ABSTRACT

This educational paper discusses a variety of indicators that can be used to measure the quality of care in renal medicine. Based on what aspect of care they reflect, indicators can be grouped into four main categories: structure, process, surrogate outcome and outcome indicators. Each category has its own advantages and disadvantages, and we give some pointers on how to balance these pros and cons while taking into account the aim of the measurement initiative. Especially within initiatives that link payment or reputation to indicator measurement, this balancing should be done with care to avoid potential, unintended consequences.

Furthermore, we suggest consideration of (i) a causal chain—i.e. subsequent aspects of care connected by evidence-based links—as a starting point for composing a performance indicator set and (ii) adequate case-mix adjustment, not only of (surrogate) outcomes, but also of process indicators in order to obtain fair comparisons between facilities and within facilities over time. Keywords: nephrology, quality indicators, quality of health care

INTRODUCTION

Initiatives worldwide are measuring the type and quality of renal care in order to identify practice patterns, engage and support clinicians in improving the quality of their local care delivery system or to provide transparency to policy-makers and the public [1–6]. Rather than focusing on individual clinicians, these measurement initiatives evaluate systems of healthcare delivery based on a set of quality indicators. Indicators can be categorized into different types, all with their own advantages and disadvantages, which we describe and illustrate in the first section of this paper. There, we also discuss how the aim of an initiative determines how the pros and cons of those indicator types should be weighed. We argue that this should be done with care to avoid potential unintended consequences, especially within initiatives that aim to facilitate external judgement of care quality.

In the second section we suggest using ‘causal chains’ as a potential point of departure when composing a set of interrelated indicators. In a causal chain, each element (i.e. an aspect of care to be translated into an indicator) is connected to the next element by an evidence-based link. We also provide some examples of indicator sets currently used for quality of care measurement in nephrology.

Finally, in the last section we advocate that—apart from (surrogate) outcome indicators—process indicators should also be adjusted for case mix in order to enable correct interpretation of clinical quality measurements.

MEASURING THE QUALITY OF CARE: BASIC CONCEPTS AND DEFINITIONS

Measures versus indicators

We can define indicators for quantifying the things we see in the world surrounding us. For the human body, for
example, you can measure its weight in kilograms. To determine whether it concerns a healthy weight, you can relate it to the body’s height in centimetres by calculating the body mass index, or—for more accurate information—take into account waist–hip ratio, skinfold thickness and body fat distribution. All are measures of the human body.

‘Quality of care’ or ‘clinical performance’, however, cannot be put on a scales, held against a measuring tape, or scanned with a device to analyse its composition. Hence, there are no direct measures of the quality of care because—unlike the human body—it is an abstract concept that is not part of our physical world. To quantify this abstract concept, we are thus dependent on the measurable aspects of health care that are only an indication of its quality. This paper is about these measurable aspects, to which we will further refer as ‘quality indicators’ or ‘clinical performance indicators’.

**Indicators referring to healthcare structures, processes and outcomes**

Besides being abstract, quality of care is also a multidimensional construct. One can distinguish three classic dimensions, resulting in three categories of quality indicators: those referring to structures, to processes and to outcomes of health care [7]. **Structure indicators** refer to characteristics of the healthcare setting that affect a system’s ability to meet healthcare needs of (a group of) patients [8]. Often they reflect the availability of services or resources. Examples are the availability of a dedicated outpatient vascular access service, the renal nurse-to-patient ratio or having a nutritional patient counselling programme in place. **Process indicators** refer to the care that is actually being delivered, for instance, the timely performance of non-invasive ultrasonography of vessels in haemodialysis (HD) patients listed for vascular access creation, or hepatitis B vaccination in seronegative patients. Lastly, **outcome indicators**—either observed or patient reported [9]—involve the ultimate health status of the patient or the occurrence of (adverse) events after having received treatment. Examples of observed outcome indicators are cardiovascular death in patients with end-stage renal disease (ESRD) and bacteraemia in HD patients with a tunnelled catheter, whereas the quality of life after kidney transplantation and satisfaction with dialysis care are typical patient-reported outcome indicators.

