Insights from ADPedKD, ERKReg and RaDaR registries provide a multi-national perspective on the presentation of childhood autosomal dominant polycystic kidney disease in high- and middle-income countries

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Data on the presentation of Autosomal Dominant Polycystic Kidney Disease (ADPKD) in children have been based on small/regional cohorts and practices regarding both asymptomatic screening in minors and genetic testing differ greatly between countries. To provide a global perspective, we analyzed over 2100 children and adolescents with ADPKD from 32 countries in six World Health Organization regions: 1060 children from the multinational ADPedKD registry were compared to 269 pediatric patients from the United Kingdom (RaDaR) and 825 from the European Rare Kidney Disease Registry (ERKReg). Asymptomatic family screening was a common mode of presentation (48% in ADPedKD, 62% in ERKReg) with broad international variability (19%-75%), but fairly stable temporal trends in both registries with no correlation to genetic testing. The national rates of genetic testing varied and correlated significantly with healthcare expenditure (odds ratio 1.030 per 100 United States Dollars/capita/year, in the ERKReg cohort), with little variation over time. Diagnosis due to prenatal abnormalities was more common than anticipated at 14% increasing steadily from 2000 onward in both registries. Realistically, a high proportion of children were diagnosed with ADPKD by active screening, underlining that families affected by ADPKD have a high need for counselling on the complex issues around presymptomatic diagnosis. Regional variations in rate of genetic testing appeared to be driven by economic factors. However, large differences in rate of active screening were not correlated to healthcare spending and probably reflect the influence of different of cultural, legal and ethical frameworks on families and clinicians in different healthcare systems.

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease and the fourth most common cause for kidney replacement therapy in adults worldwide. ADPKD represents

Lay Summary

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited disease, characterized by growth of cysts in the kidneys and usually does not progress to kidney failure until adulthood. Less is known about childhood ADPKD, and actively looking for the disease before symptoms (screening) is controversial. Ultrasound screening or genetic testing (where accessible) should only be performed in minors after careful consideration and discussion with the family about the benefits and harms of presymptomatic screening. We describe how >2100 children from 3 different registries (ADPKD registry [ADPedKD], European Rare Kidney Disease Registry [ERKReg], and National Registry of Rare Kidney Diseases [RaDaR]) were first diagnosed. Genetic testing was performed in 52% in ADPedKD and 41% in ERKReg, and differences between countries were related to health care spendings. Approximately half of the children were diagnosed by active screening, but the large international variations were not related to rate of genetic testing. Diagnoses before birth increased in both ADPedKD and ERKReg from 2000 onward, probably due to advances in prenatal diagnostics. In summary, countries with higher health care spendings were more likely to perform genetic testing, but the large regional differences in asymptomatic screening also appear to have other influences such as local health care systems, laws, cultural attitudes or beliefs of the clinicians, and families affected by ADPKD.

a major socioeconomic burden for patients, families, communities, and health care systems.[1–4] Although it is recognized that (mainly microscopic) cyst formation already starts *in utero*,[5] and hypertension is a common feature in young adults,[6] ADPKD often causes few symptoms until the third to fourth decade associated with a critical threshold for progression of kidney damage. There is a large phenotypic spectrum of childhood ADPKD that includes incidental sonographic findings of kidney cysts in many cases, but also severe neonatal presentations (resembling autosomal recessive PKD[7]) as well as mild symptomatic courses, with arterial hypertension and/or symptoms (such as macrohematuria, abdominal pain, or enuresis).[8–11] Such a broad clinical spectrum combined with inter- and intrafamiliar variability of disease progression is challenging for the collection of epidemiologic and demographic data.[12,13] Early nephroprotective strategies are a promising goal for preventing kidney damage,[14] so there is an increasing need to understand and characterize disease manifestations of early ADPKD to select those at risk of rapid progression.[15,16] Therefore, characterizing the initial mode of presentation of a large and diverse population is an important first step to map current practices and to understand the impact of different local policies.

Despite the fact that several recent initiatives have sought to standardize the management of children with ADPKD,[17–21] these recommendations need to be integrated into different health care systems in the context of local policies, legal frameworks, and financial constraints as well as diverse cultures, beliefs, and apprehensions of families and health care staff. We therefore hypothesized that there would still be large discrepancies regarding the management and diagnosis of children with ADPKD around the globe, for example, with respect to a proportion of children diagnosed by active screening or rates of genetic testing. Our aim was to analyze the baseline data of the largest pediatric ADPKD registry (ADPedKD) regarding age at diagnosis, mode of presentation, and clinical characteristics of children at presentation and evaluate differences between era of diagnosis, year of birth, and countries and their socioeconomic characteristics. To extend the geographical spectrum, these data were compared with data on the UK-based pediatric ADPKD patients collected in the National Registry of Rare Kidney Diseases (United Kingdom) (RaDaR) registry[22] and in the European Rare Kidney Disease Registry (ERKReg).[23]

METHODS

Study population and data collection

We analyzed the baseline characteristics of patients included in the multinational ADPedKD registry (https://www.adpedkd.org)[24] until June 2021. The ADPedKD registry collects data on children up to the age of 19 years diagnosed with ADPKD in Europe, Africa, and Asia in a common database. Details about the structure, data collection, and management of ADPedKD have been previously described.[24] Diagnosis of ADPKD was based on family history and imaging findings and/or molecular genetic testing. After informed consent, deidentified data were stored in secure online databases. Later the United Kingdom, North and South America, and Australia joined the initiative with their own respective regional databases, namely RaDaR,[25] National Institutes of Health (NIH)–funded Hepato-Renal Fibrocystic Disease (HRFD) Core Resource,[26] and KidGen Collaborative (KidGen).[27] For the present analysis, the NIH-HRFD and KidGen datasets were merged with the original ADPedKD registry, while patients from the RaDaR database are used as a pediatric control group, mainly because patient level data on genetic testing and mode of diagnosis were not available for RaDaR. There were no duplicate patients. The second control group was extracted from ERKReg, the investigator-led registry of the European Reference Network for rare kidney diseases (ERKNet) funded by the European Union to which both adult and pediatric nephrology centers contribute.[23] Eligible patients had a clinical and/or genetic diagnosis of ADPKD before the age of 19 years and were not also included in the ADPedKD registry. Data were extracted in October 2023.

Four modes of presentation were defined: (i) at-risk children from families with known ADPKD identified by active screening (family screening), (ii) incidental finding of kidney cysts on abdominal ultrasound in a child (postnatal incidental finding), (iii) prenatal diagnosis of ADPKD by ultrasound

screening in pregnancy (prenatal diagnosis), and (iv) children who presented with signs and/or symptoms related to ADPKD such as gross hematuria, pain, hypertension, or proteinuria (clinical signs/symptoms). In ADPedKD, the mode of presentation was classified by the local investigator, even though clinical symptoms were not always unequivocally attributable to ADPKD and some patients with later symptomatic or incidental diagnoses had records of prenatal abnormalities. In ERKReg, mode of presentation was defined according to the answers regarding previous clinical symptoms, known family history, method by which diagnosis was made, and prenatal ultrasound findings. For patients with a prenatal diagnosis, the age at diagnosis was expressed as a negative value corresponding to the time before birth at which anomalies were first noted.

