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Genomic testing in pediatric urology: Implications for diagnosis and management

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Summary

Genomic medicine is becoming increasingly relevant to pediatric urology. Developing an understanding of which children might benefit from genomic testing and how genomic results might impact clinical decision-making will become a necessary skill in the next few years. A genetic diagnosis can provide certainty, prompt screening of other organ systems, guide treatment and surveillance, enable testing of family members and inform reproductive counselling. In this review, we provide an overview of several monogenic conditions that might be encountered in the pediatric urology clinic and guidance on when to refer for genomic testing. We discuss monogenic congenital uropathies and how knowledge of the genetic basis of these conditions has improved understanding of disease pathophysiology. We summarise recommendations for genomic testing in pediatric stone formers, of whom around 20% have a monogenic cause, and show how this can facilitate access to targeted therapies (e.g. primary hyperoxaluria type 1). Finally, we review how genotype-phenotype correlations can be used to guide risk stratification, surveillance protocols and screening of other organ systems in children at risk of Wilms tumour.

Introduction

Genomic medicine is now embedded in pediatric practice, propelled by falling costs and wider access to next-generation sequencing (NGS). While genomic testing was once confined to targeted single-gene Sanger sequencing, clinicians can now access multi-gene panels, whole exome sequencing (WES), and increasingly, whole genome sequencing (WGS). WGS captures single-nucleotide/indel and structural (>50 base pairs) variation across both coding and non-coding regions, allowing the application of expertly curated 'virtual' gene panels that are continuously updated as new gene-disease associations emerge [1]. These technologies are transforming diagnostic and therapeutic pathways, especially in pediatrics where ~80% of rare diseases have a genetic basis. Large-scale initiatives, such as the Generation Study which aims to undertake WGS in 100,000 newborns, are redefining population screening and have the potential to detect ~200 rare conditions, including predisposition to Wilms tumour and primary hyperoxaluria [2].

For pediatric urologists, genomics is becoming increasingly relevant. Children with congenital anomalies of the kidneys and urinary tract (CAKUT) or unexplained bladder dysfunction may have an underlying genetic aetiology. Over 50 monogenic causes of CAKUT are known, explaining ~5-20% of cases, with the highest diagnostic yield seen in those with kidney anomalies (renal agenesis, hypodysplasia or cystic dysplasia), a family history and/or extra-renal manifestations [3]. Furthermore, kidney stones may be the first presentation of an inherited metabolic disorder in children [4], and 10-15% of children with Wilms tumour have a genetic predisposition syndrome [5]. Timely identification can inform prognosis and management, prompt surveillance of other organ systems and support counselling regarding recurrence risk and screening of family members.

Here, we provide an overview of monogenic urinary tract disorders encountered in pediatric urology (Table 1), outline who to refer for genomic testing and highlight how a molecular diagnosis can impact patient care.

Upper tract dilatation

Children with upper tract dilatation (hydronephrosis, ureteric dilatation or both) are among the most common referrals to pediatric urology to investigate for pelvi-ureteric junction obstruction (PUJO), vesico-ureteric junction obstruction (VUJO), vesico-ureteral reflux (VUR) or primary megaureter. These anomalies may occur in isolation or within the broader CAKUT spectrum, with PUJO the leading cause of antenatal hydronephrosis [6]. Clinical presentation is variable: Some children develop urinary tract infection (UTI), flank pain or hematuria; others are asymptomatic, with abnormalities detected on antenatal imaging. Impaired urinary outflow can result in progressive loss of kidney function, increased UTI susceptibility and urolithiasis [7].

Although most cases are sporadic, a subset of congenital obstructive uropathy is monogenic. A recent exome sequencing study in >700 individuals with upper tract obstructive uropathy (including PUJO and VUJO) identified a monogenic cause in 10% [8]. Pathogenic variants in *HNF1B* (hepatocyte nuclear factor 1 beta), *TNXB* (tenascin XB) and *TBX18* (T box transcription factor 18) were identified most frequently and those with extra-renal features were more likely to receive a genetic diagnosis (odds ratio ~4) [8]. Heterozygous *HNF1B* variants are the commonest cause of CAKUT and can present with bilateral hyperechogenic kidneys on antenatal ultrasound; cystic, horseshoe, or duplex kidneys; hydronephrosis; and collecting system anomalies [9]. As in other CAKUT conditions, phenotype alone rarely predicts genotype, supporting WES/WGS to evaluate a broad set of causal genes.

