TOPIC 1: DIAGNOSIS

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Disclosure of Interests

David H. Ellison, MD

< **Pfizer**>

- Invited speaker, International Aldosterone Forum, Tokyo, Japan, May 2016, includes modest honorarium

Question #1: Definition of Gitelman's Syndrome

- Gitelman's syndrome (GS) is a salt-losing tubulopathy characterized by hypokalemic alkalosis with hypomagnesemia and hypocalciuria
- GS is caused by inactivating mutations in the SLC12A3 gene that codes for the thiazide-sensitive sodium chloride cotransporter…

Question:

- Is GS a clinical diagnosis?
- Is GS defined by the presence of SLC12A3 mutations on both alleles?
- Note: Lin and colleagues could account for 65% of 'missing' mutations as deep intronic mutations, but not all.
- What do we call folks with 1 SLC12A3 and one CLCNKB mutation?
- What do we call folks in whom one or two mutations can't be found, or who are not tested?

Thought

GS-suspected
GS-proved-SLC12A3
GS-variant-SLC12A3/
CLCNKB

Literature Values from Genetic GS

| year | | 1992 | 2015 Matsunoshita, | 2015 Jiang | 2011 Balavoine | 2007 Colussi | 2007 Colussi | 2012 Favre | 2011 Lo | 2011 Vargas-Poussou |
|---|---|---|---|---|---|---|---|---|---|
| author | | Betinelli | 90 | 17 | 15 | 22 | 19 | 8 | 19 | 24 |
| N | | 16 | Adult | adult | adult | Adult | child-adol | adults | 27 | ad + child |
| age | | | | | | | | | | |
| **K** | | | | | | | | | | |
| | median | 2.7 | | | | | | | | |
| | max | 3 | | | 3.5 | | | | | |
| | min | 1.4 | | | 2.2 | | | | | |
| | mean | | 2.45 | | 2.8 | 2.6 | 2.7 | 2.9 | 2 | 2.5 |
| | SD | | 0.4 | | 0.3 | 0.3 | 0.3 | 0.3 | 0.35 | 0.49 |
| **FEK** | | | | | | | | | | |
| | median | 23.9 | | | | | | | | |
| | max | 39.1 | | | | | | | | |
| | min | 7.7 | | | | | | | | |
| | mean | | | | | | | | | |
| | SD | | | | | | | | | |
| **u ca/creat** | | | | | | | | | | |
| | median | <0.01 | | | | | | | | |
| | max | 0.06 | | 0.51 | | | | | 0.19 | 0.82 |
| | min | 0.1 | | 0.02 | | | | | 0.03 | 0.03 |
| | mean | | 0.055 | 0.11 | 0.15 | 0.16 | 0.11 | 0.15 | 0.055 | 0.14 |
| | SD | | 0.08 | 0.11 | 0.11 | 0.14 | 0.06 | 0.08 | 0.03 | 0.12 (n=13) ? Unit |
| **mg** nl (.69-.94) | | | | | | | | | | |
| | median | 0.54 | | | | | | | | |
| | max | 0.62 | | 0.91 | 0.822 | | | | 0.78 | 0.3 |
| | min | 0.41 | | 0.43 | 0.41 | | | | 0.45 | 0.01 |
| | mean | | 0.65 | 0.67 | 0.66 | 0.57 | 0.66 | 0.59 | 0.57 | 0.58 |
| | SD | | 0.14 | 0.18 | 0.14 | 0.12 | 0.12 | 0.08 | 0.09 | 0.12 (n=23) |

