What's new for children with Alports?

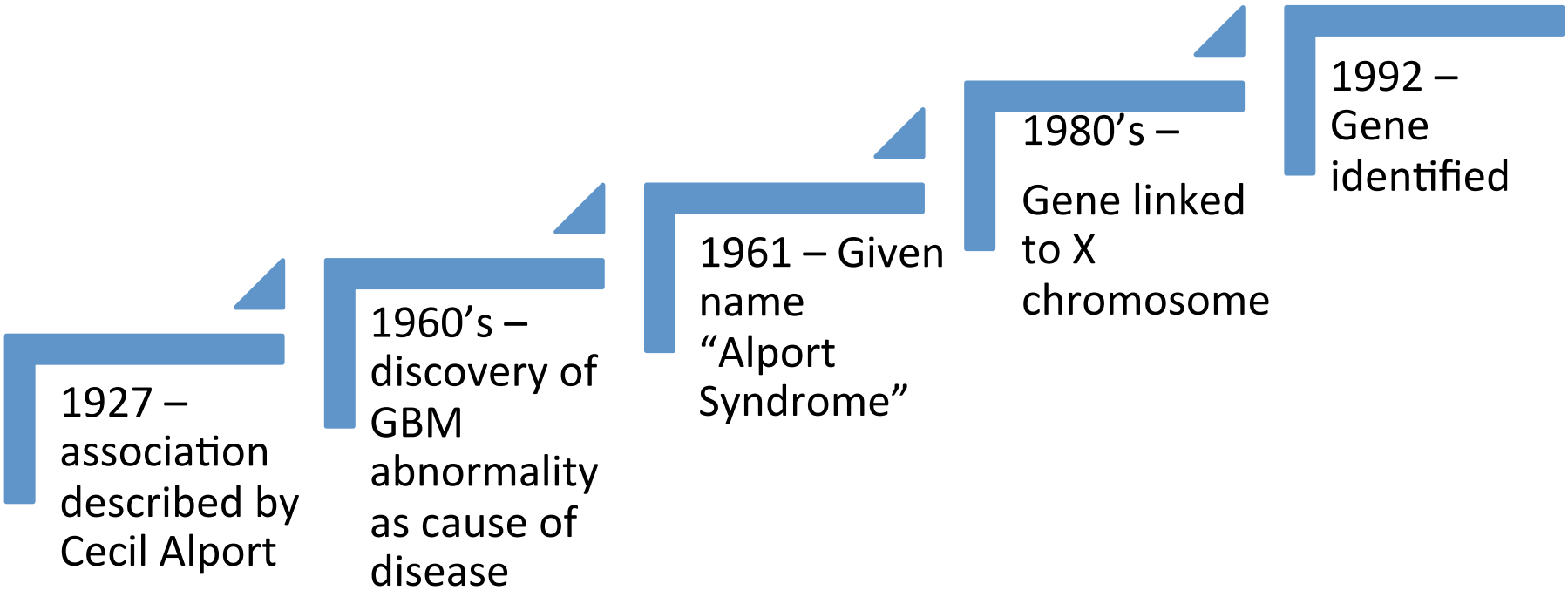
Andrew Lunn

Paediatric Nephrologist

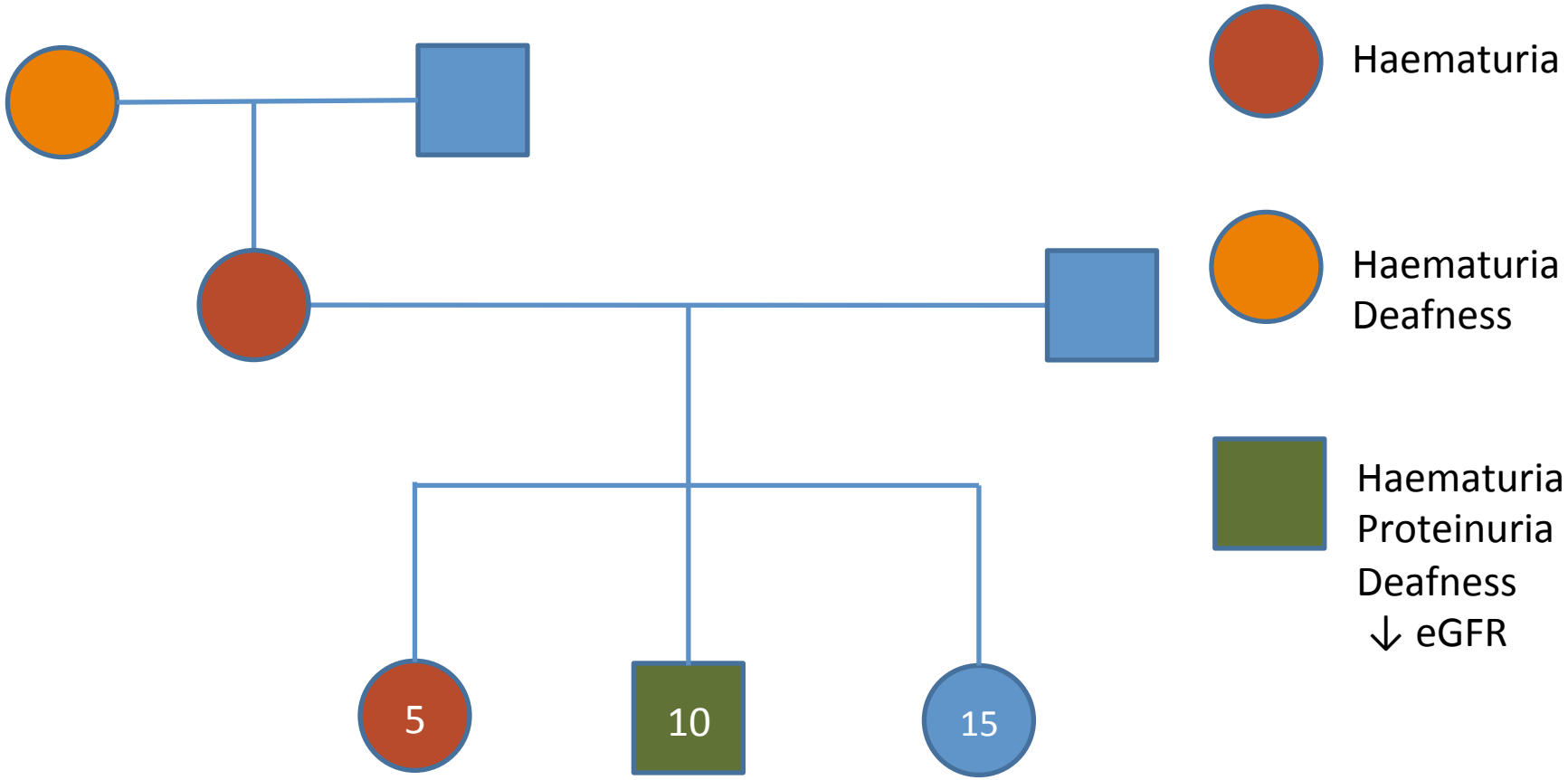
Overview

- Background
- Case study – an affected family
  - New guidelines
  - New therapies
- Future therapies

Alport Syndrome



An affected family



The 10 year old boy

- Presented with macroscopic haematuria
- BP 125/60 (>95th centile)
- Creat 67 µmol/l (eGFR 60 ml/min/1.73m^2)
- Urine protein:creat ratio 94 mg/mmol
- Would you
  - Biopsy?
  - Do genetic testing?
  - Treat him?

Lets take a look at the evidence

Expert Guidelines for the Management of Alport Syndrome and Thin Basement Membrane Nephropathy

Judy Savige,* Martin Gregory,† Oliver Gross,‡ Clifford Kashtan,§ Jie Ding,‖ and Frances Flinter¶

J Am Soc Nephrol 24: 364–375, 2013.

- 2013 guideline
  - Level D evidence (Expert opinion)
- Recommendations
  - Confirm diagnosis on biopsy
  - Confirm mode of inheritance with genetics

Lets take a look at the evidence

Table 1. The diagnosis of X-linked Alport syndrome

Criteria	Sensitivity	Specificity
Family history of Alport syndrome	High (80%)	High
Bilateral high-tone sensorineural hearing loss	High	Moderate
Lenticonus	Low to moderate (30%)	Very high
Central fleck retinopathy	Moderate (50%)	Very high
Lamellated GBM	High	Very high
$\alpha3\alpha4\alpha5$(IV) collagen chains absent from GBM	Moderate (80% of males and 60% females)	High
$\alpha5$(IV) collagen chain absent from skin	Moderate (80% of males and 60% females)	High
COL4A5 pathogenic variant	High (>90%)	High

J Am Soc Nephrol 24: 364–375, 2013.