Heterozygous variants in *TBX18* have been reported in patients with PUJO, VUJO, primary megaureter, hydronephrosis and kidney anomalies; *TBX18* is a transcriptional repressor essential for ureteric development [8,10]. In model systems, *Tbx18* regulates the condensation of undifferentiated ureteral mesenchyme around the distal ureter stalk, creating a permissive niche for smooth muscle and urothelial differentiation while repressing metanephric mesenchyme gene expression [10–12]. Null $Tbx18^{-/-}$ mice die shortly after birth, with failed ureteric mesenchymal differentiation and develop VUJO, hydroureter and hydronephrosis [11]. By contrast, $Tbx18^{+/-}$ mice show an attenuated phenotype with mild proximal hydroureter [10]. These animal models suggest that impaired ureteric smooth muscle development (which is essential for ureteric peristalsis) contribute to human obstructive phenotypes. Beyond the urinary tract, promoter variants in *Tbx18* have been associated with congenital heart defects, suggesting a broader embryonic development role though such multisystem effects have not been observed in humans [13].

Rare, heterozygous missense variants in another regulator of smooth muscle differentiation, teashirt zinc finger homeobox 3 (*TSHZ3),* have also been reported in patients with hydronephrosis and hydroureter [14]. *Tshz3* had long been a candidate CAKUT gene: null mutant mice develop PUJO with defective smooth muscle differentiation and absent peristalsis in the proximal ureter [15]. However, incomplete penetrance and phenotypic variability mean further studies are required before definitive causality can be established.

TNXB, an extracellular matrix protein expressed in vesico-ureteric junction urothelium, has been associated with VUR and rare heterozygous variants are described in familial and sporadic VUR as well as congenital obstructive uropathy [8,16,17]. Individuals with heterozygous *TNXB* variants often report joint hypermobility (biallelic variants cause Ehlers-Danlos syndrome) and it is proposed TNXB may contribute to the tensile forces

that close the vesico-ureteric junction during voiding, with defects leading to reflux and obstruction.

While monogenic causes of congenital obstructive uropathy are rare, genomic testing should be considered in the context of associated kidney anomalies, a family history, consanguinity and/or syndromic features. A genetic diagnosis can provide clarity, prompt testing of other organ systems and enables screening of family members. Looking forward, it would be interesting to investigate whether having a particular genotype impacts surgical outcome; for example, can an inherited developmental smooth muscle defect predict poor peristaltic recovery after pyeloplasty or ureteric reimplantation?

Prune Belly Syndrome and megacystis

Prune Belly Syndrome (PBS), also known as Eagle-Barrett syndrome, is defined by a triad: (1) deficient abdominal muscles, (2) megacystis and megaureters and (3) bilateral undescended testes in males. It is a rare developmental mesodermal defect affecting both smooth muscle and connective tissue of the lower urinary tract and abdominal wall. Biallelic variants in *CHRM3* (encoding the M3 muscarinic acetylcholine receptor) have been reported in consanguineous families with 'prune-belly like' syndrome [18]. CHRM3 is critical for detrusor contraction; loss of function causes atony and systemic autonomic symptoms such as non-reactive dilated pupils [19]. Another subgroup of PBS overlaps with the Megacystis-Microcolon Intestinal Hypoperistalsis Syndrome (MMIHS), a prenatal-onset disorder with high mortality. MMIHS is caused by heterozygous (often *de novo*) variants in genes regulating smooth muscle contractility, including *ACTG2* (gamma-2 smooth muscle actin) [20], *MYH11* (smooth muscle myosin heavy chain) [21], *MYLK* (myosin light chain kinase) [22], *MYL9* (myosin light chain 9) [23] and *LMOD1* (leiomodin 1) [24]. These disrupt the actin-myosin apparatus,

leading to an inert, dilated bladder and gut. *ACTG2* variants have been reported to account for over 85% of MMIHS cases with congenital megacystis [25]. Rare variants in other smooth muscle and connective tissue-regulating genes such as *ACTA2* (alpha smooth muscle actin), *FLNA* (filamin A) and *MYOCD* (myocardin) have also been linked to PBS/megacystis phenotypes [26–29].

Management of PBS remains largely surgical and supportive and routine genomic testing is not currently recommended, although in specific cases genetic testing can be considered based on clinical clues. If the individual has intestinal pseudo-obstruction, a targeted gene panel for visceral myopathy (including *ACTG2*, *MYH11*, *LMOD1*, *MYLK, MYL9*) may differentiate MMIHS from classical PBS. Similarly, in an infant with prune belly findings plus autonomic anomalies like fixed dilated pupils, *CHRM3* should be tested. In families with multiple affected males, X-linked inheritance (e.g. *FLNA*) must be considered. A molecular diagnosis can also anticipate extra-urogenital issues: e.g. cardiac and neurological anomalies in *FLNA* patients and thoracic aortic aneurysms and dissections in those with pathogenic *ACTA2* variants [30,31].

