University of Iowa Stead Family Children's Hospital

Tumor Growth in TSC: Kidneys, Liver, and Pancreas

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CONFLICT OF INTEREST – Lyndsay Harshman MD

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Grant/Research Support	NIDDK R01 (R01 DK128835-01, 2021-2026)
Consultant	**Nothing to disclose**
Speakers Bureau	**Nothing to disclose**
Stock Shareholder	**Nothing to disclose**
Other (identify)	**Nothing to disclose**

I WILL DISCUSS USE OF SELECT MEDICATIONS IN TSC-ASSOCIATED KIDNEY DISEASE:

I HAVE NO FINANCIAL INTEREST WITH THESE MEDICATIONS

PLEASE DISCUSS YOUR INDIVIDUAL THERAPY WITH YOUR TSC SPECIALTY TEAM

OBJECTIVES

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1. Describe the natural history of kidney, liver, and pancreas tumors in TSC

2. Understand the complications associated with kidney, liver, and pancreas tumors in TSC

3. Describe evidence-based monitoring and treatment strategies for kidney, liver, and pancreas tumors.

TSC……. In One Slide or Less!

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- Autosomal dominant
  - *TSC1* = hamartin
  - *TSC2* = tuberin
- Disorder of the "mTOR" pathway
  - *TSC1* and *TSC2* are required to form the TSC complex.
  - The TSC complex is a "brake" on the mTOR pathway
  - Without the "brake" there is uncontrolled cell growth
- *TSC2* gene mutations may increase risk for kidney tumors

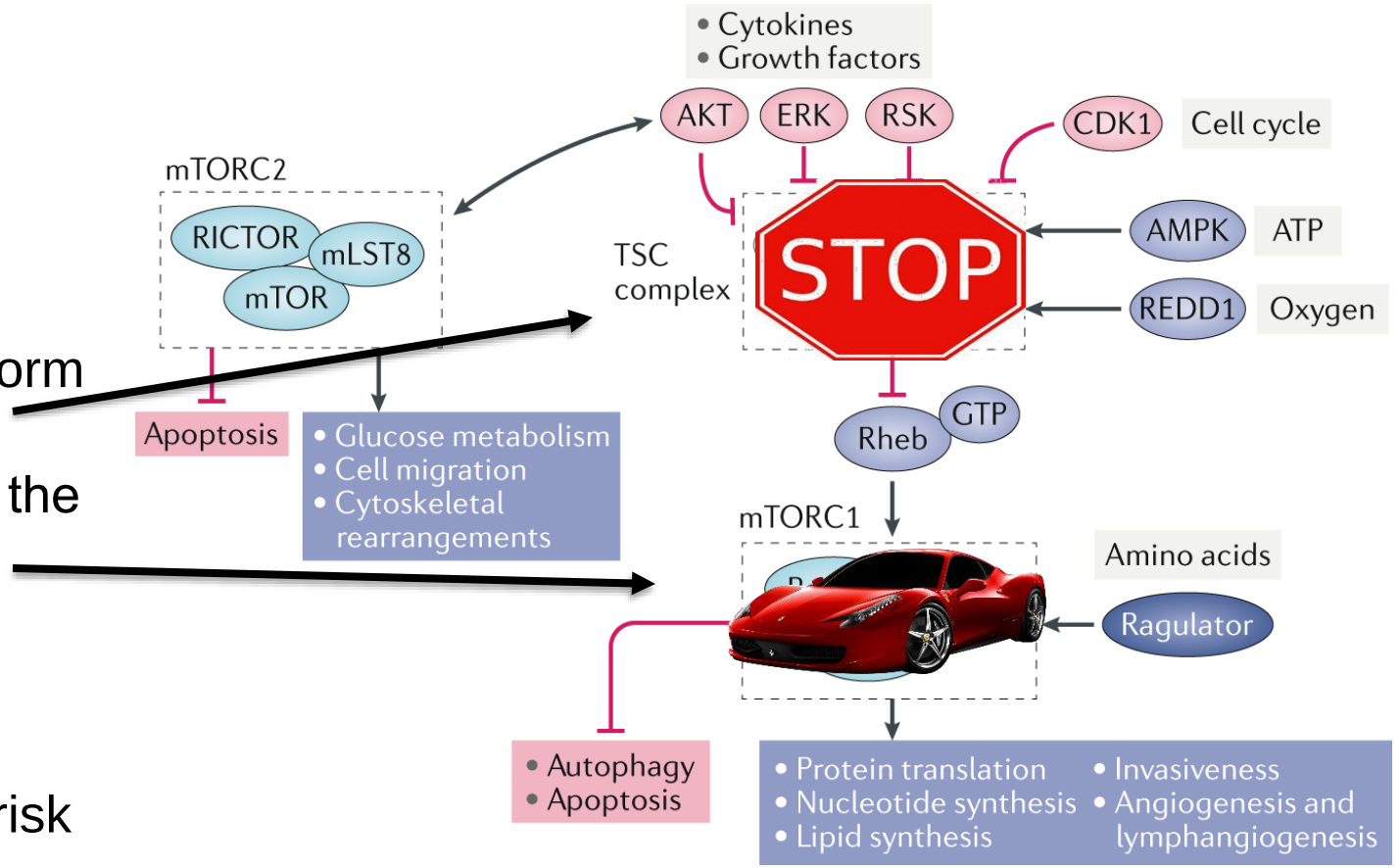

Figure: Lam HC, Siroky BJ, Henske EP. Renal Disease in tuberous sclerosis complex: pathogenesis and therapy. *Nature Reviews Nephrology* (Nov 2018).

Abdominal Tumors in TSC

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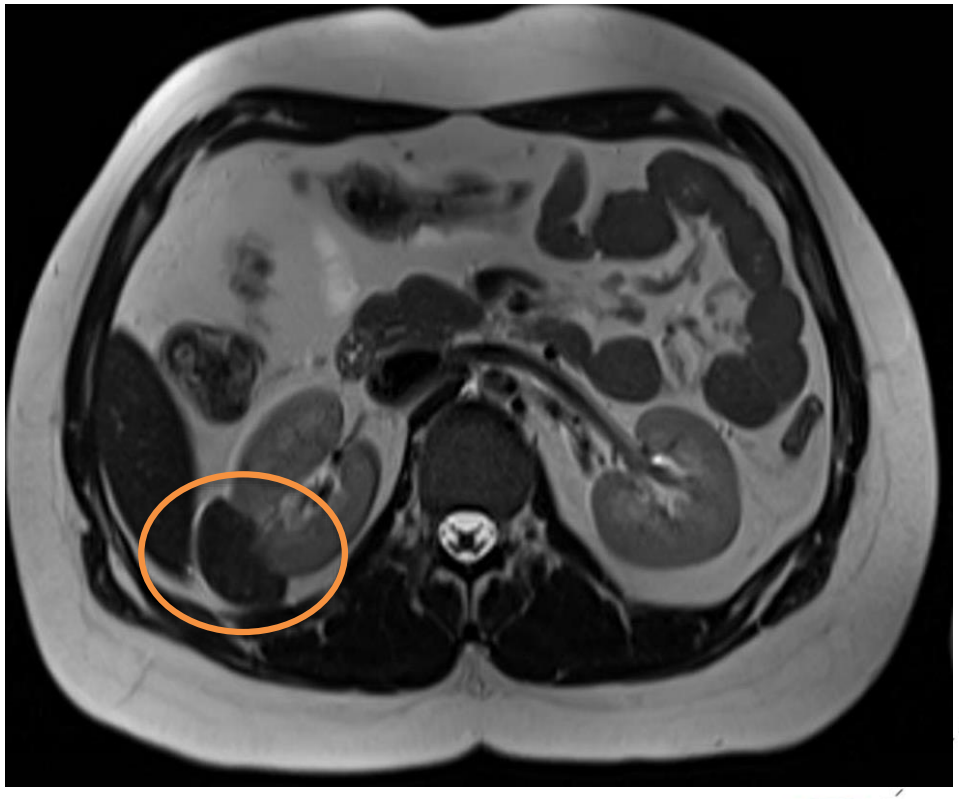

