Tuberous Sclerosis, the Kidneys, and Pregnancy

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Primer on Basic Kidney function

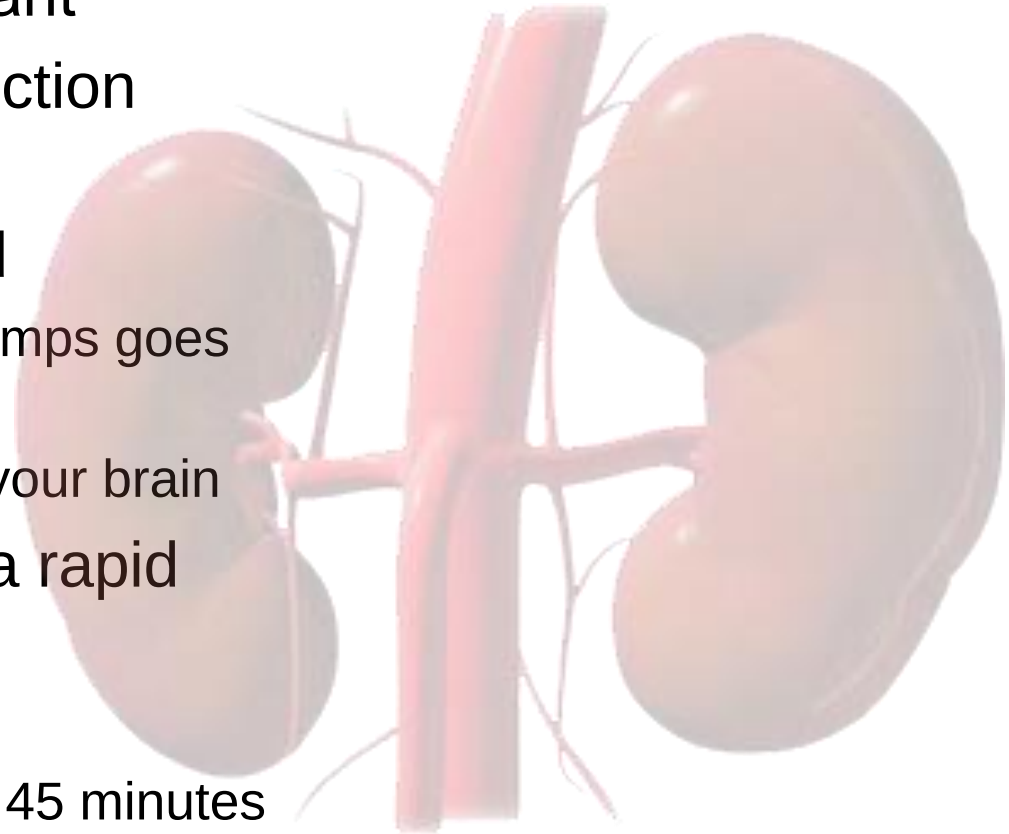
- Kidney is the body's "processing plant"
- Made up of blood vessels and collection tubes
- Processes a huge amount of blood

  Almost 20% of all the blood your heart pumps goes to the kidneys

  - More than any other organ except your brain
- Leaky capillaries filter the blood at a rapid rate

  Roughly 100 ml each minute

  Your entire blood volume is filtered every 45 minutes or so…



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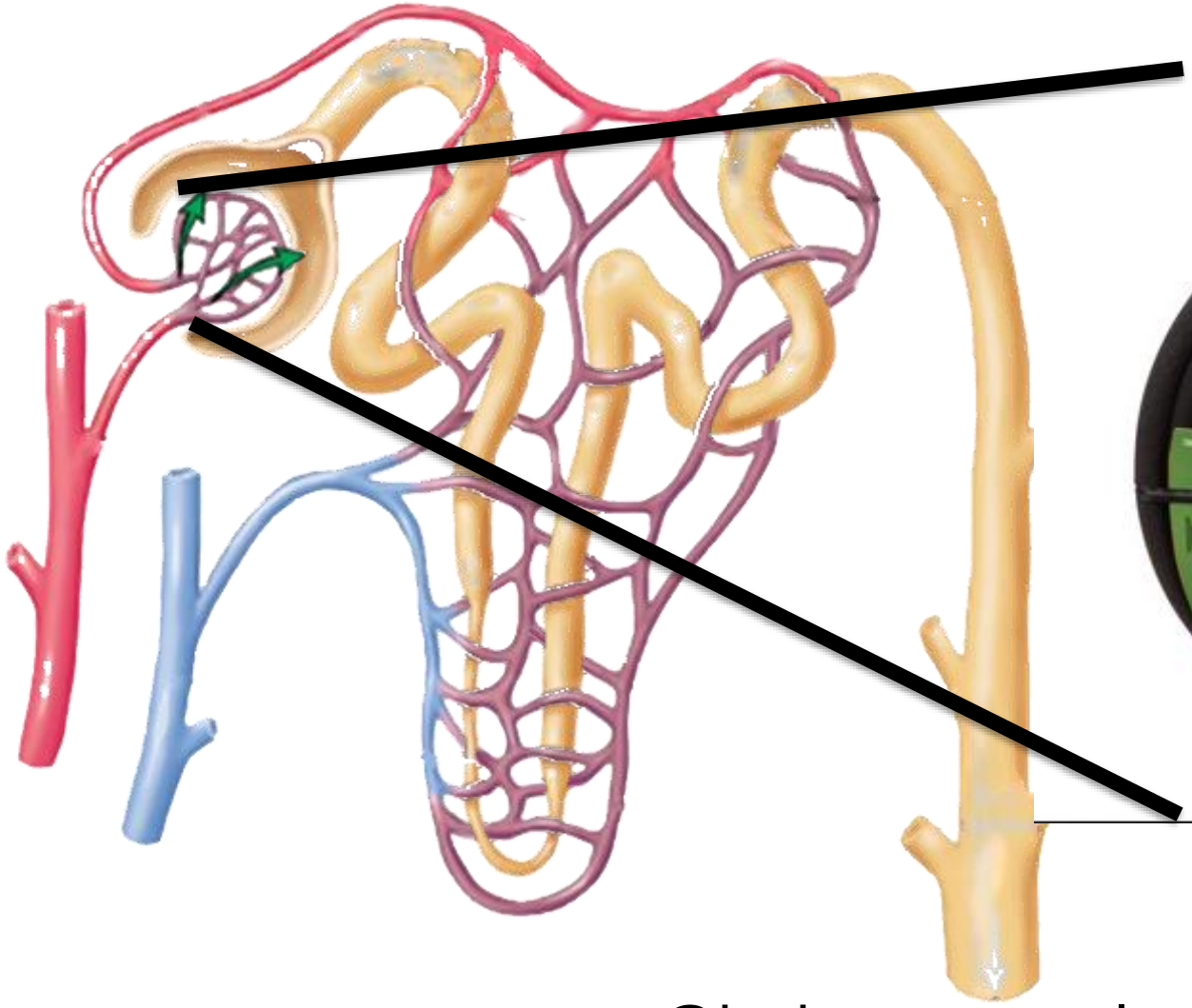
Structure of the Kidney



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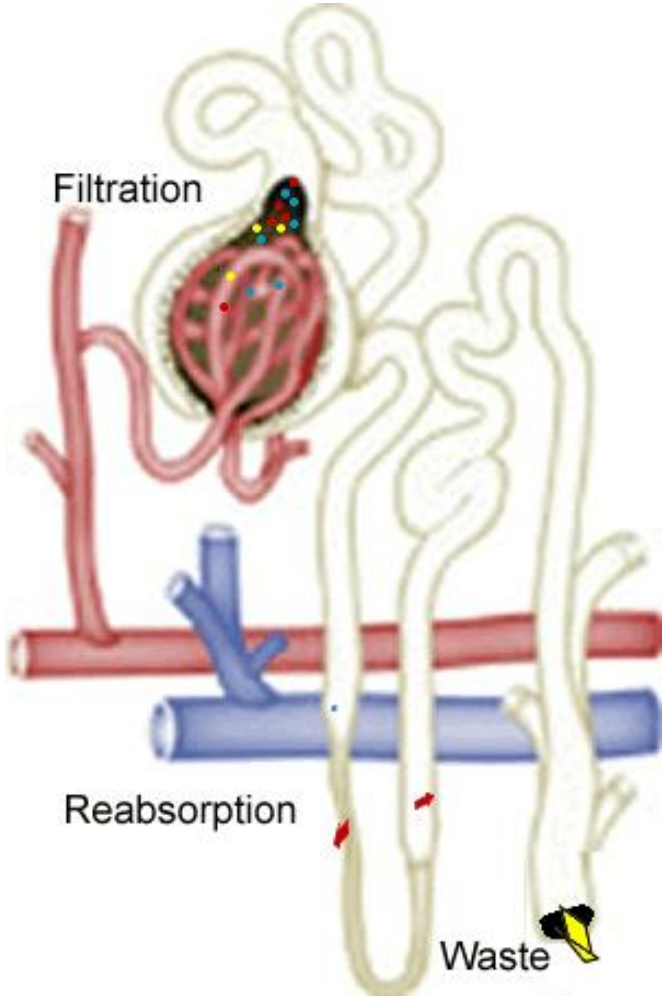
Basic kidney function

