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***Graphical Abstract***

# *A multi-national perspective on the presentation of childhood ADPKD in high- and middle-income countries: insights from the ADPedKD, ERKReg and RaDaR registries*

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

***Cohort***

***n* = 2,154**

**Children with ADPKD aged 0-19 years**

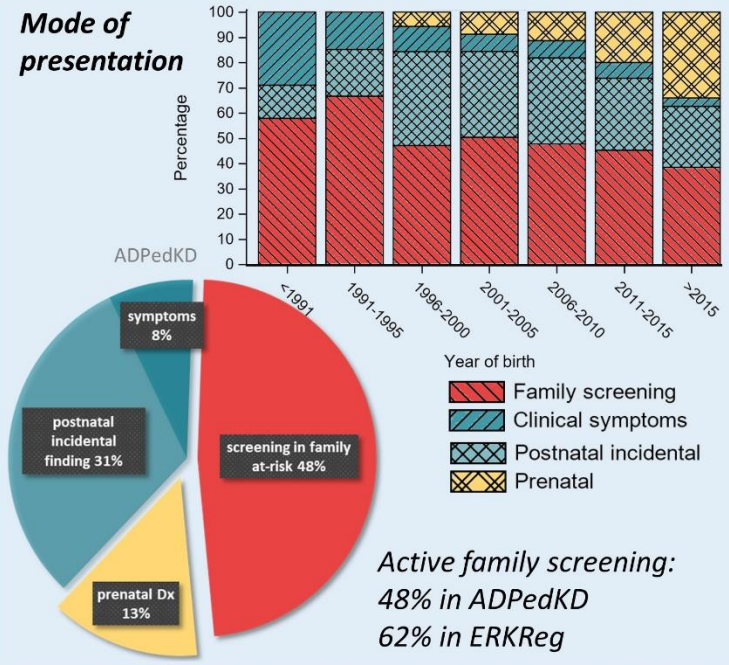
***ADPedKD*** *n* = 1,060
***ERKReg*** *n* = 825
**RaDaR** *n* = 269

**32 countries**
6 WHO world regions

24 high income
8 middle income

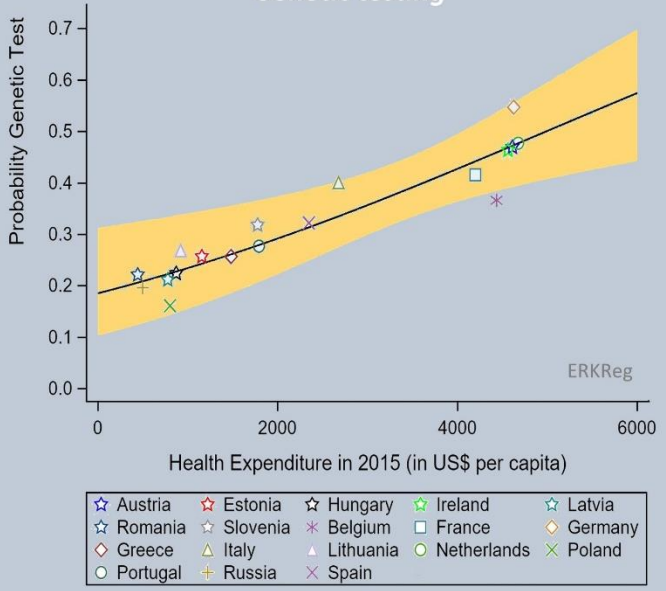
empirical Bayes estimates by world region

***Mode of presentation***




*Active family screening:*
*48% in ADPedKD*
*62% in ERKReg*

***Genetic testing***




***Gimpel, 2024***
**On behalf of the ADPedKD, ERKReg & RaDaR Consortia**

**adpedkd.org** **erknet.org** **ukkidney.org**
**@ADPedKD** **@EURefNetwork**

**CONCLUSION** *High rate of children diagnosed by active screening. Prenatal diagnoses rise after 2000. Greater geographical than temporal variations show influence of local health care systems.*

***A multi-national perspective on the presentation of childhood autosomal dominant polycystic kidney disease in high- and middle-income countries: insights from the ADPedKD, ERKReg and RaDaR registries***

**Running title:** Global presentation of childhood ADPKD

**Type of manuscript:** Original Article, Clinical Investigation

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**ABSTRACT**

Data on the presentation of Autosomal Dominant Polycystic Kidney Disease (ADPKD) in children has been based on small/regional cohorts and practices regarding both asymptomatic screening in minors and genetic testing differ greatly between countries.

We analyzed over 2100 children and adolescents with ADPKD from 32 countries in 6 WHO world regions: 1060 children from the multi-national ADPedKD registry were compared to pediatric patients from the UK (RaDaR, n=269) and the European Rare Kidney Disease Registry (ERKReg, n=825).

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 and no correlation to genetic testing.

The national rates of genetic testing were very different and correlated significantly with healthcare expenditure (odds ratio 1.030 per 100USD/capita/year, $P = 0.002$ in the ERKReg cohort), but had little variation over time.

Diagnosis due to prenatal abnormalities was more common than anticipated at 14% (8%-19%); it increased steadily from 2000 onward in both registries.

In summary, 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, while the rate of active screening was very different between countries and may reflect the influence of different of cultural, legal and ethical frameworks on families and clinicians in different healthcare systems more than economic factors alone.