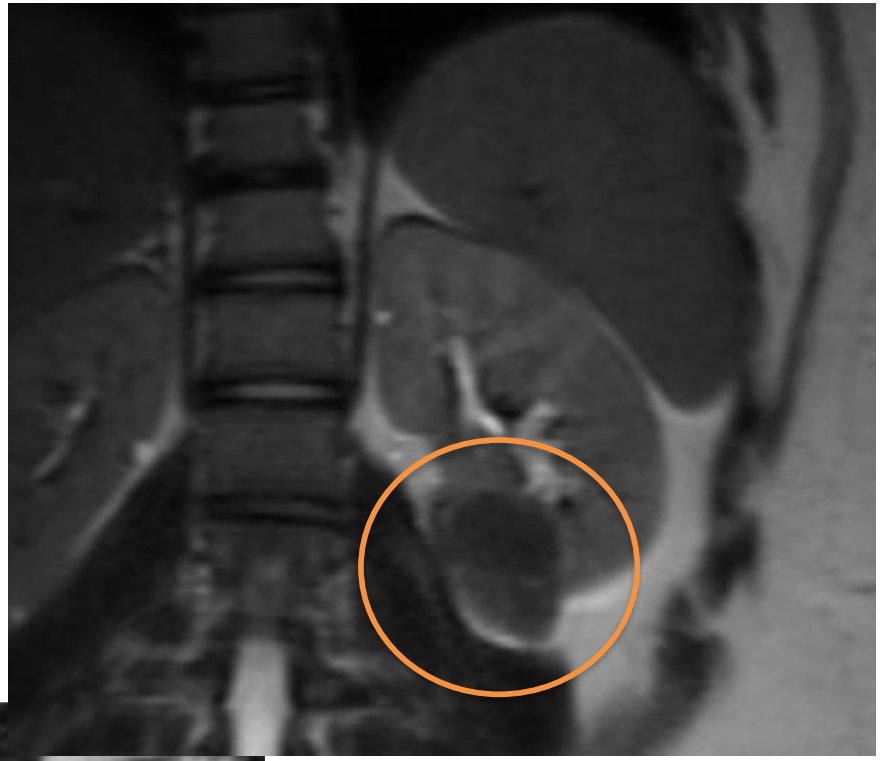

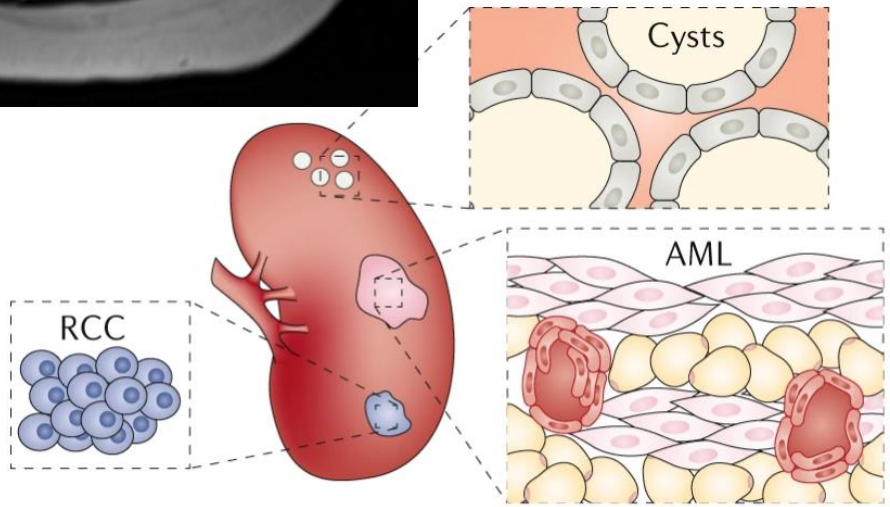

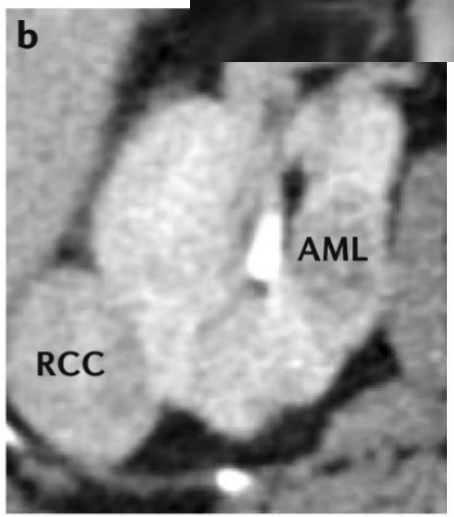

Figure: Lam HC, Siroky BJ, Henske EP. Renal Disease in tuberous sclerosis complex: pathogenesis and therapy. *Nature Reviews Nephrology* (Nov 2018).

Kidney Tumors in TSC: Angiomyolipoma (AML)

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Diagnostic Criteria

Major Criteria	Minor Criteria
Hypomelanotic macules (≥3; at least 5 mm diameter)	"Confetti" skin lesions
Angiofibroma (≥3) or fibrous cephalic plaque	Dental enamel pits (≥3)
Ungual fibromas (≥2)	Intraoral fibromas (≥2)
Shagreen patch	Retinal achromic patch
Multiple retinal hamartomas	Multiple renal cysts
Multiple cortical tubers and/or radial migration lines	Nonrenal hamartomas
Subependymal nodule (≥2)	Sclerotic bone lesions
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
LAM*	
Angiomyolipomas (≥2)*	

Routine Surveillance

Kidney	Preferred Assessment	Frequency
Imaging	1st line: MRI 2nd line: CT vs ultrasound	At diagnosis then every 1-3 years
Labs	Serum creatinine Cystatin C Urine: microscopy and protein	Every 1-2 years
Blood Pressure	Manual cuff	Every visit

Tables: Northrup, H, et al., Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations *Pediatric Neurology* (July 2021)

Kidney Tumors in TSC: Angiomyolipoma (AML)

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Major diagnostic feature of TSC

- *"fatty, vascular, muscle tissue"*
- 2+ lesions required

Usually asymptomatic in childhood

- *By the age of 10, the majority of TSC peds patients will have AML visible on imaging*
- *80% of adults will have one or more AML*

Become symptomatic as tumors grow

- *Bleeding, pain, elevated blood pressure*
- *Chronic kidney disease*
- *Rupture*

Significant cause of early death in adulthood

- Spontaneous hemorrhage → highest risk in fast-growing tumors and tumors larger than 6 centimeters

AMLs can be detected <u>early</u> with appropriate screening!

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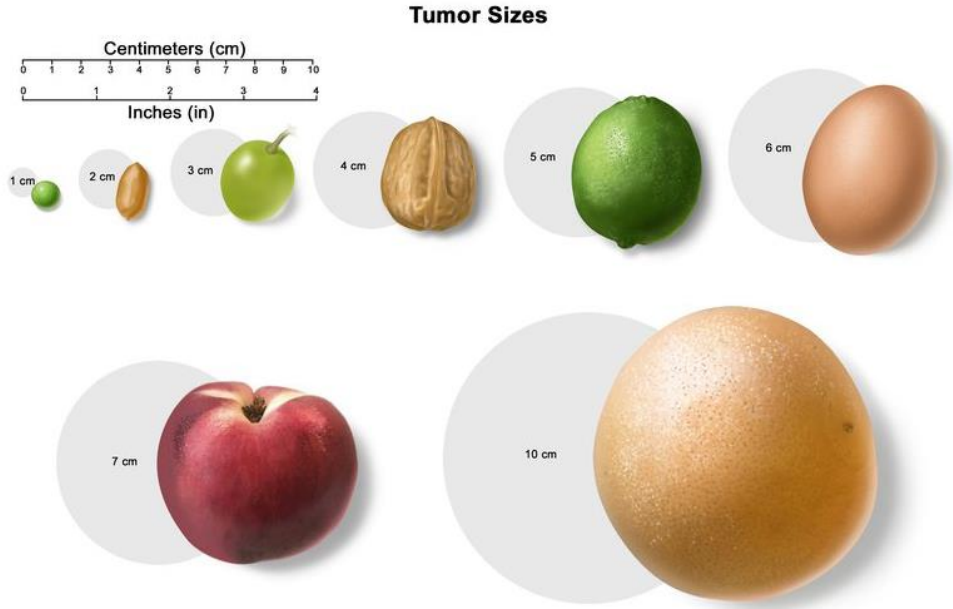
1. Abdominal imaging at time of TSC diagnosis
2. Accurate blood pressure assessment
3. Routine kidney function measurement
    - Blood labs: Creatinine and cystatin C
    - Urine labs: blood or protein



AMLs can be detected <u>early</u> with appropriate screening!

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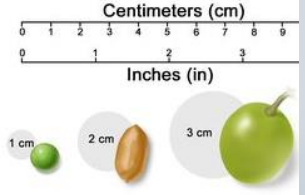

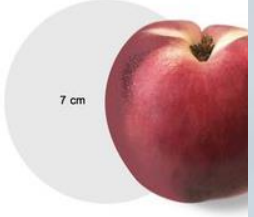

EVEN SUPERHEROES NEED THEIR BLOOD PRESSURE CHECKED AND LABS DRAWN!

Photo credit: University of Iowa DeGowin Blood Center

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Imaging Modalities for Kidney Tumors in TSC

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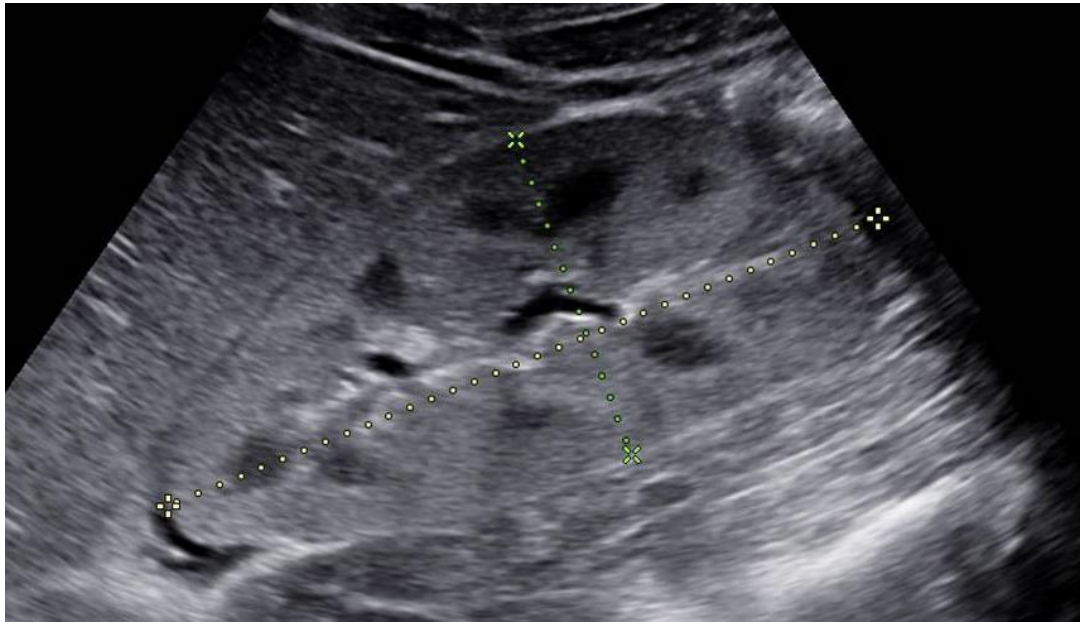

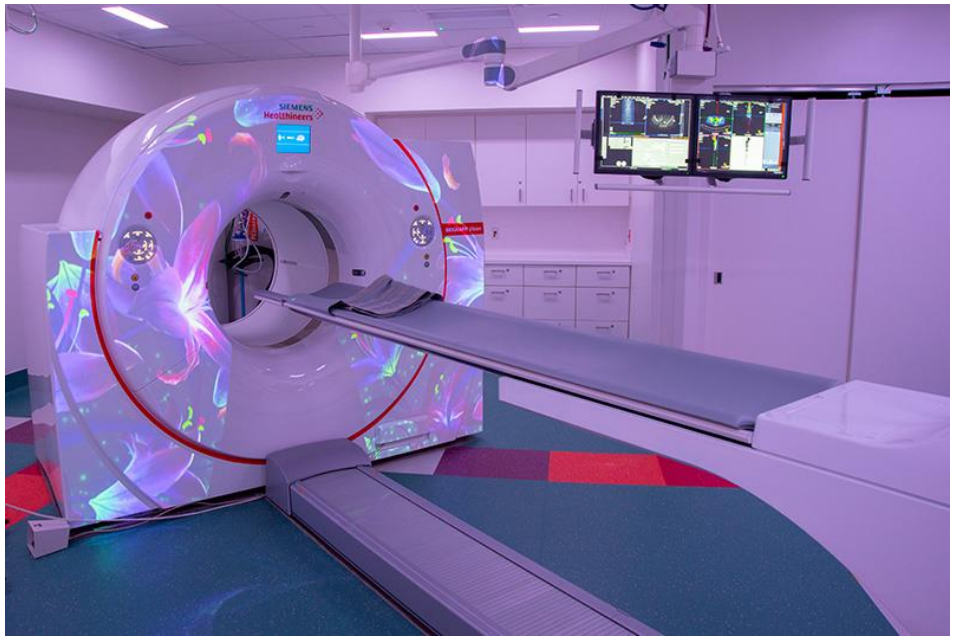

<u>MRI is the preferred imaging modality</u>

- better detection of "fat poor" AML than ultrasound

CT may be required for persons with a vagal nerve stimulator at certain centers

- ideally needs contrast administration for best delineation of AML

Top picture: University of Iowa
Bottom picture: Nicklaus Children's Hospital

Use of TSC Imaging Guidelines in the US

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Modality of Kidney Imaging Procedures