For the analysis of local geographical effects, countries were grouped according to World Health Organization (WHO) regions[28] and Europe was further subdivided according to the United Nations geoscheme.[29] Country-specific health care expenditures, expressed both as US dollar (USD) per capita or as a percentage of gross domestic product, were taken from the data repository from the WHO for 2015.[30,31]

Statistical analysis

A validation plan with automated quality checks for coherence of the submitted data was performed in both cohorts. Direct contact between responsible statisticians ensured consistent and comparable data analyses across cohorts. Descriptive statistics are given as relative and absolute frequencies of all nonmissing cases for binary/categorical variables and of mean (SD) and median (interquartile range) for the continuous variables. Unknown data were treated as missing.

To obtain country- and region-specific estimates for the probability that a genetic test was performed and for the probabilities of each mode of presentation, generalized linear mixed models (i.e., binary logistic regression models with a random country/region effect) were used. From these models, empirical Bayes estimates and 95% confidence intervals for each country/region were derived.[32] Note that the smaller the number of subjects in a region/country, the more the country-specific Bayes estimate will shift toward the overall mean of all regions/all countries.

To assess the determinants of age at diagnosis, univariable linear mixed models were used for era of diagnosis, genetic test performed, mode of presentation, positive family history, and genotype, adding a random effect of country to handle the correlation between patients of the same country. A linear mixed model with country as the only random effect was used to evaluate differences between countries. Consequently, several factors were combined without model reduction into a multivariable linear mixed model based on *a priori* variable selection. χ^2 tests were used to explore univariable relations with genetic test performed and modes of presentation. All analyses were performed using SAS software version 9.4 of the SAS System for Windows by senior statisticians (SF and JH) of the respective registries.

Ethical statement

The study was approved by the ethics committee of University Hospitals Leuven (S59638) as the leading center of ADPedKD and confirmed by the local institutional review boards of all participating centers or through the protocols for the participating regional databases. The ERKReg, RaDaR, NIH, and KidGen registries and their informed consent forms were approved by the local institutional review boards as required by local and national regulations. The study was conducted according to the 2013 Declaration of Helsinki, the guidelines of Good Clinical Practice, and all applicable regulatory requirements, including the European Union General Data Protection Regulation.

RESULTS

We analyzed 2154 children and adolescents with ADPKD from 32 countries on 4 continents. From the ADPedKD registry, data of 1060 children with ADPKD from 25 countries and 63 centers were analyzed, including 17 (1.6%) from KidGen and 16 (1.5%) from HRFD. Of these, 547 (52%) were female. The RaDaR cohort comprised 269 patients (57% female) and the ERKReg cohort 825 patients (51% female), of whom 390 (47%) came from adult centers. Patients originated from 5 of the 6 WHO world regions, with 24 countries being rated as "high income" and 8 as "middle income" with a range of yearly health care expenditure from 58 to 9383 USD per capita. The number of patients per region and mean weighted health care expenditure of each region are given in Table 1. The number of patients per country is given in Supplementary Table S1.

The data regarding demographics, mode of presentation, and genetic findings for each registry are presented in Table 2. ADPKD was genetically confirmed in children themselves in 50% of the ADPedKD cohort (525 of 1060, see Table 2). The rate of genetic confirmation in the child was lower in the RaDaR and ERKReg cohorts (30% and 33%), mainly due to a higher percentage of children with missing data on genetic results (31% and 18% vs. 4% in ADPedKD) but also because of a lower rate of genetic testing (43% and 41% vs. 52%, respectively). The ratio of *PKD1* to *PKD2* causative variants was similar to published adult cohorts with 10.6 to 1.0 in the ADPedKD group and similar in the RaDaR (12.5 to 1.0) and ERKReg cohorts (9.0 to 1.0). There was a known positive family history for ADPKD in 79% of ADPedKD children (825 of 1044), 72% of ERKReg children (595 of 825), and 97% of RaDaR children (231 of 238).

Mode and age of presentation

In the group of 950 children with data available on mode of presentation from the ADPedKD cohort, nearly half were diagnosed by family screening (455 of 950, 48%), while the second most common mode was postnatal incidental finding (293 of 950, 31%), followed by prenatal diagnosis in 129 of 950 (14%) and clinical signs or symptoms in 73 of 950 (8%, see Table 3). There was no significant difference in mode of presentation between boys and girls. Approximately half (n =

Table 1 | Number of countries, patients, and health care expenditure by world region

World region	Total number of countries (high/middle income)	Total number of patients	Range of national health care expenditures[a]	Mean weighted health care expenditure[b]
SEAR	1 (0/1)	5	58	58
EUR-East	7 (4/3)	262	157–1284	834
EMR	3 (1/2)	13	174–1439	916
EUR-South	7 (5/2)	678	447–2676	2115
EUR-North	5 (5/0)	401	776–4561	4112
EUR-West	6 (6/0)	759	4199–9383	4476
WPR	2 (2/0)	20	2279–5324	4868
AMR	1 (1/0)	16	9244	9244

WHO regions (and countries represented in the present cohorts): AMR, Region of the Americas (USA); EMR, Eastern Mediterranean Region (Egypt, Iran, UAE); EUR, European Region (Europe-East: Belarus, Czech Republic, Hungary, Poland, Romania, Russia, Ukraine; Europe-South: Greece, Italy, Portugal, Serbia, Slovenia, Spain, Turkey; Europe-North: Estonia, Ireland, Latvia, Lithuania, UK; Europe-West: Austria, Belgium, France, Germany, Netherlands, Switzerland); SEAR, South East Asian Region (India); WPR, Western Pacific Region (Australia, Singapore).
[a]Health care expenditure in US dollar per capita in 2015.[31]
[b]Weighted for number of patients from each country.

429 of 764, 56.2%) of patients with a positive family history were diagnosed via family screening, whereas 12% (92 of 764) were diagnosed prenatally, 7% (52 of 764) with clinical symptoms, and 25% (191 of 764) with postnatal incidental findings. The rate of genetic testing in the family screening group (238 of 455, 52%) was similar to the symptomatic diagnosis group (41 of 73, 56%) and the incidental finding group (142 of 293, 48%; $P = 0.057$).

By comparison, in ERKReg of the 595 patients with a positive family history, 370 (86%) were diagnosed by family screening, 3 (0.7%) prenatally, and 58 (13.5%) with clinical symptoms. Overall, family screening was more common in ERKReg than in ADPedKD (62% vs. 48%) and prenatal diagnosis less common (see Table 2). However, the combined group of family screening and prenatal presentation was similar in both (64% vs. 62%), and not all patients with prenatal abnormalities were assigned to prenatal diagnosis by the ERKReg investigators. The combined group of incidental finding and diagnosis due to symptoms (which can be hard to distinguish in clinical practice) were also similar in ERKReg

Table 2 | Demographical characteristics of the ADPedKD, RaDaR, and ERKReg cohorts

