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When should we offer antenatal sequencing for urinary tract malformations? A systematic review, cohort study and meta-analysis

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Abstract

Objective: Determine the incremental yield of prenatal exome sequencing (PES) over chromosome microarray (CMA) and/or karyotype for urinary tract malformations (UTMs).

Method: A prospective cohort study encompassing data from the English Genomic Medicine Service North Thames Laboratory Hub for fetuses with bilateral echogenic kidneys (BEKs) was combined with data from a systematic review. MEDLINE, EMBASE, Web of Science, MedRxiv and GreyLit were searched from 01/2010-02/2023 for studies reporting on the yield of PES over CMA or karyotype in fetuses with UTMs. Pooled incremental yield was determined using a random effects model. PROSPERO CRD42023364544.

Results: Fourteen studies (410 cases) were included. The incremental yield for multisystem UTMs, any isolated UTMs, and BEKs was 31% [95% CI, 18%–46%; I^2 = 78%], 16% [95% CI, 6%–26%; I^2 = 80%] and 51% [95% CI, 27%–75%; I^2 = 34%]. The most common clinical diseases and syndromes identified, based on the variant genes detected, were Bardet-Biedl syndrome (*BBS* genes), dominant and recessive polycystic kidney diseases (*PKD1*, *PKD2* and *PKHD1*) and renal cysts and diabetes syndrome (*HNF1B*).

Conclusion: There was a notable incremental genetic diagnostic yield when PES was applied to multisystem UTMs and BEKs. There was a modest incremental yield when this technique was used for UTMs other than BEKs.

Key points

What's already known about this topic?

- Bilateral echogenic kidneys (BEKs) have a recognized association with monogenetic conditions and are an indication for prenatal exome sequencing (PES) in many healthcare systems.

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What does this study add?

- For urinary tract malformations other than BEKs, there is a modest incremental yield from PES over chromosome microarray and G-banding karyotype.

1 | INTRODUCTION

Urinary tract malformations (UTMs), also known as congenital anomalies of the kidney and urinary tract (CAKUT),[1,2] account for up to 20% of all major congenital anomalies and affect around 1:1000 births.[3] UTMs comprise a wide spectrum of individual disorders including kidney malformations that themselves are divided into agenesis, when the kidney fails to form, and dysplasia, when the organ begins to form but its internal structure is immature and metaplastic.[4,5] The sonographic appearance of kidney dysplasia is a hyperechogenic or "bright" parenchyma with loss of corticomedullary distinction.[5] A variant is the multicystic dysplastic kidney where the sonographic appearance is dominated by large cysts separated by bright parenchyma. Prenatal hyper-echogenicity is not, by itself, a diagnostic of kidney dysplasia and this appearance is also described in, for example, autosomal dominant and recessive polycystic kidney diseases (ADPKD and ARPKD).[6] In the PKDs, glomeruli and tubules are generated but then become cystic, while in dysplasia glomeruli and tubules fail to form. The spectrum of UTMs also includes malformations of the lower urinary tract. As examples, a greatly distended bladder occurs with anatomical bladder outflow obstruction (BOO) due to posterior urethral valves, while a similar distended appearance can occur with failure of bladder emptying but in the absence of a true obstruction, so called "functional BOO," caused by disorders of neuromuscular differentiation of the bladder and its outflow tract.[7] Not all prenatally detected UTMs have poor prognoses. For example, many cases of hydronephrosis that are not caused by BOO can spontaneously resolve.[8] On the other hand, UTMs collectively cause around half of the cases of severe kidney failure requiring dialysis and transplantation in childhood, and they are also an important cause of severe kidney failure in young adults.[9,10] Furthermore, the most severe UTMs are associated with anhydramnios or oligohydramnios which can confer perinatal lethality due to a failure of lung maturation.[11]