- Most of that filtrate gets reabsorbed back into the blood stream by tubules
  - You don’t make a liter of urine every 10 minutes!
  - The tubules are responsible for fine tuning reabsorption to control the blood levels of many chemicals and electrolytes



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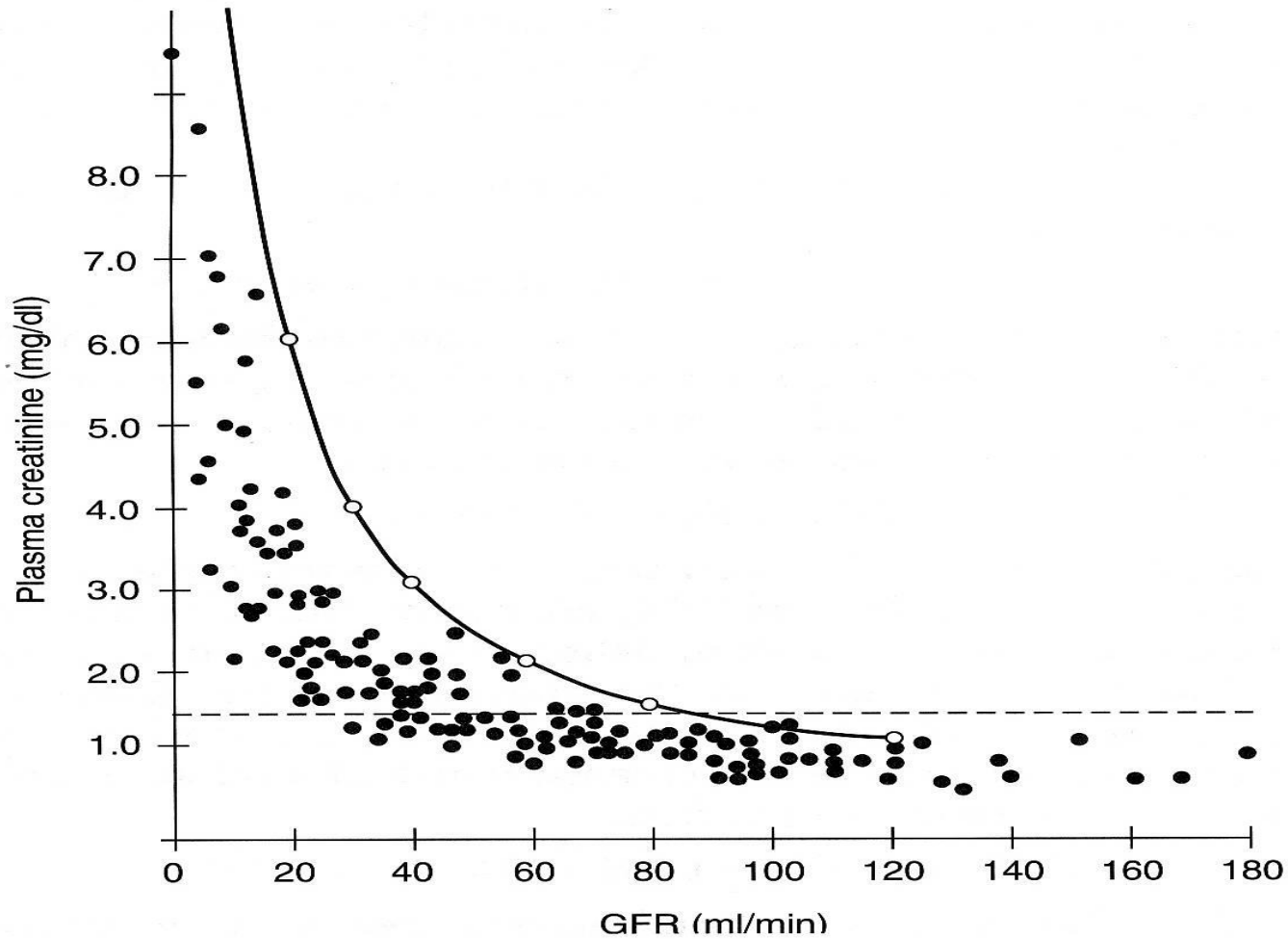
Creatinine and Clearance

- Creatinine is made at a constant rate
- It is only removed from the blood by kidney filtration
- Once filtered, it gets excreted into the urine
- Measuring the blood levels gives a good estimation of the filtration, or GFR
- Decreased filtration is noted as an increase in creatinine.

Kidney Function and Creatinine



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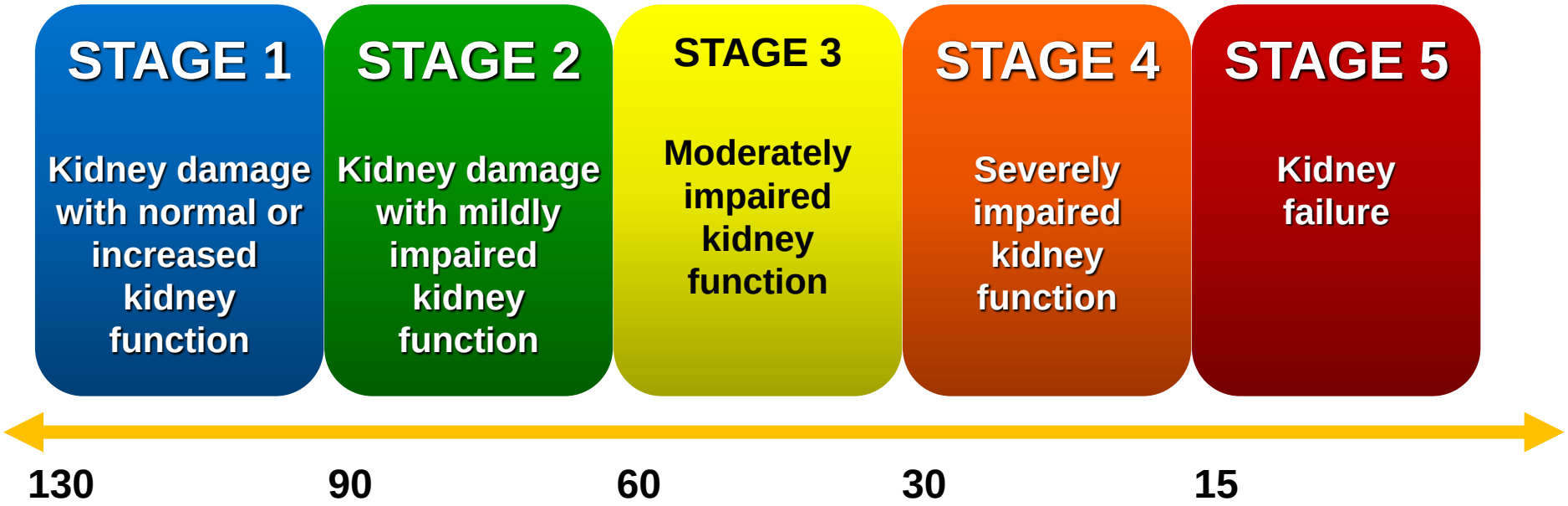
Stages of Chronic Kidney Disease[1]



1. KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. National Kidney Foundation Web site. www.kidney.org/professionals/kdoqi/guidelines_ckd/p4_class_g1.htm. Accessed May 2011.