**Keywords:** Autosomal dominant polycystic kidney disease, children, adolescents, registry, phenotype, genetic testing, demographics

**TRANSLATIONAL STATEMENT**

This current real-world map of the way that infants, children and adolescents with ADPKD are diagnosed demonstrates the large influence of regional practices on the complex ethical questions around diagnosing ADPKD in asymptomatic minors. This highlights the need for progress in specialized multidisciplinary counselling of affected families. Further longitudinal analyses should aim to characterize the benefits and harms of early asymptomatic diagnosis. In view of recent advances in delaying disease progression in high-risk individuals, the registries serve as a base for further studies to identify and validate primary endpoints, prognostic factors and predictive biomarkers for children with ADPKD in order to tailor therapy to individual risk.

**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 done in minors after careful consideration and discussion with the family about the benefits and harms of presymptomatic screening.

We describe how >2100 children from three different registries (ADPedKD, ERKReg, RaDaR) were first diagnosed.

Genetic testing was performed in 52% in ADPedKD and 41% in ERKReg, and differences between countries were related to healthcare spendings.

About 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 onwards, probably due to advances in prenatal diagnostics.

In summary, countries with higher healthcare 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.

**ABBREVIATIONS**

| | |
|---|---|
| ADPKD | Autosomal dominant polycystic kidney disease |
| KidGen | Kidneys, Genes and Generations Collaborative (Australia) |
| NIH-HRFD | NIH-funded Hepato-Renal Fibrocystic Disease Core Resource (North America) |
| RaDaR | National Registry of Rare Kidney Diseases (United Kingdom) |
| GDP | Gross domestic product |
| UN | United nations |
| USD | US dollars |
| SD | Standard deviation |
| IQR | Interquartile range |
| WHO | World health organization |

## INTRODUCTION

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 a major socio-economic 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 3rd-4th decade associated with a critical threshold for progression of kidney damage. There is a large phenotypic spectrum of childhood ADPKD which 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 intra-familiar variability of disease progression is challenging for the collection of epidemiological 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 healthcare staff. We therefore hypothesized that there are still large discrepancies regarding the management and diagnosis of children with ADPKD around the globe, e.g. with respect to 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

evaluated differences between era of diagnosis, year of birth as well as countries and their socioeconomic characteristics. To extend the geographical spectrum, these data were compared to the UK-based pediatric ADPKD patients collected in the RaDaR registry[22] and in the European Rare Kidney Disease Registry (ERKReg)[23].

## METHODS

### Study population and data collection

We analyzed baseline characteristics of patients included in the multi-national ADPedKD registry (https://www.adpedkd.org)[24] until June 2021. The ADPedKD registry collects data on children diagnosed with ADPKD up to the age of 19 years 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, de-identified 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 the UK's National Registry of Rare Kidney Diseases (RaDaR)[25], 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 was not available for genetic testing, nor mode of diagnosis 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: (1) at-risk children from families with known ADPKD identified by active screening (family screening), (2) incidental finding of kidney cysts

on abdominal ultrasound in a child (postnatal incidental finding), (3) prenatal diagnosis of ADPKD by ultrasound screening in pregnancy (prenatal diagnosis) and (4) 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 analysis of local geographical effects, countries were grouped according to world health organization (WHO) regions[28] and Europe further subdivided according to the UN geoscheme[29]. Country-specific healthcare expenditures, expressed both as US dollar (USD) per capita or as a percentage of gross domestic product (GDP), 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 non-missing cases for binary/categorical variables and of mean, standard deviation (SD), median and interquartile range (IQR) 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 stronger the country-specific Bayes estimate will shift towards 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 only with country as 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. $Chi^2$-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. 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 four 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 females. The RaDaR cohort comprised 269 patients (57%) females)

and the ERKReg cohort 825 patients (51% females), of which 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 healthcare expenditure from 58 to 9,383 USD per captia. Patient numbers per region and weighted mean healthcare expenditure of each region is 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 the child themself 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 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 children (231 of 238) of RaDaR children.

**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 (455/950, 48%), while the second most common mode was postnatal incidental finding (293/950, 31%), followed by prenatal diagnosis in 129/950 (14%) and clinical signs or symptoms in 73/950 (8%, see Table 3). There was no significant difference in mode of presentation between boys and girls. About half (*n*=429/764 (56.2%)) of patients with a positive family history were diagnosed via family screening, while 12% (92/764) were diagnosed prenatally, 7% (52 of 764) with clinical symptoms and 25% (191/764) with postnatal incidental findings. The rate of genetic testing was similar in the family screening group (238/455 (52%)) compared to the symptomatic diagnosis group (41/73 (56%)) and the incidental finding group (142/293 (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 and ADPedKD at 36% and 39%. 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, IQR 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 to family screening ($P < 0.01$). Children diagnosed by family screening were thus usually below the age of consent, i.e. at diagnosis only 3/407 (0.7%) were aged above 16 years, 24/407 (5.9%) above 14 years and 46/407 (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 healthcare 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 (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; while 162/825 (20%) were over 16 years and 86/825 (8%) over 18 years old at diagnosis.

Among the 129 patients with prenatal diagnosis in ADPedKD, the most common anomalies were hyperechogenic kidneys (52/81 (64%)), kidney cysts (55/98 (56%)) and

enlarged kidneys (43/85 (51%)), but abnormal quantity of amniotic fluid was uncommon (13/81 (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 under 18 years old.