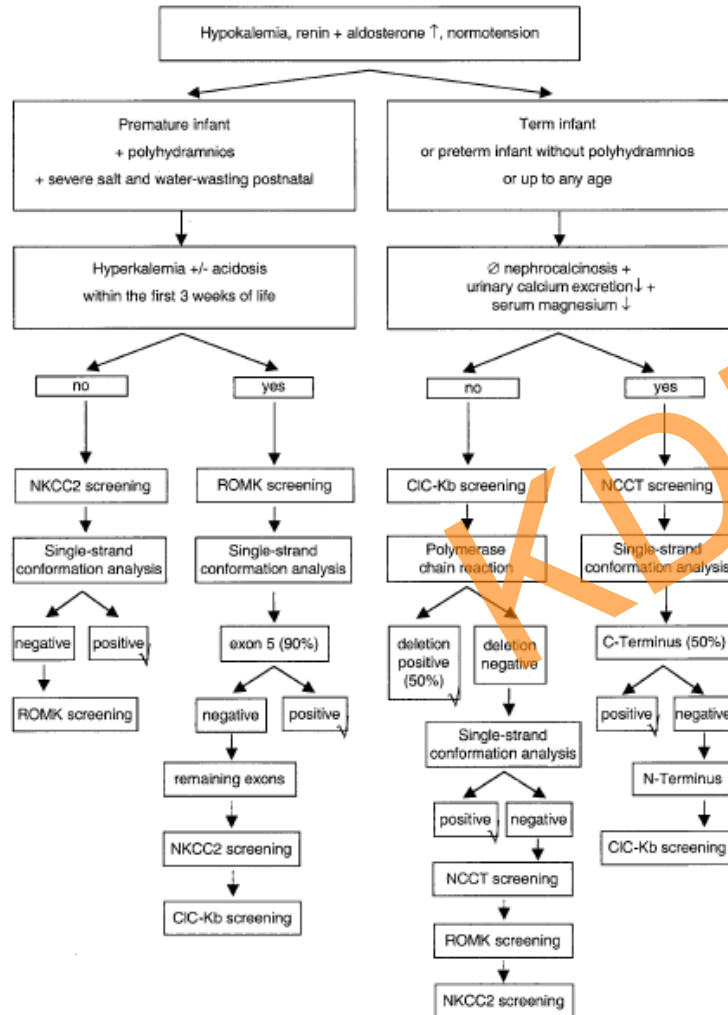# Which algorithm for hypokalemia?
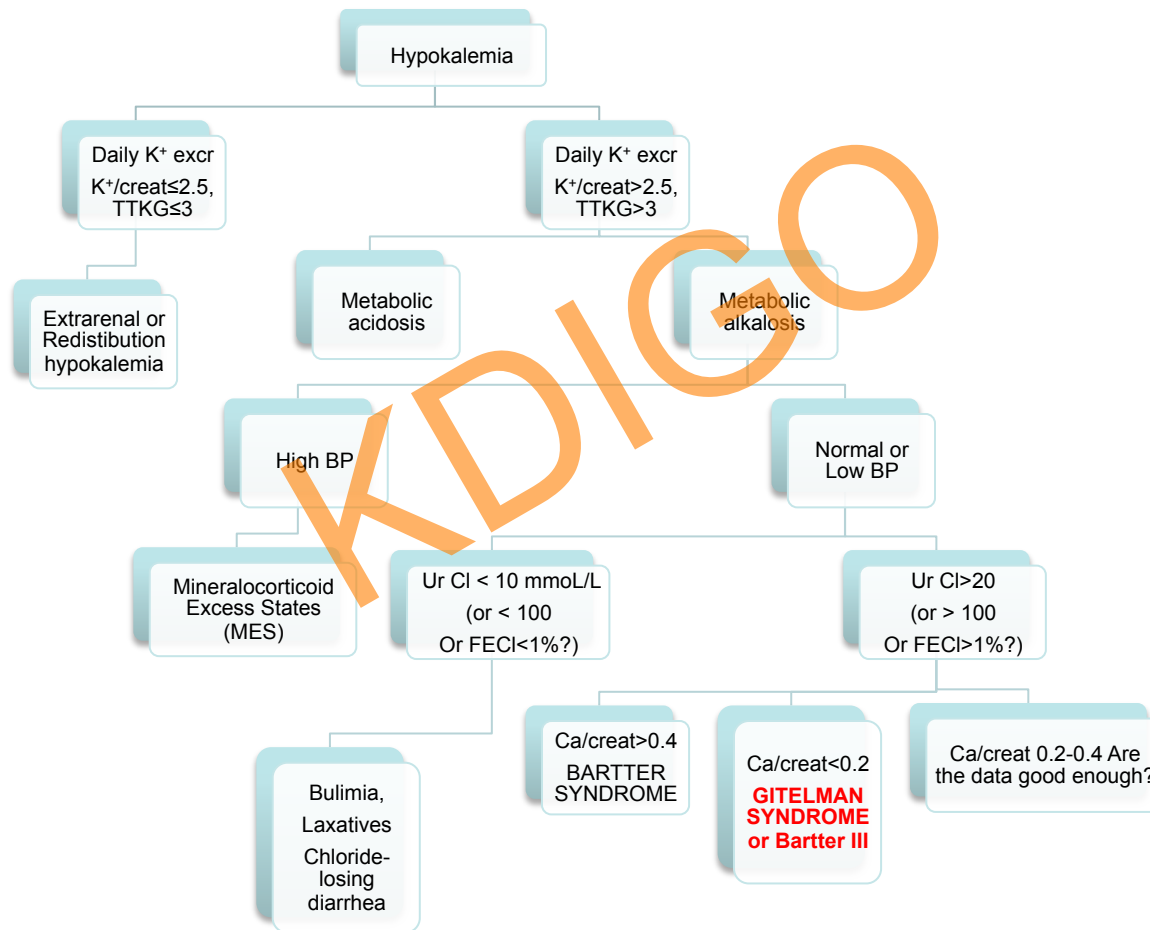

Vargas-Poussou
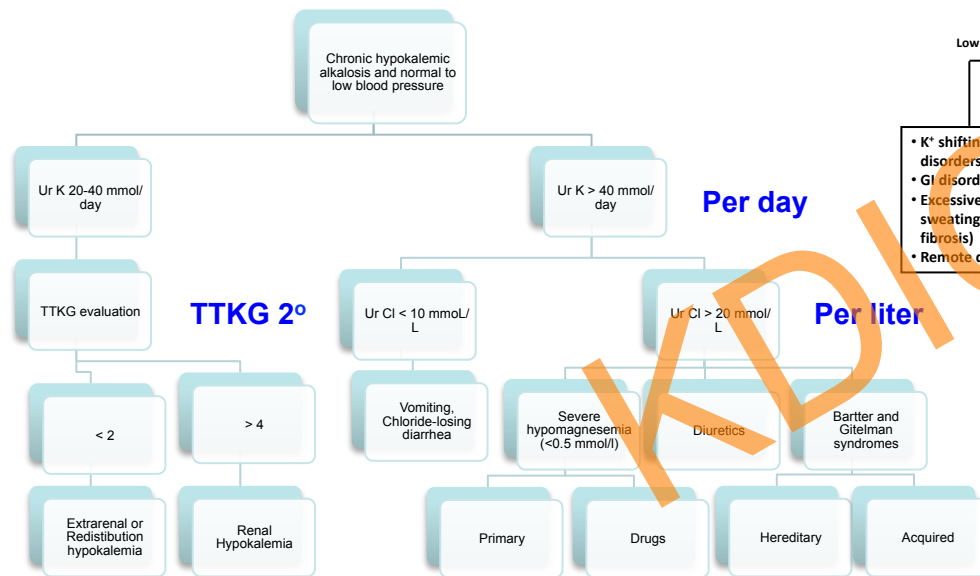
Lin
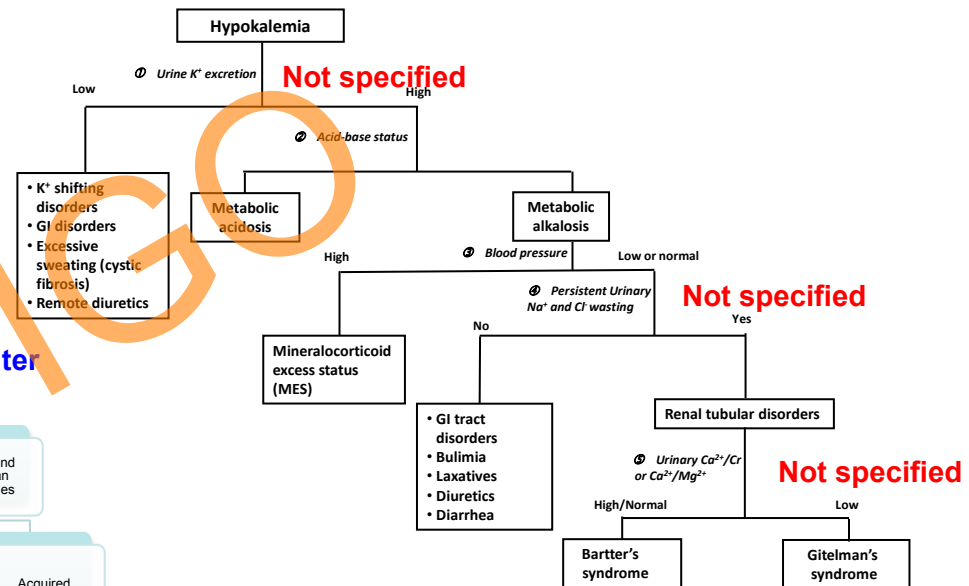
Which algorithm?

