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# Advancing Treatments for Rare Renal Diseases: New Hopes and Opportunities to Address a High Unmet Need

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**Keywords**
Chronic kidney disease · Rare disease · Glomerulonephritis · Clinical research

**Abstract**
***Introduction:*** The etiology of chronic kidney disease (CKD) is varied and complex. Diabetes and hypertension comprise 2/3 of cases and rare conditions, including inherited genetic diseases, comprise 1/3. We previously reported a 54% increase in clinical studies in CKD in the last 10 years. Hypothesizing a greater increase in rare renal disease studies, we undertook further analysis of metadata from Clinicaltrials.gov. ***Methods:*** CT.gov was searched for 49 conditions determined to be rare renal diseases posted between Jan-2003 and Dec-2022. Studies were divided into 2 time periods: P1 (2003–2012) and P2 (2013–2022) and analyzed by study type, phase, indication, primary endpoint, population, and funding. ***Results:*** Studies increased significantly in P2 versus P1 (123%, $p < 0.001$) with the greatest rise in observational studies (283%, $p < 0.001$). Interventional studies increased 93% ($p < 0.01$), with the greatest rise in early phases (205%, $p < 0.001$). The most frequent indications were LN, ADPKD, and IgA nephropathy; all increased 77–166% in P2 ($p < 0.05$ – $p < 0.001$). Proteinuria was the most frequent primary endpoint, which increased 63% ($p = 0.054$). Studies with pediatric populations increased 78% ($p < 0.01$). Most studies were nonindustry funded; however, industry-funded studies increased by 225% ($p < 0.001$). ***Conclusion:*** Clinical research in rare renal diseases has increased significantly in the last 10 years, particularly in glomerular diseases (GDs) and ADPKD. Proteinuria correlates with outcomes in GD, which explains the high percentage of studies with this primary endpoint. Rare renal diseases disproportionately affect children and the rise in studies with pediatric populations is encouraging. The rise in observational studies may signal an increased focus on understanding the natural course and pathophysiology of disease, which may lead to new potential therapeutic targets and future interventional studies. The increase in industry-funded studies suggests basic science is translating into industry-sponsored research.



## Introduction

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function present for greater than 3 months. The diagnosis of CKD may be based on measurement of serum creatinine with calculated diminished estimated glomerular filtration rate and/or the detection of blood or protein in a urine sample. The diagnosis may also be made by kidney abnormalities

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observed on radiologic imaging (e.g., ultrasound, computed tomography). CKD is common in adults, with approximately 700 million people affected by CKD worldwide in 2017 (9.1% of the population) [1]. The prevalence of CKD increased by 29.3% between 1990 and 2017 [1]. In countries with low to middle socio-demographic index, where renal replacement therapy is not available or dialysis is inadequate, patients typically die during CKD progression to end-stage renal disease (ESRD) due to cardiovascular comorbidities, such as coronary artery disease, or within months of reaching ESRD.

Nephrology has been identified as an interesting development opportunity for the pharmaceutical industry due to several factors, including high unmet need, ongoing evolution (simplification) of endpoints and faster approval tracks [2]. Furthermore, the authors have previously reported a greater than 50% increase in clinical research in CKD over the last decade compared to the previous one [3]. The etiology of CKD is varied and complex, with diabetes mellitus and hypertension responsible for the two-thirds of CKD cases in adults. Other conditions such as inherited genetic diseases (e.g., autosomal dominant polycystic kidney disease [ADPKD]), congenital anomalies of the kidney and urinary tract, and glomerulonephritis either renal limited (e.g., IgA nephropathy [IgAN]) or in the setting of systemic autoimmune diseases (e.g., lupus nephritis [LN]) make up the remaining one-third of cases.

