JSN/KDIGO Joint Symposium, Sendai, May 27, 2017

Controversies and Consensus in Rare Kidney Disorders

Prof. Dr. med. Olivier Devuyst

EUReniOmics

WGiKD

University of Zurich[UZH]

The Global Burden of Rare Diseases

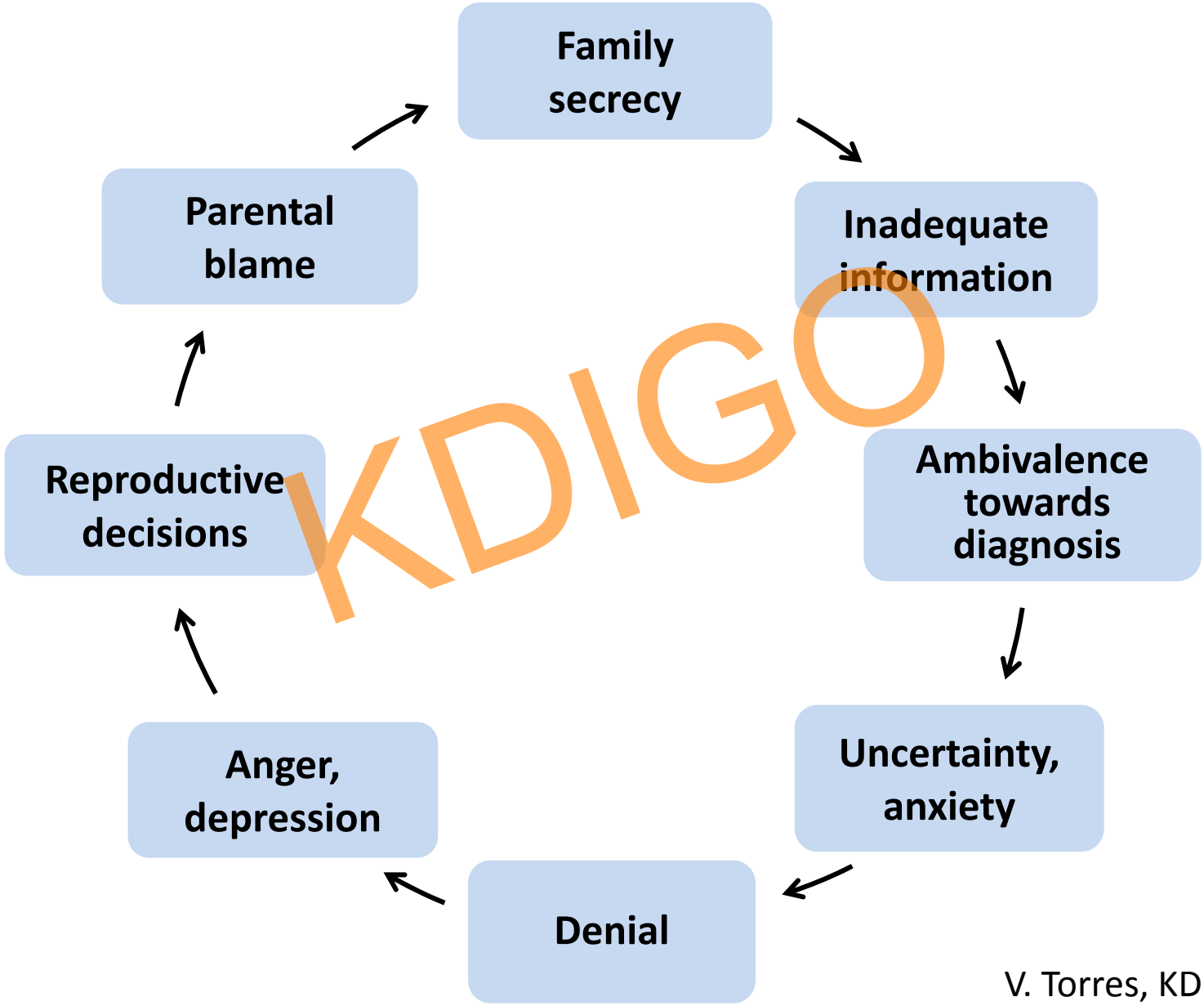
- Rare diseases: ~6,000 – 8,000 disorders
- Defined by prevalence (1:2000 - EU; 1:2500 – JPN)
- Affect ~30 M patients in EU and in the USA, > 300 M worldwide
- 80% of rare diseases have a genetic origin
- Typical challenges: variable phenotypes, fragmented data, lack of standards, poor knowledge for disease mechanisms and natural history

"Orphan diseases" : severity, insufficient resources and knowledge, specific conditions for drug development

Rare Diseases: Specific Burden

- Severe, chronic, often degenerative or life-threatening
- Onset: 50% in childhood
- Disabling: quality of life compromised – loss of autonomy
- Psychological burden: patients, families, lack of hope, lack of support
- Incurable diseases, without effective treatment (sometimes symptomatic R/)
- Difficult to diagnose and manage; heterogeneity in terms of care