Modality	Kidney Imaging Procedures ($n = 128$)	Kidney Imaging Procedures Before January 1, 2013 ($n = 99$)	Kidney Imaging Procedures on or After January 1, 2013 ($n = 29$)	*P* Value
	n (%)	*n* (%)	*n* (%)	
US	85 (66.4)	69 (69.7)	16 (55.2)	0.19
CT	31 (24.2)	23 (23.2)	8 (27.6)	
MRI	12 (9.4)	7 (7.1)	5 (17.2)	

MRI is still potentially under-utilized despite TSC Consensus recommendations

Imaging frequency is lower than recommended by TSC Consensus guidelines

Frequency of Kidney Imaging Rate (Imaging Procedures/Year) (N = 70)

Kidney Imaging Rate During the Measurement Window (Imaging Procedures/Year)	*n* (%)
0	30 (42.9)
>0 to <0.167	9 (12.9)
0.167	0
>0.167 to <0.33	7 (10)
0.33	0
>0.33	24 (34.3)

Goedken, A., et al., Kidney Imaging Surveillance in Commercially Insured Patients with Tuberous Sclerosis Complex. *Pediatric Neurology* (December 2020)

Risk factors for AML growth

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- Female sex
- Pregnancy & estrogen
- Genetics: TSC2 gene

Treatment: Angiomyolipoma in TSC

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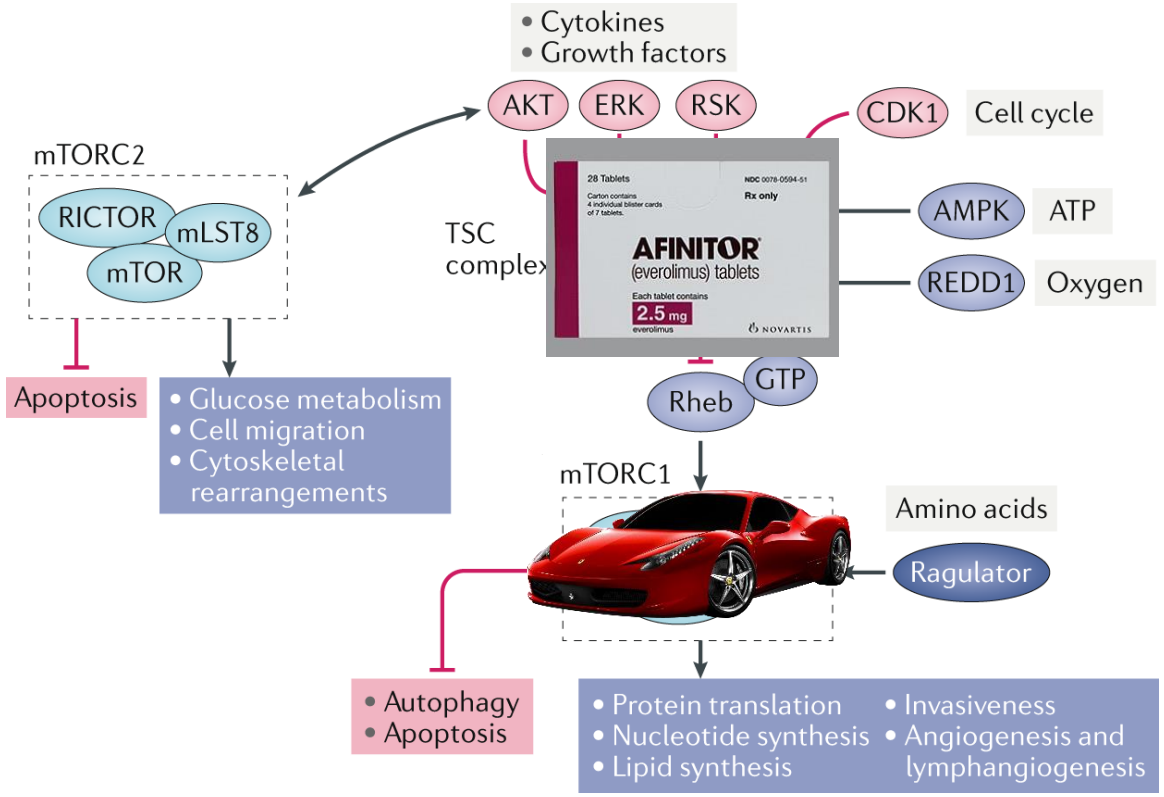

Effect of everolimus on renal angiomyolipoma volume over time.

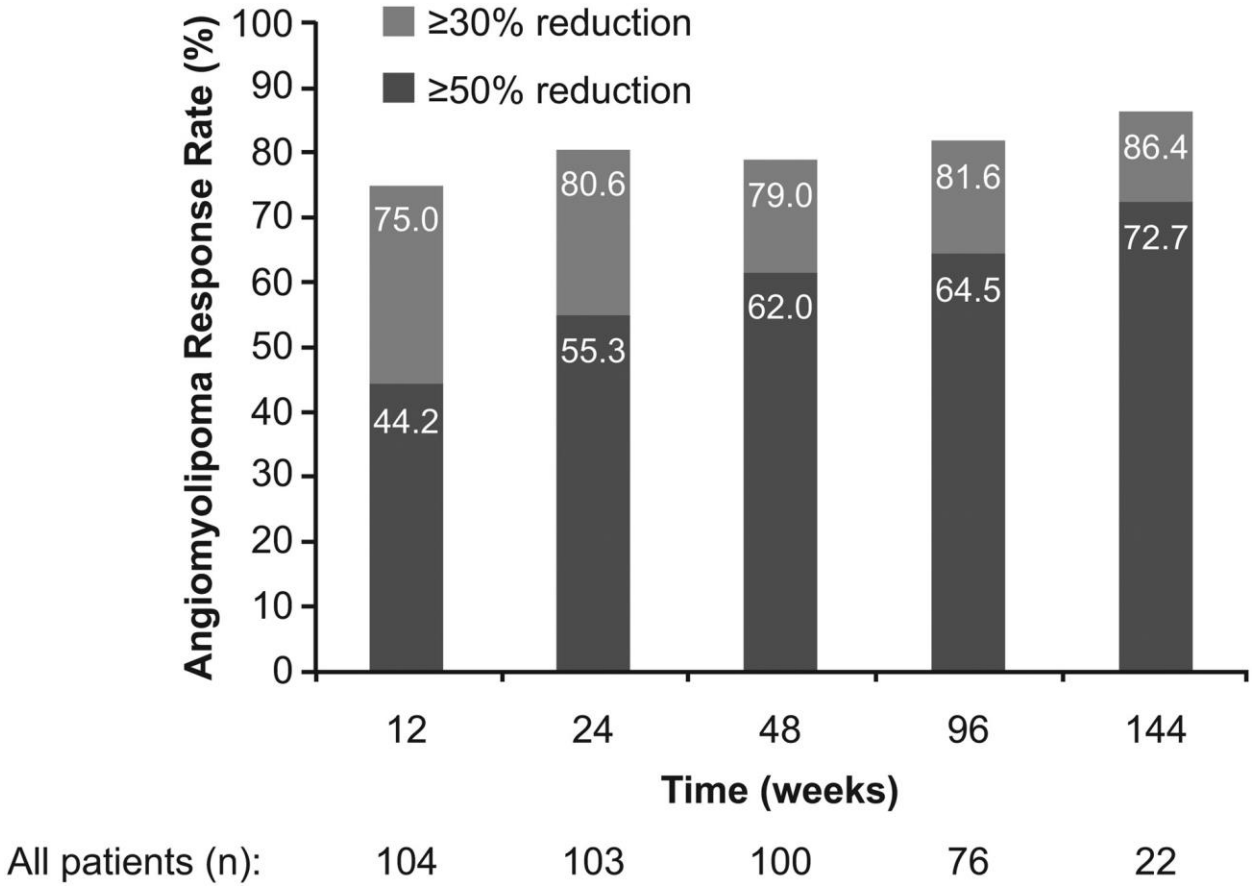

Figure: Bissler et al., Everolimus for renal angiomyolipoma in patients with tuberous sclerosis complex or sporadic LAM: extension of a randomized controlled trial. *Nephrology, Dialysis, Transplantation* (January 2016).

Effectively using mTOR inhibitors for renal AML

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"Inducers"

- Substances that can DECREASE the level of everolimus in the blood by increasing metabolism of drug in the body

Examples:

Carbamazepine, phenobarbital, phenytoin, steroids

"Inhibitors"

- Substances that can INCREASE the level of everolimus in the blood through slower drug metabolism

Examples:

Antifungals (ketoconazole), cyclosporine, verapamil, erythromycin

Effectively using mTOR inhibitors for renal AML

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Common side effects:

1. Mouth sores (stomatitis)
2. Elevated lipids
3. Elevated blood glucose
4. Elevated urine protein

Other reported side effects:

1. Pneumonitis (lung inflammation)
2. Infection

Monitoring:

1. Labs within 2-4 weeks of starting everolimus and then every 4-8 weeks until steady dose is achieved with minimal side effect(s)

Before starting:

1. Stop "ACE" inhibitors
2. Make sure vaccines up to date!
3. Review other medications with a TSC-specialty pharmacist

What do to for mTOR-associated side effects?

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Mouth Sores	Lysine	Decadron "swish and spit"	Kenalog dental paste	Consider holding medication
Elevated lipids	Weight reduction	Dietary modification	Consider fish oil or statin medication	
Infection	Hold or reduce medication dose	Antibiotics may be required		

Everolimus dosing and goal range should be decided by your provider.

