Kidney Disease in TSC

Leuven Family Meeting

2019

Declaration of Interest

- The cause of TSC
- The picture of TSC
- Therapy in TSC
- The future in TSC

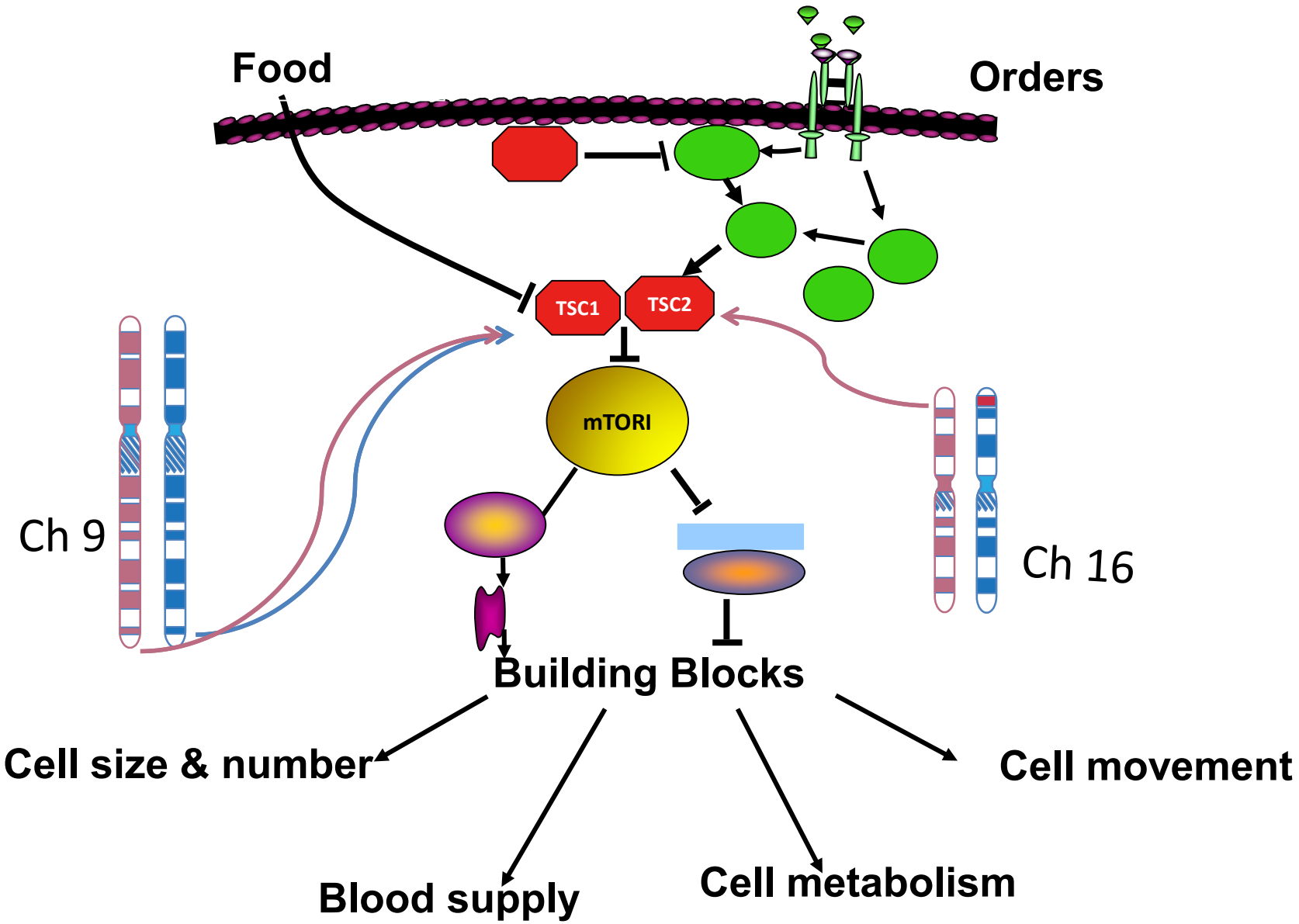
How do we know what we know?