Emotional Burden of an Inherited Disease



V. Torres, KDIGO-ADPKD

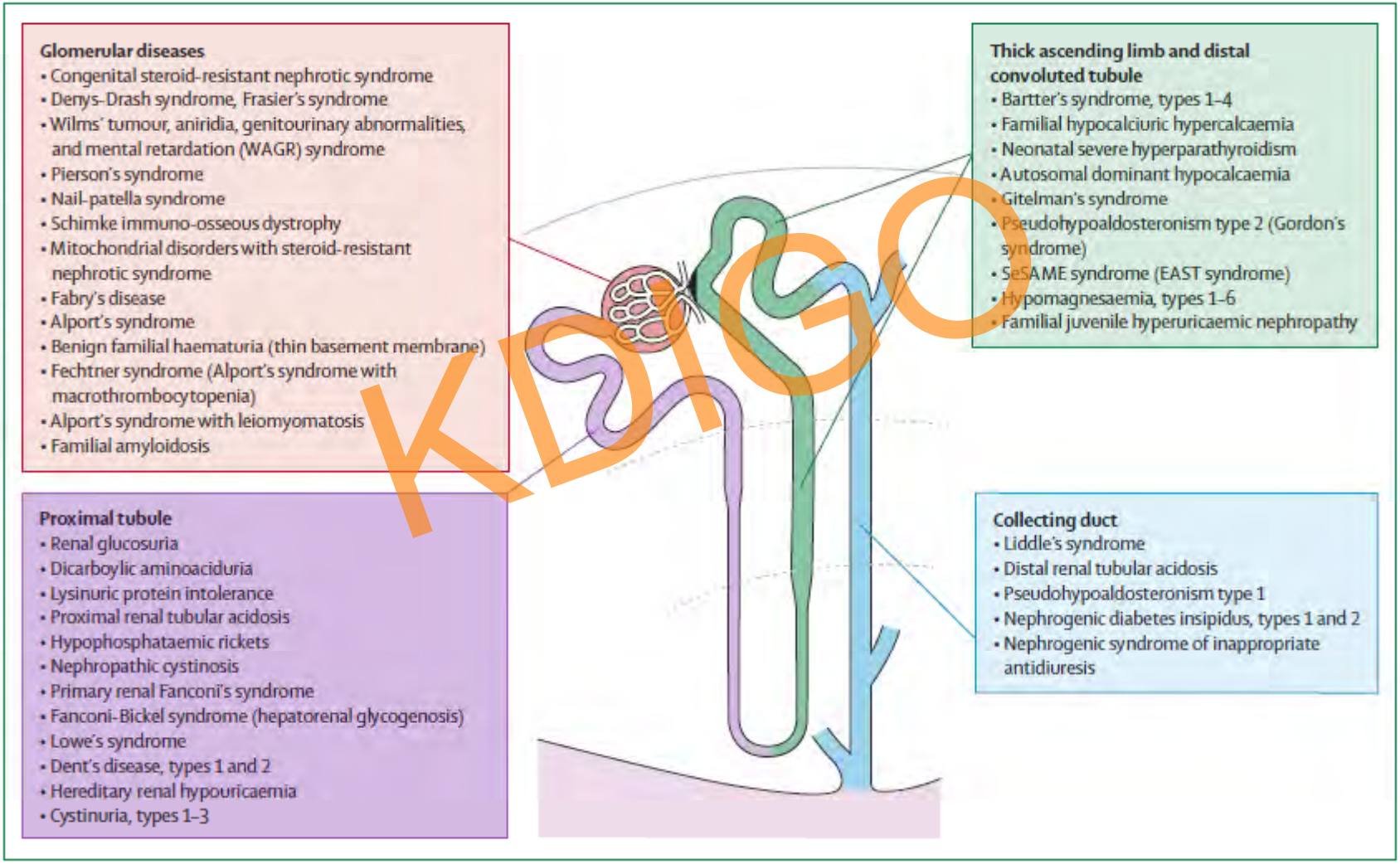
Rare Kidney Diseases

- Rare kidney diseases: > 150 disorders
- Overall prevalence: ~60-80 cases per 100,000
- At least 10% adults and virtually all children on RRT
- Fifth most common cause of ESRD (Diab > HT > GN > PyeloN)

- Patients with inherited kidney disorders rarely die (progresses in RRT)
- However: poor health, poor quality of life, multisystemic complications

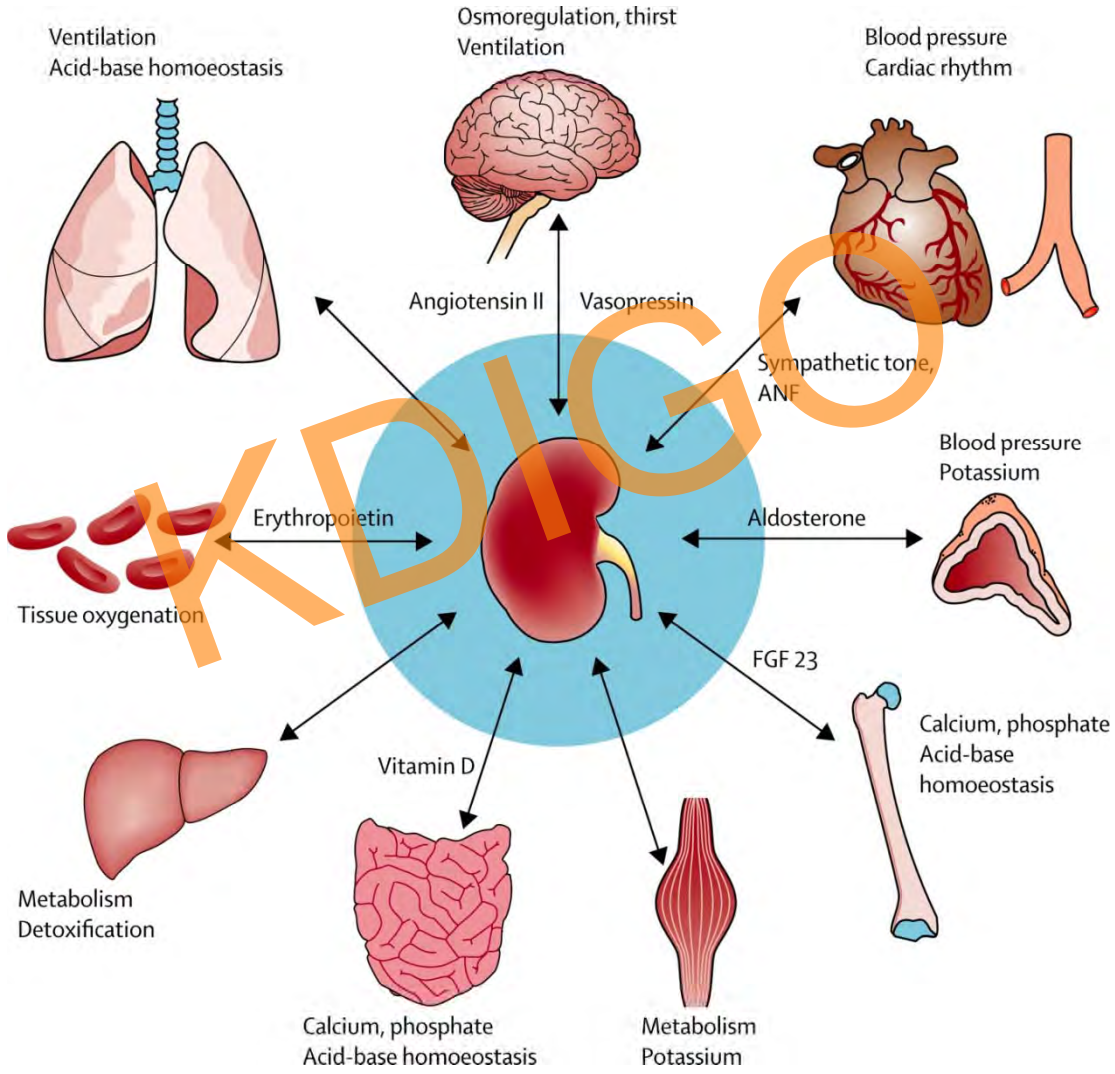
→ *children with severe congenital nephropathies can be dialysed from neonatal age onwards, but face many decades of life with ESRD and have a high likelihood of changes in physical, cognitive, and psychosocial development.*

