

External quality assurance of creatinine (and other analytes) assays

A few public/governmental institutions partake in EQA (e.g UKNEQAS, with satisfactory results); several of the modern private institutions/laboratories are partakers with satisfactory results.

Routine reporting of eGFR/ standardisation

In Nigeria, some clinical chemists and clinicians have worked on use of eGFR to determine/evaluate renal function, both in the normal or apparently healthy population and in various diseases - “the studies cited under the introduction above”. A cut-off value of ≥60ml/min/1.73m^2 for the apparently healthy (non-CKD subjects) population using the 4-variable MDRD equation has been established in some regions/

Table 2 Summary of CKD testing in Nigeria

CKD testing approach	Current assay methods/practice	Currently in routine use	Currently for research only	Remarks
Serum creatinine	Automation, Enzymatic, Kinetic Spectrophotometry, POCT (Roche Reflotron) **Jaffe End point still done in some health institutions*	YES	NO	IDMS Traceable; Commercial enzymatic assay kits; Commercial standards and controls (SRMs and CRMs), e.g. Randox; EQA results satisfactory in institutions that engage
eGFR (creatinine-based, Cockcroft-Gault)	Automation, Enzymatic, Kinetic Spectrophotometry, POCT (Roche Reflotron)	YES	NO	Still being used by some (very few) based on validation studies done in some population groups
eGFR (creatinine-based, MDRD)	Automation, Enzymatic, Kinetic Spectrophotometry, POCT (Roche Reflotron)	YES	NO	Mostly 4-variable MDRD; IDMS Traceable
eGFR (creatinine-based CKD-EPI)	Automation, Enzymatic, Kinetic Spectrophotometry, POCT (Roche Reflotron)	YES	NO	Mostly IDMS Traceable
eGFR (Cystatin C based CKD-EPI	ELISA assays	NO	YES	Mostly commercial ELISA kits with controls and calibrators
eGFR (Creatinine with cystatin C-based CKD-EPI)	Creatinine (Automation, Enzymatic, Kinetic spectrophotometry); Cystatin C: ELISA	NO	YES	Mostly commercial ELISA kits with controls and calibrators
Kidney injury molecule 1 (KIM 1)	ELISA	NO	YES	Mostly commercial ELISA kits with controls and calibrators

Urine Albumin/ creatinine ratio	Albumin: Automation, ELISA, POCT equipment	YES	NO	Mostly commercial ELISA kits with controls and calibrators
24 hour Urine protein	Spectrophotometric	YES	NO	In cases that require 24 hour quantification (e. g Nephrotic syndrome)
Urinalysis (dipstick with/without microalbuminuria template)	Strips	YES	NO	Mostly at Point-of-Care and in routine screening/medical tests

zones of the country. Available data from different studies done in Nigerian population groups is consistent with the cut-off value of <60mL/min/1.73m^2 for CKD, using the 4-varaible MDRD equation. Sanusi et al. in Ile-Ife, South- western Nigeria (27, 28), Adebisi in Ilorin, North-central Nigeria (29), and Agaba et al. in Jos, North-eastern Nigeria (30) have proved that the MDRD equation is reliable alternative to measurement of endogenous creatinine clearance (Crcl) in the estimation of GFR in Nigerians. Currently, only a few clinical chemistry laboratories report eGFR. However, in many/most institutions, the nephrologists commonly use the creatinine result from the laboratories for eGFR (mostly MDRD and CKD-EPIcr equations).

CKD task force in Nigeria

ACCN will constitute a task force.

Collaboration with nephrologists

The Nigerian Association of Nephrology (NAN) developed ***Guidelines for the Detection and Management of Chronic Kidney Disease (CKD), 2nd May, 2011,*** though without involving the clinical chemists.

However, there is a level of collaboration being practised by nephrologists and clinical chemists in some centres/institutions in reporting eGFR, especially in the aspect of creatinine assay method, standardisation and traceability to IDMS, even though there is no Laboratory/ Nephrology Working Group put in place yet.

Conclusion and way forward

Need for ACCN to have a CKD Task Force who will work towards standardization of assays of creatinine and other markers of CKD across the country, and also collaborate with the nephrologists (Nigerian Association of Nephrology) in the following areas: agreement to recommend the routine reporting of e-GFR; agreement on clinical practice guidelines; joint initiative to promote the benefits of testing for CKD; preparation of educational support materials for laboratory personnel, family doctors and patients, renal physicians (31).

ASIA

SUMMARY OF NATIONAL ACTIVITIES IN CKD TESTING IN INDIA

In the large ethnicity of India, uniformity in testing is not available for CKD, and many a time not affordable. There is no one statutory control for the laboratory diagnosis in correlation with clinical diagnosis for various reasons at present.

The testing can be categorized into the following types of laboratories generally available in line with scope of services, Basic composite/ Medium/Advanced laboratories.

Awareness and protocol of testing is available, but actual performance is seen in some teaching, corporate and centres of excellence hospitals which are not in the reach of the population specially in outreach places and lower socio economic strata. Hence most of the understanding and publications are from these laboratories which may not reflect the accurate incidence. International guidelines are followed in the best possible way available. Most of the publications are from the advanced laboratories.

The IDMS traceability creatinine is used in majority of the Medium and Advanced Laboratories (32). Though MDRD equation is used quite commonly, the appropriateness of the same in line with creatinine traceability is many a time questionable. There is variation in use of the formula of MDRD among the laboratories

In the higher centres, creatinine is reported with eGFR and vice versa. Protein creatinine ratio is done in all 3 categories of laboratories and albumin creatinine ratio in the medium and advanced laboratories. Standardization of the eGFR in institutes have been done initially by comparison with isotope renogram and found to be superior to CG formula (33). The Schwartz formula for pediatric population is well accepted clinically, CKD-EPI children has not yet taken off (34).

Serum Cystatin usage is minimal as a regular tool of evaluation mainly due to cost and eGFR using the same, is sporadic in publication.

Both medium and large laboratories have good results of proficiency testing. Laboratories are under a national accreditation programme (though not yet mandatory). With different ethnicities to arrive at national reference interval, would take time. Though study evaluations are done in different areas of the country, these may be considered cross-sectional due to the diversity of individuals living in different areas.

The distinct features to be addressed in the country under statutory guidance

1. ***Uniformity of use in creatinine assay***
2. ***Biological reference interval*** of the serum creatinine, protein creatinine ratio and albumin creatinine ratio, sex and gender wise
3. ***Selection of MDRD and CKD EPI equation uniformity*** (35)
4. ***Awareness of general medical practitioners in use of the equation*** only with standardized IDMS creatinine assay
5. ***To always correlate with regional higher centres on knowhow of*** assays, reference intervals with national and international guidelines
6. ***A regional state wise registry*** to know the CKD burden in the country (36)
7. ***To work with instrument and reagent vendors*** to help in this achievement on a Government statutory.

CONCLUSION

This short review presents some examples from worldwide national acitivities in CKD testing. Considering the fact that already mentioned treatment of CKD is cost-effective and improves outcomes, this observation argue in favor of including CKD in national guidelines and noncommunicable chronic disease (NCD) programs (5). The described activities fullfil the very first step in achieving this goal.

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