Molecular Genetics and Metabolism 116 (2015) 223–225

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Commentary

Undiagnosed Diseases Network International (UDNI): White paper for global actions to meet patient needs

Domenica Taruscio[a,*], Stephen C. Groft[b], Helene Cederroth[c], Béla Melegh[d], Paul Lasko[e], Kenjiro Kosaki[f], Gareth Baynam[g,h,i,j,k,l], Alexa McCray[m], William A. Gahl[n]

[a] National Center for Rare Diseases, Istituto Superiore di Sanità, Rome, Italy
[b] National Center for Advancing Translational Sciences, National Institutes of Health, United States
[c] Wilhelm Foundation, Sweden
[d] Department of Medical Genetics, University of Pécs, Hungary
[e] Department of Biology, McGill University, Montreal, Canada
[f] Center for Medical Genetics, Keio University School of Medicine, Tokyo, Japan
[g] Princess Margaret and King Edward Memorial Hospitals, Perth, Australia
[h] Office of Population Health, Public Health Division, WA Department of Health, Australia
[i] Telethon Kids Institute, Perth, Australia
[j] Western Australian Registry of Developmental Anomalies, Perth, Australia
[k] School of Paediatrics and Child Health, University of Western Australia, Perth, Australia
[l] Institute for Immunology and Infectious Diseases, Murdoch University, Perth, Australia
[m] Center for Biomedical Informatics, Department of Medicine, Harvard Medical School, Boston, Massachusetts, United States
[n] NIH Undiagnosed Diseases Program, National Human Genome Research Institute, National Institutes of Health, United States

ARTICLE INFO

Article history:
Received 27 October 2015
Received in revised form 4 November 2015
Accepted 4 November 2015
Available online 5 November 2015

Keywords:
Undiagnosed
Global health
Rare diseases
Omics
Ontology
Diagnosis

ABSTRACT

In 2008, the National Institutes of Health's (NIH) Undiagnosed Disease Program (UDP) was initiated to provide diagnoses for individuals who had long sought one without success. As a result of two international conferences (Rome 2014 and Budapest 2015), the Undiagnosed Diseases Network International (UDNI) was established, modeled in part after the NIH UDP. Undiagnosed diseases are a global health issue, calling for an international scientific and healthcare effort. To meet this demand, the UDNI has built a consensus framework of principles, best practices and governance; the Board of Directors reflects its international character, as it includes experts from Australia, Canada, Hungary, Italy, Japan and the USA. The UDNI involves centers with internationally recognized expertise, and its scientific resources and know-how aim to fill the knowledge gaps that impede diagnosis. Consequently, the UDNI fosters the translation of research into medical practice. Active patient involvement is critical; the Patient Advisory Group is expected to play an increasing role in UDNI activities. All information for physicians and patients will be available at the UDNI website.

In 2008, the NIH Undiagnosed Disease Program (UDP), through the efforts of the National Human Genome Research Institute, the NIH Clinical Center, the Office of Rare Diseases Research, and other NIH research institutes and centers, arose to address an unmet need, to provide a diagnosis for individuals who had long sought one without success. This program evaluates patients for whom medicine has failed to provide a diagnosis. Such patients have spent years accumulating large amounts of medical records and test results, often at great emotional and financial cost. A second, critical goal was to obtain insights into novel disease mechanisms and pathways [1]. In 2013, the Common Fund of the United States' National Institutes of Health (NIH) granted 7 years of support to establish a nationwide Undiagnosed Diseases Network (UDN), consisting of a coordinating center, 7 clinical sites (including the NIH UDP), two sequencing cores, a metabolomics core, a model systems core, and a gene function core. The NIH UDP continues to thoroughly evaluate 120–150 patients per year at the NIH Clinical Center, and the other 6 clinical sites began seeing their first patients in August 2015.

The NIH UDN is committed to sharing best practices, genomic, phenotypic and functional data, and expertise among its sites. This is accomplished through the use of a common Institutional Review Board (located at the National Human Genome Research Institute) and a consent that allows for sharing of personally identifiable data and specimens among the centers. In addition, de-identified data are shared with qualified collaborators outside of the Network [2,3].

* Corresponding author at: National Center for Rare Diseases, Istituto Superiore di Sanità, Viale Regina Elena, 299, 00161 Rome, Italy.
E-mail address: domenica.taruscio@iss.it (D. Taruscio).

http://dx.doi.org/10.1016/j.ymgme.2015.11.003
1096-7192/

Many undiagnosed patients, including patients affected by rare diseases, with unmet needs are present throughout the world. To begin to address this, the Common Fund, within the Office of the NIH Director, along with the Wilhelm Foundation, Sweden [4], has sponsored two international conferences. The first was held in Rome on September 29–30, 2014 (hosted by the National Center for Rare Diseases, Istituto Superiore di Sanità) and the second was in Budapest on June 26–27, 2015 (hosted by the National Research, Development and Innovation Office [NKFIH] and the University of Pecs, Hungary). A related workshop was held in Perth, Western Australia (August 2015). In attendance were representatives of 18 countries and 4 continents, and a firm resolve to improve the situation emanated from those meetings.