When fetal UTMs are detected, it is imperative to allow parents to make informed decisions about the pregnancy, including the decision to terminate, planning for postnatal care or to inform future pregnancies.[12] In recent decades, with advances in human genomics, attention has begun to focus on defining potential genetic causes of UTMs, including those detected before birth.[5,7,13,14] Such information, in turn, can give families a reason as to why the UTM occurred to inform genetic counseling and to help plan clinical management because the postnatal clinical trajectory of specific diseases, for example, kidney dysplasia versus ARPKD, may differ.[15]

Aneuploidy or pathogenic copy number variants are detected in 40% of prenatally detected anomalies using standard diagnostic methods, G-banding karyotyping and chromosomal microarray (CMA), respectively.[16] It is thought that a proportion of the remainder of unexplained cases could be the result of Mendelian single gene disorders. Next generation sequencing (NGS) technologies such as prenatal exome sequencing (PES) have been tested for fetal malformations and have been reported to have an incremental yield over standard testing (i.e. karyotyping and CMA) for prenatally detected anomalies of around 8.5%–18.8%.[16] The diagnostic yield varies depending on the phenotypic subgroup affected and this has not yet been collectively assessed in the urinary tract, where aneuploidy is responsible for approximately 12% of cases.[17] There have been approximately 40 genes implicated in isolated UTMs and 232 in syndromic UTMs.[18] The objective of this systematic review and meta-analysis is to determine the incremental yield of prenatally diagnosed UTM occurring with other anomalies, or in isolation, and to further subclassify UTM phenotypes based upon those which had a significant incremental yield from NGS.

2 | METHODS

2.1 | Literature search

A systematic review of the literature was carried out in accordance with PRISMA guidance[19] and prospectively registered with PROSPERO ID: CRD420233645544. The search was conducted across MEDLINE, EMBASE, Web of Science, MedRxiv and GreyLit for papers from January 2010 to February 2023. Variants of the terms "exome sequencing," "prenatal" and "abnormality" were used to capture any relevant texts. Full search criteria are available from the corresponding author on request. The papers were filtered to include only English language texts and human studies. Citations of relevant papers were searched, and clinical experts in prenatal genetics and pediatric nephrology were contacted to conduct further studies. Two reviewers (S.S. and K.R.) screened abstracts, followed by review of full texts using systematic review management software Covidence.[20] Inclusion criteria were (1) Five or more cases of fetal UTMs which were undergoing PES; (2) testing was performed based on a prenatally identified phenotype detected on ultrasound; and (3) there was a negative CMA or karyotype result.

2.2 | Additional cohorts

One cohort, which was an extended version of previously published data, was included with permission from the teams involved in the Prenatal Assessment of Exomes and Genomes[21] study. A second unpublished cohort represented prospectively collected clinical cases

from the National Health Service, England (NHSE) rapid PES pathway carried out by the North Thames NHS England Genomic Laboratory Hub from October 2020 to February 2023. For the NHSE cases trio PES was performed and interpreted as previously described in line with existing criteria with patients providing written informed consent for the collection of clinical data for research purposes. The NHSE selection criteria specify that the only isolated UTMs which should undergo PES are bilaterally echogenic kidneys (BEKs) with a normal bladder.[22,23]

The NHSE cohort used the fetal anomaly panel which has been developed from postnatal panels for phenotypic features that may present prenatally and would meet current NHSE criteria for PES. The green (diagnostic grade) genes on each of these panels are reviewed by an expert panel supported by literature search. Criteria for inclusion are "A gene with a reported structural phenotype detectable with standard ultrasound screening or other imaging modalities, for example, MRI, that could present at any stage in fetal life." The postnatal panels reviewed that are applicable to this review are Cystic renal disease, Bardet Biedl syndrome, Beckwith-Wiedemann syndrome and other congenital overgrowth disorders and CAKUT. All variants that are warm/hot class 3 (by ACGS variant classification guidelines) or above and in keeping with the expected inheritance pattern or in genes known to be associated with a condition that affects the urinary system are taken to a multidisciplinary team discussion to determine if likely to be causal of imaging findings. The methodology and bioinformatic filtering pipeline have been previously reported.[24]