Lets take a look at the evidence

- Treatment

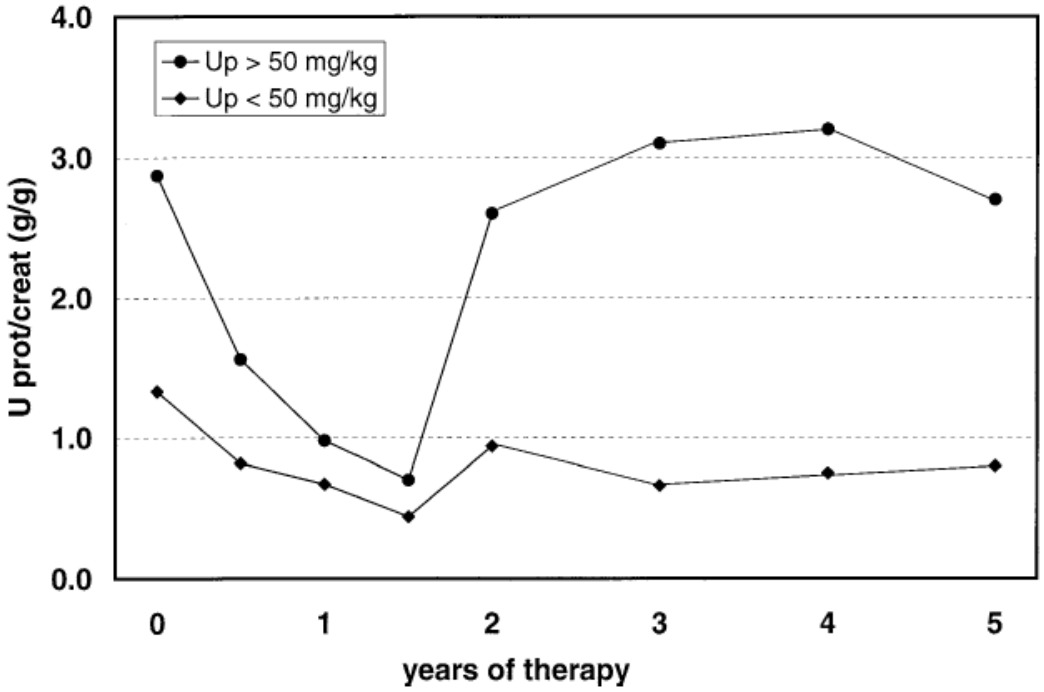


Fig. 2 Proteinuria in Alport patients treated with enalapril for 5 years. Proteinuria expressed as protein/creatinine ratio in two subgroups of patients

Pediatr Nephrol (2004) 19:271–275

Lets take a look at the evidence

- Treatment – Registry Data

Group	Number	ACE-Inhibitor	Onset of RRT
Untreated relatives	109	No	22 years
Impaired renal function	26	20 years	25 years
Proteinuria	115	13 years	40 years

The 10 year old boy

- Learning points
  - Genetic testing advisable
  - ACE-Inhibitor delays onset of RRT

The 5 year old girl

- Microscopic haematuria - family testing
- BP 100/67 (75th centile)
- Creat 32 µmol/l (eGFR 101 ml/min/1.73m^2)
- Urine protein:creat ratio 10 mg/mmol
- Mother been to family day and asks for ACE-I
- Would you
  - Biopsy?
  - Do genetic testing?
  - Treat her?

Family support

a brighter future for people living with alport syndrome

welcome to alport uk

alport uk is a patient-led organisation dedicated to empowering people living with **Alport Syndrome** to enjoy the best possible quality of life. Drawing on our continuous learning from and collaboration with individuals, families and the scientific community, this website aims to facilitate a support and information network for all those affected by **Alport Syndrome**.

latest news

Alport Information Days 2015

september 2nd, 2015

support

Following our great success of the Alport Information Day in Birmingham in February we will be holding another one in Manchester on Saturday 21st November 2015. See the flyer for more details. National Alport