Characteristic	ADPedKD	RaDaR	ERKReg
Pediatric ADPKD population size	N = 1060	N = 269	N = 825
Genetic test performed			
Yes	547 (52)	117 (43)	335 (41)
No	454 (43)	Not recorded	Not recorded
Unknown	59 (6)	152 (57)	490 (59)
Genetic results (information available)	N = 547	N = 117[a]	N = 335[a]
No information or NMD in ADPKD genes	22 (4)	36 (31)	61 (18)
PKD1 causative variant	470 (86)	73 (62)	245 (73)
PKD2 causative variant	45 (8)	6 (5)	27 (8)
PKD1+*TSC2* causative variant	6 (1)	2 (2)	0 (0)
Other causative variant	4 (1)	0 (0.0)	2 (1)
Ratio of *PKD1* to *PKD2* variants	10.6:1	12.5:1	9:1
Diagnosis (information available)	N = 950	N = 139	N = 596
Prenatal	129 (14)	15 (11)	13 (2)
Family screening	455 (48)	Unknown	370 (62)
Incidental finding	293 (31)	Unknown	126 (21)
With symptoms	73 (8)	Unknown	87 (15)
Age at diagnosis (information available)	N = 945	N = 269	N = 825
Mean age in years (SD)	5.7 (5.2)	10.5 (6.7)	9.3 (6.2)
Median age in years (IQR)	4.9 (0.5–9.8)	12.2 (4.4–16.5)	9.8 (3.5–15.0)
Min; Max	–0.7; 18.5	–0.7; 19.0	–0.3; 19.0

ADPedKD, ADPKD registry; ADPKD, autosomal dominant polycystic kidney disease; ERKReg, European Rare Kidney Disease Registry; IQR, interquartile range; Max, maximum; Min, minimum; N, number of observations with data; NMD, no causative variant detected; RaDaR, National Registry of Rare Kidney Diseases.
[a]In the RaDaR and ERKReg cohorts, no distinction was available between no genetic test performed and unknown. Hence, all patients without genetic results were considered as no genetic test performed.
Data are n (%) unless otherwise noted.

Table 3 | Age at diagnosis (in years) in the ADPedKD and ERKReg cohorts as a function of mode of diagnosis

	ADPedKD			ERKReg		
	N	Mean	SD	N	Mean	SD
Total	945	5.7	5.2	825	9.3	6.2
Prenatal	129	−0.1	0.1	13	0.1	0.2
Family screening	455	6.1	4.8	370	10.4	6.1
Incidental finding	293	7.2	5.2	126	11.0	4.0
Clinical symptoms	73	7.0	5.6	87	8.8	5.9

ADPedKD, ADPKD registry; ERKReg, European Rare Kidney Disease Registry; N, Number of observations.

and ADPedKD at 36% and 39%, respectively. For the RaDaR cohort, no details on mode of presentation were available.

The mean age at diagnosis in the ADPedKD cohort was 5.7 years (±5.2 years, median: 4.9, interquartile range: 0.5–9.8, including prenatal diagnoses). Children identified by family screening had a lower age at diagnosis than those with symptomatic and incidental diagnosis (6.1 ± 4.8 vs. 7.0 ± 5.6 and 7.2 ± 5.2 years, $P = 0.01$, see Table 3). A linear mixed model with country added as a random effect restricted to the cases with postnatal diagnosis also revealed a significantly higher age at diagnosis in children diagnosed by postnatal incidental findings compared with family screening ($P < 0.01$). Children diagnosed by family screening were thus usually below the age of consent, that is, at diagnosis, only 3 of 407 (0.7%) were aged above 16 years, 24 of 407 (5.9%) above 14 years, and 46 of 407 (11.3%) above 12 years. A multivariable linear mixed model in the ADPedKD group showed no significant relation of positive family history, performance of a genetic test, or health care spendings with age at diagnosis (see Supplementary Table S2).

Mean age at diagnosis was higher in both RaDaR and ERKReg cohorts at 10.5 and 9.3 years, respectively (see Table 2). This was not exclusively due to the lower proportion of prenatal diagnoses in ERKReg, because the mean age in the other mode of presentation subgroups was also higher in ERKReg than in ADPedKD (see Table 3). In ERKReg, 567 (69%) of patients were diagnosed before the age of 14 years, whereas 162 of 825 (20%) were over 16 years and 86 of 825 (8%) over 18 years old at diagnosis.

Among the 129 patients with prenatal diagnosis in ADPedKD, the most common anomalies were hyperechogenic kidneys (52 of 81, 64%), kidney cysts (55 of 98, 56%), and enlarged kidneys (43 of 85, 51%), but abnormal quantity of amniotic fluid was uncommon (13 of 81, 16%). Of the 73 children who were diagnosed with signs or symptoms of ADPKD, the primary reason was usually urological: 16 (22%) with urinary tract infection, 16 (22%) with flank/back pain, 12 (16%) with hematuria, 5 (7%) with enuresis/dysfunctional voiding, 2 (2.7%) with urolithiasis, and 1 (1.4%) with cyst complications. Kidney-related morbidities were less commonly the primary reason for presentation: 10 (14%) with hypertension and 2 (2.7%) with proteinuria. However, among the 376 children for whom the local investigator considered the diagnosis to have been an incidental finding, similar complaints (except cyst complications) were also common (see Supplementary Table S3).

Temporal changes

Prenatal diagnoses were very uncommon in children born before 2000 and increased until at least 2015 (Figure 1a and b). The proportion of diagnoses by family screening decreased slightly over time to be replaced mainly by prenatal diagnoses. Thus, year of birth was the most significant predictor of age at diagnosis in the multivariate model (see Supplementary Table S2). There was no association between year of diagnosis and the likelihood of genetic testing ($P = 0.56$). In comparison, in ERKReg, more patients were born before 2000, but the temporal trends were similar with less family screening over time and a significant increase of prenatal diagnoses after 2010 (Figure 1c and d). Thus, for both registries, most patients diagnosed prenatally were born after 2005 and are therefore currently still younger than 18 years.

Geographical variations

The most pronounced regional differences were between the rates of genetic testing as shown in Figure 2 (by world region) and Supplementary Figure S1 (by country). Within ADPedKD, there was a significant overall variability ($P < 0.0001$ for the likelihood-ratio test comparing the deviance of 2 nested models). Of the 12 countries represented both in ERKReg and ADPedKD, the empirical Bayes estimates overlapped in all but 2 (Belgium and Italy), with higher rates in ADPedKD than ERKReg in both.

Both in the ADPedKD and ERKReg cohorts, lower rates of genetic testing were observed in regions with lower health expenditure (in USD per capita, e.g., highest in Western Europe, followed by Southern Europe and Eastern Europe; see Figure 2 and compare mean health care expenditure in Table 1). This was also true on a country level (see Figure 3a and b). When correlation was tested with a generalized linear mixed model, this showed a significant association within the ERKReg cohort (odds ratio per 100 USD/capita = 1.030 [95% confidence interval: 1.011–1.049], $P = 0.002$) and a very similar but nonsignificant association in the ADPedKD cohort (odds ratio per 100 USD/capita and year = 1.028 [95% confidence interval: 0.996–1.060], $P = 0.09$). As is visible in Figure 3a, this can be attributed first to the inclusion of Switzerland and the United States, which both have extremely high health expenditure but low levels of genetic testing (in the United States it is not covered by health insurance, and in Switzerland costs of genetic testing are only covered after individual application). As shown in Supplementary Figure S2, the exclusion of the United States and Switzerland resulted in a significant association of genetic testing with gross domestic product in the mixed linear model (odds ratio per 100 USD/capita and year = 1.081 [95% confidence interval: 1.028–1.137], $P = 0.0024$).