Bladder Exstrophy–Epispadias Complex

The bladder exstrophy–epispadias complex (BEEC) represents a spectrum of lower abdominal wall and pelvic defects. Classic bladder exstrophy (CBE) involves an open bladder on the abdominal surface with an epispadias (split urethra); more severe variants include cloacal exstrophy where bladder is combined with bowel exstrophy and often spinal defects. Familial clustering and twin concordance suggest a heritable component [32,33]. The most common finding has been recurrent microduplications at chromosome 22q11.21 (overlapping the *DiGeorge* syndrome region), found in approximately 3% of CBE patients [34,35], although incomplete penetrance of this variant is seen. Rare variants in *SLC20A1* (encoding a phosphate transporter) have

also been identified [36], however the most robust genetic associations have been identified using genome-wide association studies (GWAS) implicating the pioneer transcription factor *ISL1* [37,38]. This reinforces a multifactorial model where maternal environment and polygenic susceptibility interact to perturb mesodermal development.

In practice, genomic testing for bladder exstrophy is mostly undertaken on a research basis. Risk of recurrence in future children is low (0.3-2.3%) unless an inherited cause is identified [39]. Detection of the 22q11.21 microduplication should prompt screening for hearing loss, neurodevelopmental delay and/or cardiac anomalies. If a *de novo* pathogenic *SLC20A1* variant is found, recurrence risk for siblings is low, whereas the affected individual has a 50% chance of transmitting it to their children. At present, a molecular diagnosis in BEEC does not change the surgical management, which remains focused on anatomical reconstruction and protecting renal function.

Posterior urethral valves and fetal lower urinary tract obstruction

Posterior urethral valves (PUV) is the commonest cause of kidney failure in childhood. Although largely considered a sporadic developmental abnormality, recent research points to a complex genetic architecture. Rare variants in the transcription factor *BNC2* (basonuclin-2) and *FLNA* have been reported in families with lower urinary tract obstruction (LUTO), PBS and PUV [28,40]. In addition, rare copy number variants (CNVs) and microduplications are enriched in PUV [41,42] and genome-wide association studies have identified non-coding variants implicating the transcription factor *TBX5* and planar cell polarity gene *PTK7* as PUV susceptibility genes [43].

From a clinical standpoint, genomic testing in boys with PUV is not routinely performed, although there is a need to improve risk stratification in this cohort as prognostic biomarkers have yet to advance beyond nadir creatinine [44]. *CDH12* (cadherin-12), a

cell-adhesion molecule, has been proposed as a candidate gene for kidney injury in PUV but further replication is required [45]. A pragmatic approach may be to undertake genomic testing in patients with associated kidney anomalies or a family history of LUTO.

Neurogenic bladder (Congenital neuropathic bladder dysfunction)

'Neurogenic bladder' refers to bladder dysfunction due to a central or peripheral lesion or neuropathy, most commonly due to spinal dysraphism. This multifactorial congenital neural tube defect (NTD) is linked to folic acid deficiency and genomic testing is generally not indicated beyond investigation of known syndromic associations.

Of interest to pediatric urologists is non-neurogenic lower urinary tract dysfunction, a diagnosis that refers to children who manifest the urodynamic profile and renal risk seen in spinal dysraphism of high storage/voiding pressures without an identifiable nervous system lesion. Most cases have no defined genetic etiology and genomic testing is not done routinely. A handful of cases have single-gene defects: Biallelic *CHRNA3* (cholinergic receptor nicotinic alpha 3) variants cause congenital autonomic neuropathy with a neurogenic-like bladder [46]; homozygous *ELP1*/*IKBKAP* variants in familial dysautonomia (Ashkenazi founder population) with autonomic and sphincter involvement [47]; and heterozygous *HLXB9/MNX1* mutations in Currarino triad, which can entail neurogenic bowel and bladder [48].

In children with severe bladder dysfunction and normal spinal imaging, a stepwise approach is reasonable: exclude occult dysraphism and cerebral causes, then consider genomic testing for targeted dysautonomia/neuropathy genes or wider syndromes if other organ systems affected, consanguinity, or family history. At present, a molecular diagnosis rarely changes urological intervention but aligns expectations (often life-long

management) and enables accurate family counselling (typically *de novo* or autosomal recessive with 25% sibling risk when biallelic).