read more

RareRenal.org

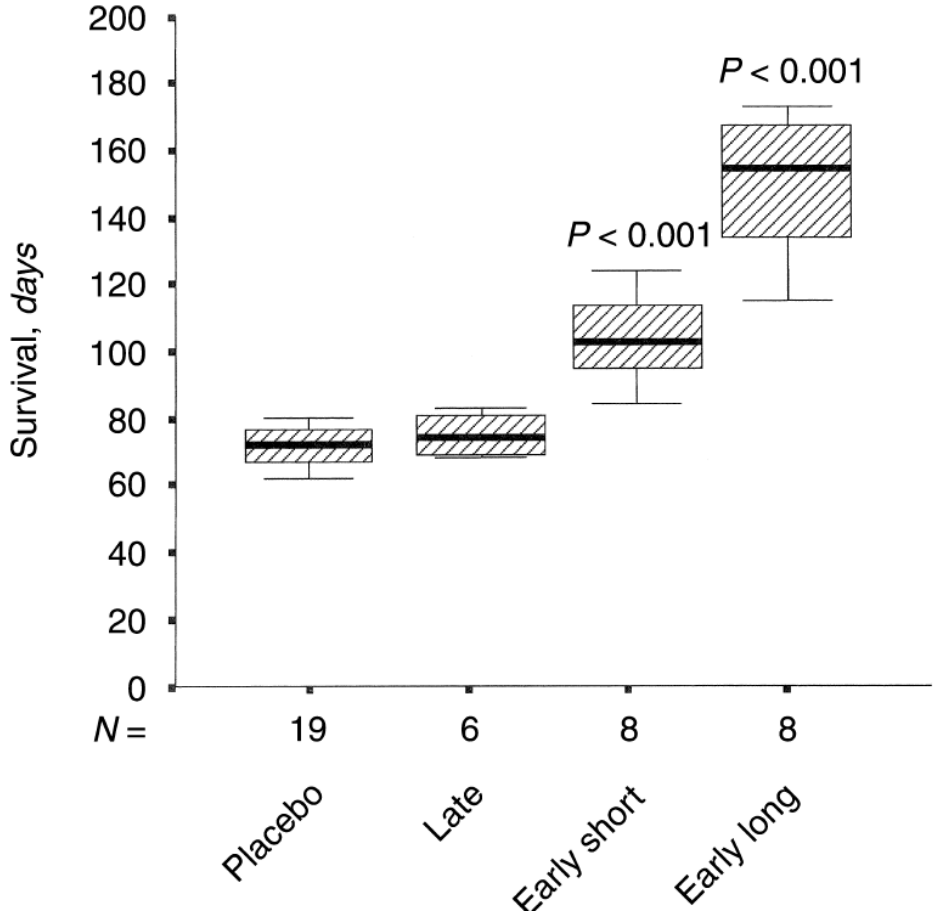
Information on rare kidney diseases

Family support

https://youtu.be/1H8Xc6DRmbs

Lets take a look at the evidence

Preemptive ramipril therapy delays renal failure and reduces renal fibrosis in COL4A3-knockout mice with Alport syndrome[1]



Kidney International, Vol. 63 (2003), pp. 438–446

Lets take a look at the evidence

- Treatment – Registry Data

Group	Number	ACE-Inhibitor	Onset of RRT
Untreated relatives	109	No	22 years
Impaired renal function	26	20 years	25 years
Proteinuria	115	13 years	40 years
Haematuria or microalbuminuria	33	8 years	None

The 5 year old girl

- Learning points
  - Good family support groups available
  - More research needed on pre-emptive treatment

The 15 year old girl – has a friend

- Microscopic haematuria – incidental finding
- BP 107/67 (<50th centile)
- Creat 53 µmol/l (eGFR 93 ml/min/1.73m^2)
- Urine protein:creat ratio 10 mg/mmol
- Mother has haematuria
- Would you
  - Biopsy?
  - Do genetic testing?
  - Treat her?
- What advice would you give about the chance of her having an affected child?
- What advice would you give about the chance of her having a more severely affected child?