- Definition of TSC
  - A collection of problems that make TSC highly likely
  - Genetic diagnosis (80 → 95%)
  - Disease causing gene mutation v normal variant
- 1:6500 newborns

The cause of TSC

- TSC2 (1993)
- TSC1 (1997)
- mTOR pathway

Pathobiology



Rapamycin or Sirolimus

The picture of TSC

TOSCA

Tuber**O**us **SC**lerosis Registry to Increase disease **A**wareness

Europe

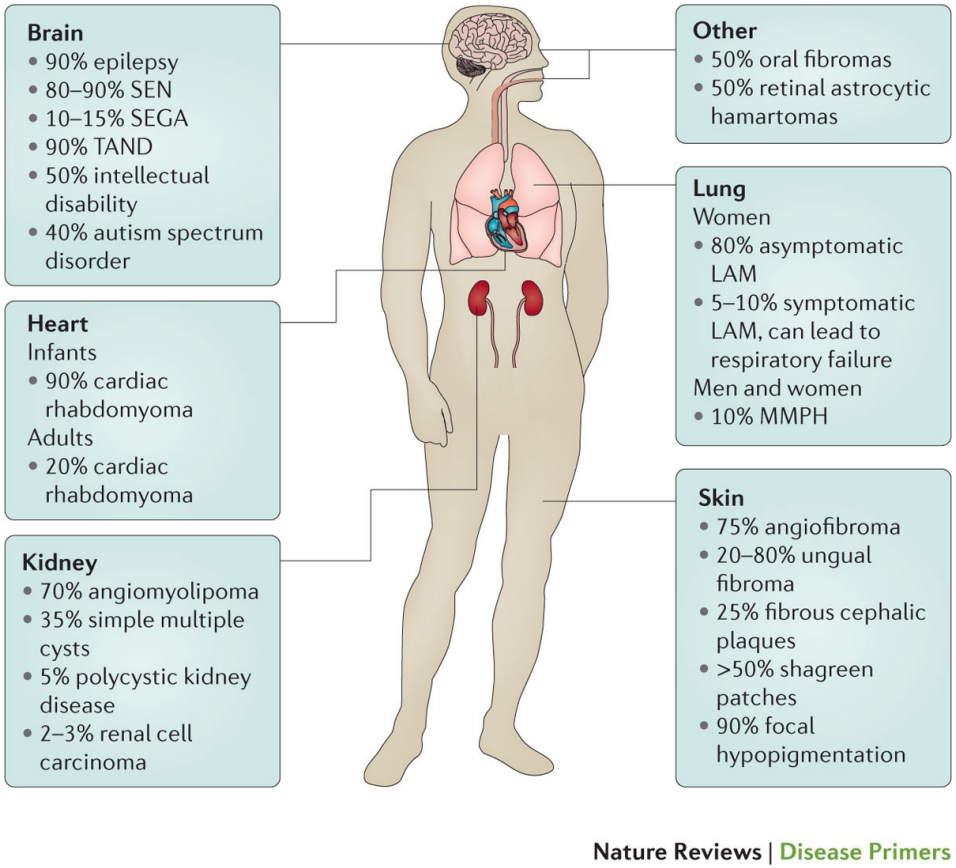
Austria*, **Belgium*,** Czech Republic*, Denmark*, Estonia, France*, Germany*, Greece*, Italy*, Latvia, Lithuania, Netherlands*, Norway*, Poland*, Portugal, Romania, Slovakia, Slovenia*, Spain*, Sweden*, United Kingdom*

EGM

Australia, China, Israel, Korea, Taiwan, Thailand, Turkey, Russia, South Africa Japan

- TOSCA: **2216** patients enrolled as of Sep 30, 2016
- TOSCA PASS: **179** patients enrolled as of Sep 30, 2016

**EU countries involved in TOSCA PASS*



Henske, E. P. *et al.* (2016) Tuberous sclerosis complex
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2016.35

Lifetime risk of serious complication from TSC before 2012

- Resistant epilepsy – 40%[5]
- Disfiguring facial rash 75%[6]
- SEGA – 10-15%[1]
- Renal (Bleed or CKD) – 40-50%[2,3]
- Symptomatic LAM – 5-40% (In women)[4]
- TAND – 90%[7]

1. Jozwiak S, 2013 Eur J Paed Neurol 17 348-52
2. Kessle OJ, 1998 *European Urology* 33**,** 572-5
3. Kingswood,JC 2014 CPRD Eur Assoc Urology
4. Cudzilo, C. J. 2013 Chest 144(2): 578-585
5. Curatolo, P.2012 Eur J Paediatr Neurol 16(6): 582-586
6. Northrup, H, 2013 Pediatr Neurol 49(4): 243-254
7. de Vries PJ, 2014 Paediatr Neurol

What we knew
Pre 2012

- AMLs approx 80% & commonest cause of death in adults with TSC [1,2]
- Risk of bleeding 25-50% [3,4]
- LAM ~30-80% of women [1,2]
- Kidney cancer ~ 1-3%
- Polycystic kidney 5%
- Needing dialysis~ 1%
- Reduced kidney function 40% (Adults)[5]
- High blood pressure 27% (Adults)[5]