2.3 | Phenotypic sub-classification

A UTM referred to any structural fetal anomaly affecting one or both kidney(s), ureter(s), bladder and or urethra with no exclusions. In the instance of the NHSE cohort, only BEK were included as these were the only cases analyzed. Cases in the current study were considered "isolated" if the prenatal ultrasound findings were confined to the urinary tract, and as "multisystem" if they had additional findings in other anatomical systems. Anatomical UTM sub-types were grouped for sub-analysis as overseen by a pediatric nephrologist (A.S.W.) as suspected BOO, hydronephrosis, kidney agenesis, kidney dysplasia and BEKs. As the cohort was small, only those with a large enough number of cases to facilitate the calculation of an incremental yield were further interrogated. It became evident that the only sub-group with an identifiable yield was that of BEKs and hence, the final sub-analysis was that of (1) isolated BEK, and (2) all non-BEK isolated UTMs as a comparison group.

2.4 | Statistical analysis and quality assessment

The incremental diagnostic yield of NGS over standard chromosome analysis was calculated via risk difference with 95% confidence intervals and pooled using a random effects model to give a total percentage using RevMan version 5.4—(Review Manager, the Cochrane Collaboration, Copenhagen, Denmark),[25] for all cases, isolated UTM cases and for phenotypic subgroups of UTM. Incremental yield was calculated using zero to reflect negative result from CMA or karyotyping.[26,27] Variants from PES results were considered positive if they were graded pathogenic or likely pathogenic, in association with guidelines from the American College of Medical Genetics and Genomics/American College of Pathology (ACMG).[28]

Heterogeneity, or consistency in findings between studies, was assessed graphically by forest plots and statistically using Higgin's I^2, and funnel plots were used to assess publication bias. Quality assessment was conducted using a modified version of Standards for Reporting of Diagnostic Accuracy (STARD)[29] Criteria with additional quality points specific to this study. These included: (1) use of trio analysis, (2) Use of ACMG guidelines for interpretation, (3) validation of variants using Sanger sequencing, (4) description of prenatal phenotype, and (5) description of the variant filtering process.

3 | RESULTS

In addition to the two extended cohorts, 12 studies were deemed fit for inclusion,[30–41] giving a total of 409 cases of prenatally diagnosed UTM (174 isolated and 235 associated with additional extra-UTMs). The screening process and studies used are detailed in the PRISMA chart in Figure 1. The characteristics of the studies are detailed in Table 1 and the quality assessment is expressed in Figure 2. Due to the limited number of cases, quality assessment was not used to inform the meta-analysis.

Where stated, the median maternal age at testing was 28 (range 20–41) years and the median gestational age was 21 (range 11–36) weeks. The mean turnaround time for NGS was 67.75 days (+/− 22.4 days). Across all studies 23 variants of unknown significance (VUS) were reported (of which two were upgraded to likely pathogenic postnatally), giving a pooled yield VUS of 4% [95% CI 0%–7%; $I^2 = 43\%$]. In addition, five secondary findings were reported, giving a incremental yield of 2% [95% CI; −1, 5%, $I^2 = 43\%$] (Supplementary Tables S1 and S2). All reported pathogenic and likely pathogenic variants are demonstrated in Supplementary Table S3.

The pooled incremental yields for all UTMs inclusive of sub-analyses are demonstrated in Table 2 and Supplementary Figure S1A–C.

Of the 88 cases with a specific monogenic diagnosis the most prevalent genes with pathogenic variants detected were *Bardet-Biedel syndrome* (*BBS*) genes encoding cilia-associated proteins ($n = 10$; 11.4%), with cases being predominantly multisystem in nature ($n = 8$) and the remainder presenting with isolated UTMs ($n = 2$); *PKHD1* encoding fibrocystin, associated with ARPKD ($n = 8$; 9.1%), with the majority isolated in nature ($n = 7$); and *PKD1* or *PKD2*, respectively encoding polycystins 1 and 2, associated with ADPKD ($n = 6$; 6.8%), all of which were isolated in nature. In addition, pathogenic variants in hepatocyte nuclear factor 1B (*HNF1B*) encoding a transcription factor expressed in the developing kidney