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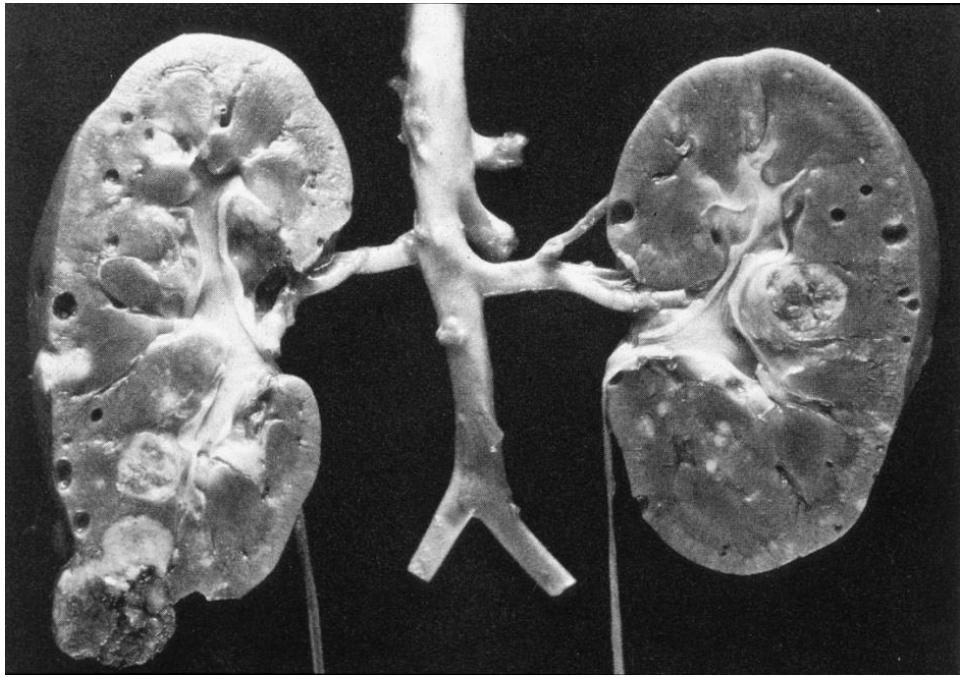
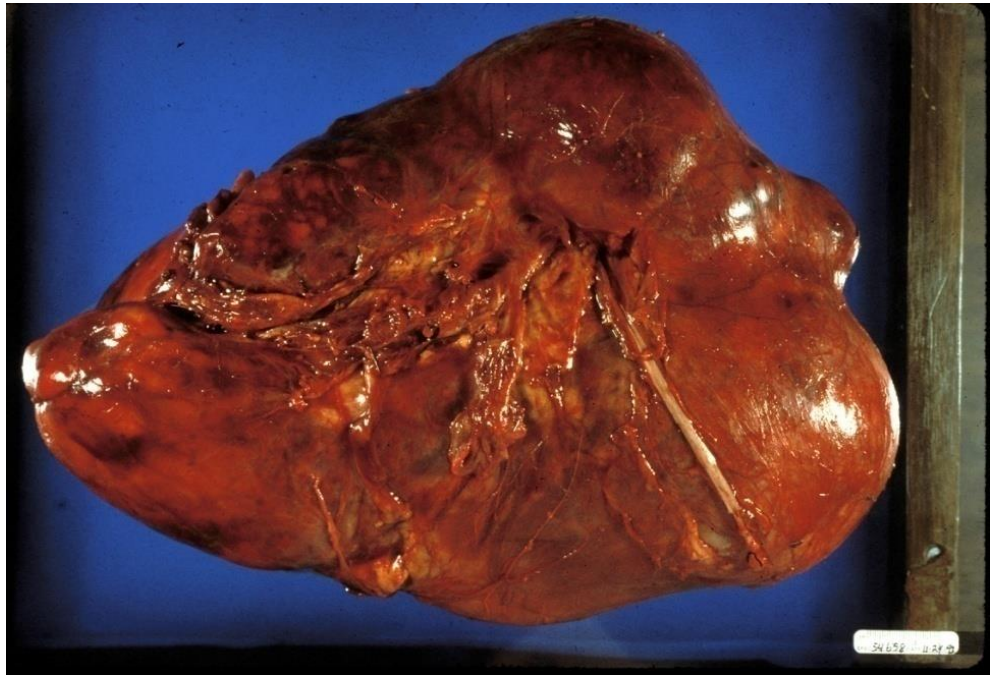
Kidney Features of Tuberous Sclerosis

Angiomyolipomas, Cysts, RCCs





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Age and Onset of Symptoms

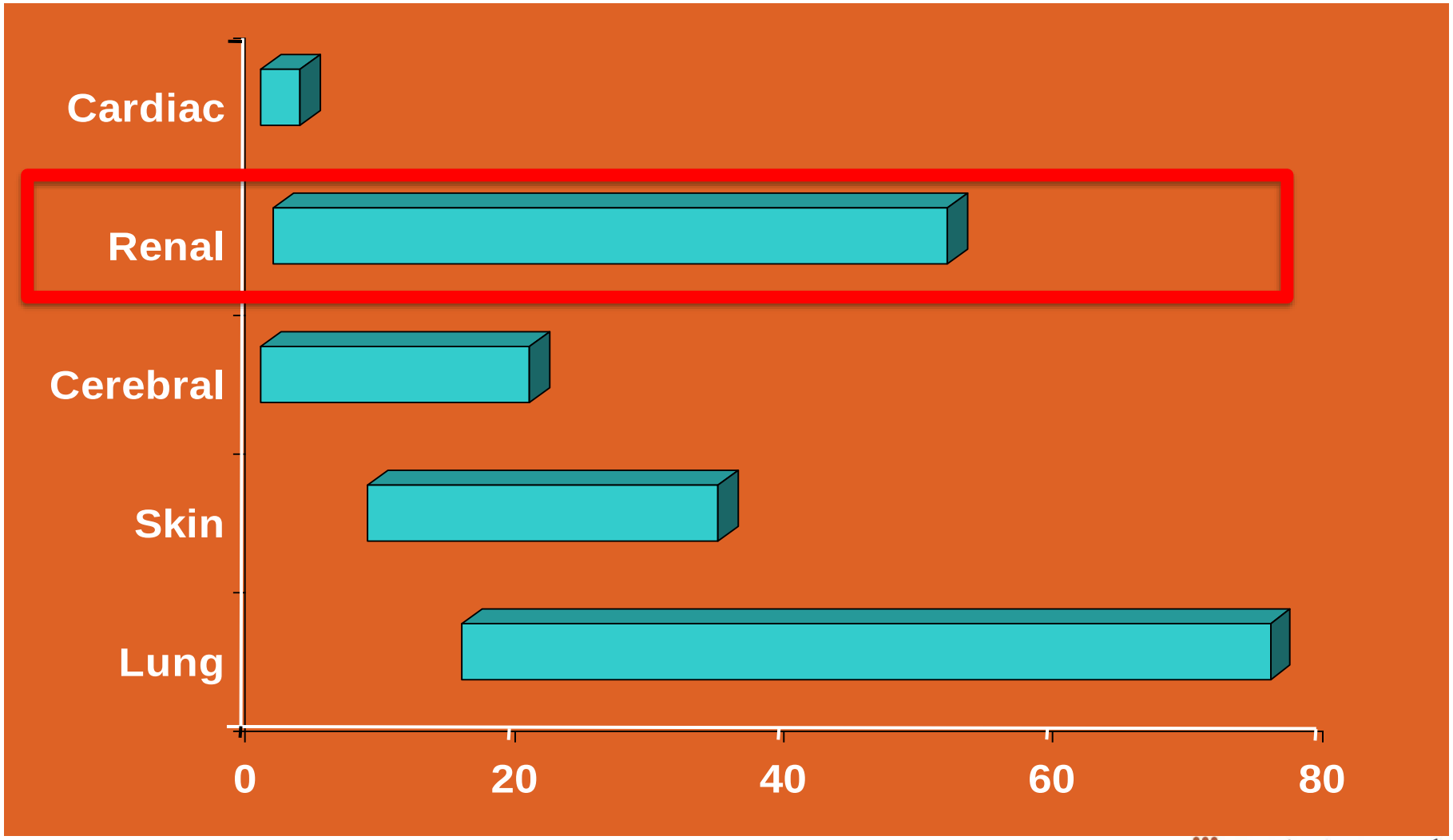

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Image courtesy of DN Franz, 2011.

