KDIGO Controversies Conference
Nephropathic Cystinosis
How can we build on existing registries? Would a global registry improve patient outcomes

Lisbon, Portugal Dec 11-13, 2014

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Chief, Pediatric Nephrology
Advancing Rare Disease Research: The Intersection of Patient Registries, Biospecimen Repositories, and Clinical Data, Office of Rare Diseases, NIH

**Workshop Objectives:** To discuss the development of an infrastructure for an Internet-based platform with common data elements utilizing a federated rare disease registry able to incorporate:

- Existing rare disease registries and any other useful patient registries
- Patient organizations with no registry looking to establish one
- Patients with no affiliation with a support group looking to belong to a registry
Expected Outcomes

- To gain acceptance of the concept of a federated rare disease patient registry by as many curators of patient registries and other stakeholders as possible and to gain their participation in creating this patient registry. Participating stakeholders will agree on a strategy to harmonize standardized common data elements, vocabulary, and open source software to enable the exchange of data and information to facilitate research collaborations.
Introduction to Objectives for the Collaborative Rare Diseases Registry (CRDR)

- Developing the Rare Diseases Registry
- Patient and Research Advocate Engagement
- Structure and Function of a Collaborative Rare Disease Patient Registry
- The National Health Information Network and its Implications for a National Rare Disease Patient
I. Standards, Informatics, and Technology

• Support for Compatibility and Interoperability
• Data Standards in Rare Disease Registries
  – Common Data Elements (CDEs) & terminology for sharing
• Global Data Aggregation: Global Unique Identifier (GUID) assigned to each patient for tracking
II. Biospecimens/Biorepositories

- Challenges and Obstacles Obtaining Rare Disease Specimens and the Use of Registries
- Rare Disease Biospecimens: Quality and Accessibility Challenges
- Rare Disease Biorepositories and Registries: The Need for Collaborative and Novel Approaches
- The Use of Patient Registries to Increase Procurements of Rare Diseases Biospecimens
III. Clinical Research, Patient Care, and Disease Management

- Role of Rare Disease Registries in Clinical Research
- Regulatory and Other Governmental Influences on Clinical Research
- Patient Registries and their Role in Understanding Health Outcomes
- Data and Test Result Validation: Reporting Research Data and Clinical Test Results to Patients (Researcher and Patient Perspectives)
IV. Patient Participation and Outreach Activities/Patient Advocacy

• Patient Advocacy Groups and Patient Registries: An Overview, NORD
• The Role of Patient Advocacy Groups in Establishing Common Infrastructure
• Legal/Bioethical Issues in Medical Research and Release of Genetic Information
V. Human Subjects: Bioethical and Legal Issues for Clinical Studies

• Human Subjects: Ethical and Legal Issues/45 CFR 46, Office of Human Protection, NIH

• Legal/Bioethical Issues in Medical Research and Release of Genetic Information
Registry Stewardship

• **Registry Coordinator:** overall manager & point person for interface with stakeholders

• **Registry Curator:** genetics experienced, oversees patient data entry, monitors investigator requests for de-identified data or specimens

• **Scientific/Medical Advisory Board:** assist with ethical & data protection, research & interface with advocacy stakeholders

• **Data Management Governance** is critical
NIH/NCATS GRDR℠ Program
Global Rare Diseases Patient Registry Data Repository

1. Patients join a registry and provide health information
2. Registry managers de-identify collected patient data and biospecimens and assign GUID
3. De-identified patient data is shared with the GRDR program
4. Patient data linked to biospecimens via the GUID interfacing with RD-HUB
5. GRDR aggregates, maps data to CDEs & national standards, integrates patient clinical information and provides access to approved researchers
6. Researchers conduct various biomedical studies within & across diseases
7. Registry owners notify identified participants and directed to study PI

Linking to other databases
Established Registries & Rare Disease Databases

• Import data from existing registries into GRDR repository: Federated model
• Provides larger opportunity for sharing of de-identified data to research community
• Use existing surveys, informed consent, research project applications, etc. via pilot participation: Nephcure
• All organizations contributing de-identified data will retain ownership of data & complete control of their registry
Barriers to Establishing a Global Registry for Cystinosis

