CONTROVERSIES AND CONSENSUS IN RARE KIDNEY DISORDERS

Prof. Dr. med. Olivier Devuyst
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

- Family secrecy
- Inadequate information
- Ambivalence towards diagnosis
- Uncertainty, anxiety
- Anger, depression
- Denial
- Reproductive decisions
- Parental blame

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

Kidney Function and Homeostasis

Rare Inherited Kidney Disorders: Opportunities
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.

The price of sequencing a whole human genome hovers around $5,000 and is expected to drop even lower.
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
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.

![Logos of Orphanet, EURORDIS, and NORD](image-url)
Initiative on Rare and Undiagnosed Diseases (IRUD): Integrating Knowledge for Diagnoses
Patient Organizations and Research on Rare Diseases

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

Comment on: Efficacy and safety of sirolimus in lymphangioleiomyomatosis.
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)
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

Anne Blanchard¹,²,³,⁴, Detlef Bockenhauer⁵,⁶, Davide Bolignano⁷, Lorenzo A. Calò⁸, Etienne Cosyns⁹, Olivier Devuyst¹⁰, David H. Ellison¹¹, Fiona E. Karet Franklin¹²,¹³, Nine Y.A.M. Knöers¹⁴, Martin Konrad¹⁵, Shih-Hua Lin¹⁶,¹⁷, and Rosa Vargas-Poussou²,¹⁸
A new familial disorder characterized by hypokalemia and hypomagnesemia.

Gitelman HJ, Graham JB, Welt LG.

PMID: 5929460 [PubMed - indexed for MEDLINE]

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

David B. Simon1,2, Carol Nelson-Williams1,2, Margaret Johnson Bia2, David Ellison2,3, Fiona E. Karet1,2, Antonio Morey Molina4, Ivar Vaara5, Fujihiko Iwata6, Howard M. Cushner7, Marianne Koolen6, Francisco J. Gainza9, Hillel J. Gitelman10 & Richard P. Lifton1,2
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
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

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**

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

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Weblinks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td><a href="http://federg.org/">http://federg.org/</a></td>
</tr>
</tbody>
</table>
| Germany        | [http://www.arpha.net/static/DE/gitelmansyndrom.html](http://www.arpha.net/static/DE/gitelmansyndrom.html)  
  [http://associazionebarttergitelman.weebly.com](http://associazionebarttergitelman.weebly.com) |
  [http://rarerenal.org/rare_disease_groups/hypokalaemie_alkalose_rdg/](http://rarerenal.org/rare_disease_groups/hypokalaemie_alkalose_rdg/)  
  [http://www.gitelmansyndrome.co.uk](http://www.gitelmansyndrome.co.uk) |
  [http://barttersite.org/category/gitelmansyndrome/](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
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 transcutaneous measurements
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
Common Elements in Rare Kidney Diseases: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

Ségolène Aymé¹, Detlef Bockenhauer², Simon Day³, Olivier Devuyst⁴, Lisa M. Guay-Woodford⁵, Julie R. Ingelfinger⁶, Jon B. Klein⁷, Nine V.A.M. Knoers⁸, Ronald D. Perrone⁹, Julia Roberts¹⁰, Franz Schaefer¹¹, Vicente E. Torres¹², Michael Cheung¹³, David C. Wheeler¹⁴, and Wolfgang C. Winkelmayer¹⁵: for Conference Participants*

*Other conference participants: Aris Angelis, Corinne Antignac, Kyongtae Bac, Carsten Bergmann, Anthony J. Bleyer, Marjolein Bos, Klemens Budde, Katherine Bull, Dominique Chauveau, Martina Cornel, Etienne Cosyns, Jane de la Rosse, 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 McKernacher, 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

<table>
<thead>
<tr>
<th>Healthcare systems</th>
<th>Well-resourced</th>
<th>Low-resourced</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early access to financial support for eligible patients. Provide patients with help in navigating the system.</strong></td>
<td></td>
<td>Knowledge of available networks and opportunities such as grants or voluntary exchange programs</td>
</tr>
</tbody>
</table>
| **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 |
| **Information** | Websites  
Webinars  
Pamphlets  
Podcasts  
Films  
Audio  
Social media | • 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 |
| **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 pathophysiologic 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

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

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

10% of the world’s population has a rare disease.