Published in final edited form as:

BJU Int. 2019 January ; 123(1): 130–139. doi:10.1111/bju.14524.

Phenotypic Severity Scoring System and Categorization for Prune Belly Syndrome: Application to a Pilot Cohort of 50 Living Patients

DG Wong¹, MK Arevalo^{1,*}, NM Passoni^{1,4}, NS Iqbal¹, T Jascur¹, AJ Kern², EJ Sanchez^{1,4}, A Satyanarayan^{1,4}, J Gattineni³, LA Baker^{1,4}

¹Department of Urology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390, USA

²Pediatric Urology, Anne Arundel Medical Center, 2001 Medical Pkwy, Annapolis, MD 21401, USA

³Pediatric Nephrology, Children's Health Dallas, 1935 Medical District Dr, Suite B5238, Dallas, TX 75235, USA

⁴Pediatric Urology, Children's Health Dallas, 2350 N. Stemmons Freeway, Suite F4300, Dallas, TX 75207, USA

Abstract

OBJECTIVE: To design a novel system of scoring Prune Belly Syndrome (PBS) phenotypic severity at any presenting age and apply it to a large pilot cohort.

PATIENTS AND METHODS: From 2000-2017, PBS patients were recruited to our prospective PBS study and medical records were cross-sectionally analyzed, generating individualized RUBACE scores. We designed the pragmatic RUBACE scoring system based on six sub-scores (R: renal, U: ureter, B: bladder/outlet, A: abdominal wall, C: cryptorchidism, E: extra-genitourinary, generating the acronym RUBACE), yielding a potential summed score of 0-31. The E score was utilized to segregate syndromic PBS and PBS-plus variants. The cohort was scored per classic Woodard criteria and RUBACE scores compared to Woodard category.

RESULTS: 48 males and two females had mean RUBACE scores of 13.8 (range: 8-25) at a mean age of 7.3 years. Segregated by phenotypic categories, there were 39 isolated PBS (76%), 6 syndromic PBS (12%) and 5 PBS-plus (10%) cases. Mean RUBACE scores for Woodard categories 1, 2 and 3 were 20.5 (n=8), 13.8 (n=25), and 10.6 (n=17), respectively (p<0.001).

CONCLUSIONS: RUBACE is a practical, organ/system level, phenotyping tool designed to grade PBS severity and categorize patients into isolated PBS, syndromic PBS, and PBS-plus groups. This standardized system will facilitate genotype-phenotype correlations and future prospective multicenter studies assessing medical and surgical treatment outcomes.

*Corresponding author. M.K. Arevalo, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390, USA, Tel.: +1 314 807 1271; fax.: +1 214 648 3800.

Conflict of Interest Statement
None.

Keywords

Prune Belly Syndrome; Cryptorchidism; Severity Score; Megacystis

Introduction:

Prune Belly Syndrome (PBS) is a phenotypically variable congenital multisystem myopathy of mild to lethal severity affecting 3.8/100,000 live male births (1). Despite advances in medical and surgical management, newborn mortality remains high at 23-29%, unimproved from mortality rates reported in earlier cohorts (1-3). And although rare, PBS contributes disproportionately to health care costs as many require renal replacement therapy (RRT) in early childhood: 2.5 percent of North American pediatric renal transplants and 4.2 percent of European pediatric RRT are for a diagnosis of PBS (4, 5). Managing PBS patients who survive the neonatal period is a formidable challenge for pediatric and adult specialists, as no consensus on treatment strategies exists. Individual practitioners may encounter only a few affected patients in the course of a career, and evidence-based guidance has been limited by small sample sizes and retrospective approach. The need for collaborative, prospective randomized studies assessing specific treatment outcomes is broadly recognized (6).

Current study designs are hindered by the wide heterogeneity of the PBS phenotype and absence of any unified method to classify phenotypic severity (7), making it difficult to compare patients and their outcomes (8). This also limits investigators' ability to identify phenotypically-distinct PBS patients whose unique features may represent a specific genetic etiology. The only existing phenotypic categorization of PBS severity, cogently devised by Woodard in 1985, divides newborns into three groups based on clinical parameters and immediacy of life-supporting surgical management required by the child (9). While Woodard's classification is useful in broadly prioritizing the patient's care and management, it is limited by lack of phenotypic granularity.

Recognizing these barriers to improved PBS research and treatment, we hypothesize that a more expansive, two-fold classification system will better describe the phenotypic diversity of PBS patients. First, to facilitate PBS phenotyping, we created a novel, pragmatic, numerically-continuous scoring system called RUBACE, designed to quantitatively grade the phenotypic severity of a PBS patient. Second, we borrowed from the genetics literature a methodology wherein patients with a complex trait are partitioned into phenotypic sub-categories. The classic prune triad (deficient midline abdominal musculature, urinary tract distension, and cryptorchidism) typically occurs in isolation – we define this group as 'isolated PBS' (Figure 1). However, many PBS patients have extra-genitourinary malformations outside the typical PBS phenotype which we have sub-classified into two categories: 'syndromic PBS' and 'PBS-Plus'. In syndromic PBS, the extra-genitourinary features meet criteria for a known genetically-defined syndrome, association or condition. In PBS-Plus, there are extra-genitourinary malformations outside the isolated PBS phenotype that fall short of a distinct genetically-defined disease/syndrome/association. We applied the RUBACE and Woodard scoring systems and these PBS sub-categories to a large pilot cohort of PBS patients for individualized phenotyping.

