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Spina Bifida Guideline

Urologic guidelines for the care and management of people with spina bifida

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Abstract.
PURPOSE: The life expectancy for people with spina bifida has increased, thus resulting in greater need for guidelines in urologic care in order to protect normal renal function, to develop strategies for urinary continence, and to advance independence through adult years.
METHODS: The English literature was assessed from 2002–2015; greater than 300 publications identified. Case reports and opinion pieces were eliminated leaving 100 for in depth review. Clinical questions were then established for each age group that allowed for focused assessment.
RESULTS: There was no Level 1 evidence for any of the defined clinical questions. This resulted in group consensus for all questions throughout all age groups. Guidelines were provided for identifying a symptomatic urinary infection, the role of urodynamic bladder testing and identification of bladder hostility, determining methods of renal function assessment and surveillance, the initiation of continence control, and transitioning to self-care through the teen and adult years.
CONCLUSION: Urologic guidelines continue to be based on clinical consensus due to the lack of high level evidence-based research. Further research is required in all aspects of urologic management. While not the "Standard of Care," these guidelines should be considered "Best Practice".

Keywords: Spina bifida, spinal dsyraphism, neurogenic bladder, myelomeningocele, neural tube defects

1. Introduction

As life expectancy in people with spina bifida has increased through advances in care by other disciplines, particularly neurosurgery, urologic morbidity and mortality have become problematic for all individuals progressing into adulthood. This places the importance of

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developing guidelines for care that will enhance urologic management of individuals with spina bifida into perspective. These guidelines focus on maintaining normal renal function through all ages, developing strategies for urinary continence, and achieving the highest level of independence with personal care through adulthood.

The majority of newborns with spina bifida have a normal upper urinary tract (kidney and ureter). Tanaka et al. reported on 188 infants with two kidneys; only 3.7% had high grade hydronephrosis in at least one kidney, 40.4% had low grade hydronephrosis in at least one kidney and 55.9% had two normal kidneys, 84.6% of infants had no reflux. Of the 66 infants who were able to obtain a dimercaptosuccinic acid (DMSA) scan, only 5 infants had defects noted on the scan [1]. Historically, we know that if left unattended, 50% of children will suffer upper urinary tract damage within 5 years due to lower urinary tract (bladder and urethra) hostility [2]. During the first several years of life, the urologic focus on a child's health is based on maintaining normal renal function at a time when the kidneys are most susceptible to damage. As the child approaches school age, interest is extended toward gaining urinary continence. Then, structured transition to self-care begins for teenage patients. Each of these urologic management milestones builds upon the last and may influence renal function in a positive or negative fashion.

The importance of maintaining normal renal function cannot be overstated. While creatinine is a good screening estimate of renal function, it is limited in the non-ambulatory child and adult with spina bifida due to low muscle mass and may provide a false sense of normality [3]. Renal function may be more accurately measured with serum cystatin C or with a nuclear medicine estimated glomerular filtration rate test (GFR) [4]. Currently, the best measure of renal function in children and adults with spina bifida is unknown.

This urologic guideline is aspirational and merges aspects of proactive and reactive philosophies based on a "best practice" methodology utilizing common resources available within most institutional settings. The guideline was developed by adult and pediatric experts with the intent to assist clinicians, patients, families and other stakeholders to achieve the Primary, Secondary and Tertiary urologic outcomes that provided the foundation for its development. Urologic care is appreciated to be dynamic and ever changing.

1.1. Outcomes

Primary

1. Maintain normal renal function throughout the lifespan.
2. Achieve urinary continence as early as socially acceptable.
3. Maximize urologic independence.

Secondary

1. Eliminate hostile bladder dynamics through medical management.
2. Reduce or eliminate operative reconstruction of the bladder.
3. Maximize renal outcome while minimizing expense of studies, staying aware of the timing and frequency of studies such as urodynamic testing, upper tract imaging, and lab studies.
4. Reduce impact of urinary tract infections (UTIs) and antibiotic overuse.
5. Establish a care program that allows for urologic independence, such as through clean intermittent self-catheterization (self-CIC).

Tertiary

1. Determine the best measure of renal function.
2. Minimize occurrence of urolithiasis.
3. Determine whether surgical interventions are effective in the long-term.

