



# Initiative on Rare and Undiagnosed Diseases (IRUD):

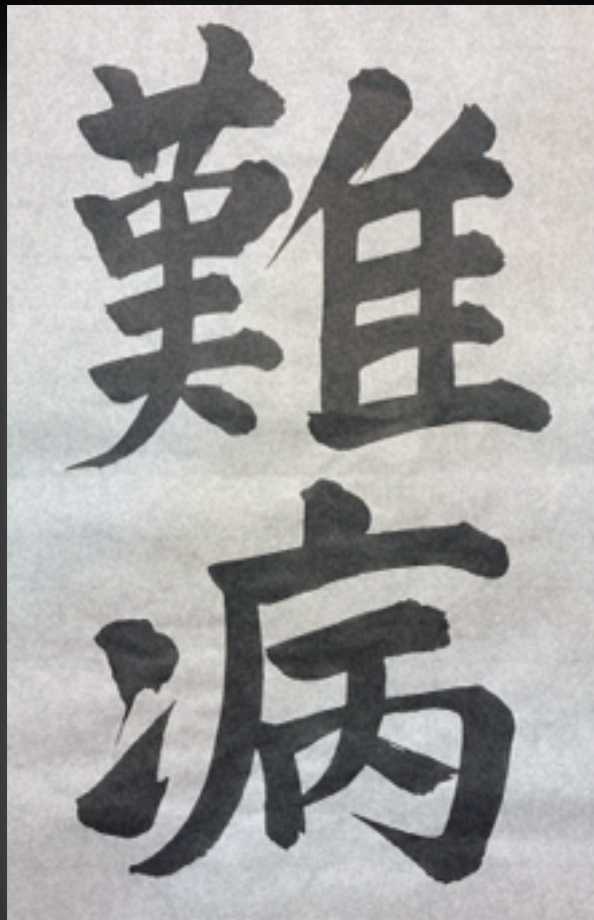
Towards integrative diagnosis network for universal healthcare system

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**G2MC: Implementing Genomic Medicine Globally**  
**April 27, 2017**

**Takeya Adachi M.D., Ph.D.**

**Japan Agency for Medical Research and Development (AMED)**



Rare

Causes and pathogenesis unclassified

Effective treatment unestablished

Long-term care required

*Nan-Byo*  
Since 1972

*Nan* = difficult / hard to handle

*Byo* = diseases / illness

THE LANCET, SEPTEMBER 4, 1971

**SUBACUTE MYELO-OPTICO-NEUROPATHY  
(S.M.O.N.) IN JAPAN**

**A Community Survey**

KIMIHIRO NAKAE  
SHUN-ICHI YAMAMOTO  
AKIHIRO IGATA

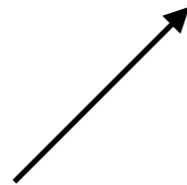
*Department of Epidemiology, University of Tokyo  
School of Health Sciences, and  
Department of Clinical Neurology,  
Brain Research Institute, University of Tokyo, Japan*

*Brain Research Institute, University of Tokyo, Japan  
Department of Clinical Neurology,  
School of Health Sciences, and*

