Questions we will address

• What is the evidence for increased risk of CKD with kidney stones?
• Are stone formers at increased risk for ESRD?
• What subgroup of stone formers have the most risk of CKD?
• Is the risk of CKD and ESRD limited to only certain types of stone formers (rare genetic diseases, struvite)?
• Are asymptomatic (incidental radiographic) stone formers at risk for CKD?
Evidence of increased risk of CKD with kidney stones

Increased risk of kidney stone history in incident CKD patients compared to community controls

- **Cases:** Newly diagnosed CKD by ICD9 codes and confirmed by two or more elevated SCr levels >1.5 mg/dl (n=548).

- **Controls:** Random digit dialing and Medicare recipient listings frequency matched to cases on age, sex, race, location (n=514).

- **History of nephrolithiasis** by chart review in cases and by interview in controls.

- **CKD risk was predominantly interstitial nephritis (pyelonephritis)**

<table>
<thead>
<tr>
<th>Disease</th>
<th>N cases (% stones)</th>
<th>OR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic renal disease (all)</td>
<td>548 (16.8)</td>
<td>1.9</td>
<td>(1.1, 3.4)</td>
</tr>
<tr>
<td>Nephrosclerosis</td>
<td>104 (12.5)</td>
<td>1.1</td>
<td>(0.4, 3.0)</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>108 (14.8)</td>
<td>2.5</td>
<td>(0.9, 7.0)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>76 (11.8)</td>
<td>0.8</td>
<td>(0.3, 2.5)</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>106 (27.4)</td>
<td>3.4</td>
<td>(1.5, 7.4)</td>
</tr>
<tr>
<td>ESRD</td>
<td>36 (13.9)</td>
<td>1.5</td>
<td>(0.3, 8.8)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>118 (17.0)</td>
<td>1.1</td>
<td>(0.4, 2.9)</td>
</tr>
</tbody>
</table>

Vupputuri S et al, AEP, 2004
eGFR lower for stone formers in the general population with BMI>27

- NHANES III sample
- 5.7% stone formers
- Adjusted for age, sex, race, BP, diuretics
- For BMI >27: eGFR lower in stone formers (-3.4 ml/min/1.73 m²) (p=0.005)
- For BMI <27: No difference (p=0.29)

Gillen DL et al, Kidney Int, 2005

Population-based studies of kidney stones as risk factors for CKD

- Risk factor for CKD in Thailand
- 3459 subjects surveyed with concurrent eGFR and UACR measures
- 5% reported a history of kidney stones
- 18% had CKD (eGFR<60 or UACR>30 or RBC >5/HPF)
- Multivariable adjusted OR = 2.7 (95% CI: 1.6 to 4.7)
- Adjusted for age, sex, diabetes, hypertension, & serum uric acid

Ingsathit et al, NDT, 2010
Rochester Epidemiology Project

- Unique and unparalleled records linkage infrastructure for research
  - Data on 753,399 Olmsted County people
  - Linking together 1,454,337 individual patient records
  - Containing over 12,967,559 Outside Source diagnoses
- Data from 40 outside sources
  - Primary sources: Mayo, Olmsted Medical Center Clinic and Hospital, Rochester Family Medicine Clinic
  - Full List of REP data sources with timeframes can be found at: Data Covering 1935-Present
- 95% of the Olmsted County population has at least one clinic visit every 2-3 years allowing nearly complete enumeration of the local population!


Risk of CKD with kidney stones (matched cohort study design)

- Identified all Olmsted County, MN residents with their first (incident) kidney stone between 1984 and 2003.
  - Stone formers by ICD-9 codes (n=5081): 592, 594.11, and 274.11.
  - Controls matched (3:1) (n=14,144) on:
    - Age and Sex
    - Length of medical record
    - Clinic visit at time of stone event (baseline date)

Rule et al, CJASN, 2009
Prevalent versus incident CKD based on a clinical diagnosis

Index Date
(stone event or clinic visit for controls)

