Identifying Individuals with a Reduced GFR Using Ambulatory Laboratory Database Surveillance

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The use of outpatient laboratory databases to identify people with a low GFR may be part of an effective strategy to increase their use of treatments to prevent kidney failure. All renal function data from 17 independent outpatient laboratories in Eastern Ontario were combined to determine the proportion of adults with at least one serum creatinine measurement during a 1-yr period. The detection rates of low GFR were measured using different algorithms, and what proportion of identified low GFR was transient was considered. Canadian census data were used to calculate rates and proportions. Renal function testing was common. Of the 1,090,000 adult residents, 32% of the entire population and 63% of seniors had at least one serum creatinine measured during the study year. Sixteen percent of the population (49% of those with tests performed) had at least one GFR <80 ml/min per 1.73 m^2, 5% (16%) had at least one GFR <60 ml/min per 1.73 m^2, and 0.6% (1.7%) had at least one GFR <30 ml/min per 1.73 m^2. Low GFR were usually not transient: 68% of individuals with subsequent testing at least 30 d later had a similar or worse GFR. Ambulatory laboratory database case finding, particularly in older patients, seems to be a promising method for easily identifying large segments of the population with persistent reductions in GFR. Whether such identification leads to improved health outcomes warrants further study.

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Chronic progressive kidney disease is an asymptomatic condition that is usually identified and managed by primary care physicians. Guidelines and position statements (1–5) recommend that family physicians regularly measure serum creatinine and urine protein in patients with diabetes, hypertension, or a family history of kidney disease to identify those with renal dysfunction. Such patients benefit from proven interventions to reduce their risk for mortality and cardiovascular disease. Angiotensin-converting enzyme inhibitors (6,7) and strict BP control (8,9) also decrease the risk for progression to ESRD.

Unfortunately, several studies confirm marked deficiencies in the current delivery of health care for at-risk patients (10–12). Physician nonadherence to accepted screening and treatment standards may stem from competing burdens in primary care practices or the perceived infrequency of incident ESRD in the population (13,14). This has prompted several ongoing trials of improved education and health care delivery. Studies of organizational change have explored the effects of separate chronic kidney disease clinics, the use of allied health professionals for specific chronic disease prevention activities (15,16), and earlier referral to nephrologists. Interventions involving patient self-management of disease have included education (17), financial incentives, and reminders. Physician education interventions have examined outreach and reminders (18–21).

For increasing the identification of segments of the population who may benefit from intensive therapy as provided by these interventions, prospective mass screening (22), renal screening at visits for other reasons, manual or electronic physician chart audit, or laboratory reporting of estimated GFR (21) all have been considered either separately or in unison. Another potential innovative strategy is laboratory-initiated screening, in which aggregate data from laboratory information systems are reviewed in real time. Laboratory-initiated case finding may be cost-effective, add value to existing data, and increase the identification of at-risk patients. Renal function testing in routine care is ubiquitous and is often performed for other reasons, thus making this strategy appealing (23). Using information that is already in a database in part circumvents difficulties of mass screening for a low prevalence condition such as advanced chronic kidney disease (24). However, the viability of screening laboratory databases for renal disease is uncertain. Within ambulatory outpatient laboratory databases, some renal insufficiency will be transient. Identifying "false-positive" elevations reduces the effectiveness of screening, and it is uncertain to what degree this strategy identifies such cases. In this study, we combined all population-based renal labora-

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tory data in a defined geographic region to determine identification rates of low GFR. We also assessed the permanence of renal insufficiency in those who were identified with low GFR.

Materials and Methods

Study Population

Ontario is Canada's most populous province and is home to approximately 12 million people, 8 million of whom are 18 yr of age and older. This study was localized to Eastern Ontario (Figure 1). Population estimates were derived from Canadian Census data as described elsewhere (23). The region was the permanent residence of 1.09 million adults during the study period.

