The Italian Telethon UDP: a pilot research program

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Background

With a population of 60 million inhabitants, Italy has an estimated number of patients with a rare genetic disease of about 300-600k, as estimated by the Ministry of Health (2014 National plan for rare diseases). Unfortunately, this number does not take into account those patients with a genetic condition without a diagnosis.

Since 1990 the Telethon Foundation, an Italian biomedical research charity, has been involved in studying neglected genetic diseases and funds projects spanning from basic science up to clinical trials. In 2016, Telethon launched the first undiagnosed diseases program (UDP) in Italy, a pediatric pilot program based on an in-depth clinical and genetic analysis of patients without diagnosis.

The program

Telethon UDP is coordinated by the Telethon Institute of Genetics and Medicine (TIGEM) and is based on a three-step assessment:

- case sheet evaluation by a dedicated web-based platform,
- clinical evaluation,
- genetic analysis by next generation exome sequencing analysis.

The first steps could lead to clinical diagnosis; if not the patients will undergo sequencing. Patients will be evaluated by one of the three participating clinical centers located in north, center and south Italy, respectively in Monza, Rome and Naples (Fig. 1). The program will rely on the technological expertise of next generation sequencing team at TIGEM.

The whole exome sequencing will be performed on family trios using Illumina platforms.

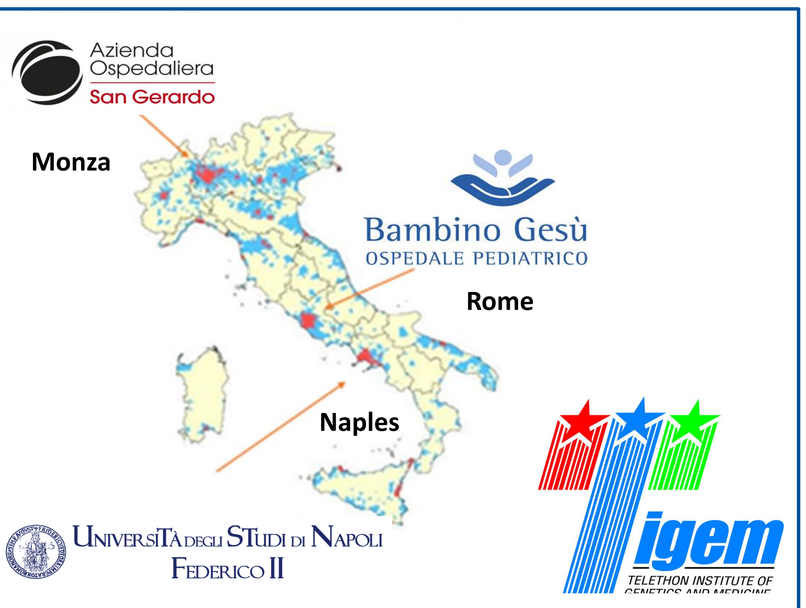

Fig. 1. Geographical distribution of participating centers.