In children, the prevalence of kidney disease ranges from 15 to 74.7 cases per one million children [4] making it extremely rare. Kidney disease can affect children in several ways, ranging from treatable disorders without long-term sequelae to life-threatening conditions. Data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) show a progression rate from CKD stages II-IV to ESRD of 17% at 1 year and 39% at 3 years, with the median time to ESRD of four and a half years. Furthermore, age-specific mortality in children with ESRD is about 30 times greater than children without ESRD [5]. Children with CKD face many challenges, such as negative self-image, behavior and learning problems, delayed language and motor skills development and delayed growth rate compared to their healthy peers. Kidney disease in children can be caused by birth defects, hereditary disease, infection, nephrotic syndrome, systemic disease, trauma, and urine blockage or reflux. The causes of ESRD in children are correlated to age range. For example, birth defects and hereditary disease are the leading causes of ESRD from birth to the age of 4. Hereditary disease, nephrotic syndrome, and systemic disease are the leading causes between the ages of 5 through 14. Glomerular disease (GD) is the most common cause between the ages of 15 and 19. However, in contrast to the positive trends in adult CKD populations in the last 10 years, increases in clinical studies in pediatric populations have been marginal [3]. Hypothesizing more marked increases in rare renal disease studies in the last 10 years compared to what has been previously reported by the authors for clinical research in CKD more broadly, we undertook a further analysis of clinical studies in rare renal indications using metadata from Clinicaltrials.gov (CT.gov).

## Methods

CT.gov was searched for interventional or observational studies with a first post date between January 01, 2003, and December 31, 2022, that included the terms in Table 1, determined to be rare renal diseases. Prior to 2003, only 14 studies in these indications had been registered. The search excluded expanded access programs as these are not considered clinical studies. Search results were divided into two time periods: period 1 (P1), which contained all studies with a first post date between 2003 and 2012 and period 2 (P2), which contained all studies with a first post date between 2013 and 2022. The two time periods were analyzed by study type, study phase (by clustering studies into early phase [phase I and phase II] and late phase [phase II/III through phase IV] categories), primary indication, primary endpoint, funding source, and population type. A Jarque-Bera test was performed on both sets of data to determine whether they were significantly different from a normal distribution. The tests returned $p$ values >0.05, which confirmed that there was insufficient evidence that the datasets were not normally distributed. Differences between the two periods were analyzed using descriptive statistics and two-tailed $t$ tests, assuming unequal variances, to test for statistical significance.

## Results

The search returned 876 records, of which 50 were excluded due the primary study indication not matching terms in the search criteria. The remaining 826 studies were included in the analysis.

*Study Type and Development Phase*

There was a 123% increase in the total number of clinical studies in P2 (570, M = 57.0 [$SD$ = 13.2] compared to P1 (256, M = 25.6 [SD = 14.9]) (shown in Fig. 1a), which was statistically significant ($t[18] = 4.99$, $p < 0.001$). The number of interventional studies increased by 93% (P2 = 417, M = 41.7 [SD = 9.4] vs. P1 = 216, M = 21.6 [SD = 13.3], $t[16] = 3.90$, $p < 0.01$), while the number of observational studies increased by 283% (P2 = 153, M = 15.3 [SD = 5.1] vs. P1 = 40, M = 4.0 [SD = 3.5], $t[16] = 5.80$, $p < 0.001$). Early phase studies (phase I and phase II) increased by 155% in P2 (189, M = 18.9 [SD = 6.6] compared to P1 (74, M = 7.4 [SD = 4.8]), which was

**Table 1.** A list of rare renal disease search terms used to extract metadata from clinicaltrials.gov

| | | |
|---|---|---|
| Adenine Phosphoribosyltransferase Deficiency | Glomerulocystic Disease | MPGN |
| APRT-D | IgA Nephropathy | Minimal Change Nephropathy |
| Alport Syndrome | IgAN | Nephronophthisis |
| Anti-Glomerular Basement Membrane Disease Vasculitis | IgA Vasculitis | Primary Hyperoxaluria |
| Goodpasture Syndrome | Henoch schonlein purpura | Hyperoxaluria |
| Atypical Haemolytic Uraemic Syndrome | Immunotactoid Glomerulopathy | Shiga toxin associated haemolytic uraemic syndrome |
| aHUS | Glomerulonephritis with Organised Microtubular Monoclonal Immunoglobulin Deposits | Small Vessel Vasculitis |
| Autosomal Dominant Polycystic Kidney Disease | GOMMID | ANCA Vasculitis |
| ADPKD | Large vessel vasculitis | Steroid resistant nephrotic syndrome |
| Autosomal Recessive Polycystic Kidney Disease | Lowe syndrome | SRNS |
| ARPKD | Medium vessel vasculitis | Steroid sensitive nephrotic syndrome |
| C3 Glomerulopathy | Membranous Nephropathy | SSNS |
| C3 Glomerulonephritis | Membranoproliferative Glomerulonephritis | Thin basement membrane nephropathy |
| Fibrillary Glomerulonephritis | Dense Deposit Disease | Type 1 Cryoglobulinaemic glomerulonephritis |
| Focal Segmental Glomerulosclerosis | Dent Disease | Monoclonal gammopathy of renal significance |
| FSGS | Lupus Nephritis | |
| Giant Vessel Arteritis | Variable vessel vasculitis | |