Urofacial (Ochoa) Syndrome

Urofacial syndrome (UFS) is a very rare autosomal recessive disorder combining a characteristic 'inverted' facial expression (appearing to grimace when attempting to smile) with severe functional bladder dysfunction. Children with UFS lack any physical blockage in the urethra, but cannot coordinate detrusor contraction with sphincter relaxation, leading to high-pressure urinary retention, VUR and kidney damage. Biallelic variants in *HPSE2* (heparanase-2) and *LRIG2* (leucine-rich repeats and Ig-like domains 2) are responsible for most cases [49,50], with these genes crucial for the development of the bladder's peripheral nerves. Mice lacking *Lrig2* or *Hpse2* exhibit abnormally-dense innervation in the bladder wall but sparse innervation at the outlet and a neuropathic bladder [51]. When UFS is clinically suspected, genomic testing should be undertaken, and molecular confirmation prompts early bladder management.

Metabolic stone disease

The prevalence of urolithiasis has demonstrated a significant upward trend over recent decades [52]. Most pediatric cases are linked to underlying metabolic abnormalities, predisposing children to kidney stones, nephrocalcinosis, chronic kidney disease, recurrent UTI, and impacting growth and development [52]. Nearly half of affected children develop a symptomatic recurrence within three years [53]. Over 35 genes have been associated with kidney stone risk and a monogenic cause can be identified in ~20% of early-onset stone formers (<25 years) [52,54,55]. Early diagnosis can guide condition-specific therapy (e.g. RNA interference (RNAi) therapy in primary hyperoxaluria) and can inform transplant decisions where living related kidney donation is being considered.

Cystinuria underlies 6-8% of kidney stone disease in the pediatric population, often presenting in adolescence [52]. It results from biallelic loss-of-function variants in the cystine transporter subunits *SLC3A1* (type AA) and *SLC7A9* (type BB), leading to defective proximal tubular reabsorption of cystine (as well as ornithine, lysine and arginine) and precipitation of insoluble cystine stones [56]. Diagnosis is typically made in the presence of increased 24-hour urinary cystine excretion (>400 mg/d) and characteristic hexagonal crystals on urine microscopy. Although genomic testing is not mandatory, it can clarify diagnosis in atypical presentations and facilitate timely initiation of cystine-binding therapy (e.g. tiopronin and D-penicillamine) in cases refractory to hydration, low-sodium diet and urinary alkalinisation with potassium citrate [56].

Biallelic loss-of-function variants in genes involved in vitamin D metabolism (*CYP24A1*), proximal tubule phosphate transport (*SLC34A1*, *SLC34A3*) or paracellular calcium and magnesium reabsorption (*CLDN16*, *CLDN19*) can also result in hypercalciuria, nephrocalcinosis, calcium oxalate/phosphate stones and a variable phenotypic spectrum including hypercalcaemia (*CYP24A1, SLC34A1*), hypophosphatemia and rickets (*SLC34A1*/*A3*), hypomagnesemia (*CLDN16/19*), polyuria, dehydration, failure to thrive and chronic kidney disease (CKD) [52]. Interestingly, rare, monoallelic variants in these genes are also associated with kidney stones implicating a possible allele-dosage mechanism [52,57].

Distal renal tubular acidosis (dRTA; *ATP6V0A4, ATP6V1B1, SLC4A1*) and X-linked recessive Dent's disease (*CLCN5*, *OCRL*) can also present with hypercalciuria, nephrocalcinosis and calcium phosphate stones; dRTA usually in association with metabolic acidosis and sensorineural hearing loss and Dent's with low-molecular-weight proteinuria and progressive CKD in males [52]. Finally, adenine phosphoribosyltransferase (*APRT*) deficiency, an autosomal recessive disorder of

adenine metabolism leading to 2,8-dihydroxyadenuria (DHA), results in radiolucent kidney stones which can present with acute kidney injury in children due to bilateral obstruction [58]. Treatment with xanthine oxidase inhibitors (e.g. allopurinol and febuxostat) can improve kidney function [59].

Primary hyperoxaluria (PH) exemplifies how genomic testing can directly inform management. This rare, autosomal recessive condition is usually caused by pathogenic variants in the hepatic enzyme alanine-glyoxylate aminotransferase (*AGXT;* PH type 1), leading to defective glyoxalate metabolism and excessive urinary oxalate resulting in nephrocalcinosis, calcium oxalate stones and kidney failure [60]. PH2 (*GRHPR*) and PH3 (*HOGA1*) are less common. Genomic testing can identify missense *AGXT* variants known to be pyridoxine-responsive for targeted vitamin B_6 supplementation [60] and a confirmed molecular diagnosis enables access to new RNAi therapies (lumasiran, nedosiran) which lower urinary oxalate excretion. Initial data suggests these RNAi therapies may reduce kidney stone recurrence and slow down progression of CKD but longer-term studies are needed to determine their true clinical impact [60].