1. Franz DN et al. *Neuropediatrics* 2010; 41(5):199-208.
2. Dixon BP et al. *Nephron Experimental Nephrology* 2011; 118(1):e15-e20.
3. Kessle OJ et al. *European Urology,* 1998 33, 572-5
4. Mouded Il et al. *Journal of Urology,* 1978 119, 684-8.
5. Kingswood,JC et al CPRD Eur Assoc Urology 2014

Therapy in TSC

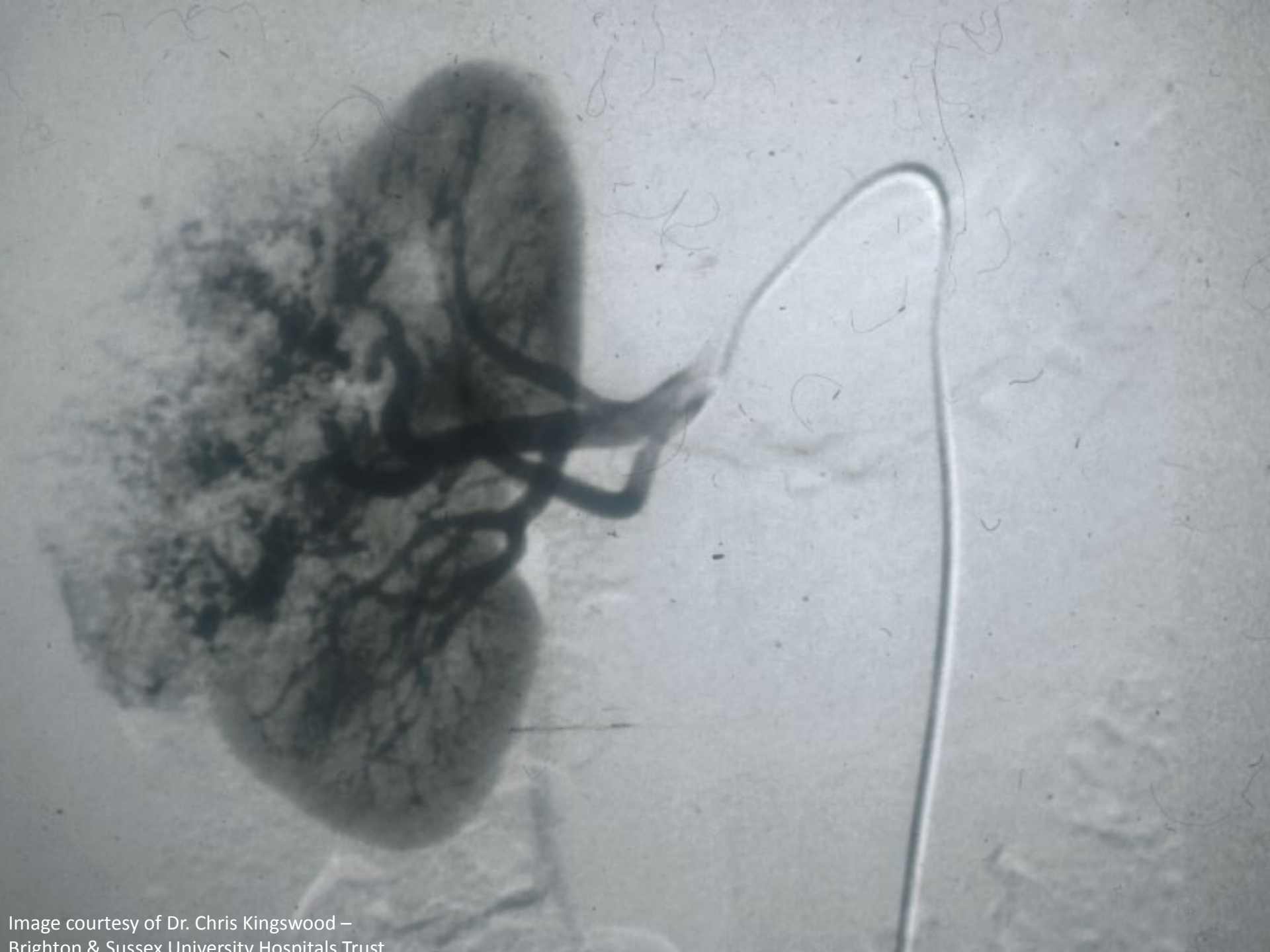
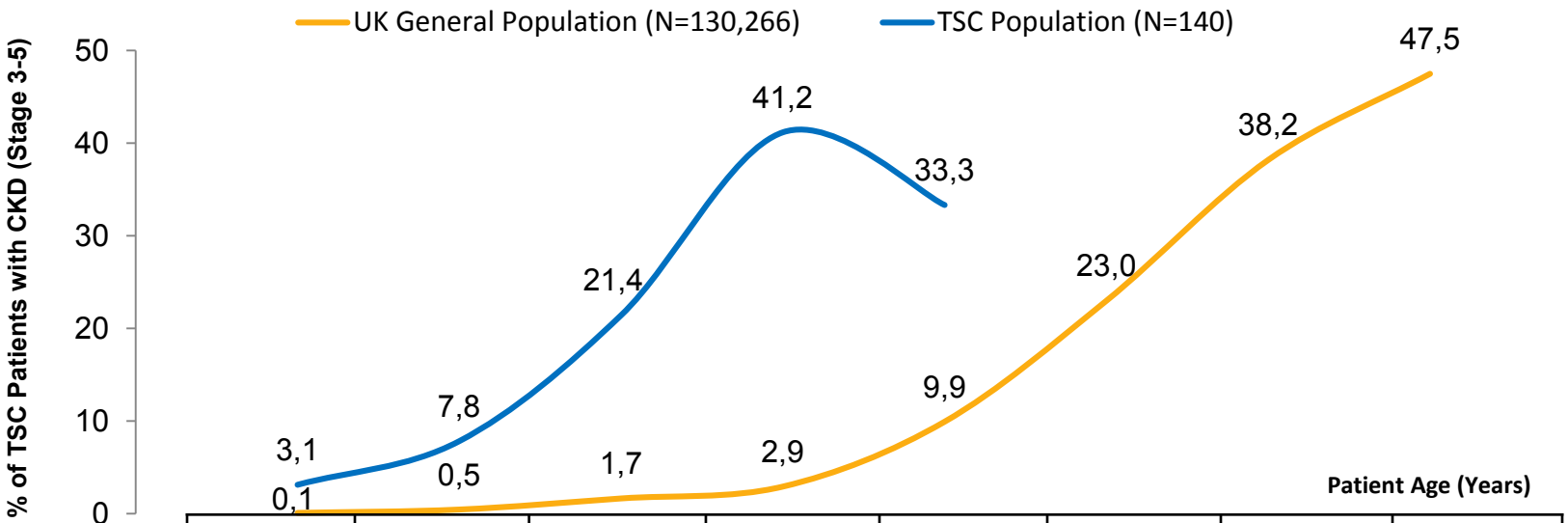