**Governmental Support**

**Subsidies and Research Projects**

Patients under  
unidentified  
conditions

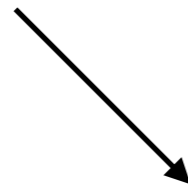


**Relatively Rare  
& Diagnosed**

Subsidies  
&  
Research  
Projects



*Nan-Byo*  
Since 1972



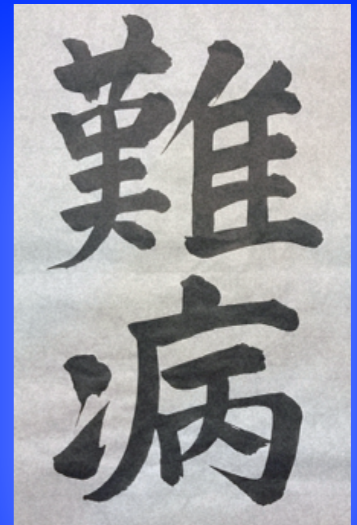
**Ultra-Rare &  
Undiagnosed**



**What is  
overlooked  
by *Nan-Byo***

Rarity

Relatively Rare  
& Diagnosed



*Nan-Byo*  
Since 1972

**IRUD**

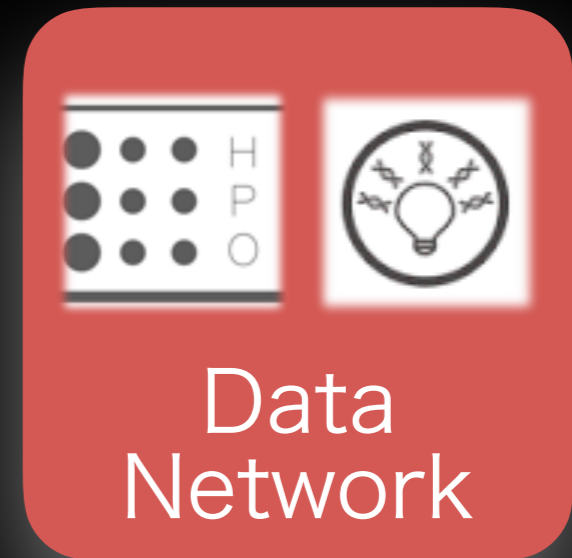


**Ultra-Rare &  
Undiagnosed**

**Diagnosis**



# Initiative on **Rare** and **Undiagnosed** Diseases IRUD since 2015





# Diagnosis network utilizing *Nan-Byo* measures

Upon Japanese Universal Healthcare System

Clinical  
Centers

**Outpatient** department-based

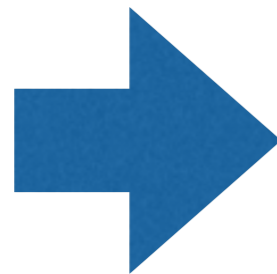
Collaboration with *Nan-Byo* researchers