At present, there is no clear guidance on which children with urolithiasis should undergo genomic testing and when in the clinical pathway that should occur. The European Association of Urology (EAU, 2025) [61] and American Urological Association (AUA, 2016) [62] recommend that all pediatric stone formers should undergo stone analysis and metabolic evaluation, with metabolic risk factors identified in up to 89% of children [4]. Ideally two 24-hour urine collections for total volume, pH, calcium, oxalate, urate, citrate, cystine and electrolytes should be performed with blood tests for calcium, phosphate, bicarbonate, magnesium, urate, renal profile and if hypercalcemia is present, parathyroid hormone (PTH) and 25-hydroxy vitamin D. Spot urine samples can be used in children who are not toilet-trained.

Although children are recognised as a high-risk group for recurrence, these guidelines do not explicitly address genomic testing. Several groups have however proposed that genomic testing should be considered in children and young people <25 years alongside standard metabolic evaluation [63,64]. Figure 1 summarises how genomic testing could be integrated into the management of children with kidney stones, although further work is needed to define optimal patient selection. Nonetheless, genomic testing offers significant potential for improving understanding of disease mechanisms and enabling access to diseases-specific treatments.

Wilms tumour predisposition syndromes

Several congenital syndromes confer an increased risk of Wilms tumour (WT; nephroblastoma) and identifying a (likely) pathogenic germline variant can directly inform screening and surveillance. WT is the most common kidney malignancy in children, characterized by persistent foci of embryonic kidney cells (nephrogenic rests) that transform to WT through a somatic 'second hit'. Although only ~2% of affected children have a positive family history, ~10–15% harbour a germline pathogenic variant in one of >20 WT predisposition genes [5,65]. These children tend to present earlier (<2 years), with bilateral disease and/or have associated syndromic features [5].

Heterozygous, usually *de novo*, variants in Wilms tumour 1 *(WT1)*, a zinc-finger transcription factor essential for urogenital development, account for 1-5% of WT [66]. *WT1*-disorders exhibit distinct genotype-phenotype correlations with truncating variants (nonsense, frameshift, splice-site) associated with the highest WT risk (~80%). Affected males frequently have disordered testicular development (hypospadias, cryptorchidism, ambiguous genitalia) and an elevated risk of gonadoblastoma [66]. Approximately 20% will have additional kidney or urinary tract malformations and some develop proteinuric glomerulopathy in adolescence. Missense variants affecting DNA-binding domains (exons 8/9) can cause diffuse mesangial sclerosis with early-onset steroid-resistant

nephrotic syndrome and rapid progression to kidney failure – historically termed Denys-Drash syndrome [66]. The mutant WT1 protein exhibits a dominant negative effect which likely explains the more severe phenotype relative to truncating variants that lead to haploinsufficiency [66]. These children carry an increased WT risk (~50%) and may have associated genitourinary anomalies such as duplex, horseshoe or ectopic kidneys, VUR or PUJO [66]. Intron 9 splice-site variants typically present a lower risk for WT (~2%), but the highest risk of gonadoblastoma in males with complete gonadal dysgenesis (formerly known as Frasier syndrome) [66]. Whole-gene *WT1* deletions - as seen in WAGR syndrome (Wilms tumour, aniridia, genitourinary anomalies, intellectual disability) involving 11p13 with contiguous *PAX6* loss—also carry a high WT risk (~50%) [5].

Children with congenital overgrowth syndromes are similarly predisposed to WT, notably Beckwith–Wiedemann syndrome (BWS), Perlman syndrome (*DIS3L2*), and Simpson–Golabi–Behmel syndrome (*GPC3*). BWS is an imprinting disorder of 11p15 characterized by activation of the normally silent maternal insulin-like growth factor 2 (*IGF2)* allele; IGF2 signalling is frequently upregulated in both overgrowth syndromes and WT [5,67]. Clinically, BWS features lateralized overgrowth, macroglossia, exomphalos, neonatal hypoglycaemia and an elevated embryonal tumour risk (~8%) [67]. WT risk varies by molecular subtype, with highest risk in those with a gain of methylation at the maternal imprinting centre 1 (IC1) allele (~20%) and segmental paternal uniparental isodisomy (upd(11)pat; 8%) where a child inherits two identical duplicated chromosomal segments from their father [67]. Renal manifestations can also include corticomedullary cysts, hypercalciuria, and nephrolithiasis [67].

