

Treatabolome: a rare diseases treatment awareness project

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INTRODUCTION

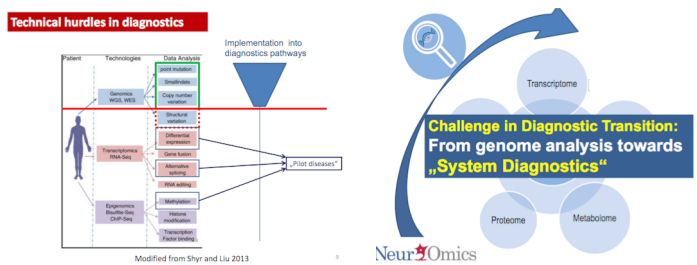
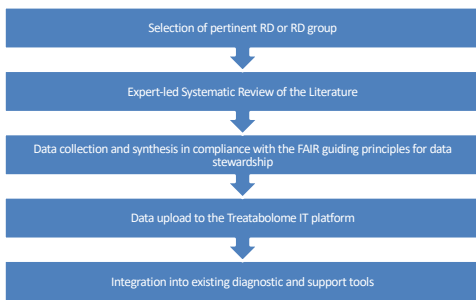
Rare diseases are individually rare but globally affect 3.5 to 5.9% of the population, i.e. 263-446 million people worldwide, according to the latest calculations. Recent estimates point to over 10000 rare diseases, of which 6172 disorders are listed in Orphanet, about 70% of which being genetic and around 70% having paediatric-onset. These diseases' rarity is contextual, varying with the population considered and also geographically. Nonetheless, disease rarity uniformly translates into a delayed diagnosis, with 25% of patients having to wait for 5 to 30 years to have one. It is essential, at the time of diagnosis, to be able to relay information about potential gene and variant-specific therapies to patients.

"Solve-RD – solving the unsolved rare diseases" is a research project funded by the European Commission for five years (2018-2022) aiming at improving the diagnostic and therapeutic management of rare diseases. It will deliver seven implementation steps, including one dedicated to treatment as part of the "genetic knowledge web". With this in mind, we propose a method of allowing clinicians to access this information promptly to benefit patients affected by rare disease and their families. The "Treatabolome" is an evidence-appraised database of rare diseases treatments for specific genes and variants to be made available through genetic diagnosis and support tools, for example, the Genome-Phenome Analysis Platform of RD-Connect. The Treatabolome aims at contributing to raising awareness and increasing the visibility of existing rare diseases' treatments to clinicians.

METHODS

Solve-RD will deliver 7 main implementation steps: (i) Collect Phenotypes, (ii) New phenotype patterns, (iii) Re-analyse exomes / genomes, (iv) Novel molecular strategies, (v) Functional analysis, (iv) Clinical utility and (vii) Towards therapy. A brokerage structure connecting clinicians, gene discoverers and basic researchers will be assembled to quickly validate novel genes and disease mechanisms through a "multomics, beyond the genome" approach.

Within this ambitious project, the **Treatabolome** is a task that aims at improving the visibility of gene and variant-specific rare diseases' treatments.



To deliver this, expert-led systematic reviews will be written as building blocks of a treatment knowledge database that will feed existing RD diagnostic tools with gene and variant specific-treatment information. This is what was piloted for Congenital Myasthenia Syndromes and will now be broadened to include other entities as well (Laminopathies, CMT Mitochondrial Disorders, Genetic Parkinson Disease, Early-onset ataxias and Channelopathies). This is possible by the collaboration of the participating ERNs that provide the experts that will write the Systematic Reviews that will be the building blocks of the Treatabolome. A system is in place to appraise the level of evidence behind each treatment proposal (GRADE; OEBML) and the data will be treated in accordance with the FAIR guiding principles of data stewardship. These implement the organization of the research data in findable, accessible, interoperable and reusable data resources, either in a repository, published or both. The principles that guide the FAIR data model are published (1) and are displayed below.