**Clinical correlates and surrogate outcomes as indicators of clinical performance**

**Clinical correlates** are clinical or laboratory signs that can be objectively measured and are associated with disease activity, but not necessarily causally related to patient outcomes. The special subgroup of clinical correlates that is thought to have a causal relationship with a subsequent health outcome is referred to as **surrogate outcomes** [10]. When carefully selected and validated, indicators based on clinical correlates and surrogate outcomes may be useful as they are more easily obtained than outcome indicators [11], while also being more directly related to patients’ health status than process indicators. However, parameters are often called ‘surrogates’ without a robust evaluation of their relation with clinical endpoints in large, well-designed studies that measure both surrogate and ultimate patient outcomes. For example, based on observational data the degree of proteinuria seems a surrogate for the decline of renal function [12, 13]. Yet, there is still debate whether aiming for a reduction in proteinuria indeed slows progression to ESRD [14, 15]. In addition, the validity of surrogate outcomes is specific to the context (e.g. type of patients, targeted outcomes) in which they were evaluated, making their interpretation complex [10]. For example, lowering blood pressure was shown to decrease cardiovascular events in patients with diabetes [16], but this was less clear for diabetes patients who also had nephropathy [17].

**Indicator definition: selecting a numerator and a denominator**

Many performance indicators are defined as the proportion of a numerator—specifying how many times preferred care was provided or events occurred—relative to a denominator reflecting the number of patients eligible or at risk. Selecting a different numerator or denominator affects the final indicator value, and thus, the conclusion on clinical performance. **Box 1** contains an illustrative example, which shows how one may account for the potential influence of patient characteristics and of care delivered by healthcare professionals other than nephrologists.

**What makes a good quality indicator?**

The perfect quality indicator does not exist as each has its own advantages and disadvantages (Table 1) [11, 18, 19]. How to balance these pros and cons depends on the aim of the measurement initiative. There are three types of initiatives [9, 20, 21]. First, **performance-monitoring initiatives**, such as (inter)national renal registries and the Dialysis Outcomes and Practice Patterns Study programme, which regularly review clinical performance based on a combination of structure, process and (surrogate) outcome indicators. They aim to formulate hypotheses on the relationships between the different aspects of care and to identify trends over time in practices and outcomes. This requires indicators that can be measured reliably in large populations over a long time period, accompanied by information on potential confounders. Secondly, **formative initiatives** focus on internal quality control—i.e. without external interference—and improving care processes [3, 4, 22]. Indicators used within such initiatives should be especially sensitive to changes in performance over time, easy to interpret and a straightforward basis for deciding which QI initiatives should be undertaken. Lastly, **summative initiatives** are characterized by external judgement of care (by governments, payers, patients, etc.) linked to direct consequences for payment or reputation [5, 6, 23]. Selection and use of indicators for this purpose should be done with the greatest possible care in order to avoid unjustified sanctions or rewards. Chassin et al. [24] suggested that in this case, indicators should reflect processes of care that (i) have a strong evidence-based link to relevant outcomes of care; (ii) can be measured reliably; (iii) are proximate to the desired outcome and (iv)
have minimal or no unintended consequences. Additionally, summative initiatives should monitor if their linking performance to (financial) incentives does not result in physicians applying a ‘one-size-fits-all’ policy just to get high indicator scores. For example, reimbursing HD via an arteriovenous (AV) fistula at a higher rate than through a catheter—which is the case in the UK—might drive dialysis centres to construct fistulae while ignoring the potential harm, e.g., in older patients [25].

To illustrate how to assess the ‘goodness’ of an indicator for specific purposes, let us look at the percentage of patients with CKD (Stage 3–5; not on dialysis) who had a fasting lipid profile performed at least once in the last year [23]. It seems suitable for a formative purpose: being a process indicator; even small sample sizes are expected to be sufficient for detecting a change in performance [11]. Moreover, since it is hardly influenced by patient-related factors (such as demographics, patient preference) its interpretation is rather straightforward as being under the influence of care providers. Also, it incorporates the preferred clinical action (performing the fasting lipid profile), thus revealing the focus of actions needed to improve the indicator.