Surveillance recommendations are risk stratified. European guidance advises abdominal ultrasound every 3 months for children with an estimated WT risk >5% until the age of 7 years, by which time >95% of WTs have presented [68]. In North America,

surveillance is offered where risk is >1% [69]. Ultrasound screening is not generally recommended for low-risk groups (e.g. intron 9 *WT1* splice variants; maternal IC2 loss of methylation in BWS). Detailed gene- and syndrome-specific surveillance protocols have been published recently [68,69].

A WT predisposition syndrome should be suspected in any child with bilateral or early-onset WT (<2 years), particularly when accompanied by disorders of testicular development (differences/disorders of sex development or complete gonadal dysgenesis), congenital kidney and urinary tract anomalies, gonadoblastoma, or an overgrowth phenotype [70]. Early recognition permits timely referral to clinical genetics for targeted testing: sequencing and copy-number analysis of *WT1* and other predisposition genes (e.g. *REST*, *TRIM28*, *DIS3L2*, *CTR9*) and DNA methylation and copy-number analysis of 11p15. A molecular diagnosis facilitates entry into tailored tumour-surveillance programmes and guides longitudinal management, including screening for proteinuria, hypertension and chronic kidney disease, as well as imaging for associated genitourinary anomalies.

Genomic testing in the clinic

Pediatric urologists are often the first point of contact for children and families with congenital urinary tract malformations, urolithiasis and WT. An awareness of the genetic basis of these conditions and maintaining a high level of vigilance can ensure that children get early referral and access to genomic testing. In the context of urinary tract malformations, the highest diagnostic yield is seen in children with kidney anomalies (agenesis, hypodysplasia or cystic dysplasia), a family history of congenital urinary tract malformations (often following an autosomal dominant inheritance pattern), consanguinity (increasing the likelihood of autosomal recessive disorders) and/or additional syndromic features such as neurodevelopmental disorders, hearing impairment, cardiac or skeletal anomalies (Box 1) [3]. Similarly, children with early-

onset, bilateral urolithiasis or WT and those with other organ system involvement are more likely to have an underlying genetic cause. Recognition of these features should prompt referral to clinical genetics or pediatric nephrology services for genomic testing, ideally within a multi-disciplinary setting.

A positive genetic result can provide clarity on diagnosis, allowing access to patient support groups, registries and clinical trials, provide prognostic information regarding risk of kidney failure and enable screening of other organ systems that may be affected. Families also benefit from clear information on inheritance patterns, enabling discussions with genetic counsellors around cascade testing in first-degree relatives, recurrence risk in future children and preimplantation genomic testing. In pediatric stone formers a molecular diagnosis of cystinuria or PH1 enables access to disease-specific therapies whereas knowledge of the underlying genetic basis of WT can inform screening and surveillance strategies.

Genomic testing is not without its challenges and variant interpretation must be undertaken according to strict international standards [71]. Pathogenic or likely pathogenic variants can be used to inform clinical, reproductive and/or life decisions and it is therefore critical to ensure any variant reported as disease-causing is done so with the utmost confidence. Variants of uncertain significance (VUS) are common, often require further investigation (e.g. segregation analysis, deeper phenotyping) and cannot be used for clinical decision-making. Furthermore, 1-2% of patients undergoing WES/WGS put themselves at risk of ‘secondary findings’, where variants are identified in ‘actionable’ genes not related to the condition being tested, commonly related to cardiovascular disease or cancer (including WT) [72]. The consent process should therefore include comprehensive discussions around uncertainty and potential for unexpected results.

Finally, access to genomic testing still varies significantly across healthcare systems with coverage often dependent on indication and insurer (or national health system) policies; high out-of-pocket costs, limited lab capacity and counselling infrastructure, and regulatory/reimbursement gaps which disproportionately restrict access in low- and middle-income settings, creating inequities despite falling sequencing prices. Ensuring equitable access to these technologies will be a key challenge for the genomic community going forward.

The future of genomics in pediatric urology

Genomic medicine is evolving beyond simple diagnostics. Population level newborn screening has the potential to identify babies at risk of WT and metabolic stone disease for early intervention and targeted surveillance [2]. Genomic risk scores, although at present largely research-based, can be used to stratify risk of progression of chronic kidney disease and urolithiasis, offering the potential to detect those at high risk of complications or recurrence for targeted follow up [73]. Future studies looking at surgical outcomes in patients with monogenic developmental smooth muscle disorders would be important to determine whether genomic testing in congenital obstructive uropathies has the potential to influence surgical decision-making. Finally, gene therapy has recently been shown to improve bladder emptying in a mouse model of urofacial syndrome, raising the exciting possibility of gene therapy for human congenital bladder disease in the future [74].