There was little regional variation in the proportion of prenatal diagnoses (see Figure 4), but the postnatal modes of

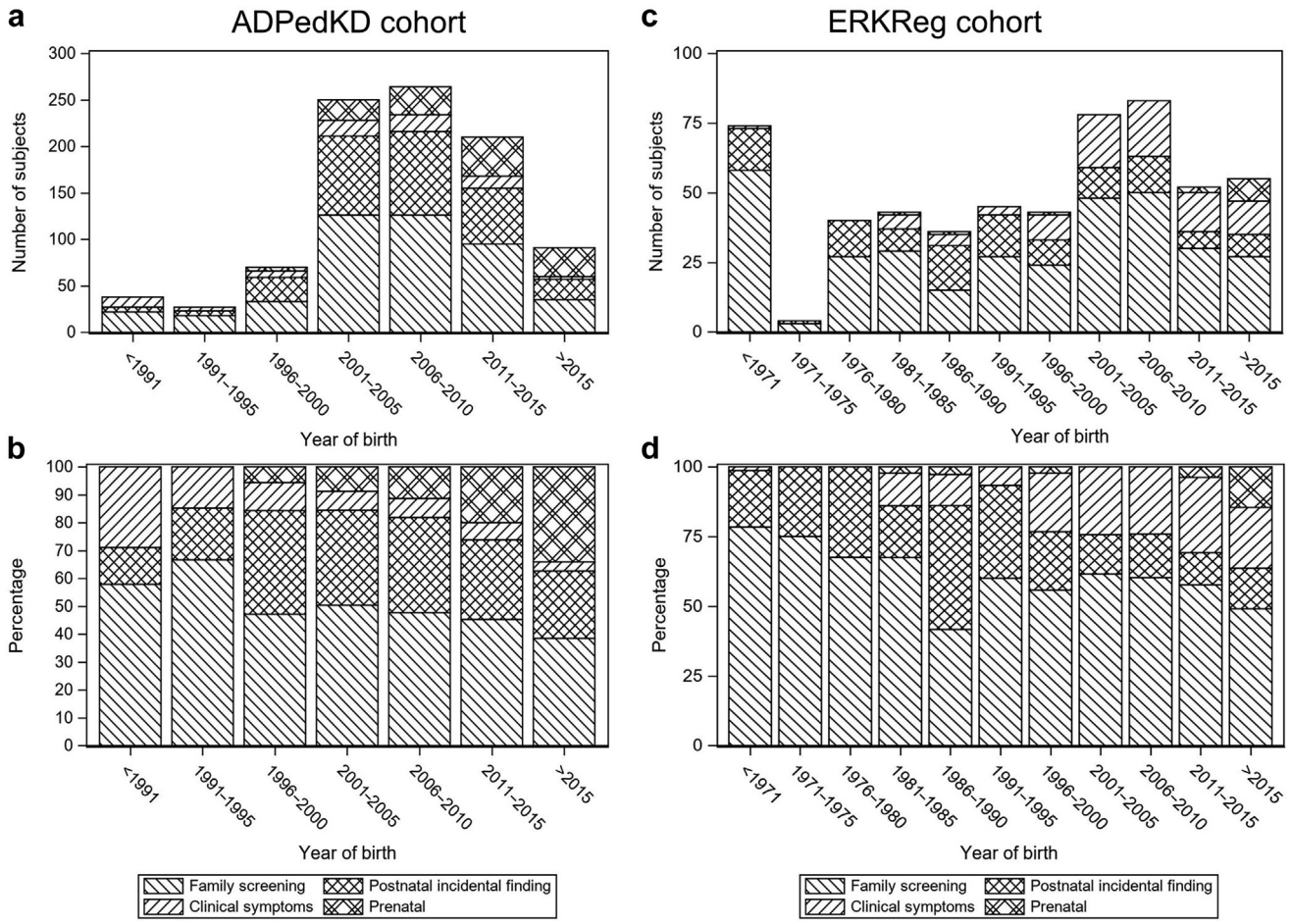

Figure 1 | Distribution of mode of presentation of autosomal dominant polycystic kidney disease (ADPKD) per year of birth for (a,b) the ADPKD registry (ADPedKD) cohort (n = 945) and (c,d) the European Rare Kidney Disease Registry (ERKReg) cohort (n = 825).

presentation differed significantly between countries, most so for the percentage of diagnoses by family screening (see Figure 5). However, family screening was less variable when countries were grouped by world region (see Supplementary Figure S3). Both within the ADPedKD and within the ERKReg cohort, the country of origin had a significant effect in the general mixed linear model for the mode of presentation (both $P < 0.0001$). Regional variations in proportion of children diagnosed by incidental finding with symptoms are shown in Supplementary Figure S4.

The empirical Bayes estimates for mean age at diagnosis per world region are shown in Figure 6. There was some heterogeneity, but no clear geographical pattern. Although there was a significant correlation in the uni- and multivariable models between age at diagnosis and country of residence ($P < 0.001$ and $P = 0.0001$), this explained only 1.03% and 1.49% of the overall variability in the uni- and multivariable model, respectively (Supplementary Table S2).

DISCUSSION

We report on the initial diagnosis of a total of over 2100 children and young persons with ADPKD who come from 32 countries on 4 continents, covering 24 high-income and 8 middle-income countries with the aim of assessing regional and temporal influences on current modes of diagnosis.

The first finding was that a high proportion of children were diagnosed by family screening (48% in ADPedKD and 62% in ERKReg), with a slight tendency to decrease over time to the benefit of prenatal diagnosis in both registries. Although there are multiple ethical, psychological, and legal challenges around actively screening for a noncurable disease in children with a lively debate since the 1990s,[33–36] and the medical benefit is unclear,[37] it appears that in real-life asymptomatic screening has nevertheless been performed for some years, and approximately half of the cases of pediatric ADPKD are diagnosed in this way. We postulate that it is a consequence of both the considerable stress some parents experience of not knowing about a child's transmission status[38] and their desire to be proactive in contributing to the best outcome for their children. With the emerging data on the relevance of hypertension and/or proteinuria for the progression of kidney disease in ADPKD, a novel potential for early intervention is becoming more widely perceived. Indeed, ADPKD can no longer be regarded as untreatable, despite still being incurable. As emphasized by international consensus statements[18,19] and the Kidney Disease: Improving Global Outcomes (KDIGO)

