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The cycle of development, publication, and implementation of clinical practice guidelines for CKD

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Implementation of clinical practice guidelines (CPGs) leads to better outcomes. The first K/DOQI guideline for chronic kidney disease (CKD) recommended the use of estimated glomerular filtration rate (eGFR) to assess kidney function, minimizing 24–h urine collections for the measurement of creatinine clearance. Kagoma *et al.* demonstrate that automatic reporting of eGFR with clinical decision support was required for implementation of this recommendation. The second cycle of development, publication, and implementation of CPGs for CKD is under way.

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Chronic kidney disease (CKD) confers adverse outcomes, particularly increased cardiovascular events, premature cardiovascular death, and chronic kidney failure.[1] Clinical practice guideline (CPG) implementation is the most promising way to improve care, leading to better outcomes. The first Kidney Disease Outcomes Quality Initiative (K/DOQI) CPG for CKD has achieved an extraordinary success in broad dissemination over a relatively short implementation since its publication in 2002,[1] providing uniform terminology for clinicians of every type to define CKD and stratify it into stages and promoting the remarkable adoption of estimated glomerular filtration rate (eGFR) reporting worldwide. However, the process of optimizing CKD care is only just beginning. There is little agreement among practitioners in a number of pivotal areas, including the definition of CKD (particularly for the elderly with eGFR of 45–60 ml/min per 1.73 m^2 in the absence of albuminuria), the key elements of primary-care management of stages 1–3 CKD, the indications for nephrology consultation,[2] and the scope of the respective roles and responsibilities of the primary-care physician and the specialist following consultation. In the absence of consensus in the community, these clinical management issues are being interpreted at the point of care to a greater degree than in longer-established chronic diseases such as diabetes and cardiovascular disease. Thus, CPG implementation in CKD is largely a subjective local process, making the systematic assessment of implementation challenging. Clinical decision support is the implementation method of the future to bridge the gap between the evidence synthesized by CPGs and patient care delivered through the electronic health record in a cyclical process (Figure 1).

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Reporting of eGFR and primary care

Making kidney-function results directly accessible to the clinician is an important step in CKD detection and management. Kagoma and colleagues[3] (this issue) evaluate the implementation of one of the key recommendations of the first CKD guideline: to assess kidney function with eGFR in routine clinical practice, reserving 24–h urine creatinine clearance collections for confirmatory testing.[1] These experienced health-service researchers use the monthly prevalence of 24–h urine collections in an adult population of more than 8 million patients in the province of Ontario, Canada, from August 1999 to July 2009 to investigate the impact of two major interventions: the publication of the K/DOQI CKD CPG in February 2002, and the introduction of eGFR reporting in all outpatient laboratories in January 2006. The authors assume a 3-month lag period following each of the two events to assess variation based on previous publications.[4,5] Each eGFR value, based on the Modification of Diet in Renal Disease (MDRD) Study equation, was accompanied by one of five corresponding prompts relating the level of kidney function to CKD. For example, results between 30 and 60 ml/min per 1.73 m^2 were followed by: 'consistent with moderate chronic kidney disease if result confirmed by repeat assessment, with persistence for 3 months or more.'[4] This form of clinical decision support assists interpretation with direct incorporation into the clinical workflow for each laboratory result. The study is well designed, and the methods are rigorous. The data capture for this large population is impressively comprehensive, feasible in part by virtue of universal health care with a single federal payer. The results from Canada's most highly populated province show no significant change following the publication of the K/DOQI CKD guideline, but a 23.5% reduction in 24-h urine collections after eGFR reporting with prompts, from 44.6 to 34.1 per 100,000 population, which remained significant after adjustment for sex and age ($P < 0.0001$). The obvious benefits are improved patient convenience, and increased accuracy of kidney-function assessment for clinical practice using eGFR rather than creatinine clearance. The estimated cost benefit was small, $5651 per month in reduced laboratory

