



HOW TO BUILD A REFERENCE CENTER

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June 16 – 19, 2016
Amsterdam, Netherlands

CASE REPORT

- On August 15, 1988 B.L, a 21-year-old-man was admitted to the Unit of Nephrology of Bergamo Hospital because of:
 - fever
 - jaundice
 - confusion
 - aphasia
 - migrating paresthesias
 - visual abnormalities
- Laboratory findings
 - Hct: 27%
 - LDH: 2343 I.U./L
 - Platelet count: $27 \times 10^3/\mu\text{l}$
- Diagnosis: TTP
- Treatment: Plasma exchange
- Outcome: Full recovery of the acute episode

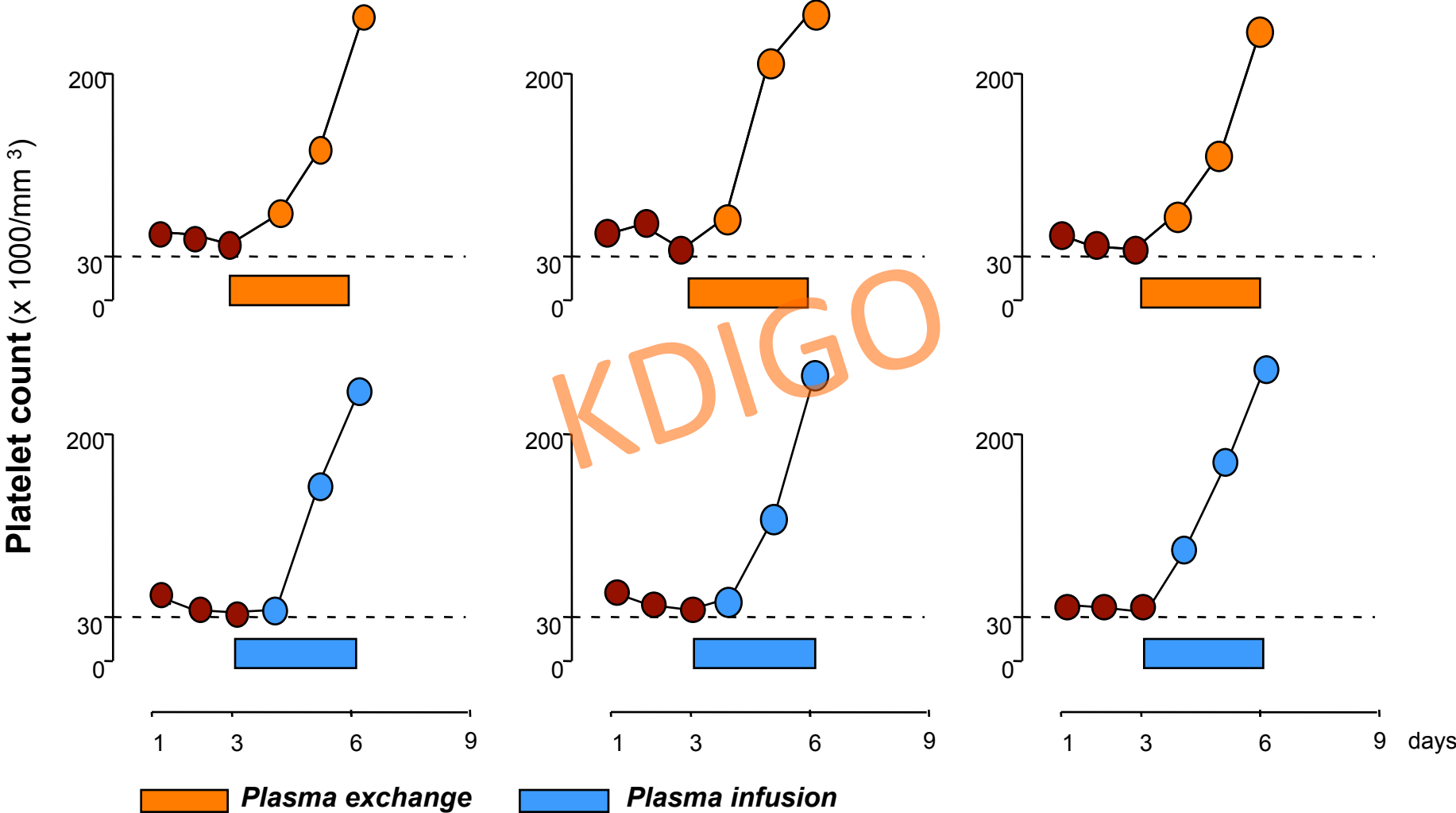
KDIGO

CLINICAL COURSE

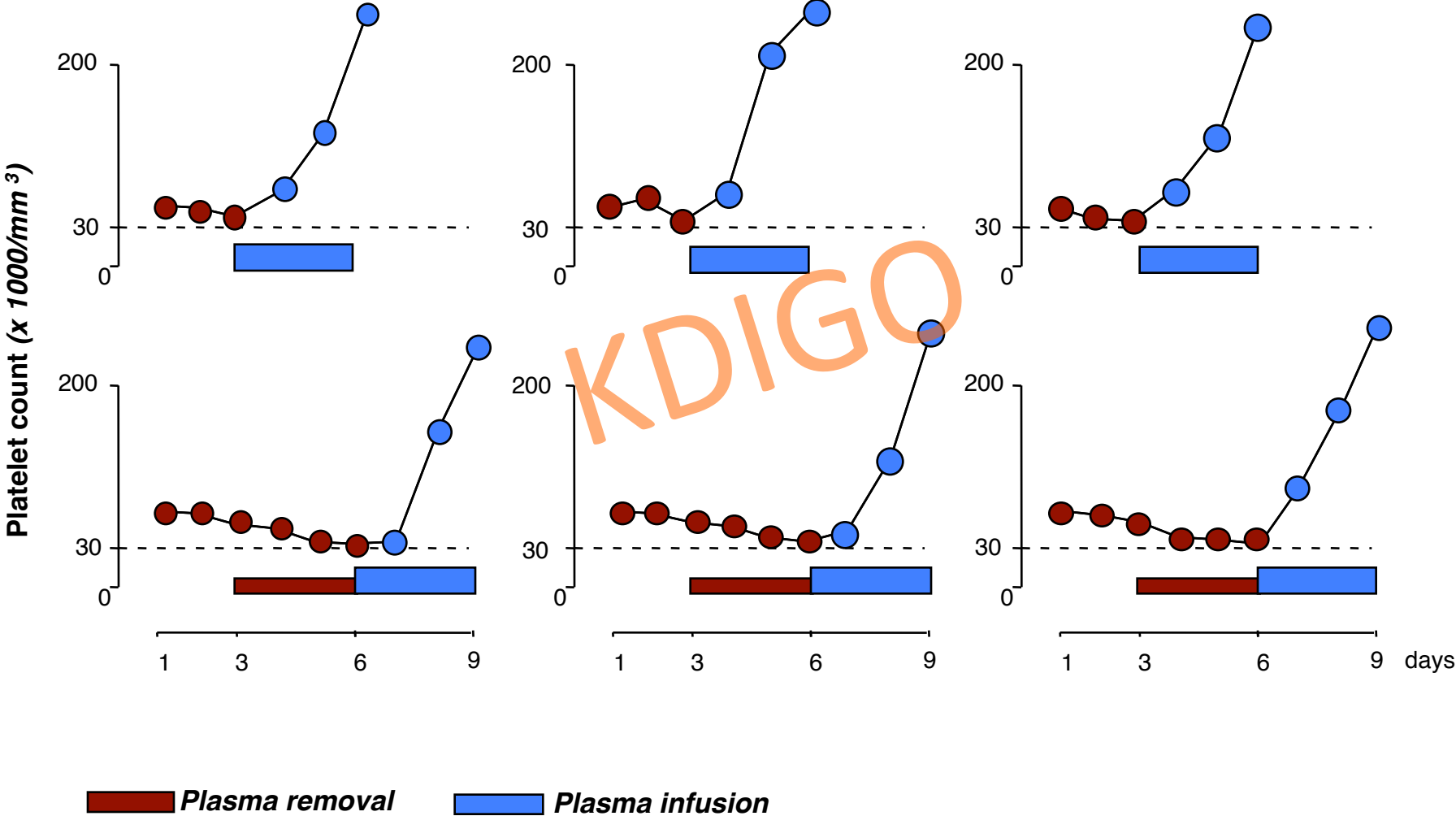
Since August 1988

- Almost 2-hundreds (monthly) recurrences of TTP
 - Recovery of acute episodes with plasma therapy
 - Progressive renal function deterioration
 - Started chronic dialysis (*March 3, 2001*)
 - Persistency of monthly recurrences with predominant gastrointestinal symptoms and occasional gastrointestinal bleeding
-