Peters et al.
Am J Med. 2002;112:183–190.

Which algorithm?

Question #2: Spot or 24 Hour Urine for K?

< Should we recommend a ‚spot' urine for diagnosis, rather than 24 hour urine or should we be agnostic?

Table 2. Comparisons between spot and 24-hour urine collections for hypokalemia

	Spot urine (Timely)	24-hour urine
Represent	Disease state	› Therapeutic course
Advantage	Faster and practical Simple and convenient More physiological Can simultaneously assess urine Na⁺, Cl⁻, divalent cation excretion Adjusted by urine creatinine (urine K⁺/Cr), osmolality (TTKG), fractional excretion (FEK⁺)	› Quantitative K⁺ balance › Can calculate creatinine clearance rate
Limitation	Diurnal urine K⁺ variation	› Time-consuming and inconvenient › Inadequate urine collection › Invalid in acute hypokalemia and emergent condition › May misdiagnose GI disorders with hypovolemic hypokalemia after volume repletion › Influenced by drugs (eg.diuretics and aminoglycoside) › May delay in diagnosis and treatment

What we'd really like to know is sensitivity, specificity, and positive and negative predictive values.
BUT few if any head to head comparisons

Question #3: What test on spot for K?

< Should we recommend a ‚spot' urine for diagnosis, rather than 24 hour urine or should we be agnostic?

Are there data to guide this decision?

For spot urines, what is the best test?

1. Fractional potassium excretion
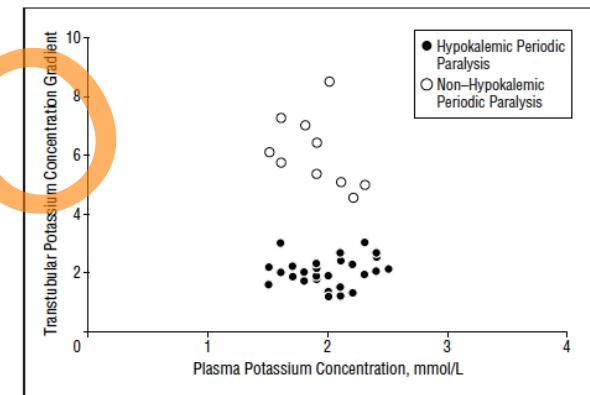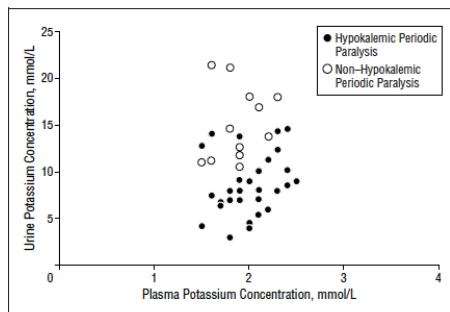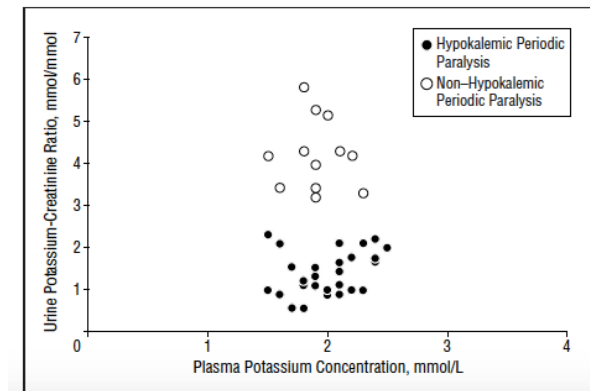
2. Urine K+/creatinine ratio (?>2.5)