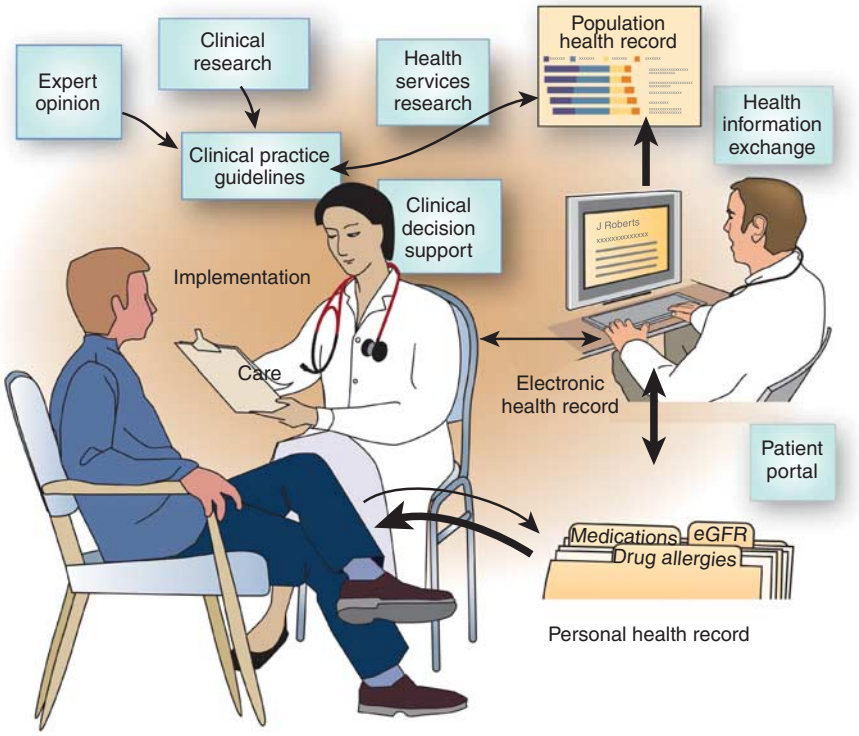

Figure 1 | The cycle of development, publication, and implementation of clinical practice guidelines. Implementation or translation into practice should contribute to the development of a subsequent guideline, primarily through health services research. Clinical decision support is shown as the implementation method that bridges the gap between the evidence synthesized by clinical practice guidelines and patient care delivered through the electronic health record. The three major components of information technology in health care are shown: the personal health record, the electronic health record, and the population health record. The arrows represent the flow of information. The arrow between the patient and the personal health record is mostly in the direction of the patient, as patient input into the electronic health record is currently limited.

fees for 24-h urine testing, based on a per-test cost of $10.35. The inability to distinguish the impact of eGFR reporting from the impact of the prompt is worth noting in addition to the comprehensive discussion of limitations by the authors. The eGFR reporting may not have influenced care in the absence of the kernel of educational information delivered by the prompt. These compelling findings should inspire ongoing rigorous implementation following future CPG publication, especially using clinical decision support.

Other aspects of primary care assessed in the literature following eGFR reporting include detection of CKD, achievement of target blood pressure, use of renin–angiotensin system (RAS) blockers (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), avoidance of nephrotoxins, drug prescription that considers the level of kidney function, and implications of a false-positive CKD diagnosis. An outpatient study by Wyatt *et al.* from the US Veterans Affairs Medical Center revealed small but significant improvements in CKD detection using administrative data collection for diagnosis codes before and after reporting (14.6 to 21.5%) and achievement of blood pressure goal (32.9 to 34.4%).[6] Although the comparison between detected and undetected CKD did not influence the achievement of target blood pressure, the use of the appropriate CKD diagnostic code was significantly associated with urinary protein testing (39.8% to 54.2%). Three of four studies demonstrated small but statistically significant increases in RAS blockade use following reporting, from 1.9 to 6%.[5–7] The authors of the negative study speculated high baseline rates of RAS blocker use as a possible explanation.[5] Studies of patient safety risk in CKD care and eGFR reporting have been limited mostly to single academic centers.[7,8] One study showed no change in nonsteroidal anti-inflammatory drug prescription rates,[7] while a systematic review of drug prescribing practices that considered the level of kidney function using clinical decision support showed promise overall, with the limitation of heterogeneous design across studies.[8] The reduction in quality-adjusted life years associated with a false-positive CKD diagnosis was considered by one interesting study that used Monte Carlo microsimulations in the transitions between six conditions: normal, false-positive CKD, true-positive or detected CKD, undetected CKD, chronic kidney failure, and death.[9] The assessment of the cost-effectiveness of eGFR reporting versus serum creatinine reporting by the authors depends on the accuracy of the model. The assumption of one outpatient nephrology consultation for all detected and false-positive CKD may not be realistic. Still, the potential negative consequences of the patient's being labeled with CKD could be addressed by the subsequent refinement of the CKD definition and/or stratification in the CPG, as well as through ongoing investigation.

