Indian Undiagnosed Diseases Program (I-UDP) – The Unmet Need

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Genomics is an integral part of many pediatric diseases spanning all sub-specialities. While many genetic disorders are diagnosed with the currently available genomic tests, there still are many patients who do not receive a definitive diagnosis. The Indian Undiagnosed Diseases Program is a multicenter effort to address these challenges and unmet needs of rare disease patients where current available genetic tests have failed to make a diagnosis. It embodies the principles of collaborative effort across multispecialty disciplines, and uses detailed phenotype. Diagnostic methods are tailored to patient specifics and the large genomic data is interrogated with precise, in-house bioinformatics pipelines using patient-specific phenotype to build the diagnostic algorithm. The inception of this research initiative in India is a step towards creating awareness and appreciation of the needs for our undiagnosed cohorts to enable appropriate management in this era of precision medicine.

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Rare diseases (RD) are conditions that affect a relatively small number of patients. It is estimated that these comprise 5000-8000 disorders and impact about 6-8% of the population [1]. Definitions of rare disorders vary in different countries and India still awaits to adopt a suitable definition [2]. Most of the rare disorders are of genetic origin. While they may be individually uncommon, as a group they substantially contribute to the healthcare burden. Rough estimates show that more than 50 million individuals in India are likely to be affected by rare disorders [3]. The biodiversity of the population groups in India, endogamous marriages, and high consanguinity rates, contribute to the high burden of genetic diseases.

Genetic tests including microarray and next generation sequencing techniques of panel/exome sequencing have made wide inroads into clinical care and there is a dynamic change in medical practice, not only of geneticists, but of many physicians at large. However, a definitive diagnosis is arrived at in only 25-50% patients using standard diagnostic procedures and these tests [4]. Many remain undiagnosed because of limited awareness, the small number of trained geneticists, inadequate representation and thereby the lack of attention, as well as limited access to diagnostic facilities within the healthcare system of the country. Other reasons for the microarray/exome negative undiagnosed cohort include mosaicism at tissue level, structural changes that are not identified by exome sequencing including variants in non-coding regions of the genome or in the regulatory regions. Complex, non-Mendelian patterns of inheritance including genetic and environmental modifiers also contribute to a negative exome analysis. Additionally, it could be a new gene for a clinically recognizable disorder or a previously undescribed syndrome awaiting gene identification [1,4].

Many emerging technologies including genome sequencing, proteomics and metabolomics, with enhanced computational expertise are gaining importance in the landscape of rare disorders. Physicians mostly work in isolation while evaluating a patient, but what is required for these disorders with multidimensional involvement is a multidisciplinary approach with specialists of different disciplines, bioinformaticians and scientists to solve the diagnostic puzzle. In absence of this, the disorders can remain unrecognized and unsolved [1].

The National Institute of Health (NIH), USA initiated an Undiagnosed Disease Program in 2008 for patients for whom diagnosis has eluded them [5]. The success of this program furthered the expansion to multiple sites in the US as well as the initiation of the Undiagnosed Diseases Network International (UDNI), in 2014, to address the worldwide needs of patients with challenging phenotypes and limited information to address this diagnostic conundrum. Many countries, including India, are members of this global call for rare disease patients. Other programs were initiated in many countries, including Deciphering Developmental Disorders in UK [6], Findings of Rare Disease Genes [7] and Care4Rare Canada Consortium [8] in Canada, contributing to the worldwide efforts.