3. TTKG (?>3)

Figure 2. Transtubular potassium concentration gradients in the patient cohort.
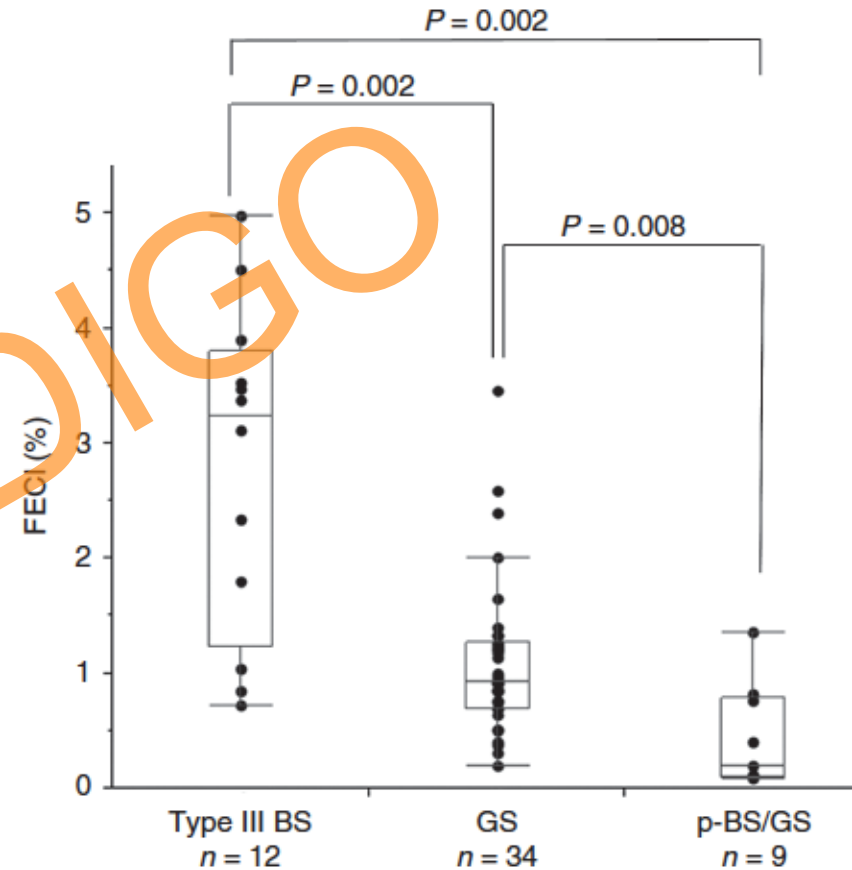
Lin et al. Arch Intern Med 2004

Question #4: Spot or 24 Hour Urine for Cl?

For 24 hour urine, what should be the cutoff? (>20, >40, >100)
For spot, should we recommend FECl?
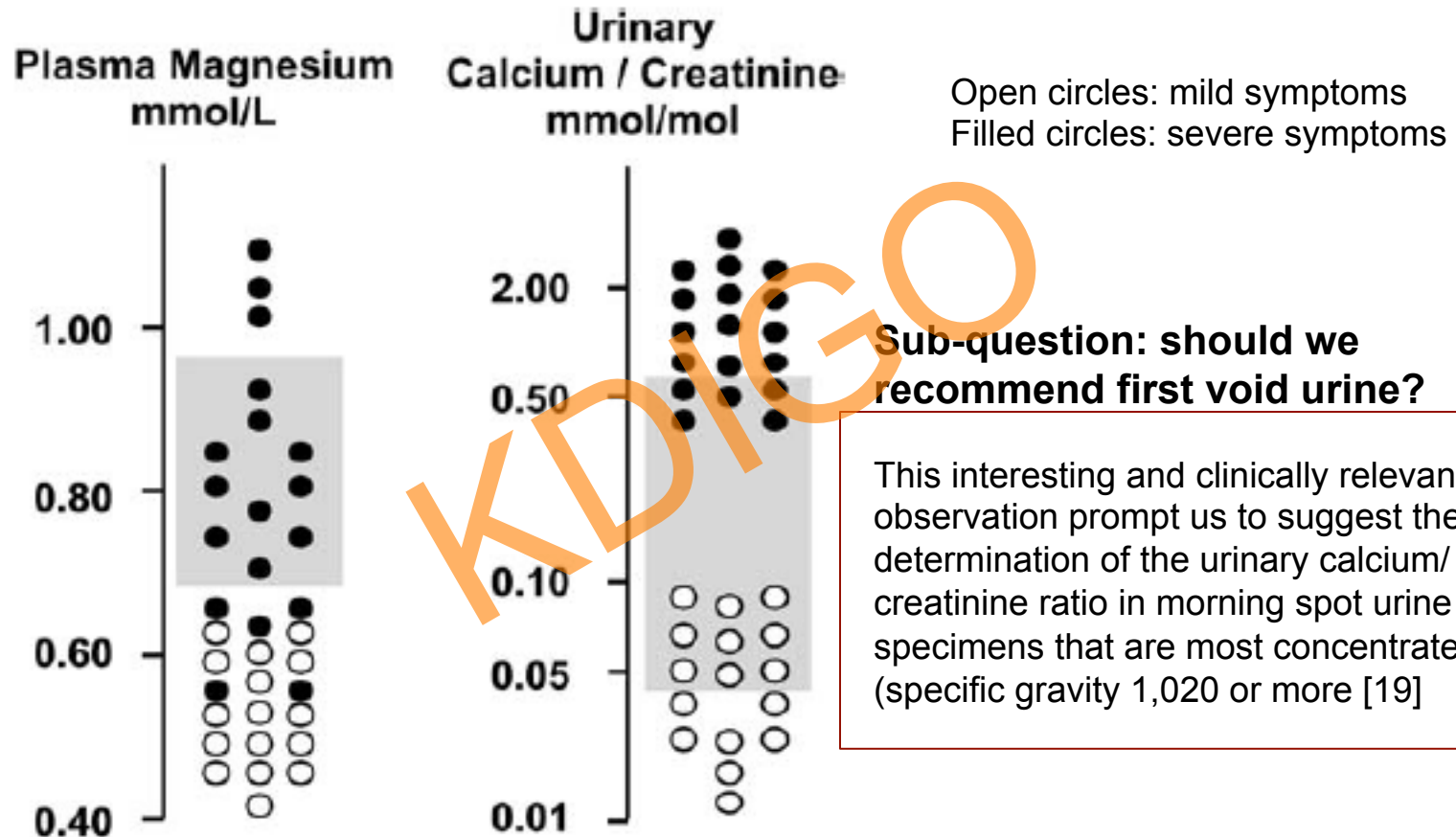
      if so, what is the cutoff?

