Our understanding of glomerular diseases has evolved over the years, in part through studies and registries developed from electronic health records (EHR). For nephrotic syndrome (NS), this has helped identify FSGS and membranous nephropathy as the leading causes in Black and White patients, respectively (1). Furthermore, these studies have demonstrated decreased kidney survival and higher mortality in patients with NS, compared with the general population (2). Like all studies, identifying patients from the EHR is potentially susceptible to selection biases.

In this work, Vestergaard et al. compared patients with biochemical features of NS to patients with hospital-recorded NS within the Danish National Patient Registry in Denmark from 2004–2018 (3). The authors hypothesized that more patients would be identified by laboratory criteria than coded diagnoses. Laboratory NS was identified by the presence of nephrotic-range proteinuria and hypoalbuminemia. Nephrotic-range proteinuria was defined as a spot urine albumin-creatinine ratio >220 mg/mmol, urine albumin excretion rate >2.2 g/d, spot urine protein-creatinine ratio >350 mg/mmol, or urine protein excretion rate >3.5 g/d. Hypoalbuminemia was defined as plasma albumin <36 g/L (<3.6 g/dl) in persons aged <70 years, and <34 g/L (<3.4 g/dl) in persons aged ≥70 years. A coded diagnosis of NS was based on the basis of International Classification of Diseases, Tenth Revision N04 or International Classification of Diseases, Eighth Revision 581.

The authors showed that patients with nephrotic-range proteinuria and hypoalbuminemia were markedly five-fold more common than those with a coded diagnosis of NS. In addition, a lower eGFR and greater comorbidity were seen in the former. Similarly, prior kidney transplant recipients were more likely to have nephrotic-range proteinuria and hypoalbuminemia (6%) than were diagnosed with NS (1%). These findings demonstrate that studies on the basis of coded diagnoses may fail to characterize fully the population with NS. Particular strengths of this study included a large dataset with inclusion of laboratory, pathology, medication, and diagnosis data linked by individual patient identifiers. Notably, 70% of individuals had a reported hospital diagnosis reflecting any nephropathy by the index date, compared with only 10% receiving a code for NS. This highlights the inherent limitations in using an arbitrary rubric, such as NS.

As most nephrologists will attest, the conventional definition of NS includes edema and hypoalbuminemia, although Kidney Disease: Improving Global Outcomes guidelines do not provide a specific albumin criterion (4). The authors acknowledge the term NS is arbitrary (Figure 1). In the 16th–18th centuries, “dropsy,” now a synonym of edema, was considered a disease (5). It was later established that the combination of kidney disease, proteinuria, and hypoproteinemia was one cause for dropsy. In 1905, the term “nephrosis” originated to distinguish the pathology of inflammatory forms of kidney disease (nephritic) from noninflammatory counterparts (5,6). The term NS was likely introduced in the 1940s, and Berman and Schreiner suggested proteinuria ≥3.5 g/d on the basis of a retrospective clinicopathologic cohort of 45 patients with glomerular diseases. Remarkably, all patients had hypoalbuminemia, but edema was absent in 27% (7).

Given the ambiguity and variability of the definition, Glassock and colleagues proposed to include two essential parameters for the diagnosis of NS: proteinuria ≥3.5 g/d and serum albumin below the lower limit of normal (usually <3.5 g/dl), thereby excluding edema as an essential clinical sign (6). By using this modern definition, Vestergaard and colleagues captured a larger population with more generalizable findings, solely on the basis of laboratory criteria. The authors found that comorbidities such as CKD, diabetes mellitus, and hypertension were more common in patients with NS identified by laboratory criteria than diagnosis codes. These patients were also less likely to undergo kidney biopsy. In essence, for example, patients with presumed diabetic kidney disease are less likely to be given a diagnosis of NS and less commonly undergo kidney biopsy than patients in whom “primary” NS, such as membranous nephropathy, is suspected. Moreover, clinicians may have coded these patients with similar, but different, codes than N04/581. For example, the use of “N03.2 Chronic nephritic syndrome with diffuse membranous

From Dopsy to Chart Biopsy: Opportunities and Pitfalls of Electronic Health Records

C. Elena Cervantes and C. John Sperati

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glomerulonephritis” would not have captured patients by diagnosis code alone.