Patients and Methods

From 2000 – 2017, living patients diagnosed with PBS were recruited to our institution's prospective clinical and genetic study (NIH grant R01 DK105068 – PI: L. Baker). To facilitate this investigation, we designed a pragmatic, numerical PBS severity scoring system to grade patients of any age based on six sub-scores (R: renal, U: ureter, B: bladder/outlet, A: abdominal wall, C: cryptorchidism, and E: extra-genitourinary [RUBACE]), yielding a potential summed score of 0-31 (Table 1). Medical records for patients were reviewed for cross-sectional application of RUBACE. Patients were scored by two providers (N.M.P and M.K.A). Any discrepancy in scoring was resolved by joint re-examination of the patient record and consensus.

Data sources and selection of the score-date

With IRB approval, complete medical records were solicited from recruited subjects on a voluntary basis. Electronic medical records (EMR) were also reviewed for recruited subjects treated at our tertiary children's hospital. Because these complex children often receive care at multiple facilities with redundancy of evaluation, patients were scored at a single point in time using an individually-assigned score date. This score date was selected based on the most recent inpatient encounter wherein there was sufficient imaging, laboratory, and physical exam and/or operative notes to establish the patient's severity in each of the six RUBACE sub-categories. Patients with records insufficient for scoring were excluded.

RUBACE subcategory grading and severity scoring

The rubric guiding PBS RUBACE scoring is seen in Table 1. In each applicable subcategory, patients with normal anatomy without pathology should receive zero points.

RUBACE Renal (R) scoring (max: 6 points) corresponds to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) GFR severity categories (reported in ml/min/1.73m²). KDIGO categories G1-2, G3a-b, G4 and kidney failure (GFR <15) receive RUBACE R scoring of 1, 2, 3, and 4, respectively (10). GFR should be calculated per KDIGO-referenced creatinine-based or cystatin C-based equations for children or adults as appropriate. Additional RUBACE R points are awarded for very young age (<2 years, 2 pts) and pre-adolescent age (<13 years, 1 pt) based on the rationale that renal stress is greater during major growth periods.

For the ureter (U) subscore (max: 3), initial and interval assessment of vesicoureteral reflux (VUR) should be per AUA guidelines (11). "High" grade VUR corresponds to an International Reflux Grading Scale of III-V. While the gold standard for VUR assessment is voiding cystourethrography and/or videourodynamics, sonographic findings may be used in proxy. Other imaging studies that measure ureter girth are also acceptable measures of severity, as distal ureteral diameter has been shown to predict breakthrough febrile UTIs and VUR outcomes (12, 13). Current ureterostomy or nephrostomy for ureteral obstruction should be scored 3 points; however, ureters status post correction (e.g. ureteroureterostomy, reimplant) merit only 2 points.

For bladder/outlet severity (B, max: 3), “urotherapy” is per International Continence Society definitions of treatment models for bowel and bladder dysfunction (14). Patients given pharmacologic therapy to aid voiding and patients given antibiotic prophylaxis against UTI are awarded 2 points. Surgical diversion such as vesicostomy merits 3 points, however, other surgical procedures such as augment or reduction cystoplasty should not receive 3 points. A child who underwent surgical diversion at an early age but currently voids per urethra should not receive 3 points.

Judgement of abdominal (A) wall laxity severity (max: 2) has not been standardized and thus we propose our subjective categorization unless an imaging modality has demonstrated clear absence of ventral abdominal wall musculature (2 points). Subjectively, the mild abdominal phenotype has a protuberant, lax, mildly contractile belly with minimal to no wall thinning or wrinkles (1 point, Figure 2a). In contrast, the severe, classic prune belly appearance (2 points, Figure 2b) is a strikingly thin, floppy, noncontractile abdominal wall with lateral sagging, protrusion of the abdominal organs, and moderate to severe skin wrinkling. Eventration in the left or right upper quadrant may be significant. Bowel loops and peristalsis are often visible beneath the skin. Children being scored status post abdominoplasty are awarded 2 points unless they are able to perform a sit-up unassisted, which receives 1 point.

Definitions and categories of cryptorchidism (C) (max: 2) are per previously-established guidelines (15). Bilateral, non-palpable testes should be scored 2 points. Patients found to have inguinoscrotal or unilaterally-undescended testes should be scored 1 point. Surgical history of orchiopexy for bilateral intra-abdominal testes (e.g. Fowler-Stephens) may be used in proxy to score older patients who have surgically descended testes. Males with normally-descended testes should not be awarded any points in this category. XX female patients are awarded 1 point to permit application of RUBACE to female prune candidates.

The five extra-genitourinary (E) sub-scores (neurologic, cardiac, gastrointestinal, musculoskeletal, and respiratory) are generated based on decades of literature reporting cases of PBS with extra-genitourinary disease, as well as the authors’ experience managing a sizable patient cohort (1, 7, 8). The E sub-score is the most variable (max: 15). It is acknowledged that subtler symptoms (e.g. constipation, asthma, scoliosis) may not announce themselves until later childhood, resulting in a score of zero in many patients, particularly newborns. Infant patients should be scored as completely as possible based on their standard-of-care evaluations and their score and categorization may be readjusted as they age.