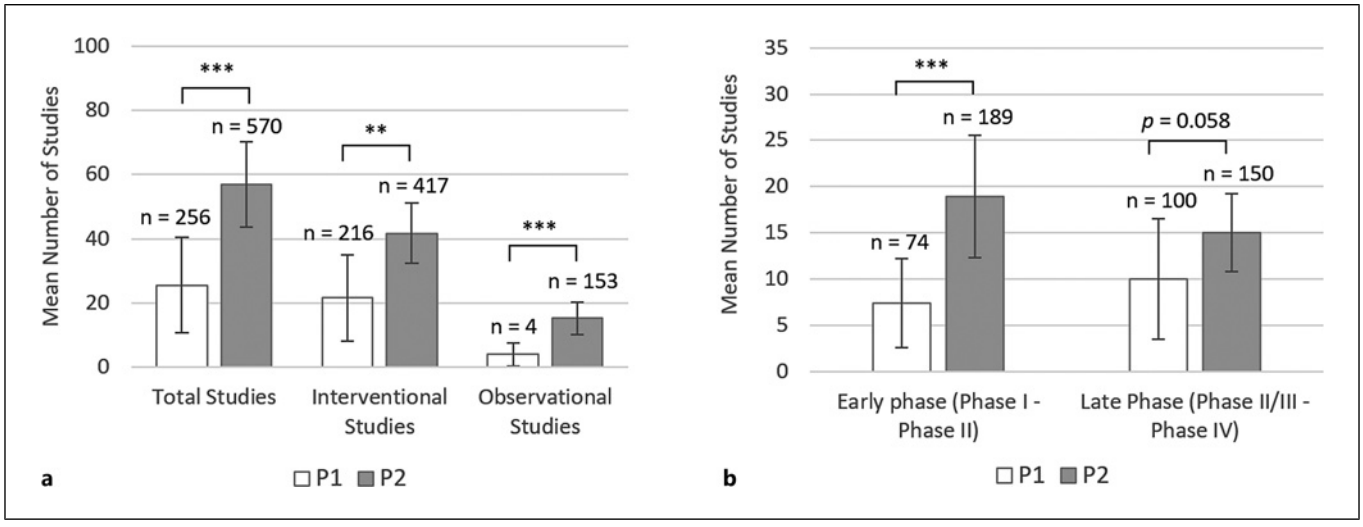


**Fig. 1.** A comparison of the distribution of clinical studies registered in CT.gov in the period 2003–2012 (P1) versus 2013–2022 (P2) by (**a**) study type and (**b**) study phase. Values represent the mean; error bars represent the standard deviation. The number of studies is denoted above each bar. ** two-tailed *t* test with unequal variances <0.01; *** two-tailed *t* test with unequal variances *p* value <0.001.