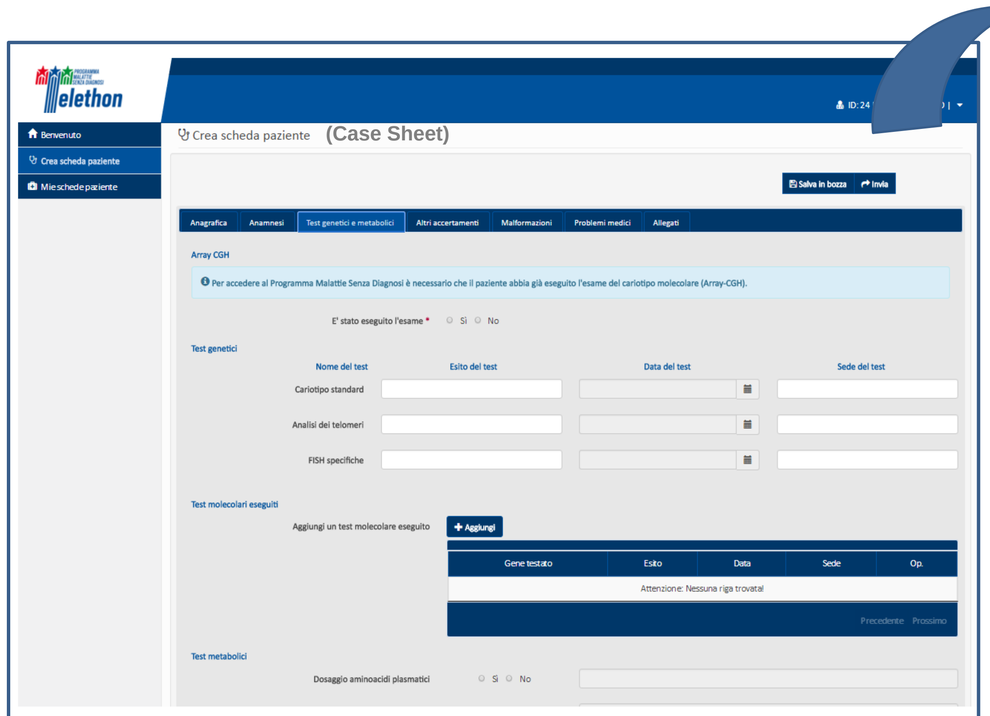

Fig. 2. The web-based platform. A case sheet.