Laboratory Data

In Ontario, private and hospital-based laboratories provide medical laboratory testing. With few exceptions, the private laboratories provide laboratory testing exclusively to community-based patients. Hospital-based laboratories provide testing primarily to hospitalized patients but also to community patients who attend hospital-based clinics or in areas where private laboratories are unavailable.

Between September 1, 1999, and September 1, 2000, one of the authors (C.V.W.) prospectively assembled relevant data from 17 independent laboratory information systems in the region for patients who were 18 yr of age and older (Figure 1). All private laboratories and hospitals operating in Eastern Ontario participated in the study with the exception of Hawkesbury and Cornwall, where limitations of their information systems precluded participation. This had a negligible effect on our results because these laboratories contributed <1.5% of data for the study area (23).

The data set included all serum creatinine measurements performed in eastern Ontario during the study year. In all laboratories, serum creatinine was assessed using the modified kinetic Jaffe assay, using various Auto-Analyzers (Vitros, Beckman, Roche-Hitachi, J&J Ortho Diagnostics). In Ontario, each laboratory aims to maintain a coefficient of variation of <4%. The typical adult serum creatinine references reported by the various laboratories varied between laboratories but approximated 60 to 125 μmol/L (0.7 to 1.4 mg/dl) in men and 50 to 110 μmol/L (0.5 to 1.2 mg/dl) in women. For the two largest laboratories in Ontario (Gamma-Dynacare and MDS International), 139 duplicate samples were sent to the Cleveland Clinic (the primary laboratory for the Modification of Diet in Renal Disease Study) (25). These laboratories were reading, on average, 3 to 5 μmol/L (0.04 to 0.06 mg/dl) higher than the Cleveland Clinic in 2002.

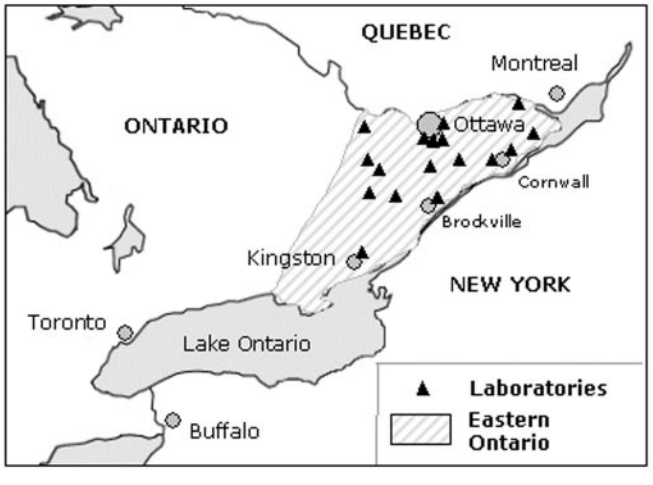


Figure 1. In 2000, there were 1.09 million adults living in Eastern Ontario (shaded in grey stripes). We combined renal testing from all independent laboratories (▲) in the region and downloaded results to a central site linked to provincial administrative data.

Linkage to Administrative Databases

Computer files of assembled laboratory tests were encrypted and transferred electronically to the Institute for Clinical Evaluative Sciences (ICES; Toronto, ON, Canada). Patients were identified by their Ontario Health Insurance Plan number. An ICES staff person with written permission to see unencrypted patient identifiers decrypted the entire data file. Physician and patient identifiers then were individually re-encrypted with a key to permit linking with other administrative data sets at ICES. Researchers used these anonymous data files, which were stored on a stand-alone computer network for the study.