Other Treatment: Angiomyolipoma in TSC

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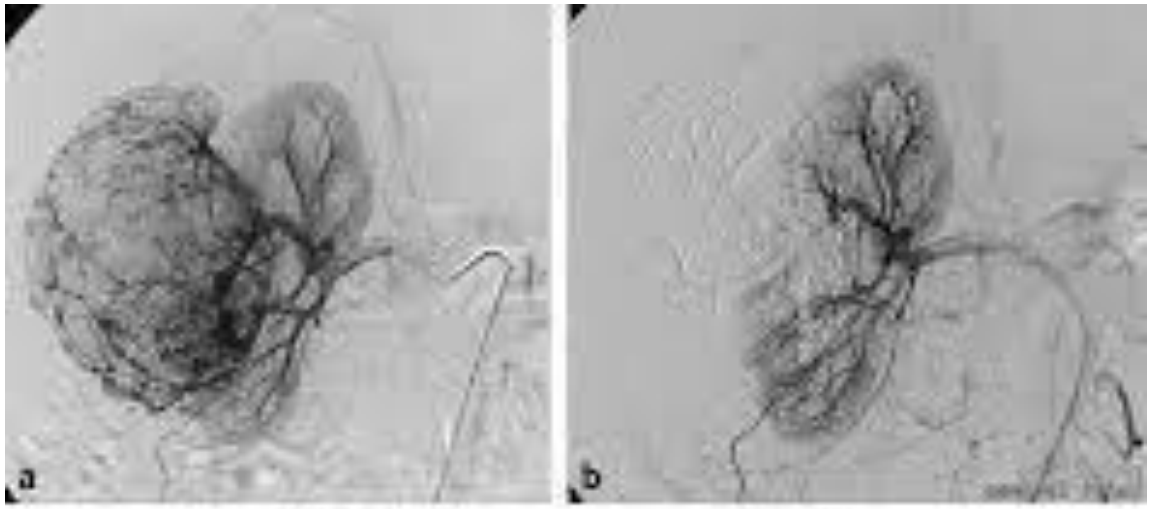
Clinical presentation	Recommendation
Management recommendations for renal angiomyolipoma	
Angiomyolipoma with acute hemorrhage	Embolization (followed by corticosteroids for 7 days to mitigate post-embolization syndrome) [3]. Embolization should be as selective as technically feasible to preserve renal parenchyma Avoid nephrectomy
Asymptomatic, growing angiomyolipoma >3 cm in diameter	First-line: mTOR inhibitor Second-line: selective embolization or kidney-sparing resection

POST EMBOLIZATION SYNDROME

- inflammatory response that causes significant fever and pain that can last for several days despite the use of acetaminophen
- Reported in 49 out of 55 patients with TSC requiring embolization (Bissler, 2002)
- Prednisone burst and taper may decrease risk for post-embolization syndrome



Real-world images

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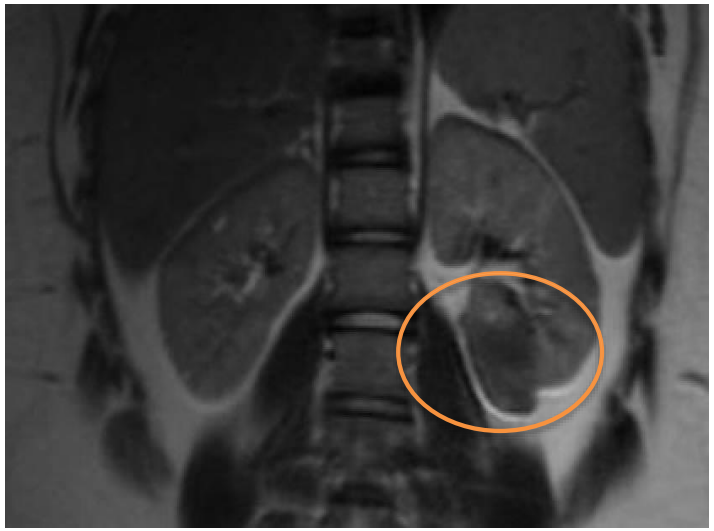
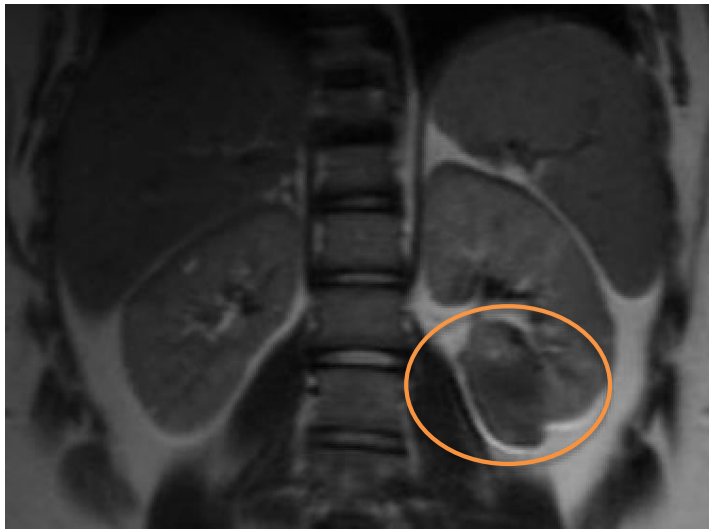
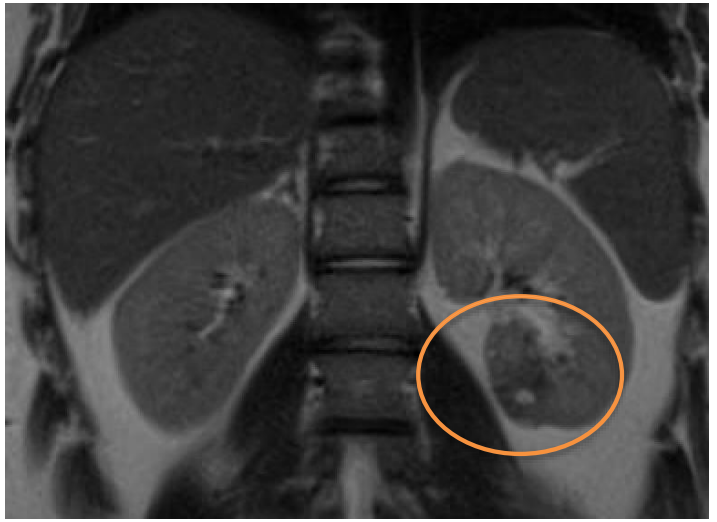