Image courtesy of Dr. Chris Kingswood –
Brighton & Sussex University Hospitals Trust

Prevalence of CKD (Stage 3-5) in the TSC Population by Age Compared to the UK General Population (Dec 1998-Nov 2003)*

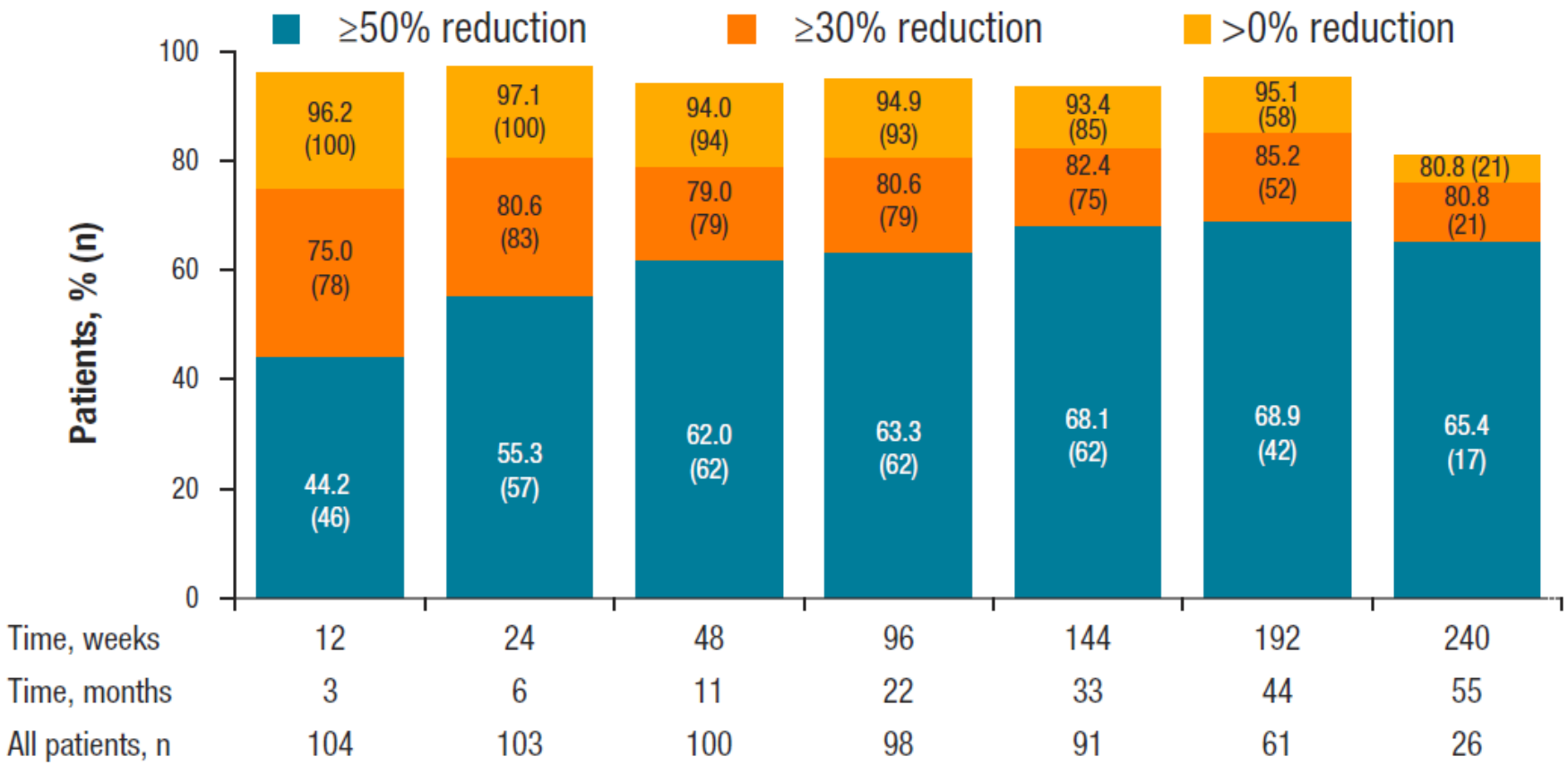


	18-24	25-34	35-44	45-54	55-64	65-74	75-84	≥85
TSC (N)	32	51	28	17	12	0	0	0
TSC (95% CI)	0.1-16.2	2.2-18.9	8.3-41.0	18.4-67.1	9.9-65.1	-	-	-
UK Gen. Pop (95% CI)	0.1-0.2	0.4-0.6	1.5-1.8	2.7-3.2	9.5-10.4	22.3-23.7	37.3-39.2	45.9-49.2

**CKD prevalence estimates in the TSC population were calculated and compared to the UK general population as reported in the NEOERICA study (Dec 1998-Nov 2003) [4].*
If a CKD (stage 3-5) record/identifier was observed prior to 1998 in a TSC patient, this patient was still considered to have a CKD case in the observational period (i.e. Dec 1998-Nov 2003).