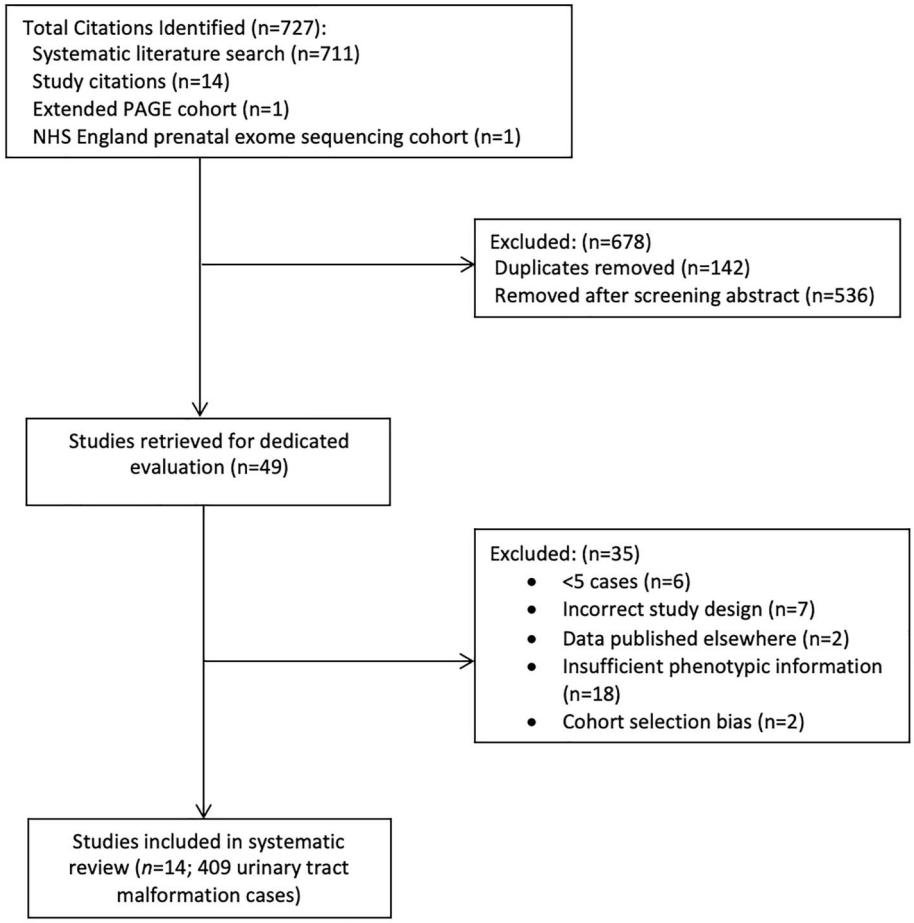

FIGURE 1 Flowchart summarising the studies included in the systematic review of incremental yield of next generation sequencing in cases of prenatally diagnosed urinary tract malformations with negative chromosomal analysis.

and implicated in the "renal cysts and diabetes syndrome" were detected in four cases of BEK (12.5%).

The predominant inheritance pattern was autosomal recessive (biallelic) in 67% ($n = 59$) with 30.7% ($n = 27$) autosomal dominant (monoallelic), of which 81.5% ($n = 22$) were *de novo*. One case (1.1%) was X-linked (Mucopolysaccharidosis Type II) and in one case the inheritance pattern was not stated.

4 | DISCUSSION

There was a notable incremental genetic diagnostic yield when PES was applied to BEK. The most common clinical diseases and syndromes identified, based on the variant genes detected, were the ciliopathies Bardet Biedl syndrome (*BBS2*, *BBS9*, *BBS7* and *BBS10* genes), dominant and recessive PKDs (*PKD1*, *PKD2* and *PKHD1*), and the renal cysts and diabetes syndrome (*HNF1B*). In contrast, there was a modest incremental yield when this technique was used for UTMs other than BEKs.