PLASMA EXCHANGE vs INFUSION IN CHRONIC RELAPSING TTP



PLASMA INFUSION vs REMOVAL IN FAMILIAL AND RECURRENT TTP

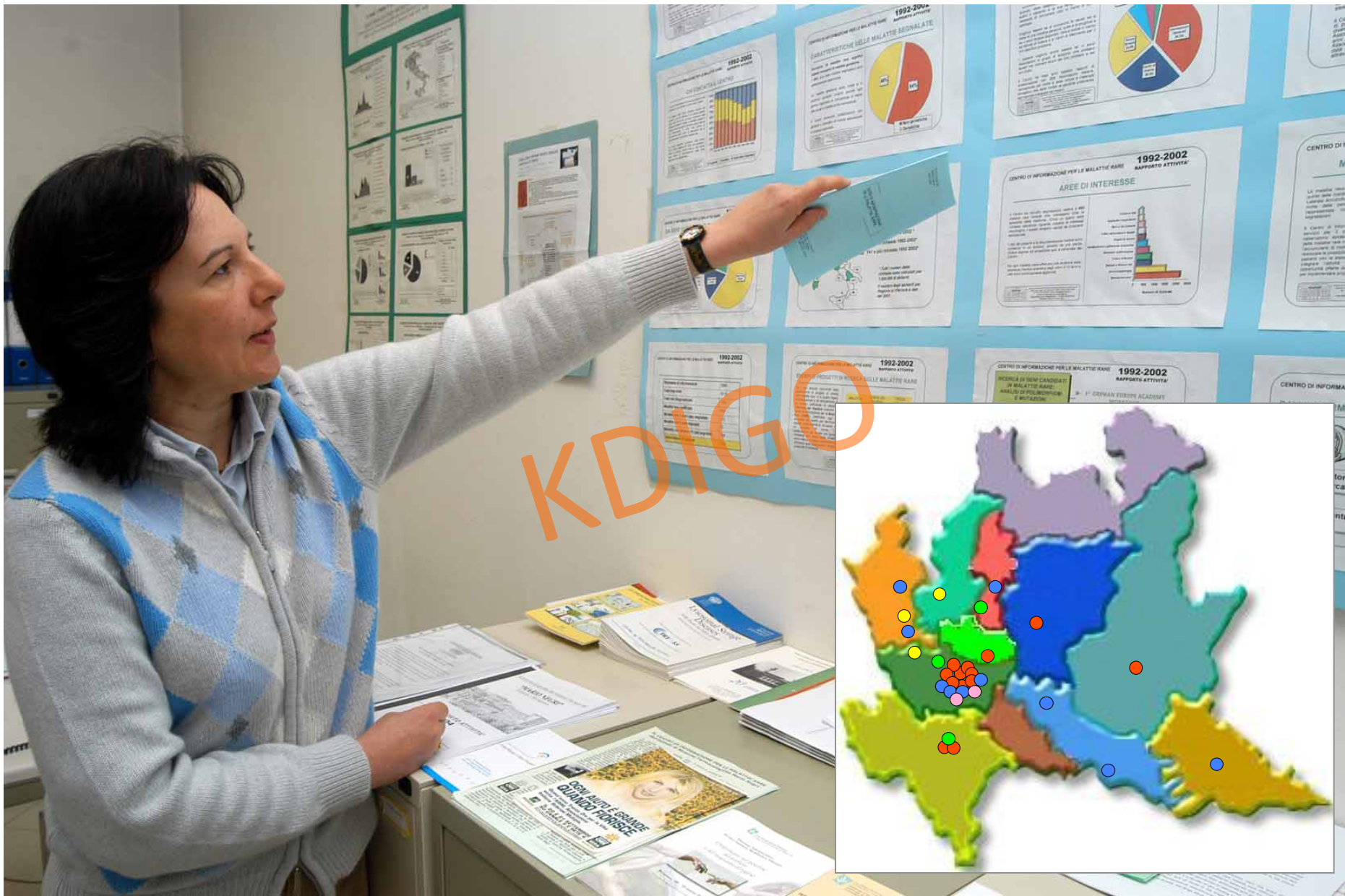




1992



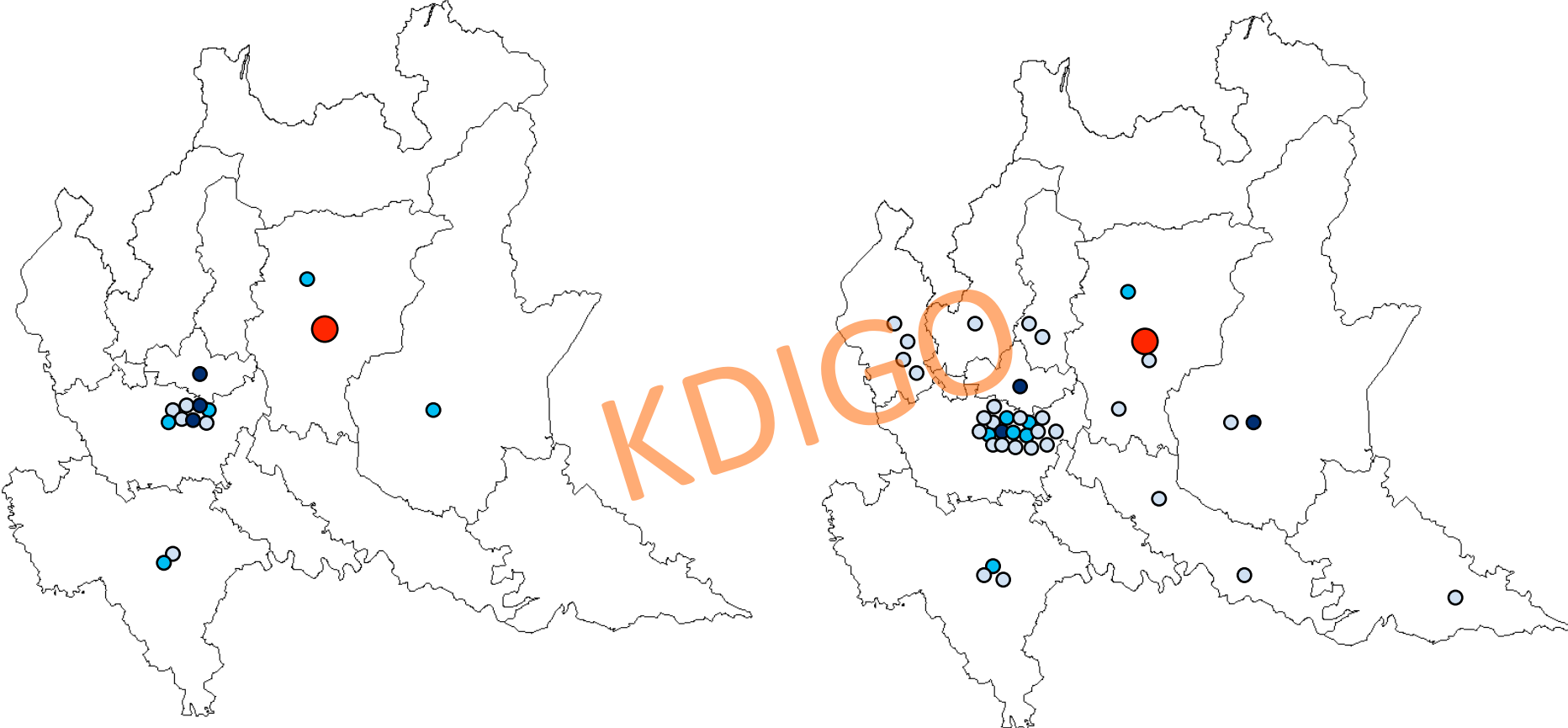




REGIONAL NETWORK FOR RARE DISEASES

2001 → 13 Presidi

2015 → 38 Presidi



● Centro di coordinamento

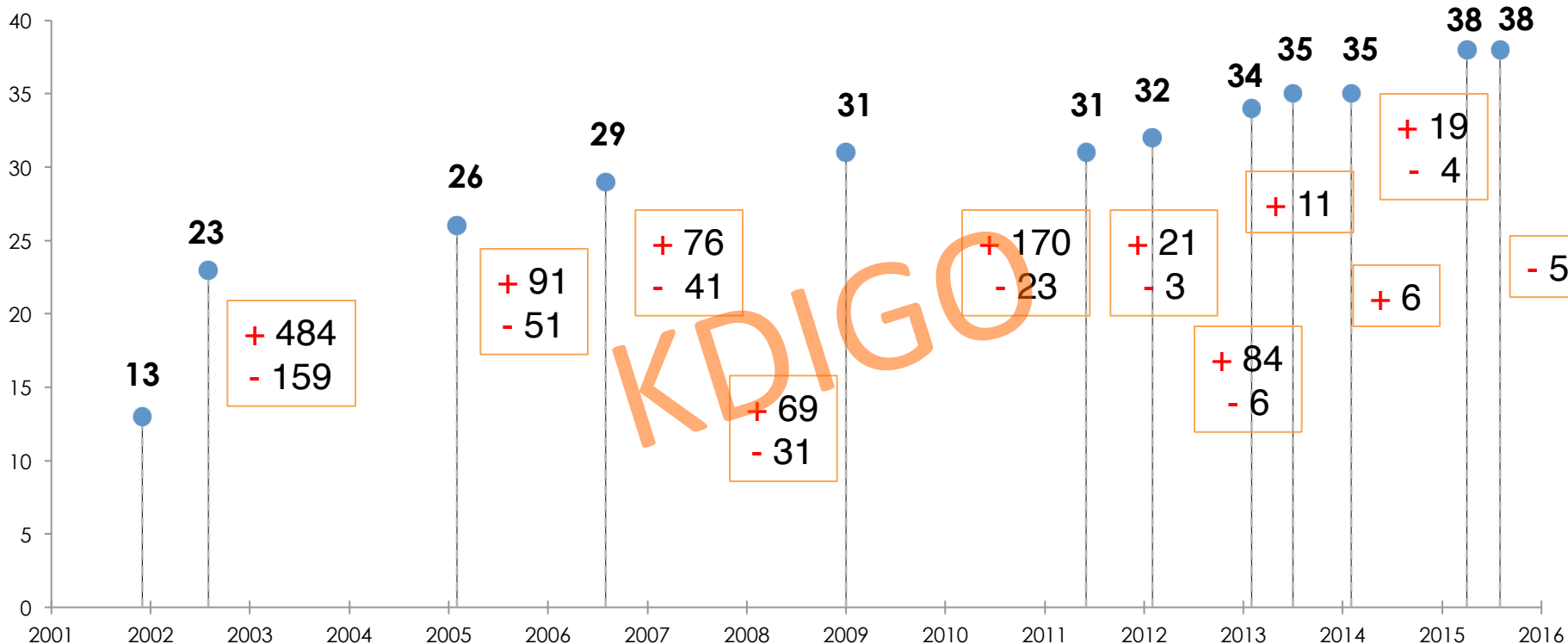
- ≤ 80
- 81 - 149
- ≥ 150

Number of diseases served by Reference centers

REGIONAL NETWORK FOR RARE DISEASES

EVOLUTION OF REFERENCE CENTERS

N° Reference centers

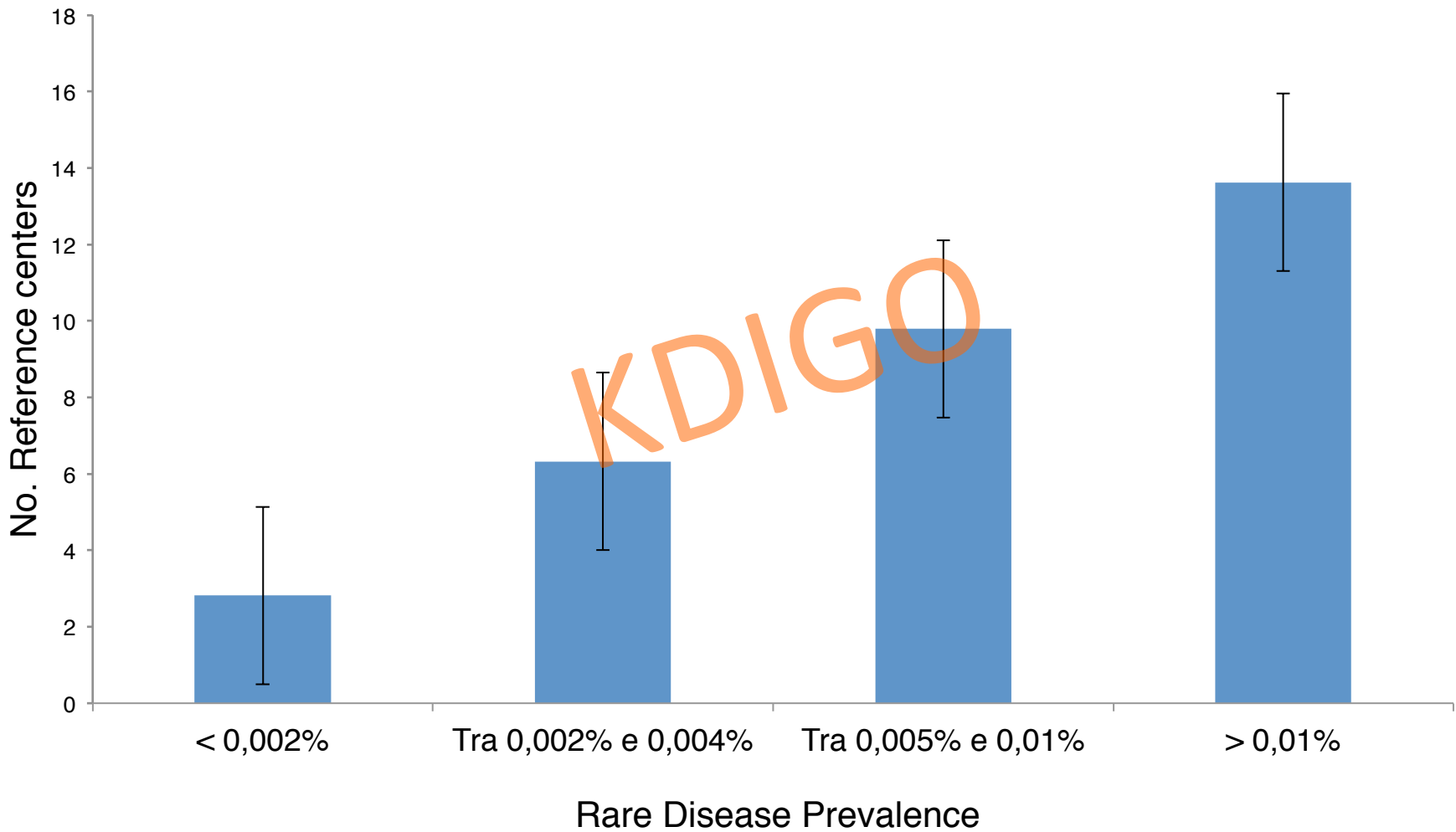


+ New endprsmnts - Withdrawal



REGIONAL NETWORK FOR RARE DISEASES

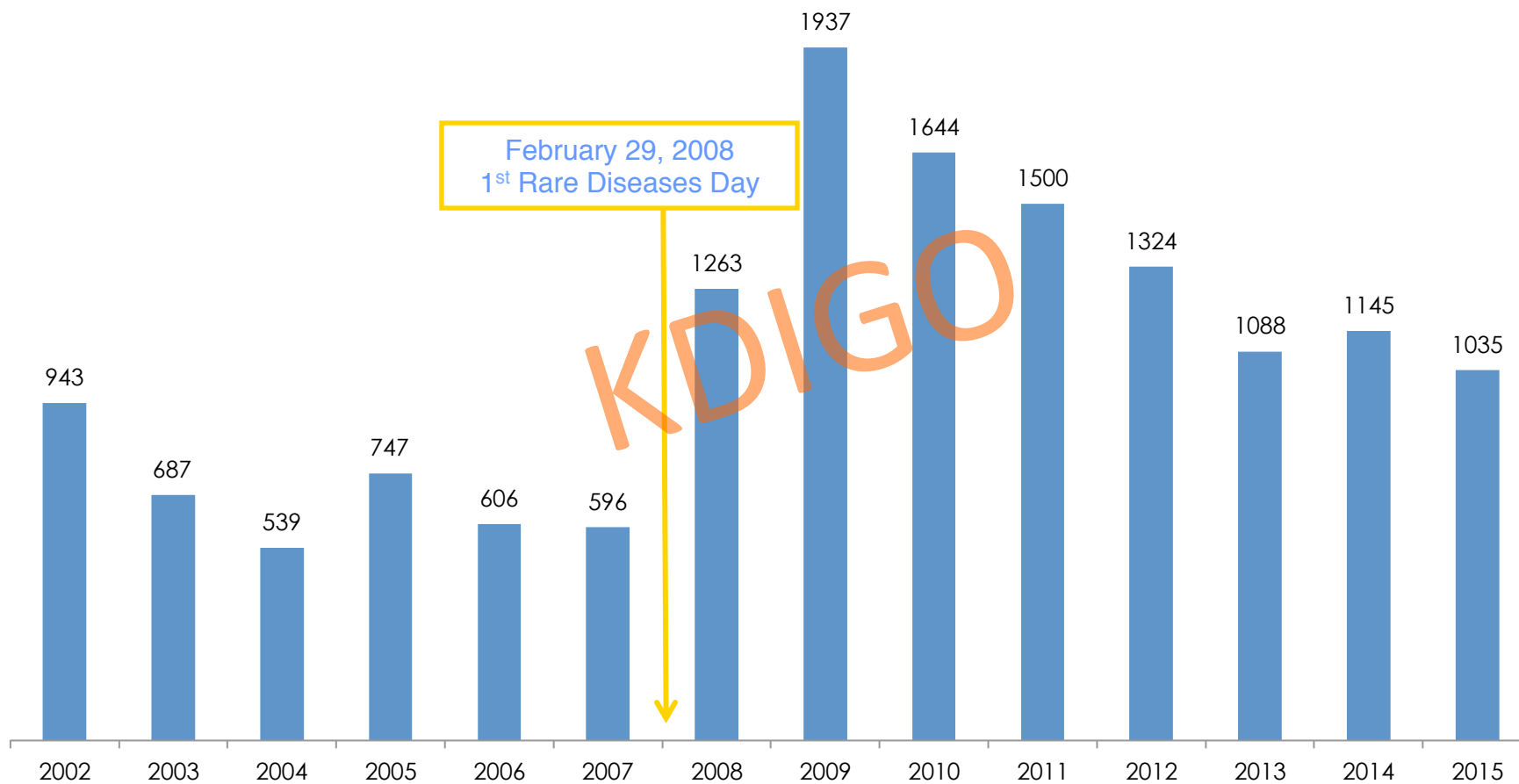
DISEASES THAT ARE LESS RARE HAVE HOWEVER MORE REFERENCE CENTERS



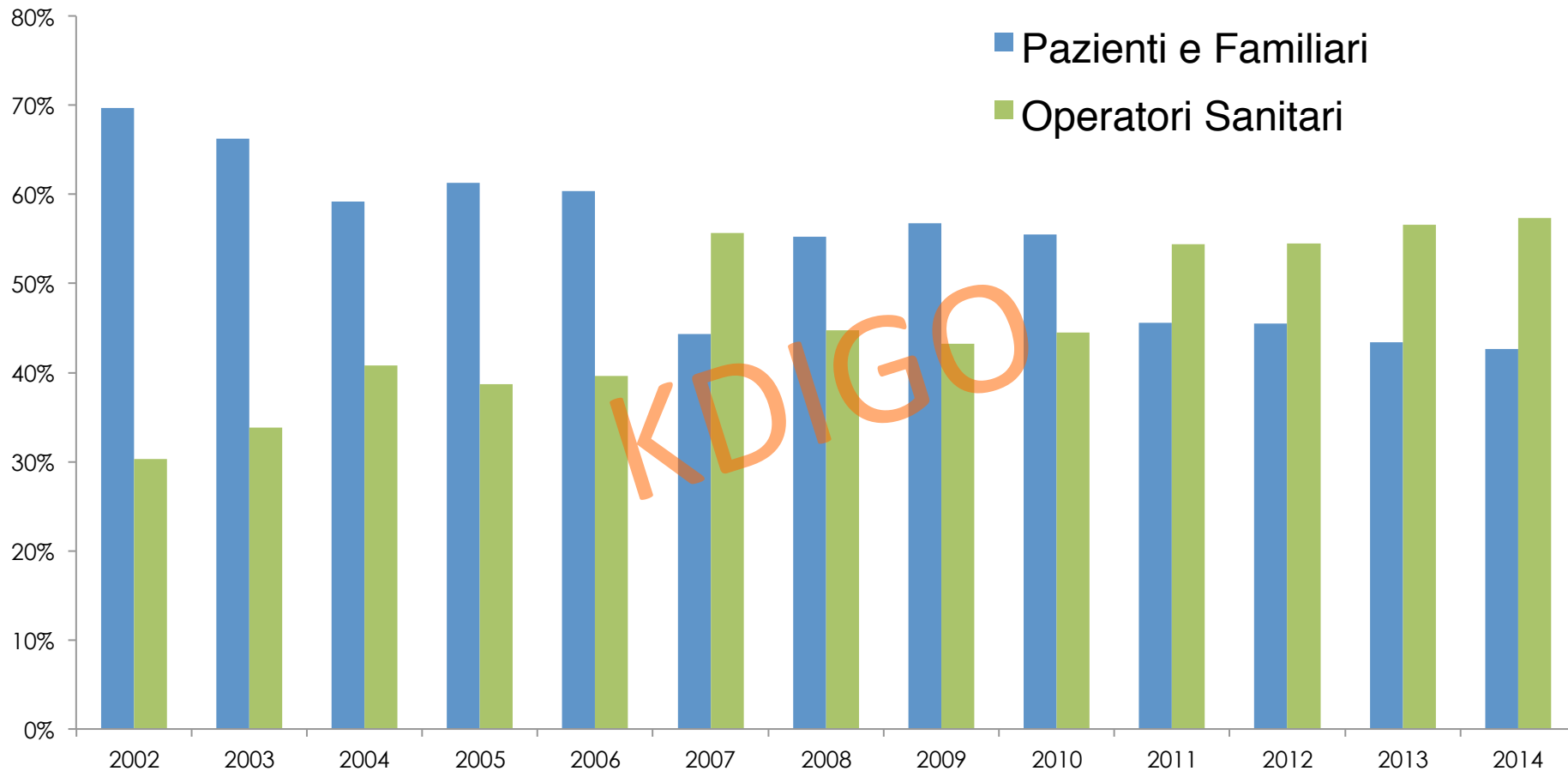
Regional Network for Rare Disease Working Group

- Goals
 - The Working Group establishes uniform strategies for the reference centers to pursue prevention, surveillance, diagnosis and treatment of rare diseases
- The Working Group is composed by representatives of
 - Region
 - Reference centers
 - Coordination Center
 - Local health authority
 - Patient associations

COORDINATION CENTER: CONSULTING ACTIVITY



COORDINATION CENTER: CONSULTING ACTIVITY



Regional Networks evolution in Italy



2001



...2007

PATIENT DISTRIBUTION BY AGE AND GENDER



Lombardy population	9.973.397*
All RD cases	54.647
Dieases	291
Prevalence	548/100.000

Diagnostic , Therapeutic and Social Care Pathways (PDTA)

Since 2012 the Regional Network has promoted the development, through conferences of experts, of shared pathways for the diagnosis, treatment and social assistance to patients with rare disease