Inherited Kidney Disorders: Segmental Distribution



Devuyst O, et al. Lancet **383**, 2014

Kidney Function and Homeostasis



Eckardt KU, et al. Lancet **382**, 2013

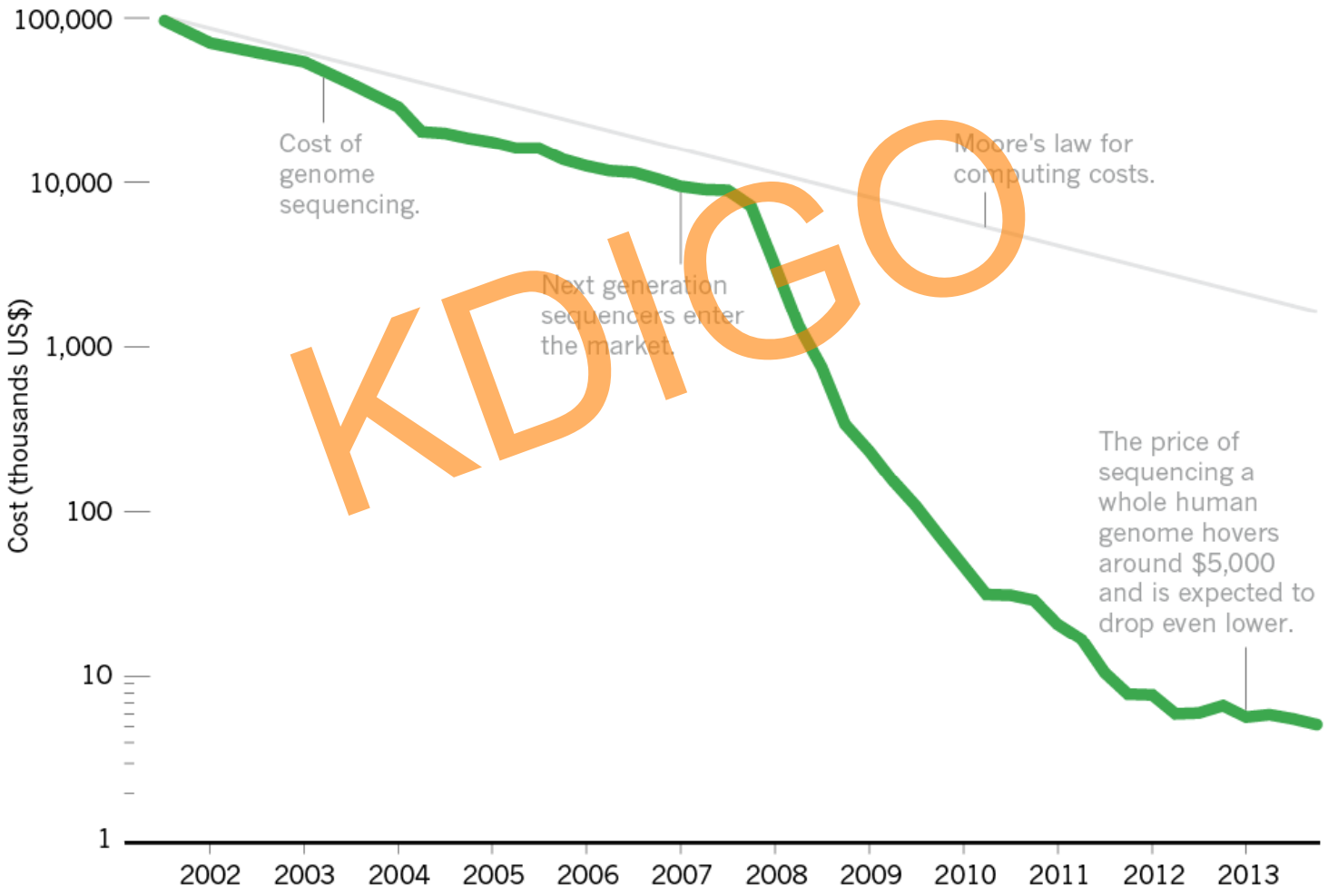
Rare Inherited Kidney Disorders:

Opportunities

Nature, 19 March 2014

Falling fast

In the first few years after the end of the Human Genome Project, the cost of genome sequencing roughly followed Moore's law, which predicts exponential declines in computing costs. After 2007, sequencing costs dropped precipitously.



Inherited Kidney Disorders: Next-generation Sequencing

- Development and validation of multigene panels: *simultaneous investigation of all relevant genes for a given phenotype*

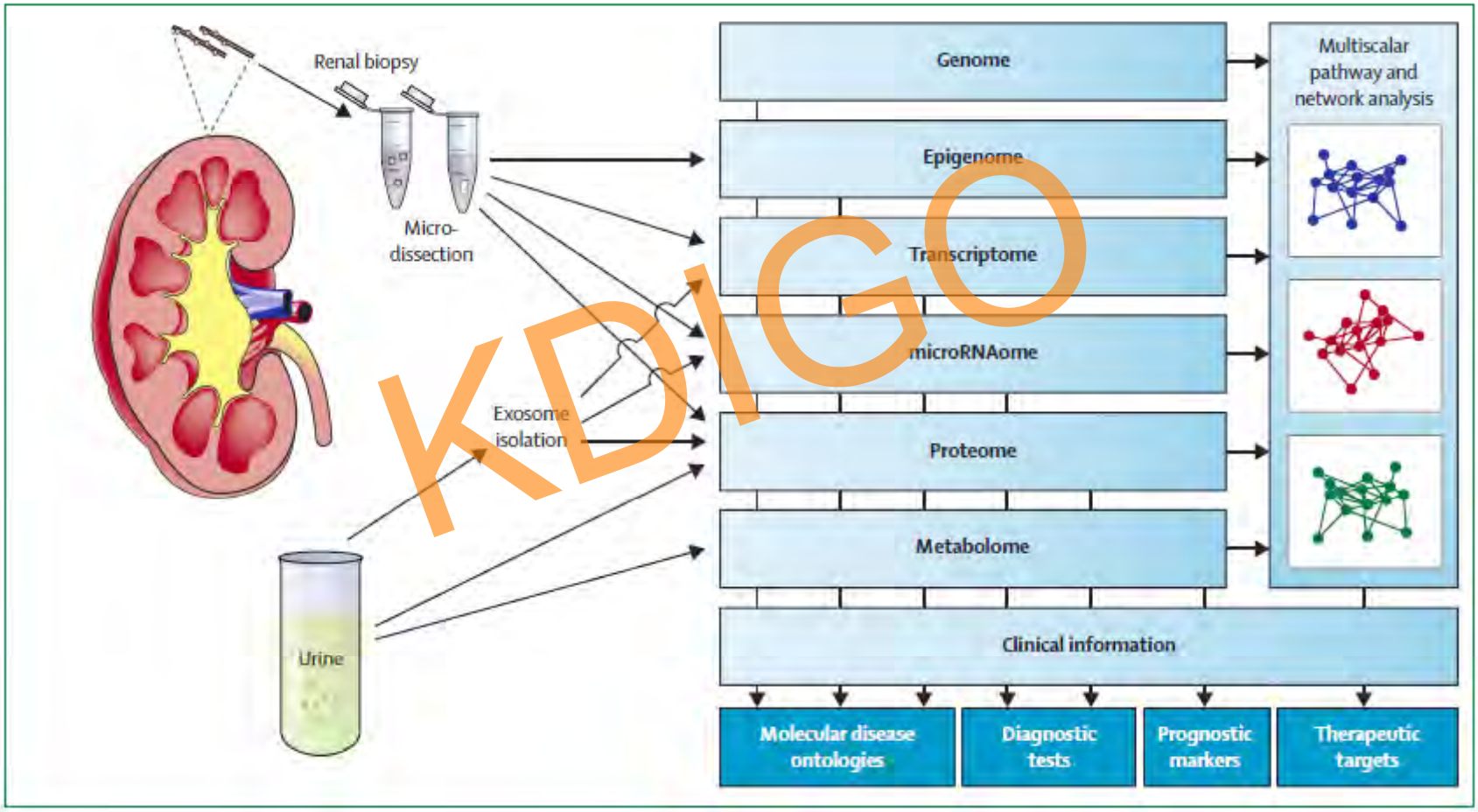
  → Reduced costs and turn-around times

- Successful application multigene panels/NGS for diagnostic:
  - Alport syndrome
  - Steroid-resistant nephrotic syndrome
  - Nephronophthisis - ciliopathies
  - Tubulopathies

- Whole exome and whole genome sequencing – new challenges

EURenOmics

Inherited Kidney Disorders: Omics Technologies



Devuyst O, et al. Lancet **383**, 2014

Research Programmes, Cohorts, Biorepositories

Fragmentation of patient-related information represents a major obstacle for rare disease research.