Clinical findings, nonetheless, are important elements of a syndrome. In fact, the absence of edema was reported as a limitation of this study. Edema in the definition of NS is problematic given its variable frequency and complex pathophysiology. Edema is often absent in patients with nephrotic-range proteinuria caused by conditions such as overflow proteinuria, adaptive segmental sclerosis, or diabetic nephropathy (6,7). One can see how these diseases, and others, might less commonly be given a coded diagnosis of NS. The work of Vestergaard and colleagues demonstrates the importance of utilizing objectively quantifiable measures in identifying and classifying participants for research. This is further strengthened by the observation that 87% of patients had a diagnosis reflecting any nephropathy by 1 year after the index date. In other words, >10% of patients would still not be identified as even having kidney disease, much less NS, if using these diagnosis codes alone. This has obvious implications for the generalizability of findings that are overly derived from diagnosis codes alone.

EHR datasets remain a work in progress. The use of billing codes alone results in an underrepresentation of the condition of interest. The EHR is often tailored to billing, quality improvement, and health care operations, and not to the capture of validated, clinical research data. A recent study across the Military Health System identified 63% of uncoded CKD that was otherwise captured by laboratory data (9). It is true that laboratory data may not be available in all patients, which would also lead to an underestimation of disease. The Cleveland Clinic Registry, adopted by 2002, defined CKD on the basis of International Classification of Diseases diagnosis or laboratory data. Remarkably, the study showed considerable agreement between the administrative dataset and actual chart review (10). As Vestergaard et al. suggest, the combination of electronically extracted clinical data with more traditional administrative datasets is key, provided the algorithm is validated.

With these challenges in mind, Shang et al. (11) designed a machine-learning algorithm for detection of CKD and manually validated it across three medical systems. The algorithm allowed observational analyses at large scale, including associations across common comorbidities and heritability of kidney diseases. Moreover, its power was demonstrated through the recovery of known risk loci associated with kidney disease through the incorporation of genome- and phenotype-wide association studies. Machine learning from big data represents a continued evolution in our ability to comprehensively recognize, categorize, and analyze. These tools may allow for improved capture of uncoded NS, permit more robust linkage to serologic, genomic, and tissue-based datasets, and permit better phenotyping and clinical prognostication through otherwise unrecognized associations. Perhaps, for example, this provides further insight into at-risk groups for thromboembolic complications, response to immunosuppression, or progression to ESKD.

In conclusion, the definition of NS is arbitrary, and the clinical significance of specific serum albumin and proteinuria thresholds require further clarification. The complex pathophysiology of proteinuric kidney disease and overlapping clinical features across specific etiologies demonstrate the need for more robust phenotyping. Large prospective observational cohort studies such as the Nephrotic Syndrome Study Network (NEPTUNE) and Cure Glomerulonephropathy (CureGN), among others, may help provide such data. As Vestergaard et al. demonstrate, the use of health-system EHR, even in a well-integrated system such as the national Danish registry, requires careful constructs for the extraction of generalizable data. Investigators should be particularly mindful for the effect of selection criteria on inclusion (or exclusion) of patients with diabetes mellitus and advanced CKD. These EHR resources, however, are often less expensive to access and easier to operate than large cohort studies. As such, they remain vitally important tools in improving human health. Advances in machine learning may quickly allow sensitive and specific mining of very large datasets across diverse populations around the world, facilitating a new era for clinical care and research.

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Author Contributions

C.E. Cervantes and C.J. Sperati conceptualized the study, wrote the original draft, and reviewed and edited the manuscript; and C.J. Sperati provided supervision.

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