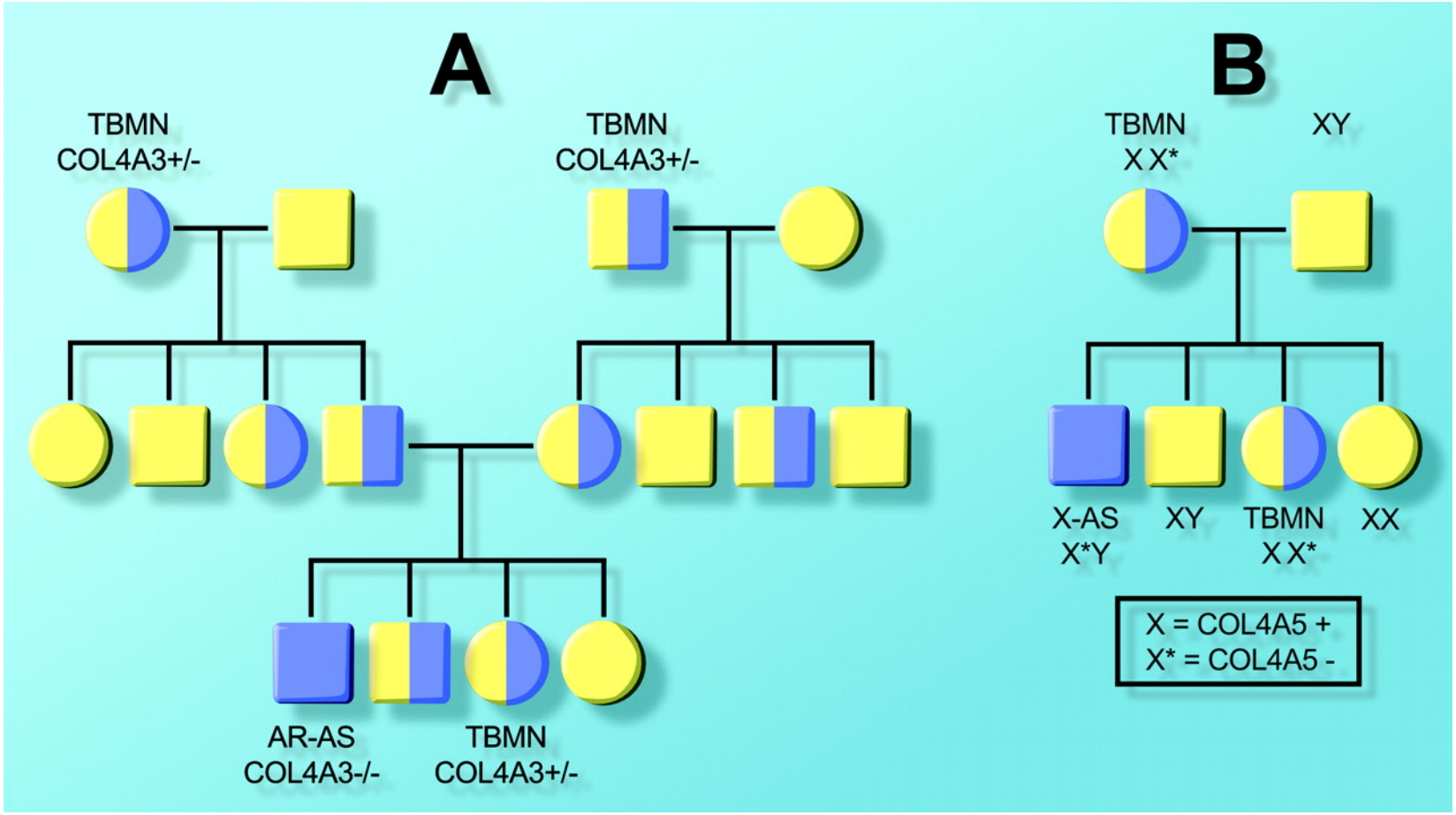
Lets take a look at the evidence

- 2013 guideline
  - Level D evidence (Expert opinion)
- Recommendations
  - Biopsy if atypical features
  - Biopsy and / or genetics if X-linked Alport syndrome cannot be excluded

Lets take a look at the evidence

- Carrier for Alport Syndrome or TBMN?
  - Prevalence of Alport syndrome; 1 in 5000
  - Prevalence of TBMN; 1 in 100
- Statistics suggests 50 x more likely to be TBMN

Illustration of possible modes of inheritance for autosomal and X-linked forms of TBMN and Alport syndrome (AS).



Karl Tryggvason, and Jaakko Patrakka JASN 2006;17:813-822

Lets take a look at the evidence

- “It would be of utmost importance to make sequencing analyses of the COL4A3, COL4A4, and COL4A5 genes available to the clinic as a routine diagnostic method of TBMN and Alport syndrome.”

J Am Soc Nephrol 17: 813–822, 2006.