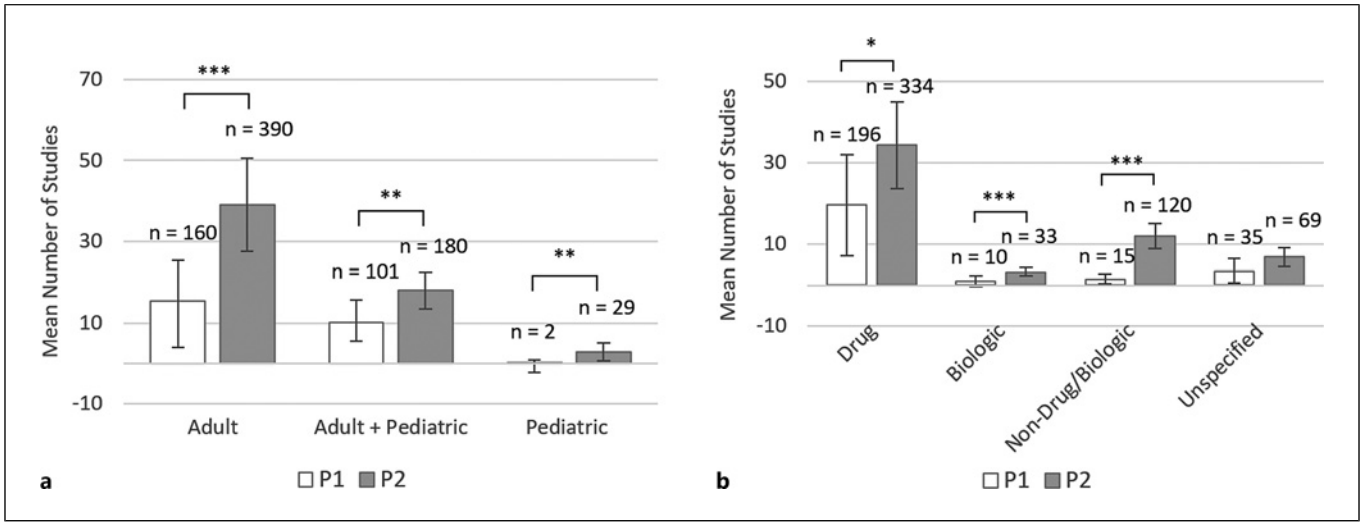


**Fig. 2.** A comparison of the distribution of clinical studies registered in CT.gov in the period 2003–2012 (P1) versus 2013–2022 (P2) by (**a**) study population type and (**b**) study intervention type. Values represent the mean; error bars represent the standard deviation. The number of studies is denoted next to each bar. ** two-tailed *t* test with unequal variances *p* value <0.01; *** two-tailed *t* test with unequal variances *p* value <0.001.

statistically significant ($t[18] = 4.99$, $p < 0.001$), while late phase studies (phase II/III – phase IV) increased by 50% in P2 (150, M = 15.0 [SD = 4.2] vs. P1 = 100, M = 10.0 [SD = 6.5]), which was approaching, but did not reach, statistical significance ($t[15] = 2.05$, $p = 0.058$) (shown in Fig. 1b).

*Population and Intervention Type*

The majority of studies in both periods were conducted in adult-only populations (P1 - 60%, P2 - 68%) (shown in Fig. 2a). However, there was a 78% increase in studies that included pediatric populations in P2 (180, M = 18.0 [SD = 5.5]) versus P1 (101, M = 10.1 [SD = 4.6]), which was statistically significant ($t[17] = 3.49$, $p < 0.01$). There was also a statistically significant increase in the number of pediatric-only studies in P2 (29, M = 2.9 [SD = 2.3]) versus P1 (2, M = 0.2 [SD = 0.6]) ($t[10] = 3.60$, $p < 0.01$) (shown in Fig. 2a). An analysis of studies by intervention type (shown in Fig. 2b) revealed that studies that investigated drug interventions (medicines manufactured through chemical synthesis) represented 67% of study interventions in P1 compared to 55% in P2. Biologic interventions (medicines manufactured from living organisms or containing components of living organisms) constituted 14% of studies in P1 compared to 12% in P2. However, although the proportion of studies investigating drug interventions and biologic interventions was lower in P2 versus P1, in absolute terms there were significant increases in both intervention types. The number of studies investigating drug interventions increased by 82% (P2 = 344, M = 34.4 [SD = 10.7] vs. P1 = 196, M = 19.6 [SD = 12.5], $t[18] = 2.85$, $p < 0.05$), whilst the number of studies investigating biologic interventions increased by 100% (P2 = 33, M = 3.3 [SD = 1.1] vs. P1 = 10, M = 1.0 [SD = 1.3], $t[17] = 4.27$, $p < 0.001$). Studies of nondrug or biologic interventions (including, but not limited to, behavioral, device, diagnostic, dietary interventions) also increased significantly in P2 compared to P1 (P2 = 120, M = 12.0 [SD = 3.2] vs. P1 = 15, M = 1.5 [SD = 1.3], $t[12] = 9.31$, $p < 0.0001$).