**Geographical variations**

The most pronounced regional differences between were 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 two 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 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 healthcare 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 100USD/capita = 1.030 (95% confidence interval: 1.011 to 1.049), $P = 0.002$), and a very similar, but non-significant association in the ADPedKD cohort (odds ratio per 100USD/capita and year = 1.028 (95% confidence interval: 0.996 to 1.060), $P = 0.09$). As is visible in Figure 3a, this can be attributed firstly to the inclusion of Switzerland and the US, which both have extremely high health expenditure, but low levels of genetic testing (in the US it is not covered by health insurance and in Switzerland costs of genetic testing are only covered after individual application). As shown in supplemental Figure S2, the exclusion of the US and Switzerland resulted in a significant association of genetic testing with GDP in the mixed linear model ((odds ratio per 100USD/capita and year = 1.081 (95% confidence interval: 1.028 to 1.137), $p = 0.0024$).

There was little regional variation in the proportion of prenatal diagnoses (see Figure 4), but the postnatal modes of 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 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. While 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 four 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 was 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. While there are multiple ethical, psychological and legal challenges around actively screening for a non-curable 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 done for some years, and about half 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] as well as their desire to be pro-active 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 KDIGO 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 pre-symptomatic 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 reference 39)] with both parents and children in an age-appropriate manner. While 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, 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 doing 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, that was not so evident when they were combined into regions of similar healthcare expenditure. We consider this to reflect the impact of local healthcare practices and ethical frameworks on physicians' and families' attitudes towards active screening in children of affected parents, which was also evident in a detailed patient focus group study from three different countries[38]. There was no correlation of screening diagnoses to rates of genetic testing, probably because abdominal ultrasound is an alternative (if less reliable) method of diagnosis in childhood. Therefore, ethical and local healthcare 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 be prenatally 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

counselling of (prospective) parents affected by ADPKD, which is also stressed in the new KDIGO guidelines on ADPKD[39]. From our data, we are unable 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 counselled to disclose this to the prenatal sonographer prior to 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 which are merely markers of disease transmission. As most patients with prenatal diagnoses were born after 2005, they are currently still under the age of 18 years and will be seen mainly in pediatric centers, which may explain the differing experiences of pediatric vs 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 healthcare expenditure (Figure 3). That genetic testing was not uniformly high in countries with high healthcare expenditure may reflect that it is not uniformly covered by insurance companies (e.g. in the US), 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, while 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 healthcare 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 genetical testing in the last two 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 countries. Knowledge about local rates of genetic testing may help national patient advocacy groups, medical organizations and/or planners in the healthcare to move towards 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 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 some authors have suggested may increase the rate of kidney incidental findings[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 as being retrospective and with unknown bias as neither randomly sampled nor covering 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 pre-implantation genetic diagnosis of ADPKD and cannot comment on their effect on the ADPKD population. 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 vs incidental findings, as it is probably not meaningful. We also did not perform a comparison of larger vs. 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 multi-center cooperation. Future perspectives for the multi-national ADPedKD registry, will be to analyze prenatal presentations in more detail, examine for genotype-phenotype correlations and to develop predictive models for identifying children at-risk of fast progression and who are likely to benefit from active therapy[15,49].

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

## DISCLOSURE STATEMENT

All the authors declared no conflicts of interest.

## SUPPLEMENTARY MATERIAL

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

**Supplementary Table S1.** Number of patients included per country.

**Supplementary Table S2.** Results from a multivariable linear mixed models for age at diagnosis with country as a random effect (ADPedKD cohort).

**Supplementary Table S3.** Symptoms and signs present at diagnosis of ADPKD in the subgroups of children with symptomatic ADPKD and incidental finding.

**Supplementary Figure S1.** Empirical Bayes country-specific estimates for relative likelihood of genetic testing by country for the (a) ADPedKD and (b) ERKReg cohorts.

**Supplementary Figure S2.** Likelihood of genetic testing being performed, as predicted by a generalized linear mixed model (binary logistic regression) with country added as a random effect in the ADPedKD cohort (without USA and Switzerland).

**Supplementary Figure S3.** Empirical Bayes country-specific estimates for relative likelihood of diagnosis of ADPKD as postnatal incidental finding by world region in the (a) ADPedKD cohort and (b) ERKReg cohort.

**Supplementary Figure S4.** Empirical Bayes country-specific estimates for relative likelihood of diagnosis of ADPKD as a result of postnatal incidental finding (a and b) or clinical symptoms per country in the (c and d) per country in the (a and c) ADPedKD cohort and (b and d) ERKReg cohort.