Matsunoshita et al. 2016

Question #5: What should the Cutoff for Ca/creat be?

Open circles: mild symptoms
Filled circles: severe symptoms

Sub-question: should we recommend first void urine?

This interesting and clinically relevant observation prompt us to suggest the determination of the urinary calcium/creatinine ratio in morning spot urine specimens that are most concentrated (specific gravity 1,020 or more [19]

Betinelli 2002

Question #5: Should we give age-dependent cut-offs?

Table 1 Suggested reference values for the definition of hypocal-ciuria in Gitelman disease. The figures given represent the lower age-dependent reference value given in the literature [17] multiplied by a factor of 3

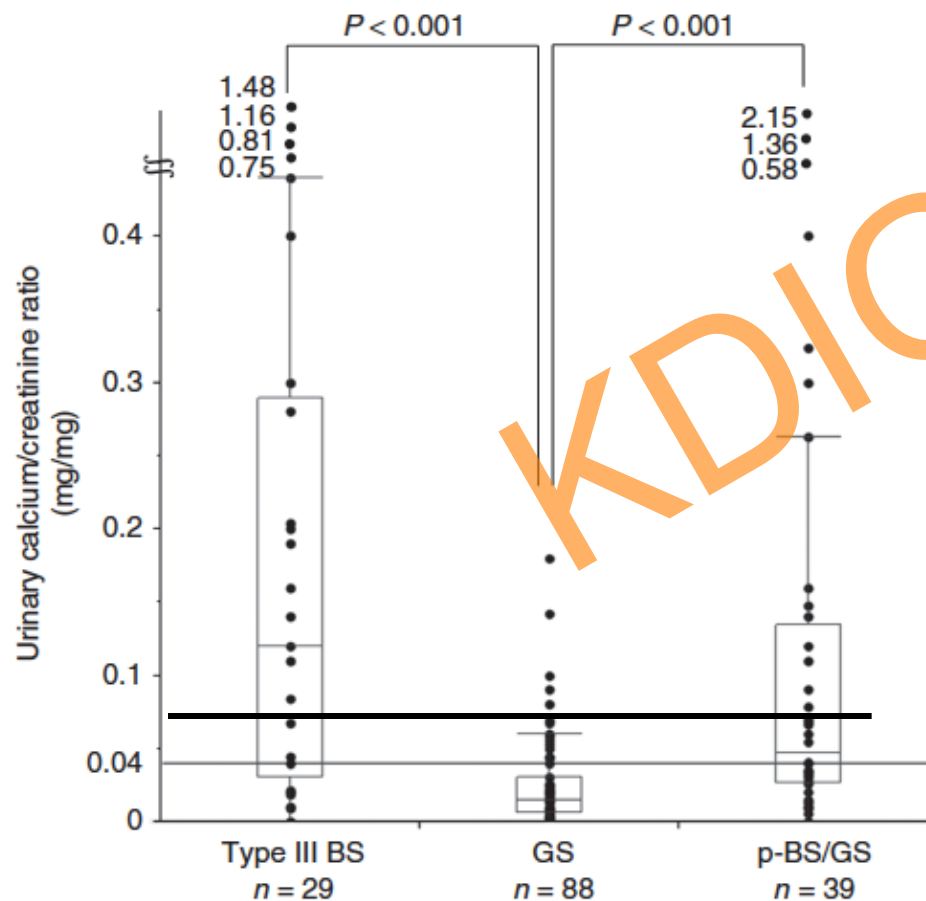| Age (years)	Calcium/creatinine (mol/mol)	Calcium/creatinine (mg/mg)
0.5–1.0	0.27	0.010
1.1–2.0	0.21	0.078
2.1–3.0	0.18	0.067
3.1–5.0	0.15	0.056
>5.1	0.12	0.044

Should be 0.1

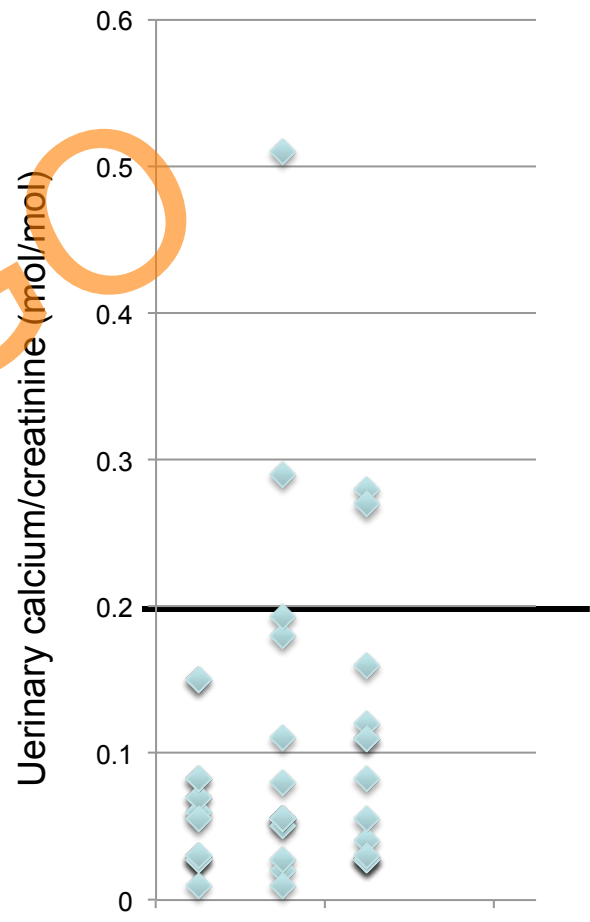Note that this is lower than 0.2, which is often recommended