2. Methods

These guidelines were developed through literature review and consensus-building methodology as described by Dicianno et al. [5] Phase 1 initiated the preparation phase with the establishment of the working group and dividing expertise into content areas. All authors participated extensively in this process. Phase 2 focused on review of the literature. The prior Guideline 3rd edition was published in 2006 with literature reviewed from mid-1970s through 2002 and did not include adults. The current guidelines are based on English language, peer-reviewed literature from 2002–2015. Clinical questions were developed for each age group in order to provide focused guidance on the assessment of evidence-based research (Table 1). After eliminating case studies and opinion pieces, the working group assessed over 300 articles, identifying approximately 100 that met criteria for review. Within that group of articles, the lack of evidence-based research created gaps requiring focus on clinical consensus for each recommendation. Phase 3 finalized the guideline development utilizing consensus building methodology. Consensus was defined as overwhelming agreement

Table 1
Clinical questions

Age group	Clinical questions
0–11 months	1. How do you define a symptomatic urinary tract infection and what is its long-term sequela? 2. Can diagnostic studies of the lower urinary tract (urodynamic) or upper urinary tract (ultrasonography) predict and prevent an adverse change in kidney function? 3. What is proactive management? 4. Is proactive management better than reactive to maintain normal upper tract?
1–2 years 11 months	1. How can providers account for neurologic bladder changes due to growth and/or tethering? 2. What diagnostic tools are reliable to assess renal function? 3. Are upper tract changes reversible once they occur? 4. How should symptomatic UTIs be defined? What is the sequela of symptomatic UTIs? What is the optimal upper and lower urinary tract surveillance? 5. Does the use of proactive CIC and antimuscarinic medication help to maintain a normal upper tract?
3–5 years 11 months	1. How can providers account for neurologic bladder changes due to growth and/or tethering? 2. What diagnostic tools are reliable to assess renal function? 3. Are upper tract changes reversible once they occur? 4. How should symptomatic UTIs be defined? What is the sequela of symptomatic UTIs? What is the optimal upper and lower urinary tract surveillance? 5. Does the use of proactive CIC and antimuscarinic medication help to maintain a normal upper tract? 6. Are the caregivers compliant with CIC? Who is performing CIC – the caregivers and/or the child?
6–12 years 11 months	1. What is the best way to measure renal function in the child that is non-ambulatory? 2. What social, environmental, and economic limitations or hurdles are encountered when working to achieve urinary continence? 3. What is worse: stool or urinary incontinence? 4. How do we define urologic continence? Is the definition of continence congruent with the perspective of the patient, family, and physician?
13–17 years 11 months	1. How is continence affected by a shift in responsibility to self-care? 2. How is a normal upper urinary tract affected by a shift in responsibility to self-care? 3. What is optimal surveillance of the upper and lower urinary tract? 4. If reconstructive continent bladder surgery was undertaken, would patients do it again? 5. If no reconstructive surgery was undertaken do patients wish it had been?
18+ years	1. What is optimal surveillance of the upper and lower urinary tract? What cancer screening is needed? 2. How do we define UTI in the adult and when do we treat? 3. How do we minimize sequelae of secondary incontinence in adulthood?

but not unanimity within the working group. This provided the foundation for the urologic guidelines recommended within the 2018 Spina Bifida Association Guidelines for the Care of People with Spina Bifida [6].

3. Results

While there is a plethora of peer reviewed urologic information, none support Level 1 clinical evidence related to the defined clinical questions. The following guidelines were based on working group consensus. Guidelines in each age group correspond to the clinical questions established for that time period (Table 1). The process that established each guideline along with any supporting literature is indicated in the parentheses (i.e., clinical consensus [5]) Guidelines by age are found in Table 2.

4. Discussion

These guidelines were created to assist care providers across disciplines with the basic requirements to maintain normal renal function, establish continence that would be considered socially acceptable, and ultimately allow for transition to self-care. Overarching goals for all guidelines across disciplines was to focus care coordination in a patient- and family-centered fashion and to develop a medical home and neighborhood founded on team-based care.