• Advocacy organization engagement/trust
• Financial metrics for sustainability
• Transparency of stewardship & oversight
• Establishing & maintaining Team Science collaboration
• Metrics of productivity: advocacy group feedback, family/patient improvements, scientific publications/grants, clinical trials
• Deliverables to industry & funding agencies: trial enrollment & completion
Research Functions that a Rare Disease Patient Registry Enables

• Knowledge dissemination: distribution of information to patients and their clinicians on new therapies, best practices, and safety issues.
• Patient recruitment: providing patient population information instructive in designing trial protocols that optimize size and length of trials.
• Clinical epidemiology: population descriptive statistics, natural history of disorders, medical practice variation.
• Clinical effectiveness: evaluation of the effects of preventive, diagnostic, and curative interventions delivered in real-world settings.
• Safety monitoring: orphan drugs are generally not tested in large Phase III studies, which makes the need for post-marketing safety surveillance using registries even more important than conventional drugs.
• Quality and Outcomes Improvement: enhancing patient outcomes by standardizing practice and reducing practice variation; CDEs common data elements.
• Genotype/Phenotype Association Studies: the registry provides phenotypic data which can be linked to genetic and other exposure data.
• Linkage to Biospecimens and Biorepositories: to detect phenotypic correlates of cell and tissue biology.
This website, designed for researchers, clinicians, policymakers and industry professionals, is a key component of the interactive nature of the Cure Cystinosis International Registry (CCIR) vision. CCIR provides clinical resources for the research community. Registered providers have access to the following website features:

**Explore Responses** - View de-identified aggregate clinical data from the entire patient registry database to learn about disease burden.  
*(Example: See how many registrants answered ‘Yes’ to ‘Has the affected person ever had a kidney transplant?’)*

**Filter Responses** - Perform limited searches of the registry in order to identify target populations for trial/study planning and recruitment.  
*(Example: See how many males answered ‘Yes’ to ‘Has the affected person ever had a kidney transplant?’)*

**Query Data** - Request a custom registry report from the Curator that includes results from more refined or complex searches, and also information such as participant location or profile curation status.  
*(Example: See a comparative analysis between different countries of males who have ever had a kidney transplant)*

**Recruit for Clinical Trials** - Post an IRB approved clinical trial recruitment material on the CCIR website or request for the material to be emailed to targeted population.
The ESPN/ERA-EDTA Registry

Cohort: 600 new pts starting RRT per year; 10,000 pts total

Central Office: Biostatistics & Epidemiology department, Amsterdam Medical Center (head: Kitty Jager)

Funding: €200k/year (ERA-EDTA, ESPN; occasional industry, EU grants)

Staffing: 1 Post-Doc (coordinator), 1-2 PhD students, 1 data manager + visiting fellows (junior ped nephrologists; 2 wks-1y) 14 fellows hosted in past 5 years
The ESPN/ERA-EDTA Registry

„Meta-Registry“ Concept:
Annual data collection from European national RRT registries

Variable extent of data items collected, according to availability
and national registry policies

Transmission of de-identified data through national contacts

Direct online data submission
also possible, used by small countries

Data quality checks and feedback

Annual reporting / benchmarking to participating countries
Data Submission and Integration

- Periodic **retrieval of data extracts** from existing national and transnational patient registries
- Variables will be mapped to central database
- **Online data entry** menu for use by centers not reporting to existing national registries
Data Privacy & Regulatory Framework

Rules of data exchange to be laid down in Data Transfer Agreement

- Data transmitted to IPNA Registry shall not contain any information that would allow to identify an individual patient or even the treatment center.

- Only National Registry representative able and conditionally authorized to relay a data entry to the treatment center.

- Only local investigators can re-identify a patient from coded entry.
IPNA Registry: Expected Output

Initial focus of analysis:

Global **socioeconomic context** determining children’s access to RRT
Country-specific RRT incidence, modality choices and outcomes vs. **key economic, developmental and health indices:** GDP, Human Development Index, total/public health expenditure, childhood mortality ...