- EPIRARE: European Platform for Rare Disease Registries (www.epirare.eu)
- PARENT: Patient Registries Initiative (www.patientregistries.eu)
- RD-CONNECT: A platform connecting databases, registries, biobanks and clinical bioinformatics
- IRDiRC: International Rare Diseases Research Consortium (www.irdic.org)
- EURenOmics: European Consortium for High-Throughput Research in Rare Kidney Diseases
- ORPHANET: The portal for rare diseases and orphan drugs (www.orpha.net)
- EURORDIS: The European Organization for Rare Diseases (www.eurordis.org)
- Center for Mendelian Genomics (www.mendelian.org)
- …

Inherited Kidney Disorders: Health Policies

- *To ensure that approaches developed at highly specialized tertiary care centers can be adopted in facilities that cover the majority of population.*

- *To promote the implementation of clinically relevant genetic testing and to ensure delivery and impact of genetic information to physicians, patients and society in general.*

orphanet

EURORDIS
Rare Diseases Europe

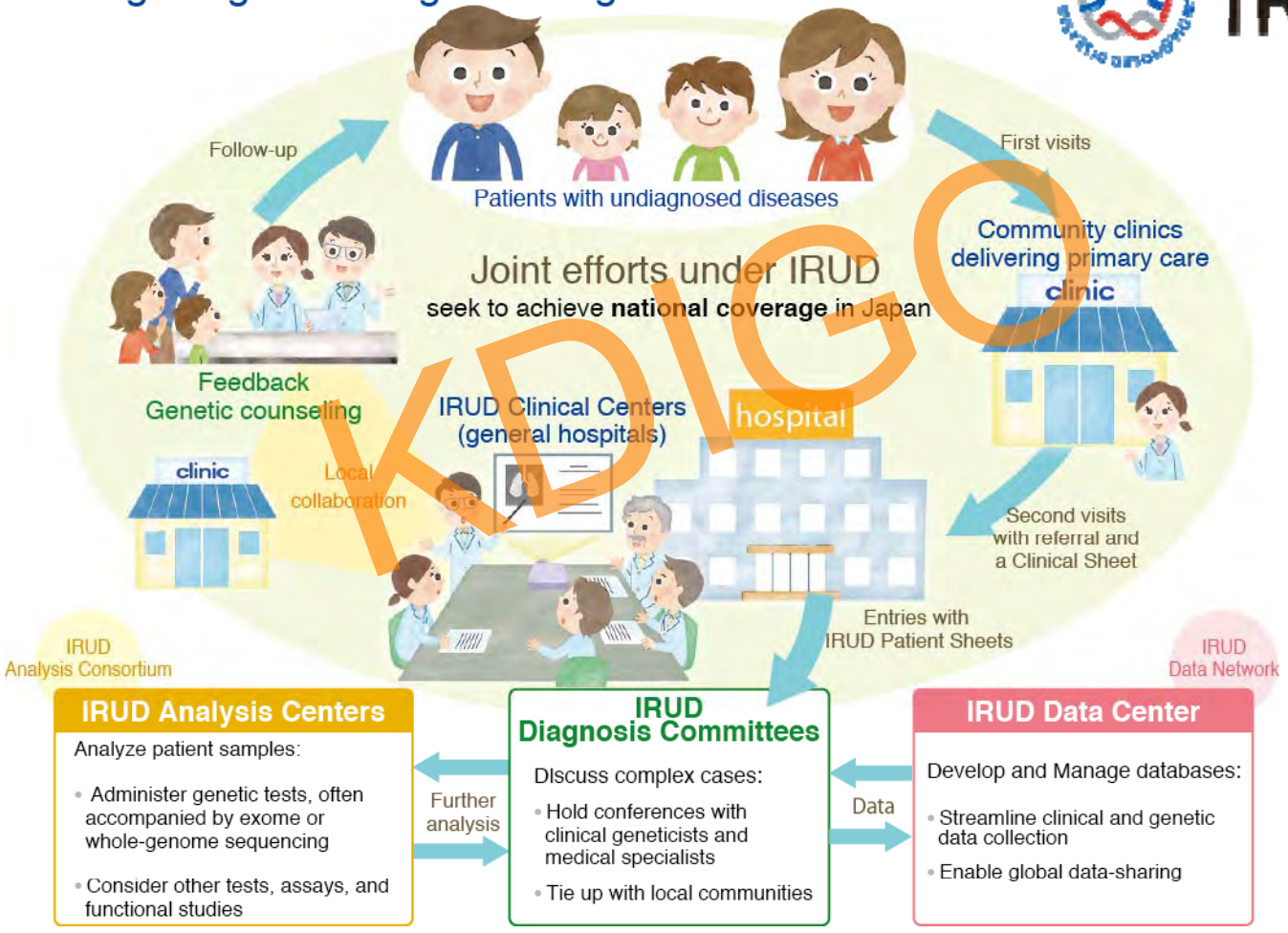
NORD
National Organization for Rare Disorders

Japan Agency for Medical Research and Development

AMED

Initiative on Rare and Undiagnosed Diseases (IRUD) : Integrating Knowledge for Diagnoses

IRUD



EDITORIAL

Patient Organizations and Research on Rare Diseases

Julie R. Ingelfinger, M.D., and Jeffrey M. Drazen, M.D.

N Engl J Med 2011; 364:1670-1671 | April 28, 2011 | DOI: 10.1056/NEJMe1102290

Comment on: Efficacy and safety of sirolimus in lymphangioleiomyomatosis.

CYSTINOSIS RESEARCH FOUNDATION

PKD FOUNDATION
Polycystic Kidney Disease

AIRG France
Association pour l'Information et la Recherche sur les maladies Rénales Génétiques

OHF
The Oxalosis & Hyperoxaluria FOUNDATION

The Lowe Syndrome Foundation

FEDERG

GEBERT RÜF STIFTUNG
WISSENSCHAFT.BEWEGEN

Common Elements in Rare Kidney Diseases:
Challenges and Topics

- Technological advances in diagnosis
- Consequences of improved genetic diagnosis
- Management of renal function, optimal pediatric transition care
- Challenges in trial design and conduct
- Development of novel biomarkers or surrogates
- Translation of new knowledge into clinical programs
- QOL issues
- Policy initiatives – various parts of the world

→ *Implementation of the resources in low-income countries ?*

Controversies Conferences examine what is known, what can be done with what is known and what needs to be known on topics of clinical relevance in nephrology.

- *Current practice recommendations*
- *Clinical questions and outstanding issues*
- *Research agenda*

- Gitelman Syndrome (Brussels, February 2016)
- Complement-Mediated Kidney Diseases (Barcelona, November 2015)
- Fabry Nephropathy (Dublin, October 2015)
- Nephropathic Cystinosis (Lisbon, December 2014)
- Autosomal Dominant Tubulointerstitial Kidney Disease (Boston, September 2014)
- Autosomal Dominant Polycystic Kidney Disease (ADPKD) (Edinburgh, January 2014)

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

KDIGO Controversies Conferences Methodology

- Scope of work – Topics – Roster (global)
- Plenary lectures covering major themes
- Balanced review of the literature: *areas of consensus, controversies, gaps of knowledge*
- Highlighting controversial issues
- Prioritized breakout questions – specific sessions
- Consensus report

Gitelman syndrome: consensus and guidance from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

OPEN

Anne Blanchard[1,2,3,4], Detlef Bockenhauer[5,6], Davide Bolignano[7], Lorenzo A. Calò[8], Etienne Cosyns[9], Olivier Devuyst[10], David H. Ellison[11], Fiona E. Karet Frankl[12,13], Nine V.A.M. Knoers[14], Martin Konrad[15], Shih-Hua Lin[16,17] and Rosa Vargas-Poussou[2,18]

Kidney International (2017) **91,** 24–33

Trans Assoc Am Physicians. 1966;79:221-35.

A new familial disorder characterized by hypokalemia and hypomagnesemia.

Gitelman HJ, Graham JB, Welt LG.