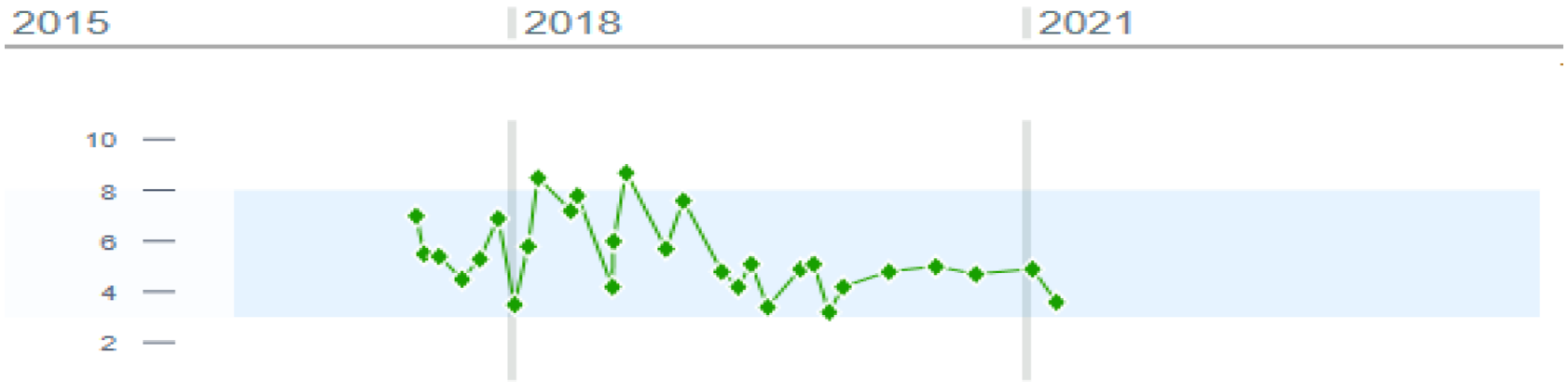




Baseline: AML 5.5 cm

12 months everolimus: AML 4.4 cm

48 months everolimus: AML 2.2 cm



Everolimus drug levels

Diagnostic Dilemmas

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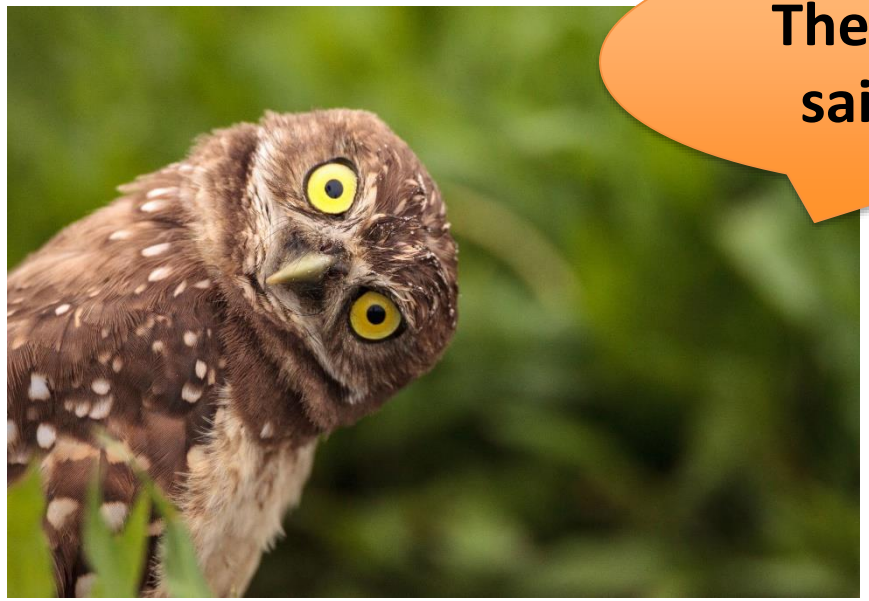
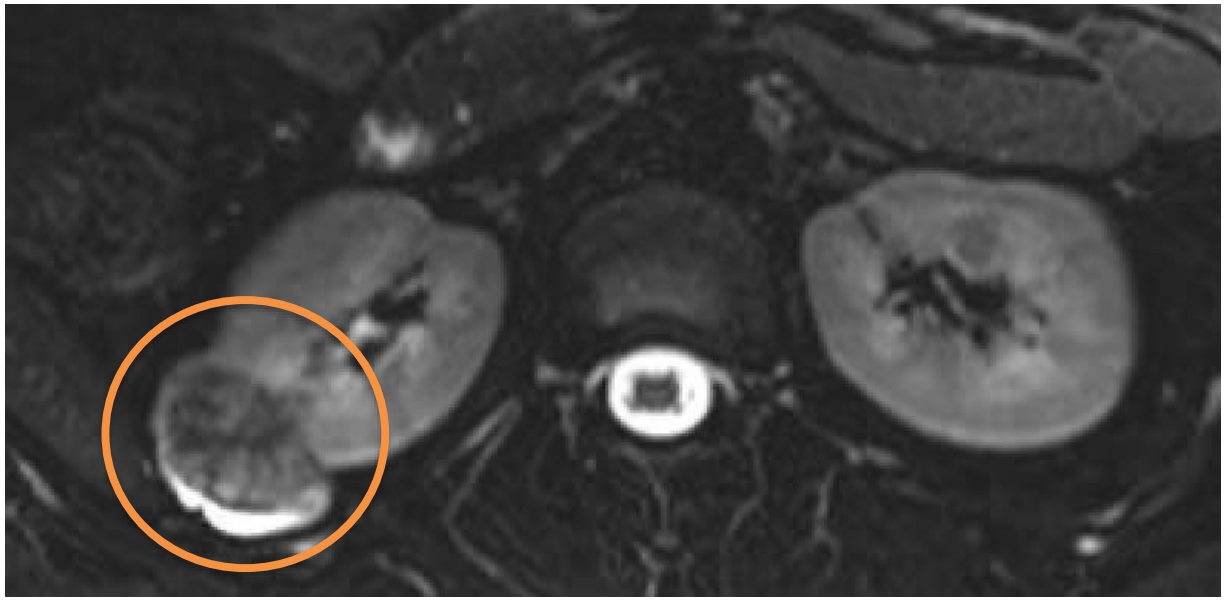


The radiologist said WHAT?!

"Fat poor angiomyolipoma versus renal cell carcinoma: clinical correlation is required"



Other tumors: Renal Cell Carcinoma

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Comparison of Imaging Characteristics for fat-poor AML and renal cell carcinoma (RCC), clear cell type

Imaging Type	Fat-Poor AML	RCC (clear cell type)
Non-contrast CT	Bright	Dull
Contrast CT	Non-uniform texture	Non-uniform texture
”standard” MRI (T2)	Dull	Bright
Diffusion MRI	Bright	Dull
Fat-suppressed MRI	Dull	Bright
Contrast MRI	Non-uniform texture	Non-uniform texture

Table adapted from: Park BK. Renal Angiomyolipoma Based on New Classification: How to Differentiate It From Renal Cell Carcinoma. AJR (March 2019).

A brief discussion to kidney cysts in TSC

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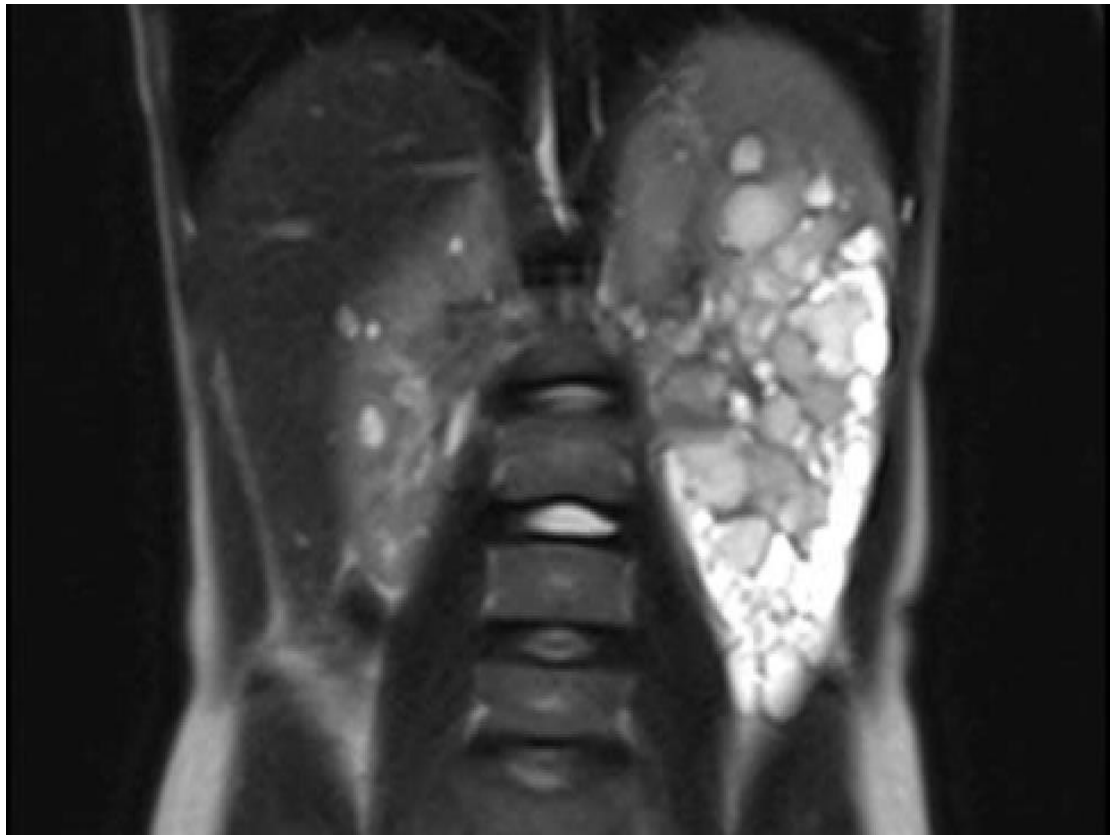
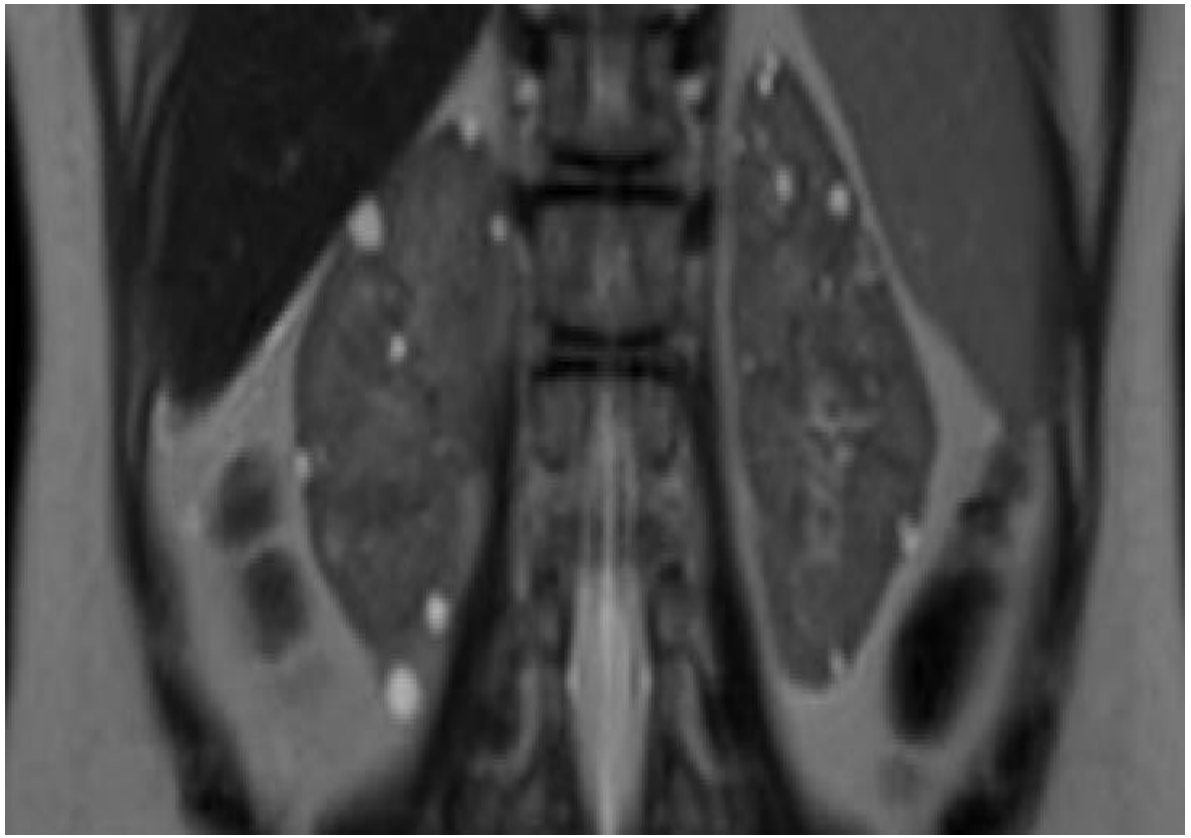
Large Cysts