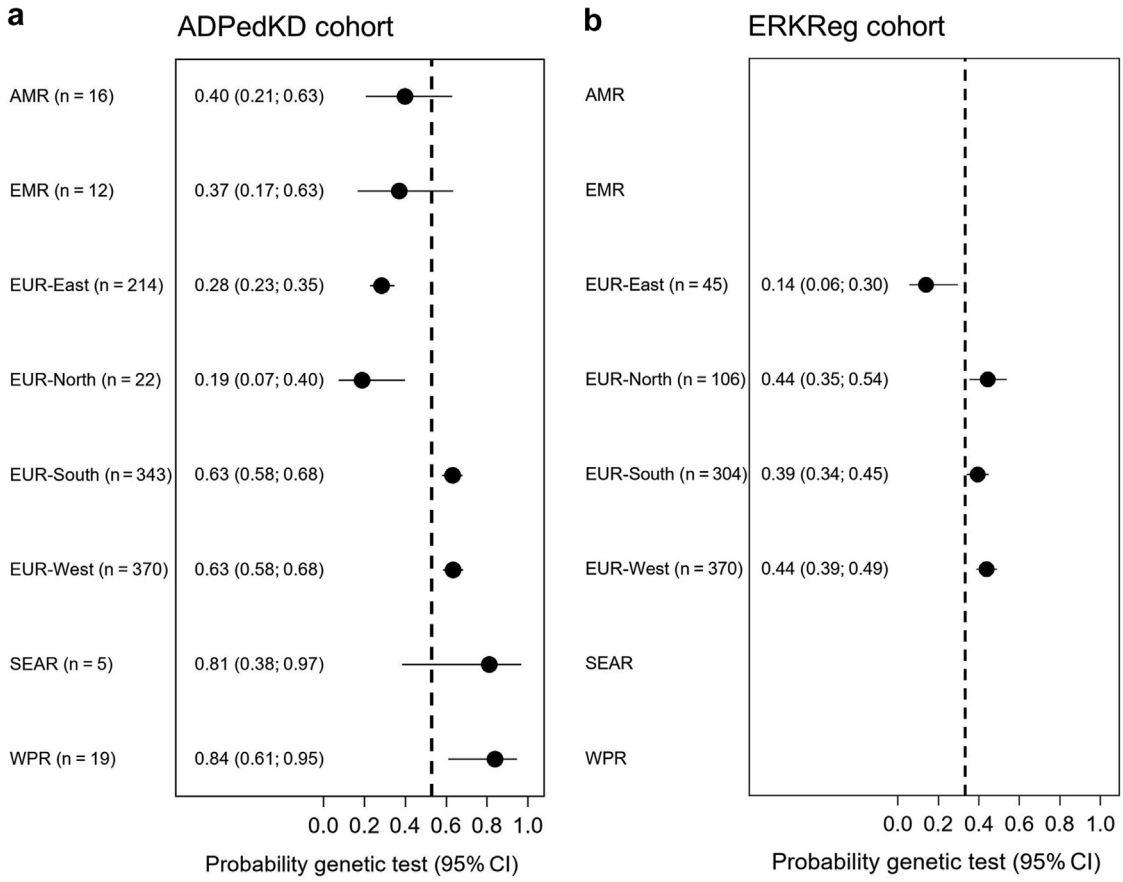

Figure 2| Bayes estimates for percentage of children receiving genetic testing by world region. (**a**) ADPKD registry (ADPedKD) cohort and (**b**) European Rare Kidney Disease Registry (ERKReg) cohort. The dashed line represents the mean over all regions. The dots and numbers indicate empirical Bayes estimates for the probability of genetic testing in that region, with horizontal lines and numbers in parentheses indicating the 95% confidence interval (CI). ADPedKD: AMR: Region of the Americas (1 country: USA, n = 16); EMR: Eastern Mediterranean Region (3 countries: Egypt, n = 1; Iran, n = 4; United Arab Emirates, n = 7); EUR-East: European Region—East (6 countries: Belarus, n = 11; Czech Republic, n = 68; Poland, n = 96; Romania, n = 13; Russia, n = 22; Ukraine, n = 4); EUR-North: European Region—North (1 country: Lithuania, n = 22); EUR-South: European Region—South (6 countries: Greece, n = 5; Italy, n = 172; Portugal, n = 10; Serbia, n = 40; Spain, n = 25; Turkey, n = 91); EUR-West: European Region—West (5 countries: Belgium, n = 155; France, n = 181; Germany, n = 18; Netherlands, n = 2; Switzerland, n = 14); SEAR: South East Asian Region (1 country: India, n = 5); WPR: Western Pacific Region (2 countries: Australia, n = 17; Singapore, n = 2). ERKReg: EUR-East: European Region—East (4 countries: Hungary, n = 1; Poland, n = 26; Romania, n = 14; Russia, n = 4); EUR-North: European Region—North (4 countries: Estonia, n = 1; Ireland, n = 91; Latvia, n = 3; Lithuania, n = 11); EUR-South: European Region—South (5 countries: Greece, n = 1; Italy, n = 225; Portugal, n = 4; Slovenia, n = 38; Spain n = 36); EUR-West: European Region—West (5 countries: Austria, n = 13; Belgium, n = 68; France, n = 159; Germany, n = 86; Netherlands, n = 44).

2025 Clinical Practice Guideline for the Evaluation, Management, and Treatment of ADPKD[39] (especially chapter 7), it is important to discuss the pros and cons of presymptomatic screening of at-risk children and the potential implications of a positive diagnosis, which are detailed in depth in the KDIGO guidelines (summarized in Table 3 of the guideline by Devuyst and Torres[39]) with both parents and children in an age-appropriate manner. Although health care professionals should counsel families about the potential adverse effects of establishing a diagnosis such as psychological burden and difficulties with private insurance or employment, they should also respectfully acknowledge families' wishes for diagnostic clarity, which may affect further medical management and family planning, and provide opportunity and motivation for early lifestyle interventions. We emphasize the importance of informed and shared decision-making by weighing the benefits and burdens of establishing a diagnosis while considering the child and family's values and situation. Screening for hypertension and proteinuria alone, without actively performing abdominal ultrasound, is a viable option, but performing presymptomatic genetic testing or ultrasound should also be discussed.[17]

There was wide variation between countries in the proportion of screening diagnoses, which was not so evident when they were combined into regions of similar health care expenditure. We consider this to reflect the impact of local health care practices and ethical frameworks on physicians' and families' attitudes toward active screening in children of affected parents, which was also evident in a detailed patient focus group study from 3 different countries.[38] There was no correlation of screening diagnoses to rates of genetic testing, probably because abdominal ultrasound is an alternative (if

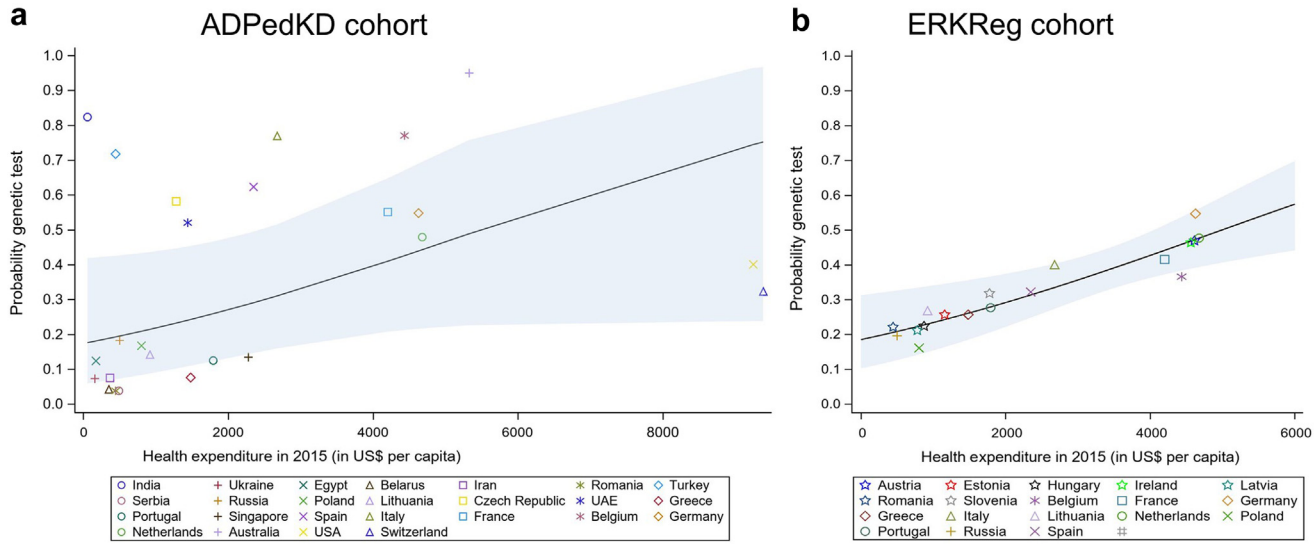

Figure 3 | Likelihood of genetic testing being performed in children with autosomal dominant polycystic kidney disease (ADPKD), as predicted by a generalized linear mixed model (binary logistic regression) with country added as a random effect in the (a) ADPKD registry (ADPedKD) cohort and (b) European Rare Kidney Disease Registry (ERKReg) cohort. Current health expenditure is expressed as US dollar per capita per year (as of 2015). Shaded area: 95% confidence interval. For number of patients per country in both cohorts, see Supplementary Table S1.

less reliable) method of diagnosis in childhood. Therefore, ethical and local health care frameworks are probably more important than economical constraints on genetic testing on determining rate of screening diagnoses.