Institutions create protocols for care based on their philosophy and available resources. Two general philosophies of early urologic management prevail: a proactive approach and a reactive approach. The proactive approach attempts to identify children at risk for upper urinary tract deterioration based on specific hostile parameters. Treatment is initiated before renal compromise occurs. The reactive approach follows a child closely and institutes management at the first sign of any adverse change [7,9,12]. Advocates of a proactive approach favor early identification of "at risk" children by assessing bladder function through urodynamic testing and managing hostile bladder parameters. This is undertaken to prevent adverse upper urinary tract

Table 2
Urologic guidelines by age

Age	Guideline	Evidence
0–11 months	1. Obtain the following baseline studies within three months of birth:	Clinical consensus [7]
	– Renal/bladder ultrasound and repeat in six months – Urodynamic testing – Serum creatinine	
	2. Initiate CIC and antimuscarinic therapy for the treatment of bladder hostility when indicated based on the above results.	Clinical consensus [7]
	3. Consider the presence of a Urinary Tract Infection (UTI)* when there is a fever (100.4 F/38.0 C) in neonates less than one month of age with failure to thrive and dehydration.	
1–2 years 11 months	1. Obtain renal/bladder ultrasound every six months when the child is under the age of two. Next, obtain an ultrasound yearly if the child is stable, without UTIs or imaging changes.	Clinical consensus
	2. Obtain a renal/bladder ultrasound, as needed if the child has recurring symptomatic UTIs or if urodynamic testing identifies bladder hostility.	Clinical consensus
	3. Obtain urodynamic testing yearly through age three. Repeat as needed if the following are noted:	Clinical consensus [2,9,10]
	– bladder hostility – upper urinary tract changes – recurrent symptomatic UTIs	
	4. Obtain a serum creatinine test if there is a change in the upper urinary tract.	Clinical consensus
	5. Assess suspected UTIs with a urine specimen obtained by sterile catheterization technique. Repeat a positive bag urine specimen with a catheterized specimen.	Clinical consensus
3–5 years 11 months	1. Obtain a renal/bladder ultrasound yearly, if the child is stable.	Clinical consensus
	2.Obtain a renal/bladder ultrasound as needed, if the child has recurrent symptomatic UTIs or if urodynamic testing identifies bladder hostility.	Clinical consensus
	3. Obtain urodynamic testing only if the following are present:	Clinical consensus
	– upper tract changes – recurring UTIs – interest in beginning a urinary continence program	
	4. If the child is on CIC, begin to involve the child in the process of self-catheterization.	Clinical consensus [11]
	5. Obtain a serum creatinine test if there is a change in imaging of the upper urinary tract.	Clinical consensus
	6. Obtain serum chemistries (includes serum creatinine) at age 5. Assess suspected UTIs with a catheterized urine specimen. Repeat a positive bag urine specimen with a catheterized specimen.	Clinical consensus
	7. Initiate CIC and antimuscarinic therapy when indicated by upper urinary tract changes, recurring symptomatic UTIs, or bladder hostility noted on urodynamic testing.	Clinical consensus [7,9,12]
	8. Introduce urinary continence and discuss interest in beginning the program and options at each visit.	Clinical consensus [11,13]
	9. Introduce bowel management and discuss interest and discuss interest and options at each visit.	Clinical consensus
6–12 years 11 months	1. Obtain a renal/bladder ultrasound yearly, if the child is stable.	Clinical consensus
	2. Obtain a renal/bladder ultrasound as needed if the child has recurrent symptomatic UTIs or if urodynamic testing identifies bladder hostility.	Clinical consensus
	3. Obtain urodynamic testing when initiating a urinary continence program, if the following are present:	Clinical consensus
	– upper urinary tract changes such as hydronephrosis or renal scarring – recurring symptomatic UTIs – changes in urinary continence status	
	4. Obtain a serum creatinine test yearly. If the child has low muscle mass, consider an alternative measure of renal function.	Clinical consensus [3]
	5. Obtain serum chemistries yearly on any child who has had urinary reconstruction.	
	6. Obtain a serum B12 level test every year beginning two years after urinary reconstruction.	Clinical consensus [14–16]
	7. Discuss a urinary continence program and interest in beginning the program and options at each visit.	Clinical consensus [11,13]
	8. Discuss a bowel management program and the interest and options at each visit.	Clinical consensus
13–17 years 11 months	1. Obtain a renal/bladder ultrasound yearly, if the child is stable.	Clinical consensus
	2. Obtain a renal/bladder ultrasound as needed, if the child has recurring symptomatic UTIs or if urodynamic testing identifies bladder hostility.	Clinical consensus
	3. Obtain a serum creatinine test yearly. If the child has low muscle mass, consider an alternative measure of renal function.	Clinical consensus [3]
	4. Obtain serum chemistries including B12 yearly on any child who has had urinary reconstruction.	Clinical consensus [14–16]
	5. Transition urologic care to self-management, if doing so is developmentally appropriate for the child.	Clinical consensus [17,18]