*Primary Indication*

The three most studied indications in both period 1 and period 2 were LN, ADPKD, and IgAN (shown in Fig. 3). Collectively, these indications accounted for 442 studies, representing 54% of total studies included in the analysis. Studies of LN increased by 77% in P2 (117, M = 11.7 [SD = 3.8]) compared to P1 (66, M = 6.6 [SD = 4.5]), which was statistically significant ($t[18] = 2.75$, $p < 0.01$). The increase in studies of ADPKD (154%) (P2 = 94, M = 9.4 [SD = 4.6] vs. P1 = 37, M = 3.7 [SD = 2.8]), $t[15] = 3.35$, $p < 0.01$) and IgAN (166%) (P2 = 93, M = 9.3 [SD = 2.4] vs. P1 = 35, M = 3.5 [SD = 2.6]), $t[18] = 5.14$, $p < 0.001$) was also statistically significant.

*Primary Outcome*

We evaluated the top ten primary outcome measures in industry sponsored studies (shown in Fig. 4) and found that urinary protein was the most frequently evaluated primary endpoint over the last 20 years. Studies

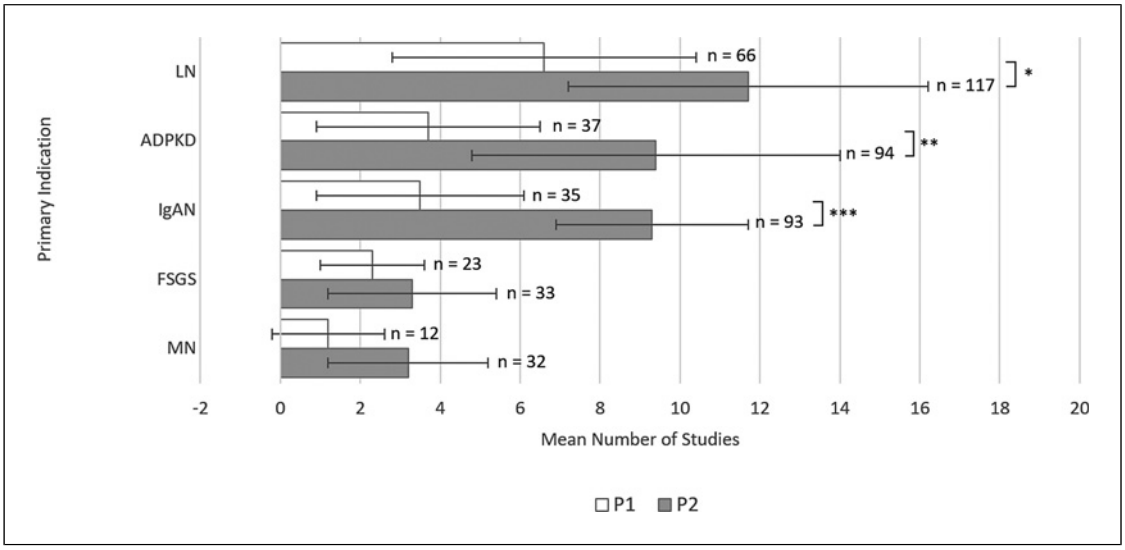


**Fig. 3.** A comparison of the distribution of clinical studies registered in CT.gov in the period 2003–2012 (P1) versus 2013–2022 (P2) according to the top five most frequently reported primary indications. Values represent the mean; error bars represent the standard deviation. The number of studies is denoted next to each bar. *two-tailed *t* test with unequal variances <0.05; ** two-tailed *t* test with unequal variances *t* test *p* value <0.01; *** two-tailed *t* test with unequal variances *p* value <0.001. LN, lupus nephritis; ADPKD, autosomal dominant polycystic kidney disease; IgAN, IgA nephropathy; FSGS, focal segmental glomerulosclerosis; MN, membranous nephropathy.

investigating the effects of therapeutics on urinary protein (including urine protein-to-creatinine ratio [UPCR]) increased by 63% in P2 (101, M = 10.1 [SD = 3.7] vs. P1 (62, M = 6.2 [SD = 4.7]), which approached, but did not quite reach, statistical significance ($t$[17] = 2.07, $p$ = 0.054). There was a significant increase in the number of studies evaluating composite endpoints (response rate, remission rate, and disease progression), which collectively increased by 107% (P2 = 95, M = 9.5 [SD = 3.9] vs. P1 = 46, M = 4.6 [SD = 3.1]), $t$[17] = 3.10, $p$ < 0.01). The number of studies evaluating adverse events as the primary outcome measure increased significantly (P2 = 55, M = 5.5 [SD = 2.4] vs. P1 = 10, M = 1.0 [SD = 0.9]), $t$[12] = 5.5, $p$ < 0.001).