The finding that 10%–20% of cases were diagnosed prenatally may seem surprising for a disorder commonly considered as an "adult" disease, but this was remarkably similar between countries. Prenatal diagnoses became increasingly common since 2000 in both the ADPedKD and ERKReg cohorts, reflecting both the rapid development of prenatal ultrasound since the 1990s[40] and reports that fetuses with ADPKD primarily present with hyperechogenic and enlarged kidneys rather than classical cysts.[41–43] A significant proportion of children in ERKReg had prenatal abnormalities recorded, yet were not considered to have a prenatal diagnosis by the local investigator. This may explain the slightly later rise of prenatal diagnoses in ERKReg. The high rate of prenatal diagnoses demonstrates that there is a high need of counseling of (prospective) parents affected by ADPKD, which is also stressed in the new KDIGO guidelines on ADPKD.[39] From our data, we are not able to differentiate deliberate prenatal screening diagnoses from "accidental findings" nor to estimate the number of terminations of pregnancies because of ADPKD. As high-resolution ultrasound is now part of routine pregnancy care in most of the countries represented here, families who consciously chose not to seek the child's (or fetus') transmission status should be counseled to disclose this to the prenatal sonographer before examination; in the same way they should advise the sonographer at other postnatal abdominal ultrasound examinations (e.g., for abdominal trauma). In future analyses of the registry, we hope to characterize patients with prenatal abnormalities more fully in order to differentiate features that are risk factors for very early onset or rapidly progressive disease and those that are merely markers of disease transmission. As most patients with prenatal diagnoses were born after 2005, they are currently still younger than 18 years and will be seen mainly in pediatric centers, which may explain the differing experiences of pediatric versus adult nephrologists when managing patients with "typical" ADPKD. However, this group of patients with prenatal diagnoses can be expected to reach clinics for adult nephrology within the next years.

The proportion of children who received genetic testing showed wide regional variation. This seems to be at least partially due to the cost of genetic testing as it was less common in countries with lower absolute health care expenditure (Figure 3). That genetic testing was not uniformly high in countries with high health care expenditure may reflect that it is not uniformly covered by insurance companies (e.g., in the United States), varying cultural and religious beliefs and wide international discrepancy in legislation around genetic and genomic testing. For example, in some countries, individuals do not have to disclose predictive genetic test results to private insurance companies, whereas in others, the law prohibits molecular testing of minors affected with monogenic disease unless there is a benefit for themselves or related individuals in their family. Thus, the local health care systems may affect the decisions on screening taken by the families and clinicians in multiple ways. Interestingly, there was no increase in the proportion of children receiving genetic testing over time despite the rapid advances in routine genetic testing in the last 2 decades, which may be due to the fact that *PKD1* and *PKD2* remain more challenging to sequence than other genes, that genotyping is still not common practice in adult nephrology (as the diagnosis is mainly based on ultrasound findings and family history[12]), and that accessibility is still limited in some