When assessing its use for a summative purpose, two of the Chassin criteria appear satisfied: availability of cholesterol and triglyceride values in the laboratory system would be a reliable way to determine if the profile indeed has been performed (criterion 2); and performing the lipid profile is unlikely to be harmful in itself (criterion 4). However, criterion 1 is only partly fulfilled: the indicator was derived from a National Kidney Foundation Kidney Disease Outcomes Quality Initiative guideline recommendation for which the strength of the evidence base was graded as only ‘moderate’ [26]. Finally, criterion 3 is violated because many clinical follow-up actions need to be executed correctly after performing the profile in order to establish improvements that are noticeable to patients, i.e. there is no direct link between the indicator and the desired outcome. So, it is questionable if rewarding or punishing healthcare providers based on this indicator is fair and will actually improve the quality of care.

### Box 1. Calculation of the percentage of patients receiving HD via an arteriovenous fistula as an indicator of dialysis centres’ performance—fictitious example

Assume we have the following vascular access data available:

<table>
<thead>
<tr>
<th>Indicator</th>
<th>All ages</th>
<th>&lt;80 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>All incident HD patients</td>
<td>536</td>
<td>429</td>
</tr>
<tr>
<td>Screened for fistula suitability at least once before start dialysis</td>
<td>418</td>
<td>364</td>
</tr>
<tr>
<td>Functioning AV fistula at start dialysis</td>
<td>171</td>
<td>156</td>
</tr>
<tr>
<td>Functioning AV fistula at day 91 of dialysis</td>
<td>240</td>
<td>227</td>
</tr>
</tbody>
</table>

We could now calculate the following values for the ‘same’ indicator by selecting different numerators and denominators:

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Numerator</th>
<th>Denominator</th>
<th>Indicator value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>171</td>
<td>536</td>
<td>32</td>
</tr>
<tr>
<td>B</td>
<td>240</td>
<td>536</td>
<td>45</td>
</tr>
<tr>
<td>C</td>
<td>227</td>
<td>429</td>
<td>53</td>
</tr>
<tr>
<td>D</td>
<td>418</td>
<td>536</td>
<td>78</td>
</tr>
</tbody>
</table>

**Indicator A**

Dividing the number of patients with an AV fistula at the start of dialysis as the numerator by the total number of incident HD patients as the denominator results in an indicator value of 32%. However, for part of the patients starting without a fistula, maturation time may have been too limited due to late referral by general practitioners. One could argue that it is unfair to attribute these cases to the clinical performance of the dialysis centre.

**Indicator B**

To limit the effect of late referrals, one could use the number of patients with an AV fistula at Day 91 of dialysis as the numerator instead. This increases the indicator value to 45%.

**Indicator C**

Patient factors may impact on a centre’s AV fistula rate. For example, in older patients it may be more difficult to establish a functioning fistula due to increased risk of maturation failure and access-related complications. Also, elderly patients might value the expected survival gain from dialysis via a fistula less than younger people. Instead of ascribing the effect of age to a centre’s performance, we could exclude octogenarians from the equation and focus on the 429 incident HD patients <80 years of age. This further increases the indicator value to 53%.

**Indicator D**

To avoid centres from using older age alone as an exclusion criterion for even considering patients for AV fistula creation, one could calculate the percentage of all incident HD patients that were screened for fistula suitability at least once before starting dialysis. This indicator is less affected by other healthcare providers and patient-related factors than indicators A–C. However, it only reflects a first step of fistula creation and not the required subsequent ones. Also, it is difficult to determine whether an improved value of this indicator means that a centre changed the way of delivering vascular access care, or that they just checked more ‘fistula screening performed’ boxes.

