**Nature Reviews Nephrology Commentary**

*Electronic Health Records advancing clinical trials for paediatric glomerular disease: are we there yet?*

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For paediatric nephrologists used to dealing with rarities, glomerular disorders can be considered one of the more ‘common’ manifestations of kidney disease in children and young people (CYP). Nephrotic syndrome, affecting 2 to 7 per 100,000 children (1), may be one of the first nephrological encounters for many paediatricians in training, thus sealing the fate of many a future nephrologist. Glomerular disease also accounts for a significant proportion of long-term injury, contributing 5-14% of all chronic kidney disease (CKD) and 15-29% of end-stage kidney disease (ESKD) worldwide (2). Despite its relative frequency, therapeutic advances in paediatric glomerular disease have not been forthcoming. Small patient numbers limit the power achievable within a clinical trial to detect a clinically significant difference: for example, a sample size of 348 patients would be needed to identify a 20% reduction in a baseline protein:creatinine ratio from 150mg/mmol between two study groups, not accounting for attrition. As such, it is of no surprise that children are often recruited alongside adults in therapeutic trials, although it is unclear how generalisable results are to the paediatric population. One systematic review identified 27 paediatric-specific clinical trials, accounting for 2.6% of all nephrology studies and 0.9% of all paediatric-specific studies (3).

Clearly, adequately powered clinical trials are required to determine the most effective strategies to prevent disease progression in children, not least for those with glomerular disease. But how can we identify sufficient numbers of eligible participants in an efficient and cost-effective manner? In an article in the *Journal of the American Society of Nephrology* *(JASN)*, Denburg and colleagues offer a solution that’s been under our noses for some time: the (almost) ubiquitous electronic health record (EHR) (4). In the article, Denburg *et al*. described the development of a computational phenotype from data elements identified in the medical records and clinical encounters of 231 confirmed cases of paediatric glomerular disease. An iterative approach was then undertaken to test the rule-based algorithm using blinded, structured chart reviews: first in a single centre with subsequent validation across 8 additional tertiary hospitals. During this period of refinement, the team modified the algorithm requirements for overactive codes (‘acute glomerulonephritis’) and removed those triggering high false positive counts (‘glomerulosclerosis’); the result is a digital phenotype comprising clinical encounters (>=3 nephrology reviews), diagnostics and kidney biopsy procedure codes that has a high overall sensitivity (96%), specificity (93%) and negative predictive value (97%) for detecting glomerular disease. Unfortunately, the data published in the paper are not entirely transparent as total patient numbers used for validation quoted in the abstract do not match those given in the tables. Nevertheless, in theory, the use of robust computational phenotypes to identify disease-specific cohorts could accelerate identification of potential participants for clinical trials.

However, limitations to EHR data and computational phenotypes exist. EHRs are designed primarily to record clinical interactions and audit and improve healthcare provision, and this has a number of implications. First, there is a legal dimension. For example, under the terms of the European General Data Protection Regulation, without prior patient consent for use of their EHR for research with an explicit statement that they may be approached for inclusion into trials at some unspecified time-point in the future, patients identified by this algorithm in this research could not be directly approached for trial inclusion. Patients must be offered the opportunity to opt out of such data use (5). There are ways around this, e.g. by implementing alerts in local EHR systems at source that then prompt local clinicians to consent and recruit participants when they see the patient.

Second, we must be mindful that for any diagnostic algorithm, a trade-off between sensitivity and specificity occurs resulting in false positive and negative results. Approaching a falsely positive case for recruitment could result in increased anxiety, additional tests and, in the worst-case scenario, exposure to an unnecessary treatment for a child and their family. Detection of a ‘case’ may not automatically equate to a patient fully informed about their condition. Clearly, rigorous checks in close collaboration with local teams will be required for confirmation of a patient’s eligibility and recruitment before patients are approached.

Third, any algorithm can only be used in settings that deliver care similar to that seen in the settings that the algorithm was developed for. For settings where there may be a different pathway of work-up, the restriction to more than 3 clinical encounters may miss cases (e.g. if patients are hospitalised for prolonged periods), and also issues around billing/funding incentives may lead to particular codes being used in some settings more often than in others. A requirement for attending a nephrologist on three or more occasions, as included in this study’s algorithm, may mean that non-health seeking or non-attending populations, which may include disadvantaged children, are under-represented in trial recruitment. Although children from low-income families may benefit from government-funded healthcare initiatives such as Medicaid or the Children’s Health Initiative Programme (CHIP), eligibility criteria and benefits offered vary by jurisdiction, which may also affect validity across regions.

Fourth, the use of a well-designed and validated phenotype is only as good as the data captured within an EHR system. For example, if a particular type of disease has been associated with having a particular ethnicity – this may in turn mean that the rate of false-positives may vary by ethnicity(6). Data capture of important confounding variables such as ethnicity or measures of socio-economic deprivation and high rates of missingness and/or misclassification are ongoing challenges for EHR research (7).

In summary, Denburg and colleagues have demonstrated it is possible to identify, with a high degree of accuracy, patient populations for whom pragmatic clinical trials are needed. Moving now from identification to recruitment requires working with patients and their families, healthcare professionals, clinical trialists and data providers to ensure solutions to these issues are acceptable to patients, their families and the wider public.

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