Fetal renal echogenicity is a relatively common prenatal sonographic finding, seen in 1.6 per 1000 ultrasound scans.[42,43] Of relevance to the current report, it can be associated with genetic syndromes such as PKD and other ciliopathies, as well as the renal cysts and diabetes syndrome.[6,13] With the lower yield for all other anomalies pooled together excluding BEK being less than 10% collectively, it appears that the most common prenatal presentation for a single gene disorder affecting the urinary tract is that of BEK. This would, furthermore, justify this as inclusion criteria for the NHSE PES case selection.[23,43]

ADPKD is the most common monogenic kidney disease, occurring in 1 in 500 to 1 in 1000 live births.[44] Early detection from before birth up to 15 years-of-age, however occurs in only 2%–5% of cases.[14] Although fetuses with ADPKD may present with BEK in-utero most affected individuals do not present with renal impairment for some years postnatally. Making a definitive diagnosis of ADPKD, based on finding variants of *PKD1* or *PKD2*, warrants careful follow up throughout childhood and beyond, especially given the increased risk of hypertension before adulthood.[45] *PKHD1* variant ARPKD is rarer, occurring in an estimated 1 in 20,000 live births.[46] There is a clear significant risk of perinatal demise when fetal kidneys are enlarged of more than four standard deviations associated with oligohydramnios leading to pulmonary hypoplasia.[47] The prenatal phenotypes of both ADPKD and ARPKD are similar, that is, BEKs identified on ultrasound, therefore genetic testing and obtaining a

TABLE 1 Characteristics of the studies included in the final meta-analysis reporting on the diagnostic yield of next generation sequencing in prenatally diagnosed urinary tract malformations with negative chromosomal microarray or karyotype.

Study	Next generation sequencing approach and variant filtering pipeline	Number of urinary tract anomalies		
		All urinary tract	Isolated	Multi-system
Lei et al.[37]	Proband NEXTflex™ Rapid DNA Sequencing Kit (5144-02) HiSeq2500 sequencer, version 3, Illumina	30	21	9
Zhou et al.[41]	Trio AgilentSureSelect QXT ALL Human Exon V6 kit. Illumina Hiseq 2500	41	41	0
Deng et al.[34]	Trio WES "Routine Operation." Illumina HiSeq2500	19	13	6
Chen et al.[32]	Trio SolPure Blood DNA kit. 4000 disease-related genes. NextSeq500	7	6	1
Corsten-Janssen et al.[33]	SureSelect Human All Exon V6. Illumina NextSeq500 Filtered with Alissa NGS-Bench Lab software—virtual panel of ~3850 genes	5	0	5
Marangoni et al.[38]	Trio KAPA HyperPrep/HyperPlus Library Preparation Kit and SeqCap EZ Choice XL Probes. Illumina HiSeq 1500/NovaSeq 6000 *in-silico* panel of 1273 genes	34	12	22
Meier et al.[39]	Trio Agilent SureSelect^{XT} Library Prep Kit. Agilent SureSelect^{XT} Human All Exon V6. HiSeq 2500 or HiSeq 4000 platform	7	1	6
Boissel et al.[31]	Agilent SureSelect (V4 or V5) exome capture kit. 100bp paired-end sequencing on the Illumina HiSeq (2000 or 2500). Filtered for coverage ≥10×	40	14	26
Greenbaum et al.[35]	Majority Trio. WES using Illumina platform. Filtered out low quality reads and artifacts.	18	3	15
Becher et al.[30]	Trio WES KAPA HTP library kit. SeqCap EZ MedExome Plus Illumina NextSeq 500. Ingenuity Variant Analysis	8	4	4
Petrovski et al.[40]	KAPA Biosystem's library preparation kits, and whole-exome capture was done with Nimblegen SeqCap EZ version 3.0 rapid or Nimblegen SeqC Illumina HiSeq 2500ap EZ version 4	25	13	12
Lord et al.[21]	Agilent SureSelect XT Human All Exon V5 Plus with custom ELID#0337431 Illumina HiSeq 2500). Modified list of genes associated with developmental disorder.	126	35	91
NHS England North Thames[22]	Twist Human comprehensive exome capture kit. Fetal anomaly gene panel V1.92 panelapp. Illuminia NGS platform x20 depth Focus on panel of 1205 genes (Genomics England PanelApp	35	6	29
Kuchinska Chanwan et al.[36]	Oligonucleotide array platform CytoSure Constitutional v3 (8 × 60 k). Resolution of 120kb. Novaseq6000 using sureselect human all exon v.6	14	5	9
Total		409	174	235