Clinical identification: 1966

PMID: 5929460 [PubMed - indexed for MEDLINE]

Genetics: 1996

article

Gitelman's variant of Bartter's syndrome, inherited hypokalaemic alkalosis, is caused by mutations in the thiazide-sensitive Na–Cl cotransporter

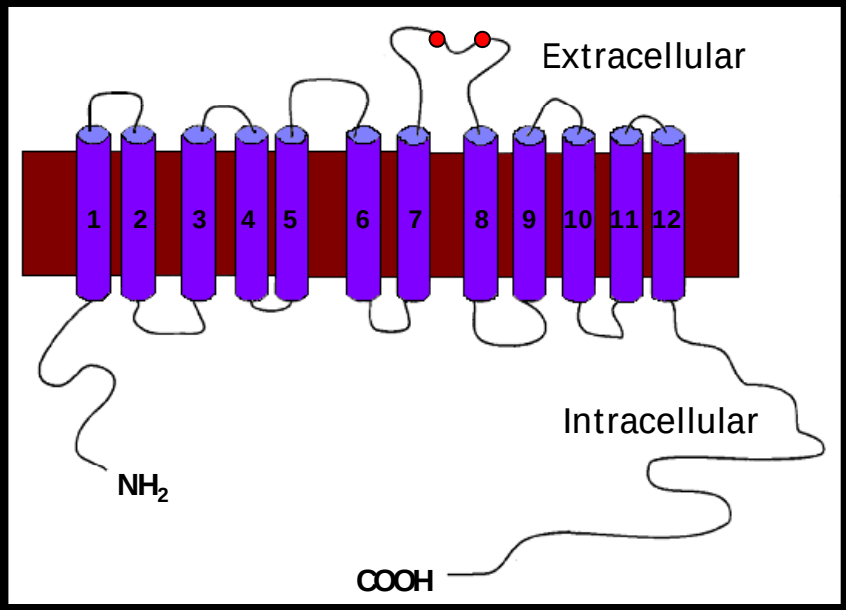
[1]Howard Hughes Medical Institute, Department of Genetics, Boyer Center for Molecular Medicine, [2]Section of Nephrology, Department of Medicine,

David B. Simon[1,2], Carol Nelson-Williams[1,2], Margaret Johnson Bia[2], David Ellison[2,3], Fiona E. Karet[1,2], Antonio Morey Molina[4], Ivar Vaara[5], Fujihiko Iwata[6], Howard M. Cushner[7], Marianne Koolen[8], Francisco J. Gainza[9], Hillel J. Gitelman[10] & Richard P. Lifton[1,2]

Gitelman's Syndrome

- The most frequent inherited tubulopathy : 1:40,000 (HZ 1% in Europe)
- Autosomal recessive transmission
- Mutations in *SLC12A3* coding for NCC (16q13)

- Phenotype similar to thiazide administration :
  - « Mild » salt-losing
  - Hypokalemia, hypomagnesemia
  - Inappropriate kaliuresis
  - Metabolic alkalosis
  - Hypocalciuria



BASIC RESEARCH www.jasn.org

J Am Soc Nephrol (2011) 22: 693-703

Spectrum of Mutations in Gitelman Syndrome

Rosa Vargas-Poussou,*†‡ Karin Dahan,§‖ Diana Kahila,*† Annabelle Venisse,*
Eva Riveira-Munoz,§ Huguette Debaix,§ Bernard Grisart,‖ Franck Bridoux,¶ Robert Unwin,**
Bruno Moulin,†† Jean-Philippe Haymann,‡‡ Marie-Christine Vantyghem,§§ Claire Rigothier,‖‖
Bertrand Dussol,¶¶ Michel Godin,*** Hubert Nivet,††† Laurence Dubourg,‡‡‡ Ivan Tack,§§§
Anne-Paule Gimenez-Roqueplo,*†‡ Pascal Houillier‡‖‖‖ Anne Blanchard,‡¶¶¶ Olivier Devuyst,§
and Xavier Jeunemaitre*†‡

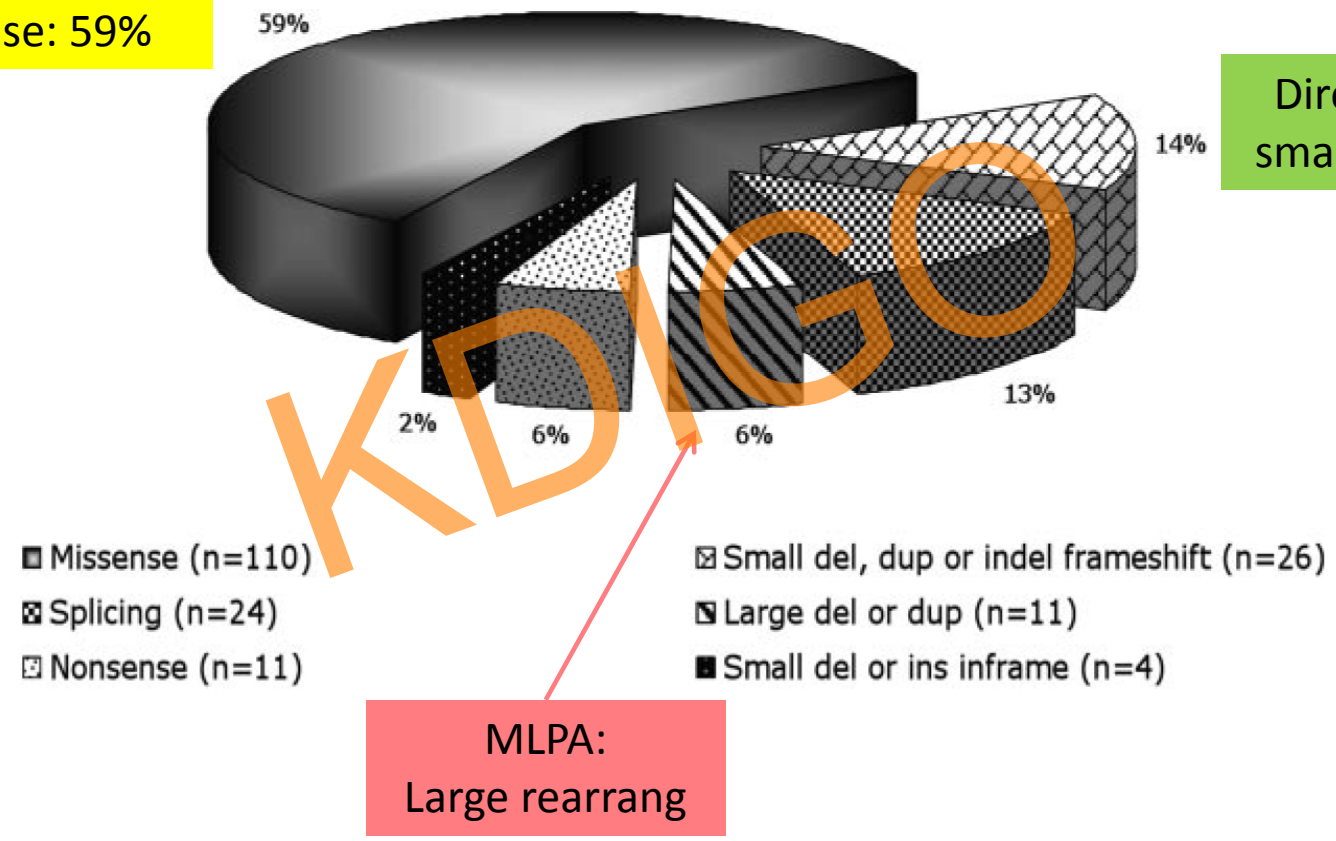
Largest cohort thus far: 448 unrelated patients from *EUNEFRON*

→ ***Direct sequencing of genomic DNA:***

- 70% (315/448): two mutations
  - 25% homozygous – 75% compound heterozygous
- 18% (81/448): one mutation
- 12% (52/448): no mutation

Spectrum of Mutations in Gitelman Syndrome

Missense: 59%



Direct seq: small ins/del

MLPA: Large rearrang

Largest cohort thus far: 448 unrelated patients

J Am Soc Nephrol (2011) 22: 693-703

Gitelman Syndrome: *Many Unsolved Issues*

- Diagnostic criteria and methods
- Clinical workup and follow-up
- Phenotypic heterogeneity
- Nature and severity of the
- Biochemical abnormalities and clinical manifestations
- Treatment and long-term consequences of the disease

Kidney Disease: Improving Global Outcome (KDIGO) controversies conference to assess the current state of knowledge related to GS, identify knowledge gaps, and propose a research agenda.