The provincial Registered Persons Database records basic demographic information for each Ontarian. The Registered Persons Database was used to identify the age and gender of each person who had a creatinine measurement. To exclude tests that were conducted while an individual was in hospital, we linked to the Discharge Abstract Database. The Discharge Abstract Database records the admission and discharge date of all hospitalizations (including same-day surgeries) in Ontario. All creatinine measures that were conducted while the patient was in hospital were classified as "hospital tests" and were excluded from the study. To identify tests that were conducted while the patient was in the emergency department, we linked to the Physicians Services Database (PSD) and used a published algorithm to identify emergency department visits (26). The PSD database records claims for physician services. Services that were conducted in emergency departments were identified by special claim codes. Tests that were ordered on the same date by the same physician who claimed an emergency assessment were classified as emergency tests and were excluded from the analysis. We used PSD to identify patients who had or were continuing renal replacement therapy. Using claim codes described elsewhere (27), we identified patients who received hemo- or peritoneal dialysis or a transplant. When a patient had a least two of these claims before or during the study period, we labeled them as ESRD and excluded them from subsequent analyses. We identified patients with diabetes using the Ontario Diabetes Database, a data-derived registry that uses a validated administrative algorithm defined elsewhere (28).

Case-Finding Criteria

Different algorithms for identifying individuals with low GFR were generated using different threshold values of age, gender, and serum creatinine. To calculate GFR, we used the abbreviated Modification of Diet in Renal Disease (MDRD) formula (GFR [ml/min per 1.73 m^2] = 186 × serum creatinine [mg/dl]$^{-1.154}$ × age [years]$^{-0.203}$ × 0.742 [if female] × 1.21 [if black]) (29), an equation with strong predictive validity for death, cardiovascular disease, hospitalization, and ESRD when used in laboratory data sets (30,31). Race was not available in the laboratory data, and we used the MDRD equation for nonblack individuals. This had a negligible effect on our categorized MDRD estimates given that <3% of adults in the region were black (Canadian Census). GFR was categorized according Kidney Disease Outcome Quality Initiative cutoff points (60 to 80, 30 to 59, and <30 ml/min per 1.73 m^2) (32). In addition, individuals were grouped into similar strata of GFR using serum creatinine Couchoud cutoff points that have been previously validated against inulin clearance (33). (For men, serum creatinine of 137 μmol/L [1.5 mg/dl] for a GFR <60 ml/min per 1.73

m^2 and 177 μmol/L [2.0 mg/dl] for a GFR <30 ml/min per 1.73 m^2; for women, 104 μmol/L [1.2 mg/dl] for a GFR <60 ml/min per 1.73 m^2 and 146 μmol/L [1.6 mg/dl] for a GFR <30 ml/min per 1.73 m^2).

In patients with more than one measurement, an individual's highest serum creatinine was used to determine the proportion of patients who would be identified using an algorithm. To assess whether reductions in GFR were transient or sustained, we compared the first low GFR with another measurement at least 30 d later.

Statistical Analyses

Descriptive statistics were used to characterize the study population examined. χ^2 tests were used to compare differences in detection rates among the different algorithms. The ethics review board of Sunnybrook and Women's College Health Sciences Centre Toronto approved the research protocol.

Results

Between September 1, 1999, and September 1, 2000, the participating laboratories conducted a total of 859,738 serum creatinine tests on adults with a valid patient identifier. A total of 292,868 (34.1%) tests were excluded because the test was performed while the patient was in hospital (n = 238,861), the test was done while the patient was in the emergency department (n = 36,991), or tests were performed in patients who were or had been receiving renal replacement therapy (n = 17,016).

A total of 566,870 creatinine tests were included in the study. A total of 73.4% of these tests were done in commercial laboratories. The tests were performed in 349,513 different adults, or 32.1% of adults in the population. The median age was 54 yr (interquartile range, 41 to 69 yr), 57.2% of patients were female, and 13.3% had diabetes. The proportion of the population who had renal function testing increased with age from 17.1% of patients who younger than 35 yr to 54.4% of those who were older than 65 yr (χ^2 test for trend, $P < 0.0001$). The number of adults with one, two, three, and four or more serum creatinine measurements was 252,650 (72.3%), 55,920 (16.0%), 19,184 (5.5%), and 21,759 (6.2%), respectively.