*Funding Source*

The majority of studies in both periods were nonindustry funded (P1 64%; P2 57%) (shown in Fig. 5). The number of nonindustry funded studies increased by 98% in P2 (327, M = 32.7 [SD = 6.9]) compared to P1 (162, M = 16.2 [SD = 9.6]), which was statistically significant ($t$[16] = 4.32, $p$ < 0.001) The number of industry-only funded studies increased by 225% (P2 = 202, M = 20.2 [SD = 8.5] vs. P1 = 62, M = 6.2 [SD = 4.7], $t$[14] = 4.57, $p$ < 0.001). Co-funded studies (studies that received funding from a combination of industry and nonindustry sources) did not increase significantly between the 2 periods (P2 = 41, M = 4.1 [SD = 1.9] vs. P1 = 29, M = 2.9 [SD = 3.1], $t$[15] = 1.06, $p$ = 0.31).

## Discussion

Our data provide evidence of marked, statistically significant increases in clinical research in rare renal disease indications in the last 10 years compared to the previous ten. The rise in observational studies may signal an increased focus on understanding the natural course of disease with standard of care and assist with planning of future interventional studies. For GDs, proteinuria, measured by 24-h urine protein excretion and/or UPCR, has become the gold standard following acceptance by the FDA as a surrogate endpoint for renal outcomes. Interestingly, studies using UPCR as the primary endpoint only appeared in P2; however, it is possible that composite endpoints may also include urinary protein or UPCR and could therefore fall under the broader definition of "response rate," "remission rate," or "disease progression," which collectively also increased significantly in P2. The increase in the number of studies evaluating AEs as the primary outcome may reflect an increase in the number of open-label extension or long-term follow-up studies designed to primarily assess safety. The increase in industry-funded studies suggests basic science, conducted in academia, is translating into industry-sponsored research. The absolute increase in studies investigating biologic interventions is consistent with the growing number of