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**DATA AVAILABILITY STATEMENT**

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

**Table 1** | Number of countries, patients and healthcare expenditure by world region

| World region | Total number of countries (high/ middle income) | Total number of patients | Range of national healthcare expenditures * | Mean weighted healthcare expenditure** |
|---|---|---|---|---|
| SEAR | 1 (0/1) | 5 | 58 | 58 |
| EUR-East | 7 (4/3) | 262 | 157-1,284 | 834 |
| EMR | 3 (1/2) | 13 | 174-1,439 | 916 |
| EUR-South | 7 (5/2) | 678 | 447-2,676 | 2,115 |
| EUR-North | 5 (5/0) | 401 | 776-4,561 | 4,112 |
| EUR-West | 6 (6/0) | 759 | 4,199-9,383 | 4,476 |
| WPR | 2 (2/0) | 20 | 2,279-5,324 | 4,868 |
| AMR | 1 (1/0) | 16 | 9,244 | 9,244 |

* healthcare expenditure in USD per capita in 2015[31]

** weighted for number of patients from each country

WHO regions (and countries represented in the present cohorts):
SEAR: South East Asian Region (India)
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)
EMR: Eastern Mediterranean Region (Egypt, Iran, UAE)
WPR: Western Pacific Region (Australia, Singapore)
AMR: Region of the Americas (USA)

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

| | **ADPedKD** | **RaDaR** | **ERKReg** |
|---|---|---|---|
| **Pediatric ADPKD population size, N** | **1060** | **269** | **825** |
| **Genetic test performed** | | | |
| Yes, N | 547 (52%) | 117 (43%) | 335 (41%) |
| No, N | 454 (43%) | Not recorded | Not recorded |
| Unknown, N | 59 (6%) | 152 (57%) | 490 (59%) |
| **Genetic results** (information available), N | **547** | **117**[1] | **335**[1] |
| No information or NMD in ADPKD genes, N | 22 (4%) | 36 (31%) | 61 (18%) |
| *PKD1* causative variant, N | 470 (86%) | 73 (62%) | 245 (73%) |
| *PKD2* causative variant, N | 45 (8%) | 6 (5%) | 27 (8%) |
| *PKD1+TSC2* causative variant, N | 6 (1%) | 2 (2%) | 0 (0%) |
| Other causative variant, N | 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 | 139 | 596 |
| Prenatal, N | 129 (14%) | 15 (11%) | 13 (2%) |
| Family screening, N | 455 (48%) | unknown | 370 (62%) |
| Incidental finding, N | 293 (31%) | unknown | 126 (21%) |
| With symptoms, N | 73 (8%) | unknown | 87 (15%) |
| **Age at diagnosis** (information available), N | 945 | 269 | 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 |

*ADPKD,* autosomal dominant polycystic kidney disease*; IQR,* interquartile range*; Max,* maximum *Min,* minimum*; NMD,* no causative variant detected*; N*, number of observations with data; *SD*, standard deviation.

[1]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.

**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 |

N, Number of observations; SD, standard deviation

**Figure legends**

**Figure 1** | **Distribution of mode of presentation of ADPKD per year of birth for (a) & (b) ADPedKD cohort** (*n*=945) **and (c) & (d) ERKReg cohort** (*n*=825)

**Figure 2** | **Bayes estimates for percentage of children receiving genetic testing by world region. (a) ADPedKD cohort (b) ERKReg cohort.**

The dashed line represents the mean over all regions. Dots and numbers indicate empirical Bayes estimates for the probability of genetic testing in that region with horizontal lines and numbers in brackets 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)

**Figure 3** | **Likelihood of genetic testing being performed in children with ADPKD, as predicted by a generalised linear mixed model (binary logistic regression) with country added as a random effect in the (a) ADPedKD cohort and (b) ERKReg cohort.**

Current health expenditure is expressed as USD 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.

**Figure 4** | **Bayes estimates for the relative likelihood of a prenatal diagnosis of ADPKD by world region in the (a) ADPedKD cohort and (b) ERKReg cohort**

The dashed line represents the mean over all regions. Dots and numbers indicate empirical Bayes country-specific estimates for the probability of genetic testing with horizontal lines and numbers in brackets 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)

**Figure 6** | **Bayes estimates for mean age (in years) at diagnosis of ADPKD in the (a) ADPedKD cohort and (b) ERKReg cohort by world region**

The dashed line represents the mean over all regions. Dots and numbers indicate empirical Bayes estimates for the age at diagnosis in this world region with horizontal lines and numbers in brackets 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)

# *A multi-national perspective on the presentation of childhood autosomal dominant polycystic kidney disease in high- and middle-income countries: insights from the ADPedKD, ERKReg and RaDaR registries*

## Supplementary Material

**Supplementary Table S1.** Number of patients included per country.

| *Country* | *World region* | *ADPedKD* | *RaDaR* | *ERKReg* | *WHO classification income group* |
|---|---|---|---|---|---|
| Australia | WPR | 17 | | | High |
| Austria | EUR-West | | | 13 | High |
| Belarus | EUR-East | 11 | | | Upper middle |
| Belgium | EUR-West | 156 | | 68 | High |
| Czech Republic | EUR-East | 69 | | | High |
| Egypt | EMR | 2 | | | Lower middle |
| Estonia | EUR-North | | | 1 | High |
| France | EUR-West | 190 | | 159 | High |
| Germany | EUR-West | 25 | | 86 | High |
| Greece | EUR-South | 5 | | 1 | High |
| Hungary | EUR-East | | | 1 | High |
| India | SEAR | 5 | | | Lower middle |
| Iran | EMR | 4 | | | Lower middle |
| Ireland | EUR-North | | | 91 | High |
| Italy | EUR-South | 195 | | 225 | High |
| Latvia | EUR-North | | | 3 | High |
| Lithuania | EUR-North | 26 | | 11 | High |
| Netherlands | EUR-West | 2 | | 44 | High |
| Poland | EUR-East | 98 | | 26 | High |
| Portugal | EUR-South | 11 | | 4 | High |
| Romania | EUR-East | 13 | | 14 | High |
| Russia | EUR-East | 22 | | 4 | Upper middle |
| Serbia | EUR-South | 42 | | | Upper middle |
| Singapore | WPR | 3 | | | High |
| Slovenia | EUR-South | | | 38 | High |
| Spain | EUR-South | 25 | | 36 | High |
| Switzerland | EUR-West | 16 | | | High |
| Turkey | EUR-South | 96 | | | Upper middle |
| UAE | EMR | 7 | | | High |
| UK | EUR-North | | 269 | | High |
| Ukraine | EUR-East | 4 | | | Lower middle |
| USA | AMR | 16 | | | High |