Eligible  
Criteria

1. Undiagnosed for >6 months; AND,
  - 2-1. **Multiple organ** symptoms; OR
  - 2-2. Genetic disorders suspected



# Field Survey for potential target of IRUD



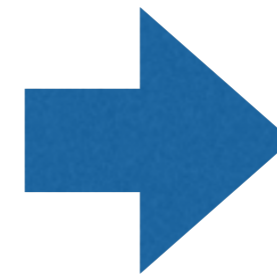
National Universities



Private Universities



Local Clinics



At most

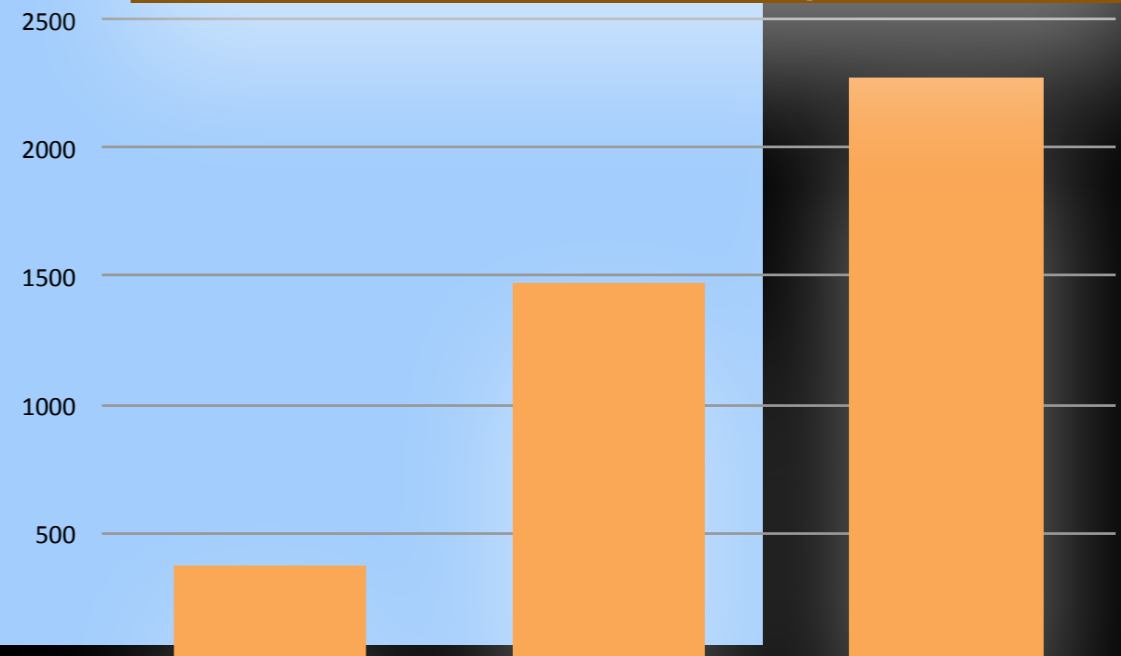
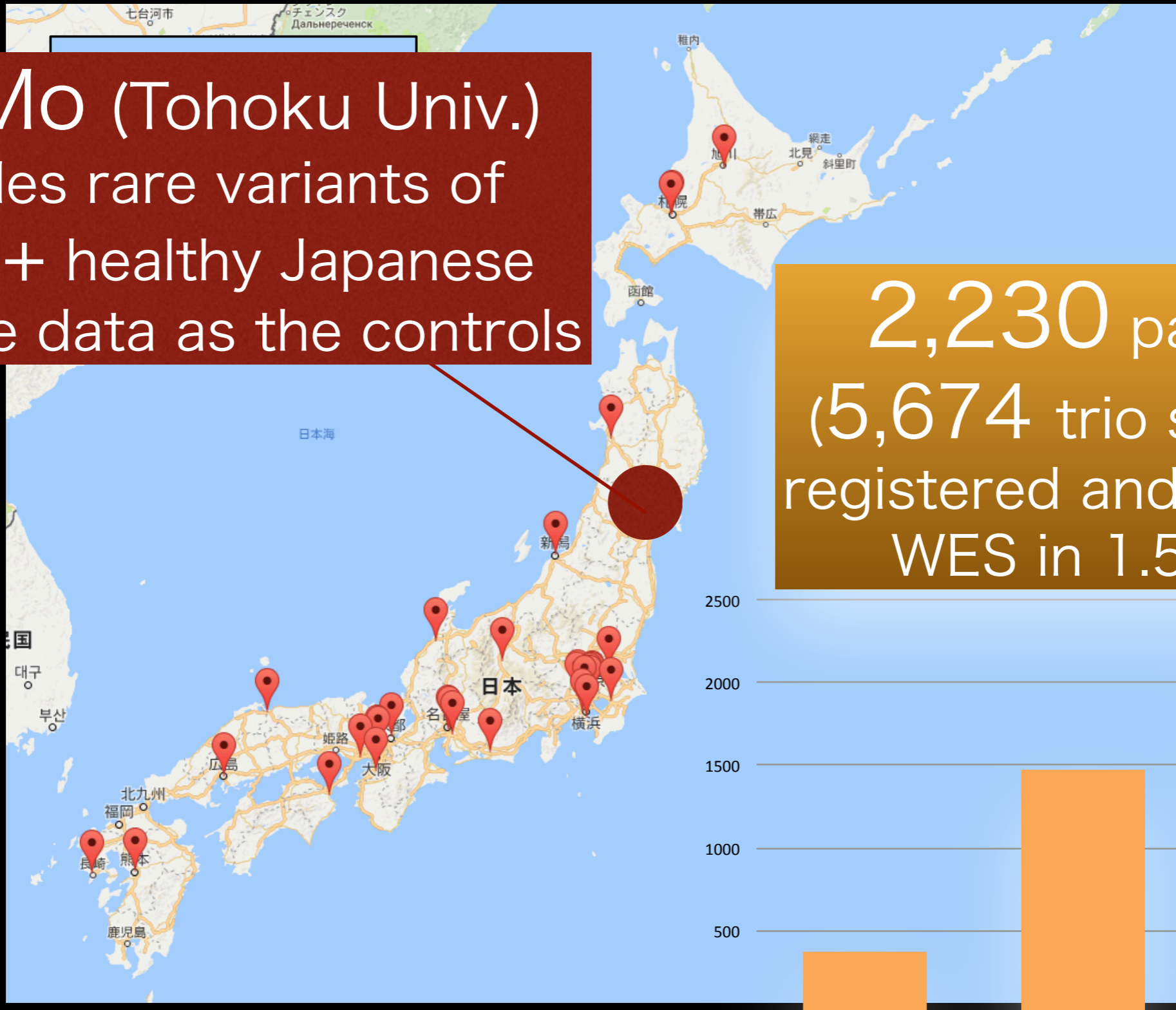