Results will enable informed **discussions with stakeholders:**
- Hospital administrators
- Health care providers
- Policy makers
- Advocacy groups
- Pharmaceutical industry
"Mature" phase of Registry:

- Data collection sufficiently large and detailed to analyze rare diseases, therapies and clinical topics impossible to study on national or regional level

- Registry will be source of information on RCT feasibility, facilitated identification of pediatric D and Tx trial populations

→ Increased pharma interest to support IPNA activities

- Global research infrastructure created by IPNA Registry project expected to prompt further global research initiatives: e.g. clinical practice surveys, novel rare kidney disease registries
Proposed Governance

- IPNA Council
- Scientific Advisory Board
- Executive Committee
- Registry Office
- IPNA Registry Committee
  - Nat’l registry representatives
  - IPNA leadership
- Coordinator, SAB Chairs
Frost Valley YMCA Kidney Summer Camp
http://www.frostvalley.org
CEMARA cystinosis registry

P Niaudet, C Antignac, E Levchenko, F Emma,
P Landais, W van’t Hoff
• A registry exists in UK (William Van't Hoff)

• A group including Corinne Antignac, Elena Levchenko, William Van't Hoff, Francesco Emma and Patrick Niaudet worked together to create an European registry

• The registry was created in the CEMARA database with Paul Landais

• Help from AIRG and Orphan Europe
Cystinosis database

- Collect individual data of cystinotic patients, including late onset forms
- Long-term evolution in adulthood
- Therapies with efficacy and tolerance
- Initial data
- Clinical evaluation
- Therapies
- Side-effects
- Genetic data
### Family

- Country of father: France
- Country of mother: France
- Consanguinity: Yes
- Height of father: 183 cm
- Height of mother: 155 cm
- Another sibling affected with cystinosis: No

### At time of diagnosis

- Date of diagnosis: 16/06/2000
- Age: 43 jours
- Height: cm
- Weight: kg
- Corneal deposits: No
- Clinical signs of rickets: No
- Other symptoms:

### Cystine leucocyte content before treatment

- Content: 4,700 mmol/1/2 cystine/mg proteins

### Fanconi syndrome

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natremia</td>
<td>136,000</td>
<td></td>
</tr>
<tr>
<td>Calcemia</td>
<td>2,680</td>
<td></td>
</tr>
<tr>
<td>Creatininemia</td>
<td>29,000</td>
<td>μmol/l</td>
</tr>
<tr>
<td>Creatinuria</td>
<td>2,400</td>
<td>mmol/l</td>
</tr>
<tr>
<td>Urine albumin/creatinine ratio</td>
<td>0,254</td>
<td>g/mmol</td>
</tr>
<tr>
<td>Glycosuria</td>
<td>4,300</td>
<td>mmol/l</td>
</tr>
</tbody>
</table>

### Bicarbonates

- Proteinuria: 0,610 g/l
- Albumin: mmol/l
- Calcium: 8,740 mmol/l

### Cysteamine treatment

- Date of start of cysteamine treatment: 08/07/2000
- Phosphocysteamin: Yes
- Cystagon: Yes
Follow-up before RRT
### Initial Data

<table>
<thead>
<tr>
<th>Field</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date at Review</td>
<td>DD/MM/YYYY</td>
</tr>
<tr>
<td>Weight</td>
<td>kg</td>
</tr>
<tr>
<td>Height</td>
<td>cm</td>
</tr>
<tr>
<td>Blood pressure maxima</td>
<td>mm Hg</td>
</tr>
<tr>
<td>Blood pressure minima</td>
<td>mm Hg</td>
</tr>
<tr>
<td>Signs of rickets</td>
<td>Yes, No, Unknown</td>
</tr>
<tr>
<td>Cystine leucocyte content</td>
<td>nmol 1/2 cystine/mg proteins</td>
</tr>
<tr>
<td>Dosage technique</td>
<td>Unknown</td>
</tr>
<tr>
<td>Residual cysteamine blood level</td>
<td>μmol/l</td>
</tr>
</tbody>
</table>