Small Cysts



Contiguous Gene Deletion Syndrome

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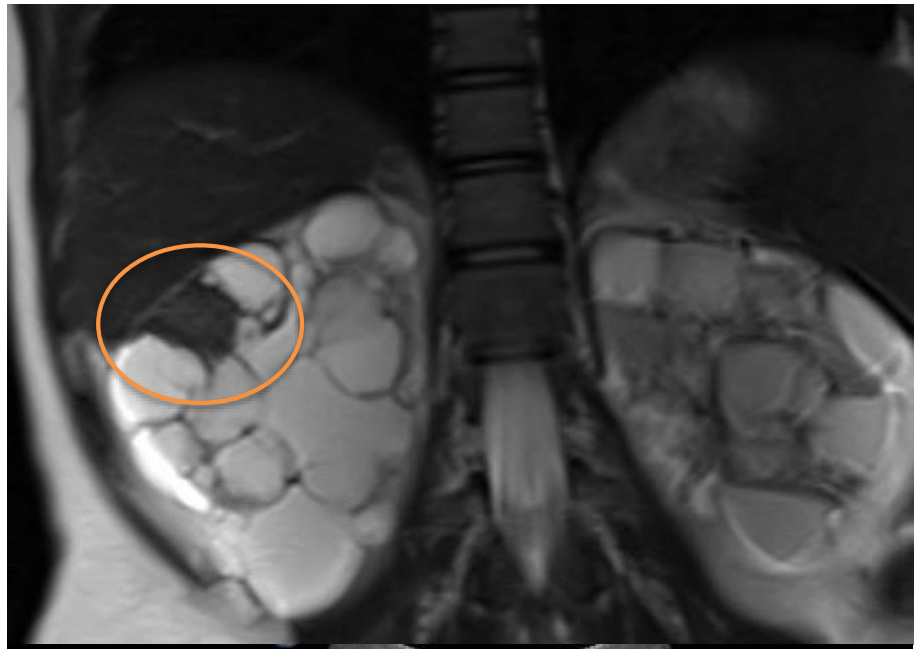
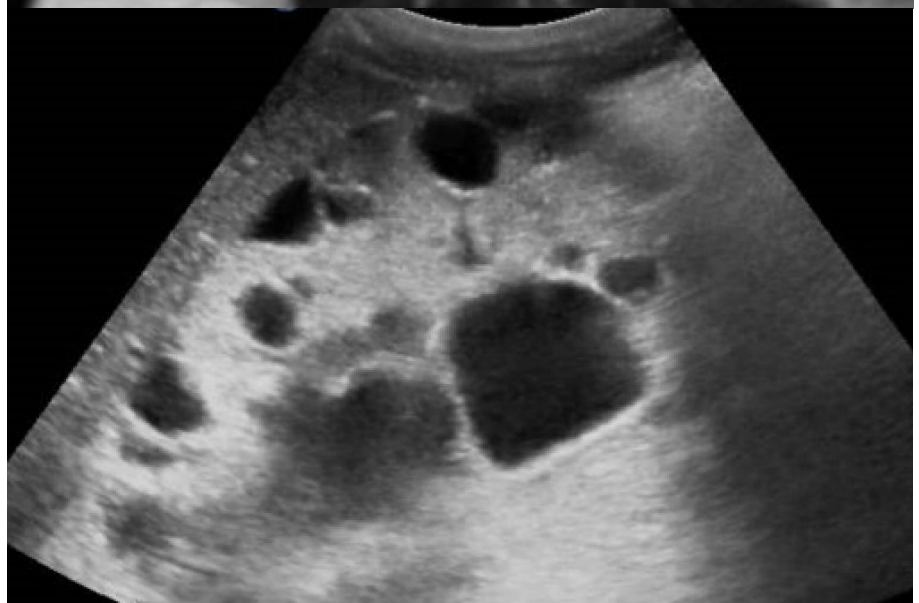
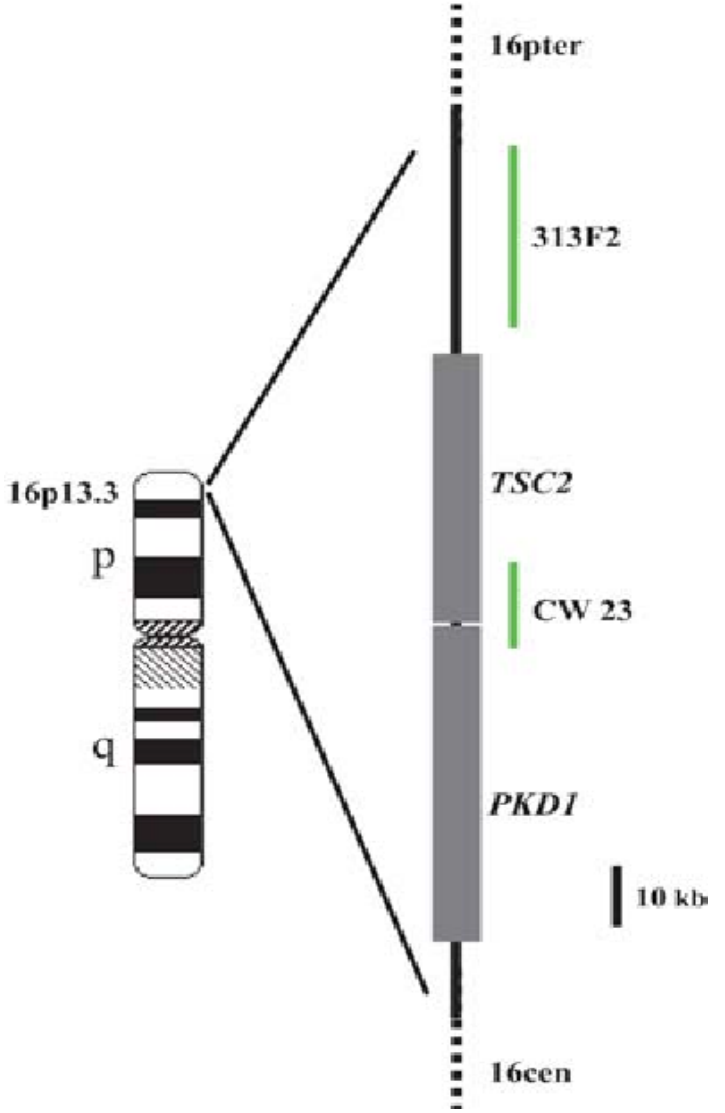




Deletion of both the *TSC2* gene and *PKD1* genes on chromosome 16

The *PKD1* gene is associated with more severe cystic kidney disease.



Is there a role for mTOR inhibition in cystic kidney disease?

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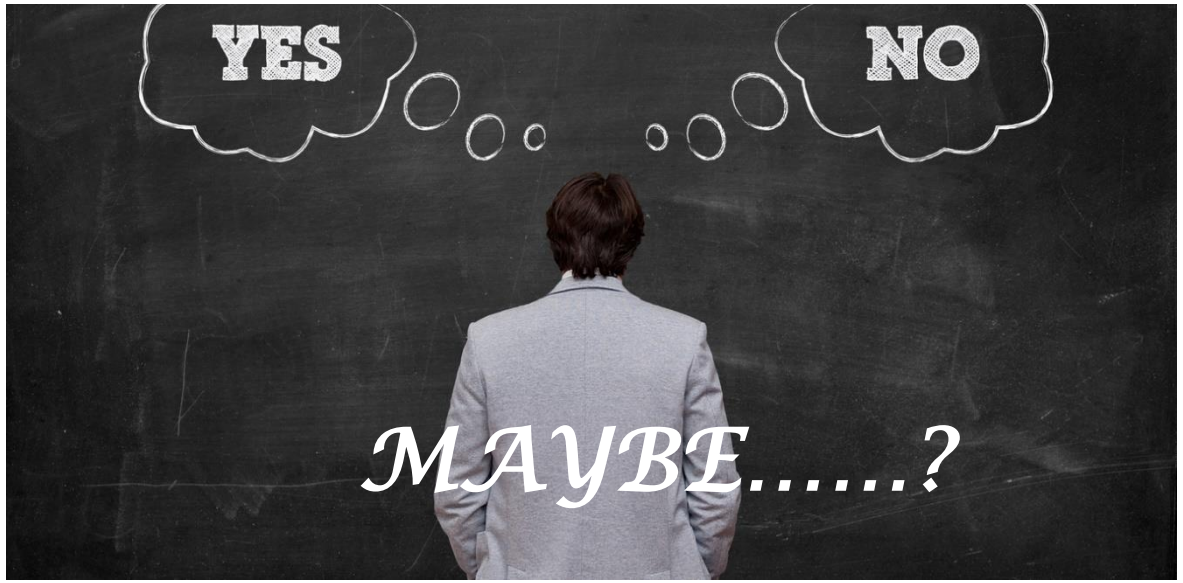

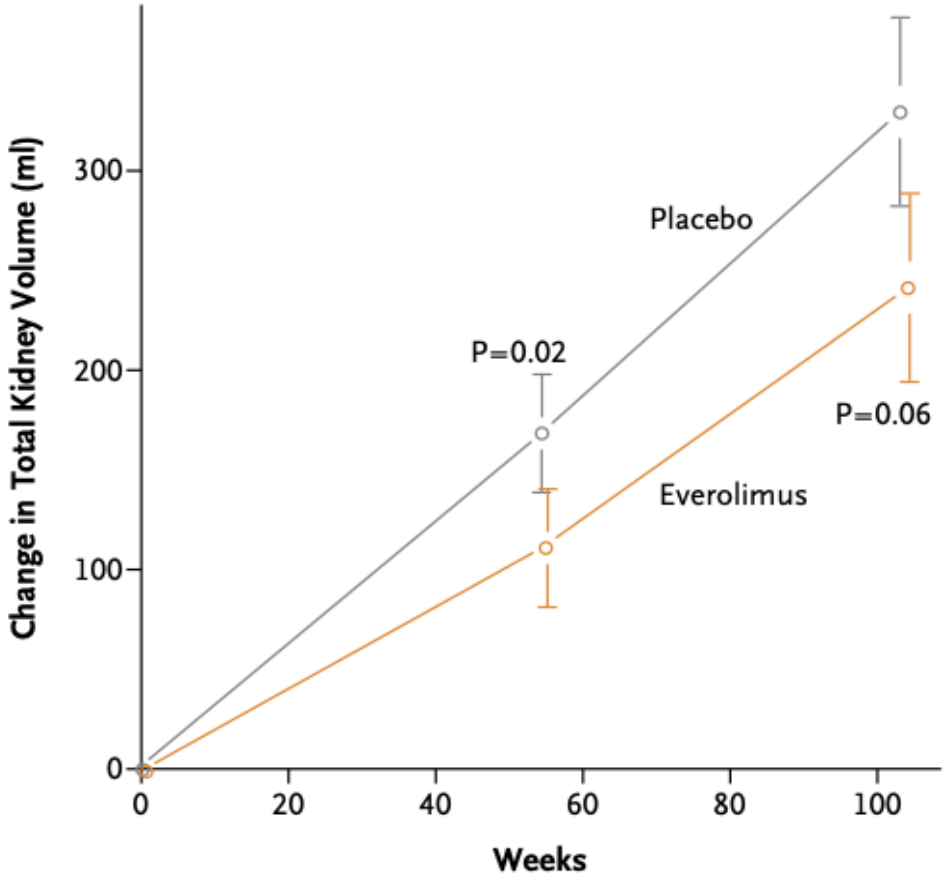

Figure: Walz G., et al., Everolimus in Patients with Autosomal Dominant Polycystic Kidney Disease. *New England Journal of Medicine* (Nov 2010).