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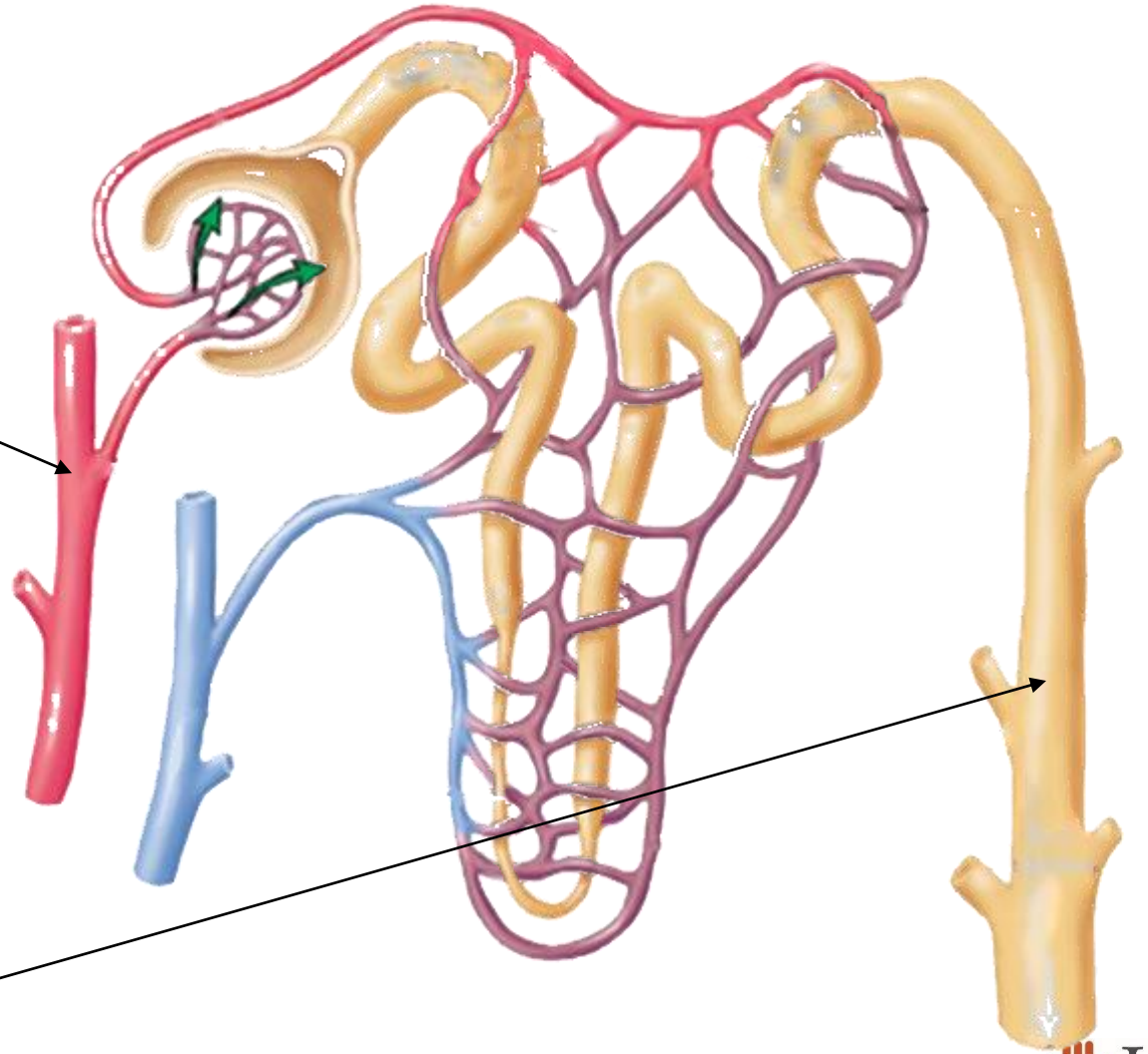
Origin of TSC Renal Disease

Blood Vessels
- Angiomyolipoma



Epithelial Cell:
- Cyst
- RCC
- Oncocytoma

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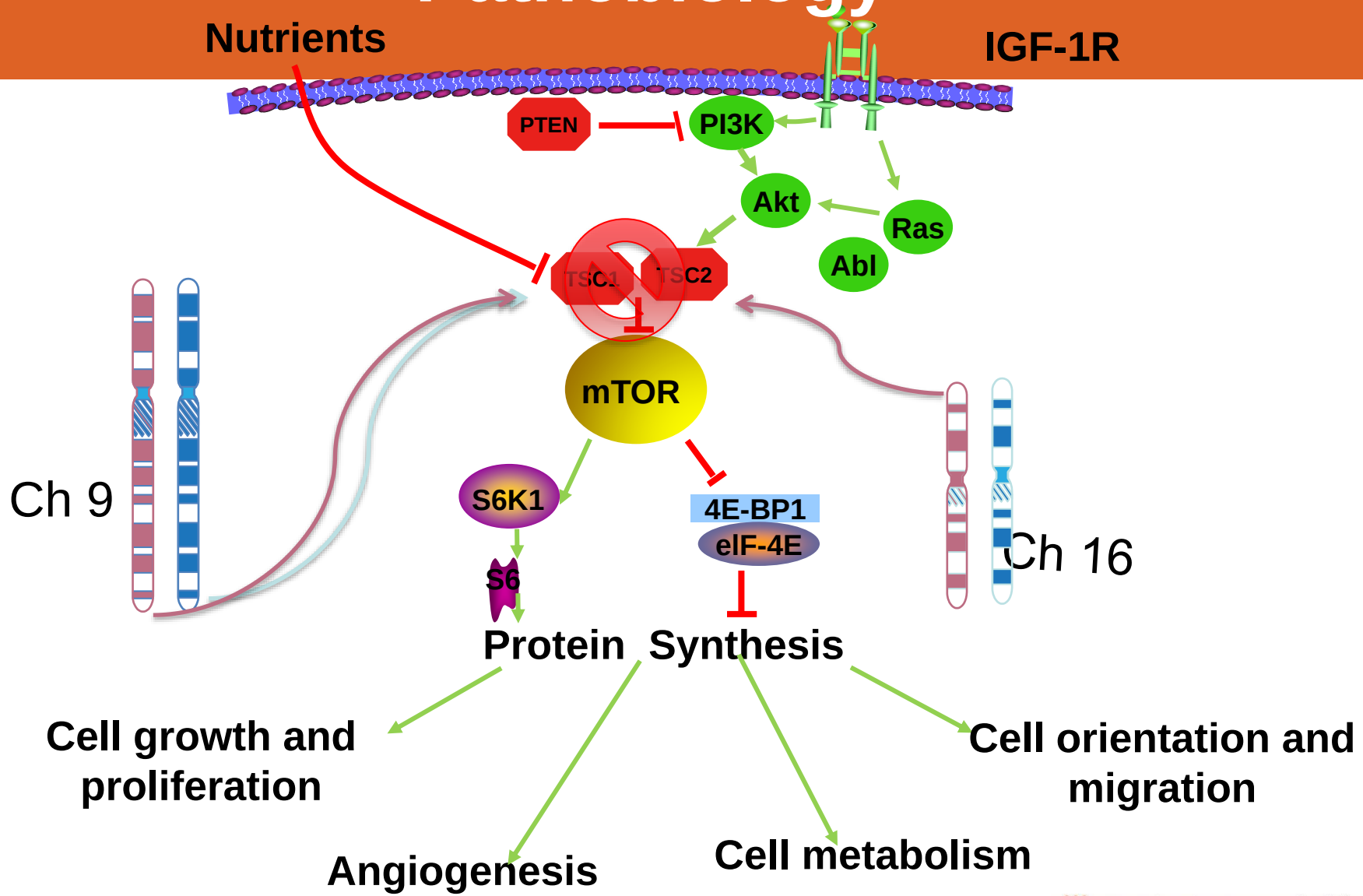
Angiomyolipoma

- Solid tumors that grow from kidneys
- Made up of 3 distinct cell types
  - Blood vessel cells (Angio)
  - Muscle cells (myo)
  - Fat cells (lipoma)
- Loss of TSC gene function leads to deregulation of mTOR pathway
  - Overactivity of mTOR at center of AML growth