Prevalent CKD

Incident CKD

-19 years

0

+3 months

Incident CKD

Prevalent CKD

Prevalent Co-morbidities
(based on ICD9, HICDA, and Berkson codes)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incident Stone Formers</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>9.6%</td>
<td>7.4%</td>
</tr>
<tr>
<td>Obesity</td>
<td>24.3%</td>
<td>20.9%</td>
</tr>
<tr>
<td>Gout</td>
<td>3.4%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19.9%</td>
<td>17.0%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>21.4%</td>
<td>18.3%</td>
</tr>
<tr>
<td>Alcohol Dependency</td>
<td>5.5%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Tobacco</td>
<td>14.8%</td>
<td>15.7%</td>
</tr>
<tr>
<td>CAD</td>
<td>7.4%</td>
<td>6.7%</td>
</tr>
<tr>
<td>CHF</td>
<td>2.3%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Stroke</td>
<td>3.1%</td>
<td>2.8%</td>
</tr>
<tr>
<td>PVD</td>
<td>4.6%</td>
<td>4.3%</td>
</tr>
</tbody>
</table>

Rule et al, CJASN, 2009
### Prevalent CKD (clinical diagnosis)

<table>
<thead>
<tr>
<th>CKD timing prior to index date</th>
<th>Stone Former</th>
<th>Controls</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior CKD</td>
<td>4746 (93.3%)</td>
<td>13713 (96.9%)</td>
<td>1.00</td>
<td>NA</td>
</tr>
<tr>
<td>&gt; 5 years prior</td>
<td>73 (1.44%)</td>
<td>170 (1.20%)</td>
<td>1.20</td>
<td>0.91, 1.58</td>
</tr>
<tr>
<td>1 to 5 years prior</td>
<td>76 (1.50%)</td>
<td>157 (1.11%)</td>
<td>1.35</td>
<td>1.03, 1.78</td>
</tr>
<tr>
<td>0 to 1 years</td>
<td>46 (0.90%)</td>
<td>47 (0.33%)</td>
<td>2.74</td>
<td>1.82, 4.12</td>
</tr>
<tr>
<td>0 to 90 days after index date</td>
<td>142 (2.79%)</td>
<td>60 (0.42%)</td>
<td>6.75</td>
<td>4.98, 9.14</td>
</tr>
<tr>
<td>Overall Prior CKD</td>
<td>337 (6.63%)</td>
<td>434 (3.07%)</td>
<td>2.24</td>
<td>1.94, 2.60</td>
</tr>
</tbody>
</table>

Rule et al, CJASN, 2009

### Incident stone formers (years 1986-2003) n=4,774

- Baseline clinical chronic kidney disease (CKD)
- Baseline elevated serum creatinine (Scr)
- Follow up <90 days

**Event:** Clinical CKD or Elevated Scr

**Censoring:** Last clinic visit

<table>
<thead>
<tr>
<th>Stone formers n=4,066</th>
<th>Non-stone formers n=10,150</th>
</tr>
</thead>
<tbody>
<tr>
<td>-331</td>
<td>-403</td>
</tr>
<tr>
<td>-81</td>
<td>-127</td>
</tr>
<tr>
<td>-296</td>
<td>-2,295</td>
</tr>
</tbody>
</table>

Matched non-stone formers (3:1 on age, sex, index date) n=12,975
Risk of clinically diagnosed CKD in stone formers adjusting for baseline & time-dependent co-morbidities

<table>
<thead>
<tr>
<th>Adjusting factors</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>1.66</td>
<td>1.49, 1.86</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>age, sex, Diabetes</td>
<td>1.66</td>
<td>1.48, 1.85</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>age, sex, Obesity</td>
<td>1.65</td>
<td>1.48, 1.85</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>age, sex, Essential Hypertension</td>
<td>1.63</td>
<td>1.46, 1.82</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>age, sex, Gout</td>
<td>1.65</td>
<td>1.48, 1.85</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>age, sex, Tobacco Use</td>
<td>1.68</td>
<td>1.50, 1.87</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>age, sex, Coronary Artery Disease</td>
<td>1.62</td>
<td>1.45, 1.81</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>age, sex, Cerebral Infarct</td>
<td>1.66</td>
<td>1.49, 1.85</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>age, sex, CHF</td>
<td>1.64</td>
<td>1.47, 1.84</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>age, sex, Alcohol Dependency</td>
<td>1.68</td>
<td>1.51, 1.88</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>age, sex, Hyperlipidemia</td>
<td>1.63</td>
<td>1.46, 1.82</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>age, sex, Peripheral Vascular Disease</td>
<td>1.65</td>
<td>1.48, 1.85</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>fully adjusted</td>
<td>1.60</td>
<td>1.43, 1.79</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
Prevalent versus incident CKD based on SCr

Index Date
(stone event or clinic visit for controls)

-3 years -1 month 0 +3 months

Prevalent ↑SCr
Ignore SCr
Incident ↑SCr
Risk of Sustained $\uparrow$SCr ($>1.3$ M, $>1.1$ F)