The distribution of testing and GFR results are presented in Figure 2. During the study year, 172,414 (16.3% of the population; 49.3% of those with tests performed) were flagged with at least one MDRD GFR <80 ml/min per 1.73 m^2. Similarly, 54,471 (5.0% of population; 15.6% of tested) had a GFR of <60 ml/min per 1.73 m^2, and 6096 (0.5% of population; 1.7% of tested) had a GFR of <30 ml/min per 1.73 m^2. The Couchoud cutoffs resulted in lower proportions of people with decreased renal function with 24,297 (2.2% of the population; 7.0% of those tested) having at least one Couchoud GFR of <60 ml/min per 1.73 m^2 and 8157 (0.8% of the population; 2.3% of those tested) having at least one Couchoud GFR <30 ml/min per 1.73 m^2.

A total of 54,576 individuals with a MDRD GFR <80 ml/min per 1.73 m^2 had another measurement at least 30 d later. The natural history of GFR values that initially were identified as low is presented in Table 1. In the majority of cases identified, low GFR was not transient. With subsequent testing, the GFR was similar or lower in 68% of individuals. Only 18% of those with initially identified low GFR had an increase of 10 ml/min per 1.73 m^2 or more with subsequent testing. The proportion of people with transient reductions in GFR was not appreciably higher in those with an initial GFR between 60 and 79 ml/min per 1.73 m^2 compared with an initial GFR <30 ml/min per 1.73 m^2.

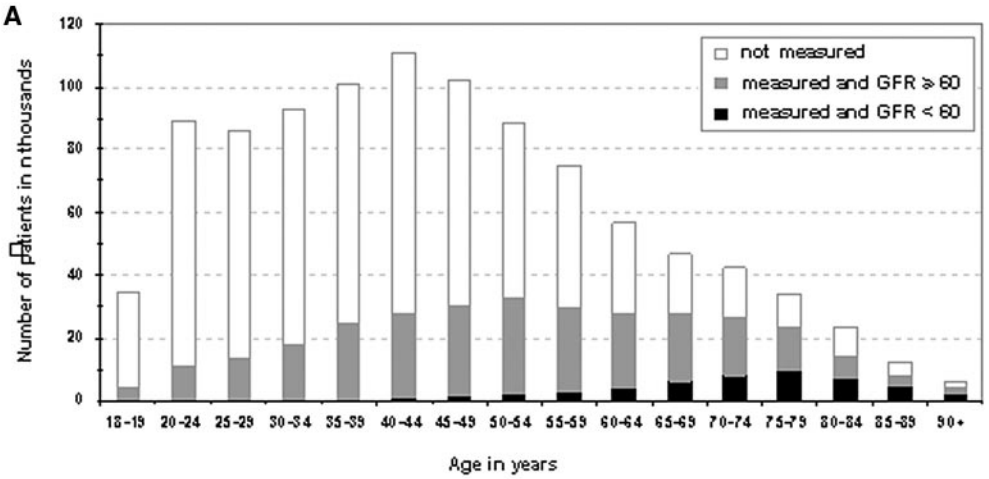
Discussion

Laboratory-initiated database screening may help to identify at-risk segments of the population who benefit most from intensive therapy to prevent premature death, cardiovascular disease, and ESRD. Here, ambulatory laboratory case finding seemed to be a promising strategy especially in identifying large numbers of older people with persistent reductions in GFR. During the study year, for every 100,000 adults 65 yr or older, approximately 63,000 had at least one serum creatinine measured, 23,000 were flagged with at least one MDRD GFR <60 ml/min per 1.73 m^2, and 2600 were flagged with at least one MDRD GFR <30 ml/min per 1.73 m^2.