AV, arteriovenous; HD, haemodialysis.
Table 1. Categories of quality indicators and their main (dis)advantages

<table>
<thead>
<tr>
<th>Category</th>
<th>Refer to</th>
<th>Examples</th>
<th>Advantagesa</th>
<th>Disadvantagesa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structures</td>
<td>Healthcare setting characteristics that affect the systems’ ability to meet health care needs of patients</td>
<td>• Availability of dedicated outpatient vascular access service&lt;br&gt;• Renal nurse-to-patient ratio&lt;br&gt;• Having nutritional patient counselling programme in place&lt;br&gt;• Hepatitis B vaccination in HD patients&lt;br&gt;• Prescription of ACE inhibitors in CKD patients with hypertension and proteinuria&lt;br&gt;• Performing non-invasive ultrasonography of vessels in HD patients listed for vascular access creation</td>
<td>• Easy to record&lt;br&gt;• Not influenced by patient case mix</td>
<td>• Difficult and costly to change&lt;br&gt;• Additional information required to understand the indicator</td>
</tr>
<tr>
<td>Processes</td>
<td>Care that is actually being delivered</td>
<td>• LDL cholesterol&lt;br&gt;• Blood pressure&lt;br&gt;• Serum phosphorus</td>
<td>• Sensitive to a change in practice&lt;br&gt;• Limited delay between delivering care and measuring performance&lt;br&gt;• Incorporate preferred clinical action</td>
<td>• Clinical relevance is subject to changing trends&lt;br&gt;• Directly influenced by patient preference&lt;br&gt;• Process indicators that regard the performance of tests do not reflect if necessary subsequent clinical actions are performed.</td>
</tr>
<tr>
<td>Clinical correlates</td>
<td>Objectively measured clinical or laboratory signs associated with disease activity, but not causally related to outcomes</td>
<td>• Cardiovascular mortality in CKD patients&lt;br&gt;• Occurrence of bacteraemia in HD patients with a tunnelled catheter&lt;br&gt;• Quality of life after kidney transplantation&lt;br&gt;• Satisfaction with dialysis care</td>
<td>• More directly related to ultimate health status than process indicators&lt;br&gt;• More sensitive to differences in quality of care than outcomes</td>
<td>• Requires incorporation of a target value/range, which is often subject to discussion&lt;br&gt;• Influenced by patient factors (e.g. genetic profile, environmental factors, compliance to treatment)</td>
</tr>
<tr>
<td>Surrogate outcomes</td>
<td>Clinical correlates that have a causal relationship with outcomes</td>
<td>• Hepatitis B vaccination in HD patients, non-invasive ultrasonography of vessels in HD patients listed for vascular access creation</td>
<td>• Relevant and noticeable to patients&lt;br&gt;• Provide global assessment of performance</td>
<td>• Long observation period and large sample size required to detect change&lt;br&gt;• Influenced by many other factors, e.g. patient case mix, other care providers&lt;br&gt;• Potential reasons for ‘underperformance’ are not immediately obvious</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting-enzyme; CKD, chronic kidney disease; HD, haemodialysis; LDL, low-density lipoprotein; PTH, parathyroid hormone.

aBased on refs [11, 18, 19].

INDICATORS AS PART OF A CLINICAL PERFORMANCE INDICATOR SET

No single indicator covers all relevant dimensions of clinical performance. Also, different stakeholders—clinicians, patients, payers, policy-makers—may value certain aspects of care differently. Therefore, measurement initiatives are commonly built around a set of indicators to create a comprehensive picture of the quality of care provided.

Meaningful structure indicators for these sets are likely to be found in systematic reviews of strategies to implement best practices into daily renal care [27, 28], or in individual observational studies on the association between healthcare facility characteristics and (surrogate) outcomes [29, 30]. For identifying process and surrogate outcome indicators Grade ‘1A’ or ‘1B’ recommendations from rigorously developed renal clinical practice guidelines may be a useful starting point [31]. These are the recommendations, which were based on evidence of high-to-moderate quality and which are expected to apply to and be preferred by the majority of patients [32]. Finally, selection of relevant outcome indicators should be primarily guided by the purpose of the provided care. For example, when measuring the quality of care for CKD patients (Stages 3–5; not on dialysis), progression to ESRD is one of the potential outcome indicators, whereas the quality of vascular access care may be reflected in the number of access-related infections and hospitalizations.