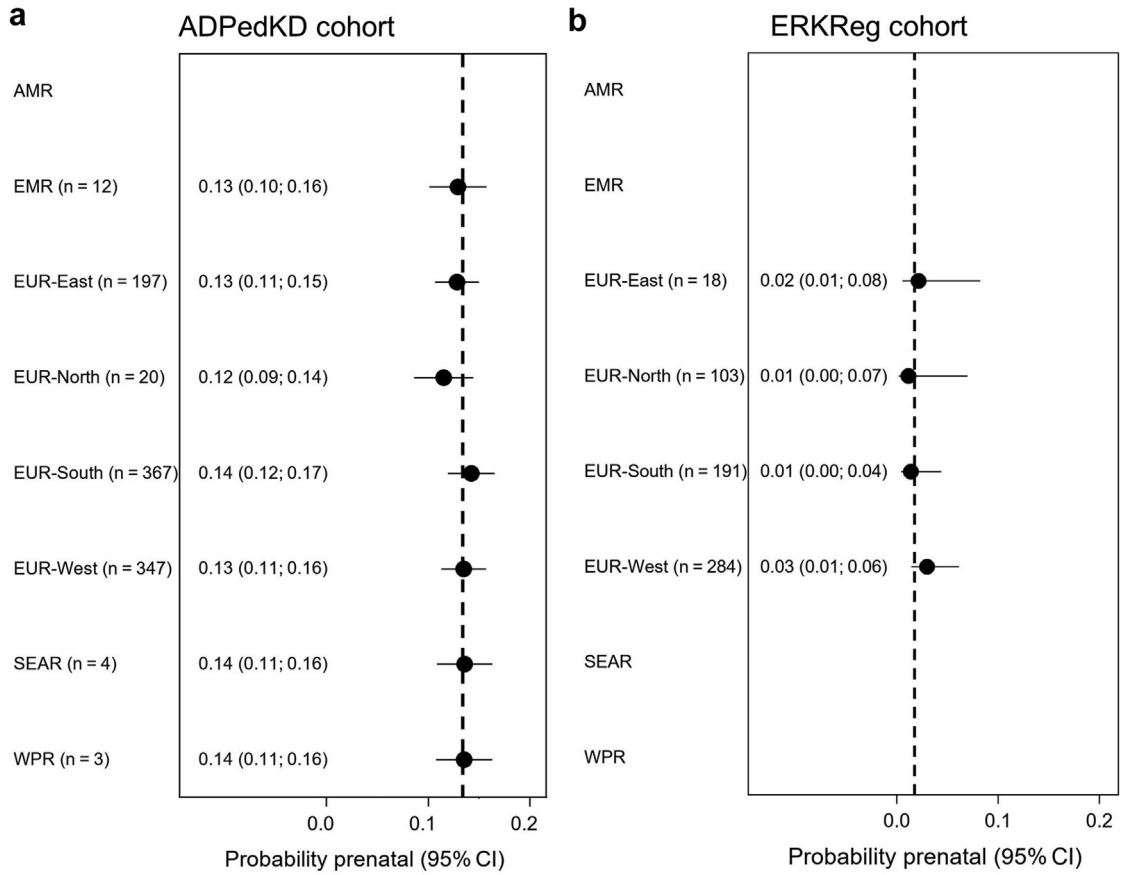

Figure 4 | Bayes estimates for the relative likelihood of a prenatal diagnosis of autosomal dominant polycystic kidney disease (ADPKD) by world region in the (a) ADPKD registry (ADPedKD) cohort and (b) European Rare Kidney Disease Registry (ERKReg) cohort. The dashed line represents the mean over all regions. The dots and numbers indicate empirical Bayes country-specific estimates for the probability of genetic testing, with horizontal lines and numbers in parentheses indicating the 95% confidence interval (CI). ADPedKD: EMR: Eastern Mediterranean Region (3 countries: Egypt, n = 1; Iran, n = 4; United Arab Emirates, n = 7); EUR-East: European Region—East (6 countries: Belarus, n = 11; Czech Republic, n = 68; Poland, n = 89; Romania, n = 13; Russia, n = 12; Ukraine, n = 4); EUR-North: European Region—North (1 country: Lithuania, n = 20); EUR-South: European Region—South (6 countries: Greece, n = 5; Italy, n = 195; Portugal, n = 11; Serbia, n = 39; Spain, n = 25; Turkey, n = 92); EUR-West: European Region—West (5 countries: Belgium, n = 154; France, n = 159; Germany, n = 16; Netherlands, n = 2; Switzerland, n = 16); SEAR: South East Asian Region (1 country: India, n = 4); WPR: Western Pacific Region (1 country: Singapore, n = 3). ERKReg: EUR-East: European Region—East (3 countries: Hungary, n = 1; Poland, n = 7; Romania, n = 10); EUR-North: European Region—North (4 countries: Estonia, n = 1; Ireland, n = 90; Latvia, n = 2; Lithuania n = 10); EUR-South: European Region—South (4 countries: Italy, n = 141; Portugal, n = 1; Slovenia, n = 22; Spain, n = 27); EUR-West: European Region—West (5 countries: Austria, n = 5; Belgium, n = 59; France, n = 129; Germany, n = 53; Netherlands, n = 38).

countries. Knowledge about local rates of genetic testing may help national patient advocacy groups, medical organizations, and/or planners in the health care to move toward improving patient care.

Children who were diagnosed with ADPKD due to signs or symptoms presented with similar problems to those in previous smaller case series, which mainly reported symptoms during the course of the disease rather than exclusively at the time of presentation.[37,41,44–47] The increase in postnatal incidental diagnoses from 2001 to 2021 may reflect improvements in quality and availability of pediatric ultrasound, which, as some authors have suggested, may increase the rate of incidental findings in the kidneys.[48] However, we would be hesitant to infer this, especially in children investigated for abdominal pain, as it can be very hard to distinguish a symptomatic diagnosis of ADPKD from an incidental finding and even a classical sign of ADPKD such as hypertension may have an alternate underlying cause. We respected the treating physician's classification of mode of presentation as either postnatal incidental finding or diagnosis with symptoms, but postulate that there is considerable overlap between both groups.

Limitations of this study are related to the inherent nature of registry data, being retrospective and with unknown bias, as they are neither randomly sampled nor cover the entire population. Therefore, it is impossible to separate whether the rise in absolute patient numbers over time was due to the success of the registry or a real increase in children diagnosed with ADPKD due to increasing awareness of treatable disease manifestations during childhood. Also, we do not have data on terminations of pregnancy or preimplantation genetic diagnosis of ADPKD and the effect on the number of people

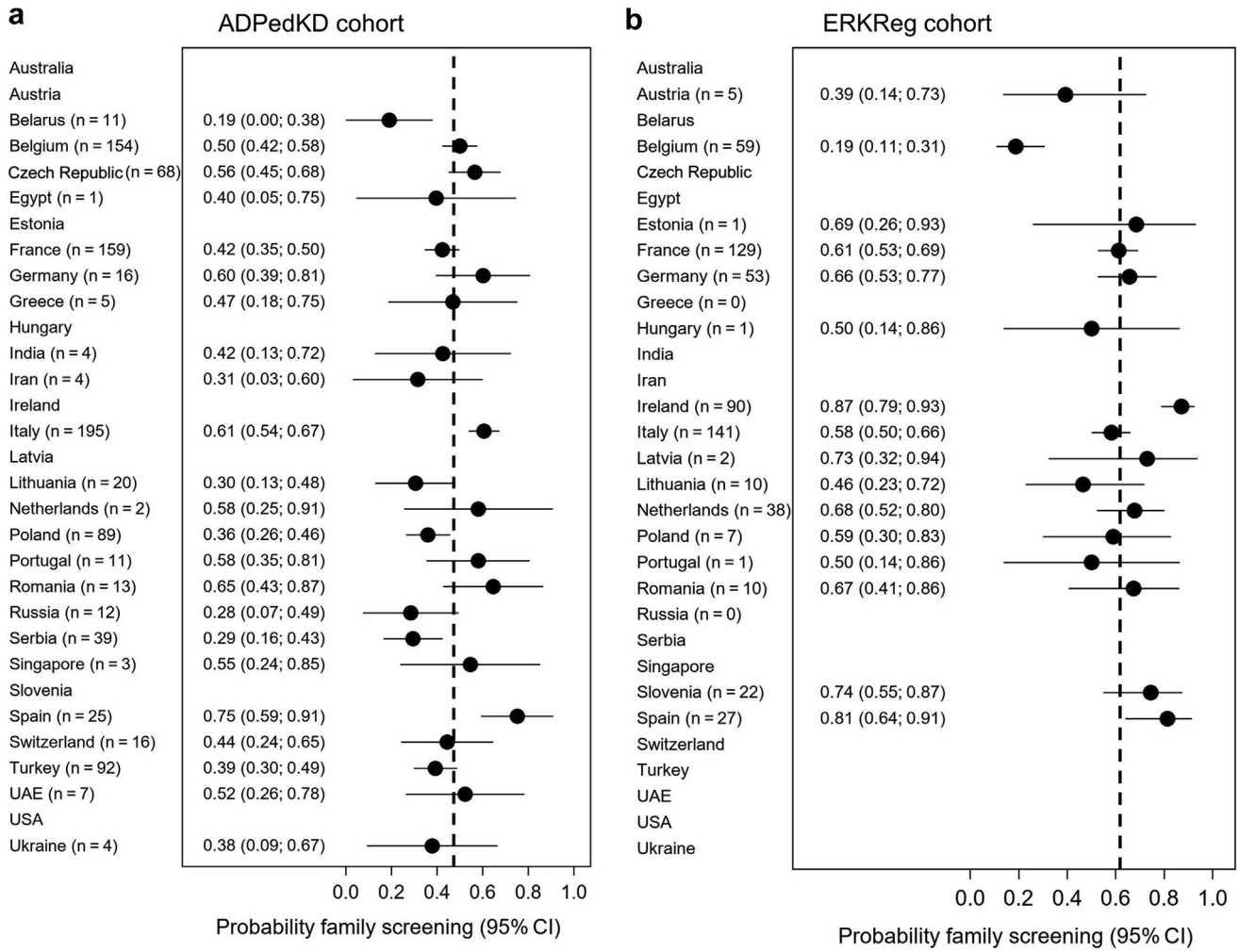

Figure 5 | Bayes estimates for the relative likelihood of diagnosis of autosomal dominant polycystic kidney disease (ADPKD) by family screening per country in the (a) ADPKD registry (ADPedKD) cohort and (b) European Rare Kidney Disease Registry (ERKReg) cohort. The dashed line represents the mean over all countries. The dots and numbers indicate empirical Bayes country-specific estimates for the probability of genetic testing, with horizontal lines and numbers in parentheses indicating the 95% confidence interval (CI).