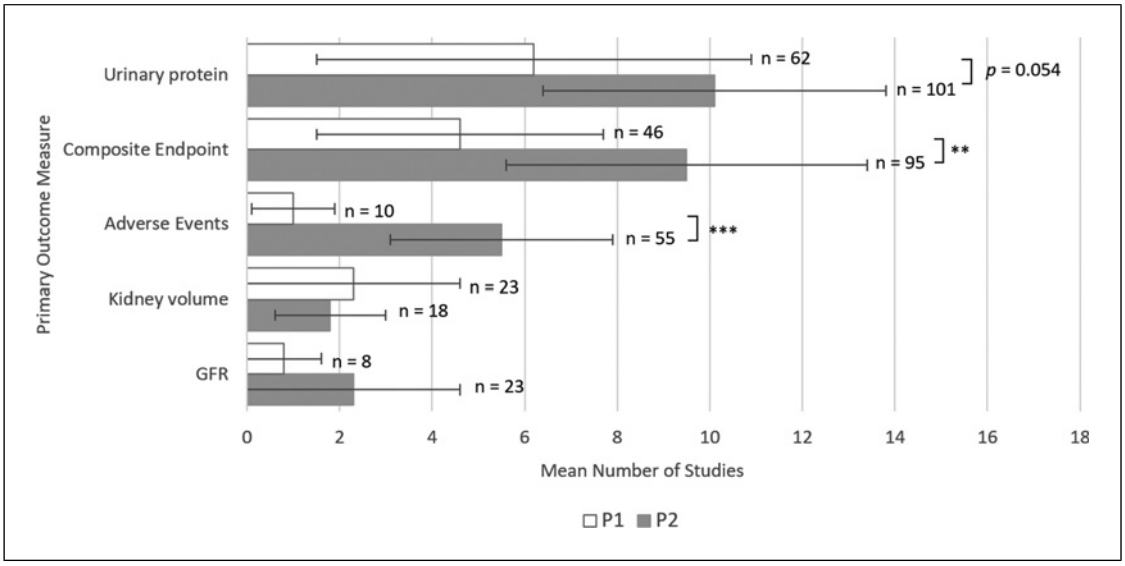


**Fig. 4.** A comparison of the distribution of clinical studies registered in CT.gov in the period 2003–2012 (P1) versus 2013–2022 (P2) according to the top five most frequently reported primary outcome measures. Values represent the mean; error bars represent the standard deviation. The number of studies is denoted above each bar. ** two-tailed *t* test with unequal variances *p* value <0.01; *** two-tailed *t* test with unequal variances *p* value <0.001. GFR, glomerular filtration rate.

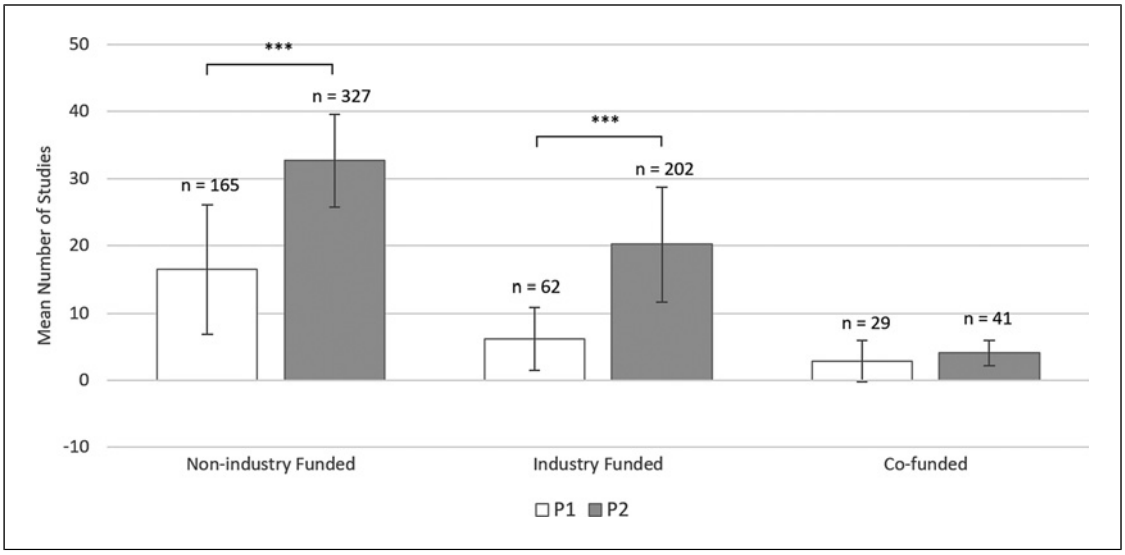


**Fig. 5.** A comparison of the distribution of clinical studies registered in CT.gov in the period 2003–2012 (P1) versus 2013–2022 (P2) according to funding source. Values represent the mean; error bars represent the standard deviation. The number of studies is denoted above each bar. *** two-tailed *t* test with unequal variances *p* value <0.001.

investments and development of this class of medications, which are forecasted to overcome sales of "standard technology" products in the next 5 years and are best designed to precisely target complex pathways in disease pathophysiology.

The significant increase in clinical studies of rare renal indications in the last 10 years that included pediatric populations, including pediatric-only studies, contrasts with trends in the broader CKD population, where increases have been small [3]. This finding supports our hypothesis

that a more targeted analysis of studies of rare renal disease, including those with a genetic component, would yield a different result. The approach to the treatment of CKD in children broadly follows the same approaches used in adults, i.e., renin-angiotensin-aldosterone system inhibitors (RAASi) with or without diuretics to slow progression and optimize blood pressure, and corticosteroids and immunosuppressive agents to treat nephrotic syndrome and systemic diseases that affect the kidneys (e.g., vasculitis). However, based on the differing etiologies of pediatric CKD compared to adults and less supporting data, these traditional approaches may be of limited use. The positive trend identified in our analysis is encouraging and reinforces hopes that with continued efforts to study the effects of novel treatments in children and better understand of the pathophysiology of rare renal disease will support earlier therapeutic interventions, delaying, or even potentially halting, disease progression in this vulnerable population.