Table 2, continued

Age	Guideline	Evidence
13–17 years 11 months	6. Transition bowel program to self-management, if doing so is developmentally appropriate for the child.	Clinical consensus
18+ years	1. Obtain a renal/bladder ultrasound yearly.	Clinical consensus
	2. Obtain a renal/bladder ultrasound, as needed if the adult has recurring symptomatic UTIs or if urodynamic testing identifies bladder hostility.	Clinical consensus
	3. Obtain a serum creatinine test yearly. If the adult has low muscle mass, consider an alternative measure of renal function.	Clinical consensus [3]
	4. Obtain serum chemistries including B12 yearly on anyone who has had urinary reconstruction.	Clinical consensus [14–16]
	5. Undertake cystoscopy and appropriate upper tract imaging in adults who have had a bladder augmentation when the following are present: – clinically-noted change in upper or lower urinary tract status – gross hematuria – recurrent symptomatic UTIs – increasing incontinence – pelvic pain – the adult has had a renal transplant with the presence of BK/polyomavirus	Clinical consensus [19–21]
	6. Evaluate patterns of continence/incontinence and address issues collaboratively with the individual and family. Include assessment of amount (volume) of incontinence as the volume in adults may be more bothersome than frequency.	Clinical consensus [22]
	7. Continue to support self-management and independent living.	Clinical consensus

*The working group recognized the lack of consistency with defining a symptomatic UTI, positive UA and urine culture. This is a critical management parameter for each age group. Therefore, the working group utilized the recommendation by Madden-Fuentes et al. regarding a symptomatic UTI in the spina bifida population [8]. Urinary Tract Infection:

– a positive UA, and
– a positive urine culture (UC) on a catheterized specimen, and
– leakage between CIC, and
– onset of pelvic or back pain, and
– fever (100.4 F/38.0 C).

Positive UA (+UA):

– > trace nitrite or leukocyte esterase on dip UA, and
– > 10 white blood cells/high power field (WBCs/hpf), uncentrifuged specimen, or
– > 5 WBCs/hpf, centrifuged specimen.

Positive UC (+UC) as:

– > 50,000 colony forming units/milliliter (CFUs/mL) (sterile specimen obtained by catheter or suprapubic catheter aspirate).
– > 100,000 CFUs/mL in a clean voided specimen [8].

changes and preserve normal renal function, thus minimizing possible irreversible upper tract deterioration. It is known that some individuals will be subjected to the consequences of intervention that were unnecessary, exposing them to associated risks, and may needlessly utilize resources. Institutions favoring a reactive approach rely on close evaluation of the upper urinary tract, renal function, and documentation of urinary infections. They feel adverse upper urinary tract changes and renal compromise can be detected early utilizing minimally invasive assessment, renal ultrasonography, and assessing renal function parameters with a serum renal function study. Adverse changes are assumed to be reversed with medical, pharmacologic, and operative management. This approach involves treating children reactively, "as needed," and allows for a more precise selective management model limiting the stress and potential side effects of invasive procedures, medications, catheterization, and surgery. However, it is not known if all adverse renal changes noted on ultrasonography can be reversed, and if current renal function studies, particularly serum creatinine, truly reflect the renal status in patients with spina bifida. The urologic guidelines merge aspects of both proactive and reactive management.

People with spina bifida are at risk for progressive renal damage secondary to recurrent urinary tract infections and a hostile neurogenic bladder. Bladder hostility may result in upper urinary tract deterioration, hydronephrosis, recurrent pyelonephritis and renal scarring. Some patients may progress to end stage renal disease requiring dialysis or renal transplantation [23,24]. Infants with spina bifida demonstrate overall normal baseline imaging (including renal US and baseline DMSA) [1]. Hence management of bladder function to prevent adverse upper urinary tract changes to preserve renal function is critical [1,25].