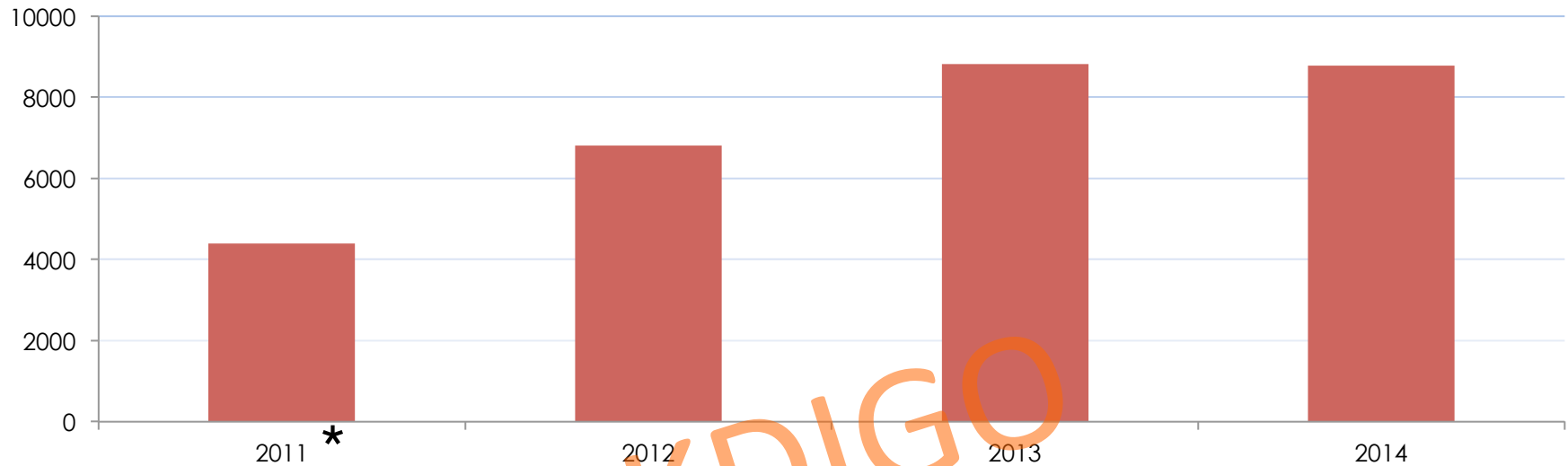
These pathways are intended to offer the best quality of care whereby optimizing the use of resources

- **632** health care professional were involved
- **31** reference centers
- **33** patient associations

- **110** PDTA were prepared

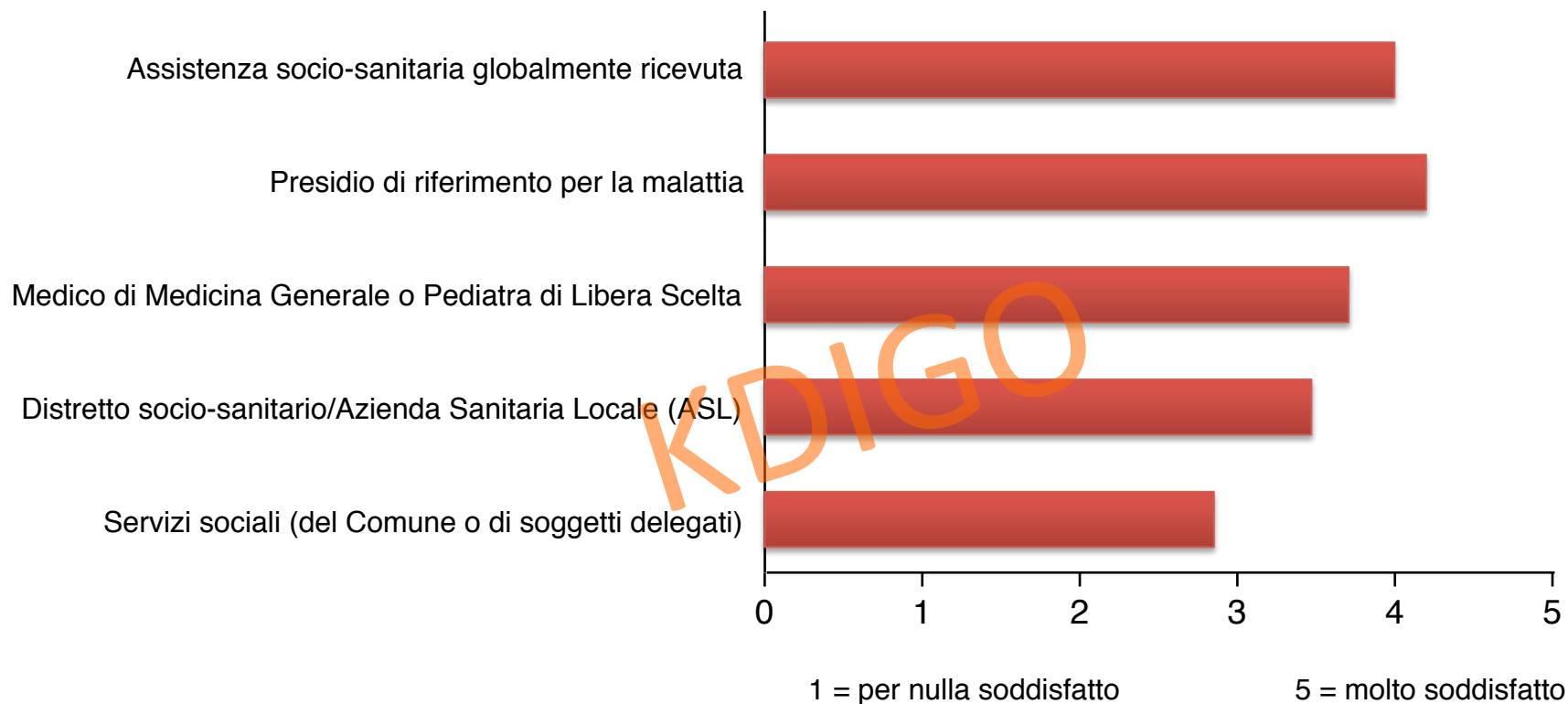
- They cover approximately **72 – 87%** of rare disease recorded in Lombardy

PDTA ARE AVAILABLE AT THE COORDINATION WEBSITE



* dal 30 marzo 2011

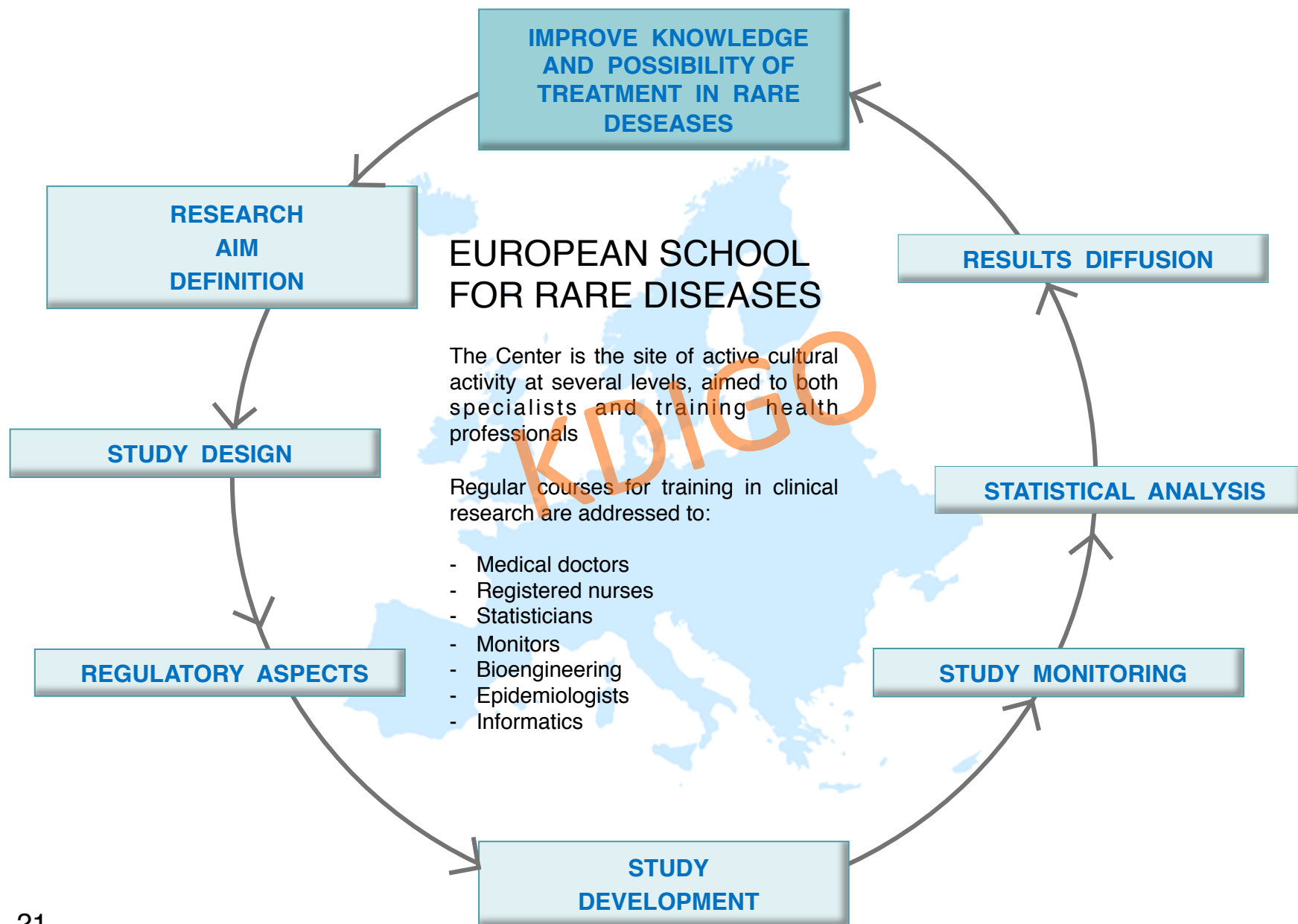
HOW THE REGIONAL NETWORK IS EVALUATED BY THE PATIENTS



"Malattie rare: rilevazione dei bisogni assistenziali e definizione di misure a sostegno". Decreto n. 7771 del 11.09.2012, Direzione Generale Sanità, Regione Lombardia