family pedigree is imperative in making a definitive diagnosis,[48] planning the course of the pregnancy and determining risk of recurrence. Under 10% of cases of ADPKD arise from *de novo* mutations[49] and 25% of patients are diagnosed without a knowledge of family history.[50,51] Our current analysis confirms that fetal BEK can also occur in the presence of heterozygous *HNF1B* sequence variants. It confirms an earlier report that this gene is a common cause of BEK detected before birth.[6] The diagnosis is an important one, not least because of the propensity for affected children to develop kidney electrolyte wasting in the teenage years, and diabetes mellitus through their life course.[15,52]

Other sub-categories of UTM had a modest yield. For instance, isolated kidney dysplasia (not manifesting as BEK) had a yield of 1%. Indeed, a recent consensus statement on kidney dysplasia that is not associated with BOO did not recommend prenatal genetic testing unless in a syndromic case and/or with BEK or amniotic fluid anomalies.[5] Isolated kidney agenesis also showed a low yield of 2%. One unilateral case was associated with biallelic variants of *FRAS1*, a gene encoding an extracellular matrix protein first found to be mutated in the multi-organ Fraser syndrome.[53] Another agenesis case, this time bilateral, carried a heterozygous variant in *GREB1L*, a gene involved in retinoic acid signaling and already associated with kidney agenesis.[54] Determining the prognosis and outcome of the pregnancy for UTM anomalies outside of BEK therefore appears dependant on deep phenotyping rather than determining a genetic cause. It is interesting that PES uncovered at least 26 different syndromes with a wide spectrum of genes and phenotypes, many of which would not typically present to pediatric nephrology services, meaning that these cases may be terminated or die in utero or their care is managed in specific metabolic, clinical genetics or rare disease clinics.

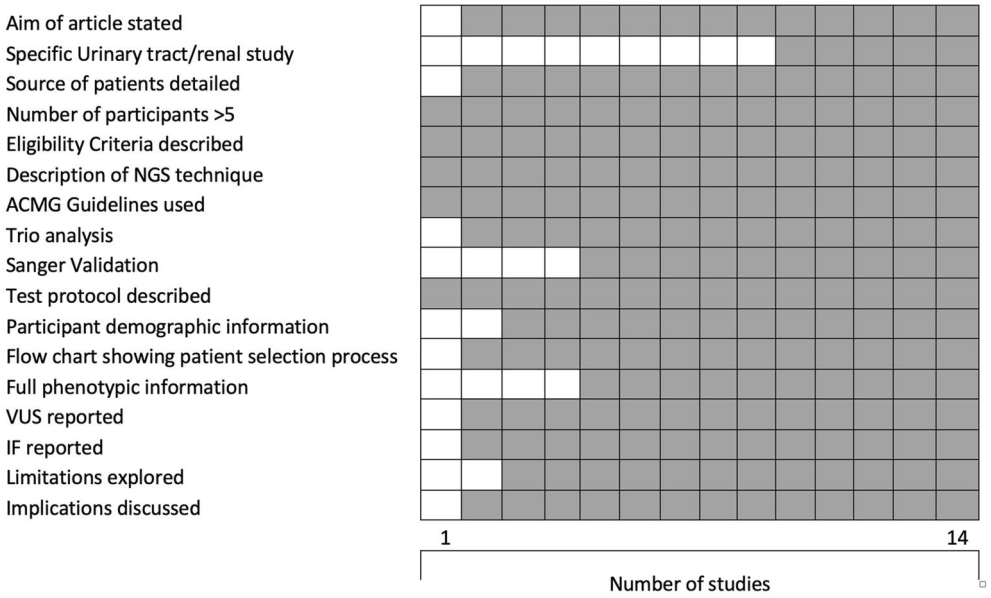

FIGURE 2 Quality assessment of the 14 studies included in this systematic review using a modified Standards for Reporting of Diagnostic Accuracy (STARD) criteria. ACMG, American College of Medical Genetics and Genomics; IF, incidental finding; VUS, variant of unknown significance.