Gitelman Syndrome: Clinical Manifestations

Most common (>50% of patients)	Prominent (20 to 50% of patients)	Occasional (Less than 20%)	Rare (Case reports)
Salt carving	Fainting	Early onset (before age 6)	Seizure
Cramps, muscle weakness, pain	Polyuria	Failure to thrive	Ventricular tachycardia
Fatigue	Arthralgia	Growth retardation	Rhabdomyolysis
Dizziness	Chondrocalcinosis	Vertigo, ataxia	Blurred vision
Nocturia	Prolonged corrected QT interval	Carpopedal spasm, tetany	Pseudotumor cerebri
Thirst, polydipsia	Febrile episodes	Vomiting	Sclerochoroidal calcifications
Paresthesia, numbness		Constipation	
Palpitations		Enuresis	
Low blood pressure		Paralysis	

Positive Criteria for suspecting Gitelman Syndrome

- Chronic hypokalemia (<3.5 mmol/l) with renal potassium wasting
- Metabolic alkalosis
- Hypomagnesemia (<0.7 mmol/l) with renal magnesium wasting
- Hypocalciuria
- High plasma renin activity or levels
- Fractional excretion of chloride > 0.5%
- Low or normal-low blood pressure
- Normal renal ultrasound

Features against a Diagnostic of Gitelman Syndrome

- Use of thiazide diuretics or laxatives
- Family history of autosomal dominant kidney disease
- Absence or inconsistent hypokalemia in absence of substitutive therapy
- Absence of metabolic alkalosis
- Low renin values
- Urine: low urinary potassium excretion; hypercalciuria
- Hypertension, increased extracellular fluid volume
- Ultrasound: nephrocalcinosis, nephrolithiasis, unilateral or cystic kidneys
- Prenatal history of polyhydramnios, hyperechogenic kidneys
- Presentation before age 3 years

Gitelman Syndrome: Diagnostic

Identification of biallelic inactivating mutations in *SLC12A3*

Recommend: NGS-based gene panel to sequence at least *SLC12A3*, *CLCNKB*, and *HNF1B*.

In view of the rapid progress of genetic testing, hydrochlorothiazide testing is no longer recommended : related risks of acute volume depletion; limitations in patients taking medications affecting tubular transport processes; risk of acute interstitial nephritis and hypersensitivity reactions.
Unless significant proteinuria, renal biopsy is not necessary for the diagnosis of GS.

Gitelman Syndrome: Recognized Complications

Most of the clinical problems in GS are linked to chronic salt loss, hypokalemia, or hypomagnesemia.

Increasingly recognized complications:

- Chondrocalcinosis and sclerochoroidal calcifications
- Higher bone mineral density, decreased rate of bone remodeling
- Growth retardation, pubertal delay, and short stature
- Hypokalemic rhabdomyolysis
- Prolonged QT interval in 50%, increased risk for ventricular arrhythmias
- Glucose intolerance or insulin resistance or both
- Glomerular proteinuria due to abnormalities of the GBM
- Chronic kidney disease

→ ***Appropriate workup***

Gitelman Syndrome: Treatment

- ad libitum NaCl intake - ? benefit of pharmacological NaCl supplements
- Individualized lifelong oral potassium or magnesium supplementation
- If hypomagnesemia, magnesium supplementation should be considered first
- Advice on type of supplements (tolerability and bioavailability of Mg)

Targets: for potassium 3.0 mmol/l and magnesium 0.6 mmol/l

→ *Additional drugs if needed and adherence verified:*

- Potassium-sparing diuretics amiloride, spironolactone, potassium canrenoate, and eplerenone can be useful (both for potassium and magnesium depletion)
- Renin angiotensin system inhibitors
- Indomethacin - caution

Gitelman syndrome: consensus and guidance from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

OPEN

SUPPLEMENTARY MATERIAL

Table S1. Conversion table.
Table S2. Normal ranges of urinary calcium-creatinine ratio in children.
Table S3. Foods rich in potassium, with glucose, magnesium, and caloric content.
Table S4. Magnesium content by various salts.
Table S5. Foods rich in magnesium, with glucose, potassium, and caloric content.

+ List of drugs to avoid: HypoK and HypoMg

Supplementary Table 7: Sick day rules

Do not stop taking your medication unless advised by your doctor

Get your potassium and magnesium checked as soon as possible if you feel unwell for any reason

If you have diarrhea or vomiting, increase your fluid intake but ensure that you add a pinch of salt, or some electrolyte powder, to anything you drink

If you are vomiting and cannot keep anything down for 24 h or more, you should seek immediate medical advice

Also, seek immediate medical advice if you pass out/faint, or:

- become dizzy
- develop tingling or muscle weakness
- notice an irregular heartbeat (palpitations)
- have painful muscular spasms

and cannot relieve these symptoms with extra potassium/magnesium supplements

See your doctor if you notice any unusual symptoms, as your medication dosage might need altering; a simple blood test might be all that is needed

Quotes from Patients in Conference

GS can compromise school performance (e.g., absence, difficulty in concentration).

Low adherence to the supplements due to socioeconomic difficulties, lack of reimbursement, transition phase (pediatric – adult).

Antiandrogenic effects of spironolactone (inlc. gynecomastia, hirsutism, erectile dysfunction), particularly difficult in adolescents and young adults.

Aggravation of hypokalemia and hypomagnesemia during pregnancy: need for management plan involving nephrology and specialized obstetrics.

GS can compromise work performance. Fatigue makes working an 8-hour day impossible. Work shifts may be particularly difficult. Patients are afraid to disclose their condition because they fear losing their job.

Education - Patient Empowerment

Country/Region	Weblinks
Belgium	http://www.airg-belgique.org/
	https://www.facebook.com/AIRG-Belgique-107206356021095/?fref=ts
Europe	http://federg.org/
France	http://www.airg-france.fr/
	http://www.soc-nephrologie.org/marhea/
	http://www.soc-nephrologie.org/nephrogone/
	http://www.chu-toulouse.fr/-centre-de-reference-des-maladies-renales-rares-
Germany	http://www.orpha.net/static/DE/gitelmansyndrom.html
	http://www.kindernetzwerk.de/.../Krankheitsuebersichten-bartter-syndrom.pdf
Italy	http://www.iss.it/cnmr/index.php?lang=1
	http://associazionebarttergitelman.weebly.com
UK	http://rarerenal.org/patient-information/gitelman-and-type-3-bartter-syndromes-patient-information/
	http://rarerenal.org/rare-disease-groups/hypokalaemic-alkaloses-rdg/
	http://www.gitelmansyndrome.co.uk
USA	http://rarediseases.org/rare-diseases/gitelman-syndrome/
	http://ghr.nlm.nih.gov/condition/gitelman-syndrome
	http://barttersite.org/category/gitelmansyndrome/

Research Agenda (I)

Diagnostic and biomarkers

- Urinary exosomes, including assessment of NCC and pNCC
- Urine values or creatinine ratios establishing wasting for potassium, sodium, chloride (spot)
- Value of ionized versus total magnesium measurement