Pathobiology



Foster KG, et al. *J Biol Chem*. 2010;285:14071-14077
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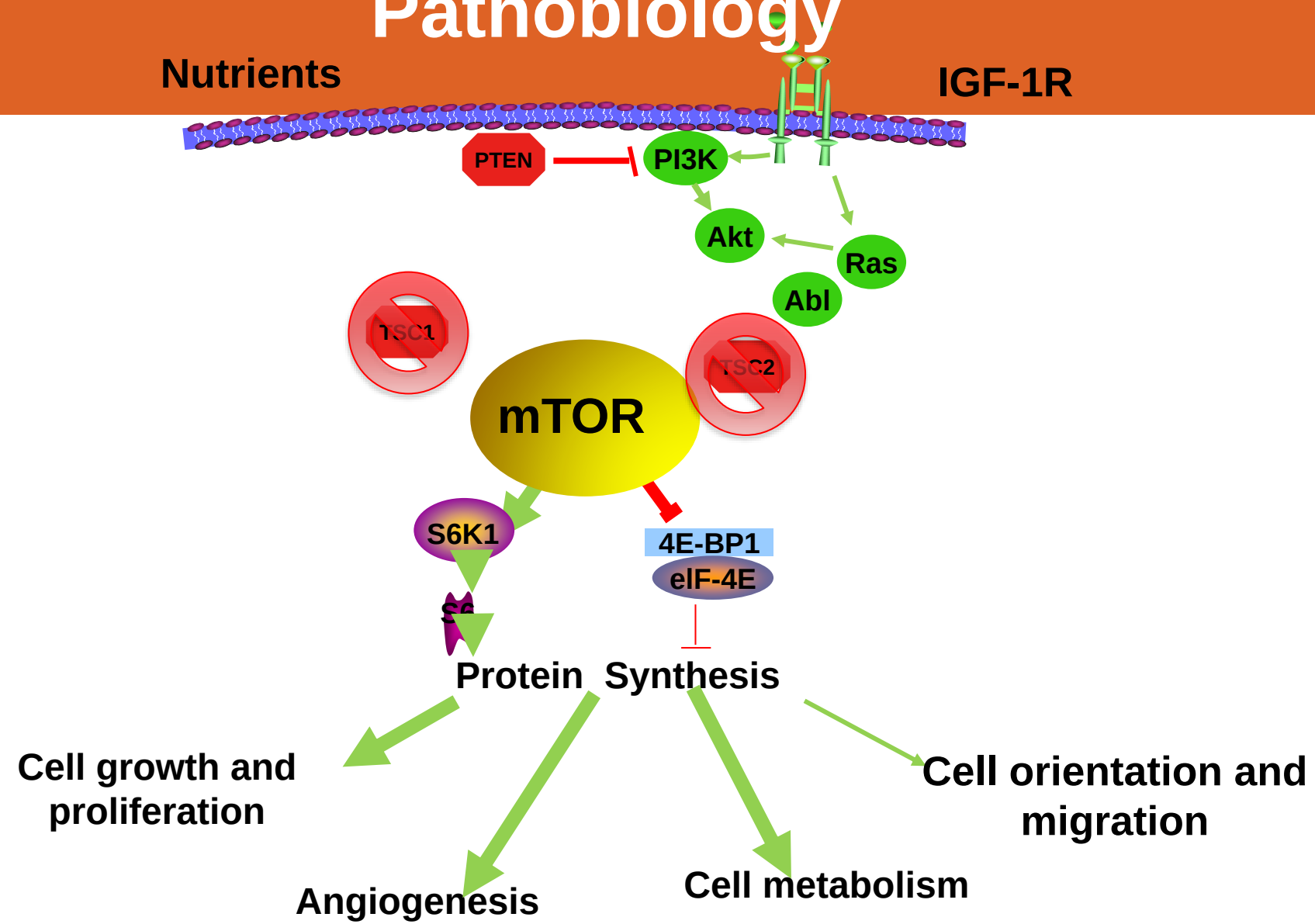

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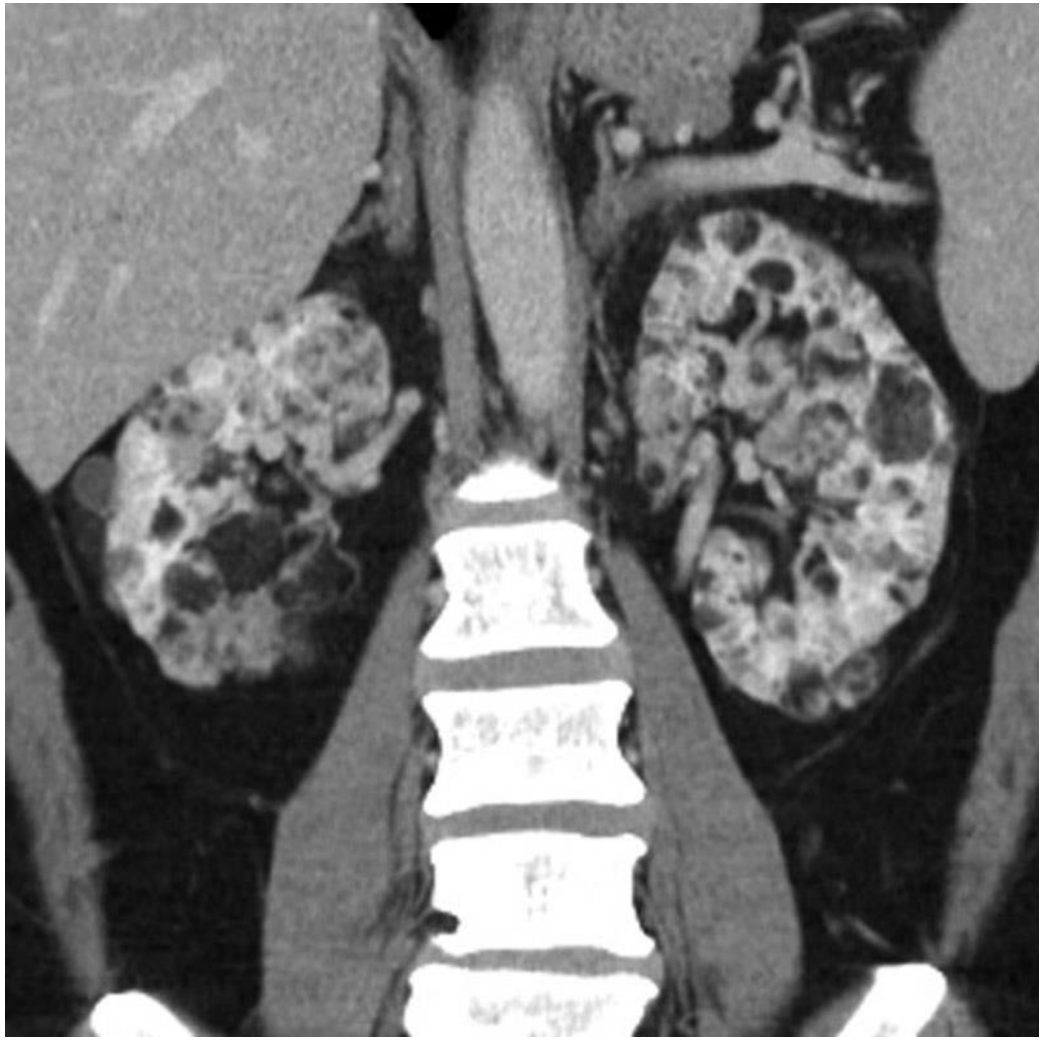
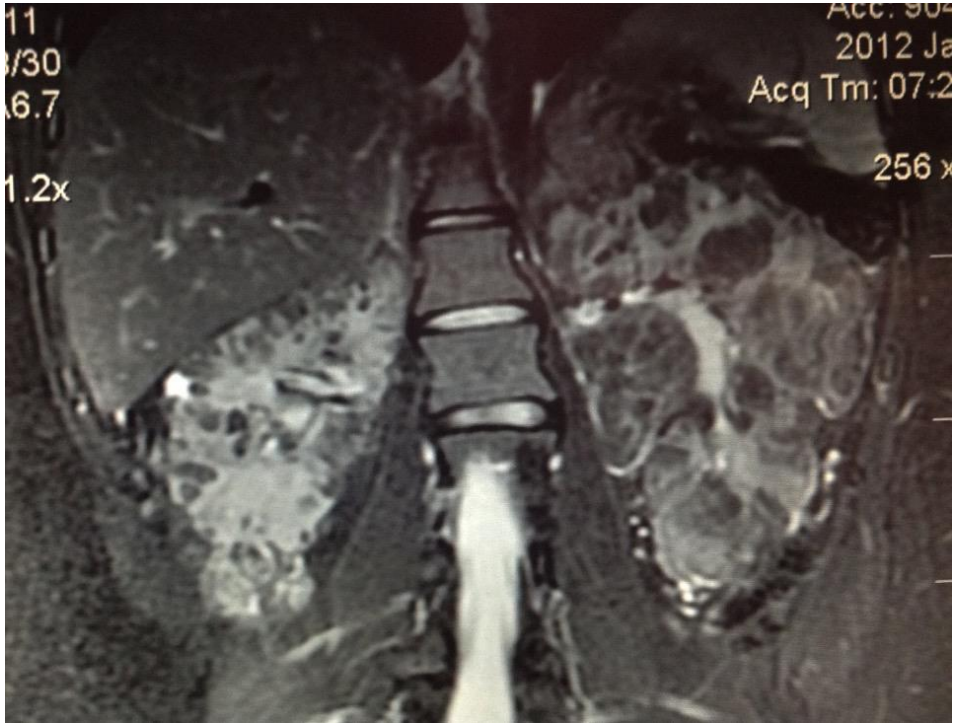
Renal Angiomyolipomas in TSC





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Consensus Guidelines

Original Article

Tuberous Sclerosis Complex Surveillance and Management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference☆

Darcy A. Krueger MD PhD [a,*], Hope Northrup MD [b], on behalf of the International Tuberous Sclerosis Complex Consensus Group

[a] *Division of Neurology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio*
[b] *Division of Medical Genetics, Department of Pediatrics, University of Texas Medical School at Houston, Houston, Texas*

- At the time of diagnosis, abdominal imaging should be obtained regardless of age. As for brain, MRI is the preferred modality for evaluation of angiomyolipomata because many can be fat-poor and hence missed when abdominal CT or US are performed.