Betinelli 2002

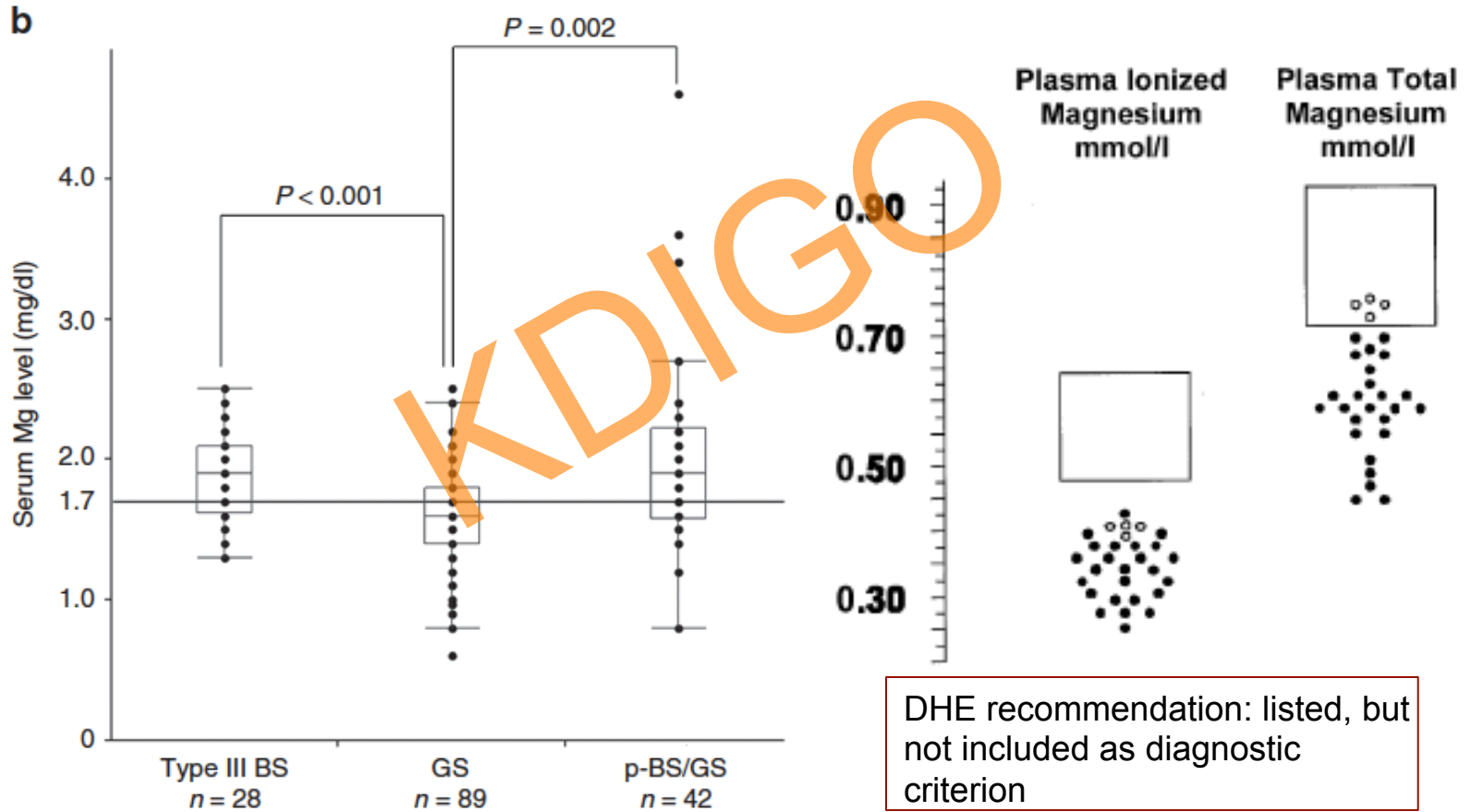# Question #5: What should the Cutoff for Ca/creat be?

From Jiang et al, 2015

Compiled From: Vargas, Lo, Jiang

Should magnesium be included?

P = 0.002

P < 0.001

Serum Mg level (mg/dl)