*SEAR:* South East Asian Region, *EUR:* European Region, *EMR:* Eastern Mediterranean Region, *WPR:* Western Pacific Region, *AMR:* Region of the Americas

*UAE*, United Arab Emirates*; UK*, United Kingdom*; USA*, United States of America.

**Supplementary Table S2.** Results from a multivariable linear mixed models for age at diagnosis with country as a random effect (ADPedKD cohort).

| | | ***Estimate (SE)*** | ***P-value*** |
|---|---|---|---|
| **Year of birth** | | | <.0001 |
| | <1991 | 11.593 (SE=0.947) | <.0001 |
| | 1991-1995 | 8.409 (SE=0.958) | <.0001 |
| | 1996-2000 | 8.483 (SE=0.679) | <.0001 |
| | 2001-2005 | 7.711 (SE=0.524) | <.0001 |
| | 2006-2010 | 4.395 (SE=0.518) | <.0001 |
| | 2011-2015 | 1.625 (SE=0.540) | 0.0027 |
| | >2015 | # | |
| **Genetic test performed** | | | 0.8743 |
| | No | 0.117 (SE=0.679) | 0.8635 |
| | Yes | -0.423 (SE=1.239) | 0.7328 |
| | Unknown | # | |
| **Positive family history** | | | 0.3336 |
| | No | 0.351 (SE=0.363) | |
| | Yes | # | |
| **Genetic grouping** | | | 0.0306 |
| | No evidence or information on ADPDK related mutations | -7.759 (SE=4.320) | 0.0729 |
| | *PKD1* or (*PKD1*+*PDK2*) | -7.660 (SE=4.196) | 0.0682 |
| | Only *PDK2* | -5.997 (SE=4.249) | 0.1585 |
| | *PKD1+TSC2* | -9.918 (SE=4.531) | 0.0289 |
| | Other | # | |
| **Current Health Expenditure (per 100 dollar/person)** | | -0.014 (SE=0.015) | 0.3693 |

The multivariable linear mixed model was fitted on 913 observations. Children with prenatal diagnosis are excluded, as they have a different age at diagnosis per se.
Random effect of country: $X^2$= 13.71, p-value=0.0001. Explained variability by random effect derived from the $X^2$ statistic: 1.49%.

*ADPKD,* autosomal dominant polycystic kidney disease*; SE*, standard error; *#,* reference category

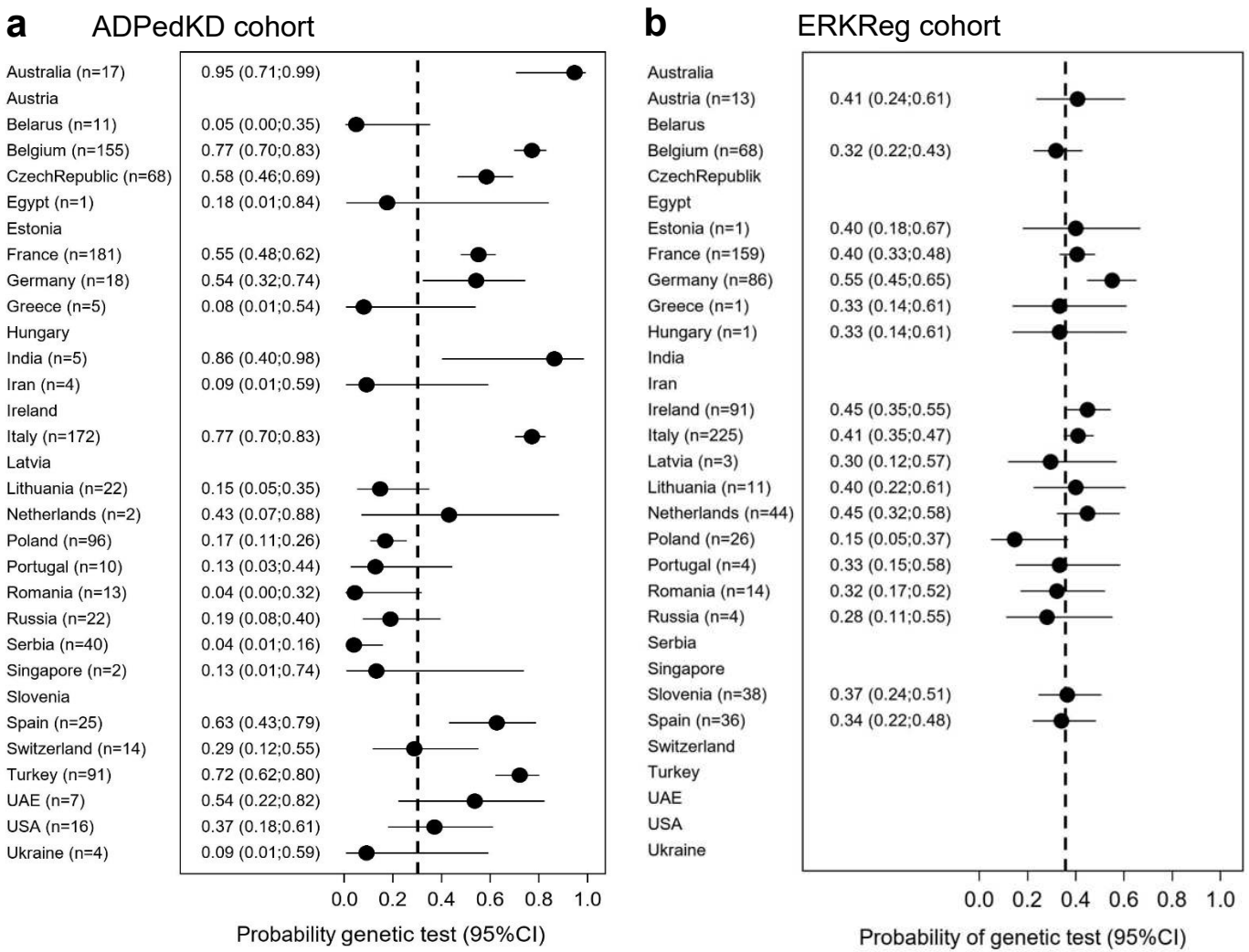
**Supplementary Table S3.** Symptoms and signs present at diagnosis of ADPKD in the subgroups of children with symptomatic ADPKD and incidental finding.