### Renal

<table>
<thead>
<tr>
<th>Field</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natremia</td>
<td>mmol/l</td>
</tr>
<tr>
<td>Kalemia</td>
<td>mmol/l</td>
</tr>
<tr>
<td>Bicarbonates</td>
<td>mmol/l</td>
</tr>
<tr>
<td>Calcemia</td>
<td>mmol/l</td>
</tr>
<tr>
<td>Phosphoremia</td>
<td>mmol/l</td>
</tr>
<tr>
<td>Creatininemia</td>
<td>mmol/l</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>ml/min/1.73 m²</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>g/l</td>
</tr>
<tr>
<td>Creatininuria</td>
<td>mmol/l</td>
</tr>
<tr>
<td>Urine protein/creatinine ratio</td>
<td>g/mmol</td>
</tr>
<tr>
<td>Glucosuria</td>
<td>mmol/l</td>
</tr>
<tr>
<td>Calcium</td>
<td>mmol/l</td>
</tr>
<tr>
<td>Calcium/creatinine ratio</td>
<td>mmol/mmol</td>
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</tbody>
</table>

### Eyes

<table>
<thead>
<tr>
<th>Field</th>
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<tbody>
<tr>
<td>Photophobia</td>
<td>Yes, No, Unknown</td>
</tr>
<tr>
<td>Visual Impairment</td>
<td>Yes, No, Unknown</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>Yes, No, Unknown</td>
</tr>
<tr>
<td>Ophthalmologic examination</td>
<td>Yes, No, Unknown</td>
</tr>
<tr>
<td>Side-effects of eye drops</td>
<td>Yes, No, Unknown</td>
</tr>
</tbody>
</table>

### Endocrine

<table>
<thead>
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<th>Field</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Pubertal staging pubic hair (Tanner)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Genitalia (Tanner)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Menarche</td>
<td>Yes, No, Unknown</td>
</tr>
<tr>
<td>Age at Start</td>
<td>Unknown</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Yes, No, Unknown</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>Yes, No, Unknown</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Yes, No, Unknown</td>
</tr>
<tr>
<td>Product</td>
<td>Date at start</td>
</tr>
<tr>
<td>-----------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Gastric tube</td>
<td>22/11/2000</td>
</tr>
</tbody>
</table>

**Treatment**

- Gastric tube
- Gastronomy
- Proton pump inhibitor
- Indomethacin
- Thyroxin supplements
- Growth hormone
- ACE inhibitors
- ARA2
### Cysteamine ocular drop

<table>
<thead>
<tr>
<th>Date at start</th>
<th>End date</th>
<th>Number of applications per day</th>
<th>Formulation &amp; co</th>
</tr>
</thead>
<tbody>
<tr>
<td>13/10/2010</td>
<td></td>
<td>6</td>
<td>+</td>
</tr>
</tbody>
</table>

### Cystamine treatment

<table>
<thead>
<tr>
<th>Type</th>
<th>Date at start</th>
<th>End date</th>
<th>Daily dose</th>
<th>Dose frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystagon</td>
<td>26/09/2014</td>
<td>26/09/2014</td>
<td>1000</td>
<td>4</td>
</tr>
<tr>
<td>Cystagon</td>
<td>25/01/2013</td>
<td>26/09/2014</td>
<td>800</td>
<td>4</td>
</tr>
<tr>
<td>Cystagon</td>
<td>10/10/2011</td>
<td>25/01/2013</td>
<td>600</td>
<td>4</td>
</tr>
<tr>
<td>Cystagon</td>
<td>08/07/2009</td>
<td>10/10/2011</td>
<td>400</td>
<td>4</td>
</tr>
</tbody>
</table>

### Cystamine treatment

<table>
<thead>
<tr>
<th>Type</th>
<th>Date at start</th>
<th>End date</th>
<th>Daily dose</th>
<th>Dose frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Daily dose</th>
<th>Dose frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Renal replacement therapy