Clinical aspects

- Blood pressure control, hypertension (incidence, cause, etc.)
- Cardiovascular complications: conduction, myocardium, predictive effort ECG, reproducibility, age effect, QT interval, and electrolyte levels
- Metabolic complications: glucose tolerance, role of magnesium balance

Patient-related outcomes

- Quality of life, disability, sociology, perception of symptoms
- Disability scores
- Self-management techniques

Genetic aspects

- Genetic heterogeneity, causal genes, or modifier genes
- Assessment of the pathogenicity of variants
- Prevalence of *SLC12A3* mutations in exome database
- Effect of the carrier state, geographic variations
- Genotype-phenotype correlations, including effect of triple *SLC12A3* mutations
- Sex effect
- Establishing prevalence of the disease and the carrier state

Kidney International (2017) **91,** 24–33

Research Agenda (II)

Intervention

- Effect of high NaCl supplementation
- Effect of sport, increased muscular mass, potassium supplementation after exercise
- Define optimal target values for potassium and magnesium

Outcome and natural history

- Registry, biobanking
- Growth, activity, sports
- Glucose intolerance and metabolic profile
- Renal function, concentration defect, proteinuria, chronic kidney disease, cysts
- Cardiovascular complications
- Rare complications: pseudotumor cerebri, pectus excavatum, link with autoimmunity

Mother and child

- Pregnancy and fetal development

Monitoring

- Improve monitoring: noninvasive, frequency, possible trans-cutaneous measurements

Kidney International (2017) **91,** 24–33

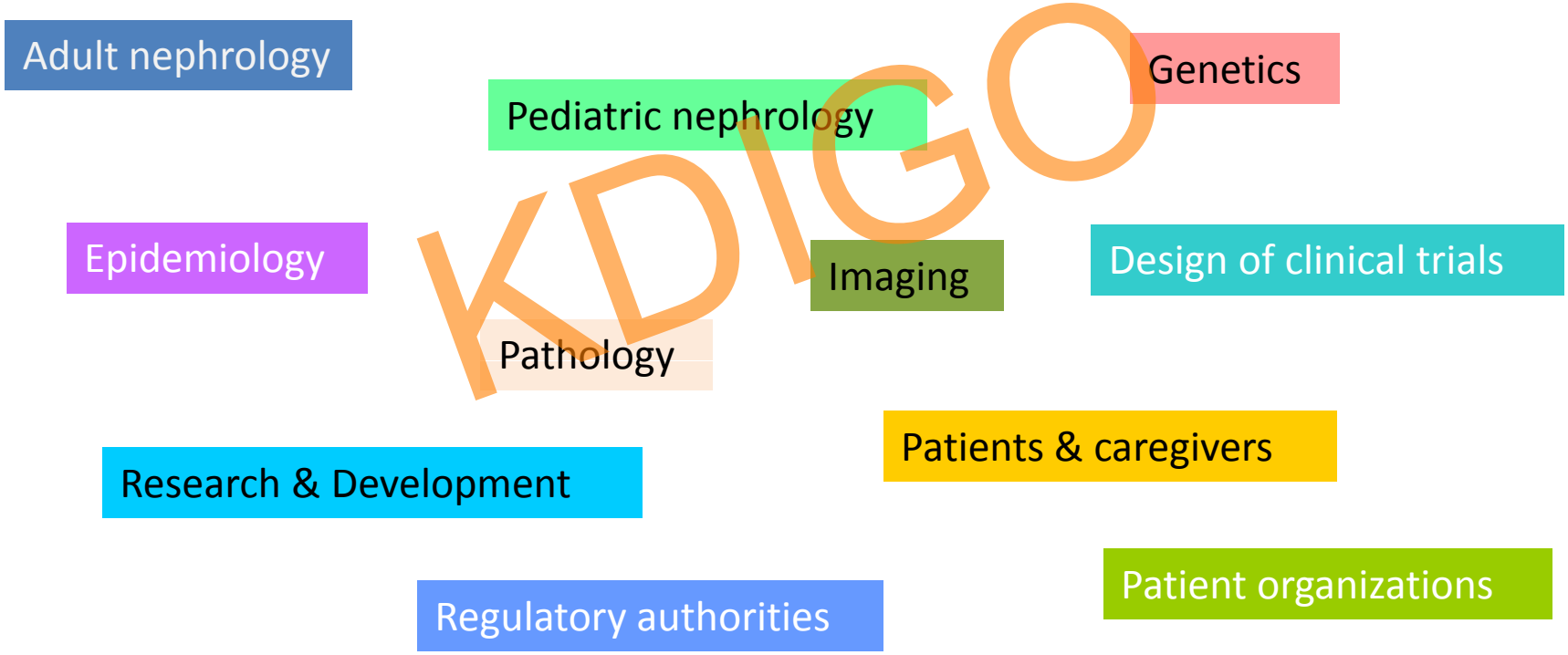
KDIGO Amsterdam, June 16-19, 2016

Common Elements in Uncommon Kidney Diseases

- Address common clinical and patient issues across the field of rare kidney diseases.
- Identify controversial topics and outstanding knowledge gaps
- Propose a research agenda to resolve these issues
- Determine whether there is sufficient evidence base for providing guidance in clinical management
- Systematically integrate patient perspectives

KDIGO Controversies Conference
Common Elements in Uncommon Kidney Diseases

Global panel – Multidisciplinary expertise



Common Elements in Rare Kidney Diseases: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

Ségolène Aymé[1], Detlef Bockenhauer[2], Simon Day[3], Olivier Devuyst[4], Lisa M. Guay-Woodford[5], Julie R. Ingelfinger[6], Jon B. Klein[7], Nine V.A.M. Knoers[8], Ronald D. Perrone[9], Julia Roberts[10], Franz Schaefer[11], Vicente E. Torres[12], Michael Cheung[13], David C. Wheeler[14], and Wolfgang C. Winkelmayer[15]; for Conference Participants[*]

[*]Other conference participants: Aris Angelis, Corinne Antignac, Kyongtae Bae, Carsten Bergmann, Anthony J. Bleyer, Marjolein Bos, Klemens Budde, Katherine Bull, Dominique Chauveau, Martina Cornel, Etienne Cosyns, Jane de la Fosse, Jie Ding, Bruno Flamion, Susie Gear, Timothy H.J. Goodship, Paul Goodyer, Oliver Gross, Nicole Harr, Peter C. Harris, Tess Harris, Julia Höfele, Marie C. Hogan, Ewout Hoorn, Shigeo Horie, Clifford E. Kashtan, Larissa Kerecuk, Robert Kleta, Martin Konrad, Craig B. Langman, Segundo Mariz, Gayle McKerracher, Annet Nieuwenhoven, Dwight Odland, Eric Olinger, Alberto Ortiz, York Pei, Yves Pirson, Brian L. Rayner, Giuseppe Remuzzi, Daniel Renault, Rémi Salomon, Aude Servais, Richard J. Smith, Neveen A. Soliman, Bénédicte Stengel, Marjolein Storm, Roser Torra, William van't Hoff, Rosa Vargas-Poussou, Elizabeth Vroom, Christoph Wanner, Hui-Kim Yap

Amsterdam, June 16-19, 2016

Increasing Role of Genetic Testing in Diagnosis

- Confirming clinical diagnosis
- Differentiating heterogeneous disorders
- Determining appropriate treatment
- Guiding decisions about family planning
- Determining the cause of unexplained familial renal disorders
- Identifying risk factors for recurrence in kidney transplantation
- Evaluating family members' suitability for kidney donation
- Prompting evaluation for extrarenal features

Presymptomatic genetic screening

- Counseling about reproductive options, respect of individual beliefs
- Consequences for health insurance