Type III BS
n = 28

GS
n = 89

p-BS/GS
n = 42

Plasma Ionized Magnesium mmol/l

Plasma Total Magnesium mmol/l

0.90

0.70

0.50

0.30

MATSUNOSHITA, 2015

DHE recommendation: listed, but not included as diagnostic criterion

Bettinelli, 2004

Diuretic Tests

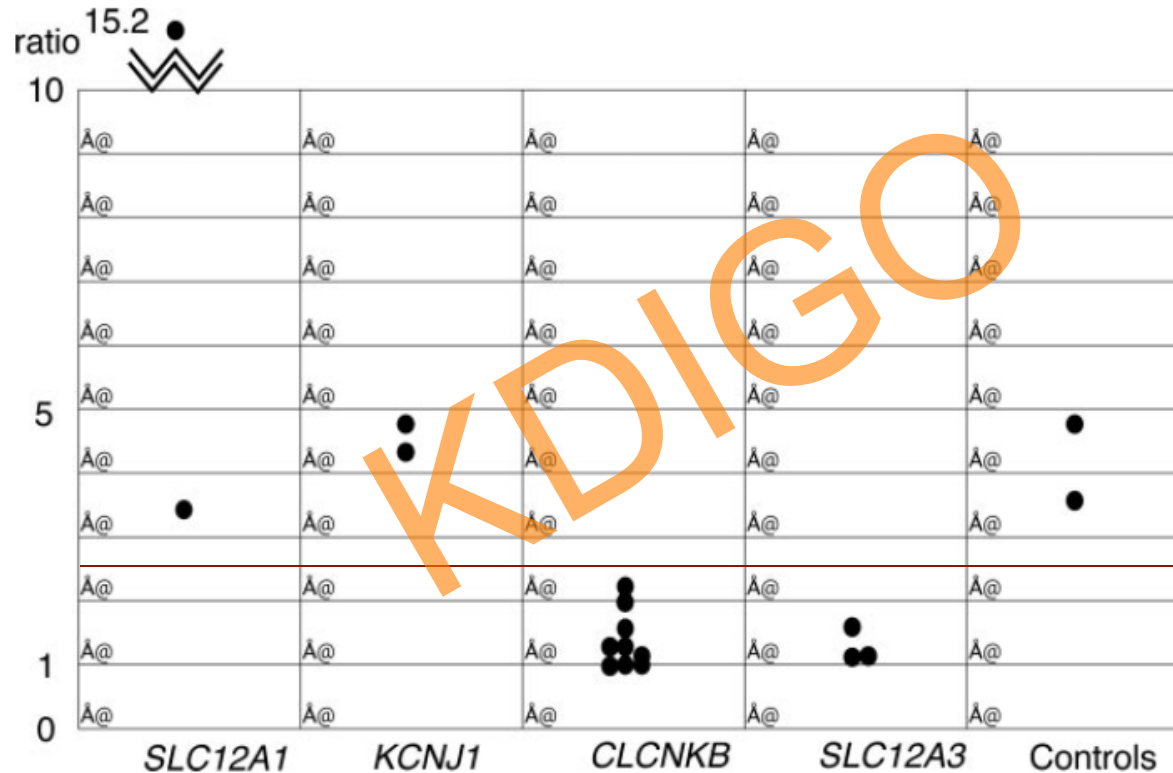|	2007	2014	2007	Total
	CJASN	Endo Prac	AJKD	
	Colussi	Jiang	Joo	
	Delta FECl <2.3%	Delta FECl <2.51	Delta FECl <2.3%	
TP	38	15	3	56
FN	3	2	2	7
TN	22	20		42
FP	0	0		0
Sens	93%	88%	60%	89%
Spec	100%	100%		100%