Éupolis Lombardia, Edizione: aprile 2014

EXPERTISE AND ORGANIZATIONAL SUPPORT FOR CLINICAL STUDIES



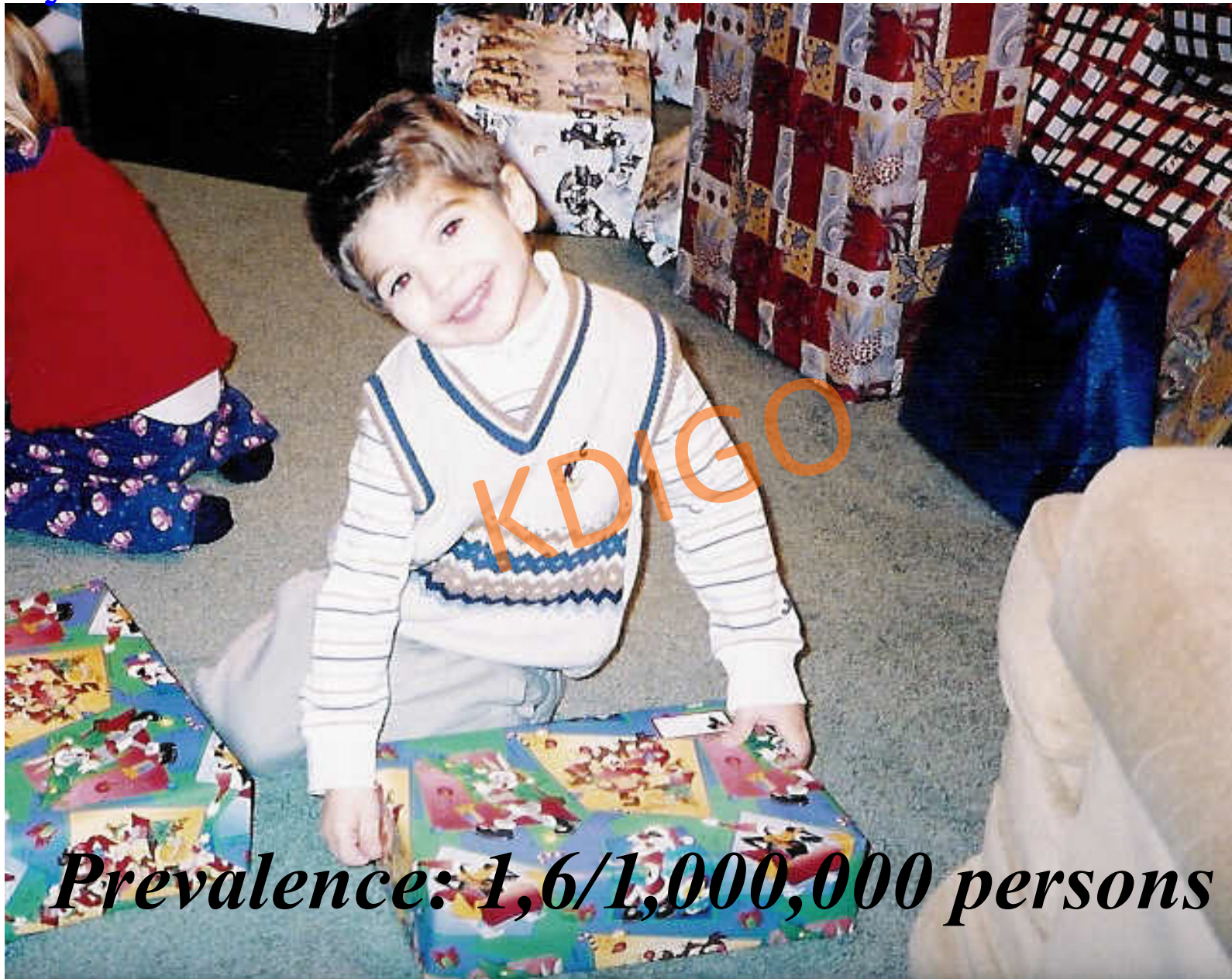
22,765

KDIGO

1992 - 2015

KDIGO 3

Ryan



Prevalence: 1,6/1,000,000 persons

**INTERNATIONAL REGISTRY OF
HUS/TTP**

Participating Centers 180

HUS/TTP patients 1160

Italian cases 780

Foreign cases 380

09/2015



**Italy
765 cases**



**UK
9 cases**



**Belgium
1 case**



**Spain
5 cases**



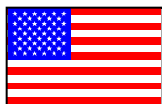
**Portugal
11 cases**



**Brazil
2 cases**



**Canada
4 cases**



**USA
58 cases**



**Argentina
23 cases**



**Chile
3 cases**



**UAE
1 case**



**South Africa
2 cases**



**India
5 cases**



**Australia
14 cases**



**Japan
2 cases**



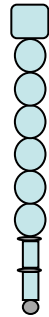
**Malaysia
2 cases**



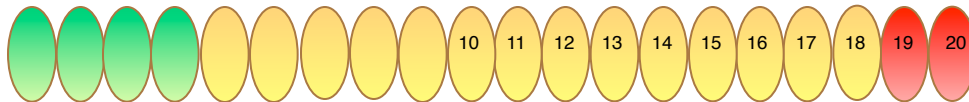
MCP 28 mutations



TM 6 mutations



CFH 76 mutations



CFI 23 mutations



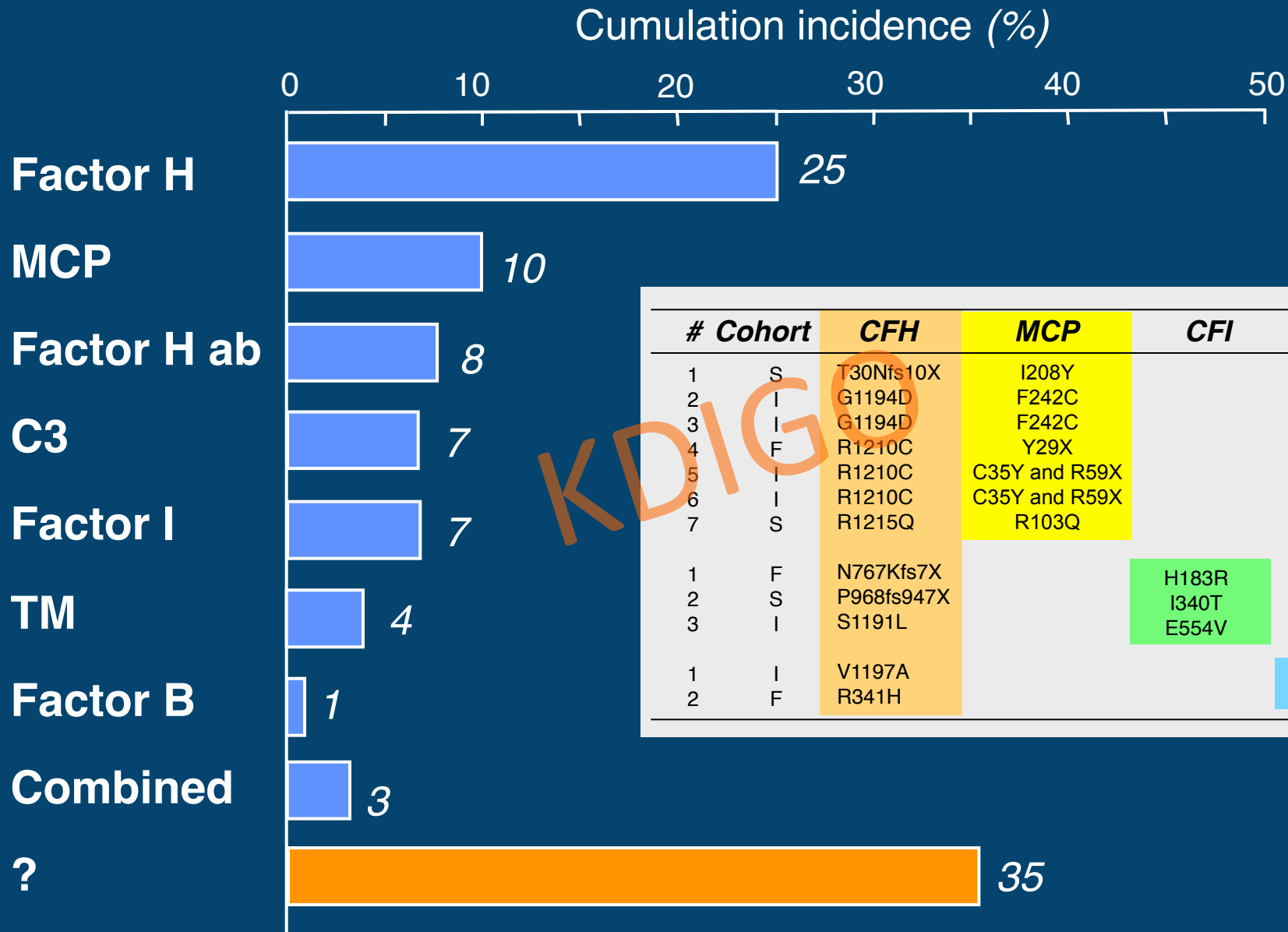
CFB 5 mutations



C3 12 mutations

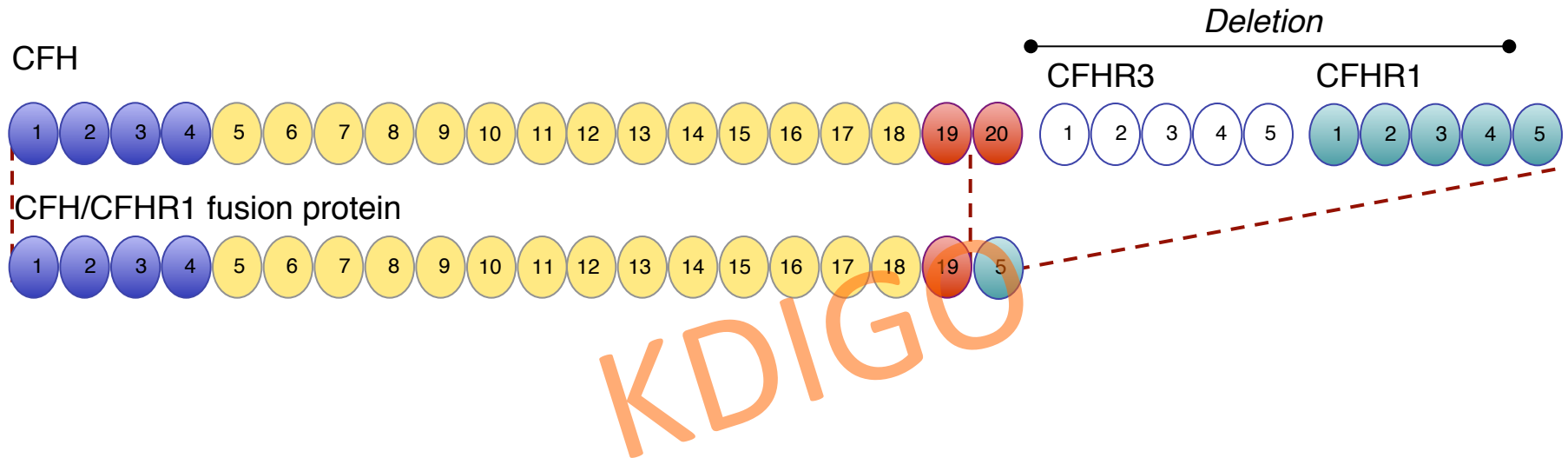


COMPLEMENT ABNORMALITIES IN 272 PATIENTS



#	Cohort	CFH	MCP	CFI	C3
1	S	T30Nfs10X	I208Y		
2	I	G1194D	F242C		
3	I	G1194D	F242C		
4	F	R1210C	Y29X		
5	I	R1210C	C35Y and R59X		
6	I	R1210C	C35Y and R59X		
7	S	R1215Q	R103Q		
1	F	N767Kfs7X		H183R	
2	S	P968fs947X		I340T	
3	I	S1191L		E554V	
1	I	V1197A			G1094R
2	F	R341H			R161W

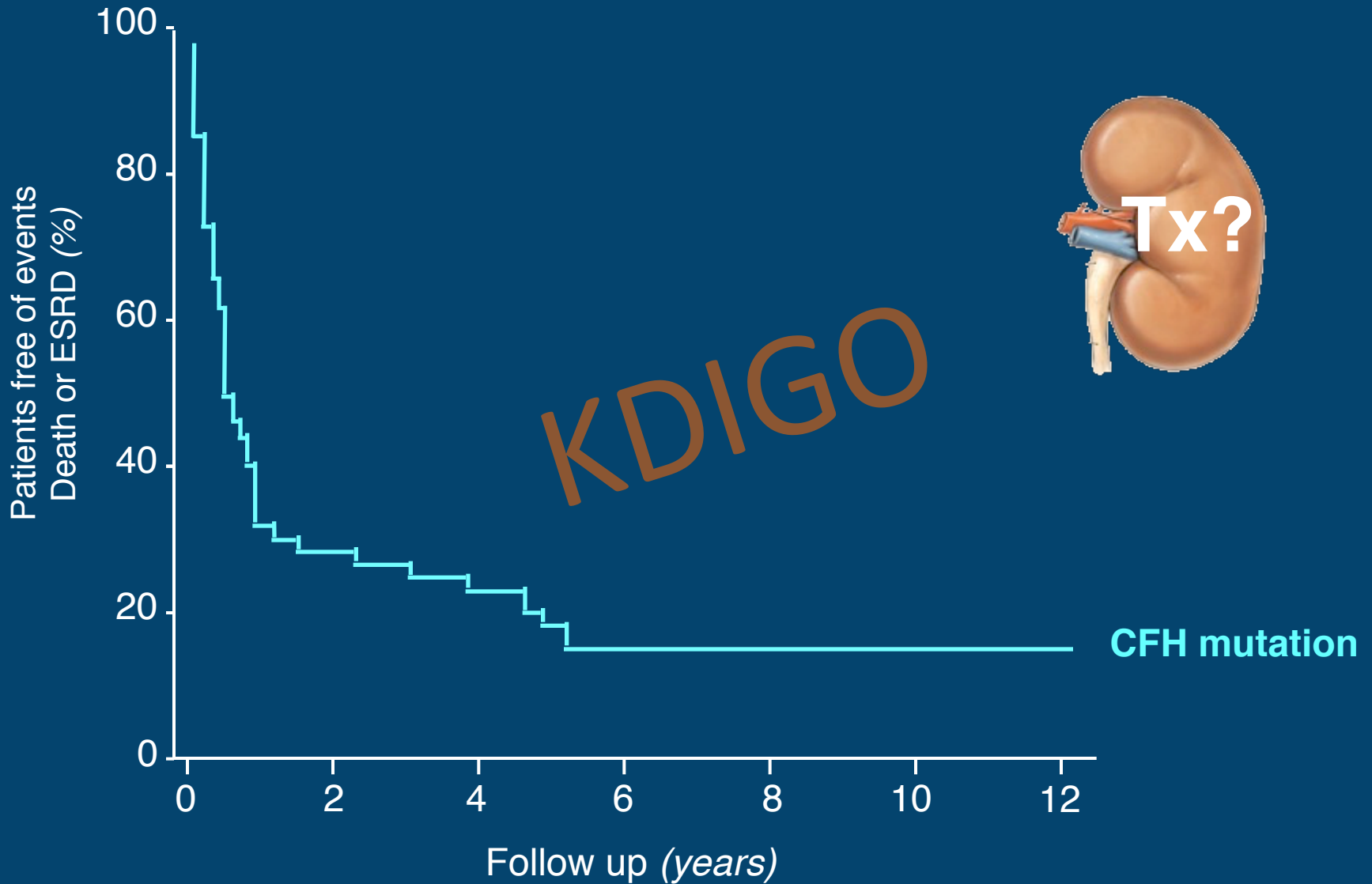
ATYPICAL HEMOLYTIC UREMIC SYNDROME ASSOCIATED WITH A HYBRID COMPLEMENT GENE



The patient and the unaffected mother and brother carry a a very rare genomic rearrangement between CFH and CFHR1 genes generating heterozygous CFH/CFHR1 hybrid protein in which SCR 1-19 are derived from CFH and SCR 20 from SCR 5 of CFHR1 by non allelic homologous recombination

Valoti et al., *JASN*, 2015

LONG-TERM OUTCOMES FOR aHUS PATIENTS



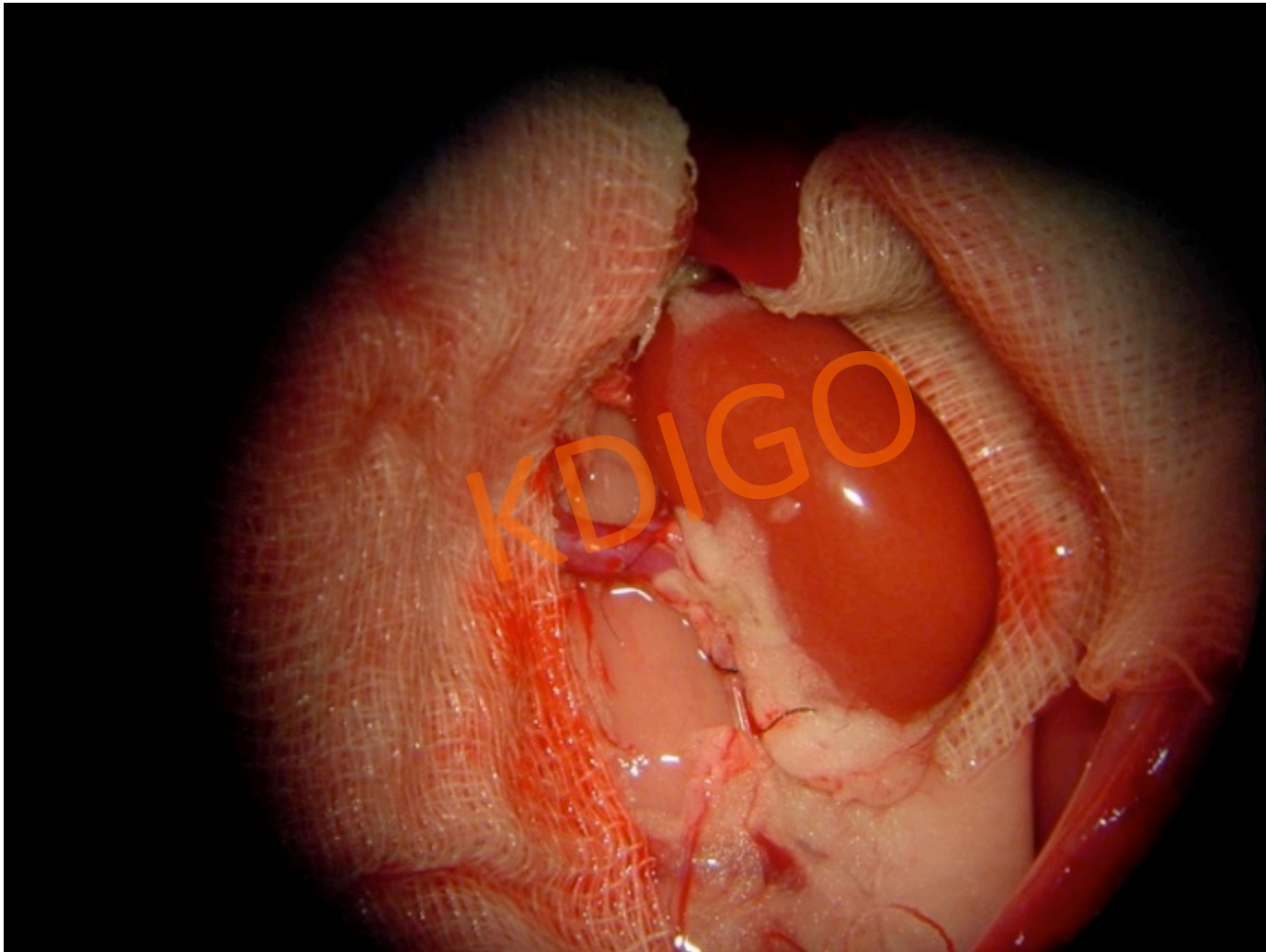


Lancet 2002; **359**: 1671–72

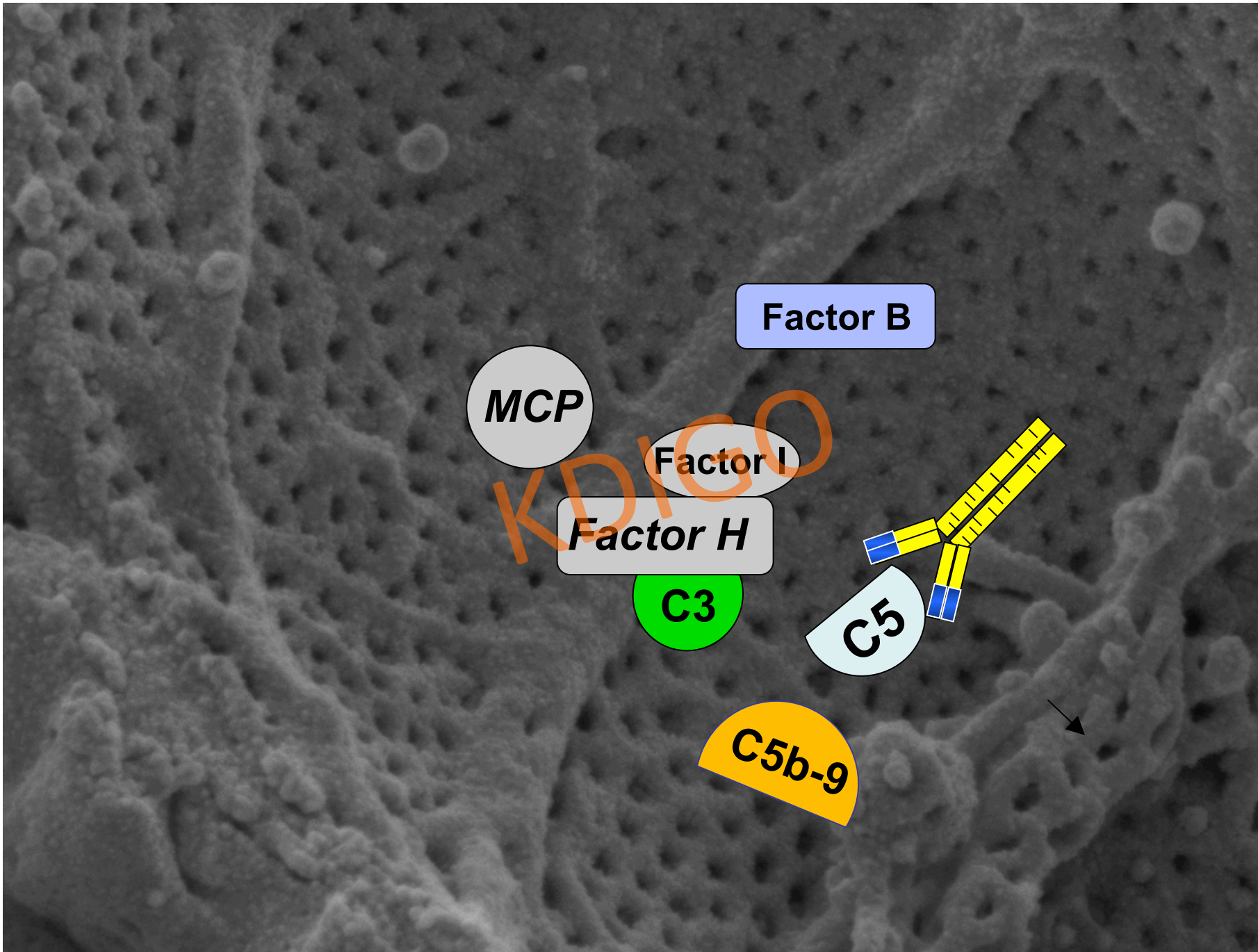
Combined kidney and liver transplantation for familial haemolytic uraemic syndrome

Giuseppe Remuzzi, Piero Ruggenenti, Daniela Codazzi, Marina Noris, Jessica Caprioli, Giuseppe Locatelli, Bruno Gridelli

ORTHOTOPIC KIDNEY TRANSPLANTATION IN RATS



Rat kidney reperfusion



EFFECTS OF 52 WEEKS OF ECULIZUMAB THERAPY IN PATIENTS WITH PLASMA DEPENDENT OR PLASMA RESISTANT ATYPICAL HUS

	Dependent (n = 20)	Resistant (n = 17)
Persistent remission	17	15
Need for plasma therapy	0	0
Serious treatment-related adverse events	0	0

Licht et al., *J Am Soc Nephrol*, 2011
Greenbaum et al., *J Am Soc Nephrol*, 2011
Legendre et al., *N Engl J Med*, 2013





330,000

KDIGO

euro per patient per year



460.000

Rare diseases and effective treatments: are we delivering?

