Orphan Drug Development Guidebook

Building Block I426

This document defines the content of the Building Block created for each identified tool, incentives, initiative or practice introduced by public bodies or used by developers to expedite drug development in Rare Diseases (RDs).

ITEM	DESCRIPTION
Building Block (BB) Title	Initiatives for undiagnosed diseases
References	https://undiagnosed.hms.harvard.edu/ http://www.udninternational.org/ http://care4rare.ca/ http://solve-rd.eu/ https://www.amed.go.jp/en/program/IRUD/ Am J Hum Genet. 2014 Jun 5;94(6):809-17. doi: 10.1016/j.ajhg.2014.05.003. Mol Genet Metab. 2016 Apr;117(4):393-400. doi: 10.1016/j.ymgme.2016.01.007. Epub 2016 Jan 22. **IRDiRC vision** Future of Rare Diseases Research 2017-2027: An IRDiRC Perspective. DOI: 10.1111/cts.12500
Description	The purposes of Undiagnosed Diseases Programs (UDPs) are to provide patients with an unknown genetic condition a diagnosis and to find the correlation between genotype and phenotype; to share globally the information to facilitate the diagnosis through a *matchmaking* for finding possible *second cases.* Worldwide the UDPs are performed primarily using Next Generation Sequencing (NGS) approaches (whole exome or whole genome sequencing) applied to the family trio or quartet UDPs shorten the time to reach a diagnosis, the so-called “diagnostic odyssey”, from years to weeks.

	The early diagnosis of an ultra-rare disease gives to the physician the possibility of choosing the most adequate treatment, if available and to the patient the possibility to benefit from the treatment before the possible worsening of the clinical condition. Further insights on genetic diseases could trigger new therapeutic approaches. The matchmaking allows the identification of other overlapping cases that can confirm diagnosis and therefore provide relevant information regarding available treatments.
Category	Development Practices Building Block
Geographical scope	International
Availability	Applicants developing medicines for rare and non-rare diseases.
Scope of use	– Identification of molecular diagnosis by NGS and other OMICS approaches – Genotype-phenotype data sharing to find a second case through matchmaking – Generation of new diagnostic technologies for genetic diseases – Generation of new informatics approaches (analysis pipeline and artificial intelligence) to shorten the "diagnostic odyssey".
Stakeholders	• Healthcare professionals, • Pharmaceutical industries, • Genomics and bioinformatics centers, • Patient organizations, • Policy makers, • NHS
Enablers/ Requirements	Enablers: healthcare professionals' organizations, National Health Systems - NHS, research institutes, genomics centers. Requirements: • Inform (e.g. announcement of guidance on UDPs); • Consult and involve (direct interactions – e.g. stakeholder meetings, workshops, stakeholder conferences); • Cooperate / participate (direct interactions - e.g. technical expert groups and networks) • Genotype and phenotype data sharing

Output	The number of enrolled patients and diagnosis provided are UDPs outputs. Report on the mapping of the scenario of UDPs and networks worldwide, generation of recommendation regarding the need of applying NGS approaches to undiagnosed patients as first-tier test.
Best time to apply and time window	The tool should be applied as soon as possible.
Expert tips	Strategic considerations: - UDPs must be embedded in a multidisciplinary network, including clinicians, bioinformaticians, psychologists etc DOs: - UDP adopted by NHS as of limited value if performed only in the research environment - Increased awareness on available programs among any interested stakeholders (i.e., patients) - Data sharing is crucial - Awareness and empowerment of patients enrolled in the UDPs, extended also after the positive/negative response received, through appropriate genetic and/or psychological counseling. - A cost-effective analysis to be conducted DON'Ts: - Do not limit to the "pure research" environment - Do not limit to genomics analysis only, but consider alternative diagnostic approaches PROs: – Shortening the time to reach the diagnosis, early treatment if available, generation of data about ultra-rare disease, more adequate choice of the treatment if available, better follow up with supportive therapies, prevention of life-threatening events and casualties. – Data sharing to allow research on disease mechanisms and to find other ultra-rare cases worldwide.

	CONs: – UDPs kept as research programs vs. NHS adoption; increase of diagnostic cost for the NHS; unmet patients' expectations (unsolved cases; possible lack of available treatments for diagnosed patients).