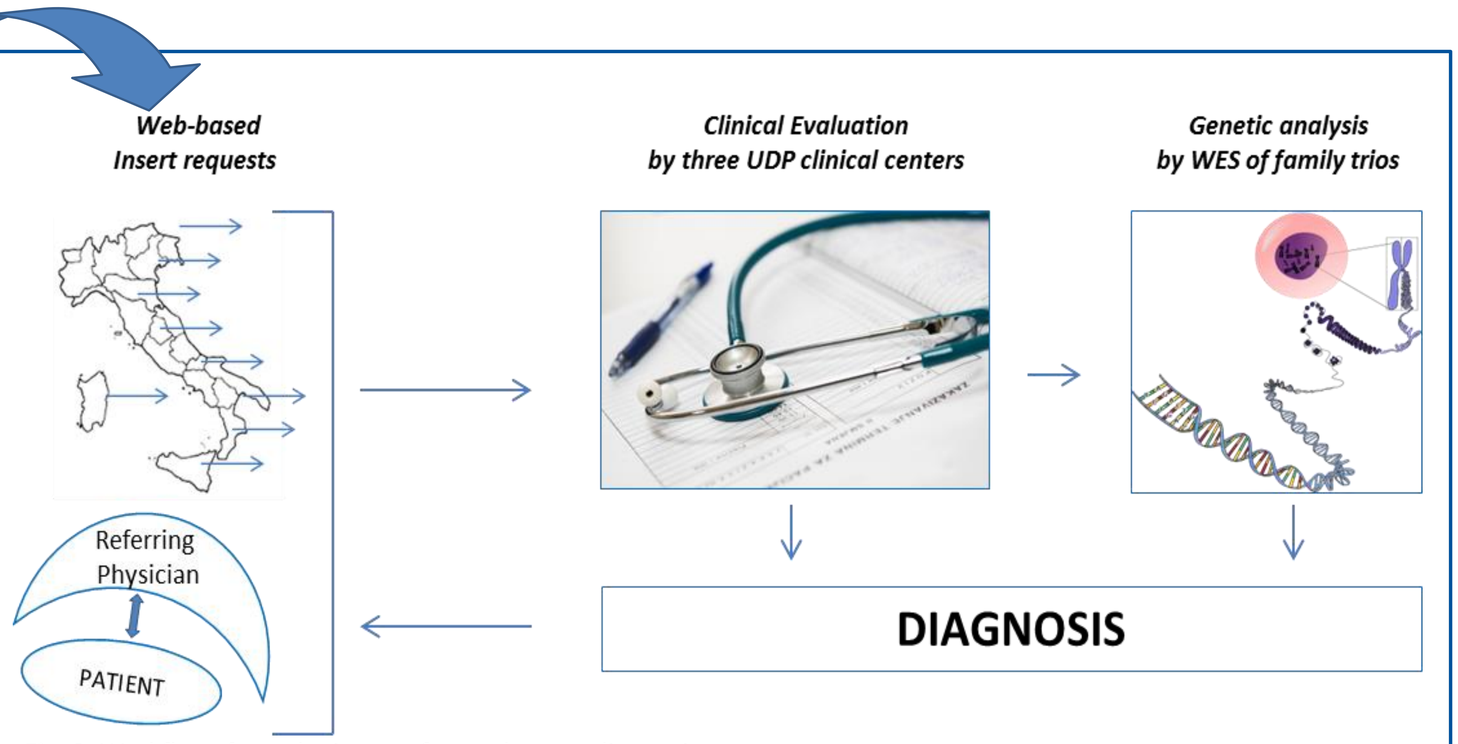

Fig. 3. Workflow: from the insert of case sheet to diagnosis.

Experimental Plan

This study will include pediatric patients affected by complex diseases of unknown etiology.

- Referring physician will candidate patients affected by suspect orphan and genetic diseases (OGD) by a web-based platform, creating a "case sheet" (Fig. 2).
- Clinical geneticists will evaluate the "case sheet" for the identification of a candidate OGD patient (Fig. 3).
- Candidate OGD patients will be clinically evaluated in one of the centers and will be classified as either bona fide OGD or possibly affected by a known disease.
- Blood/DNA samples will be collected from the OGD patient and his/her parents and available sisters and brothers for the genetic analysis.
- WES analysis in trio will be performed by high-coverage NGS.
- DNA variants will be shared and matched with those of similar phenotypes throughout the world (Fig 4).
- Results will then be returned to families.

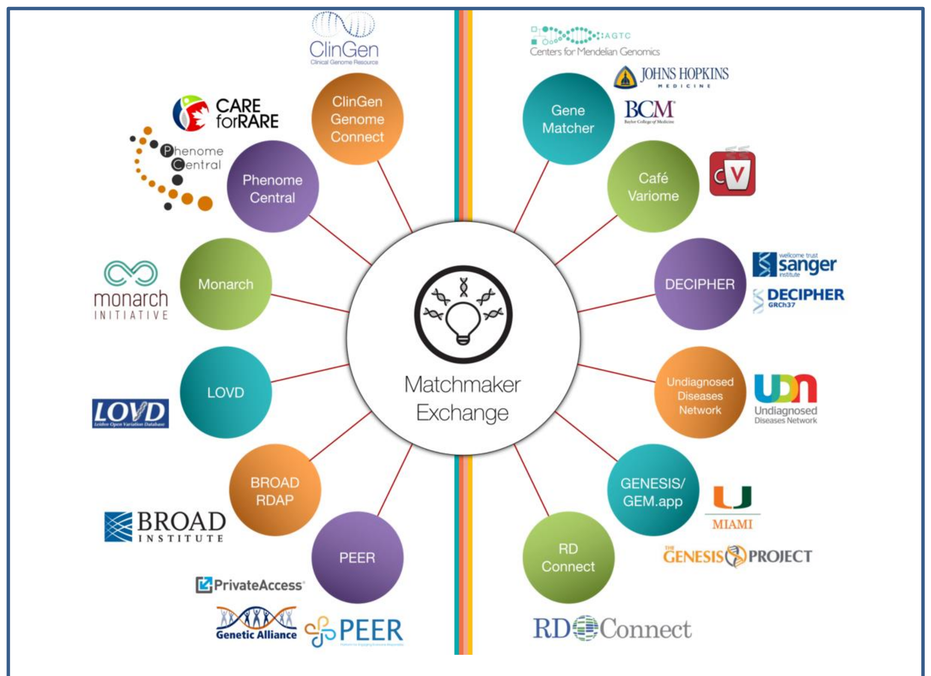

Fig. 4. Sharing data and looking for the "second case": MatchMakerExchange.

Expected Results

In a time-frame of three years, the Telethon UDP aims at identifying the causes of undiagnosed genetic diseases in an estimated number of about 350-400 families (1200-1500 individuals).

The UDP team will collaborate with international programs and specific efforts will be focused on data sharing with the goal of identifying "second cases". This task will be accomplished by the use of internationally adopted bioinformatics tools (databases, repositories, softwares) such as Phenotips and MatchMakerExchange (Fig. 4).

This program will respond to the strong needs of patients without diagnosis while providing new knowledge on extremely rare genetic diseases.

Info :

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