Reporting of eGFR and nephrology care

The effects of eGFR reporting on nephrology consultation may not be the best metric at this juncture in the absence of consensus,[2,7] despite comprehensive indications from CPGs.[1,10] A recent systematic review of the impact of eGFR reporting with and without prompts demonstrated an overall increase in nephrology consultations in the range of 13% to 270% from 13 of 16 studies.[7] Most studies also showed a change in the distribution of patients, including more elderly and women, as would be expected on the basis of the variables of the MDRD Study equation. In the publications that provided data, there was a trend for a decrease in stage 1 and 2 consultations with increases in stages 3–5.[7] Whether or not this is seen as a welcome shift reflects the subjectivity in evaluation, as supported by the variability in the definition of an appropriate

consult. Studies were heterogeneous with regard to the predefined use of appropriate nephrology consultation indications; one study used discharge from nephrology care within one year of consultation as the definition of an inappropriate use of resources.[7] Two studies evaluated changes in the timing of referral relative to the onset of chronic kidney failure following reporting, but the use of significantly different definitions of early and late consultation complicated the assessment.[7]

Assessment of the future impact of eGFR reporting

These preliminary studies are encouraging in the overall trend for a benefit of eGFR reporting. Data are needed on the impact of reporting on patient and public awareness of CKD and its risk factors and outcomes.[10] Evaluation of the impact of reporting will be essential for the refinement of methods of estimating GFR, such as the CKD Epidemiology Collaboration (CKD-EPI) 2009 creatinine equation and the 2012 CKD-EPI cystatin C equation. It will also be important to investigate patient safety, but the metrics will need to be more precisely defined. What is the impact of eGFR reporting on the timing of dialysis initiation? Will there be an influence of reporting when enough time has elapsed to accrue adequate hard end points for cardiovascular events, onset of chronic kidney failure, and mortality? Future studies of eGFR reporting should further explore the impact of the prompt as a form of clinical decision support. There is advance notice to consider the implementation before publication of an updated CKD CPG anticipated in 2012 from Kidney Disease: Improving Global Outcomes and the corresponding K/DOQI US Commentary. This will provide an opportunity to reframe the discussion regarding the controversies and adoption challenges for routine primary and nephrology CKD care in a second cycle of development, publication, and implementation.

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Double-edged sword: a p53 regulator mediates both harmful and beneficial effects in experimental acute kidney injury

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Acute kidney injury triggers activation of innate immune responses and of proapoptotic programs such as the p53 pathway. Mulay *et al.* examine the effects of blocking murine double minute-2 (mdm2), a negative regulator of p53, using a novel chemotherapeutic agent, nutlin-3a, in mouse ischemia–reperfusion injury. Their results indicate that mdm2 promotes renal regeneration by limiting p53-mediated apoptosis but also enhances early inflammation by facilitating DNA binding of nuclear factor-κB independently of p53.

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There continues to be intense interest in furthering our understanding of the cellular and molecular mechanisms underlying acute kidney injury (AKI) through the use of animal models.[1] Although attempts at translation of laboratory research findings to patient populations with AKI have yet to yield dramatic clinical benefits, there is now a clearer appreciation of the complexity of this challenge.[1] There is also an emerging consensus that robust preventative or therapeutic interventions may require the manipulation of multiple pathways to renal injury—either simultaneously or at different stages of the process.[1] Two mechanisms of injury that may be of specific interest in this regard are the

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