Exist-2. Renal Angiomyolipoma Response Rate With Everolimus Over Time

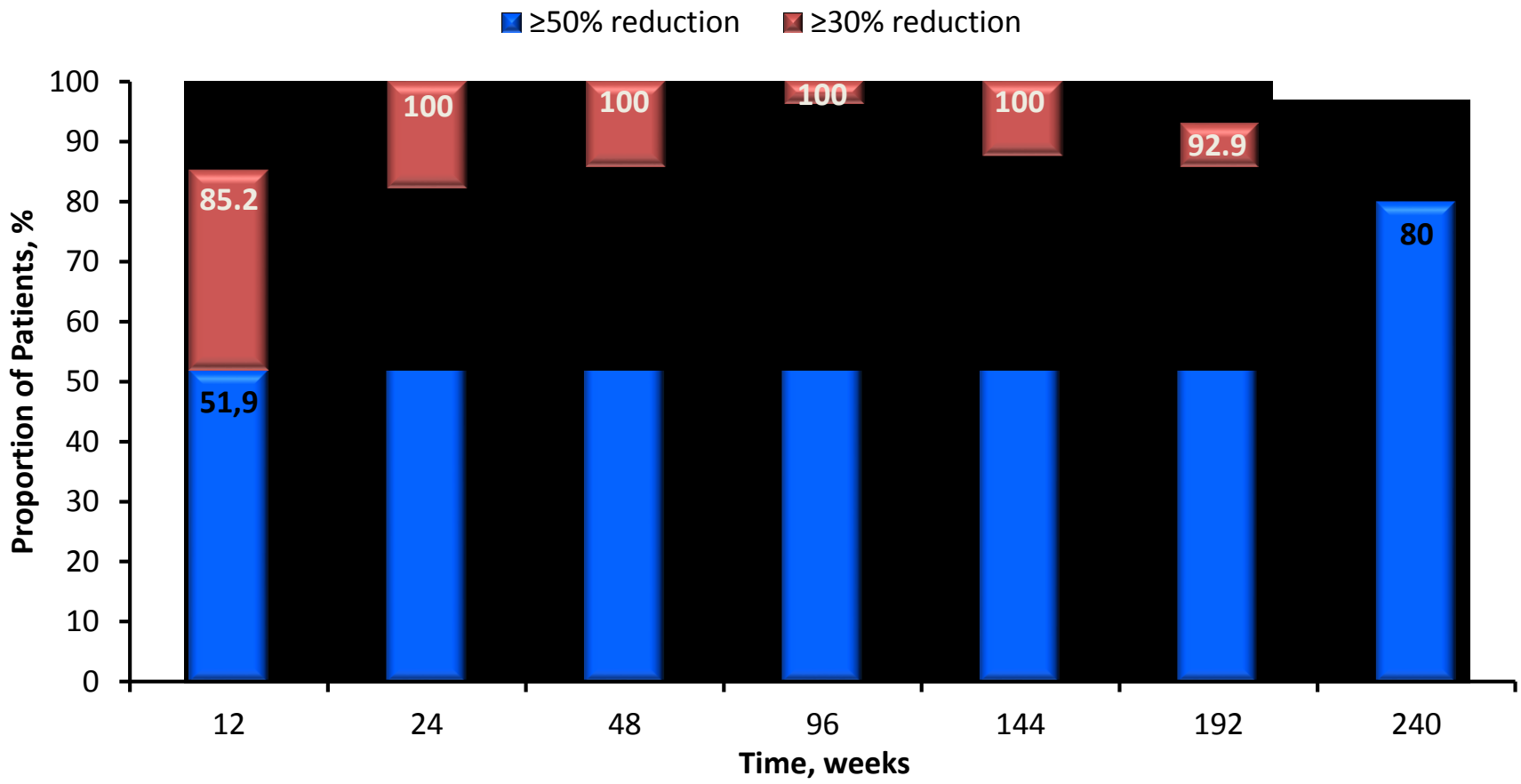
- The proportion of patients with a ≥ 50% reduction in renal angiomyolipoma increased over time, while ≥ 30% reduction was achieved in ≥ 75% of patients at all time points, except at week 240



AEs in > 15% patients by year of emergence (3.5 years)

	≤12 Months N = 112	13-24 Months n = 101	25-36 Months n = 100	37-48 Months n = 71	49-60 Months n = 15
Adverse events, n (%)	112 (100)	95 (94.1)	85 (85.0)	49 (69.0)	8 (53.3)
Stomatitis	46 (41.1)	9 (8.9)	4 (4.0)	5 (7.0)	0
Nasopharyngitis	36 (32.1)	21 (20.8)	20 (20.0)	11 (15.5)	3 (20.0)
Acne	28 (25.0)	8 (7.9)	6 (6.0)	1 (1.4)	0
Headache	26 (23.2)	11 (10.9)	5 (5.0)	1 (1.4)	0
Hypercholesterolemia	25 (22.3)	13 (12.9)	11 (11.0)	5 (7.0)	1 (6.7)
Aphthous stomatitis	21 (18.8)	15 (14.9)	8 (8.0)	4 (5.6)	1 (6.7)
Fatigue	19 (17.0)	2 (2.0)	3 (3.0)	1 (1.4)	0
Cough	18 (16.1)	4 (4.0)	4 (4.0)	2 (2.8)	0
Diarrhea	17 (15.2)	7 (6.9)	6 (6.0)	2 (2.8)	0
Mouth ulceration	17 (15.2)	5 (5.0)	4 (4.0)	2 (2.8)	0
Nausea	17 (15.2)	5 (5.0)	2 (2.0)	3 (4.2)	0