| | **ADPKD diagnosed with symptoms / signs** N=73 | **ADPKD diagnosed as an incidental finding** N=376 |
|---|---|---|
| **Urinary tract infection** | 16 (22%) | 41 (11%) |
| **Enuresis or dysfunctional voiding** | 5 (7%) | 7 (2%) |
| **Flank/ back/ abdominal pain[1]** | 16 (22%) | 84 (22%) |
| **Urolithiasis** | 2 (3%) | 4 (1%) |
| **Hematuria** | 12 (16%) | 13 (3%) |
| **Cyst complications** | 1 (1%) | 0 |
| **Hypertension** | 10 (14%) | 6 (2%) |
| **Proteinuria** | 2 (3%) | 3 (1%) |

Assignment to either diagnosis group (with symptoms/ incidental) as classified by local investigator.

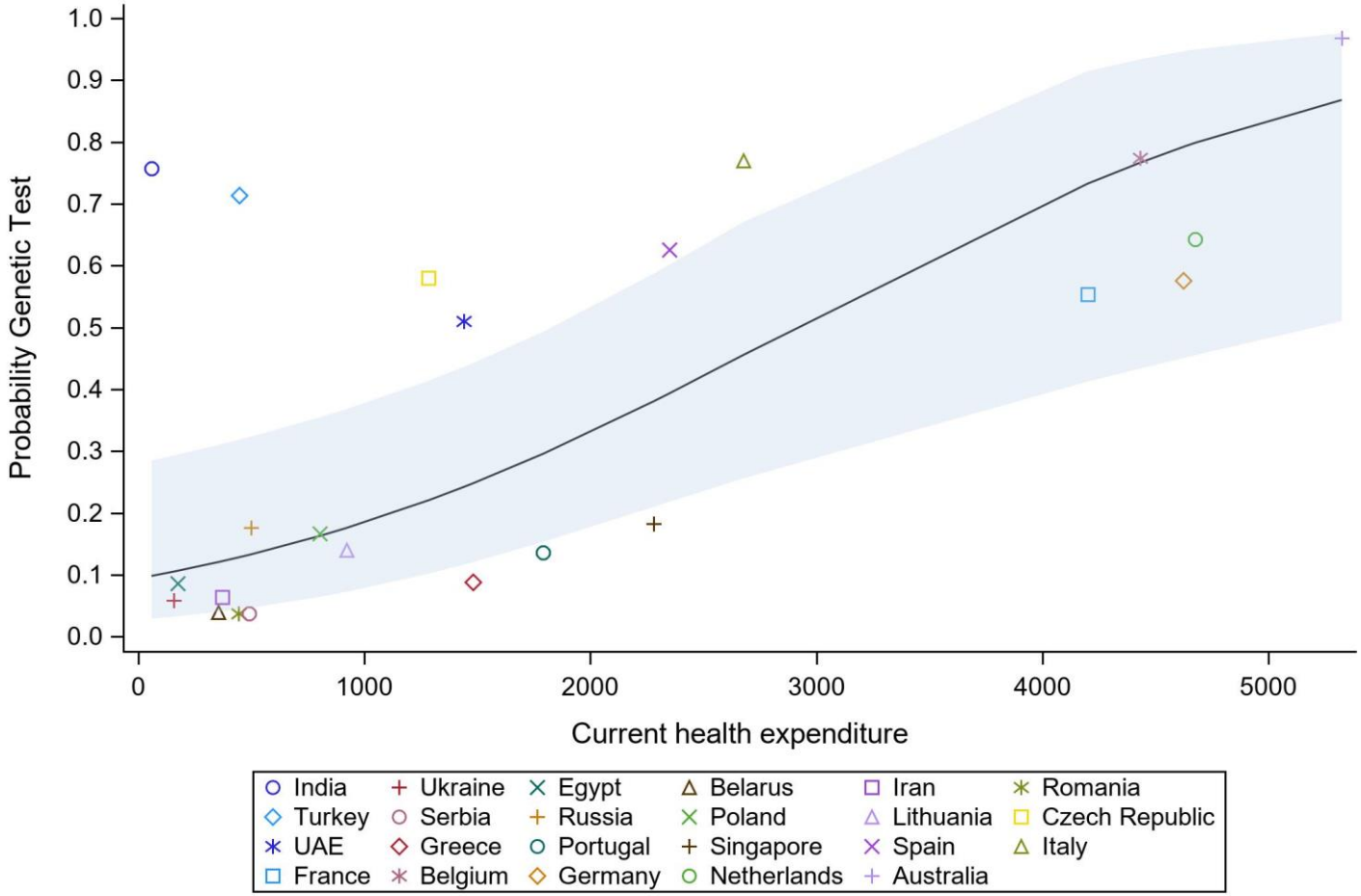
[1]Children who presented with abdominal pain for a named other reason (e.g. appendicitis, constipation, trauma, pancreatitis or malignancy are not included).