living with ADPKD. The fact that within each world region ADPedKD and ERKReg did not always cover identical countries limits the statistical comparability. This applies mainly to Europe-North, which in ADPedKD included only Lithuania as UK data were included in RaDaR, while for ERKReg it included Ireland, Estonia, Latvia, and Lithuania. Other limitations were linked to clinical challenges in pediatric ADPKD, such as difficulty in reliably distinguishing whether an individual's symptoms (e.g., flank pain) are attributable to ADPKD or an incidental finding. Therefore, we draw no conclusions from the comparison of children diagnosed with ADPKD due to symptoms versus incidental findings, as it is probably not meaningful. We also did not perform a comparison of larger versus smaller centers within countries, as this is mainly of local interest. Internationally, coverage of middle-income countries was much more limited than that of high-income countries, even though collaboration with centers in low- and middle-income countries was actively sought. Regrettably, no patients from low-income countries were included here, as at the time of data analysis, only few centers from low-income countries had joined the ADPedKD and only started including patients later on. We hope to be able to fill the gap of data on whether and how ADPKD is diagnosed in low-income countries in the future. Especially in resource-limited settings, provision of advanced nephrological care and participation in investigator-led research activities remains challenging. However, as the largest pediatric ADPKD cohort to date, this study provides an international reflection of ADPKD in children and demonstrates the success of multicenter cooperation. Future perspectives for the multinational ADPedKD registry will be to analyze prenatal presentations in more detail, examine for genotype-phenotype correlations, and develop predictive models for identifying children at risk of fast progression and who are most likely to benefit from active therapy.[15,49]

In summary, since the 1990s, a high and stable proportion of children with ADPKD were diagnosed by active screening, indicating that a significant number of parents and health care

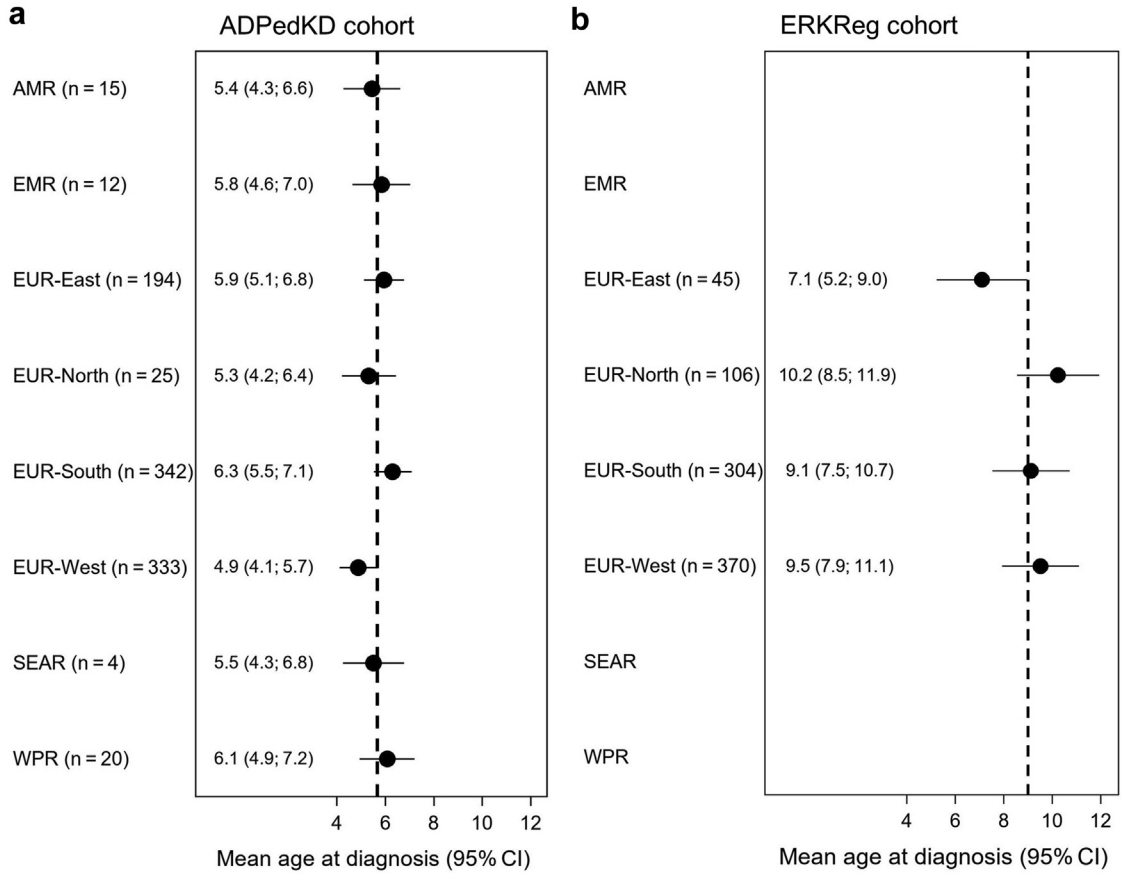

Figure 6 | Bayes estimates for mean age (in years) at diagnosis of autosomal dominant polycystic kidney disease (ADPKD) in the (a) ADPKD registry (ADPedKD) cohort and (b) European Rare Kidney Disease Registry (ERKReg) cohort by world region. The dashed line represents the mean over all regions. The dots and numbers indicate empirical Bayes estimates for the age at diagnosis in this world region, with horizontal lines and numbers in parentheses indicating the 95% confidence interval (CI). ADPedKD: AMR: Region of the Americas (1 country: USA, n = 15); EMR: Eastern Mediterranean Region (3 countries: Egypt, n = 2; Iran n = 3; United Arab Emirates, n = 7); EUR-East: European Region—East (6 countries: Belarus, n = 11; Czech Republic, n = 64; Poland, n = 82; Romania, n = 13; Russia, n = 20; Ukraine, n = 4); EUR-North: European Region—North (1 country: Lithuania, n = 25); EUR-South: European Region—South (6 countries: Greece, n = 5; Italy, n = 179; Portugal, n = 11; Serbia, n = 39; Spain, n = 25; Turkey, n = 83); EUR-West: European Region—West (5 countries: Belgium, n = 144; France, n = 164; Germany, n = 8; Netherlands, n = 2; Switzerland, n = 15); SEAR: South East Asian Region (1 country: India, n = 4); WPR: Western Pacific Region (2 countries: Australia, n = 17; Singapore, n = 3). ERKReg: EUR-East: European Region—East (4 countries: Hungary, n = 1; Poland, n = 26; Romania, n = 14; Russia, n = 4); EUR-North: European Region—North (4 countries: Estonia, n = 1; Ireland, n = 91; Latvia, n = 3; Lithuania, n = 11); EUR-South: European Region—South (5 countries: Greece, n = 1; Italy, n = 225; Portugal, n = 4; Slovenia, n = 38; Spain, n = 36); EUR-West: European Region—West (5 countries: Austria, n = 13; Belgium, n = 68; France, n = 159; Germany, n = 86; Netherlands, n = 44).

professionals opt for this management choice. Regional variations in mode and age of presentation were more pronounced than temporal variations; thus technical advances seem to play a smaller role than the cultural attitudes within health care systems and the economic and legal frameworks in which they operate. Patients with a prenatal diagnosis of ADPKD are starting to constitute a significant proportion of pediatric cohorts and counseling families will be very important.

APPENDIX

ADPedKD Collaborators

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DISCLOSURE

All the authors declared no competing interests.

DATA STATEMENT

Data of the ADPedKD, ERKReg, and RaDaR registries are not publicly available. Access can be requested from the respective coordinators (see the author list).

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Supplementary material is available online at www.kidney-international.org.

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