Pediatr Neurol 2013; 49: 255-265

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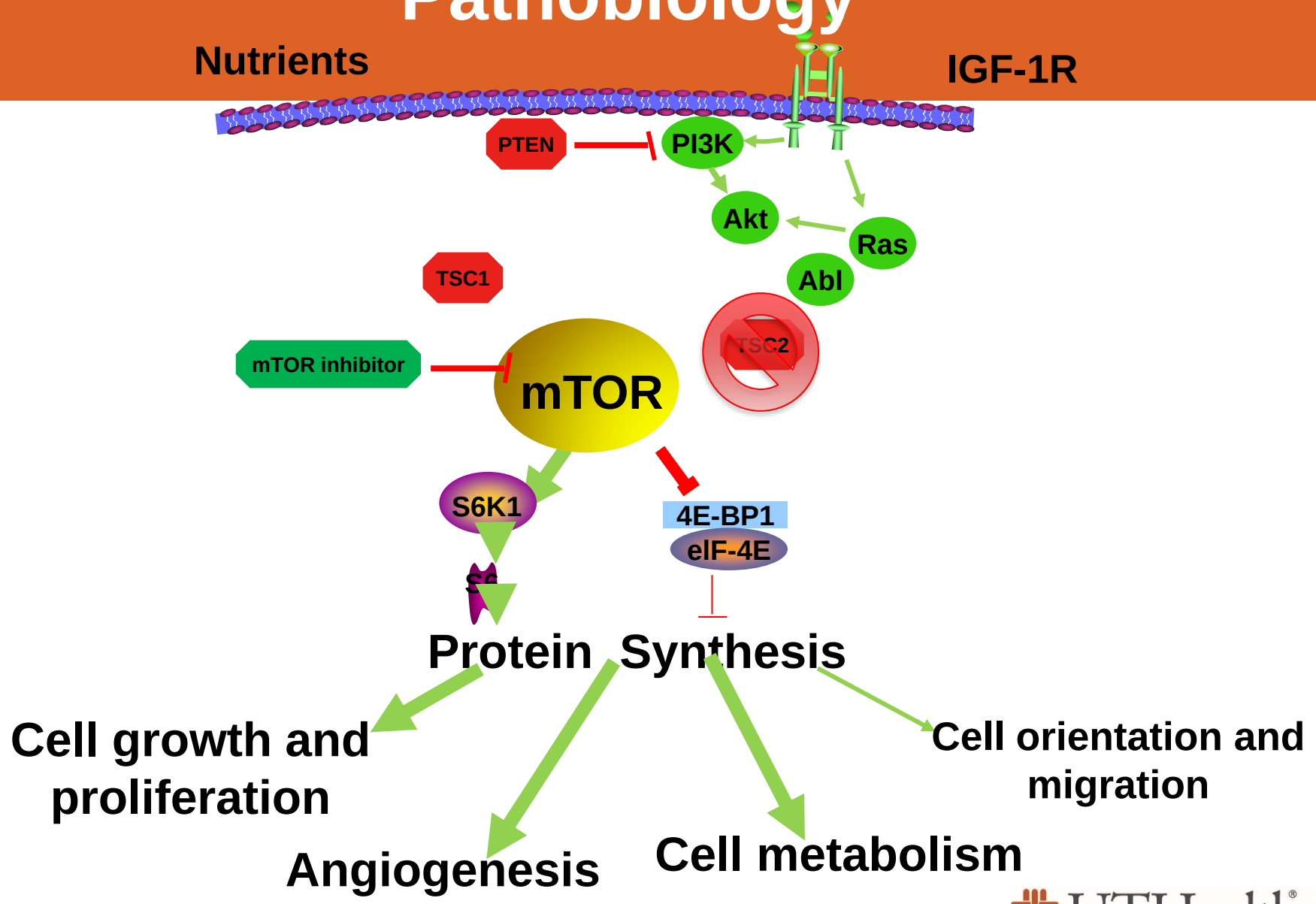
- Obtain MRI of the abdomen to assess for the progression of angiomyolipoma and renal cystic disease every 1-3 yr throughout lifetime.
- Assess kidney function and blood pressure at least annually.

Pediatr Neurol 2013; 49: 255-265

Pathobiology



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- For asymptomatic, growing angiomyolipoma measuring larger than 3 cm in diameter, treatment with an mTOR inhibitor is the recommended first line therapy.

Pediatr Neurol 2013; 49: 255-265

EXIST-2 Long Term Follow up

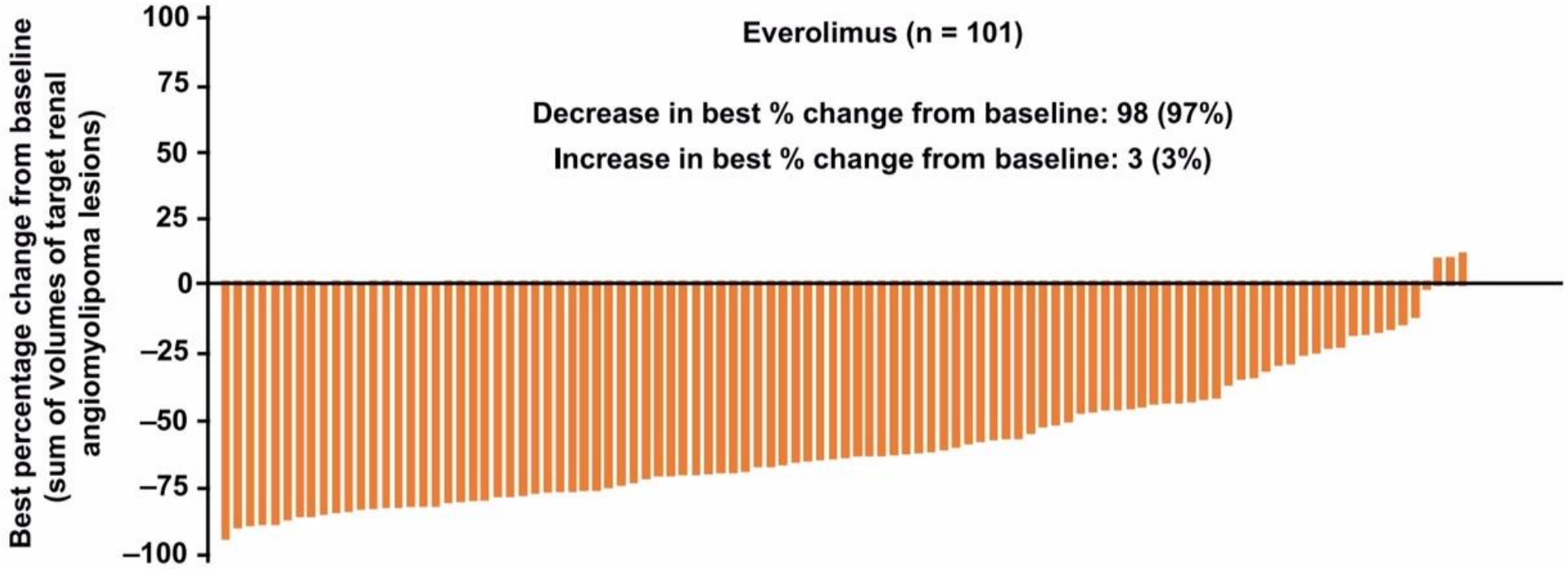

Fig 2. Best percentage reduction in the sum volume of target renal angiomyolipomas each individual patient reported at any time point in the study in 101 evaluable patients.[a] [a]11 patients were considered "non-evaluable" due to missing overall angiomyolipoma response status at each radiological assessment. Among the 12 patients with a best overall response with the status "not evaluable", only one patient reported at least one radiological assessment with a non-missing overall angiomyolipoma response status.

https://doi.org/10.1371/journal.pone.0180939.g002

Bissler, JJ, etal. PLoS ONE 12(8): e0180939

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Kidney function = pregnancy

- With TSC, most young women who are of child-bearing age will have kidney tumors but still have normal kidney function (CKD 1 or 2)
  - Likely means normal pregnancy
  - Will HAVE to stop mTOR inhibition BEFORE pregnancy
    - Risk of angiomyolipoma growth during pregnancy
    - Risk of CKD progression during pregnancy
  - MAY need to adjust blood pressure medications
    - Risk of high blood pressure during pregnancy