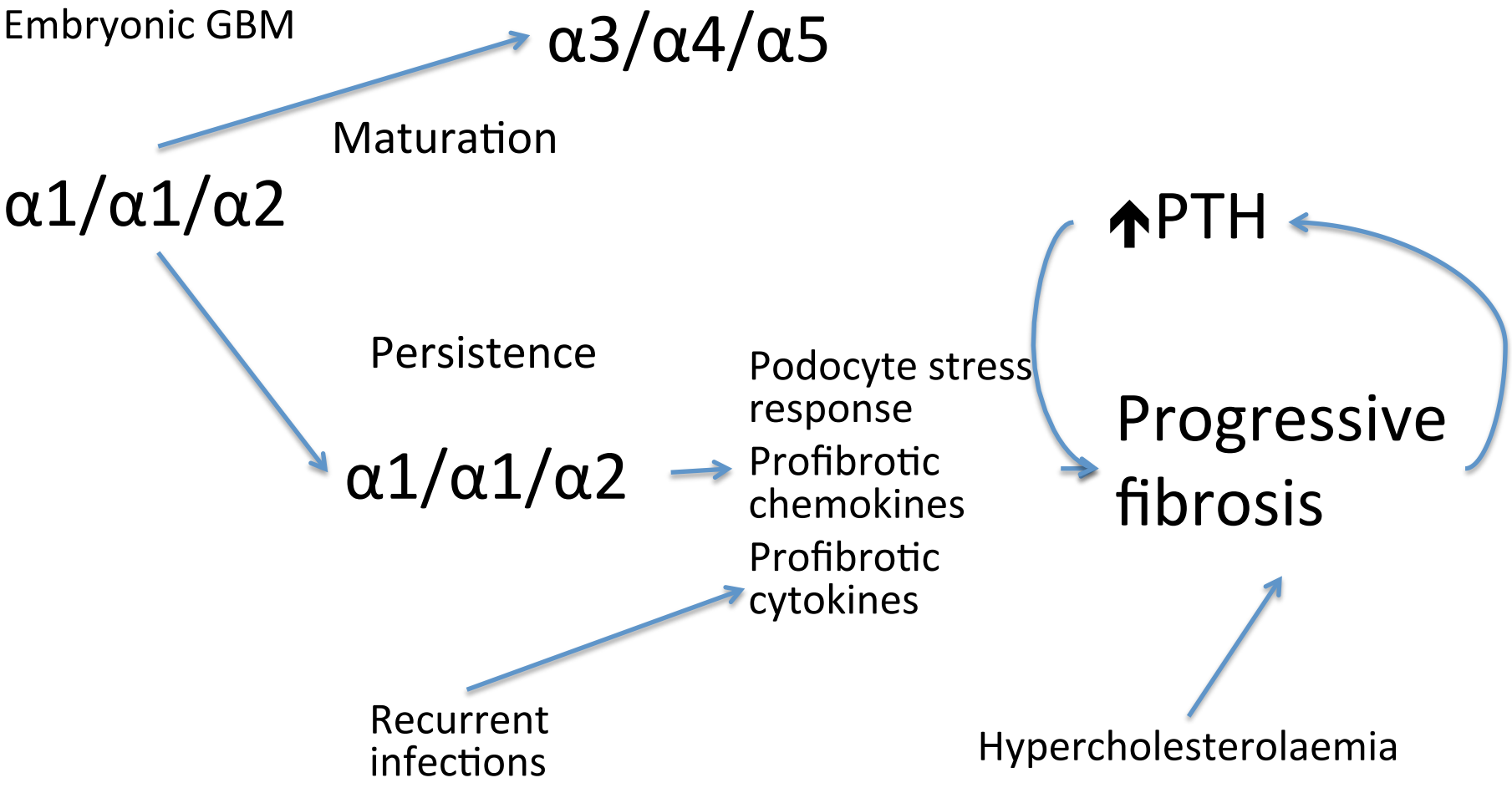
The 15 year old girl – has a friend

- Learning point;
  - Should she be getting genetic testing to inform her choices when she has children?

