NORD (National Organization for Rare Disorders),

- 501(c)(3) organization,
- patient advocacy organization dedicated to individuals with rare diseases and the organizations that serve them.

The patient odyssey: 7 challenges

Challenge 1. Finding the expert. Where does a patient go to find help? How does a patient navigate the healthcare system? How can social care services be navigated? What are the geographical constraints? How does a patient or parent keep their job?

Challenge 2. Quality of healthcare. Rehabilitation facilities, competent multidisciplinary teams, competent support staff such as psychologists and social workers.

Challenge 3. Education. Most healthcare workers will not have knowledge of rare diseases. There is diversity and heterogeneity of each disease. Uncertainty about the management and prognosis of disease especially in an emerging therapeutic environment. The Internet provides chaos.

The patient odyssey: 7 challenges

Challenge 4. **Expert guidance.** Key parental concerns may not be addressed. Realistic expectations. Informed decision-making is often not truly informed. Forward planning is complicated because of displacement. Family screening adds complexity and stress.

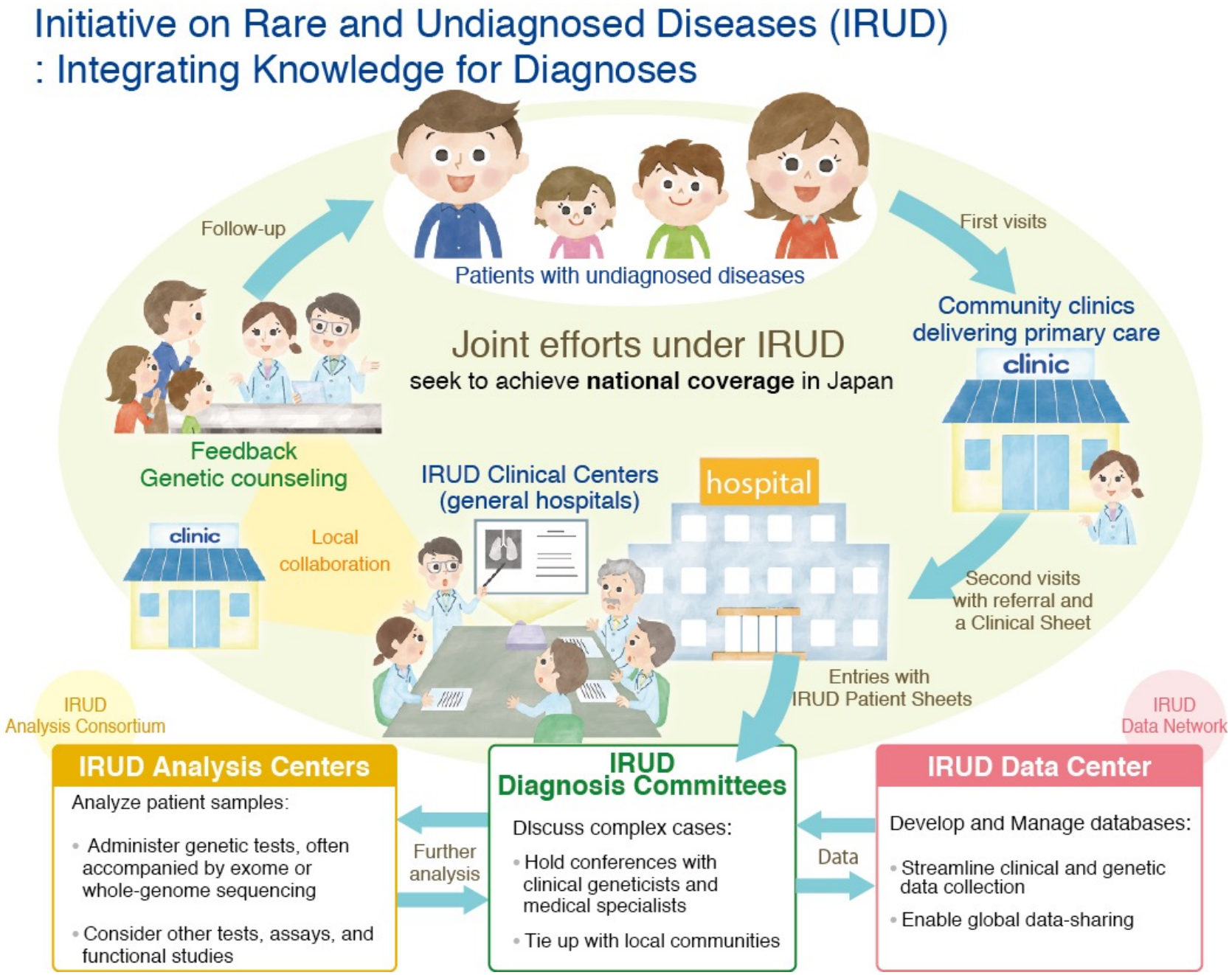
Challenge 5. Treatment options. 90% of diseases do not have an FDA approved treatment. Many diseases may not be curable at all. Effective medicines may not be available. Etiological versus symptomatic treatment is often a challenge. Cost. Lifestyle treatment is often ignored (e.g. shopping, sexuality). Access to clinical trials - particularly internationally - is complex.