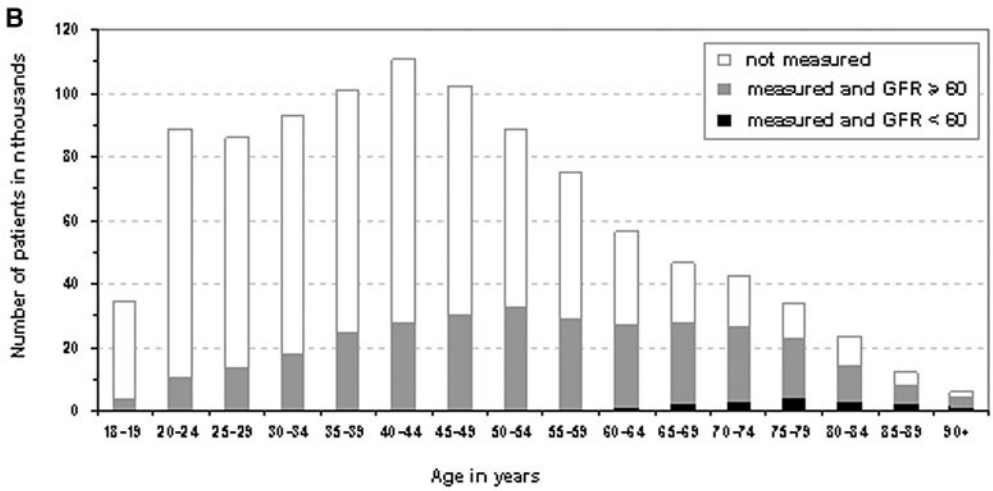
Laboratory-initiated screening will not comprehensively identify all cases of reduced GFR in the community. Just as primary care screening is effective only for those who see their physician, so, too, do laboratory screening assess only individuals who have a serum creatinine measured. However, unlike many other assays, this study confirms that serum creatinine testing is ubiquitous in health care. In our study, almost two thirds of the senior population had their renal function tested in a given year. Population coverage would certainly improve if screening were extended over many years. Thus, laboratory-initiated case detection may be viable as a supplementary method of identifying those who are at risk and may be particularly effective if coupled with alternative methods of health care delivery that increase the use of efficacious therapies.

In clinical practice, many acute conditions such as infection, dehydration, and cardiac ischemia cause transient renal insufficiency that improves with treatment. Statistically, it might also be anticipated that a group of individuals who are initially flagged with a low GFR would have an improved GFR at subsequent testing—a concept often referred to as "regression to the mean." Thus, laboratory database case finding may identify a large proportion of patients with transient reductions in GFR, thereby rendering it ineffective as a surveillance strategy. Although this is a potential concern for hospitalized patients, we found that the majority of community patients had true reductions in GFR. On repeat testing, the GFR was similar or worse in more than two thirds of individuals who were flagged with an initial low GFR. In this study, the proportion of transient reductions in GFR was not appreciably different in those with an initial GFR of 60 to 80 compared with those with a GFR <30 ml/min per 1.73 m^2.

This report is notable for successfully combining all ambulatory laboratories for a well-defined population that consisted geographically of both rural and urban communities. We also successfully excluded patients with ESRD, a deficiency found in many other renal population studies (34). However, a number of existing limitations need to be considered before laboratory-initiated case finding can prove viable in routine care. Current global health policy and legislation are fragmented in reconciling patient and physician privacy with the public good of human health. Personal data that are available in laboratory



Age	18-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90+	Total
Proportion of population with at least one serum creatinine measurement																	
	11%	12%	16%	19%	24%	25%	29%	37%	39%	48%	59%	63%	68%	60%	68%	64%	32%
Of those with at least one serum creatinine measurement, proportion who were flagged with at least one low GFR																	
GFR 60-79	4.7%	7.0%	11.1%	14.6%	20.2%	26.6%	33.0%	38.6%	43.3%	46.5%	47.1%	45.7%	41.0%	35.7%	29.6%	25.2%	33.7%
GFR 30-59	0.72%	0.93%	1.3%	1.6%	2.1%	2.7%	3.6%	5.9%	8.7%	12.2%	19.5%	27.0%	36.6%	43.6%	51.3%	52.5%	13.3%
GFR < 30	0.26%	0.34%	0.35%	0.34%	0.42%	0.51%	0.51%	0.64%	0.89%	1.30%	1.8%	2.8%	4.2%	6.3%	8.2%	11.1%	1.7%



