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Rare Disease Research Roadmap: Navigating the bioinformatics and translational challenges for improved patient health outcomes

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Abbreviations: CORD, Canadian Organisation for Rare Disease; EURORDIS, FP7, EU Framework 7 Programme; ICD, International Classification of Diseases; IRDiRC, International Rare Disease Research Consortium; NCATS, National Center for Advancing Translational Sciences; NORD, National Organisation for Rare Diseases

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Abstract
Rare disease registries have now been recognized as a global priority for progress both in monitoring and documenting the natural course, and preventing and treating rare diseases. However, a disease registry is only one element of rare disease translational research. Here, we outline what we believe are ten key components in comprehensive rare disease translational research and describe critical relationships between them. These components are: (i) client-practitioner partnerships; (ii) disease registries; (iii) biobanks; (iv) genomics and other *-omics* platforms; (v) community-based and population-wide studies; (vi) bioinformatics and high performance computing; (vii) interactions with pharma to facilitate drug discovery; (viii) personalized treatments based on genotype-phenotype correlations; (ix) eHealth and a whole of life record; and (x) regulatory frameworks, particularly with regard to specimen and data sharing, and the return of results. Each component has its own inherent complexity, but if effectively integrated they will provide a comprehensive approach to the future management of rare diseases, and aid health care providers in delivering services to individuals affected with rare diseases. We demonstrate that navigation through the roadmap can provide relevant health stakeholders with a blueprint to understand the challenges and barriers which need to be overcome within and across the constituent components. The rare disease roadmap will assist decision-making at all health stakeholder levels and enable the seamless integration of new knowledge, standard operating procedures and the implementation of best practice.

Introduction

Our understanding and appreciation of the complexity of the genetic basis of human disease, including rare diseases, is increasing rapidly. There are overlapping operational definitions of RDs and, for example, in Europe, an estimated prevalence of five or fewer affected persons in 10,000 is used. Using this definition, some 7–10% of people have one of the approximately 7000 rare diseases identified to date, 80% of which are genetic in origin [1].

The low incidence of each individual RD provides inherent challenges in ascertaining epidemiological data and recruiting sufficiently large cohorts for clinical trials or translational research. To address this shortcoming, there is for a need to establish global inclusive RD registries and biobanks [2–5] that facilitate the coordinated acquisition of fundamental disease information and research specimens to: (i) assess the health and economic impact of rare disorders individually or collectively; (ii) devise best practice disease management strategies; (iii) engage complementary national/international expertise; (iv) build sustainable academic, government and/or industry partnerships; and (v) develop large sustainable resources for translational research. Challenges and barriers that need to be overcome to facilitate these approaches include the international harmonization of informed consent, and specimen- and data-sharing practices.

In 2010, at the workshop, 'Advancing Rare Disease Research: The Intersection of Patient Registries, Biospecimen Repositories, and Clinical Data', the Office of Rare Disease Research (ORDR) at the National Center for Advancing Translational Sciences (NCATS)/NIH initiated a movement to create a global RD patient registry [3]. The workshop produced a set of recommendations, which are being implemented through the NIH/NCATS GRDRSM Program (The Global Rare Diseases Patient Registry Data Repository-GRDR – program – see https://grdr.ncats.nih.gov/).

More recently, EURORDIS, NORD and CORD issued a Joint Declaration of 10 Key Principles for Rare Disease Patient Registries [6], building on the European policy on rare disease.[1] This initiative is an important strategic step in enabling the diagnosis and treatment of patients with an RD. Additional considerations that can complement the principles of the Declaration include how registries interact with orphan drug development [7]; personalized and therapeutic interventions [8]; RD diagnostics and novel phenotyping strategies [9]; population-wide association studies [10]; rapidly evolving integrated bioinformatics advances [11]; public policy [12]; and international standardization [13]. We argue that, to make substantial advances in the translation of RD research to clinical practice, all of these activities must coalesce to avoid duplication, and that key conceptual and methodological advances need to be effectively shared and harmonized to promote rapid adaption to the ever-changing RD landscape.

In this paper we identify ten key components necessary for successful RD translational research and development. The ten components are: (i) client-practitioner partnerships; (ii) disease registries; (iii) biobanks; (iv) genomics and other *-omics* platforms; (v) community-based and population-wide studies; (vi) bioinformatics and high performance computing; (vii) interactions with pharma to facilitate drug discovery; (viii) personalized treatments based on genotype-phenotype correlations; (ix) eHealth and a whole of life record; and (x) regulatory frameworks, particularly with regard to specimen- and data-sharing and the return of results. The implementation of each component is extremely complex and all have associated challenges (or noise, to use an engineering analysis) that are

[1] http://www.eucerd.eu/?post_type=document&p=1234, http://www.eucerd.eu/?post_type=document&p=1218, http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_RDRegistryDataCollection_adopted.pdf