Cumulative incidence (%) vs. Years

- Stone formers
- Controls

Rule et al, CJASN, 2009

Risk of Sustained eGFR$<60$ ml/min/1.73 m$^2$

Cumulative incidence (%) vs. Years

- Stone formers
- Controls

Rule et al, CJASN, 2009
Incident stone formers (years 1986-2003) 
\[ n = 4,774 \]

Matched non-stone formers (3:1 on age, sex, index date) 
\[ n = 12,975 \]

-331
-81
-296
-403
-127
-2,295

Prevalent clinical chronic kidney disease (CKD)
Prevalent elevated serum creatinine (Scr)
Follow up <90 days

Study Design

Event: Clinical CKD or Elevated Scr
Censoring: Last clinic visit

Stone formers 
\[ n = 4,066 \]

Non-stone formers 
\[ n = 10,150 \]

-1,097

Event: Elevated Scr
Censoring: Last Scr test

Stone formers 
\[ n = 2,969 \]

Non-stone formers 
\[ n = 6,171 \]

-3,979

Risk of CKD with kidney stones independent of co-morbidities

<table>
<thead>
<tr>
<th>CKD Definition</th>
<th>Unadjusted HR (95%CI)</th>
<th>Co-morbidity Adjusted HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical CKD by Diagnostic code</td>
<td>1.67 (1.48, 1.88)</td>
<td>1.56 (1.39, 1.77)</td>
</tr>
<tr>
<td>Clinical CKD by Diagnostic code Limited to persons with follow-up Scr levels</td>
<td>1.59 (1.41, 1.80)</td>
<td>1.31 (1.10, 1.57)</td>
</tr>
<tr>
<td>Sustained elevated Scr</td>
<td>1.46 (1.22, 1.74)</td>
<td>1.36 (1.13, 1.62)</td>
</tr>
<tr>
<td>Sustained elevated Scr Limited to persons with follow-up Scr levels</td>
<td>1.26 (1.05, 1.51)</td>
<td>1.25 (1.04, 1.49)</td>
</tr>
</tbody>
</table>

Trade-off between a detection bias or a selection bias.
Evidence of an increased risk of ESRD with kidney stones

Population-based study of kidney stones as risk factors for ESRD

- Risk factors for incident CKD in England & Wales
- QResearch Database (775,091 women in clinical database)
- 0.7% had kidney stones by diagnosis/procedure at baseline
- CKD defined by ESRD or eGFR<45 or proteinuria
- CKD Incidence 58/10,000 women-yrs
  - Multivariable adjusted Risk of CKD: HR=1.3 (95% CI 1.1 to 1.5)
- ESRD incidence 3/10,000 person-yrs
  - Multivariable adjusted Risk of ESRD: HR=2.1 (95% CI 1.3 to 3.2)
- No independent risk of CKD or ESRD with stones in men

Hippisley-Cox et al, BMC Fam Prac, 2010
History of kidney stones more prevalent in African Americans with ESRD

- **Cases**: 300 African Americans undergoing outpatient hemodialysis at the University of Chicago.
- **Controls**: 5,341 African Americans participating in NHANES III national survey.
- **Exposure**: “Have you ever had a kidney stone?” on a questionnaire.
- **Results**:
  - Prevalence of kidney stones:
    - ESRD: 8% vs Controls: 3% (p<0.001)
  - Of the 25 ESRD patients with stones:
    - 5 had a stone episode within 3 years of starting dialysis.
    - 2 had ESRD attributed to stones.
    - No staghorn, primary hyperoxaluria, cystinuria, or bowel disease stones.

End-Stage Renal Disease (Dialysis, Transplant, or Death with CKD)

- **Cumulative incidence (%)**
  - **Stone formers**: P=0.25
  - **Controls**

Rule et al, CJASN, 2009
Risk of ESRD revisited

- Prior analysis relied on internal databases for ESRD and excluded baseline CKD.
- Repeated analysis USRDS database and internal ESRD databases with chart review (92 events).
- Incidence of ESRD
  - **Stone formers**: 1.0 (95% CI: 0.7 to 1.4) events per 1000 person-years
  - **Controls**: 0.5 (95% CI: 0.4 to 0.7) events per 1000 person-years
- Age-sex-adjusted HR=1.9 (95% CI: 1.3 to 2.9)
- Fully-adjusted HR=1.8 (95% CI: 1.2 to 2.7)
- Of the 41 stone formers who developed ESRD, only 3 had kidney stones as primary cause