# IRUD Regional Alliance Hospital Network includes **200** hospitals in Japan

ToMMo (Tohoku Univ.) provides rare variants of 2,000+ healthy Japanese sequence data as the controls

2,230 patients (5,674 trio samples) registered and received WES in 1.5 year



2015.12.25      2016.1.29      2016.3.31



**500 physicians  
&  
50 coordinators**

## -Multidisciplinary Diagnostic Approach

**Medical  
Geneticists**

**Neurologists**

**Cardiologists**

**Dermatologists**

**Pediatricians**

**Nephrologists**

**Immunologists**

**Genetic  
Counselors**

**Hemato-  
Oncologists**

**Pulmonologists**

**Pulmonologists**

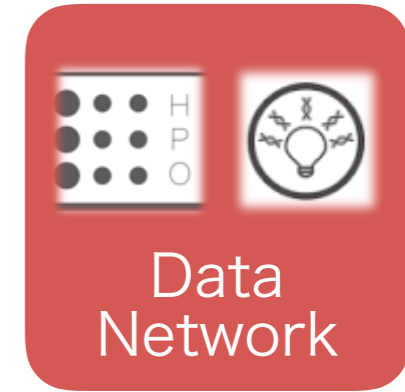
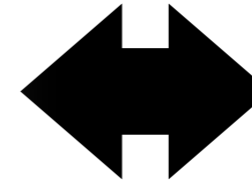
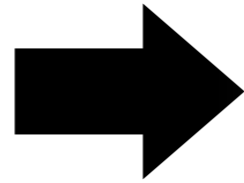
**Gastro-  
enterologists**