Evaluating causal chains in daily practice

‘Causal chains’ can be used as a starting point for composing an indicator set [33]. Figure 1 shows an example of such a chain for managing cardiovascular risk in adult CKD patients not on dialysis. It consists of four elements, each belonging to a different (indicator) category; per element, we suggested a potential indicator. The links between the elements have been evaluated in (a meta-analysis of) randomized controlled trials (RCTs) [34–36]. The main advantage of building an indicator set around causal chains is that it increases the probability that a focus on improving structure, process and surrogate outcomes within the chain actually results in a better patient outcome. Also, the use of a chain facilitates the evaluation of the chain in the context of daily care in addition to previous evaluations of the links within the often rather controlled contexts of RCTs [37]. For example, the MASTERPLAN [34] and the SHARP studies [35] excluded patients who were reluctant to change drug therapy, and poorly compliant to clinic visits or prescribed
medication, respectively. Although often excluded in RCTs, non-compliant patients are not uncommon in daily practice. Therefore, it would be of interest to include this subpopulation when monitoring performance, and evaluate if, e.g. having a nurse practitioner is still equally effective in improving statin prescription. However, strictly speaking, the causal chain is not generalizable to non-compliant patients. Some initiatives address this by having ‘patient decline’ and ‘other patient reasons’ as criteria to exclude patients from the denominator when calculating indicators [23], but allowing this ‘exception coding’ is controversial. First, because it creates an opportunity for healthcare providers to ‘game’ indicator values by excluding all patients that did not meet the targets; especially within summative initiatives there might be an incentive to do this [38]. And secondly because it may seem to relieve physicians from the responsibility to make an effort to convince patients to take their medication or stop smoking [39]. So, the practice of exception coding at least warrants close monitoring to determine whether its use was appropriate. For example, by identifying providers with outlying exception rates or—more qualitatively—by reviewing the medical records of samples of excluded patients.

**Indicator sets in nephrology: two examples**

An example of a set used for performance monitoring is the NephroQUEST indicator data set, which resulted from the NephroQUEST project initiated in 2007 by the European Renal Association–European Dialysis and Transplant Association (ERA–EDTA) Registry with support from the European Union [40]. Prior to NephroQUEST, the Registry primarily collected data on case mix and outcomes of patients on renal replacement therapy (RRT). In order to also enable the composition of other types of indicators, clinical and registry experts defined additional data items (Box 2), using international renal guidelines as the starting point. To increase the set’s sustainability over a longer period of time, the data item definitions leave room to incorporate treatment targets at a later stage because recommendations on which targets to achieve are constantly evolving. As the influence of advancing insights also applies to processes of care, the number of items to compose process indicators is limited. The set lacks items related to characteristics of dialysis centres for composing structure indicators, which may be a valuable addition in the future. For instance, frequent routine multidisciplinary conferences, or clinical decision support systems for drug prescription have been suggested to positively affect processes and outcomes of renal care [28, 29, 41].

The extended ERA-EDTA Registry data set may be used for evaluating parts of causal chains in daily practice. For example, by assessing the association between achieving a certain target and survival in European RRT patients or by investigating the relationship between potential surrogate and final outcomes. Moreover, the data set enables exploring practice patterns among European dialysis centres, and for subsequently determining between-centre or country variation.

![Causal chain of reducing the cardiovascular risk in adult CKD patients not receiving dialysis, including examples of potential performance indicators.](https://academic.oup.com/ndt/article-abstract/29/8/1460/1938386)

**FIGURE 1:** Causal chain of reducing the cardiovascular risk in adult CKD patients not receiving dialysis, including examples of potential performance indicators.
Box 2. ERA-EDTA registry data set, including the additional NephroQUEST items