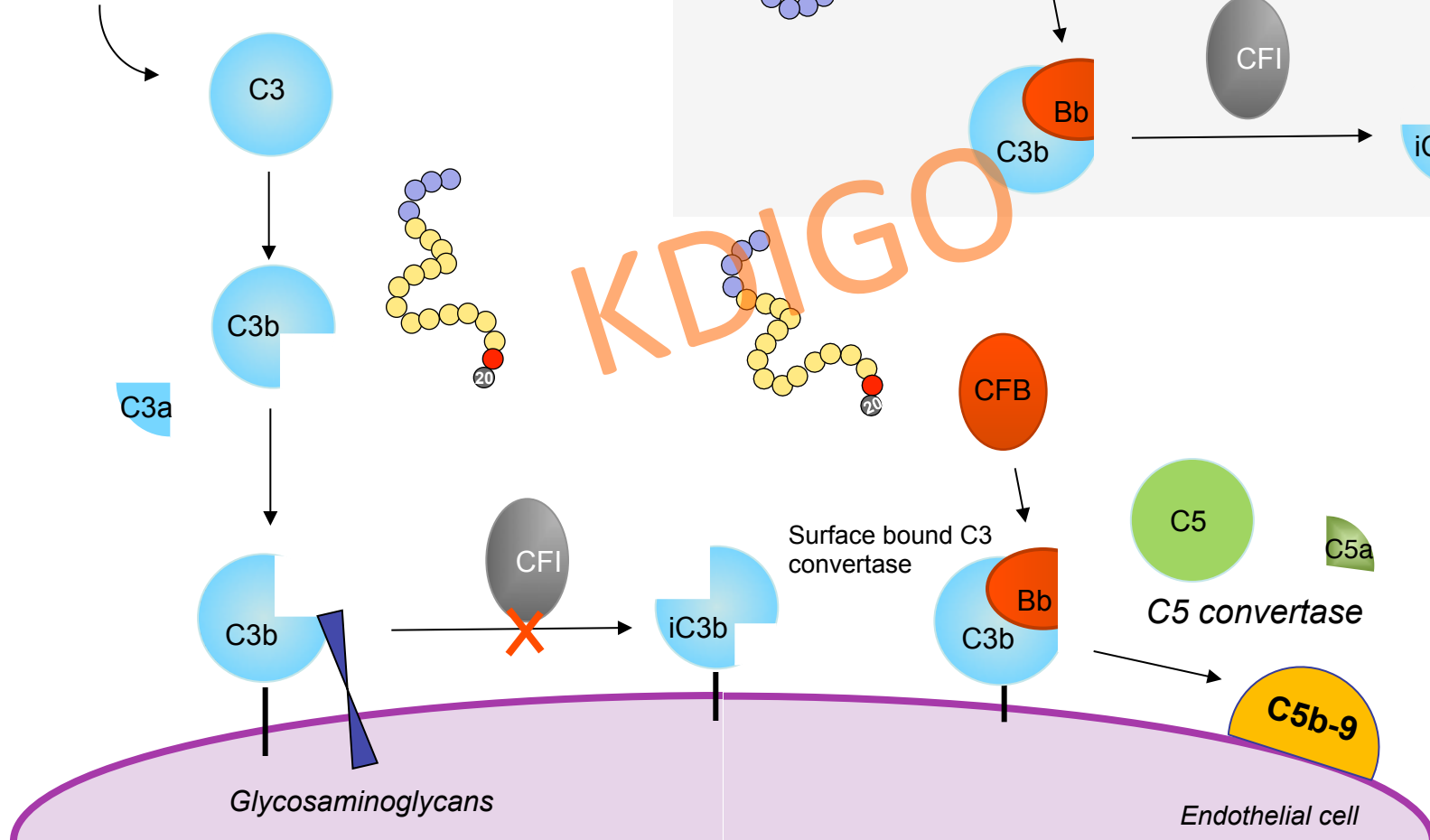
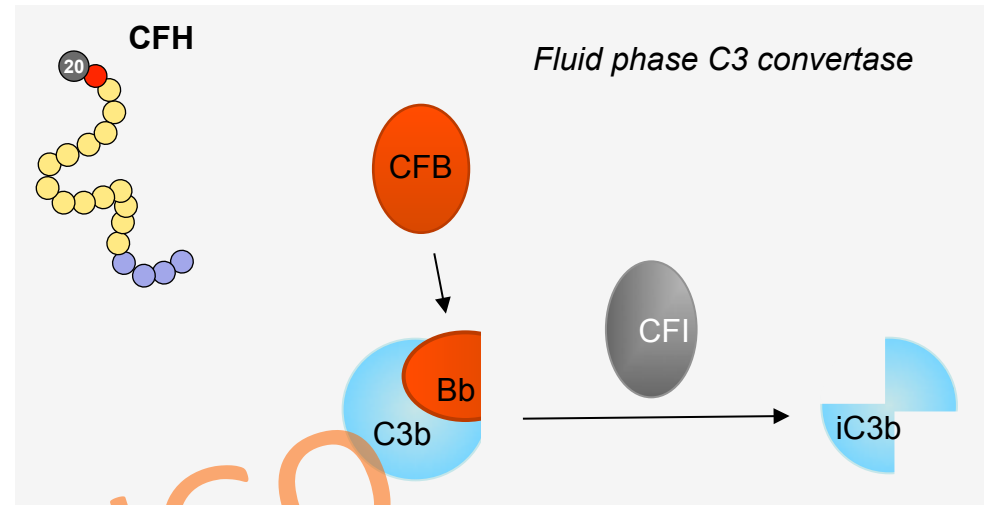
Lucio Luzzatto, Carla E M Hollak, Timothy M Cox, Arrigo Schieppati, Christoph Licht, Helena Kääriäinen, Giampaolo Merlini, Franz Schaefer, Steven Simoens, Luca Pani, Silvio Garattini, Giuseppe Remuzzi



Ogni 15 giorni per sempre?

ALTERNATIVE PATHWAY ACTIVATION IS IMPAIRED IN SOLID BUT NOT IN FLUID PHASE

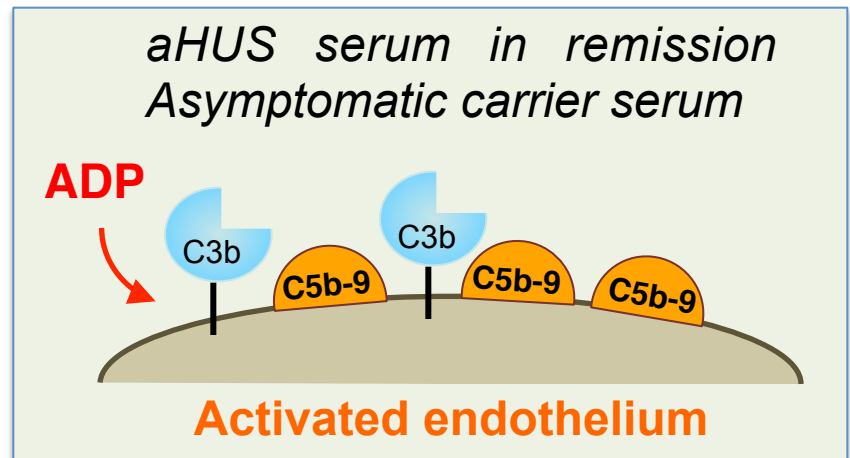
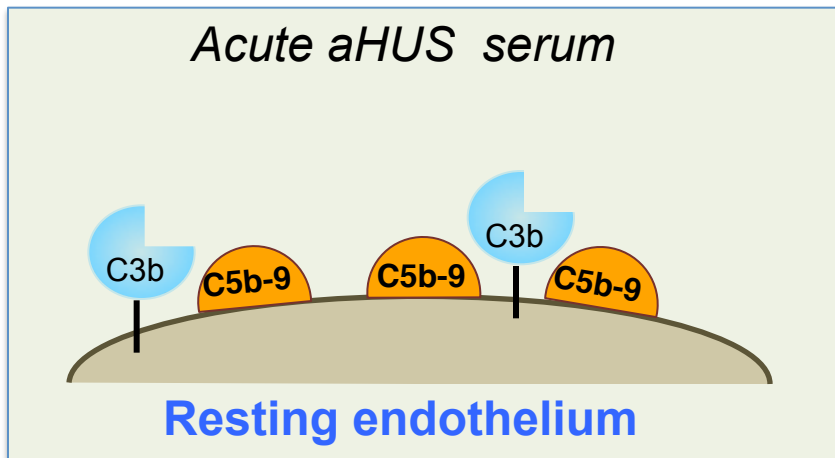
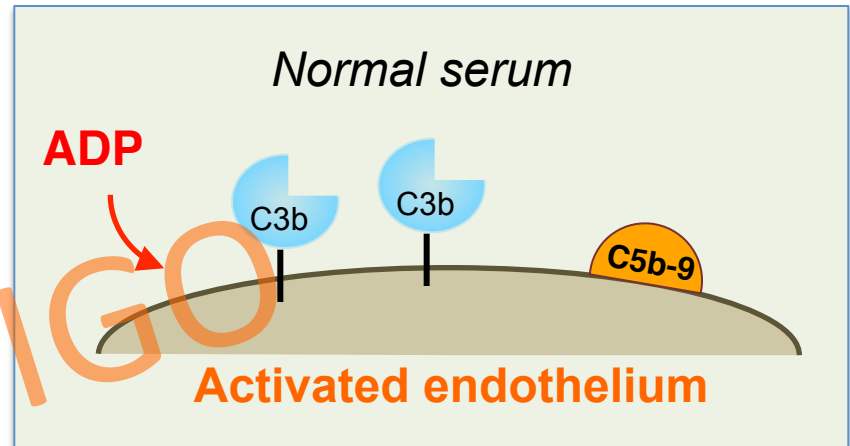
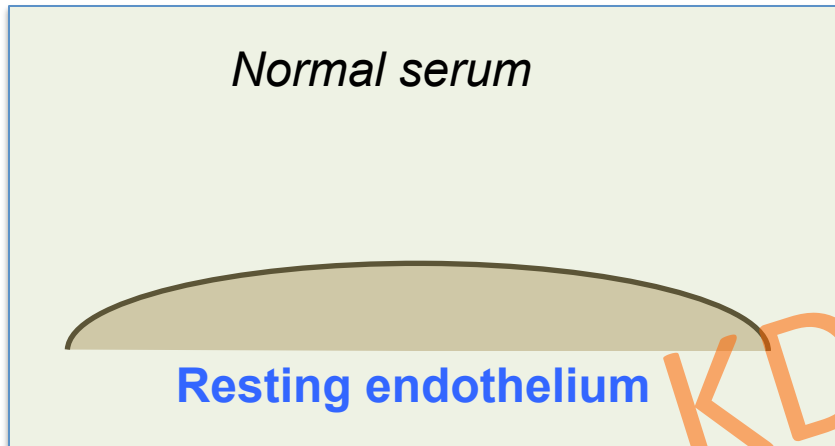
Alternative pathway activation
(spontaneous hydrolysis,
bacteria, viruses)



KDIGO

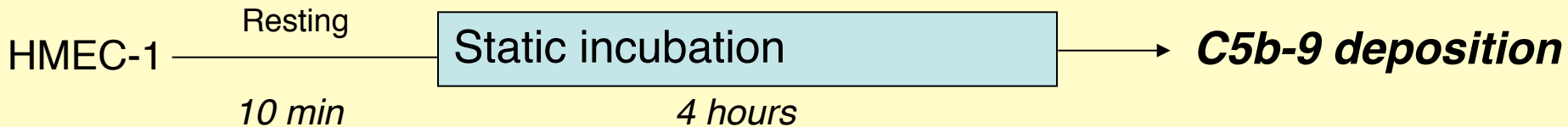
COMPLEMENTING the diagnosis of aHUS

Vahid Afshar-Kharghan THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER

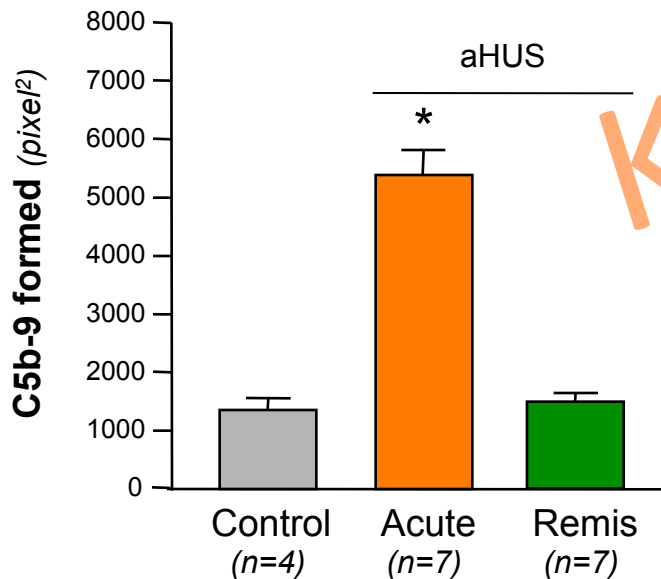


-Control or aHUS serum

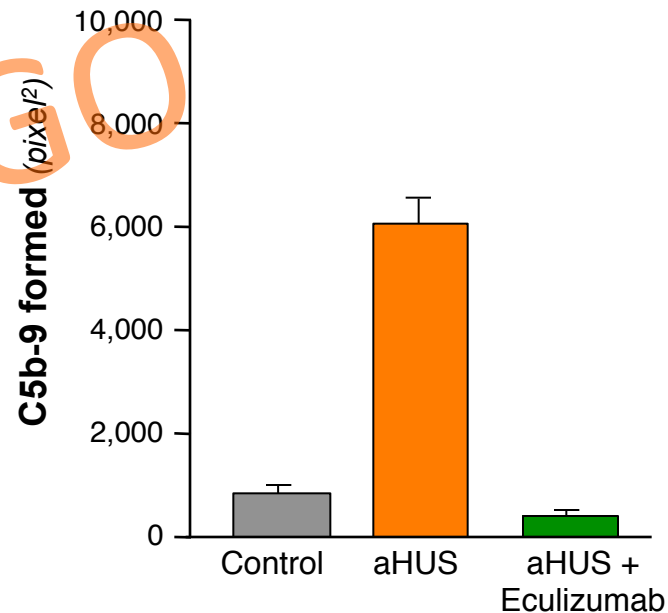
- anti-C5b-9 Ab staining
- Confocal microscopy