In these international meetings, participants decided to establish the Undiagnosed Diseases Network International (UDNI), modeled in part after the NIH UDN. The objectives of the NIH UDN are to:

1) improve the level of diagnosis and care for patients with undiagnosed diseases through the development of common protocols designed by a community of investigators;
2) facilitate research into the etiology of undiagnosed diseases, by collecting and sharing standardized, high-quality clinical and laboratory data including genotyping, phenotyping, and documentation of environmental exposures; and.
3) create an integrated and collaborative research community across multiple clinical sites and among laboratory and clinical investigators prepared to investigate the pathophysiology of these new and rare diseases and share this understanding to identify improved options for optimal patient management.

The oncoming UDNI meeting will be in Vienna on February 18, 2016.

1. Principles

Table 1 shows the general principles of the newly formed UDN International (UDNI).

1. Patients enrolled in the UDNI should be selected for the unique characteristics of their disorder and for its potential to inform new aspects of cell biology, pathogenetic mechanism(s) and therapy. Candidate patients should have been extensively examined already, so that obvious diagnoses have been eliminated.
2. Accepted patients should be thoroughly evaluated by the UDNI, preferably at no cost to the patient.
3. Patients should consent to share their data with other investigators within the group, according to the tenets of the Helsinki Declaration and/or of Good Clinical Practices [6,7]. Patient phenotypes should be expressed using a standard ontology system in order to build up a highly integrated database [8,9]
4. Next-generation sequencing and other -omics analyses (e.g., proteomics, glycomics, lipidomics) should be performed on enrolled families/patients (trios or quartets when possible), and analyzed with some uniformity and according to state-of-the-art protocols. New tools will be applied in some cases, including when a non-genetic undiagnosed disease (e.g., rare infections or poisonings) is suspected. Return of results will conform to site-specific consents.
5. The -omics and phenotypic data should be shared among members of the UDNI.
6. Functional studies should be performed to substantiate causal relationships between a candidate gene and the phenotype and address novel therapies.

2. Practices

The UDNI will adhere to the following best practices.

1. Applications will be specific to member sites, but should include core information described in Appendix A.
2. Clinical site evaluations will be comprehensive and include clinical and basic research approaches, including specimen collection for future studies, as described in Appendix B.
3. A list of clinical experts will be created for advice and referral both within the UDNI and outside of it.
4. A list of basic research topic experts will be compiled to serve as a potential collaborator pool; de-identified cases can be shared with these authorities if they have variants in genes within a particular basic researcher's area of expertise.
5. The UDNI will maintain a website with information for physicians and patients [5].
6. The NIH UDN will make available its Manual of Operations to the UDNI.

Table 1
UDNI principles and implementation approaches.

UDN principles	UDN implementation approaches
Engage centers of excellence	Seven centers of clinical excellence Two centers of genomic sequencing excellence One center of informatics excellence
Foster a collaborative research community	Monthly steering committee conference calls Regular face-to-face meetings Ongoing working group activities, training and educational issues Weekly clinical case review conference calls
Establish a cooperative governance structure	Steering committee comprising the principal investigators of each center All major decisions made by steering committee vote (one vote per center)
Design a common research protocol	Central institutional review board Protocol amended by agreement as necessary Network-wide patient consents
Provide a uniform patient experience	Patient portal for applying to the network Network-wide acceptance criteria Network-wide clinical evaluation methods Patients can participate irrespective of their health insurance status Patient advisory group
Collect data in accordance with recognized data standards	Human Phenotype Ontology for clinical data Genetic data consistent with National Center for Biotechnology Information standards Biospecimens in accordance with UDN standard protocol Standard environmental exposure survey
Protect patient data, general ELSI issues	Security procedures for personally-identifiable information and personal health information in accordance with federal guidelines[a]
Expect broad data sharing	Data sharing and use agreement for freely sharing data within the network De-identified data deposited in publicly available databases
Stimulate dissemination of research results	Policies for publications, presentations, and UDN-related grant applications
Ensure a high-functioning network	Executive committee meets weekly to review and monitor progress Performance metrics for intermediate goals Performance metrics for overall success of the network

[a] HIPAA (Health Insurance Portability and Accountability Act), NIST (National Institute of Standards and Technology), and FISMA (Federal Information Security Management Act).