**Endocrio-**

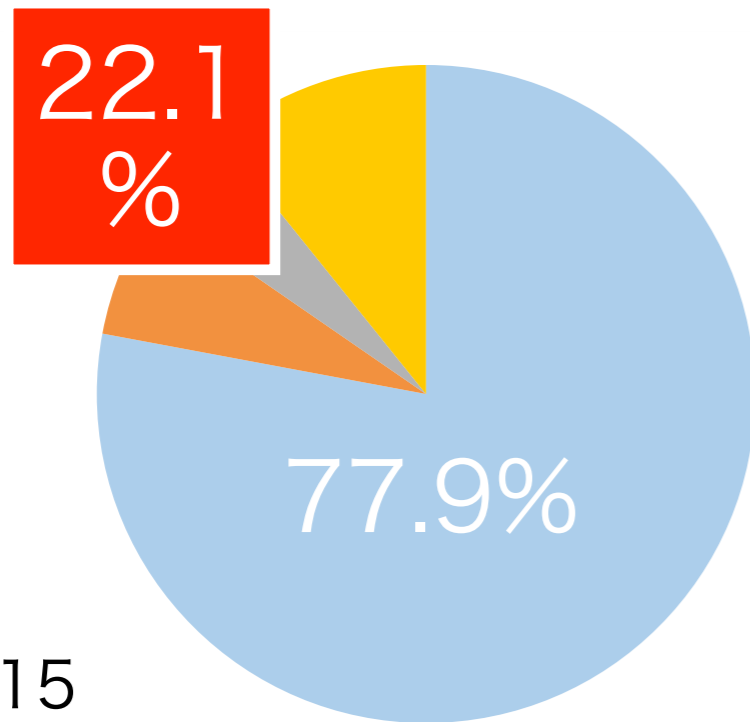
**Allergologists**

**Orthopedists**

**Ophthalmologists**



Diagnosed



n = 15

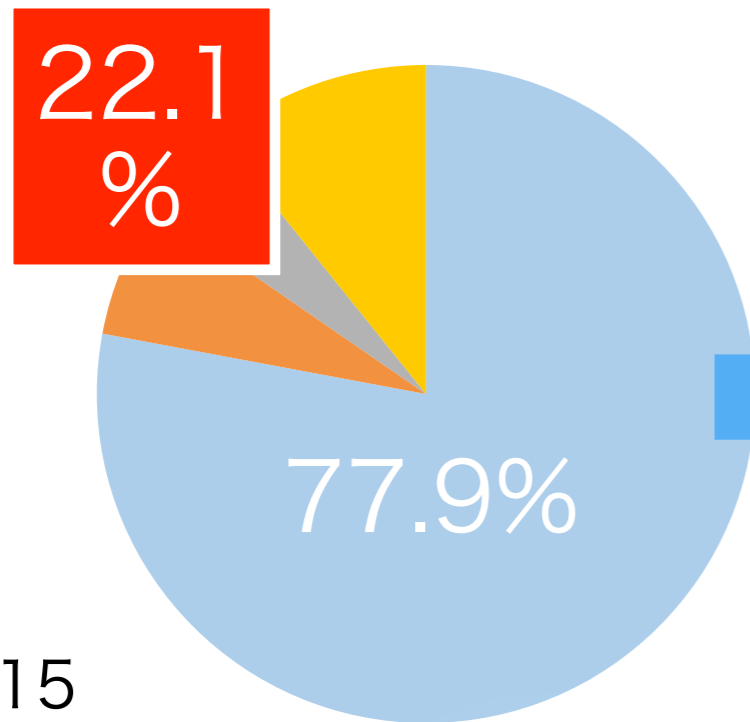
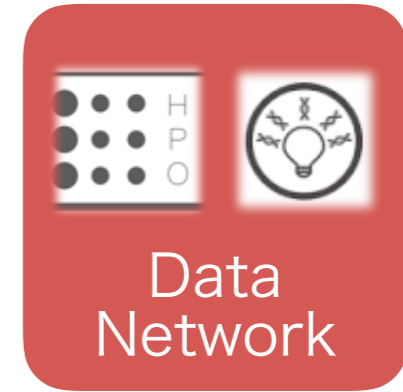
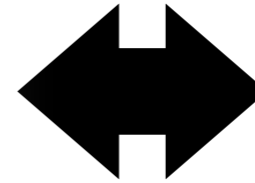
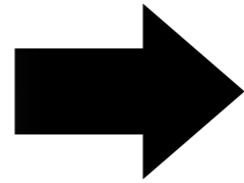
Aug. 2016

-Whole Exome Sequence (WES)

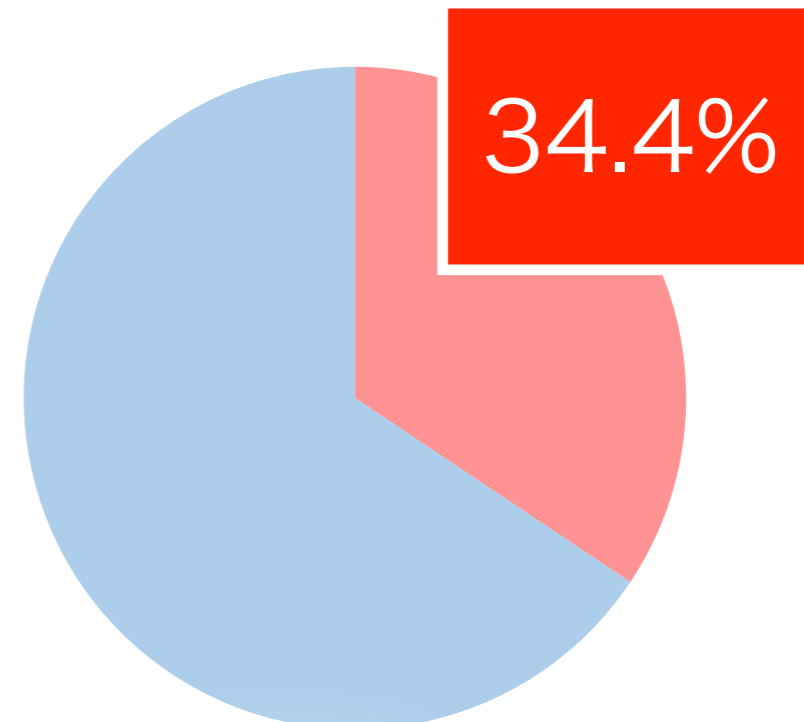
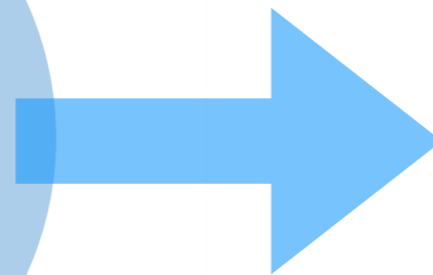
-Patient matching via Patient Archives and MatchMaker Exchange