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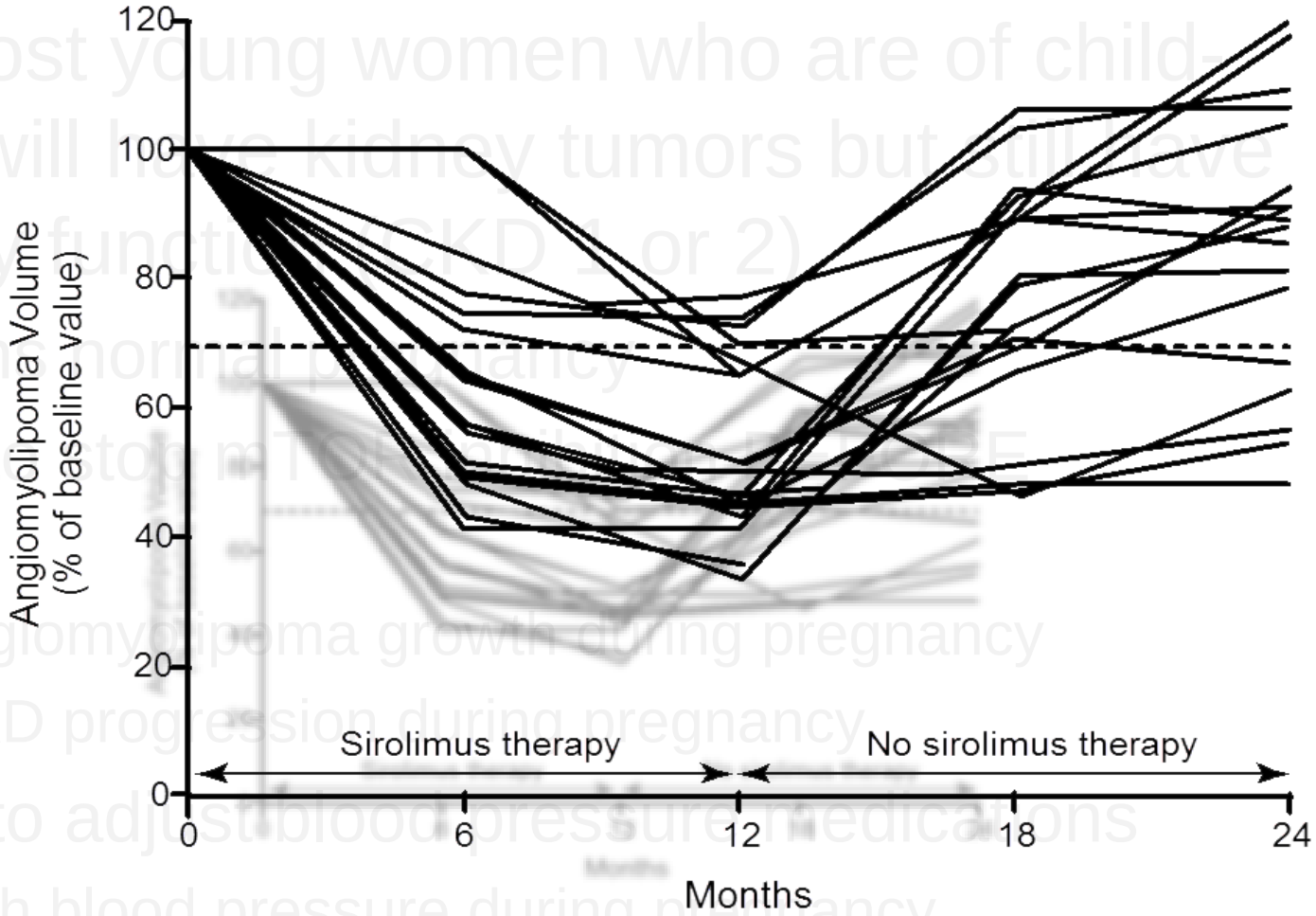
Kidney function = pregnancy



Bissler JJ, et al. *N Engl J Med*. 2008;358(2):140-151

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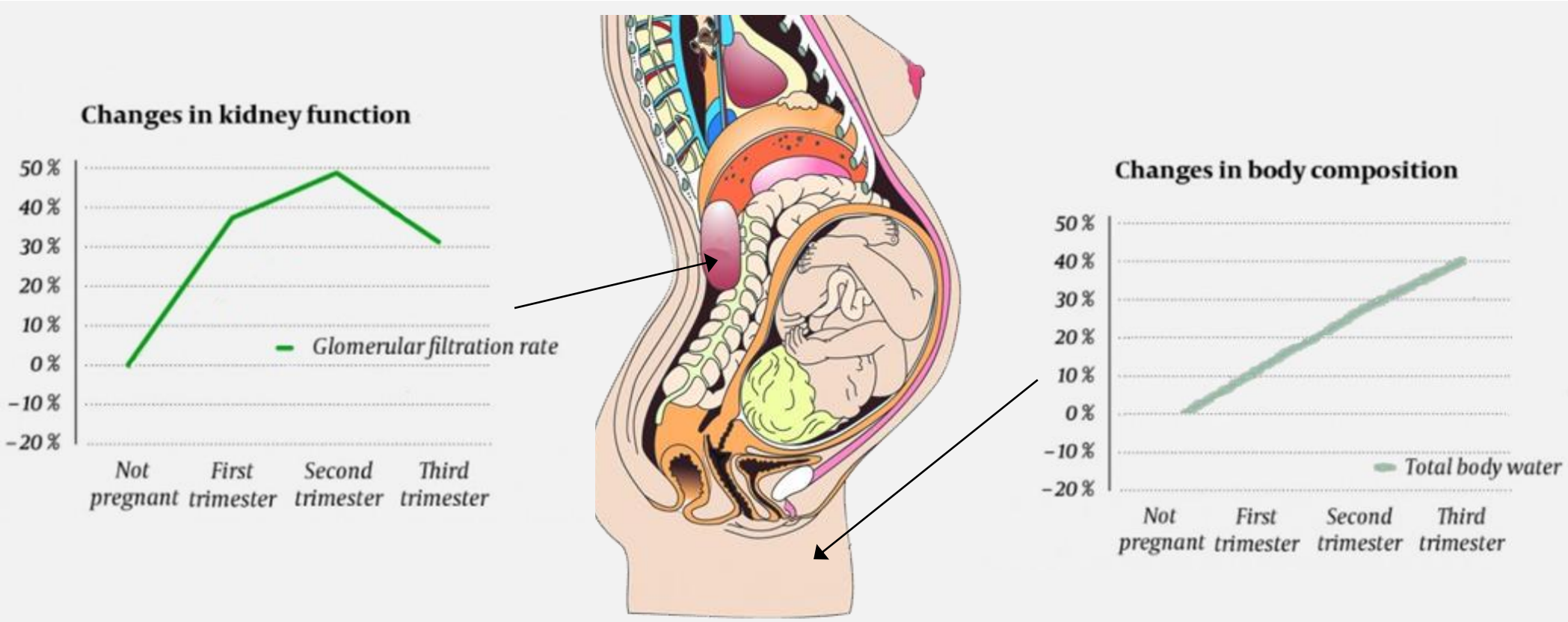
Changes during pregnancy



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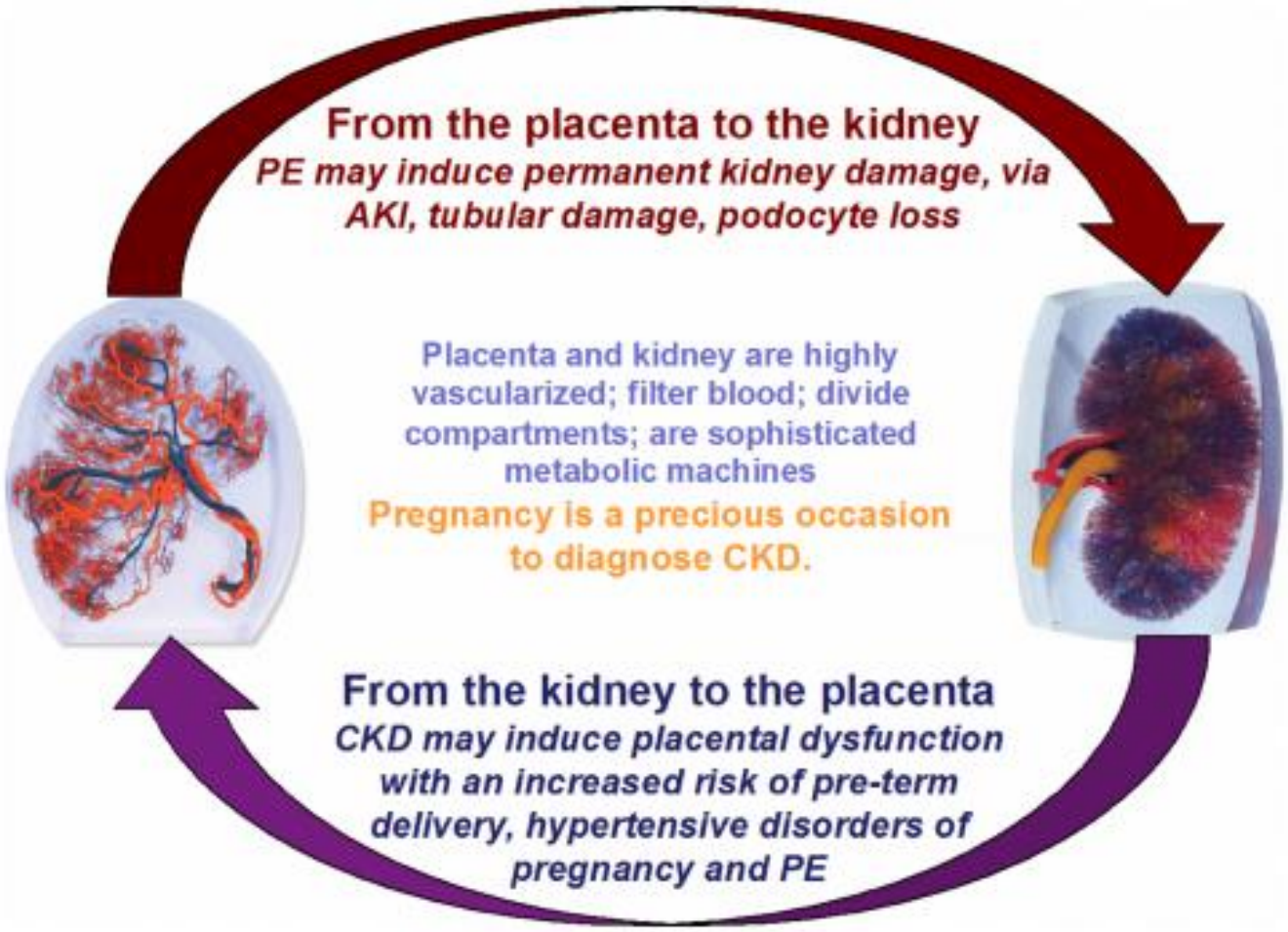
Kidney function = pregnancy