Brief detour: What is chronic kidney disease?

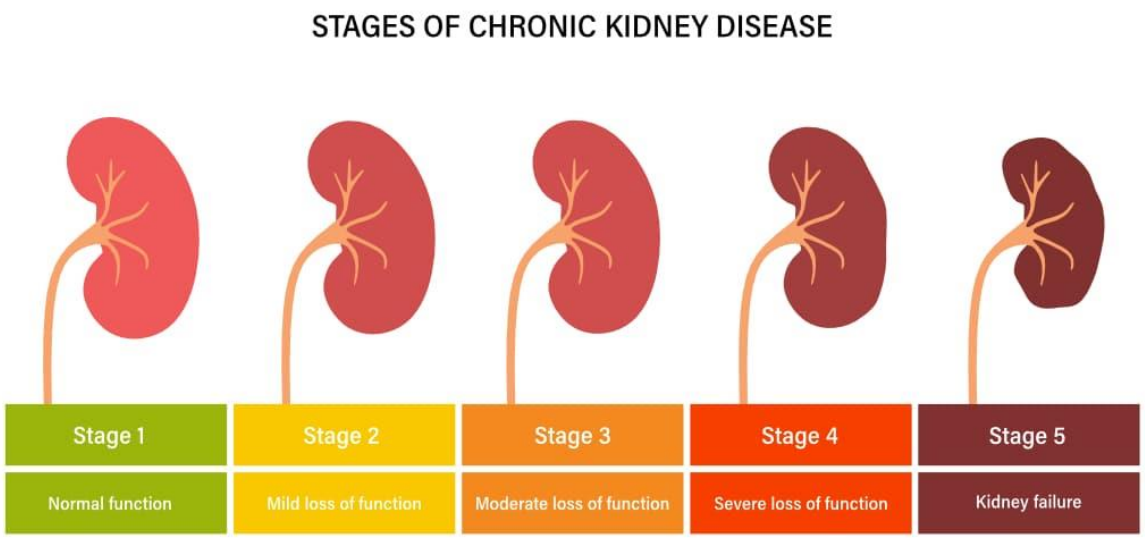

Figure: Miskawaan Health (online)

- Strong association between development of CKD and:
  - Older age
  - Angiomyolipoma size/number
  - History of embolization
  - Partial or full nephrectomy
- Regular kidney labs and urine studies are needed to detect CKD early!

Briefly: Kidney Transplantation in TSC

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Images courtesy University of Iowa

WHY WOULD A TSC PATIENT HAVE KIDNEY FAILURE?

CAN TSC PATIENTS GET A KIDNEY TRANSPLANT?

HOW OFTEN DOES KIDNEY TRANSPLANT OCCUR IN TSC?

CAN EVEROLIMUS STILL BE USED AFTER TRANSPLANT?

Liver & Pancreas in TSC

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This topic is like an iceberg – there is little published data and likely much more that remains to be discovered.

Pancreas Tumors in TSC: nonfunctional pancreatic neuroendocrine tumors (PNET)

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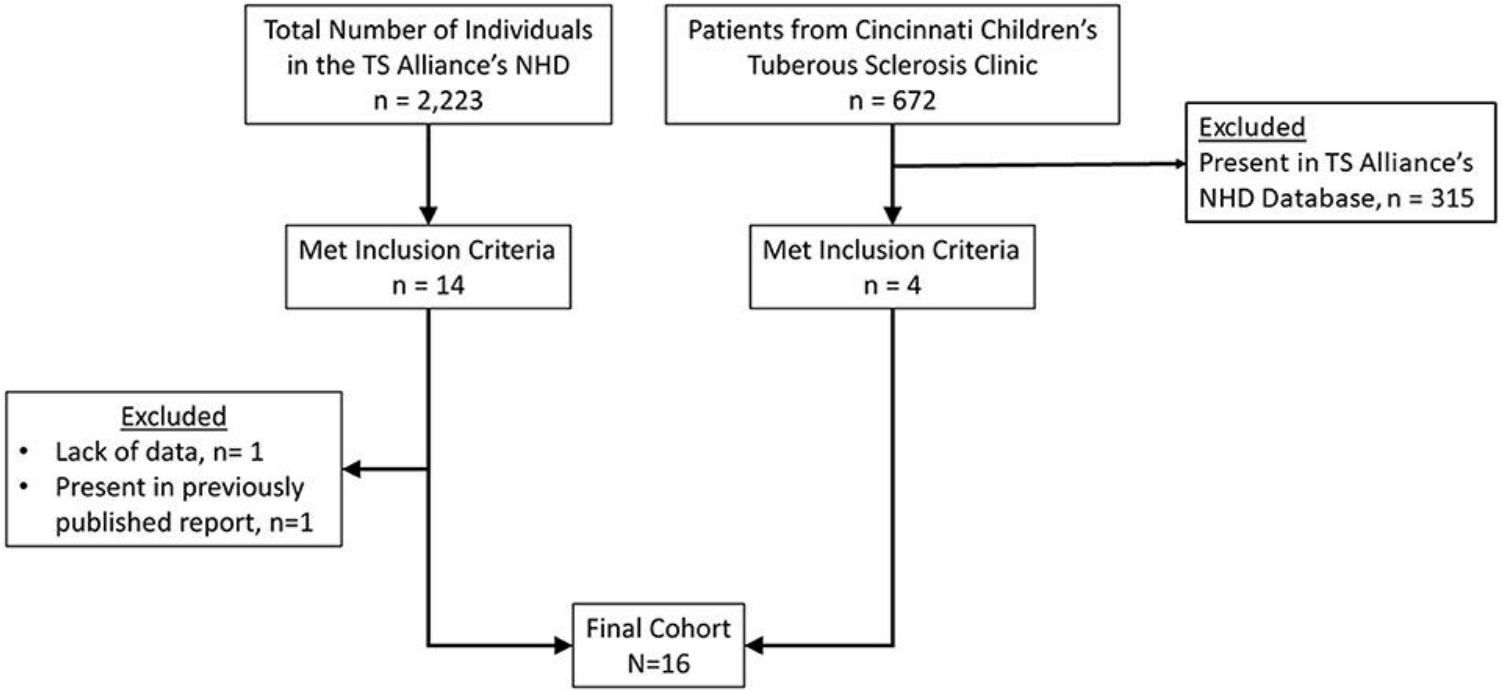
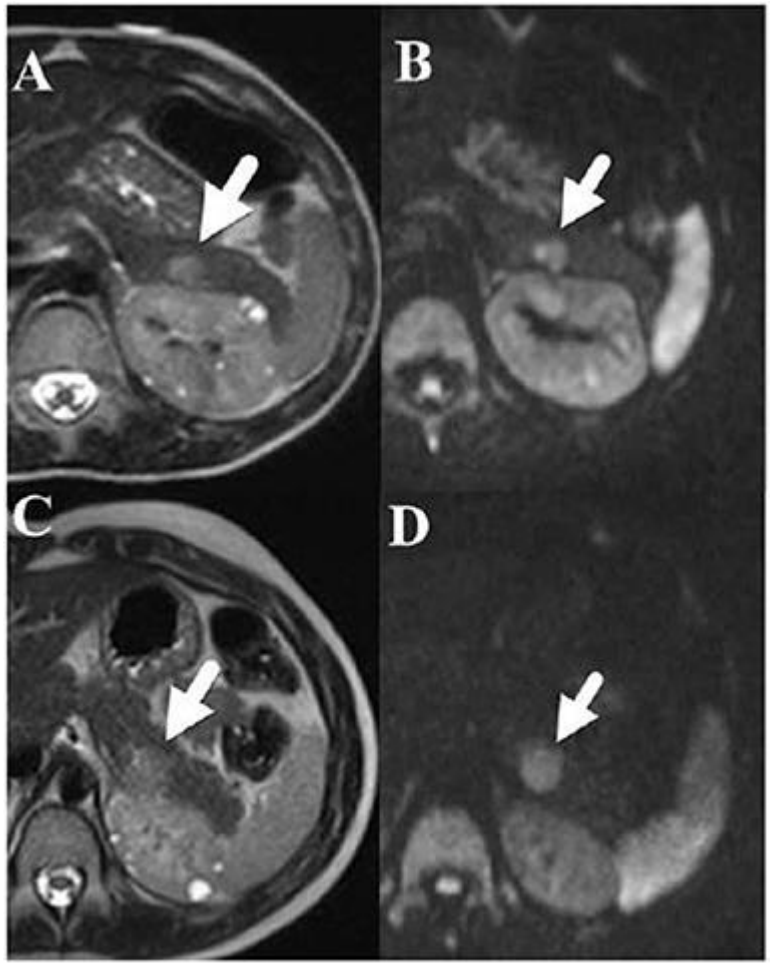


- Number of reported PNETs associated with TSC has increased in the last 10 years

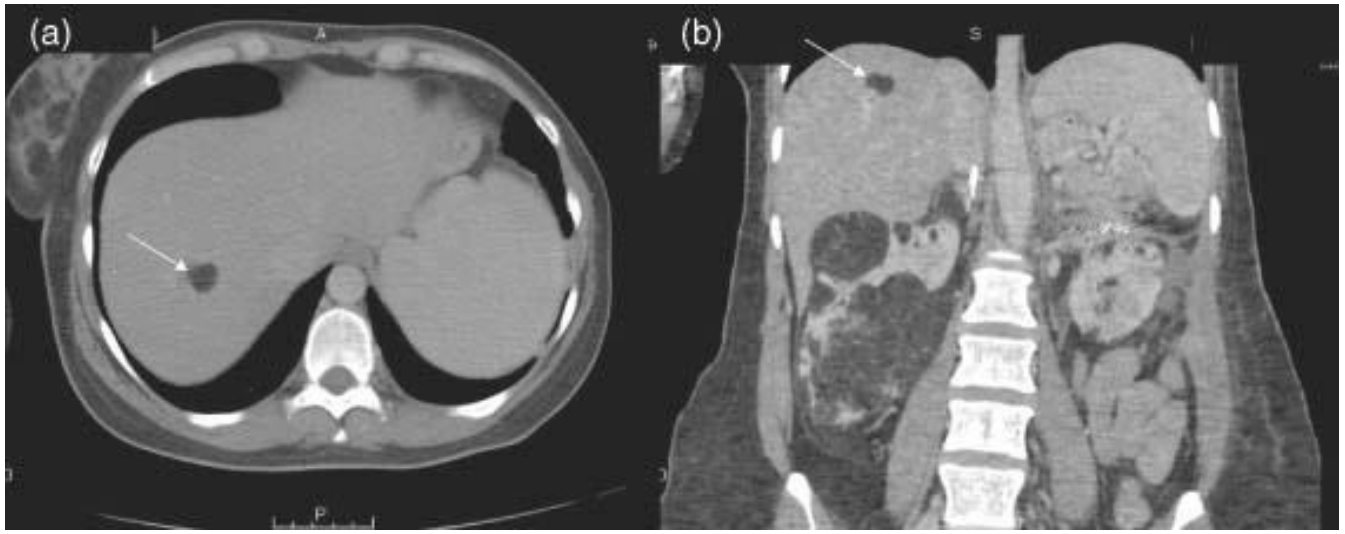
- Estimated frequency of nonfunctional PNET is 0.65%
  - *Prevalence in general population: 0.003%*
  - *Other studies suggest up to ~1.6% frequency in TSC*