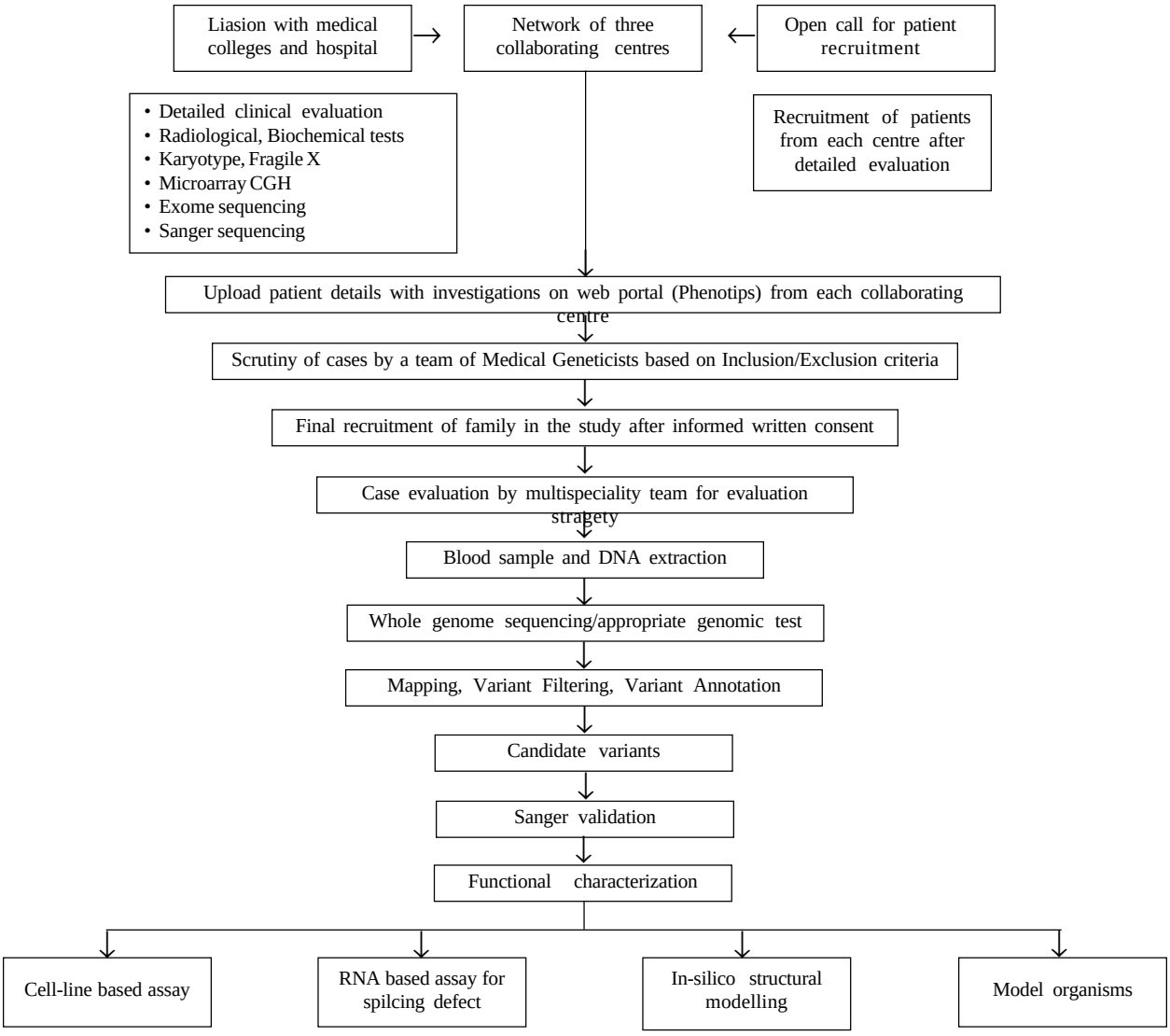

Fig. 1 Flowchart of work planned in I-UDP project.

There is a vast unmet need for rare disease gene discovery in India despite many novel genes having been described in the country [9]. These patients have long diagnostic odysseys, multiple physician visits, repeated laboratory tests with accumulated old documents, and families are spent emotionally and financially to understand the reason for their child's disorder [10,11].

There are two important concepts in working with patients with RD. Firstly, functioning within a multi-disciplinary, multi-specialty expert group allows precise phenotypic characterization. Secondly, delineating clinical features in a standardized vocabulary of clinical phenotypes, the Human Phenotype Ontology (HPO) [12], enables deep phenotyping for appropriate database search, as well as a bench-to-bedside approach to gene prioritization and discovery. Enabling a rare disorder diagnosis requires exchanging thoughts on phenotypes, and understanding etiological pathways, methods of gene identification and tools used for this to help in resolving some of these challenging cases.

The Indian Undiagnosed Diseases Program (I-UDP) was conceptualized on similar lines. This research project, funded by the Indian Council of Medical Research, commenced in February, 2021 with three participating sites - genetic units at Sir Ganga Ram Hospital, New Delhi; Sanjay Gandhi Postgraduate Institute (SGPGIMS, Lucknow, UP) and two centers at Hyderabad, Centre for DNA Fingerprinting and Diagnosis (CDFD) and Nizam's Institute of Medical Sciences (NIMS). The methodology involves a review of the submitted cases by the team of I-UDP. The challenging cases are

discussed first by a group of relevant multidisciplinary experts, followed by video conferencing between the participating sites. The aim is to enable a case-specific tailored approach and formulate a highly collaborative and coordinated format for clinical evaluation, detailed and standardized docu-mentation of patient phenotype with close bedside and bench collaborations (**Fig. 1)**. The undiagnosed diseases program enables a one-time, one patient, focused opinion, assessment, and advanced genetic testing. The strengths of this program are collaboration across multiple centers with multidisciplinary experts working together to enhance case-specific diagnostic algorithms, and allows access to all physicians in India to apply for inclusion of their patients with challenging genetic disorders in this program. This collaborative effort is expected to harness novel methods for providing diagnoses to patients, and also help science by identification of new genetic etio-logies using vast clinical material in India.

This initiative on rare and undiagnosed diseases is a great opportunity for identification of patients with rare disorders. Today, precision medicine requires gene mutation information, as a definite diagnosis has far reaching consequences for appropriate disease management, prognosis, recurrence risk and future reproductive options [13]. Additionally, the family looks to a closure of their prolonged diagnostic quest.

The I-UDP is important for patients who are spent emotionally and financially to find an answer to their disorder, the scientific community of doctors and researchers to further understand biology, and for our country, where the recent Rare Disease Policy 2021 [2] emphasizes the cognizance by the government about rare disorders and possibility of funding for treatment in the near future. In India, the realization of the important role of patient-parent organizations in supporting families with genetic disorders is coming forth and we want to use this opportunity of the change in landscape of patient care in the country. With the discovery of novel genes and identification of disease mechanisms and pathways, there is possibility of a future silver lining of therapies and precision medicine in the years to come.

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