-Screening of candidate variants

-Whole Genome Sequence (WGS)

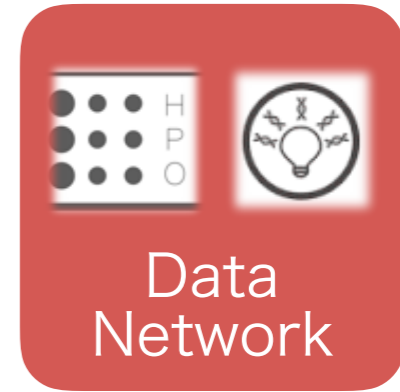
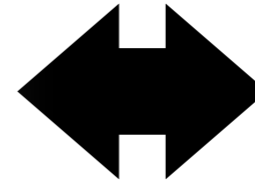
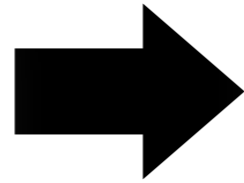


n = 15  
Aug. 2016



n = 4  
Dec. 2016

~25% of patients received the results within 6 months

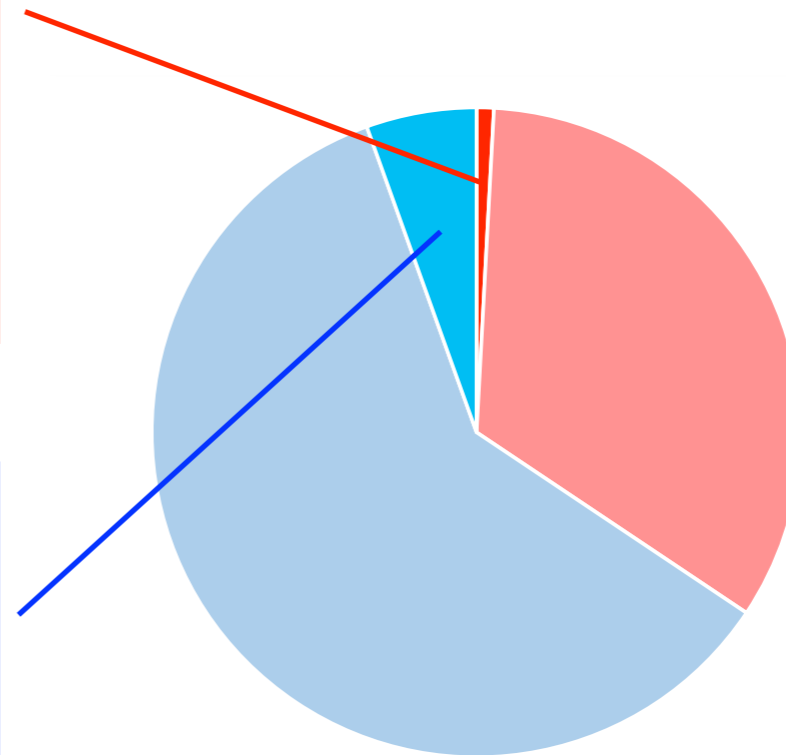


Novel Diseases  
in collaboration  
with US, Europe,  
and Asia

Suggested  
Novel Diseases  
(Candidate genes < 5)