Standard of care for all causes of CKD always includes optimal blood pressure control. Antihypertensives, specifically RAASi, have been a mainstay of therapy in CKD for over 20 years, particularly in those with proteinuria. However, in the past five to 7 years, there has been important progress in identifying additional therapeutic options for the treatment of CKD aside from RAASi. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) such as dapagliflozin and empagliflozin are being incorporated into practice guidelines for management of CKD with proteinuria. In those with diabetic kidney disease and persistent proteinuria, the nonsteroidal mineralocorticoid antagonist finerenone was approved by the FDA in 2022 as an add on therapy to further delay progression.

LN, ADPKD, IgAN, and now focal segmental glomerulosclerosis are rare renal indications with the highest number of clinical trials of novel medicinal products that will ideally demonstrate efficacy and safety to receive approval and become available on the market for patients' treatment. TFR-Budesonide, an oral targeted-release steroid, was approved in the USA in 2021 for the treatment of IgAN with high levels of proteinuria that are at risk for rapid progression. In Feb 2023, sparsentan, an oral dual endothelin angiotensin receptor antagonist, received accelerated approval as the first non-immunosuppressive therapy in the USA for this at risk population. Similar agents (e.g., atresentan) are being studied in IgAN and other indications. While these recent approvals are promising, gaps remain. For particular etiologies, there are obvious therapies (e.g., antivirals for HCV-related membranoproliferative glomerulonephritis). For others, due to the complex pathophysiology, it is less clear. However, due to research and improved understanding of the mechanisms of injury from immune dysregulation and inflammation, there has been increased interest in drug development, particularly for GDs. As a result, there are several new classes of drugs in early phase development. Promising phase 2 and 3 results could lead to a paradigm shift in the therapeutic approach to GD. Currently, there are 18 different drugs with diverse mechanism of actions under investigation for IgAN. Similarly for LN, there are 19 drugs in clinical development with diverse molecular targets and with a special focus on complement and complement cascade inhibition. The important role of complement in LN and the interest in clinical development is supported by 3 different pathways and 33 potential targets.

In the future, we anticipate the investigation of new combination drugs with a synergistic and perhaps more potent clinical effects, achieved by acting on more than one target and/or molecular pathways. Aside from therapeutics, we anticipate that this research will pave the way for the development and validation of new biomarkers that will improve diagnosis and prognosis of a wide variety of kidney disease.

## Statement of Ethics

An ethics statement is not applicable because this research is based exclusively on an analysis of metadata from a publicly available clinical trial register.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.


## Funding Sources

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## Author Contributions

D.G. and C.A. contributed to the conception and design of the work and interpretation of data, as well as the preparation of the manuscript. A.B. contributed to the analysis and interpretation of data, as well as the preparation of the manuscript.

## Data Availability Statement

All data generated or analyzed in this research are included in this article. Further inquiries can be directed to the corresponding author.

## References


1 Cockwell P, Fisher LA. The global burden of chronic kidney disease. Lancet. 2020;395(10225):662–4.
2 Wisniowska A, Singhania A. Nephrology sector of the immunology market: a major biopharma development opportunity. Bioprocess Online. 2020 nov. Available from: https://www.bioprocessonline.com/doc/nephrology-sector-of-the-immunology-market-a-major-biopharma-development-opportunity-0001 [Accessed 5 September 2023].
3 Bevan A, Garrisi D, Angeles C. Advancing treatments for CKD: trends and opportunities [Abstract]. J Am Soc Nephrol. 2022;33:49. Available from: https://www.asn-online.org/education/kidneyweek/archives/KW22Abstracts.pdf [Accessed 5 September 2023].
4 Harambat J, van Stralen KJ, Kim JJ, Tizard EJ. Epidemiology of chronic kidney disease in children. Pediatr Nephrol. 2012;27(3):363–73.
5 Gulati S. Chronic disease in children; 2020. Available from: https://emedicine.medscape.com/article/984358-overview#a6 [Accessed 27 November 2022].