Phenotypic categorization of PBS: isolated PBS, syndromic PBS, and PBS-plus

Patients were assigned to one of three categories (isolated PBS, syndromic PBS, or PBS-plus) based on the following criteria. Scores of 0-2 in any E sub-category and a score of 0-3 in the respiratory category were consistent with the typical PBS phenotype (isolated PBS). A score of 3 points in either the neurologic, cardiac, gastrointestinal, or musculoskeletal E categories indicated syndromic PBS or PBS-plus.

Comparison to Woodard categorization

Using the same medical records, patients were assigned Woodard categories based on his original description of the PBS spectrum (9). Mean RUBACE scores for each Woodard category were compared with one-way ANOVA. All statistical analysis was performed with GraphPad Prism (GraphPad Software, La Jolla, California).

Results

Of 138 prune belly patients recruited to our study, medical records were acquired for 54 patients: 30 patients with local EMR and 24 with external hospital records from 19 cities including two international patients. Four patients were excluded for incomplete records. Fifty patients (48 male, two female) with a diagnosis of PBS were scored at a median age of 6.0 years (IQR: 1.1 - 11.8). Eighteen patients were younger than two years of age at scoring, and four were scored during the first month of life. Patient cohort characteristics and demographics are described in Table 2.

The histogram of RUBACE scores as well as distributions of RUBAC and E scores are seen in Figure 3. Distribution by individual sub-score is shown in Supplementary Figure 1. When stratified by Woodard category, mean RUBACE scores were 20.5 (n=8), 13.8 (n=25), and 10.6 (n=17), for categories 1, 2 and 3 respectively ($p<0.001$, Figure 4). Segregated by phenotypic categories, 39 patients were isolated PBS (78%), six were syndromic PBS (12%), and five were PBS-plus (10%). The syndromic PBS included three patients with VACTERL association, two with familial Pierre Robin Sequence (PRS), and one with Duchenne's muscular dystrophy (DMD).

The two lowest RUBAC scoring patients had unconvincing phenotype for full classic PBS triad (Figure 3b): one non-cryptorchid male with posterior urethral valves (PUV) whose kidney and ureteral function normalized following cystoscopic valve ablation, and one female with complex large chromosomal rearrangement (6q deletion and 11p duplication), multiple congenital anomalies, and absent ventral abdominal musculature but normal kidneys, ureters, and bladder.

Discussion

During our NIH-funded genetics investigation on PBS, we realized improved phenotyping would be required to advance research and treatment for these diverse, medically- and surgically-complex patients. Thus, we developed the first detailed histogram to illustrate prune severity in a population, stratifying the severity of the classic Eagle-Barrett "triad" (RUBAC) as well as the severity of extra-genitourinary features (E). Combined, these two numbers yield the patient's RUBACE score. In its simplest application, this graphic (Figure 3) allows parents and healthcare providers to demonstrate where a new PBS child's severity lies in reference to an established cohort. Incidentally, we noted that an individual RUBAC score lower than seven may suggest an alternative primary diagnosis besides PBS, despite a prior clinical diagnosis by their healthcare provider of PBS. Only two in our cohort fell below that threshold and were notable outliers in their medical histories. One 46, XX female with an unbalanced chromosomal translocation (6.3 Mb terminal deletion of 6q27 and 13.3

Mb terminal gain of 11p15.5-p15.2) had multiple congenital anomalies, isolated low-grade hydronephrosis without VUR and a thin lax abdominal wall. Severe neurologic and cardiopulmonary defects contributed to a high E score, flagging her as PBS-plus. However, in the setting of her very low RUBAC score, we would suggest she is not a true PBS patient. The other outlier was a male born with “lax” abdomen and bilateral hydroureteronephrosis, prompting a clinical diagnosis of PBS despite normally-descended testes. His urinary tract dysfunction improved completely after ablation of cystoscopically-identified PUV. These two cases illustrate that often the PBS diagnosis is applied when the abdominal wall is lax, irrespective of the remainder of the phenotype. Essentially, the lax abdominal wall is a prominent, grossly visible feature that the parents and caregivers often mistake as pathognomonic for PBS. However, we would encourage our stricter diagnostic criteria, as bladder outlet obstruction from other etiologies (posterior urethral valves, cloaca, etc) may be part of or mimic the classic PBS phenotype. A future direction of this study will be to validate the RUBACE scoring system against unaffected children and children with PBS mimickers in order to establish diagnostic cut-offs.

The overlying goal of RUBACE was to transform PBS care, as suboptimal clinical management of this chronic disease contributes to major healthcare burdens like dialysis or transplant. We thus desired to add functional breadth to the classic Woodard spectrum without violating his original principles. In this we were successful: as expected, higher RUBACE scores significantly and inversely correlated with Woodard category (Figure 4). Woodard 1 patients had distinguishably higher RUBACE scores than Woodard 2 patients due to characteristic renal or respiratory failure. In contrast, overlap was observed in the RUBACE ranges of the Woodard 2 and 3 patients. To illustrate: of the four patients that scored a RUBACE 13, two were Woodard 2, with impaired renal function, prominent VUR, and either vesicostomy or APV, and two were Woodard 3, with much better urologic function but also possessing skeletal and GI features. While the overall RUBACE scores of all were equal, comparison of these patients side by side via the granular, separate, system-based RUBACE score yields a detailed phenotypic picture of each child, much of which is lost in the Woodard classification. The Woodard 2 and 3 categories are primarily segregated by progressive loss versus maintenance of renal function. By incorporating the KDIGO classification, renal function is clearly quantified. Thus, RUBACE was not designed to copy the Woodard classification but instead to spread out and grade the phenotypic spectrum that these patients exhibit. Spreading out the PBS phenotypic spectrum will be highly useful as PBS cohorts could be case matched based either on summative RUBACE or on individual sub-scores to target specific treatment outcomes in multi-center prospective or case-controlled studies.