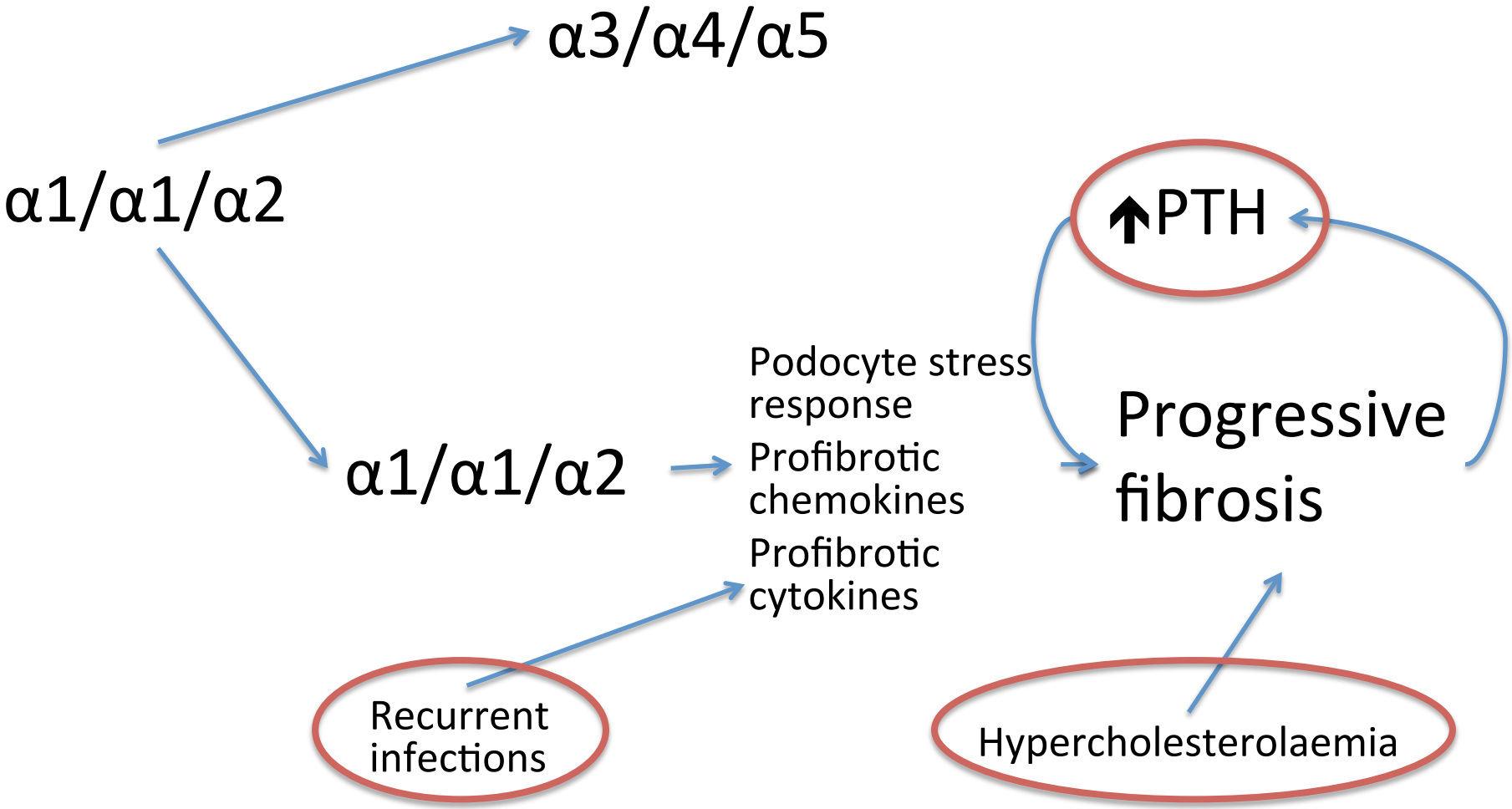
Future Therapies?

Dumbledore said
“Divination is turning out to be much more trouble than I could have foreseen”