Implementing access to diagnostic services in low-income regions

- Telemedicine, mini-gene panels,…

Helping Patients in Healthcare Systems with Differing Resources

Healthcare systems	
Well-resourced	**Low-resourced**
Early access to financial support for eligible patients. Provide patients with help in navigating the system.	**Knowledge of available networks and opportunities such as grants or voluntary exchange programs**
Multidisciplinary care • Joined-up appointments • Multi-modal resources • Face-to-face, groups, workshops • Research, trials, registries • Lots of liaison: teams, hospitals, education, employer	**Maximum use of technology and links with Specialized Centers** • Engage routine resources • Make as much information available as possible • Engage key groups/systems already available, such as church, community groups and leaders, or schools
Information • Websites • Webinars • Pamphlets • Podcasts • Films • Audio • Social media	**Information** • Simple film, audio and print information targeting visual or auditory learners may be most effective
Patient associations • Involved at every level • Provide support • Research and development • Registries • Advice • Financial • Strategic as well as supportive • Seek representativeness	**Facilitate access globally to information and learning** • Proactively seek connections with groups or individuals affiliated with Specialized Centers

Challenges in Clinical Study Design

Limitations for research in rare kidney diseases: small sample sizes, need for long duration of follow-up, paucity of outcome measures.

- Study design considerations
- Prognostic and predictive enrichment strategies to recruit patients
- Disease entities defined by common pathophysiological mechanisms

  → extrapolation of drug MOA
- Patient insights and input are essential for designing clinical trials
- Outcome measures, kidney-specific PROMs

Possible Quantitative Renal Endpoints for Clinical Trials in Rare Kidney Diseases

Condition	Endpoint	Minimum observation period
Glomerular diseases	Percent or absolute reduction in albuminuria	3 months
Tubulopathies	Mean serum electrolyte levels, urine osmolality, urine electrolyte levels	3 months
	Daily urine volume	3 months
	Incidence of electrolyte excess episodes requiring intervention	6 months
	Composite score reflecting physical functions (e.g., muscle strength, muscle cramps, headaches)	6 months
	Incidence of clinical events related to electrolyte imbalance	1 year
	Children: Change in length/height Z score	1 year
Autosomal dominant polycystic kidney disease	Percent change in total kidney volume	2-5 years
Chronic kidney disease (any etiology)	*Prevention:* Time to CKD G3	2-3 years
	Slowing of progression: > 30% or > 40% GFR loss. Consider combining with start of RRT	2-3 years

CKD, chronic kidney disease; GFR, glomerular filtration rate; RRT, renal replacement therapy.

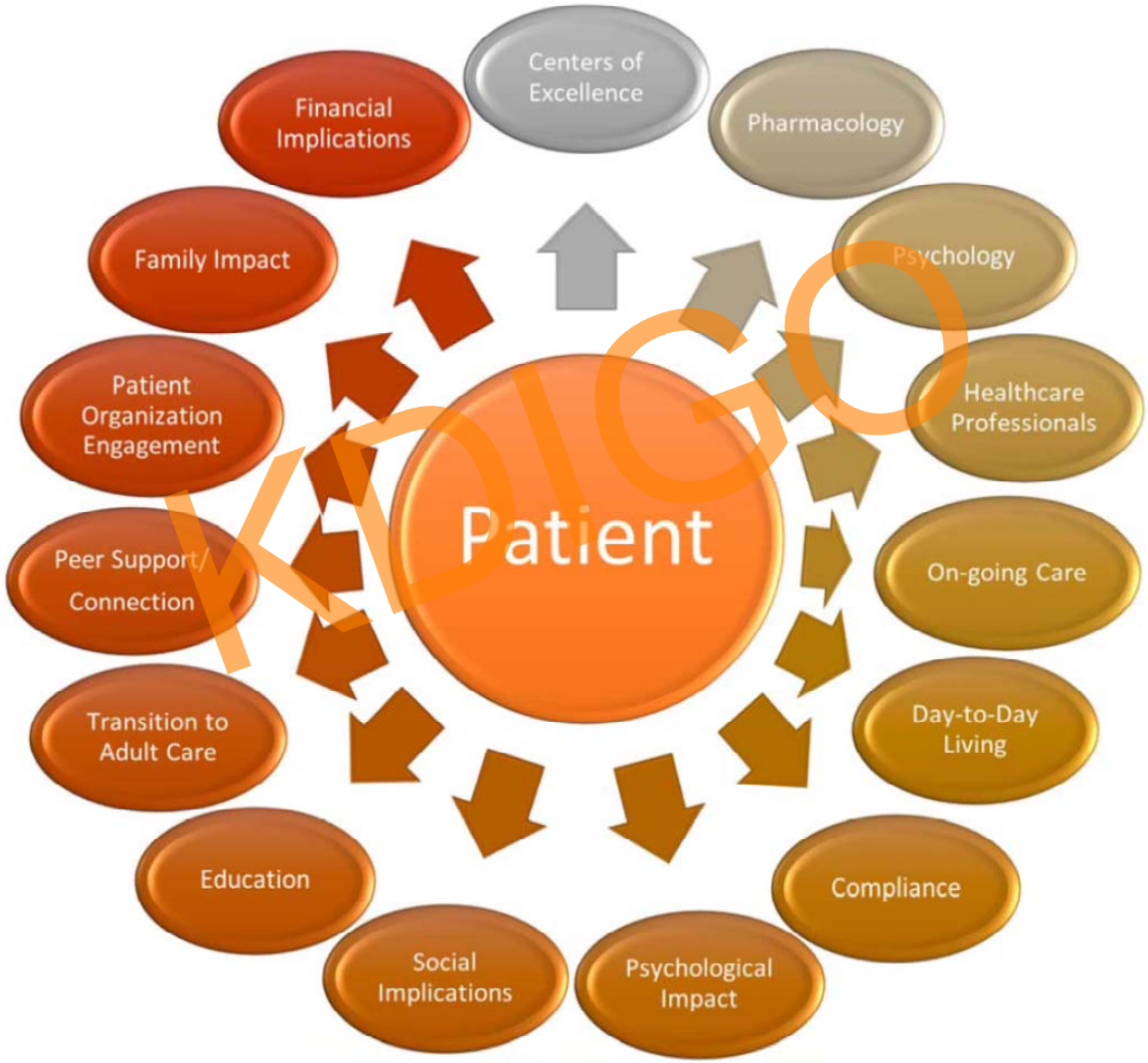
TRANSLATION OF RESEARCH TO CLINICAL CARE

- Specialized Centers, registries and biobanks
- Instruments and standards:
  - Informed consent
  - Standard of care for each disease
  - Patient-reported outcome measures
- Providers and patients: training, awareness, empowerment
- Psychological support for patients and families
- Patient organizations

Quality criteria for Centers of Excellence/Expertise/Reference

Standard	Metrics for Assessment
Comprehensive care	
Renal and extrarenal care specific for the disorder Genetics, including genetic testing Dietetics Psychosocial support Coordinated by dedicated team leader	Availability of ancillary services and non-renal specialties needed for the specific disorder
Expertise	
Care is coordinated by a multidisciplinary team with relevant expertise in the disorder	Publication record, number of patients with specific disease treated
Clinical trials	
Patients should be offered the opportunity to participate in clinical trials relevant to the specific disorder	Involvement in clinical trials for the specific disorder (if any)
Education	
Creation and distribution of information material for patients, families, and professionals, as well as education and training	Availability of informational material, courses, lectures, and training
Patient involvement	
Direct patient involvement to ensure center serves the needs of the patient	Involvement of patients and patient organizations in establishing and managing the center
Facilitate transition from pediatric to adult care	Provision of multidisciplinary age-appropriate support services

Issues with Patient Care in Rare Diseases



Thank you for your attention