Conclusion

Genomic testing is becoming increasingly relevant in pediatric urology. Identification of children with potential monogenic urinary tract disorders can facilitate early referral for genomic testing, clarifying diagnoses and allowing access to targeted treatments. A fundamental understanding of how to interpret genomic results and their implications

for clinical decision-making will become essential. The challenge now lies in ensuring genomics is integrated effectively into routine clinical practice with robust evaluation of its impact on surgical outcomes in pediatric urology.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT-5 for rephrasing and editing to improve readability and make paragraphs more concise. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Conflict of interest statement

None.

Glossary of Terms:

Copy number variant (CNV) - A deletion or duplication of a segment of DNA (>50 base pairs) that alters the number of copies of a gene.

Next-generation sequencing (NGS) - high-throughput sequencing technology that performs massively parallel sequencing (reading millions to billions of fragments simultaneously) and encompasses targeted panels, whole-exome sequencing (WES) and whole-genome sequencing (WGS).

Whole exome sequencing (WES) - NGS approach that selectively captures and sequences the protein-coding regions (exons) of the genome - about 1–2% of DNA.

Whole genome sequencing (WGS) - NGS approach that sequences (nearly) all coding and non-coding DNA and can detect single-nucleotide, indel and structural variants.

RNA interference (RNAi) - Specially designed small interfering RNA (siRNA) is delivered to cells where it targets and degrades specific mRNA. Used therapeutically to reduce expression of a specific target gene and protein e.g. lumasiran.

Variant of uncertain significance (VUS) - A genetic variant for which there is insufficient evidence to classify it as either benign or pathogenic and further testing may be required. A VUS should not be used to inform clinical or reproductive decisions.

Figure 1. Proposed Algorithm for Genomic Testing in Children with Kidney Stones. Adapted from [64]. FHHNC, familial hypomagnesaemia with hypercalciuria and nephrocalcinosis.

Box 1. When to suspect a genetic diagnosis in the pediatric urology clinic

Family history of urinary tract malformations, stones or unexplained kidney failure

Consanguinity

Syndromic features (craniofacial, neurodevelopmental, cardiac, limb anomalies)

Unexplained bladder dysfunction with normal spinal imaging

Early-onset (< 25 years), bilateral or recurrent kidney stones

Early-onset (< 2 years) or bilateral Wilms tumour

Table 1. Overview of monogenic urinary tract disorders encountered in pediatric urology. AR, autosomal recessive; AD, autosomal dominant; CAKUT, congenital anomalies of the kidneys and urinary tract; CIC, clean intermittent catheterization; CNV, copy number variant; GWAS, genome-wide association study; MMIHS, Megacystis-Microcolon Intestinal Hypoperistalsis Syndrome; PUJO, pelvi-ureteric junction obstruction; RNAi, RNA interference; VUJO, vesico-ureteric junction obstruction; VUR, vesico-ureteric reflux; WES, whole exome sequencing; XLR, X-linked recessive.