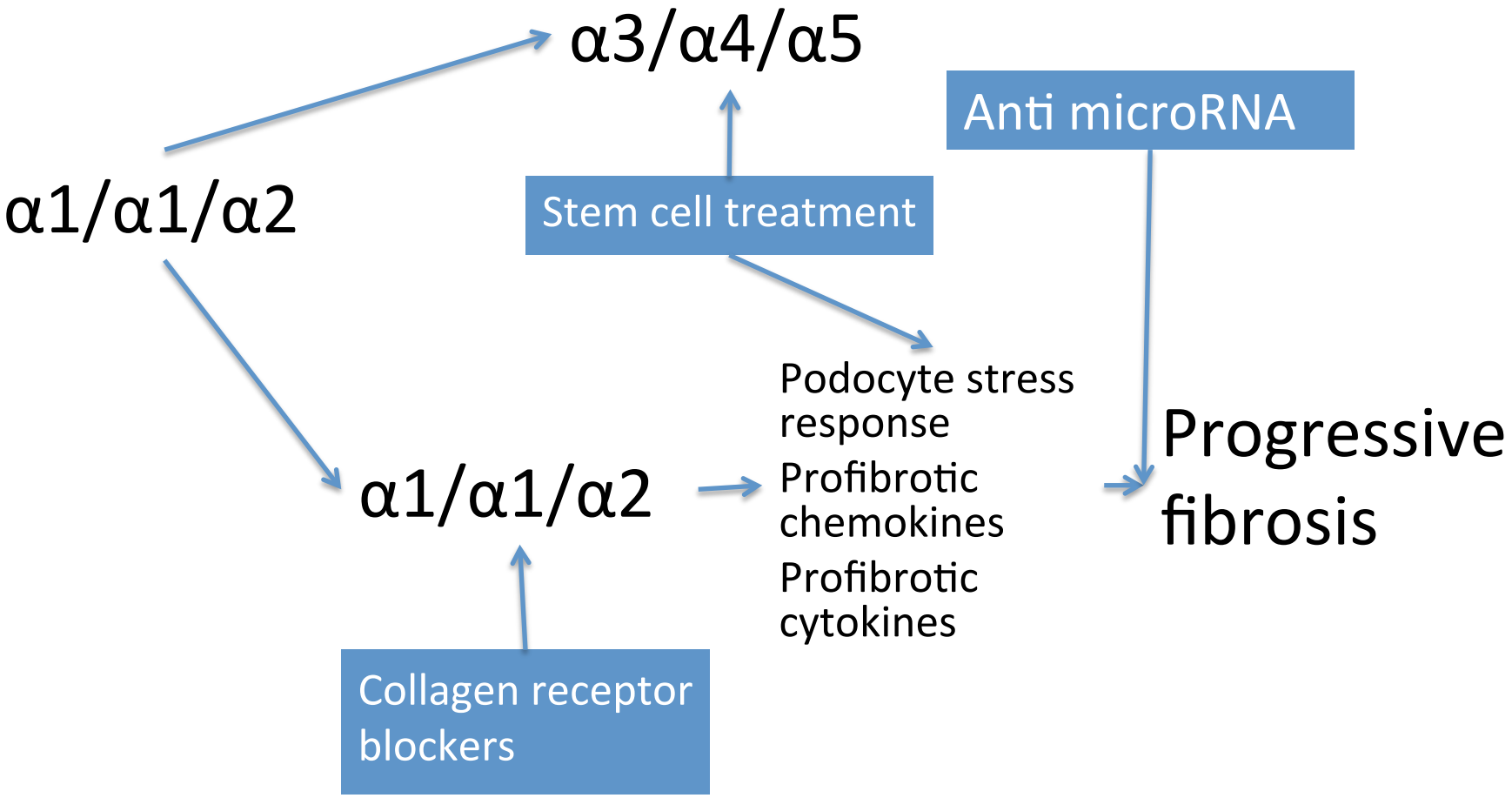
Future therapies



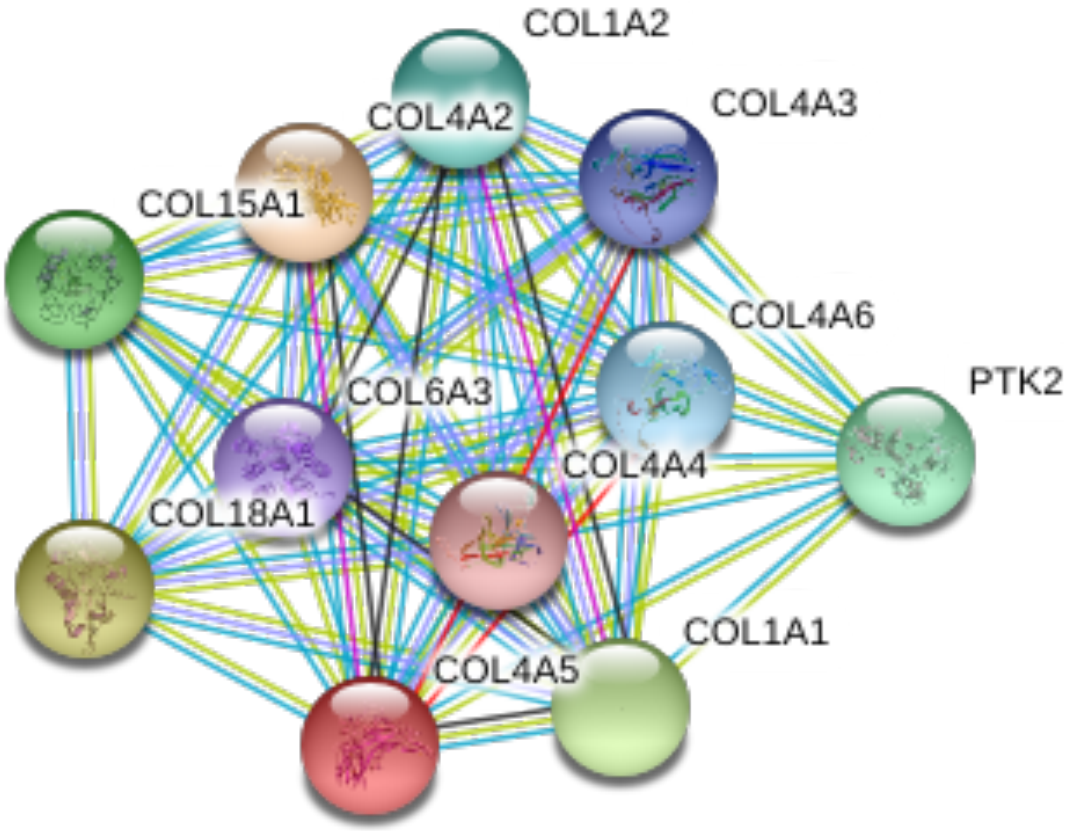
Future therapies



Future therapies



Before I summarise – any questions



What's new for children with Alport Syndrome?

- Good family support available
- Genetics have increasing role in diagnosis
- Patients with proteinuria
  - ACE – inhibitors
- More research needed
  - Treatment before onset of proteinuria
  - New therapies