The patient odyssey: 7 challenges

Challenge 6. Psychological support. Most psychologists are not skilled dealing with patients and families regarding rare disease. Impact on family is poorly understood. **Social stigmatization**. Patients often feel isolated and excluded and invisible. Patient support is often limited and patients often do not access advocacy groups. Family planning.

Challenge 7. Social aspects. School, leisure time, future work, relationships, insurance discrimination and limited professional opportunities greatly impact quality of life.

The patient odyssey: Japan



https://www.amed.go.jp/en/program/IRUD/

The patient odyssey: European Reference Networks

Platform for the development of guidelines, training and knowledge sharing

Access to >900 expert centers, 24 thematic networks and virtual advisory boards

Mobility of expertise across borders; the patient need not travel to find the expert

The European Commission supports member states by pooling knowledge and expertise, registries, data and funding

The patient odyssey: 7 recommendations

1. Encourage patient voices to be heard.
2. Organize psychological workshops
3. Distribute educational materials through all channels
4. Endorse national and international collaborations
5. Support research
6. Use data sharing and cutting edge technology and IT systems
7. Adopter wider policy alignment to include mental health support, social care and reimbursements

Diversity, equity and inclusion
Trials – medications - access

- **Diversity** is the presence of difference that may include protected characteristics such as age, race, disability and sexuality.
- **Equity** is the process of fairness, justness and impartiality
- **Inclusion** is an outcome to ensure that everyone feels represented & welcome.

Diversity, equity and inclusion

- Build trust
- Repair mistrust
- Equitable access
- Clinical databases – data sharing
- Clinical trial diversity
- Collaboration across sector

- Science of Relationship building
  - Years to build relationships
  - Customized approach
  - Bidirectional relationships
  - One size does not fit all