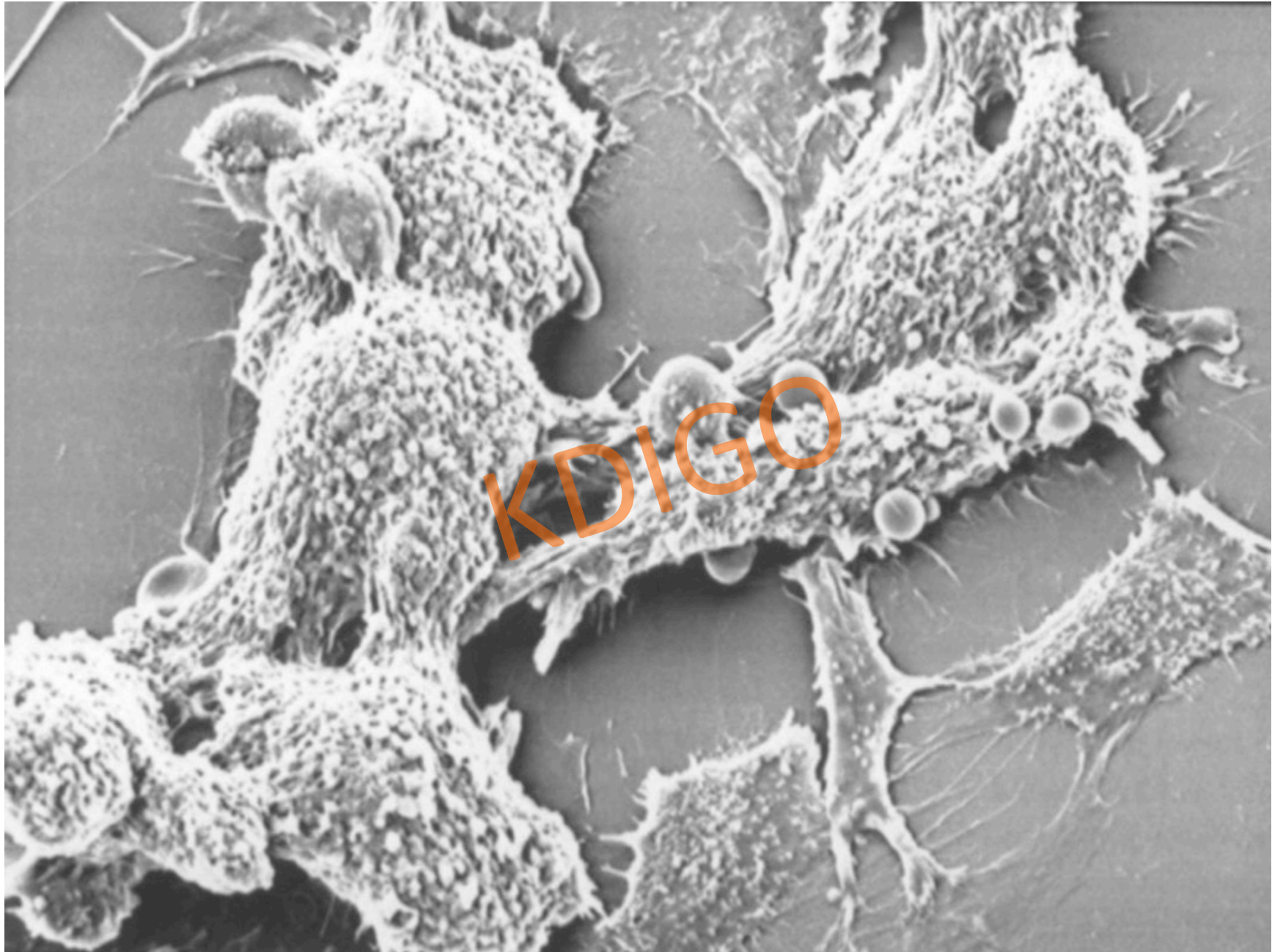


Resting endothelium



Activated endothelium



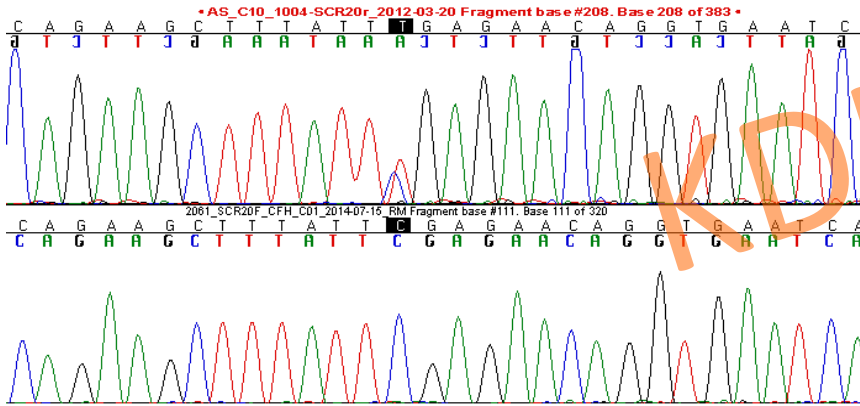




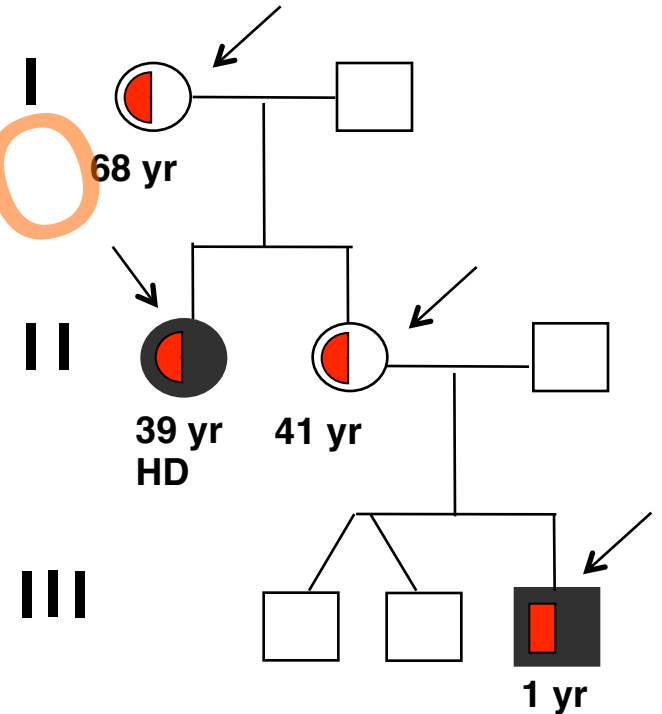
KDIGO

April 2007

A 1-year old child was admitted with familial aHUS and a heterozygous loss of function mutation in complement factor H gene (3645C>T) and developed aHUS at 6 months of age



c.3572 C>T
p.Ser1191Leu



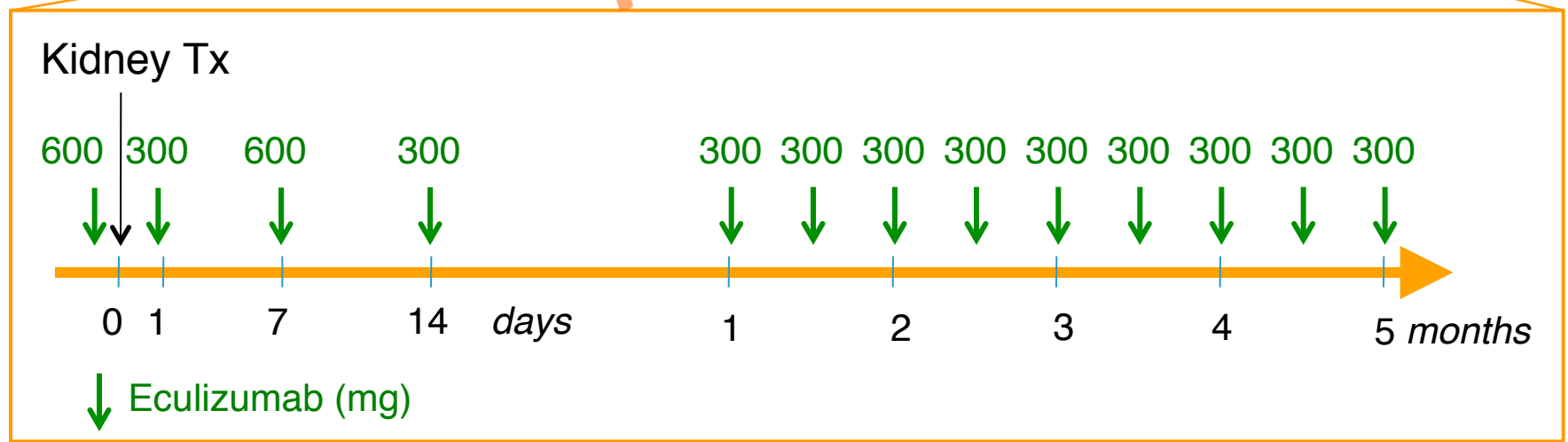
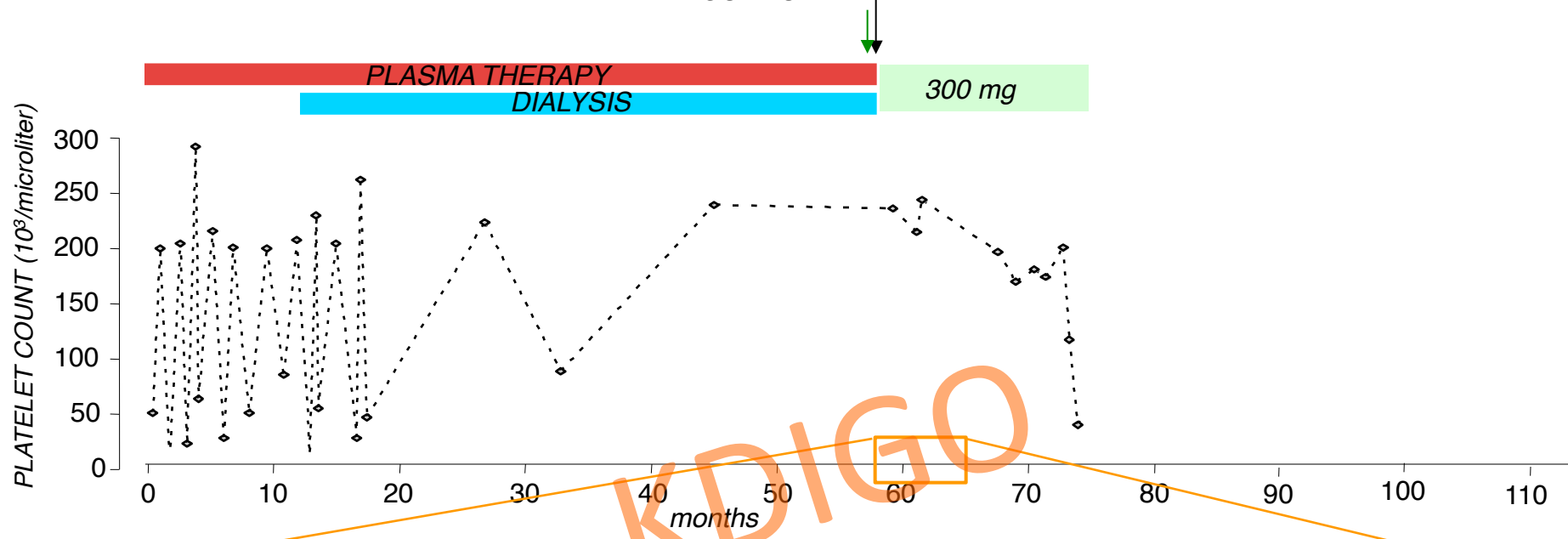
S1191L
mutation in CFH

Pediatric case

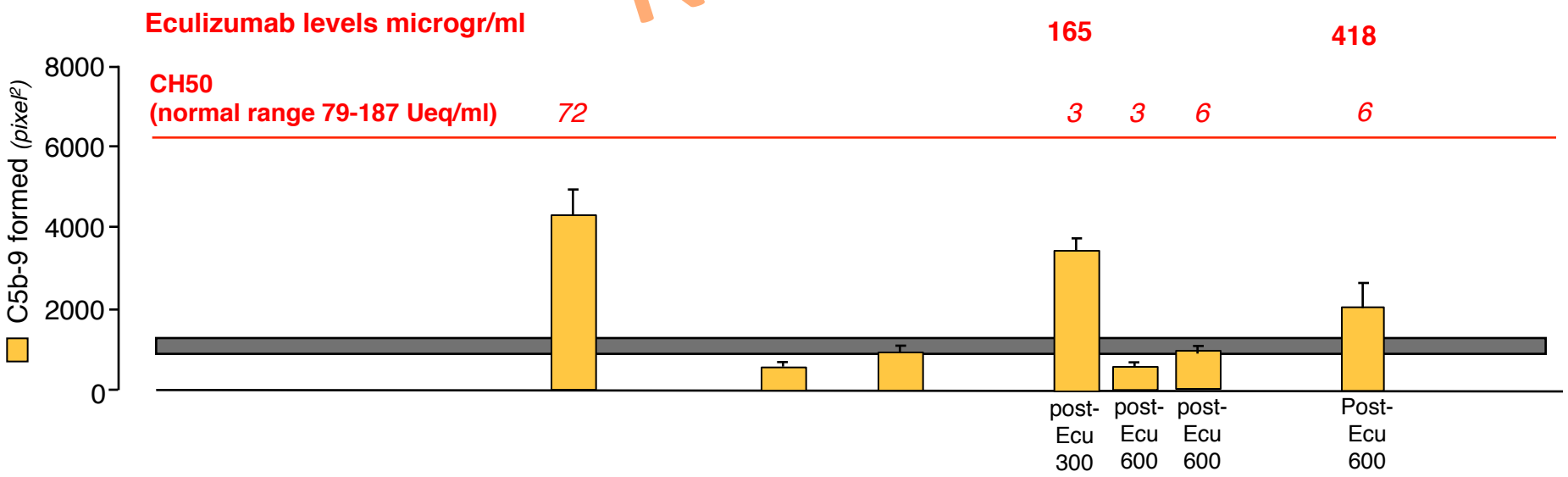
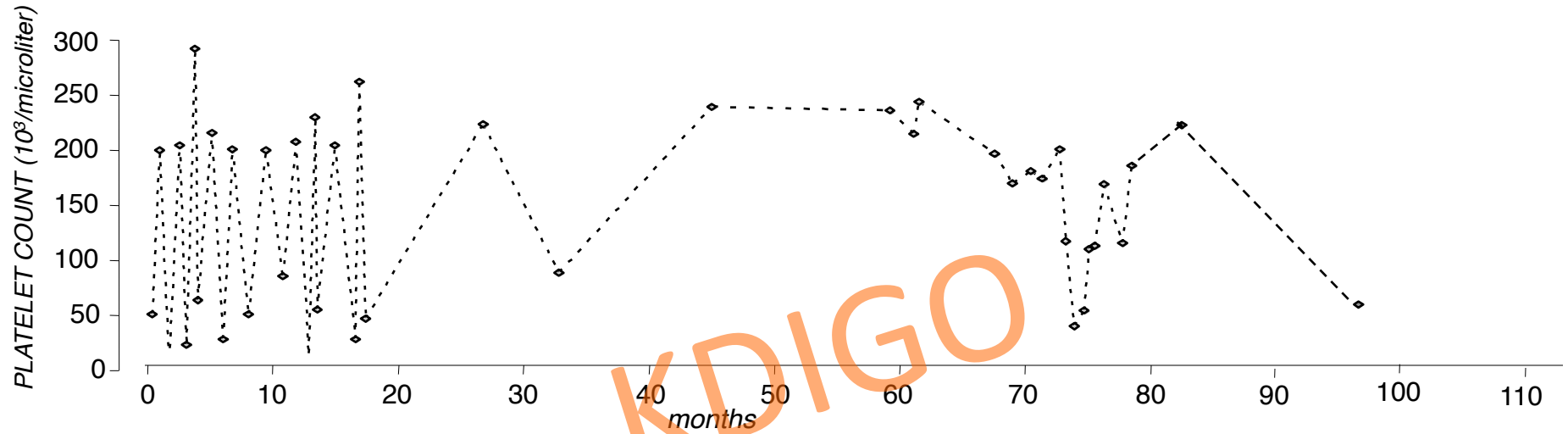
Aug 19, 2011 – 5 years of age