<table>
<thead>
<tr>
<th>Type</th>
<th>Date at start</th>
<th>End date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemodialysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living donor transplantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceased donor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Follow-up after RRT

<table>
<thead>
<tr>
<th>Date</th>
<th>DD/MM/YYYY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure maxima</td>
<td>mm Hg</td>
</tr>
<tr>
<td>Cystine leucocyte content</td>
<td>nmol 1/2 cystine/mg proteins</td>
</tr>
<tr>
<td>Dosage technique</td>
<td>Unknown</td>
</tr>
<tr>
<td>Residual cysteamine blood level</td>
<td>μmol/l</td>
</tr>
<tr>
<td>Age at review</td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>cm</td>
</tr>
<tr>
<td>Weight</td>
<td>kg</td>
</tr>
</tbody>
</table>

**Kidney**

<table>
<thead>
<tr>
<th>Type</th>
<th>Date at start</th>
<th>End date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatininemia</td>
<td>μmol/l</td>
<td>eGFr</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>g/l</td>
<td>Renal stones</td>
</tr>
</tbody>
</table>

**Eyes**

Photophobia | Yes | No | Unknown |
Visual impairment | Yes | No | Unknown |
Nystagmus | Yes | No | Unknown |
Ophthalmologic examination | Yes | No | Unknown |
Side-effects of eye drops | Yes | No | Unknown |
# Social life

## Education

- **Attendance (as appropriate)**
  - Full time
  - Part time
  - Not at school
  - Unknown

- **Performance (as appropriate)**
  - Normal
  - Mild/moderate difficulties
  - Severe difficulties
  - Unknown

## Diploma

- Secondary school education diploma (as appropriate)
  - Yes
  - No
  - Unknown
- Further education (but below the level of higher education)
  - Yes
  - No
  - Unknown
- Higher education (masters, phd, medicine, dentistry,..)
  - Yes
  - No
  - Unknown

## Extra-curricular activities

- Participation in sports/physical games activities
  - Normal
  - Impaired
  - Not appropriate
  - Unknown
- Employment (for those who have left school/college/university)
  - Full time work
  - Part time work
  - Occasional work
  - Not employed
  - Unknown
- Lodging
  - Parent’s home
  - Independent
  - Unknown
- Marital life
  - Yes
  - No
  - Unknown
Molecular data

Death
## Eunefron Cystinosis Cohort Study 2012

<table>
<thead>
<tr>
<th>Centre/Country</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>93</td>
</tr>
<tr>
<td>Rome</td>
<td>28</td>
</tr>
<tr>
<td>Belgium</td>
<td>41</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>153</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>312</strong></td>
</tr>
</tbody>
</table>
The 10 year survival of an affected individual born in the 1990s is significantly better than that of an individual born in 1980s.
**CEMARA registry as to december 2014**

<table>
<thead>
<tr>
<th>Country</th>
<th>N° patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>41</td>
</tr>
<tr>
<td>Italy</td>
<td>29</td>
</tr>
<tr>
<td>France</td>
<td>150</td>
</tr>
<tr>
<td>Total</td>
<td>220</td>
</tr>
</tbody>
</table>
Renal survival for French patients

Median survival: 70’s = 10 years
80’s = 12 years
90’s = 18 years
## RRT

<table>
<thead>
<tr>
<th>Type</th>
<th>Nº patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD</td>
<td>30</td>
<td>54.5</td>
</tr>
<tr>
<td>PD</td>
<td>3</td>
<td>5.5</td>
</tr>
<tr>
<td>RT deceased donor</td>
<td>9</td>
<td>16.4</td>
</tr>
<tr>
<td>RT living donor</td>
<td>13</td>
<td>23.6</td>
</tr>
</tbody>
</table>
Future work

1. Maintenance and development of this unique resource
2. Further data analysis (genotype, cysteamine dose)
3. Feedback to clinicians and patients