<table>
<thead>
<tr>
<th>Structures</th>
<th>Processes</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>[None]</td>
<td>• Treatment with ESAs</td>
<td>• Treatment modality</td>
</tr>
<tr>
<td></td>
<td>• Dialysis duration and frequency</td>
<td>•Time on RRT</td>
</tr>
<tr>
<td></td>
<td>• Vascular access type</td>
<td>• Survival on RRT</td>
</tr>
<tr>
<td>(Potential) Surrogate outcomes</td>
<td>• Systolic and diastolic blood pressure</td>
<td>• Source of kidney donor</td>
</tr>
<tr>
<td></td>
<td>• Serum albumin</td>
<td>• Graft survival of kidney transplants</td>
</tr>
<tr>
<td></td>
<td>• C-reactive protein</td>
<td>Patient case mix</td>
</tr>
<tr>
<td></td>
<td>• Total cholesterol; high-density lipid cholesterol; triglycerides</td>
<td>• Age; gender</td>
</tr>
<tr>
<td></td>
<td>• Haemoglobin; ferritin</td>
<td>• Height; dry weight; major amputations</td>
</tr>
<tr>
<td></td>
<td>• Calcium; phosphorus; parathormone</td>
<td>• Smoking status</td>
</tr>
<tr>
<td></td>
<td>• Urea clearance</td>
<td>• Primary renal disease</td>
</tr>
<tr>
<td></td>
<td>• Creatinine clearance</td>
<td>Comorbidities at start RRT</td>
</tr>
</tbody>
</table>

*aCollected only in the context of HD.

*bCollected only in the context of peritoneal dialysis.

*cAlready collected prior to the NephroQUEST project.

*dDerived from items: date of first RRT; date/type of event or treatment; cause of death.

supporting QI efforts among dialysis providers, the CMS clinical performance measurement project also aims to enable patients to participate in making healthcare decisions. This summative aspect of the initiative has been further emphasized since the start of the CMS Quality Incentive Program [6], which links four process indicators to reimbursement: percentage of erythropoietin-stimulating agent (ESA)-treated patients with haemoglobin ≥12 g/dL (with higher percentages getting lower quality scores); percentage of patients with a urea reduction ratio (URR) ≥65%; percentage of patients using a bipuncture AV fistula during the last treatment of the month; percentage of HD patients with an intravenous catheter in use for 90 days before the last dialysis session. However, Fishbane et al. clearly showed that none of these indicators fulfils all four Chassin criteria, which makes their use for summative purposes by CMS questionable [6].

**INTERPRETING RESULTS OF PERFORMANCE MEASUREMENTS: ADJUSTING FOR PATIENT CHARACTERISTICS**

Besides the clinical quality of the provided care, characteristics of the patient population can significantly affect the results of clinical performance measurements. For example, patient factors may explain a substantial part of differences between CMS dialysis centres in achievement of a target URR ≥65% [43]. For this reason, the values of performance indicators should be adjusted for patient factors as adequately as possible to prevent interpretation of differences in case mix as differences in performance. The ERA-EDTA indicator data set (Box 2) contains patient characteristics frequently used for risk adjustment in RRT populations. However, unknown, and thus unmeasured, case-mix factors hamper complete risk correction. This is known as the ‘case-mix fallacy’ [9]. In addition, registration of risk factors, such as comorbidities, might differ substantially between nephrologists and dialysis centres, either unintended or intended [44].

Risk adjustment usually seems to concern (surrogate) outcome indicators. Although structure indicators, like having a ‘nurse practitioner trained in cardiovascular risk management’ (Figure 1), are rarely affected by patient case mix, process indicators may be. Sicker patients need more (complex) care, which can justify a deviation from care as described in guidelines, as well as increase the susceptibility of their treatment to errors [9]. In addition, process indicators are more directly influenced by patient preference than outcome indicators. For example, older CKD patients often have more comorbidities and are being prescribed a larger variety of medications compared with their younger, healthier counterparts. A higher degree of multimorbidity and polypharmacy in such patients makes it more likely that the nephrologist will decide not to prescribe statins either to avoid adverse interactions with drug treatments recommended by different guidelines [45], or because the patient prefers not to take ‘yet another pill’. Also, it increases the chance that statins are omitted unintentionally from the drug regimen. So, in Figure 1, not only the (surrogate) outcomes ‘LDL cholesterol level’ and ‘risk of cardiovascular events’, but also the process indicator ‘percentage of patients being prescribed statins’ requires case-mix adjustment in order to be interpreted correctly as an aspect of the quality of care provided to CKD patient who are not on dialysis. Unfortunately, the lack of accepted risk-adjustment methods on the one hand, and mostly unavailable patient preference data on the other hand hinder adequate adjustment of process indicators for patient factors. The fact that this impedes fair comparisons between facilities and within facilities over time is especially problematic when using such process indicators for summative purposes.