Establishing guidelines to follow evidence-based management is logical. In 2003, sponsors from the NIH, CDC and SBA convened a conference of 100 authorities across multiple disciplines tasked with creating a research agenda for spina bifida based on what was known and lacking in evidence-based care [26]. Universally, evidence-based management was found to be lacking. Directives in 2003 were provided to help position research that would enhance the level of care based on sound evidence. Those goals had not been achieved through 2015 when work began on these guidelines. Therefore, the guidelines remain by consensus and they are not meant to represent a standard of care.

It is important to understand that these guidelines remain primarily a tool for assessment. Clearly, direction is lacking regarding treatment related to a medical, pharmaceutical, or surgical intervention. Diversity in patient population, regional differences, institutional resources, and local urologic philosophy all play a role in care and prevented the working group from establishing a consensus.

"Clinical questions" were the driving metric used to establish the guidelines. A prevailing question within all age groups was related to urinary tract infections. Our intent was to support a common definition for a urinary tract infection based on symptoms along with objective urinalysis and culture of urine that could be maintained throughout the lifespan. We identified the work of Madden-Fuentes et al. as the most relevant and reflective definition [8]. It is appreciated that intermittent catheterization and other clinical symptoms (abdominal pain, new onset of leakage, etc.) may be additional guiding factors when assessing a positive urine culture. Identifying what truly is a symptomatic urinary tract infection requiring treatment allows for early judicious antibiotic therapy, and hopefully will reduce the cycle of over treating asymptomatic bacteriuria.

The underlying goal of the urologic guidelines is to maintain normal renal function starting from birth. The glaring absence of evidence-based care of newborns, toddlers and young children prompted the CDC to develop a management protocol [27]. Now recognized as UMPIRE (urologic management to preserve initial renal function), the longitudinal protocol was established in 2014 at 9 centers throughout the United States following children from birth through the age of 5 years [25]. This is an iterative quality improvement consensus-based protocol utilizing prospective treatment. Outcomes are routinely assessed based on evidence with adjustments made to optimize care. UMPIRE has primary outcomes focused on urinary tract infection, renal function and bladder characteristics. The role of urodynamic testing is critical to the protocol. The appreciation of nuances related to testing and interpretation has already impacted the standardization of technical aspects of the procedure and objective identification of common urodynamic parameters (i.e., detrusor over activity, detrusor leak point pressure, end fill pressure, detrusor-sphincter-dyssynergy). The CDC has recently extended UMPIRE through 10 years of age. It is envisioned that UMPIRE will provide the lacking evidence to support proactive care.

The foundation of all urologic care is based on maintaining normal renal function, and increased monitoring in people with spina bifida is also one of the guideline goals. We appreciate that a significant deficiency exists within these guidelines regarding the establishment of objective renal function. The Kidney Disease Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the evaluation and management of chronic kidney disease emphasizes the importance of assessing renal function in all patients with chronic kidney disease [28], which is defined as abnormalities of kidney structure or function present for greater than 3 months. Chu et al. suggest that providers are not assessing kidney function in most practices in the spina bifida registry [29].

Currently, there is no consensus on how to best monitor for renal function in children with spina bifida. The UMPIRE study will be assessing serial radiologic imaging studies, urodynamics, renal scarring by DMSA renal scan and various measures of GFR over time [1,25]. KDIGO guidelines suggest using serum creatinine and a GFR estimating equation (eGFR) for initial assessment, with additional tests such as cystatin C or clearance measurement for confirmatory testing in circumstances when eGFR based on serum creatinine is less accurate. Formulas to calculate eGFR, including Schwartz formula, 2012 CKD-EPI cystatin C formula and CKD-EPI creatinine-cystatin C equation, and alternate cystatin C based GFR equations, are found in the KDIGO guideline paper [28].