- Some women with TSC have large kidney lesions and suffer from diminished kidney function (CKD 3-5)
  - More difficult to get pregnant
  - More difficult to stay pregnant
- During pregnancy, CKD can have multiple effects
  - On mother
  - On baby

Impact of pregnancy in women with CKD

- Maternal
  - Worsening kidney function
  - Hypertensive disorders of pregnancy
    - Gestational HTN
    - Preeclampsia
    - HELLP
  - Miscarriage
- Fetal
  - Preterm birth
  - Stillbirth or neonatal death
  - Low birthweight
    - SGA
    - Fetal growth restriction

Interactions: Kidneys and Placenta



Piccoli *J Nephro* (2018) 31:173–184

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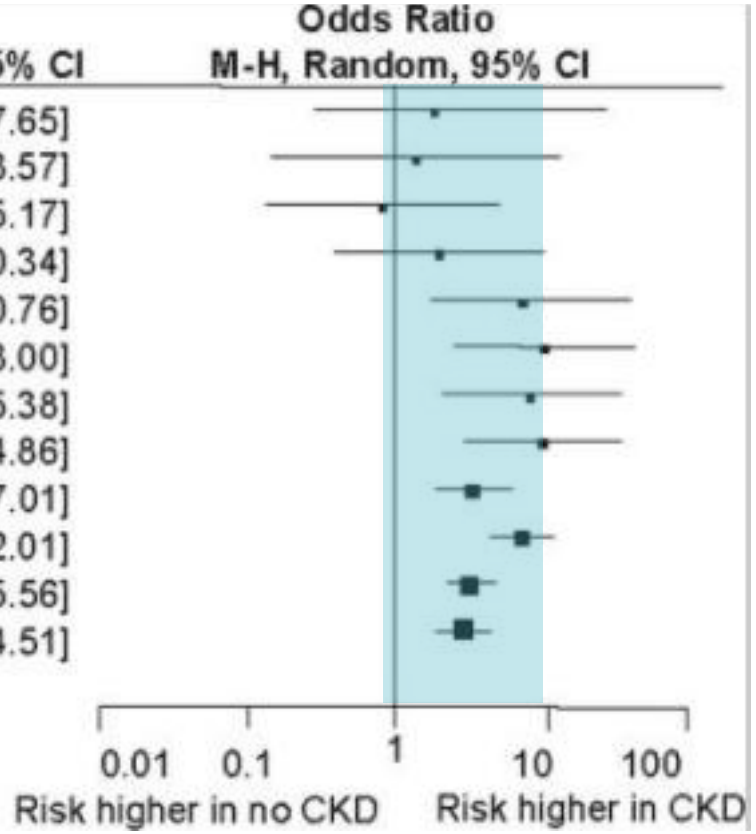
Pregnancy complications in CKD

Study	CKD Events	CKD Total	No CKD Events	No CKD Total	Weight	Odds Ratio M-H, Random, 95% CI
Piccoli	1	36	3	297	1.4%	2.80 [0.28, 27.65]
Houser	2	7	2	9	1.4%	1.40 [0.14, 13.57]
Nagai	5	11	4	8	2.2%	0.83 [0.13, 5.17]
Leppert	6	88	2	57	2.7%	2.01 [0.39, 10.34]
Gladman	10	50	2	70	2.9%	8.50 [1.77, 40.76]
Trevisan	10	25	3	50	3.5%	10.44 [2.54, 43.00]
Kimmerlee	7	36	3	110	3.5%	8.61 [2.09, 35.38]
Murakami	15	19	18	67	4.4%	10.21 [2.99, 34.86]
Rosenn	32	73	54	335	14.3%	4.06 [2.35, 7.01]
Fink	55	169	31	506	16.2%	7.39 [4.55, 12.01]
Gazarek	44	1257	181	20034	21.8%	3.98 [2.85, 5.56]
Fischer	125	911	197	4606	25.8%	3.56 [2.81, 4.51]



Adverse maternal outcomes: Hypertension, pre-eclampsia, eclampsia, mortality

Nevis *CJASN (2011)* 6: 2587–2598

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Clinical Guidelines for CKD and Pregnancy

Wiles *et al. BMC Nephrology* (2019) 20:401
https://doi.org/10.1186/s12882-019-1560-2

BMC Nephrology

GUIDELINES Open Access

Clinical practice guideline on pregnancy and renal disease

Kate Wiles[1*], Lucy Chappell[2], Katherine Clark[3], Louise Elman[4], Matt Hall[5], Liz Lightstone[6], Germin Mohamed[4], Durba Mukherjee[4], Catherine Nelson-Piercy[7], Philip Webster[8], Rebecca Whybrow[9] and Kate Bramham[10]

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UK Guidelines

- Guideline 3.3.1 We suggest women with CKD considering pregnancy are offered pre-pregnancy counselling by a multidisciplinary team including a consultant obstetrician and nephrologist or expert physician (2D).

- Guideline 3.3.2 We recommend women with CKD are advised there is an increased risk of complications in pregnancy including pre-eclampsia, preterm birth, fetal growth restriction, and neonatal unit (NNU) admission, and that they are more likely to require caesarean delivery (1C).

Wiles *BMC Nephrology* (2019) 20:401

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UK Guidelines

- Guideline 3.3.3 We recommend women with known or suspected inheritable renal diseases are offered genetic counselling including inheritance risk, prognosis, and intervention options including pre-implantation genetic diagnosis (1C).

- Guideline 3.2.4 We recommend single-embryo transfer is performed to reduce risk of complications associated with multi-fetal pregnancies in women with CKD (1C).

Wiles *BMC Nephrology* (2019) 20:401

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UK Guidelines

- Guideline 3.3.4 We recommend pre-pregnancy counselling for the optimization of maternal and neonatal outcomes in women with CKD, which may include:
  - Stabilizing disease activity in advance of pregnancy on minimized doses of pregnancy-appropriate medications (1B).
  - Optimizing blood pressure control (< 140/90 mmHg) on pregnancy-appropriate medications (1B).
  - Minimizing risk of exposure to teratogenic medications (1C) (see section 2).

Wiles *BMC Nephrology* (2019) 20:401

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UK Guidelines

- Guideline 4.3.1 We recommend women with CKD are offered low-dose aspirin (75-150 mg) in pregnancy to reduce the risk of pre-eclampsia (1B).

- Guideline 4.4.1 We recommend that the target blood pressure during pregnancy for women with CKD is 135/ 85 mmHg or less, which should be documented in the woman's healthcare record (1D).

Wiles *BMC Nephrology* (2019) 20:401

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Summary

- Kidneys are an important target of damage in TSC
- Some medications require discontinuation before pregnancy
- With normal kidney function, pregnancy often normal
- With diminished kidney function, pregnancy often complicated
- Regardless of fetal/baby outcomes, pregnancy is a strenuous metabolic process for mother and kidney function may decline
- Pregnancy brings many growth factors which may accelerate kidney tumor growth

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Questions

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