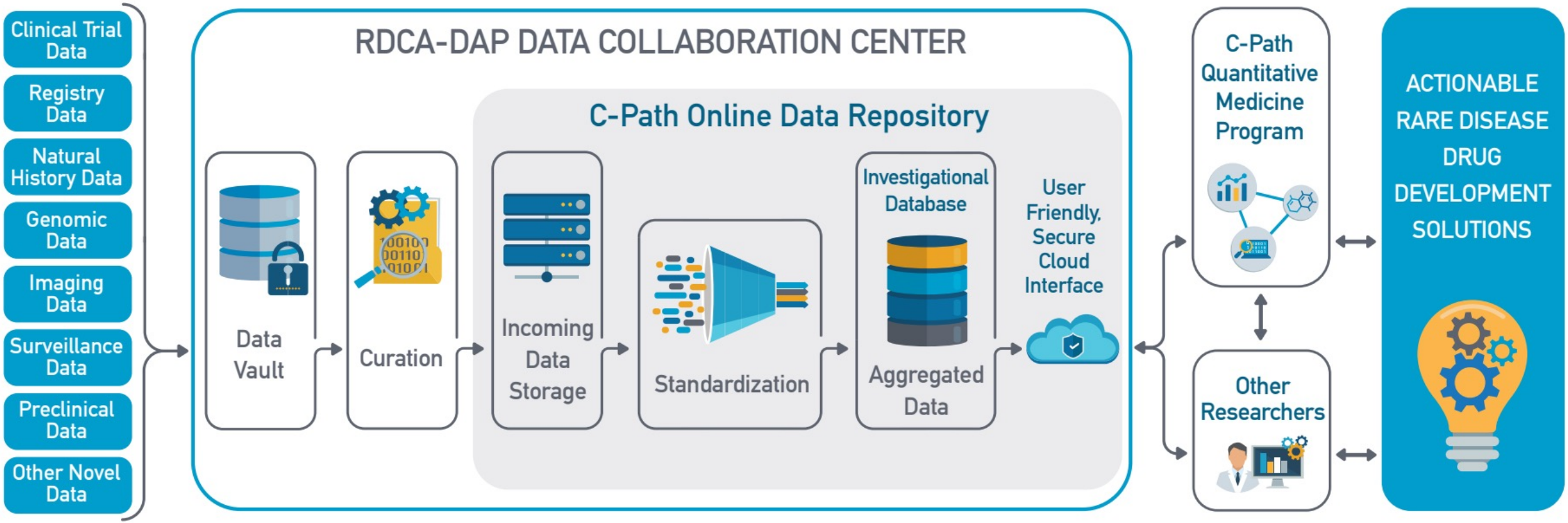
Data sharing

Patient perspective:

- Multiple registries
- Multiple overlap
- Multiple questionnaires
- “Overwhelming”
- Difficult to find data
- One patient – multiple centers
- Chaos

- Patients highly supportive about patient data sharing

Data sharing



https://rarediseases.org/wp-content/uploads/2020/04/RDCA_DAP_Program_Web-1.pdf

ACCESS: Problems in the regional health systems (remote areas)

Regional health systems particularly challenging:

- Long distances
- Lack of highly specialized medical staff
- Lack of specialized medical centers
- Lack of access to specialize testing
- Lack of access to specialized support staff e.g. psychologist

ACCESS: Problems with access to health services

STARTING AT HOME:

- Diagnosis; often there is a misdiagnosis
- Treatment: Often not properly provided or wrong
- Follow up often has gaps or hiatuses
- “The Big City” visit

ACCESS: Big City Visit (*Center or Excellence*)

- Cost of prolonged stay away from home
- Absence from occupation
- Finding appropriate doctor and or medical provider
- Elevated and uncovered costs in imaging exams laboratory tests and sophisticated DNA testing
- Costs may not be covered or only partially covered (prohibitive)
- Social insurance services do not always support the Big City Visit

ACCESS: Big City Visit: returning home

- After returning home an appropriate medical provider may not be available
- Patients need to teach their condition to health provider (not Vice Versa)
- Physicians are especially bad at admitting what they do not know
- Even with an established diagnosis , a vicious circle occurs with problematic treatment follow up, support and cost

FDA

- >7,000 rare diseases - more than 30 million people in US.
- Drug, biologic, and device development in rare diseases is complex
- Small population of patients with a rare disease makes clinical trials difficult
- Most rare diseases do not have FDA-approved treatments
- The FDA works with: patients, caregivers, and drug and device manufactures
- Orphan Drug Act of 1983: FDA approved hundreds of drugs for rare diseases

FDA: What is an orphan drug?

- An orphan drug is a drug for a rare disease or condition.
- Some rare disease treatments have been “orphaned” or discontinued because there was not enough financial incentive to continue development or production.
- The Orphan Drug Act incentivizes drug development for rare diseases.

FDA: Orphan Drug Act - Relevant Excerpts

- Companies and other drug developers can request orphan drug designation from FDA.
- Orphan designation qualifies sponsors for various incentives:
  - Tax credits for qualified clinical (in humans) testing
  - Waiver of the Prescription Drug User Fee ($3 million per drug)
  - Potential 7 years of market exclusivity after approval

https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/orphan-drug-act-relevant-excerpts

FDA: Real world data/evidence for clinical trials

- Electronic health records
- Registries
- Real world experience
- Reasonable assurance of safety
- Data standards (evidence)
- Regulatory considerations - FLEXIBILITY
- Flexible but rigorous - Fit for purpose