While it is a great challenge to improve clinical care, outcomes and research in a rare disease such as PBS, the concept is not unproven. Cystic fibrosis (CF) is another heterogeneous disease conferring great medical socioeconomic burden particularly in patients progressing to respiratory failure and lung transplant (16). Outcomes for CF patients have improved dramatically in recent years, with a 17% reduction in mortality from 2000 to 2010 (17). Though partially owed to new technology and medications, improvements stem from enhancements in the delivery of care. The lynchpin of this enhancement was the creation of a sophisticated patient clinical research registry that unified center processes and outcomes,

facilitating higher-level evidence which eventually produced treatment guidelines and proven standards of care (18). While it may take years more to achieve enhanced healthcare for PBS, RUBACE offers a common language to providers worldwide and provides the framework for a sophisticated PBS patient registry to design long-awaited prospective studies.

A second framework we hope to provide with RUBACE is the ability to bridge phenotype to genotype. RUBACE is not the first proposed bridge to genotype in rare disease: integrating detailed standardized phenotypic severity scores with genotype has been previously demonstrated for conditions such as X-linked myotubular myopathy and fascioscapulohumeral muscular dystrophy (19, 20). The use of detailed phenotyping to identify phenotypically unique sub-groups has been highly successful at identifying causal DNA variants. Urologists have encountered this concept previously in the case of Wilms' tumor, a genetically-heterogeneous disease that occurs both in isolation and also as part of more complex syndromes such as WAGR, Beckwith-Weidemann (BWS), and Denys-Drash (DDS) (21). In the case of WAGR (Wilms' tumor, aniridia, genitourinary abnormalities/gonadoblastoma, and mental retardation), a contiguous gene syndrome, the constellation of multisystem anomalies was found to occur in individuals with deletions in 11p13 (22). Years of focused study using these syndromic subjects was integral to discovery and mapping of the WT1 tumor suppressor gene—mutations in which were causal for both WAGR, DDS, and some sporadic cases of Wilms'—as well as the locus for mutations causing familial aniridia (later discovered to be PAX6) (23, 24). Concomitantly, this mapping yielded the causal mutation for BWS in 11p15.5 (25, 26). In a similar fashion, investigation of six patients possessing both tuberous sclerosis (TSC) and severe infantile polycystic disease led to greater understanding of the role PKD1 deletions play in TSC patients with profound phenotypic severity (27). Targeting children with PRS-plus, namely those with extra skeletal anomalies, similarly supported the theory that dysregulation of SOX9 is responsible for PRS's pathogenesis (28). Though genetic understanding of PBS is still in its early stages, stratifying patients for targeted candidate gene investigation is an important collaborative effort for this rare disease, and a current aim of our NIH study.

We found that 12 percent of our cohort had syndromic PBS: three had VACTERL association, two half-brothers had PRS, and one patient had DMD (Figure 1). Five patients met criteria for PBS-plus: one child with PBS plus hepatoblastoma and autism, one with PBS plus seizures, infantile stroke, and optic nerve atrophy, two with PBS plus hearing loss, and finally the one female patient we suspect is not PBS. With respect to syndromic, there have been prior cases of VACTERL reported in association with PBS, though the cause behind this is still undetermined (29, 30). Additionally, a prior case series reported four patients with PBS plus hepatoblastoma (31). However, while the genetic and molecular bases of DMD are well established (OMIM#310200, Xp21.2-21.1) and causal genes for PRS have been recently described (28), neither DMD nor PRS have yet been shown to have association with PBS. With continued application, RUBACE may uncover additional syndromes not previously reflected in the literature, giving new leads into the etiology of this complex disorder.

There were several controversial points to be addressed in designing RUBACE. One controversy was the decision to include and score female patients. There is a case to be made for female patients not meeting the diagnostic criteria for PBS, as they cannot be cryptorchid. This, in conjunction with evidence of X-linked recessive inheritance in several multiplex families (32), has led some to suspect that females cannot have true PBS. However, we believe it is important to continue studying female prunes and female pseudo-prunes for several reasons. First, the literature describes several cases of female PBS patients; due to their rarity, these descriptions have been very phenotypically detailed including the variant Mullerian anatomy and also extra-genitourinary features such as malformations suggestive of VACTERL (33-36). These extra-genitourinary features (particularly those that appear syndromic) provide salient targets for genetic investigation—even for pseudo prunes, as they may represent a milder expression of causal mutations verses other syndromes with overlapping pathogenesis. Furthermore, DNA variations in four autosomal genes, *CHRM3*, *HNFI β* , *ACTA2*, and *ACTG2*, have been associated with five sporadic PBS cases (32, 37, 38) and one PBS multiplex consanguineous kindred (39). DNA variants in these autosomal genes would manifest theoretically in females at near equal frequency as in males. Including females also allows us to test RUBACE as a diagnostic tool: validation against known non-PBS female uropathies could yield firm score cutoffs, which would be of great value to the urologist presented with the rare female patient.