Furosemide Test
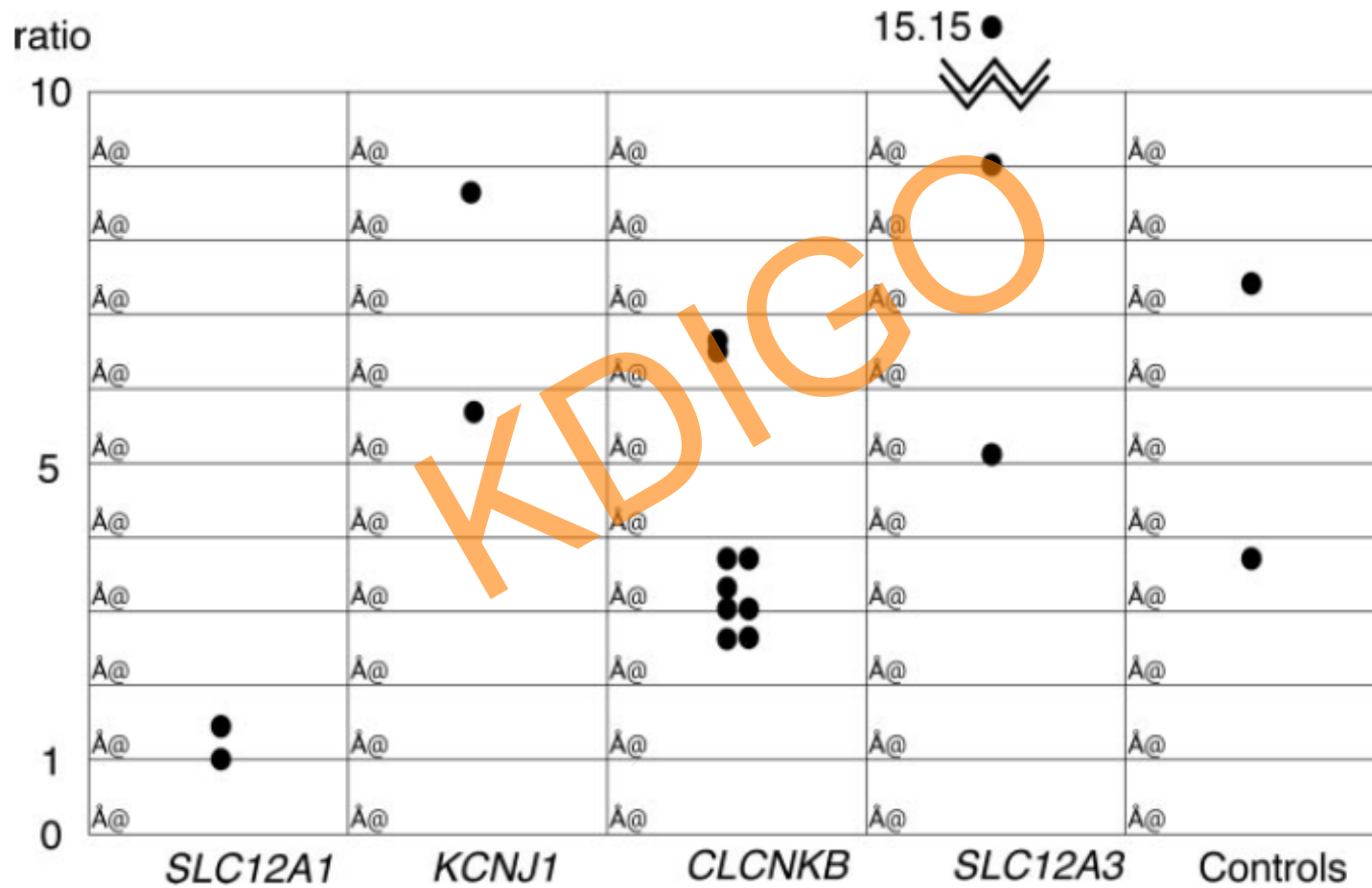
Nozu 2010

Thiazide Test

FIG. 2. Thiazide test results in the patient groups. The FECl ratio was calculated as the value after testing divided by the value before testing. Values of 1 indicate no changes of FECl after the administration of thiazide.

Note: most CLCNKB dx'd before age 3

Nozu 2010

Final Questions

Question	Proposed Answer
Spot or 24 hour	Spot: no evidence for superiority of 24 hour
K wasting	Urine K/creatinine ratio (no need to check osm) and just as good
Chloride	Use FECl not [Cl], but still only marginal
Hypomagnesemia	Not an exclusionary criterion
Ca/creatinine	?0.2 (pretty good with respect to BS except type III)
What about thiazide test?	Good as supplement
What about CLCNKB?	Use age as criterion

Proposed algorithm
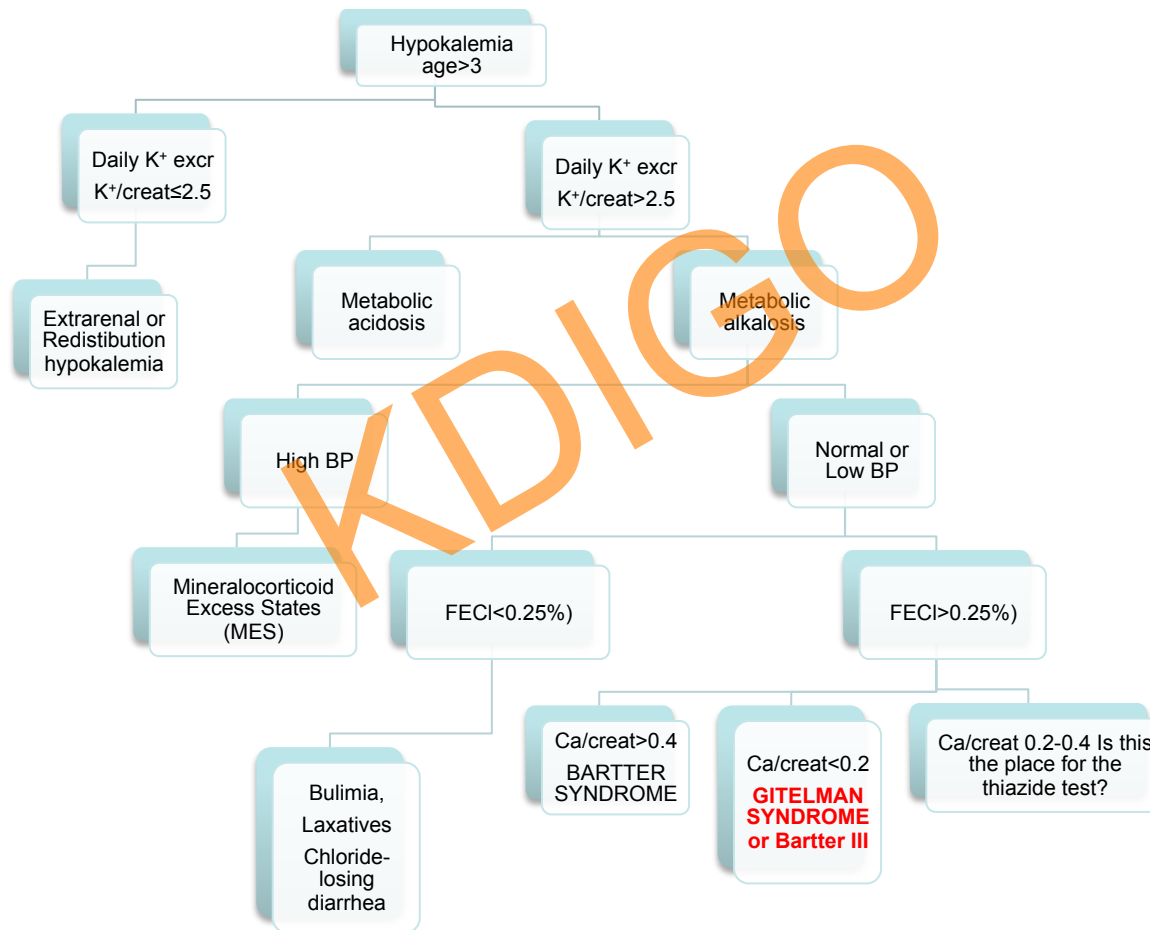
Exclusion Criteria?

Table 3. Proposed exclusion criteria for GS

History	The use of thiazide or loop diuretics
Physical examination	Increased ECF, hypertension (unless middle age or elderly)
Radiological finding	Nephrocalcinosis/nephrolithiasis
Laboratory data	
Blood	Hyperkalemia (unless high K^+ diet plus AKI)
	Metabolic acidosis (unless coexisting $HCO3^-$ losing or acid gain)
	Low renin or low aldosterone
Urine	Low urinary K^+ excretion
	Inappropriate (unparallel) urinary Na^+ vs. Cl^- excretion
	Hypomagnesiuria
	Marked hypercalciuria

ECF: extracellular fluid; AKI: acute kidney injury; IV: intravenous;