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CONDITION	KEY GENES (INHERITANCE)	TESTING APPROACH	MANAGEMENT IMPLICATIONS
Upper tract dilatation: PUJO, VUJO, VUR, megaureter.	*HNF1B (AD)* *TBX18* (AD) *TNXB* (AD) *TSHZ3* (AD)	CAKUT gene panel (including CNVs) if associated kidney anomalies, extra-renal features, consanguinity or family history. *TNXB* if joint hypermobility and VUR.	Informs recurrence risk in future children, testing of relatives and screening for extra-renal manifestations (e.g. diabetes, genital anomalies, hyperuricemia in *HNF1B*-related disease).
Prune-Belly syndrome, megacystis and Megacystis-Microcolon intestinal hypoperistalsis syndrome (MMIHS)	*ACTA2* (AD) *ACTG2* (AR) *CHRM3* (AR) *FLNA* (XLR) *LMOD1* (AR) *MYH11* (AR) *MYL9* (AR) *MYLK* (AD) *MYOCD* (AD/AR)	Phenotype-driven testing: visceral smooth muscle (*ACTG2*, *MYH11*, *MYL9*, *LMOD1*, *MYLK*) panel if gastrointestinal involvement, *CHRM3* if autonomic features, *FLNA* if X-linked inheritance, *ACTA2* if patent ductus arteriosus or aortic aneurysm/dissection. Consider WES/CNV testing in syndromic cases.	If smooth muscle contractility gene affected, this may predict poor peristalsis and need for long-term parenteral nutrition (MMIHS). If *CHRM3* – focus on CIC as anti-cholinergics may be ineffective. If *FLNA*, investigate for associated skeletal/cardiac issues.
Bladder exstrophy-epispadias complex (BEEC)	22q11.21 microduplication *SLC20A1* (AD) Polygenic risk loci (*ISL1)*	Testing currently undertaken on a research basis. Chromosomal microarray for 22q11.21 microduplication.	22q11.21/DiGeorge syndrome prompts screening for hearing, neurodevelopmental delay and cardiac anomalies.
Posterior urethral valves (PUV) and congenital lower urinary tract obstruction	*BNC2* (AD) *FLNA* (XLR) Polygenic risk loci (*TBX5, PTK7*)	Routine genomic testing not currently indicated. Broad CAKUT gene panel (including CNVs) if family history of congenital lower urinary tract obstruction.	Standard of care remains surgical/supportive.
Neurogenic bladder (non-dysraphism)	*CHRNA3* (AR) *ELP1/IKBKAP* (AR) *HLXB9/MNX1* (AD)	If work-up shows no structural lesion, then a genetic cause can be considered but very rarely monogenic: *CHRNA3* if primary autonomic dysfunction, *ELP1* if familial dysautonomia, *HLXB9/MNX1* if anorectal malformation, sacral defect, presacral mass.	Directs care beyond urology: e.g. *ELP1* requires autonomic support measures. Standard of care remains long-term bladder management and renal protection.
Urofacial syndrome	*HPSE2 (AR)* *LRIG2* (AR)	Targeted gene panel if classic facies (grimacing on smiling) and neurogenic bladder.	Early CIC – surgical/supportive management of bladder dysfunction.
Metabolic stone disease	>35 genes identified	Nephrolithiasis/nephrocalcinosis gene panel if young onset (<25 years), bilateral, recurrent or family history.	Can allow access to disease-specific treatments e.g. RNAi therapy in primary hyperoxaluria type 1 (PH1)
Wilms tumour predisposition	*WT1* (AD) *TRIM28* (AD) *REST* (AD) 11p13 deletion 11p15 imprinting disorder	Targeted gene panel if early onset (<2 years), bilateral or family history. Chromosomal microarray for 11p13 deletion if aniridia, intellectual disability, genitourinary anomalies (WAGR syndrome). 11p15 DNA methylation analysis if overgrowth/Beckwith-Wiedemann syndrome.	Genotype guides surveillance strategy, gonadal management and screening for proteinuria and kidney disease.

Initial Evaluation
- Medical and nutritional history
- Medication history
- Urinalysis and microscopy
- Blood tests: calcium, phosphate, magnesium, urate, bicarbonate, PTH, 25-hydroxy vitamin D

Stone Analysis

Metabolic Evaluation
24-hour urine collection (two consecutive samples) measuring:
- pH, volume, osmolality, creatinine
- calcium, oxalate, urate, citrate, cystine
- sodium, potassium, magnesium, phosphate

Spot urine in children not toilet trained

Consider genomic testing if:
- < 25 years old
- Positive family history
- Bilateral or recurrent kidney stones
- 24hr urine: hypercalciuria, hyperoxaluria, cystinuria

If uncertain which gene panel to send refer to pediatric nephrology or clinical genetics

Differential diagnoses:
- Hypercalciuria with hypercalcemia: infantile hypercalcemia (*CYP24A1)*
- Hypercalciuria with normocalcemia: distal renal tubular acidosis, FHHNC (*CLDN16*, *CLDN19)*
- Hypercalciuria with hypophosphatemia: *SLC34A1*, *SLC34A3,* Dent's disease/Lowe syndrome (*CLCN5*, *OCRL)*
- Hyperoxaluria: PH1 (*AGXT),* PH2 (*GRHPR),* PH3 (*HOGA1)*
- Cystinuria: *SLC3A1*, *SLC7A9*

Refer to multidisciplinary renal genetics clinic:
- Variant interpretation
- Screening for other syndromic features
- Family counselling
- Cascade testing

Management:
- Lifestyle & diet: hydration, salt restriction, normal calcium intake
- Pharmacologic therapy: potassium citrate, allopurinol (APRT deficiency), tiopronin (cystinuria)
- RNA interference therapy for PH1 (lumasiran/nedosiran)
- Targeted follow-up