An additional controversial point was how to create scoring applicable to newborns, young children prior to surgery, and those of any age after surgeries. By testing the severity score on this broad age range at a single point in time, it improved the rubric by challenging us to consider all contingencies and surgical states. However, some of our assigned scores can be debated. For example, we scored ureteral reconstruction a U score of 2pts (U2) on the assumption that the surgery improved the previous ureteral pathology. In contrast, we scored ureterostomy (U3) on the belief that this indicated severe ureteral disease with a “yet to be decided” long term outcome. Similarly, a B2 score for a child on urethral CIC could be considered to be equally pathological as CIC via APV (which we scored B3). However, we feel these are different, as urethral CIC may be only needed temporarily until the child ages and becomes cooperative for urotherapy such as double/triple timed voiding. In our eyes, the creation of an APV indicates that the incomplete bladder emptying is felt to be a fixed problem warranting a permanent surgical solution. Concerning preemptive vesicostomy (which we scored B3), it typically indicates a severely affected PBS bladder and outlet; however this could be debated as the long term outcome is also yet to be decided. Likely, PBS patients will need to be rescored intermittently. Should RUBACE be universally adopted to score PBS newborns, scoring for various segments of care can be created and the proxies we have created could be eliminated. Thus, RUBACE could be used longitudinally to evaluate treatment outcomes.

The RUBACE system has several limitations. While every attempt was made to incorporate professional/expert guidelines into the scoring, components of RUBACE are supported by expert opinion. For example, the least defined subcategory is the abdomen, with highly subjective scoring criteria and undeniable impact upon several of the extra-genitourinary scores. More qualitative and quantitative functional measures need to be developed for the abdominal phenotype, as the diminished muscular function of the PBS ventral abdominal

wall plays key roles in respiratory, musculoskeletal, gastrointestinal and urinary tract health. Additionally, RUBACE was designed to be a pragmatic score, derivable from the medical record of any PBS patient receiving the standard of care. While some of the RUBACE subgroup scores could have been defined using more quantitative studies that are occasionally used and needed in the clinical care of PBS patients (e.g. urodynamics or pulmonary function tests), these were not incorporated into the scoring system due to limited global availability. As our study was a cross-sectional study, we did not try to show that RUBACE correlates with outcomes. We hope that longitudinal studies of PBS cohorts employing this scoring system or future revisions of it can define whether RUBACE correlates with outcomes. Finally, as we only scored living patients, RUBACE may not be generalizable to PBS patients who died *in utero* or in the perinatal period.

Conclusion

The RUBACE score is a practical phenotyping tool that grades individual patient severity at the organ/system level, illustrates the full distribution of PBS severity within a cohort, aids phenotypic categorization into isolated PBS, syndromic PBS, and PBS-plus groups and lays the groundwork on which genotype-phenotype correlations and standardized, quality studies assessing medical and surgical treatment outcomes may be built.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Our sincerest thanks to the stalwart Prune Belly survivors and their families, as well as the entire Prune Belly Syndrome Network (www.prunebelly.org), for their enthusiastic and tireless support of and participation in this study. We welcome additional study participation from PBS families and collaborations with healthcare providers and major centers nationally and internationally. For more information, please contact emma.sanchez@childrens.com and/or linda.baker@childrens.com.

Funding Source

This study was supported in part by NIH grant R01 DK105068 (PI: L. Baker).

References

1. Routh JC, Huang L, Retik AB, Nelson CP. Contemporary epidemiology and characterization of newborn males with prune belly syndrome. *Urology*. 2010;76(1):44–8. [PubMed: 20381841]
2. Fallat ME, Skoog SJ, Belman AB, Eng G, Randolph JG. The prune belly syndrome: a comprehensive approach to management. *J Urol* 1989;142(3):802–5. [PubMed: 2769864]
3. Burbige KA, Amodio J, Berdon WE, Hensle TW, Blanc W, Lattimer JK. Prune belly syndrome: 35 years of experience. *J Urol* 1987;137(1):86–90. [PubMed: 2879047]
4. North American Pediatric Renal Trials and Collaborative Studies. NAPRTCS 2014 Annual Transplant Report. 2014.
5. Yalcinkaya F, Bonthuis M, Erdogan BD, van Stralen KJ, Baiko S, Chehade H, et al. Outcomes of renal replacement therapy in boys with prune belly syndrome: findings from the ESPN/ERA-EDTA Registry. *Pediatr Nephrol*. 2018;33(1):117–24. [PubMed: 28779237]
6. Hassett S, Smith GH, Holland AJ. Prune belly syndrome. *Pediatr Surg Int*. 2012;28(3):219–28. [PubMed: 22198807]