**CONCLUSION**

In this paper, we distinguished indicators referring to structures, processes, surrogate outcomes and outcomes of care. No single indicator provides a comprehensive picture of clinical performance. Therefore, indicators ought to be part of an indicator set that ideally covers elements of care that are connected by evidence-based links. The advantages and disadvantages of the different indicators should be balanced depending on the aim of the measurement initiative. This is particularly important within summative initiatives, which directly link external accountability indicator. However, we did not find any
examples within renal medicine that would meet such criteria. When additionally taking into account the need for and difficulty of adequate case-mix adjustment of process indicators, we feel that it is questionable for clinical performance indicators to be used for summative purposes at all. Instead, measurement initiatives should rather focus on facilitating observational research and monitoring trends over time, and aim to improve patient care whilst avoiding unwarranted penalization of healthcare professionals.

**CONFLICT OF INTEREST STATEMENT**

None declared. Furthermore, the authors declare that this paper has not been published previously in whole or part.

**REFERENCES**

1. Dialysis Outcomes and Practice Patterns Study program (2 September 2013, date last accessed)
15. Thompson A. Proteinuria as a surrogate end-point—more data are needed. Nat Rev Nephrol 2012; 8: 306–309
43. Tangri N, Tighiouart H, Meyer KB et al. Both patient and facility contribute to achieving the centers for medicare and medicaid services’ pay-for-
Integrated genomics and metabolomics in nephrology

Dorothee Atzler¹,², Edzard Schwedhelm¹,² and Tanja Zeller²,³

¹Department of Clinical Pharmacology and Toxicology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, ²German Center for Cardiovascular Research (DZHK), Partner Side Hamburg/Lübeck/Kiel and ³Clinic for General and Interventional Cardiology, University Heart Center Hamburg, Hamburg, Germany

Correspondence and offprint requests to: Tanja Zeller; E-mail: t.zeller@uke.de

ABSTRACT

Applying ‘omics’ approaches such as genome-wide association studies (GWAS) and metabolome analyses, genes and metabolites have been identified to be associated with renal pathophysiology. Meta-analyses of GWAS from large epidemiologic cohorts uncovered several novel loci linked with estimated glomerular filtration rate and chronic kidney disease (CKD). Sophisticated analytical technologies, including mass spectrometry and nuclear magnetic resonance spectroscopy, allow the analyses of up to 4000 targeted and non-targeted metabolites in plasma, serum and urine. Several uraemic toxins were found that were increased in CKD. Among them, arginine derivatives like asymmetric dimethylarginine or tryptophane metabolites have been identified as promising candidates to target mechanisms of kidney disease progression. This review aims to summarize recent findings in clinical kidney diseases research revealed by ‘omics’ approaches with a clear focus on recent genomics and metabolomics efforts.

Keywords: chronic kidney disease, genomics, metabolomics, nephrology

INTRODUCTION

Complex kidney diseases like chronic kidney disease (CKD), diabetic nephropathy (DN) or renal hypertension, involve a complex bundle of underlying pathophysiological mechanisms. Valuable insight has been acquired from candidate gene approaches to genome-wide association studies (GWAS); however, the underlying pathophysiological mechanisms do not only involve different genotypes but also changes in cellular, blood and urinary metabolites. Metabolomics complements other ‘omics’ data and as a downstream result of gene expression, changes in the metabolome are considered to reflect the activities of the cell at a functional level (Figure 1). Building on a substantive body of work over the past few years, we discuss herein the current knowledge of genomics and metabolomics in kidney diseases.

GENOME-WIDE ASSOCIATION STUDIES

Great progress has been made in mapping genomic variations of common disease at a genome-wide level. GWAS use genomic variations, termed single nucleotide polymorphisms (SNPs), to identify regions of the genome associated with the disease status or a clinical phenotype [1, 2].

GWAS: THEORETICAL ASPECTS

By design, GWAS provide an unbiased survey of the effects of common genetic variants. SNPs chosen for GWAS typically have a minor allele frequency (MAF) of ≥0.05 and are selected to ‘tag’ the most common haplotypes. However, the power of detection depends directly on the sample size of the study...