KIDNEY TRANSPLANT

ECULIZUMAB *ECULIZUMAB*

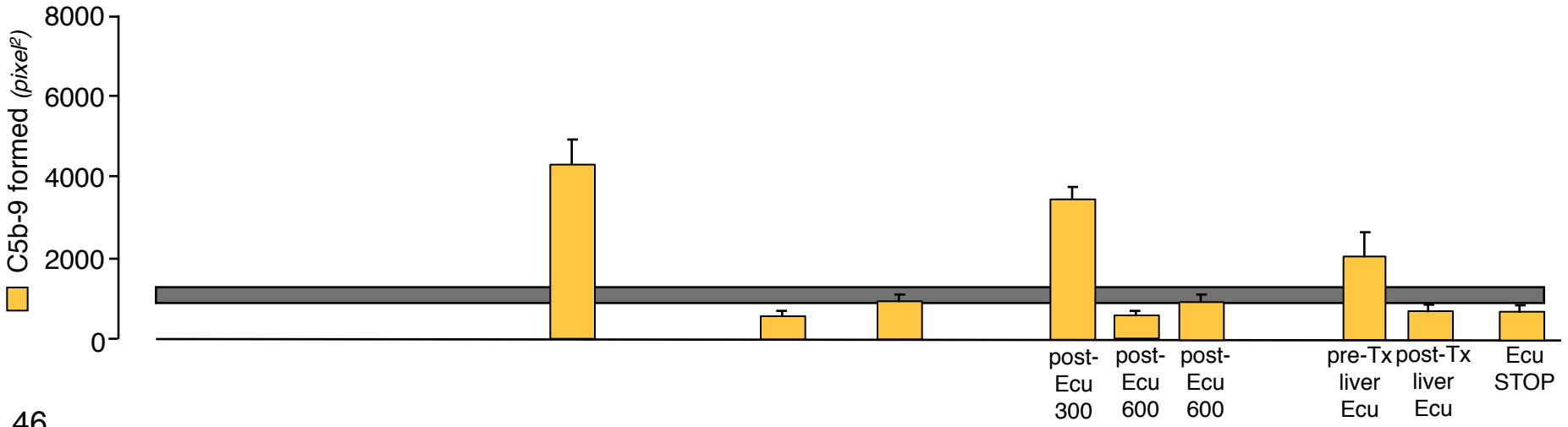
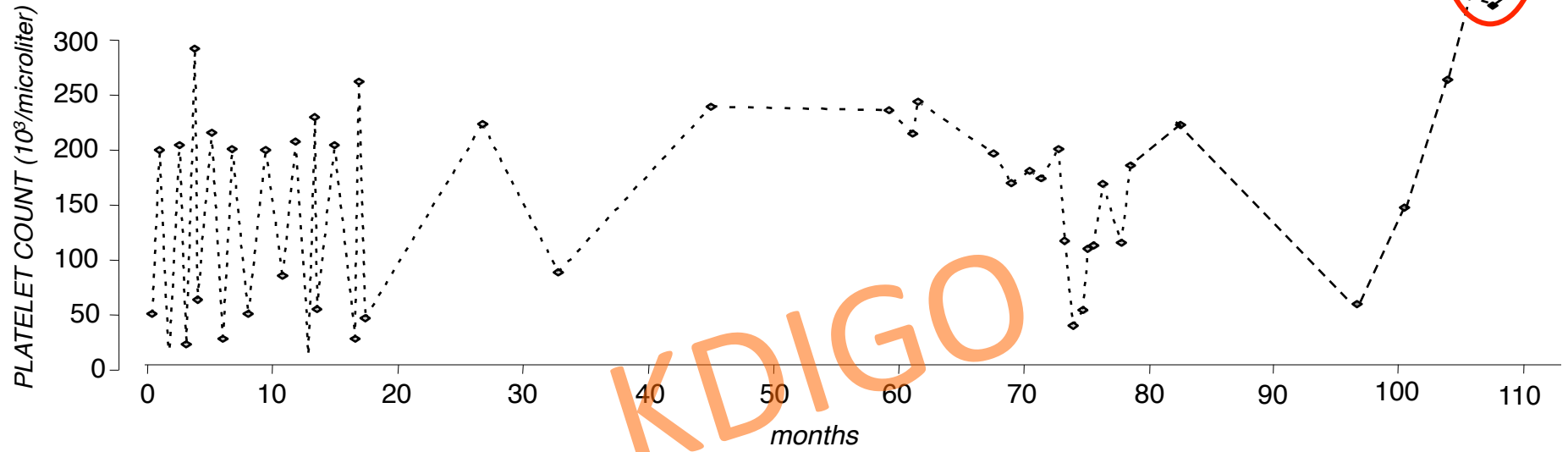


Pediatric case



Pediatric case

Sept 18, 2014 – 8 years of age

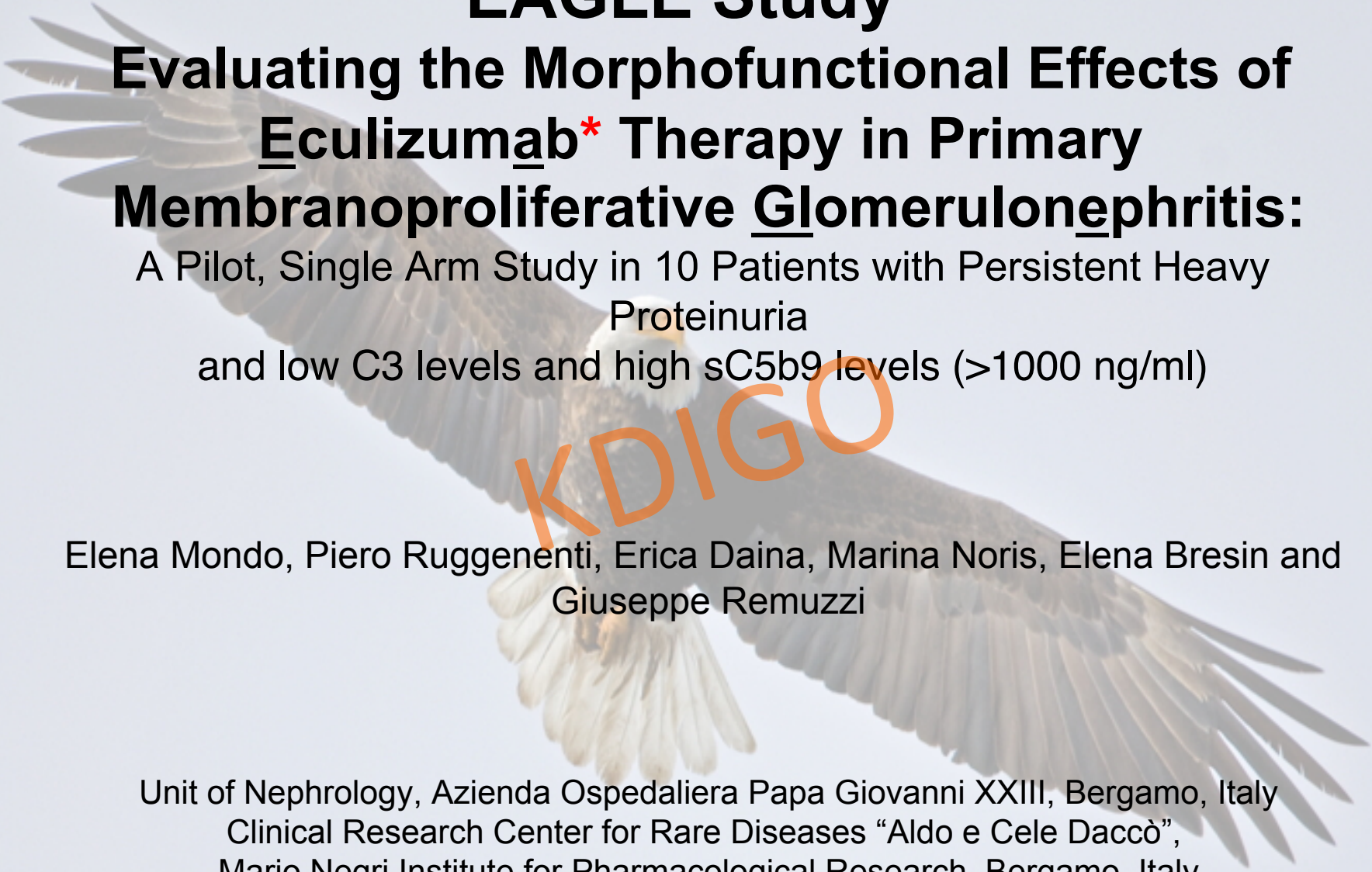


REGISTRY OF MPGN/C3G

Participating Centers	50
Ig-MPGN/C3G patients	227
<i>Italian cases</i>	204
<i>Foreign cases</i>	23

09/2014





EAGLE Study

Evaluating the Morphofunctional Effects of Eculizumab* Therapy in Primary Membranoproliferative Glomerulonephritis:

A Pilot, Single Arm Study in 10 Patients with Persistent Heavy Proteinuria and low C3 levels and high sC5b9 levels (>1000 ng/ml)

Elena Mondo, Piero Ruggenenti, Erica Daina, Marina Noris, Elena Bresin and Giuseppe Remuzzi

Unit of Nephrology, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy
Clinical Research Center for Rare Diseases “Aldo e Cele Daccò”,
Mario Negri Institute for Pharmacological Research, Bergamo, Italy

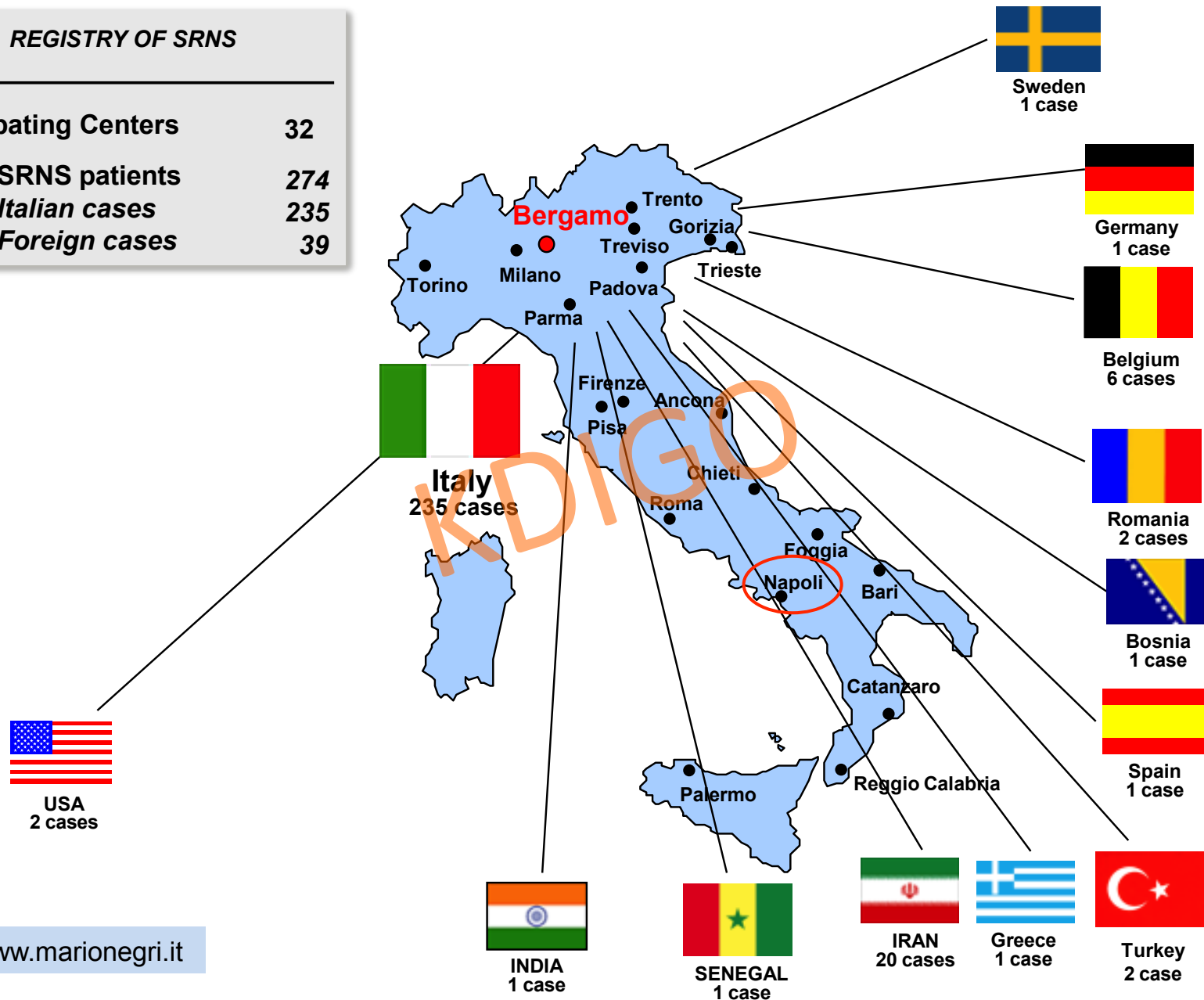
* 900 mg weekly for four infusion and maintenance phase 1200 mg at week 5; then 1200 mg every 2 weeks for 1 years

THE REGISTRY OF STEROID RESISTANT NEPHROTIC SYNDROME

REGISTRY OF SRNS

Participating Centers	32
SRNS patients	274
<i>Italian cases</i>	235
<i>Foreign cases</i>	39

07/2015



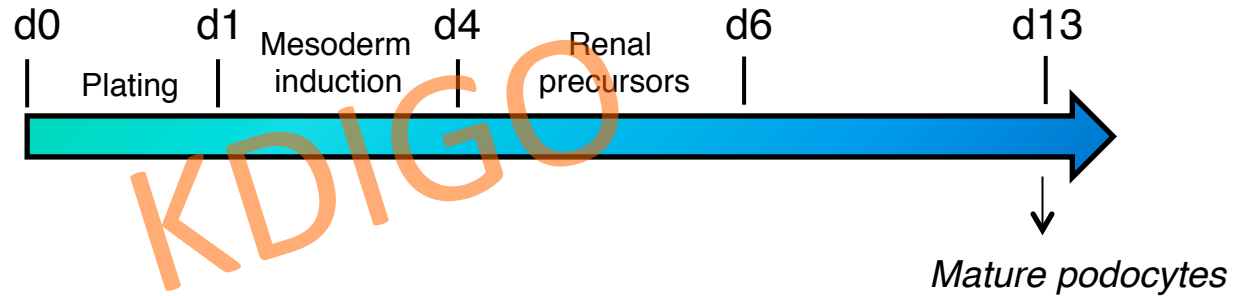
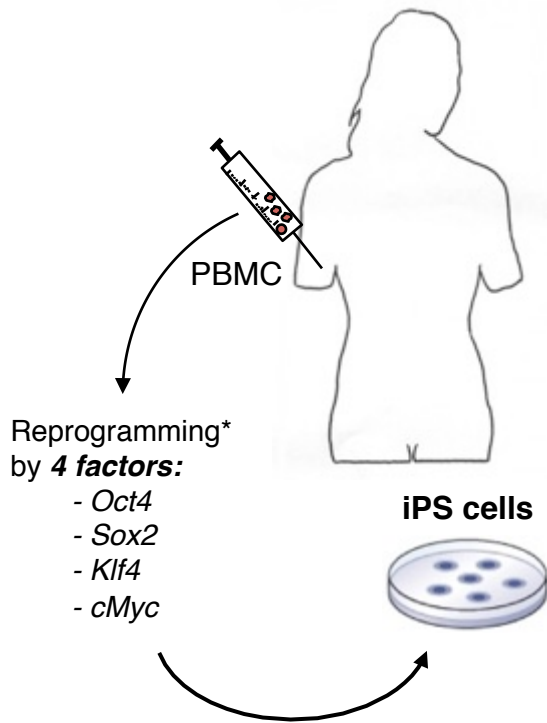
<http://www.marionegri.it>

J Am Soc Nephrol, 2014

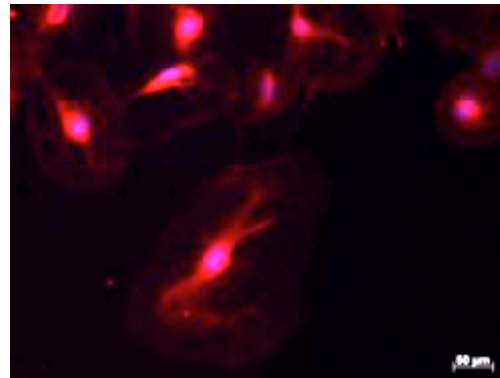
Rituximab in Steroid-Dependent or Frequently Relapsing Idiopathic Nephrotic Syndrome