3. Implementation of principles and practices

Table 1 lists basic principles and their implementation in the NIH UDN. The UDNI is expected to operate under the same principles with similar approaches to implementation.

4. Governance

The UDNI will be organized as a consortium with membership and committees.

1. Membership will be open to clinical investigators who serve undiagnosed disease patients from all countries.
2. Members agree to adhere to the principles mentioned above.
3. The initial Board of Directors will consist of Gareth Baynam (Australia), William Gahl (USA), Stephen Groft (USA), Kenjiro Kosaki (Japan), Paul Lasko (Canada), Bela Melegh (Hungary), and Domenica Taruscio (Italy). Half the board members are expected to be replaced every two years. Board members can apply for re-election.
4. Committees will have chairs and will include:
   a. Advocacy Groups
   b. Clinical management
   c. Sequencing and analysis
   d. Database
   e. Biospecimens

5. Support

Funding for the UDNI database will be requested from the NIH Common Fund, which supports the NIH UDN. The UDNI website is provided by the Istituto Superiore di Sanità. Members of the UDNI will seek their own funding for their clinical/sequencing/research sites.

The UDNI principles, actions and governance are intended to address several priority health issues. Firstly, undiagnosed diseases are a global health problem, so undiagnosed diseases call for an international framework of scientific co-operation and a consistent transnational healthcare approach. Second, undiagnosed diseases require standards of the highest quality; UDNI involves centers with internationally recognized expertise, robust scientific resources, and specialized experience directed toward filling the knowledge gaps that delay diagnosis. Consequently, the UDNI fosters the translation of research into medical practice. Finally, active patient involvement is crucial; the Patient Advisory Group is expected to play an increasing role in UDNI activities. Generally, patients' participation and experiences contribute to improved health care, and this holds true particularly for patients with undiagnosed diseases that require specialized, coordinated efforts.

All authors are involved in the Undiagnosed Diseases Network International (UDNI).

Appendix A. Applications in the UDNI should include:

1. Demographic information such as name, date of birth, gender, self-described race and ethnicity, contact information;
2. Physician referral letter relating chief complaint, history, and what is undiagnosed;
3. Pertinent medical problems and prior diagnoses;
4. Medical records of physical examinations, hospitalizations, pertinent office visits, specialist consultations;
5. Laboratory test results;
6. Imaging on disks;
7. Biopsy slides when available;
8. Video of speech, gait, hand movements when impaired.

Appendix B. Clinical site evaluation should include:

1. Review of recent medical records, tests results, pathology, imaging;
2. Medical and family history;
3. Medication list (doses, schedule);
4. Environmental and nutritional assessment;
5. Thorough physical examination;
6. Medically indicated and research laboratory studies;
7. Radiographic studies;
8. Disease-specific consultations;
9. Pertinent procedures, e.g., lumbar puncture, muscle biopsy, bone marrow;
10. Commercial genetic & biochemical testing as indicated;
11. DNA collection (proband and family) for exome/genome sequencing;
12. Specimen procurement, e.g., skin biopsy for fibroblast culture, lymphocytes for transformation, serum, plasma, CSF;
13. Pediatric sedation day for ophthalmic examination, biopsies, MRI, etc.

References

[1] W.A. Gahl, C.J. Tifft, The NIH Undiagnosed Diseases Program: lessons learned, J. Am. Med. Assoc. 305 (2011) 1904–1905.
[2] C.J. Tifft, D.R. Adams, The National Institutes of Health undiagnosed diseases program, Curr. Opin. Pediatr. 26 (6) (2014) 626–633.
[3] W.A. Gahl, A.L. Wise, E.A. Ashley, The Undiagnosed Diseases Network of the National Institutes of Health: a national extension, JAMA 16 (2015) 1–2.
[4] The Wilhelm Foundation, http://www.wilhelmfoundation.org/wf.aspx
[5] The UDNI website, http://www.udninternational.org
[6] World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects (http://www.wma.net/en/30publications/10policies/b3/17c.pdf (accessed October 10, 2015))
[7] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline for Good Clinical Practice. (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf (accessed October 10, 2015))
[8] P.N. Robinson, S. Mundlos, The human phenotype ontology, Clin. Genet. 77 (6) (2010) 525–534.
[9] O.J. Buske, M. Girdea, S. Dumitriu, B. Gallinger, T. Hartley, H. Trang, A. Misyura, T. Friedman, C. Beaulieu, W.P. Bone, A.E. Links, N.L. Washington, M.A. Haendel, P.N. Robinson, C.F. Boerkoel, D. Adams, W.A. Gahl, K.M. Boycott, M. Brudno, PhenomeCentral: a portal for phenotypic and genotypic matchmaking of patients with rare genetic diseases, Hum. Mutat. 36 (10) (2015) 931–940.