“N-of-2”  
||  
6

“N-of-1”  
||  
83





-WGS

-Other Omics

Transcriptomics

Metabolomics

Proteomics

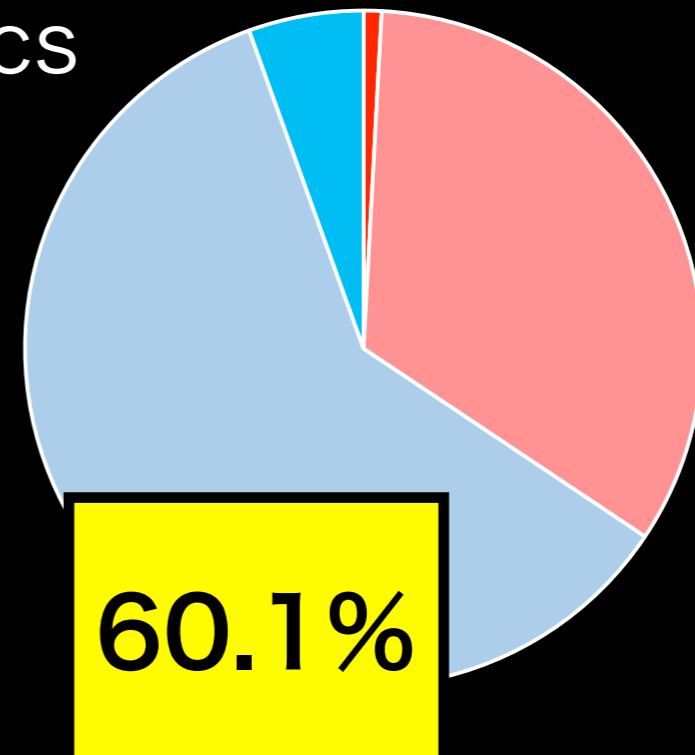
Glycomics

Lipidomics

⋮

-Further patient matching

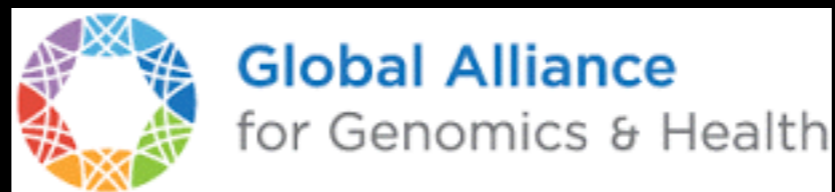
**What is overlooked by NGS?**



**Undiagnosed**



IRUD



Automatable  
Discovery and  
Access-Matrix  
**(ADA-M)**

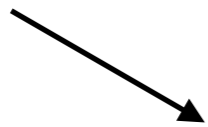
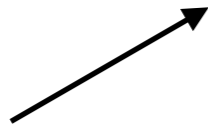
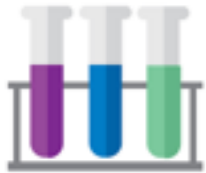
ADA-M



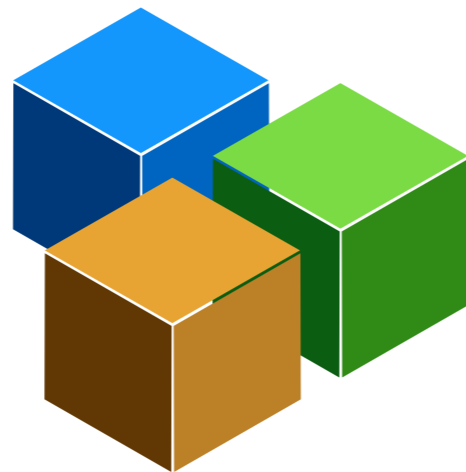
Global Alliance  
for Genomics & Health



**IRDiRC**  
INTERNATIONAL  
RARE DISEASES RESEARCH  
CONSORTIUM



Use for  
Methods  
Development?  
Profit Purpose?



Requirements of  
Linking to  
Other Datasets?



# IRUD



Accommodate information about the use of resources in discovery and/or access scenarios

+

## ADA-M



*FINAL (15 December 2016)*

**Automatable Discovery and Access Matrix ("ADA-M") v1.0**

**GUIDANCE DOCUMENT**

*Global Alliance for Genomics & Health (GA4GH)  
International Rare Disease Research Consortium (IRDiRC)*



# IRUD *Beyond*



for ALL  
Rare &  
Undiagnosed  
Patients