SUMMARY

Congenital anomalies of the kidney and urinary tract are the leading cause of end-stage renal disease in childhood. The solitary functioning kidney represents an important condition among the broad spectrum of urinary tract malformations, and has been associated with an impaired renal prognosis. Nevertheless, evidence-based clinical guidelines for individuals with solitary functioning kidneys have not been established.

To study the clinical outcome of solitary functioning kidney, the following research questions are addressed in this thesis:
1. What is the incidence of a solitary functioning kidney in childhood?
2. What is the incidence of renal injury in children with a solitary functioning kidney?
3. What are the risk factors for renal injury in children with a solitary functioning kidney?
4. Are estimating equations for GFR and office blood pressure measurement accurate applications in the clinical monitoring of children with a solitary functioning kidney?
5. What known and novel genetic factors can be identified in children with a solitary functioning kidney?

The rationale behind this thesis is further described in Chapter 1. This chapter provides a comprehensive overview of human and animal studies on renal mass reduction from childhood. Furthermore, the introduction describes the well-defined glomerular hyperfiltration hypothesis, which may underlie the impaired renal outcome of children with a solitary functioning kidney. Finally, recommendations for the clinical management of these patients are presented. In Chapter 2, the aims and outline of this thesis are presented with a brief overview of the methodology used.

In Chapter 3, we performed a systematic review on associated malformations of the kidney and urinary tract as well as extra-renal anomalies in patients with unilateral renal agenesis. Unilateral renal agenesis is a frequent cause of the congenital type of a solitary functioning kidney. Based on 43 eligible studies, 32% of individuals had associated urinary tract malformations. Of these, vesicoureteral reflux was the most commonly found anomaly (24%). Extra-renal manifestations were identified in 31% of patients. Moreover, the general incidence of unilateral renal agenesis was determined by analysis of the reported literature, and calculated to be 1 in ~2,000 births.

In Chapter 4, a similar approach was used to determine additional urinary tract malformations and extra-renal anomalies in patients with a unilateral multicystic dysplastic kidney. Together with unilateral renal agenesis, the multicystic dysplastic kidney represents the spectrum of conditions leading to a congenital solitary functioning kidney. Based on data from 19 populations, the general incidence of a unilateral multicystic dysplastic kidney was determined to be 1 in ~4,300 births. Associated urinary tract mal-
formations were found in 31% of patients, with vesicoureteral reflux identified as the most frequent anomaly (20% of cases). Extra-renal anomalies were detected in 15% of individuals.

The incidence of renal dysfunction in children with a solitary functioning kidney was studied in Chapter 5. In this retrospective study, we identified signs of renal injury, defined as the presence of hypertension and/or albuminuria and the use of antihypertensive/antiproteinuric agents, in 32% of children with a solitary functioning kidney. Moreover, we demonstrated that glomerular filtration rate declines from the beginning of puberty onwards. This decline is even more pronounced when children had additional urinary tract malformations.

The prognosis of individuals with solitary functioning kidneys is often derived from the excellent outcome of adult uninephric kidney donors. However, fundamental differences exist between both patient groups, which make it inadequate to assume that a solitary functioning kidney from childhood is harmless. In Chapter 6, we describe these discrepancies and emphasize why it is highly desirable to be born with two kidneys.

In Chapter 7, renal injury development during childhood was investigated in the largest cohort of solitary functioning kidney patients known to date (n=407). By performing Kaplan-Meier analysis, we identified that 50% of the children had developed at least one sign of renal injury at a median age of 15 years. This prognosis is even further impaired when ipsilateral urinary tract anomalies are present (median age toward renal injury: 13 years). Moreover, risk factors for renal injury development were age, associated malformations of the kidney and urinary tract and a small renal size. Low birth weight and a history of urinary tract infections showed a trend to increase the risk for renal injury. These findings imply that children with a solitary functioning kidney require regular clinical follow-up. At the time of diagnosis, an evaluation of risk factors should be made in order to improve the clinical outcome.

Gender differences in the incidence of congenital anomalies of the kidney and the urinary tract have been well established. However, it is unclear whether these gender differences also impact the renal prognosis. Although there is a male predominance in the incidence of solitary functioning kidney patients, no differences in the outcome between boys and girls were identified (Chapter 8).

The measurement of true glomerular filtration rate is cumbersome and costly, and therefore not routinely performed in children. As an alternative, pediatricians use equations to estimate glomerular filtration rate in daily clinical care. However, these equations have exclusively been designed in children with two kidneys, and, thus, using them in solitary functioning kidney patients may be inaccurate. In Chapter 9, we tested six commonly used equations for glomerular filtration rate by comparing them to a true measurement of renal function. Five of these common equations can be safely used in the monitoring of renal function of children with a solitary functioning kidney.
Blood pressure is an important clinical parameter in the development of renal dysfunction of solitary functioning kidney patients. We presented the blood pressure profiles of 24-hour ambulatory measurements of children with a solitary functioning kidney and compared them to the commonly used office blood pressure measurement (Chapter 10). Our findings indicate that regular 24h-ambulatory measurement is recommended in the clinical follow-up of solitary functioning kidney patients.

Genetic factors are increasingly recognized as the cause of a solitary functioning kidney from childhood. We described the difficulties in the discovery of genes that are implicated in renal and urinary tract malformations in Chapter 11. Furthermore, we presented important recommendations in order to unravel the genetic architecture of congenital anomalies of the kidney and urinary tract.

In Chapter 12, we performed genetic studies on the incidence of structural variants in children with both types of a solitary functioning kidney. We demonstrate that a genomic disorder can be identified in 14% of study subjects. Although this proportion appears low, this finding is a relatively important addition to our current understanding of genetic disease in solitary functioning kidney patients. Furthermore, we prioritized new disease-causing genes for renal malformations by performing a systematic computational approach and determining expression levels of candidate genes in the embryonic mouse kidney. The findings from this study are an important first step in unraveling the molecular mechanisms of renal maldevelopment.

Conclusions from our studies as well as methodological considerations, recommendations for future research and clinical management are described in Chapter 13:

1. The incidence of a congenital solitary functioning kidney should be divided into unilateral renal agenesis: 1 in ~2,000 births; and unilateral multicystic dysplastic kidney: 1 in ~4,300 births.
2. Based on two systematic reviews of the literature, as well as the largest cohort study performed to date, 1 in 3 children with a solitary functioning kidney has at least one sign of renal injury in childhood.
3. Renal injury is associated with increasing age, the presence of additional congenital anomalies of the kidney and urinary tract and a small renal size. Low birth weight and urinary tract infections show a trend with renal injury.
4. Glomerular filtration rate should be monitored by equations that combine serum creatinine and serum cystatin C. If serum cystatin C is not available, the commonly used estimating equation by Schwartz et al. provides an appropriate alternative. The urinary clearance of creatinine however, should be abandoned. Office blood pressure measurement may miss hypertension in a substantial proportion of children. Therefore, we recommend regular determination of blood pressure profiles by 24h-ambulatory blood pressure monitoring.
5. Disease-causing mutations in common genes were absent in our cohort. However, copy-number disorders (deletions and duplications) play an important role in the development of renal malformations. By using a systematic approach, these deletions and duplications allow us to define new genetic causes for a solitary functioning kidney.