7. Seidel NE, Arlen AM, Smith EA, Kirsch AJ. Clinical manifestations and management of prune-belly syndrome in a large contemporary pediatric population. *Urology*. 2015;85(1):211–5. [PubMed: 25444629]
8. Grimsby GM, Harrison SM, Granberg CF, Bernstein IH, Baker LA. Impact and frequency of extra-genitourinary manifestations of prune belly syndrome. *J Pediatr Urol*. 2015;11(5):280 e1–6. [PubMed: 26231776]
9. Woodard JR. Prune belly syndrome In: Kelalis PP, King LR, Belman AB, editors. *Clinical Pediatric Urology*. 2nd ed. Philadelphia: Saunders; 1985 p. 805–24.
10. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney inter, Suppl*. 2013;3:1–150.
11. Peters CA, Skoog SJ, Arant BS Jr., Copp HL, Elder JS, Hudson RG, et al. Summary of the AUA Guideline on Management of Primary Vesicoureteral Reflux in Children. *J Urol*. 2010;184(3):1134–44. [PubMed: 20650499]
12. Cooper CS, Birusingh KK, Austin JC, Knudson MJ, Brophy PD. Distal ureteral diameter measurement objectively predicts vesicoureteral reflux outcome. *J Pediatr Urol*. 2013;9(1):99–103. [PubMed: 22236467]
13. Arlen AM, Leong T, Guidos PJ, Alexander SE, Cooper CS. Distal Ureteral Diameter Ratio is Predictive of Breakthrough Febrile Urinary Tract Infection. *J Urol*. 2017;198(6):1418–23. [PubMed: 28694079]
14. Austin PF, Bauer SB, Bower W, Chase J, Franco I, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: Update report from the standardization committee of the International Children's Continence Society. *Neurourol Urodyn*. 2016;35(4):471–81. [PubMed: 25772695]
15. Kolon TF, Herndon CD, Baker LA, Baskin LS, Baxter CG, Cheng EY, et al. Evaluation and treatment of cryptorchidism: AUA guideline. *J Urol*. 2014;192(2):337–45. [PubMed: 24857650]
16. Hirche TO, Knoop C, Hebestreit H, Shimmin D, Solé A, Elborn JS, et al. Practical Guidelines: Lung Transplantation in Patients with Cystic Fibrosis. *Pulmonary Medicine*. 2014;2014.
17. MacKenzie T, Gifford AH, Sabadosa KA, Quinton HB, Knapp EA, Goss CH, et al. Longevity of Patients With Cystic Fibrosis in 2000 to 2010 and Beyond: Survival Analysis of the Cystic Fibrosis Foundation Patient Registry. *Annals of internal medicine*. 2014;161(4):233–41. [PubMed: 25133359]
18. Schechter MS, Gutierrez HH. Improving the quality of care for patients with cystic fibrosis. *Current opinion in pediatrics*. 2010;22(3):296–301. [PubMed: 20414114]
19. McEntagart M, Parsons G, Buj-Bello A, Biancalana V, Fenton I, Little M, et al. Genotype-phenotype correlations in X-linked myotubular myopathy. *Neuromuscul Disord*. 2002;12(10):939–46. [PubMed: 12467749]
20. Nikolic A, Ricci G, Sera F, Bucci E, Govi M, Mele F, et al. Clinical expression of facioscapulohumeral muscular dystrophy in carriers of 1-3 D4Z4 reduced alleles: experience of the FSHD Italian National Registry. *BMJ Open*. 2016;6(1):e007798.
21. Campbell MF, Wein AJ, Kavoussi LR. *Campbell-Walsh urology / editor-in-chief, Wein Alan J. ; editors, Kavoussi Louis R. ... [et al.] 9th ed.* Philadelphia: W.B. Saunders; 2007.
22. Turleau C, de Grouchy J, Tournade MF, Gagnadoux MF, Junien C. Del 11p/aniridia complex. Report of three patients and review of 37 observations from the literature. *Clin Genet*. 1984;26(4):356–62. [PubMed: 6094051]
23. Francke U Molecular genetics. A gene for Wilms tumour? *Nature*. 1990;343(6260):692–4. [PubMed: 2154698]
24. Mannens M, Bleeker-Wagemakers EM, Blik J, Hoovers J, Mandjes I, van Tol S, et al. Autosomal dominant aniridia linked to the chromosome 11p13 markers catalase and D11S151 in a large Dutch family. *Cytogenet Cell Genet*. 1989;52(1-2):32–6. [PubMed: 2575483]
25. Koufos A, Grundy P, Morgan K, Aleck KA, Hadro T, Lampkin BC, et al. Familial Wiedemann-Beckwith syndrome and a second Wilms tumor locus both map to 11p15.5. *Am J Hum Genet*. 1989;44(5):711–9. [PubMed: 2539717]