TABLE 2 Table showing the incremental yield for urinary tract anomaly sub-group analyses.

Phenotypic subgroup	Incremental yield [95% CI]	Heterogeneity (I^2)
All cases	26% [95% CI, 16%–37%]	84%
Isolated urinary tract	16% [95% CI, 6%–26%]	70%
Multisystem anomalies	32% [95% CI, 18%–46%]	78%
Isolated bilateral echogenic kidneys	51% [95% CI, 27%–75%]	34%
Isolated cases (non-hyperechogenic kidneys)	8% [95% CI, 0%–16%]	53%
Isolated renal dysplasia	1% [95% CI, −5%–7%]	0%
Isolated renal agenesis	2% [95% CI, −12%–17%]	0%

There were a total of 20 cases of isolated lower UTMs included of which none received a diagnosis. However, when cases of lower UTM with additional anomalies were considered, there were two cases associated with pathogenic variants in the *ACTA2* and *ACTG2* genes, which encode smooth muscle proteins. Such pathogenic variants are well recognized etiologies of monogenic failure of bladder emptying in the absence of a true obstruction.[7]

Of the 61 multisystem cases (from the North Thames cases and literature search) which reached a diagnosis, the most common associated anatomical subgroup was that of the central nervous system (CNS) in $n = 31$ (51%) cases. Of the CNS anomalies, the occipital encephalocele was the most commonly encountered with eight cases. An occipital encephalocele in association with renal findings, generally bilateral cystic kidneys, may be indicative of Meckel Gruber syndrome, a lethal ciliopathy[55] and within our cohort, eight cases (87.5%) had pathogenic variants in genes associated with Meckel Gruber.

To our knowledge this is the first meta-analysis assessing the incremental yield of PES for UTMs, strengthened by the addition of unpublished data from prospective cohort studies. There is also strength in noting the variant filtering pipelines associated with the studies included. Exome sequencing has a straightforward workflow, and it is the analysis pipeline where labs will differ, and this will ultimately affect their yield. All studies included gave a description of the pathway used, which is useful for comparison, and this was reflected in the STARD quality assessment. The main limitation of this study is the low number and high heterogeneity of cases. This is partly due to PES being an emerging technology and a low tendency to opt for PES in the presence of an isolated UTM other than BEK. UTM in itself represents a wide spectrum of disorders with variable phenotypic presentations and underlying pathologies; hence, there is limited benefit to grouping them together. There is currently no universally agreed upon classification system for CAKUT or prenatal UTMs.[12,29] Older anatomically based classification systems of

prenatally identified UTMs have utility but obvious limitations in terms of identifying specific diagnoses. Clinicians are now beginning to categorize UTMs as genetic or non-genetic,[13] and future classifications of UTMs, as will be true in other organ systems, are sure to be classified by the disorders as defined by their underlying genetic etiologies. The most significant study limitation as evident from the emerging dominant subgroup of BEKs, is that of selection bias of cases within all studies, including the NHSE cohort, hence the incremental yield of non-BEKs should be interpreted with caution as it represents a potential under-representation as such cases may not have been selected for PES in the first instance.

5 | CONCLUSION

There was a notable incremental genetic diagnostic yield when PES was applied to multisystem UTMs and BEKs (51%). There was a modest incremental yield when this technique was used for UTMs other than BEKs (8%). This should be considered when offering next-generation sequencing in resource limited settings.

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CONFLICT OF INTEREST STATEMENT

FM and KR received funding from Randox for a separate study with no involvement from Randox in this study.

DATA AVAILABILITY STATEMENT

The completed dataset is available from the corresponding author on request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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