**Supplementary Figure S1.** Empirical Bayes country-specific estimates for relative likelihood of genetic testing being performed in children with ADPKD by country for the (a) ADPedKD and (b) ERKReg cohorts.

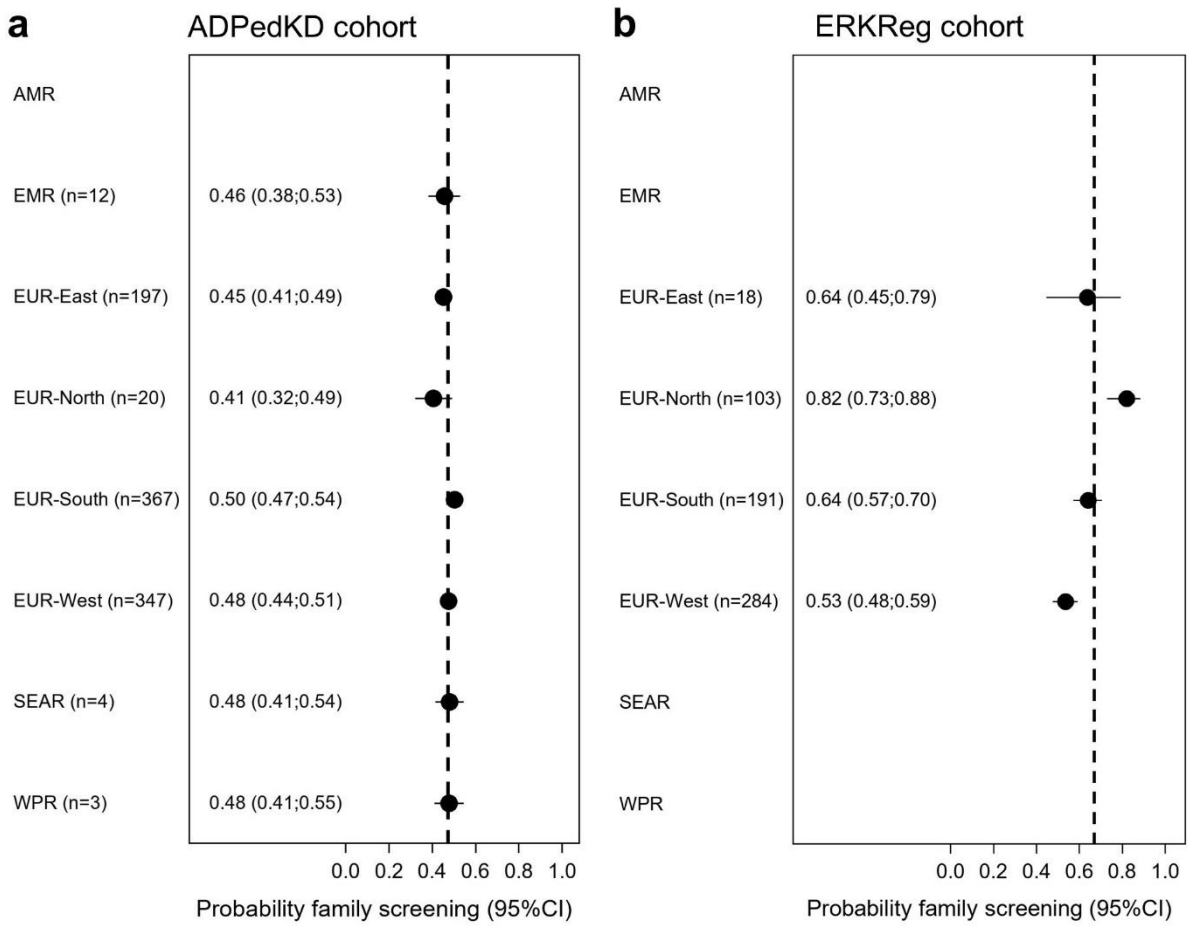



Dots/numbers indicate country-specific estimates for the probability of this mode of presentation with horizontal lines/numbers in brackets referring to the 95% confidence interval. The dashed line represents the mean over all countries

**Supplementary Figure S2.** Likelihood of genetic testing being performed, as predicted by a generalized linear mixed model (binary logistic regression) with country added as a random effect in the ADPedKD cohort (without USA and Switzerland)