Age	18-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90+	Total
Proportion of population with at least one serum creatinine measurement																	
	11%	12%	16%	19%	24%	25%	29%	37%	39%	48%	59%	63%	68%	60%	68%	64%	32%
Of those with at least one serum creatinine measurement, proportion who were flagged with at least one low GFR																	
GFR 30-59	0.70%	0.64%	0.9%	0.9%	1.0%	1.0%	1.1%	1.7%	2.5%	3.3%	5.5%	8.1%	12.2%	16.3%	20.0%	23.7%	4.8%
GFR < 30	0.60%	0.71%	0.63%	0.59%	0.70%	0.77%	0.79%	0.93%	1.19%	1.80%	2.6%	3.7%	5.6%	7.9%	10.1%	12.5%	2.3%

Figure 2. (A) The frequency of serum creatinine testing in the study year and the number of patients for whom at least one measured Modification of Diet in Renal Disease (MDRD) GFR was <60 ml/min per 1.73 m^2. Results are standardized per million adult population. (B) The frequency of serum creatinine testing in the study year and the number of patients for whom at least one measured Couchoud GFR was <60 ml/min per 1.73 m^2. Results are standardized per million adult population.

databases could be used for surveillance and quality improvement programs without explicit patient or physician consent, if approved under a regional public interest mandate and performed in a secure, confidential manner (35–37).

Interlaboratory variability complicates the interpretation of serum creatinine values (38,39). For example, consider hypothetically that in the year 2000, all laboratories in Eastern Ontario were consistently reading 5 μmol/L (0.06 mg/dl) higher than the MDRD reference laboratory, where a systematic drift in serum creatinine measurement has occurred over the past decade (38). The proportion of patients with serum creatinine testing identified with a GFR <80, <60, and <30 ml/min per

Table 1. Identified low GFR was usually not transient

	GFR Increased			No Change	GFR Decreased		
	>15	10 to 15	5 to 10	5 to −5	5 to 10	10 to 15	>15
Initial GFR <80	10%	8%	15%	45%	12%	6%	5%
Initial GFR 60 to 80	10%	8%	15%	41%	13%	6%	6%
Initial GFR 30 to 59	10%	8%	15%	48%	11%	5%	4%
Initial GFR <30	10%	4%	11%	63%	8%	2%	0.7%

A total of 54,576 individuals with a MDRD GFR <80 ml/min per 1.73 m^2 had another measurement at least 30 days later. Only 18% of those with initially identified low GFR had an increase of 10 ml/min per 1.73 m^2 or more with subsequent testing. The proportion of people with transient reductions in GFR was not appreciably higher in those with an initial GFR between 60 and 79 ml/min per 1.73 m^2 compared with an initial GFR <30 ml/min per 1.73 m^2.

1.73 m^2 would change from 49, 15.6, and 1.7% to 26, 8.6, and 1.2%, respectively. The development of a universally adopted, reliable assay of serum creatinine, which when used in GFR estimating equations demonstrates high concurrent and predictive validity, is an ongoing issue challenging the profession.

Although it is likely that identified low GFR is persistent in those with only a single serum creatinine measurement in a database (as was the case with those with two or more measurements separated by 30 d in our study), this cannot be stated with certainty given that follow-up testing was not performed in a majority of participants. Furthermore, competing events of death and emigration would require consideration when acting on flagged results.

The accuracy of administrative and census data, the logistics of timely "real-time" data management, and the sustainability of this approach all would require detailed review. Although plausible (12), it remains uncertain that opportunities exist to improve care in patients who are identified with a low GFR through this method. Patients with frequent laboratory testing may already be well managed by their primary care physicians.

Finally, the detection methods to flag low GFR used here were kept simple deliberately. In the future, it may be possible to construct better, more sophisticated case-finding algorithms using additional data such as hemoglobin, proteinuria, and serial changes in GFR, as well as drug and resource utilization in administrative databases.

In conclusion, ambulatory laboratory database screening, particularly in older patients, is a promising strategy for case finding large segments of the population with reduced GFR. Whether such identification leads to improved health outcomes warrants further study.

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