Table 1 The meaning of the FAIR principles, based on Wilkinson et al. and Mons et al

Principle	Explanation	Example in human genetics and genomics
Findability	Datasets should be described, identified and registered or indexed in a clear and unequivocal manner	BBMRI-ERIC Directory
Accessibility	Datasets should be accessible through a clearly defined access procedure, ideally using automated means. Metadata should always remain accessible	European genome-phenome archive
Interoperability	Data and metadata are conceptualised, expressed and structured using common, published standards	GA4GH Genomic Data Toolkit
Reusability	Characteristics of data and their provenance are described in detail according to domain-relevant community standards, with clear and accessible conditions for use	BRCA exchange

BOECKHOUT, M., ZIELHUIS, G. A. & BREDENOORD, A. L. 2018. The FAIR guiding principles for data stewardship: fair enough? *Eur J Hum Genet*, 26, 931-936

The different systematic reviews will be published in a special issue of the Journal of Neuromuscular Diseases in the beginning of 2021. The treatabolome dataset will be uploaded to a web platform designed by CNAG-CRG and the data will be made available as well for other platforms that provide genetic diagnostic and other support tools. The Genome-Phenome Analysis Platform will be one of those and it will allow any listed treatment to be flagged at the stage of diagnosis at a granular level.

CONCLUSIONS

- The Treatabolome will enhance visibility of rare diseases' specific treatments at the moment of diagnosis by integrating with existing support tools.
- The initial build of the Treatabolome will be possible through expert-led systematic reviews of the literature and treatment-associated evidence appraisal.
- The cross-mapping of the Treatabolome data will allow to articulate it with other data resources like HPO, OMIM and ORDO. Possible future collaboration with treatment ontologies is being assessed.
- The futures updates of the Treatabolome will evolve to a data-mining approach that will allow automatic extraction from the scientific literature. A vision of a pilot is being developed by one of the work package partners (Jackson Institute).

REFERENCES

1. WILKINSON, M. D., DUMONTIER, M., AALBERSBERG, I. J., APPLETON, G., AXTON, M., BAAK, A., BLOMBERG, N., BOITEN, J. W., DA SILVA SANTOS, L. B., BOURNE, P. E., BOUWMAN, J., BROOKES, A. J., CLARK, T., CROSAS, M., DILLO, I., DUMON, O., EDMUNDS, S., EVELO, C. T., FINKERS, R., GONZALEZ-BELTRAN, A., GRAY, A. J., GROTH, P., GOBLE, C., GRETHE, J. S., HERINGA, J., T HOEN, P. A., HOOFT, R., KUHN, T., KOK, R., KOK, J., LUSHER, S. J., MARTONE, M. E., MONS, A., PACKER, A. L., PERSSON, B., ROCCA-SERRA, P., ROOS, M., VAN SCHAİK, R., SANSONE, S. A., SCHULTES, E., SENGSTAG, T., SLATER, T., STRAWN, G., SWERTZ, M. A., THOMPSON, M., VAN DER LEI, J., VAN MULLIGEN, E., VELTEROP, J., WAAGMEESTER, A., WITTENBURG, P., WOLSTENCROFT, K., ZHAO, J. & MONS, B. 2016. The FAIR Guiding Principles for scientific data management and stewardship. *Sci Data*, 3, 160018.
2. THOMPSON, R., ABLCHT, A., BEESON, D., ENGEL, A. G., EYMARD, B., MAXIME, E. & LOCHMULLER, H. 2018. A nomenclature and classification for the congenital myasthenic syndromes: preparing for FAIR data in the genomic era. *Orphanet J Rare Dis*, 13, 211.
3. THOMPSON, R., BONNE, G., MISSIER, P. & LOCHMULLER, H. 2019. Targeted therapies for congenital myasthenic syndromes: systematic review and steps towards a treatabolome. *Emerg Top Life Sci*, 3, 19-37

• G. Bonne, R. Ben Yaou, A. Atalaia: **Laminopathies**
 • M. Jenkins, A. Lochmuller, R. Horvath: **CMT**
 • J-F. Desaphy, B. Fontaine: **Channelopathies**
 • K. Lohman: **Genetic Parkinson's Disease**
 • D. Gomez Andrez, A. Moncaya, C. Reinhard: **Early-onset ataxias**
 • T. Ratnaik, K. Schon, R. Horvath, P. Chinnery: **Mitochondrial Diseases**

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