26. Henry I, Grandjouan S, Couillin P, Barichard F, Huerre-Jeanpierre C, Glaser T, et al. Tumor-specific loss of 11p15.5 alleles in del11p13 Wilms tumor and in familial adrenocortical carcinoma. *Proc Natl Acad Sci U S A*. 1989;86(9):3247–51. [PubMed: 2566168]
27. Brook-Carter PT, Peral B, Ward CJ, Thompson P, Hughes J, Maheshwar MM, et al. Deletion of the TSC2 and PKD1 genes associated with severe infantile polycystic kidney disease--a contiguous gene syndrome. *Nat Genet*. 1994;8(4):328–32. [PubMed: 7894481]
28. Xu JX, Kilpatrick N, Baker NL, Penington A, Farlie PG, Tan TY. Clinical and Molecular Characterisation of Children with Pierre Robin Sequence and Additional Anomalies. *Mol Syndromol*. 2016;7(6):322–8. [PubMed: 27920635]
29. Younous S, Zarrouki Y, Boutbaoucht M, Mouaffak Y, El Idrissi KE, Aboussair N, et al. Prune Belly Syndrome Associated with Full Spectrum of VACTERL in a New Born. *J Clin Neonatol*. 2012;1(1):49–51. [PubMed: 24027688]
30. Awad K, Lall A. It's not All Doom and Gloom: Prune Belly Syndrome Associated with VACTERL. *J Neonatal Surg*. 2016;5(3):33. [PubMed: 27433451]
31. Becknell B, Pais P, Onimoe G, Rangarajan H, Schwaderer AL, McHugh K, et al. Hepatoblastoma and prune belly syndrome: a potential association. *Pediatr Nephrol*. 2011;26(8):1269–73. [PubMed: 21597971]
32. Granberg CF, Harrison SM, Dajusta D, Zhang S, Hajarnis S, Igarashi P, et al. Genetic basis of prune belly syndrome: screening for HNF1beta gene. *J Urol*. 2012;187(1):272–8. [PubMed: 22114815]
33. Reinberg Y, Shapiro E, Manivel JC, Manley CB, Pettinato G, Gonzalez R. Prune belly syndrome in females: a triad of abdominal musculature deficiency and anomalies of the urinary and genital systems. *J Pediatr*. 1991;118(3):395–8. [PubMed: 1825673]
34. Aaronson IA, Cremin BJ. Prune belly syndrome in young females. *Urol Radiol*. 1979;1(3):151–5. [PubMed: 162311]
35. Lubinsky M, Rapoport P. Transient fetal hydrops and "prune belly" in one identical female twin. *N Engl J Med*. 1983;308(5):256–7. [PubMed: 6336828]
36. Rabinowitz R, Schillinger JF. Prune belly syndrome in the female subject. *J Urol*. 1977;118(3):454–6. [PubMed: 143543]
37. Richer J, Milewicz DM, Gow R, de Nanassy J, Maharajh G, Miller E, et al. R179H mutation in ACTA2 expanding the phenotype to include prune-belly sequence and skin manifestations. *Am J Med Genet A*. 2012;158A(3):664–8. [PubMed: 22302747]
38. Wangler MF, Gonzaga-Jauregui C, Gambin T, Penney S, Moss T, Chopra A, et al. Heterozygous de novo and inherited mutations in the smooth muscle actin (ACTG2) gene underlie megacystis-microcolon-intestinal hypoperistalsis syndrome. *PLoS Genet*. 2014;10(3):e1004258. [PubMed: 24676022]
39. Weber S, Thiele H, Mir S, Toliat MR, Sozeri B, Reutter H, et al. Muscarinic Acetylcholine Receptor M3 Mutation Causes Urinary Bladder Disease and a Prune-Belly-like Syndrome. *Am J Hum Genet*. 2011;89(5):668–74. [PubMed: 22077972]

Figure 1.

Overview: the PBS phenotype may be categorized into isolated, PBS-plus, and syndromic PBS based on the presence of additional malformations outside the classic triad. Patterns observed in the present cohort (denoted by * asterisks) as well as in prior literature are listed.

A) Becknell et al. 2018 B) Ortiz et al. 2018 C) Murray et al. 2008 (gene proposed: HNF1 β)

D) Weber et al. 2011 (gene proposed: CHRM3) E) Brodsky et al. 2014 (gene proposed:

ACTA2) F) Awad and Lall, 2016 G) Wangler et al. 2014 (gene proposed: ACTG2).

Figure 2. Abdominal wall scoring in PBS.

A) Protuberant abdomen with laxity, suggestive of but not convincing for PBS phenotype, 1 pt. B) Abdomen with classic PBS appearance, 2 pt.

Figure 3. Distribution of RUBACE scores:

Histogram representation of phenotypic severity within our cohort of 50 patients. Syndromic PBS (n=6), PBS-plus patients (n=5), and patients in whom an alternate primary diagnosis other than PBS is suspected (n=2) are highlighted. A) Total RUBACE scores (RUBAC + Extra-GU); B) RUBAC "Triad" scores (not including Extra-GU score); C) Extra-GU scores.

Woodard Classification of PBS Cohort (n=50)	N of pts. (%)	RUBACE Score Mean $\pm$ SD
Category 1	8 (16)	20.5 $\pm$ 2.8*
Category 2	25 (50)	13.8 $\pm$ 3.5*
Category 3	17 (34)	10.6 $\pm$ 2.0*

*one-way ANOVA ($p < 0.001$)

Figure 4. Woodard Category vs RUBACE score for our PBS cohort.

As per original Woodard criteria [10], Category 1 includes PBS cases having severe renal dysplasia leading to oligohydramnios with resultant pulmonary hypoplasia and Potter sequence typically with neonatal demise; Category 2 PBS cases have the full triad with minimal renal dysplasia and no prominent pulmonary hypoplasia but progressive loss of renal function; and Category 3 PBS cases have incomplete or mild triad features, well maintained renal function and no pulmonary insufficiency.