In patients with spina bifida, creatinine is a poor marker of eGFR due to low muscle mass, particularly those who are non-ambulatory. This was initially suggested in 1997 by Quan et al., where authors described poor correlation with diethylenetriamine pentaacetate (DTPA) eGFR and the creatinine based Schwartz formula [30]. In addition, creatinine based Schwartz formulas required an accurate height measurement, which can be difficult to obtain in many non-ambulatory patients with spina bifida. Cystatin C, another marker of

renal function, is a protein produced at a constant rate by all nucleated cells. It is freely filtered by the glomerulus and not secreted at the renal tubule and is nearly entirely catabolized within the proximal tubule [31,32]. Several small studies have suggested that cystatin C based eGFR equations may be better in patients with spina bifida. Clearance studies have been considered the gold standard. They require injection of a substance with multiple timed blood draws. Inulin clearance may be the most accurate, but has limited availability [33]. Iohexol, 51-cr-EDTA and 99Tc-DTPA are also options, but require body surface area calculations to give GFR in ml/min/1.73m2 that require accurate weight and height measurements. Lastly, Zappitelli et al. developed a specific spina bifida formula which was studied in a small cohort and also assessed recently in a single center study [29,31]. Variability in assessment of eGFR in children and adults based on the formula used has been reported [34].

Urinary continence increasingly becomes relevant as children age into adolescence, the teen years, and adult life [35]. It impairs quality of life, ability to function in school and work, and increasingly impacts health quality with aging [36]. For many people with spina bifida, attaining continence requires engagement of the patient and family members. A dedication to self-management skills and careful decision-making with the urologic team regarding the need for and timing of interventions must be established. Nursing support and education for the patient and family before and after continence procedures must be expected. The guidelines recommend that discussions are initiated early in childhood and continue through adult life. It is well documented that continence is not stable throughout the lifespan and declines in adult life in people with spina bifida as well as the general population. Regular discussion with urologic providers related to urinary incontinence episodes, complications associated with leakage, and patient bother is recommended [37,38]. Data are lacking regarding the optimal definition of continence in patients with spina bifida. However, studies suggest that volume and frequency of leakage events is proportional to quality of life impact [39]. Therefore, patients should be evaluated annually for both frequency and quantity (volume) of leakage events, occurrence of skin breakdown associated with urinary incontinence, and bother associated with urinary incontinence. The goals for continence should be discussed regularly with the urological care team.

The increased lifespan of patients with spina bifida awakened the medical community about the importance and urgent need of transitioning care from the caregiver to young adult, and from the pediatric Urologist to the adult Urologist. Several transition programs have been introduced throughout the nation that focus on educating the young adults about their disease and need for lifelong medical management [40,41]. Equally important is the involvement of the adult providers in the often-complicated care of these patients as they leave pediatric practices. Transition programs focus on involving the patients and their families in achieving maximal independence and comfort within the adult medical system with the major goal of maintaining compliance with follow up to avert preventable long-term problems.

It has been noted that the primary limitation with these guidelines is the fact they are not directed by evidence-based practice. The small patient population within individual spina bifida centers and the inability to create prospective randomized trials with control groups that withhold care prevents establishment of evidence-based recommendations. Moving forward, multi-institutional assessments and studies (e.g. UMPIRE) will be needed for greater direction in objective care. The CDC's National Spina Bifida Patient Registry provides a platform to collate patient data in a standardized fashion in hopes of ratifying best practice methodologies [42]. Adding to that, a standardized approach to urologic assessment as these Guidelines provide, should help limit some of the common variables that exist between centers.

5. Conclusion

The urologic guidelines were developed on a platform of clinical questions based on age. The lack of evidence-based studies necessitated our utilization of consensus opinion in order to direct care surrounding our clinical questions. This sheds light on the major gaps in urologic clinical care that need further research. While not the "Standard of Care," there is justification for utilizing these guidelines as "Best Practice."

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guidelines to be published in this forum and making them Open Access.

The Spina Bifida Association has already embarked on a systematic process for reviewing and updating the guidelines. Future guidelines updates will be made available as they are completed.

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Conflict of interest

David Joseph is a Principal Investigator at UAB/Childrens' of Alabama for the CDC protocols: Component B-Improving the Care and Outcomes of People Living with SB-National Spina Bifida Patient Registry U01DD001237-02; Component C-Research Approaches to Improve the Care and Outcomes of People Living with Spina Bifida- (UMPIRE) U01DD001236-02.

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