ESRD attributed to kidney stones

- **Sample**: 1391 consecutive ESRD patients from 1989 to 2000 (Paris, France)
- ESRD attributed primarily to kidney stones in 3.2% (n=45)
  - Struvite stones in 42% (n=19)
  - Calcium stones in 27% (n=12)
    - 4 severe hypercalcuria
    - 2 primary hyperparathyroidism with nephrocalcinosis
    - 5 medullary sponge kidney with hypercalcuria
    - 2 recurrent UTIs
    - 1 distal RTA (sjogren’s)
  - Uric acid stones in 18% (n=8)
  - Hereditary stones in 13.3% (n=6)
    - 4 primary hyperoxaluria
    - 2 cystinuria
- Solitary functioning kidney in 40% (n=18)
Risk of CKD by stone type

Creatinine clearance lower in stone former (n=1856) compared to normals (n=153)

Worcester EM et al, J Urol, 2006
**Nested Case/Control study with in stone former cohort**

- What type of stone formers are at increased risk of CKD?
- 53 stone formers with CKD matched to 106 controls without CKD.
- Hypertension, diabetes, frequent UTIs, struvite stones, and allopurinol use were associated with CKD.
- **Stone type unknown in 50% of community stone formers**
- Number of stone episodes and surgical procedures not associated with CKD
- Study was had limited power (could only detect OR > 3)

---

**Kidney loss in stone formers**

- **Sample:** 3266 stone formers at a stone clinic (Univ. of Chicago)
- 115 (3.5%) had loss of function in one kidney:
  - 29% from stones (staghorn or high burden)
  - 23% from infection
  - 21% from obstruction
- More rapid decline in urinary creatinine clearance with age in stone formers over age 45 years.
Asymptomatic stone formers

General population

Known CKD, severe stone disease, some risk factors, or poor health

Potential kidney donors

Kidney Measurements Available
- Serum Creatinine
- Urine albumin (spot)
- ESRD
- Symptomatic stones
- GFR (iothalamate)
- CT Angio/urogram (Asymptomatic stones)
- 24-h urine studies
- Ambulatory BP

Restricted range of pathology (similar to healthy volunteer bias), but potentially more valid measurements for renal injury
Kidney stones may be the most common incidental radiological abnormalities that contribute to potential kidney donor exclusion

n=132

- Parenchymal abnormality (n=38)
- Kidney stones with or without associated abnormalities (n=51)
- Congenital abnormality of kidney position or solitary kidney (n=5)
- Upper urinary tract dilatation (n=2)
- Renal artery abnormality (n=36)

Lorenz E et al., CJASN, 2010

- 1957 potential kidney donors
- 53 (3%) past symptomatic stones
- 25 had radiographic stones
- 185 (10%) had radiographic stones only
- 1719 (87%) had no evidence of stones

Among persons with radiographic stones, past symptomatic stones were predictive of more stones and of larger stones:

A. Total number of radiographic stones

B. Diameter of largest stone (mm)
## Kidney stones and kidney function/morphology

<table>
<thead>
<tr>
<th>Kidney function measure</th>
<th>Group 1: No radiographic or past symptomatic stones (N=1719)</th>
<th>Group 2: Asymptomatic radiographic stones only (N=185)</th>
<th>Group 3: Past symptomatic stones (N=53)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR, ml/min/1.73 m²</td>
<td>Mean or %</td>
<td>Mean or %</td>
<td>Mean or %</td>
<td>Group 1 vs 2</td>
</tr>
<tr>
<td></td>
<td>101</td>
<td>102</td>
<td>102</td>
<td>0.29</td>
</tr>
<tr>
<td>24-h urine alb &gt;15 mg</td>
<td>9.0%</td>
<td>11%</td>
<td>23%</td>
<td>0.49</td>
</tr>
<tr>
<td>24-h urine alb &gt;30 mg</td>
<td>3.5%</td>
<td>3.6%</td>
<td>13%</td>
<td>0.96</td>
</tr>
<tr>
<td>Focal scarring</td>
<td>2.9%</td>
<td>8.1%</td>
<td>11%</td>
<td>0.0002</td>
</tr>
<tr>
<td>Parenchymal thinning</td>
<td>0.6%</td>
<td>2.7%</td>
<td>1.9%</td>
<td>0.004</td>
</tr>
</tbody>
</table>

## Population based study of radiographic stones and CKD

- Risk factors for CKD in China
- 2596 subjects randomly recruited for a survey with eGFR and UACR measures
- 2.2% had kidney stones **by ultrasound**
- 12% had CKD (eGFR<60 or UACR>30)
- Prevalence of sonographic kidney stones:
  - CKD 5.6%
  - No CKD 1.7%
  - Multivariable adjusted OR=2.9 (p=0.02)

Chen et al, NDT, 2009
Conclusion

• As a group, symptomatic stone formers are at increased risk of developing CKD and ESRD.