**Supplementary Figure S3.** Empirical Bayes estimates for relative likelihood of diagnosis of ADPKD as postnatal incidental finding by world region in the (a) ADPedKD cohort and (b) ERKReg cohort

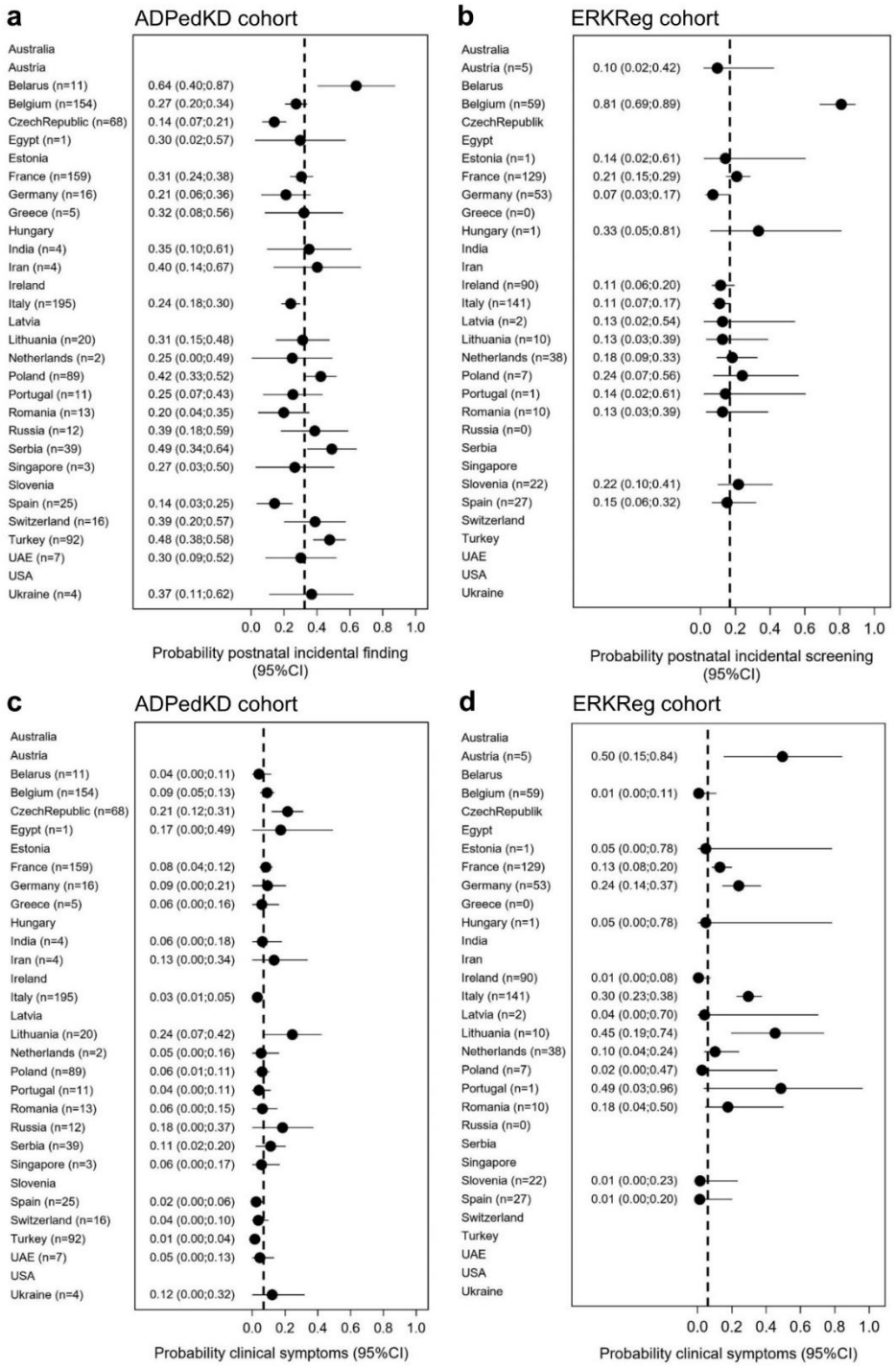



ADPedKD
EMR: Eastern Mediterranean Region (3 countries: Egypt *n*= 1; Iran *n*= 4; United Arab Emirates *n*= 7)
EUR-East: European Region - East (6 countries: Belarus *n*= 11; Czech Republic *n*= 68; Poland *n*= 89; Romania *n*= 13; Russia *n*= 12; Ukraine *n*= 4)
EUR-North: European Region - North (1 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)

Dots/numbers indicate region-specific estimates for the probability of this mode of presentation with horizontal lines/numbers in brackets referring to the 95% confidence interval. The dashed line represents the mean over all regions. *CI*, confidence interval

**Supplementary Figure S4.** Empiricial Bayes country-specific estimates for relative likelihood of diagnosis of ADPKD as a result of postnatal incidental finding (a and b) or clinical symptoms (c and d) per country in the (a and c) ADPedKD cohort and (b and d) ERKReg cohort




Dots/numbers indicate country-specific estimates for the probability of this mode of presentation with horizontal lines/numbers in brackets referring to the 95% confidence interval. The dashed line represents the mean over all countries.
*CI*, confidence interval; *UAE*, United Arab Emirates; *UK*, United Kingdom; *USA*, United States of America.