- PNET cases may be under-reported among TSC patients



Mowrey K., et al., Frequency, progression and current management: Report of 16 new cases of nonfunctional pancreatic neuroendocrine tumors in tuberous sclerosis complex and comparison with previous reports. *Frontiers in Neurology* (April 2021)

Liver Tumors in TSC:



Most common liver tumor:

- Angiomyolipoma
- Cysts

Frequency of findings:

- 30% of cohort
- high rates of asymptomatic lesions

Risk for hepatic AML:

- *TSC2* gene mutation
- Older age
- Associated with presence of renal AML

No patients in the cohort had clinically symptoms or complications from hepatic lesions.

Figure: Clinical Genetics, Volume: 82, Issue: 6, Pages: 552-557, First published: 17 January 2012, DOI: (10.1111/j.1399-0004.2012.01845.x)

Research & Educational Opportunities

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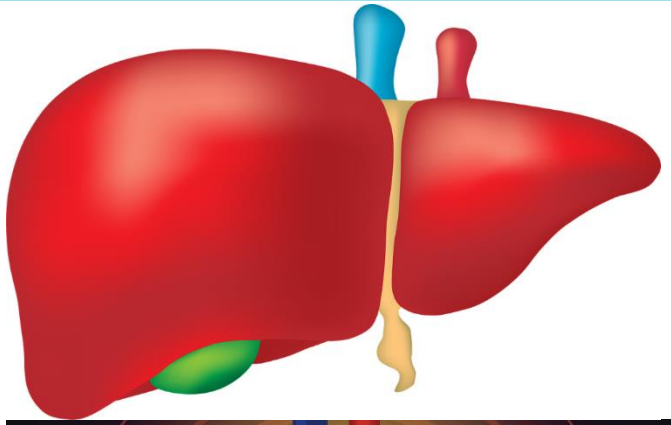

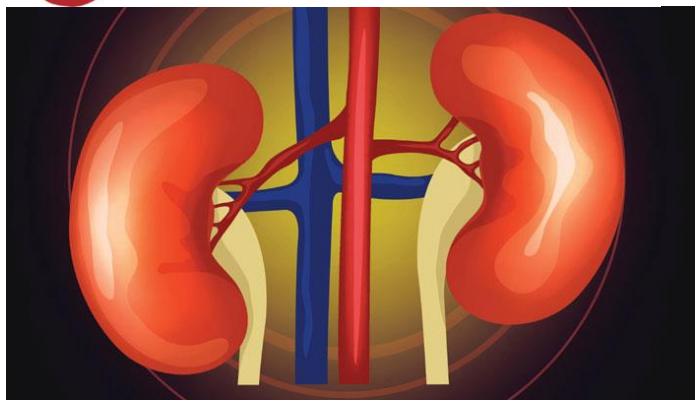

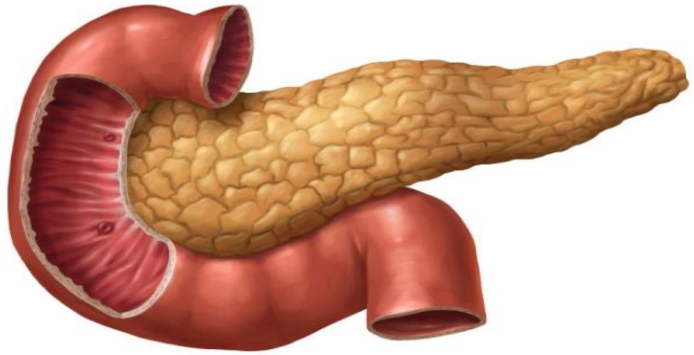

- Imaging protocols to better detect hepatic and pancreatic tumors?
- How to educate radiologists and other medical professionals about TSC-associated tumors within the liver & pancreas?
- Defining the actual risk for end-stage kidney disease in TSC?

TAKE HOME POINTS

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- Kidney tumors, including angiomyolipoma and renal cell carcinoma, can occur prior to age 30 and lead to premature death in the TSC population.

- Abdominal imaging surveillance is a critical component in the care of TSC patients.

- mTOR inhibitors are safe and effective for TSC-associated abdominal tumors within the kidney, pancreas, and liver

- There is a significant gap in the literature regarding the natural history of hepatic and pancreatic tumors associated with TSC.
  - This is a major research opportunity

Open floor for discussion

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1. What part of your TSC nephrology management do you wish you would have known about earlier?

2. How could nephrologists better educate patients/families with TSC about kidney-related complications?

Thank you! Questions are welcome!

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Dr. Alpa Sidhu
Geneticist

Dr. Lyndsay Harshman
Pediatric Nephrologist

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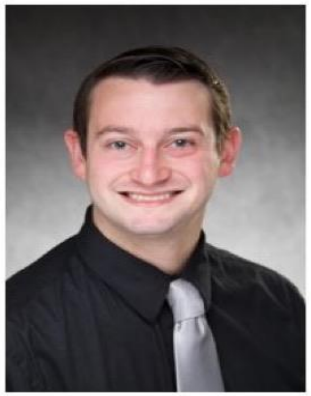

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Q&A Session with Dr. Harshman

University of Iowa Stead Family Children's Hospital

Q: My son has no mutations but kidney cysts and AMLs. Should we repeat the genetic testing?

A: *Great question. I would continue to discuss with your local team. Genetic panels change over time – meaning, new gene polymorphisms are included to panels. You may want to discuss whether any newer genetic panels could give you insight to your child's TSC diagnosis.*

Q: Our son has TSC2 and ADPKD. We are being closely monitored at Stanford. Recently the protein in his urine has been increased, but his creatinine and other labs are stable. He has no AMLs to date but has many simple cysts and very large kidneys. He's on several blood pressure medications. Is it possible to predict with some certainty when our son will need a kidney transplant?

A: *You have a wonderful care team at Stanford! A couple of things: make sure to always take a "first morning" urine sample to your clinic. Your child should urinate within a few moments of getting up. You can collect it in any container – doesn't need to be sterile. Using "ACE-inhibitors" is a good way to help with proteinuria but sometimes (unfortunately) we just can't get that protein level down and must optimize the rest of a child's kidney care including managing blood pressure to keep the kidneys as healthy as possible. Here is a nice online calculator to predict kidney disease progression risk: https://form.jotform.us/81565256783164*

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Q: What about edema with Afinitor?

A: *I personally have not had any patients experience edema on Afinitor. Medications such as amlodipine can also cause edema so that would be something to consider as well. Make sure also that your child does not have significant protein in the urine (this can be seen in rare cases with everolimus) as that could potentially contribute to edema.*

Q: We were advised not to use contrast with our annual MRI scans because of TSC, therefore someone looking at the images should recognize AMLs regardless of the contrast, correct?

A: *Unless you/your child has advanced CKD on dialysis the use of contrast for MRI should be entirely safe. The American College of Radiology guidelines also reinforces the safety of newer MRI (gadolinium) contrast agents in CKD. We do imaging as "with and without" contrast sequences at our center.*

Q: Would intermittent everolimus therapy be as effective as taking it daily?

A: *Everolimus should really be taken on a consistent, daily basis to get the most effect from the drug.*

Q&A Session with Dr. Harshman

University of Iowa Stead Family Children's Hospital

Q: Would you advise taking everolimus as prophylactic therapy once cysts are identified/or even before the onset of cysts?

A: *In full transparency, I find everolimus to be a fantastic medication, but all medications have risk for side effect, etc. So, based on currently available data (especially in the pediatric population), I would not recommend prophylactic everolimus. Understanding the role of everolimus on TSC-associated kidney cysts is likely a really important area of research for the TSC community to pursue.*

Q: My son is 20 y.o. On sirolimus x many years. AMLs stable to < 2 cm, and hair hypopigment is gone, but if we stopped the meds for a month, the hair patch is back! Time to stop the meds? Or not just for the benefit of the hair patch? His dose of sirolimus is 2.5 mg a day. If higher dose, mouth sores.

A: *If he is doing well with sirolimus re: AML or other TSC-associated disease then I would try to hold the course with it. You could discuss converting to everolimus with your physician to see if that minimizes the hair patch concerns.*

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Q: Is there any data regarding whether or not female hormones, estrogen or progestin have an effect on AMLs or reduce the incidence of renal bleeds (ruptures)?

A: *Yes! Estrogen, in particular, may increase the rate of AML growth (and subsequently risk for rupture). Similarly, female hormones may also increase growth of other tumors such as LAM.*

Q: So, an MRI is a better tool to track AMLs than ultrasound?

A: *Yes! MRI is the "gold standard" for tracking AMLs. Fat-poor AMLs are less easily detectable on ultrasound.*

Q: It shows prior to 30 years of age for kidney tumors, does it lessen my son's chance of getting the kidney tumors if he makes it past 30 with no tumors?

A: *Some people may not develop AML – this seems to be a little more likely for persons with TSC1 mutations (e.g., lower risk). But, I would still strongly suggest routine MRI to follow up risk for other tumors aside from AML such as renal cell carcinoma.*

Q&A Session with Dr. Harshman

Q: Should all patients with kidney AMLs and cysts check AD PKD1 for the cysts?

A: *I would suggest that persons with a TSC2 gene mutation and LARGE cysts be screened for a contiguous gene deletion (TSC2-PKD1 deletion). If a patient has small cysts and AML then it is unlikely to be a TSC2-PKD1 gene deletion. The cysts associated with PKD1 are "large and in charge!"*

This concludes the Q&A session.