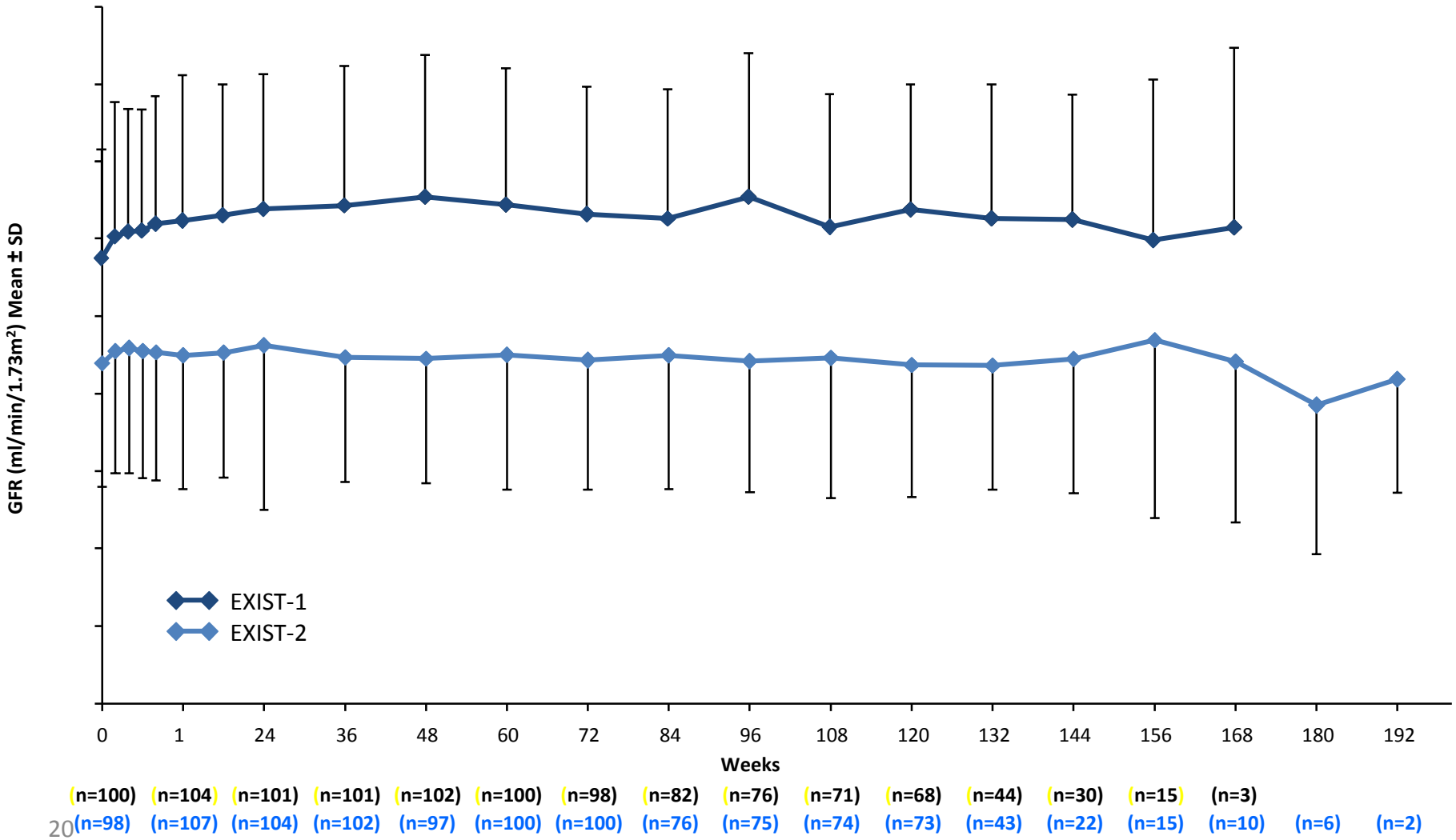
Exist-1 Angiomyolipoma Reduction was Maintained Over Time



All patients, n	27	28	28	26	24	14	5

Amazing!

EXIST-1/2: Mean Glomerular Filtration Rate During Extended Everolimus Treatment (Safety Sets)



mTORIs the silver bullet?

- Almost
- Side effects (5-10% discontinued)
  - Known short term risks
  - Longer term?
- mTORIs control but do not kill TS cells

Possible long term concerns

- Low blood phosphate
- Sexual maturation & fertility
- Kidney function / protein in the urine

Exist-1 & 2 Outcome

- 10 years on
  - No bleeding
  - Kidney function stable (In most)

Exist-1 & Exist-2

- In 95% of people with SEGA or AMLs problems halted by Everolimus
- Over 15 years experience
- This is a unique result

2010 / 2018

- Everolimus funded for AMLs, SEGA & Epilepsy
- Well done!

Lifetime risk of serious complication from TSC

- SEGA – 10-15%[1] ✓
- Renal (Bleed or CKD) – 40-50%[2,3] ✓
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- Resistant epilepsy – 40%[5] ✓
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- TAND – 90%[7] ?

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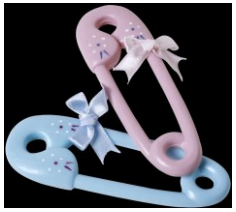
- Winston Churchill
- “This is not the end, but it is the beginning of the end”

The future in TSC

What is a “Cure”?