• Nephrolithiasis and CKD share many of the same risk factors (hypertension, diabetes, obesity, hyperuricemia) but there is an association independent of these risk factors.

• The risk of CKD varies by type of kidney stone.
  • Rare genetic diseases and struvite stone formers clearly have increased risk.
  • It is unknown if common calcium stone formers with infrequent episodes have an increased risk.

• Unlike symptomatic stone formers, persons with small incidental asymptomatic stones may not have the same risk of CKD.

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• Eric Bergstralh
• Bill Li
• Joseph Melton

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• Janell Keehn
• Brittni Barnett
• Diane Carlson
• Cynthia Nosek
• Tamara Ellefson-Briske

Laboratory Technologists
• Zejfa Haskic
• Samuel Edeh

Programmers
• Brian Crownhart
• Jeremy Palbicki
Characteristics of radiographic vs symptomatic stone formers

• 11% (n=210) of potential donors had radiographic stones
  - Age >45 y 11%, ≤45 y 10% (p=0.62)
  - Men 11%, Women 11% (p=0.80)
  - Whites 11%, Other 7% (p=0.023)

• 2.7% (n=53) had past symptomatic stones
  - Age >45 y 3.9%, ≤45 y 1.7% (p=0.003)
  - Men 3.4%, Women 2.2% (p=0.12)
  - Whites 2.9%, Other 2.4% (p=0.74)

Validation of stone former classification by dx codes

• 1698 charts of Olmsted County stone formers by diagnostic code (1984-2003) reviewed over 5/09 to 9/10
  - 848 (50%) were incident symptomatic stone formers with radiographic or clinical evidence of a stone.
  - 288 (17%) were prevalent (prior to Olmsted County or 1984)
  - 245 (14%) suspect stone formers (clinical diagnosis)
  - 124 (7%) were asymptomatic radiographic stones
  - 63 (4%) were bladder stones only
  - 134 (8%) Not valid - nothing to suggest stone disease
  - Conversely, 92% have “urolithiasis”

• Had only planned to review 1000 charts from 1984-1990.
• Added another nurse abstractor to target all 4900 charts (Currently reviewing 180 charts per month).
Prevalence of radiographic abnormalities of the renal arteries or kidneys and their impact on approval for donation (n=1957)

- Abnormality perceived as absolute contraindication and contributed to exclusion (n=10)
- Abnormality perceived as relative contraindication and contributed to exclusion (n=122)
- Abnormality perceived as relative contraindication but did not contribute to approval or exclusion (n=356)
- No abnormality (n=1469)

Lorenz E et al., CJASN, 2010

Kidney Measurements Available
- Serum Creatinine
- Urine albumin (spot)
- ESRD
- Symptomatic stones
- GFR (iothalamate)
- CT Angio/urogram (Asymptomatic stones)
- 24-h urine studies
- Ambulatory BP

- Renal Histology → ‘Nephrosclerosis’
An operational definition for ‘nephrosclerosis’ in kidney donors

- Determined number of different microstructures in the renal cortex with abnormalities:
  - Glomeruli (any global sclerosis)
  - Tubules (any atrophy)
  - Interstitium (fibrosis >5%)
  - Arteries (any arteriosclerosis)

- Sclerosis score = sum of abnormalities (0-4)

- Nephrosclerosis = 2 or more different abnormalities

Rule AD et al, Ann Intern Med, 2010

Sclerosis score by age group

Nephrosclerosis defined by a sclerosis score of 2 or higher has an overall prevalence of 28%.
Kidney stones and renal histology

- 1159 actual kidney donors with implantation renal biopsies (manually reviewed)
- 107 (9.4%) had radiographic stones (CT scan)
- 21 (1.8%) have past symptomatic stones
- Urine albumin excretion and nocturnal blood pressure were associated with nephrosclerosis after age-adjustment
- Radiographic and past symptomatic stones were not associated with nephrosclerosis.