NEJM May 5 2022

FDA: recognize challenges for real world data/evidence in clinical trials

- Supports direct comparison – historical benchmark
- Isolating treatment effect
  - Natural History guidance
  - Statistical problems
- Feasibility challenges
- Ethical
- “Majority model” for data registries

Treatment: Newborn screening

- Ethical issues are unresolved
- Gene therapy does not eliminate transmission
- Voluntary sterilization
- The ethics of DNA screening at birth for conditions many decades later
- State-sponsored discouragement to screen

Treatment: Gene therapy

- Gene therapy is an evolving strategy for disorders caused by a missing or faulty gene.
- Gene therapies can be one-time treatments and are designed to target the genetic root cause of diseases.

Gene replacement
Gene replacement uses a new, working gene to replace the function of a nonworking or missing gene. This gene instructs the body to make the missing protein.

Gene addition
Gene addition involves the introduction of a new gene into the body to target the specific cause of disease.

Gene inhibition
Gene inhibition involves deactivating or "silencing" the expression of a mutated or faulty gene that codes for a toxic protein or too much protein.

Gene editing
Gene editing corrects the mutation in a gene that is causing disease.

Gene therapy: potential benefits

Gene therapies may offer greater one time clinical benefits than those offered by conventional therapies*.

Patients:

- Eliminating or reducing clinical burden of disease
- Improving quality of life
- Potentially increasing life expectancy
- *The correct treatment negates the use of the wrong treatments and unnecessary testing and despair*

* Not all gene therapies are single administration

Gene therapy: potential benefits

Healthcare systems:

- Reduce the need for ongoing treatment (supportive)
- Decrease disease related complications
- Decrease healthcare utilization
- *The wrong treatment can be associated with unnecessary complications plus healthcare cost and detriment*

Gene therapy: potential benefits

Caregivers:

- Improve the quality of life for caregivers
- Caregivers return to work.
- Family relationships can benefit

Society:

- Patient and caregivers return to productive societal benefit
- *Gene therapy does not eliminate transmissibility*

Gene therapy: additional considerations

1. Results are variable
2. Long-term follow-up required
3. Some gene therapy is limit]‘once only’ others, multidose
4. The genetic disorder can still be passed on
5. Durability of effect

Reimbursement for gene therapies

NO ONE HAS ANY ANSWERS

Struggling

Medicaid

- “Not set up from a financial standpoint to absorb …lifetime treatment.”
- No question of significant value
- “Not set up to absorb all those costs”
- “Need to think creatively”
- “Trade offs” from the budget
- Other factors such as, housing support, childcare

Reimbursement for gene therapies

- Extreme prices (eg >$1M/person/yr)
- Healthcare insurers:
  - People change plans – across payer plans
  - Partnerships
  - Value-based agreement
  - Shared about 50:50 pay models and capping 150K$/year
- Operational challenges
- Infrastructure and capacity challenges
- State purchasing agreements – pay-over-time (like a student loan)
- Investment paradigm

Please give our patients a voice.

How does the FDA encourage the development of medical products to diagnose and treat rare diseases

- The FDA works with stakeholders, including patients, patient advocates, product developers, and researchers, to support the development of safe and effective drugs, biologics, and devices for rare diseases.
- The FDA is one part of the many parts involved in finding and developing treatments for rare diseases. Specifically, the FDA:
- Administers Laws and Regulations
- Carries out the Orphan Drug Act and related laws and regulations
- Reviews and Grants Designations to Rare Disease Drugs, Rare Pediatric Diseases, and Devices
- Evaluates whether a drug or device qualifies for designation, based on whether both the product and the disease must meet certain criteria specified in the relevant laws. Relevant designation programs for rare diseases include the orphan drug, rare pediatric disease, and humanitarian use device designation programs. Also, FDA reviews and awards Rare Pediatric Disease Priority Review Vouchers.
- Regulates Drugs and Devices
- Protects the public health by ensuring the safety, efficacy, and security of drugs, biological products, and medical devices
- Gives Research Grants
- Awards grants for research on rare diseases, including grants for clinical trials, natural history studies, and pediatric device consortium
- Conducts Outreach
- Communicates with professional organizations, patients, and rare disease advocacy groups about rare disease issues