- Effective control of established problems
- Prevention of new problems
- Reversal of problems

TS STOP



- mTORI for infants
  - To prevent infantile spasms, epilepsy, ID, ASD
- mTORI in young children
  - To halt PKD/TSC
- mTORI for 5-6 year olds
  - To prevent progression of renal-lung disease
- mTORI for older women
  - To halt LAM

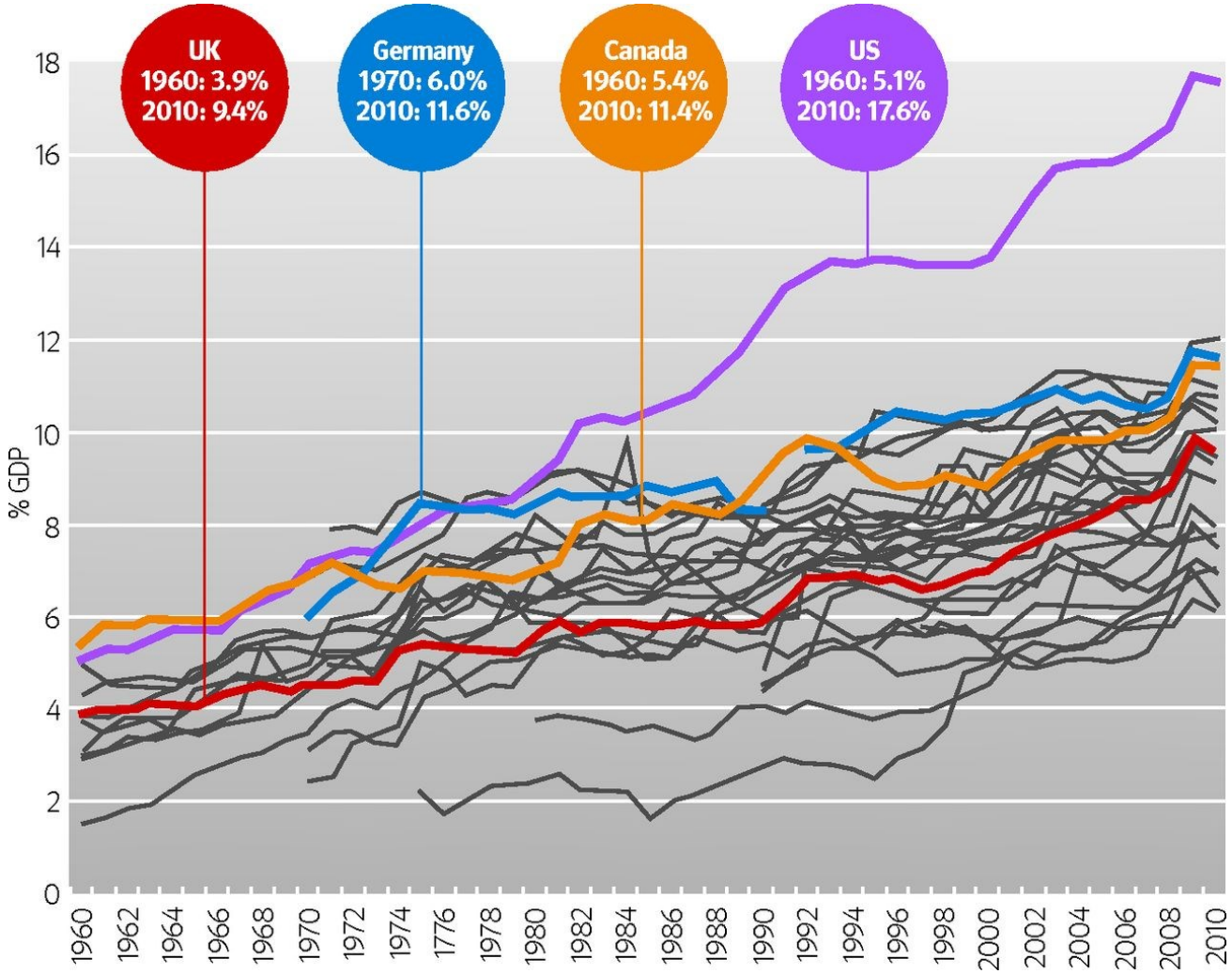
tsa tuberous sclerosis association

Tuberous Sclerosis Alliance

Reversal

- Drugs to kill TS cells
- Gene therapy
- Other ways to improve organ function

Fig 1 Total (public plus private) health spending as a percentage of GDP in OECD countries, 1960-2010.



Appleby J BMJ 2012;345:bmj.e7127

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Successful Advocacy

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association

UK International TSC Research Conference

12-15th November 2020

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