Piero Ruggenti,^{*†} Barbara Ruggiero,^{*} Paolo Cravedi,^{*} Marina Vivarelli,[‡] Laura Massella,[‡] Maddalena Marasà,[†] Antonietta Chianca,^{*} Nadia Rubis,^{*} Bogdan Ene-lordache,^{*} Michael Rudnicki,[§] Rosa Maria Pollastro,^{||} Giovambattista Capasso,^{||} Antonio Pisani,[¶] Marco Pennesi,^{**} Francesco Emma,[‡] and Giuseppe Remuzzi,^{*†} for the Rituximab in Nephrotic Syndrome of Steroid-Dependent or Frequently Relapsing Minimal Change Disease Or Focal Segmental Glomerulosclerosis (NEMO) Study Group

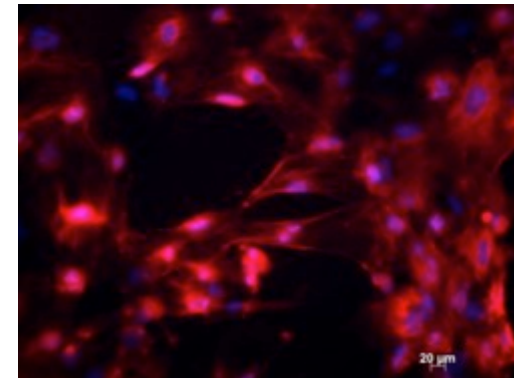
DERIVATION OF HUMAN iPSC-DERIVED PODOCYTES

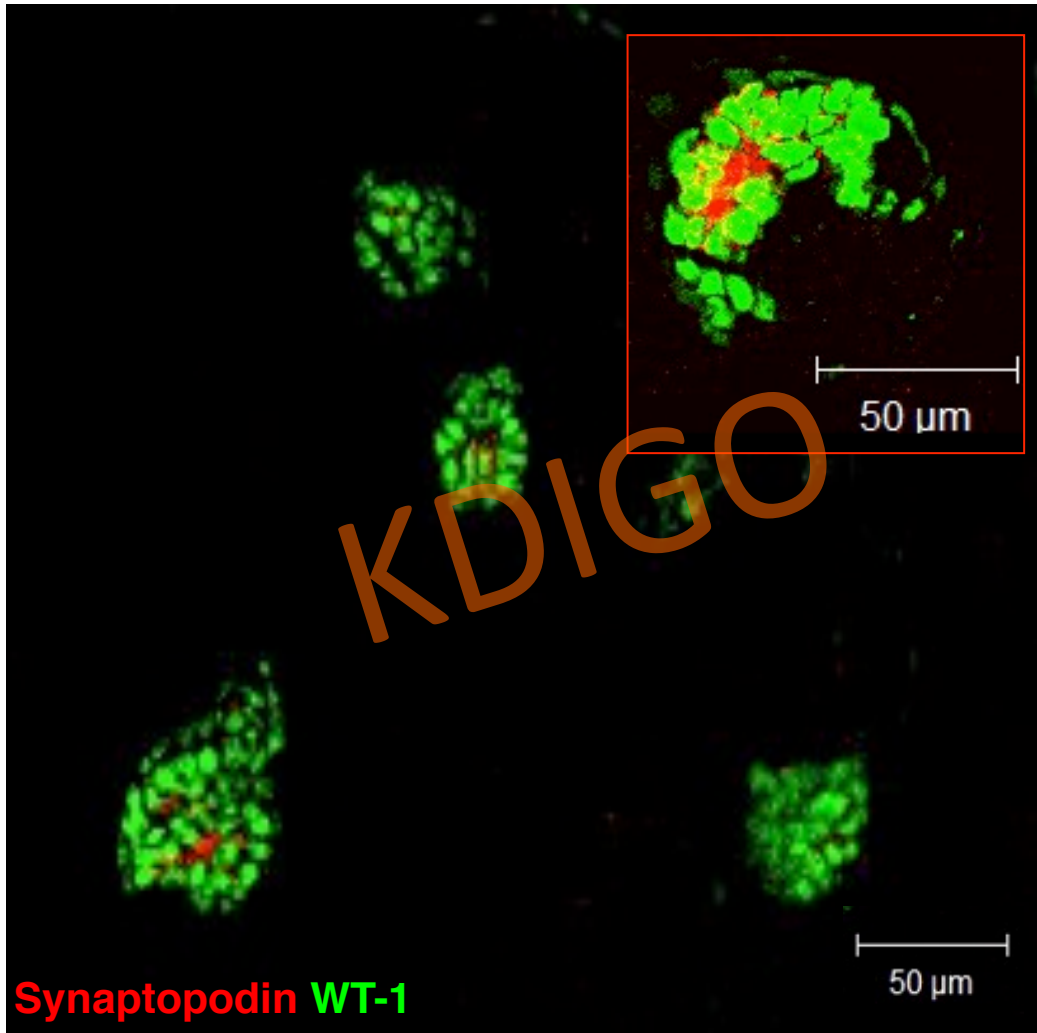


Synaptopodin/DAPI

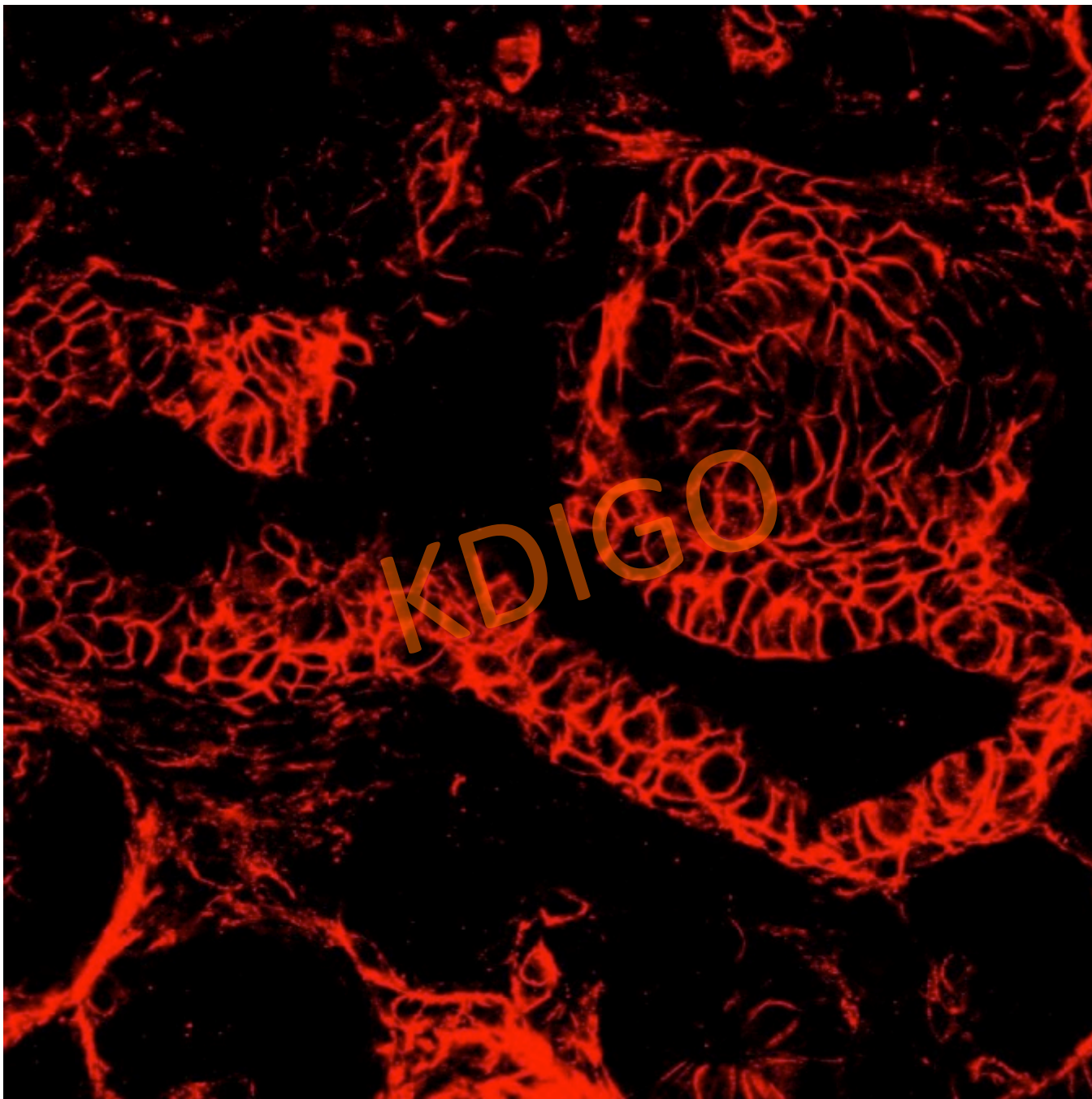


Nephrin/DAPI





In vitro
15 days



Adaptative Designs: Examples

- **Ranking and selection designs**

- *“Pick-the-winner”, “drop-the-losers” designs are used for treatment/dose selection for a subsequent randomized study)*

- **Internal pilot designs**

- *The sample size is calculated during the pilot phase and patients of the pilot study are maintained in the subsequent trial*

- **Sequential designs**

- *Continuous sequential analyses are planned with pre-set stopping criteria*

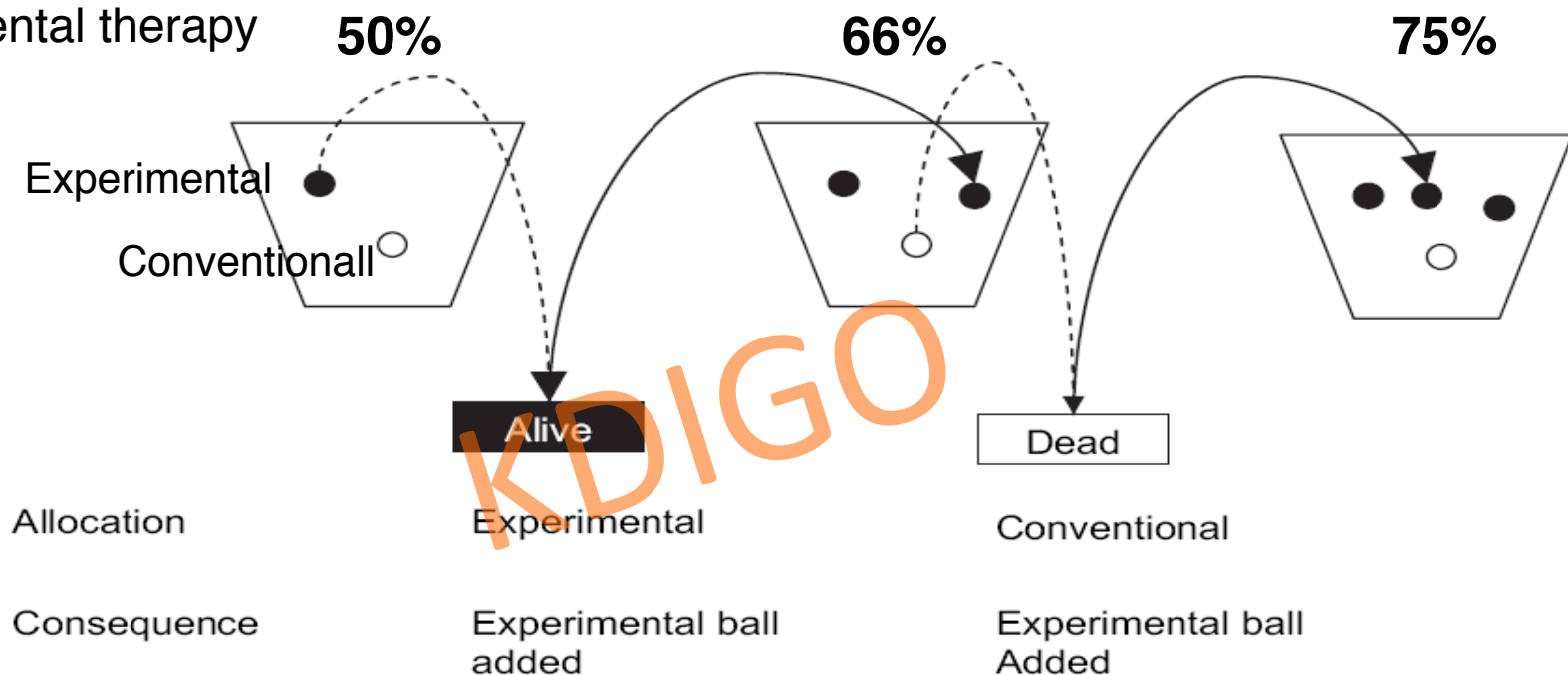
- **Response-adaptative randomization designs**

- *Possibility to adapt the study design according to preliminary outcomes*

Gupta et al, *J Clin Epidemiol* 2011

BALLS-IN-URN RESPONSE-ADAPTATIVE RANDOMIZATION DESIGNS

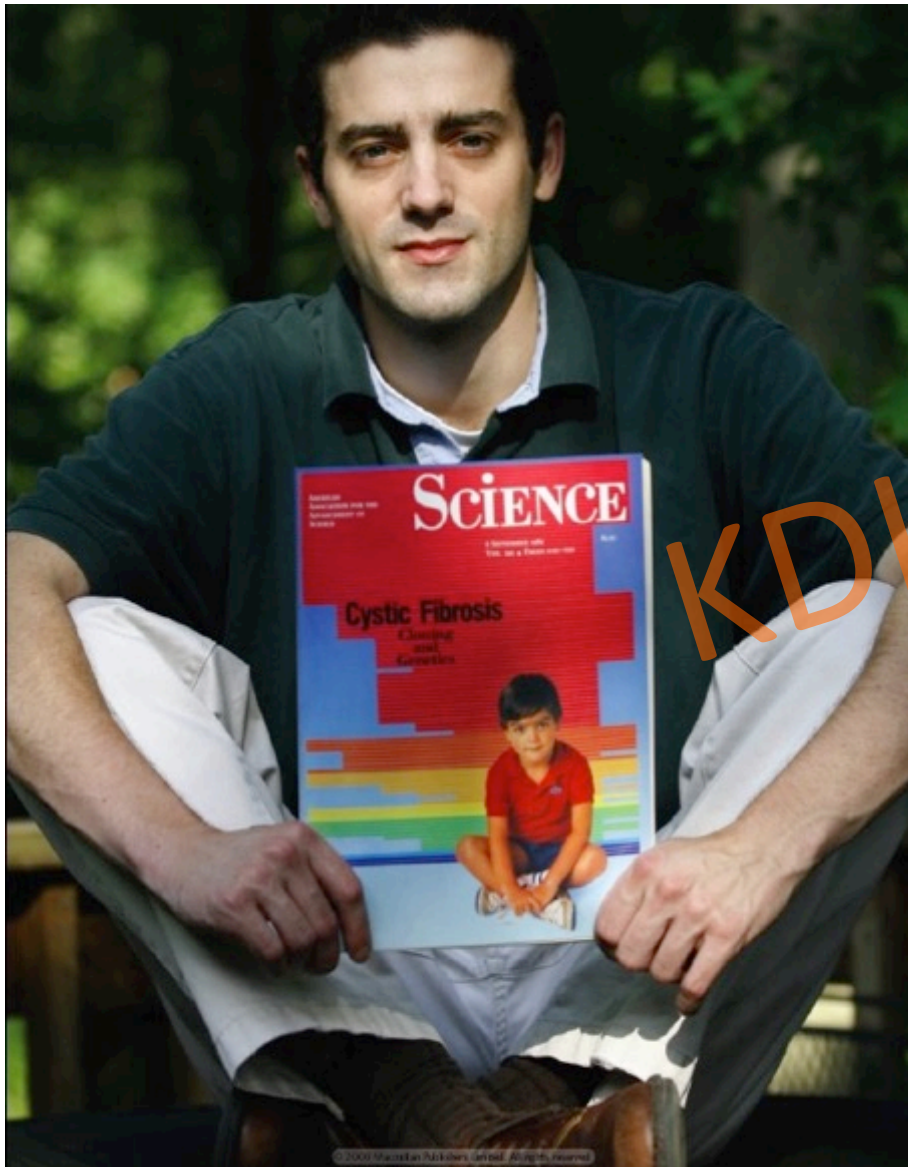
Probability of being allocated to experimental therapy



- Black balls are added whenever a patient assigned to experimental therapy survives or one allocated to conventional therapy dies
- White balls are added whenever a patient assigned to experimental therapy dies or one allocated to conventional therapy survives
- The process continues until a preset stopping criterion is met

330
KDIG

KDIGO



**“The disease
has contributed
much more to
science than
science has
contributed to
the disease.”**

— Jack Riordan

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