TABLE 1:

The PBS RUBACE Severity Scoring Rubric

EAGLE-BARRETT SYNDROME PBS TRIAD ("RUBAC") MAX SCORE: 16						EXTRA-GENITOURINARY MANIFESTATIONS ("E") MAX SCORE: 15				
No subcategory points are awarded for normal anatomy with absent pathology						No subcategory points are awarded for normal anatomy with absent pathology				
Renal Max Score: 6	Ureteral Max Score: 3	Bladder/Outlet Max Score: 3	Abdominal Wall Max Score: 2	Cryptorchidism Max Score: 2	Neurologic Max Score: 3	Cardiac Max Score: 3	Gastrointestinal Max Score: 3	Musculoskeletal Max Score: 3	Respiratory Max Score: 3	
1 pt: G1-G2: Structural damage (dilation, dysplasia, scarring) with preserved GFR 60	1 pt: Low grade VUR, or absent VUR, or distal ureter 7-10mm	1 pt: urotherapy required to empty bladder, or bladder size is 100-200% of normal	1 pt: Can do "sit-up" exercise before or after abdominoplasty, musculature mostly intact, minimal laxity, or mild/nonconvincing prune appearance	1 pt: History of or current unilateral or palpable undescended testicle(s), or patient is female		1 pt: congenital septal defects (PDA, ASD, VSD) which are spontaneously resolved	1 pt: mild to moderate constipation, managed with diet or laxatives	1 pt: mild facies, abnormally shaped fingers or toes (no loss of function), or rib flaring	1 pt: minimal respiratory support at birth, some difficulty coughing, mild intermittent asthma, or mild reactive airway disease	
2 pts: G3a-b: Kidney damage with decreased GFR 30-59	2 pts: Persistent high grade VUR (no surgery), s/p lower tract ureteral reconstruction, or distal ureter 1-2 cm	2 pts: Urethral-catheterization or pharmacologic empty, bladder size >200% normal, or patient takes antibiotic prophylaxis for recurrent UTI	2 pts: Severe abdominal laxity with obvious thinning of classic prune appearance, or s/p abdominoplasty + cannot do a "sit-up"	2 pts: History of or current bilateral nonpalpable testes		2 pts: small septal defects which are not spontaneously resolved, minimal L to R shunting, or PDA requiring surgical management	2 pts: MACE/cecostomy required, or malrotation s/p Ladd's	2 pts: scoliosis, hip dysplasia, club foot, rockerbottom foot, genu valgum, pectus excavatum or carinatum	2 pts: persistent/moderate asthma, frequent respiratory tract infections (3/ year), or 2 hospitalizations for pneumonia	
3 pts: G4: Severe loss of kidney function with GFR 15-29					PBS-PLUS OR CONGENITAL/GENETIC SYNDROME OR ASSOCIATION					
4 pts: Renal failure with GFR <15, or on dialysis or s/p renal transplant	3 pts: Persistent high grade VUR despite surgery, distal ureter 2+ cm girth, or current diverting ureterostomy or nephrostomy	3 pts: current surgical diversion (e.g. s/p tube, vesicostomy, APV), urethral atresia, or megalourethra requiring repair			3 pts: seizures, tethered cord, spina bifida, hearing loss, intellectual delay, autism, or severe neurologic condition not otherwise specified	3 pts: severe congenital or cyanotic heart disease-Tetralogy of Fallot, left sided obstructive lesions, reversed shunt, CHF or severe cardiologic conditions not otherwise specified	3 pts: required surgical bowel diversion (e.g. imperforate anus, anal atresia), gastrointestinal malignancy (e.g. hepatoblastoma), or severe GI condition not otherwise specified	3 pts: arthrogryposis, muscular dystrophy, or severe musculoskeletal malformation not otherwise specified	3 pts: ventilator-dependent > 1 week, tracheostomy, history of pneumothorax, or severe asthma	
Additional Points for Young Age: if patient is <2 years, add +2 pt and if patient										

EAGLE-BARRETT SYNDROME PBS TRIAD ("RUBAC") MAX SCORE: 16					EXTRA-GENITOURINARY MANIFESTATIONS ("E") MAX SCORE: 15				
No subcategory points are awarded for normal anatomy with absent pathology					No subcategory points are awarded for normal anatomy with absent pathology				
Renal Max Score: 6	Ureteral Max Score: 3	Bladder/Outlet Max Score: 3	Abdominal Wall Max Score: 2	Cryptorchidism Max Score: 2	Neurologic Max Score: 3	Cardiac Max Score: 3	Gastrointestinal Max Score: 3	Musculoskeletal Max Score: 3	Respiratory Max Score: 3
is <13 years, add +1 pt									
TOTAL TRIAD RUBAC SCORE: _____					TOTAL E SCORE: _____				
TOTAL TRIAD RUBAC SCORE _____ + TOTAL E SCORE _____ = TOTAL RUBACE SCORE _____									

Table 2.

Patient Demographics, Phenotypic Categories, and Scores

<i>Age (yrs)</i>	
Median (IQR)	6.0 (1.1 - 11.8)
Mean (range)	7.3 (0.0 - 35.0)
<i>Gender</i>	
Male	48 (96%)
Female	2 (4%)
<i>Race/ethnicity</i>	
White	26 (52%)
Black	13 (26%)
Hispanic	8 (16%)
Other	3 (6%)
<i>Phenotypic Category</i>	
Isolated	39 (78%)
PBS-plus	6 (12%)
Syndromic	5 (10%)
<i>Mean Scores and Ranges</i>	
RUBACE (RUBAC + E)	13.8 (8-25)
RUBAC ("triad") only	10.5 (5-15)
Extra-genitourinary (E) only	3.3 (0-13)