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 funding projects on basic and clinical research. In 2016, **Telethon launched the first undiagnosed diseases program (UDP) in Italy**, a **paediatric pilot program** based on an **in-depth clinical and genetic analysis of patients without diagnosis**.

The program

Telethon UDP is a **three years** pilot program started on **April 4th 2016**. Its **goal** is to provide a diagnosis to **patients** with a **genetic disease without a name.** This task will be accomplished through the collaboration among **three Italian clinical centers** leaded by doctors Bruno Dallapiccola, Angelo Selicorni and Nicola Brunetti-Pierri in **center, north and south Italy**, respectively in Rome, Monza and Naples (Fig. 1). The program is coordinated by Prof. Vincenzo Nigro at the intramural Telethon Institute of Genetics and Medicine (Tigem) in Pozzuoli – Naples, where the DNA sequencing will take place.

The genetic analysis is focused on the sequencing of the most informative part of human genome, the **exome**. The **DNA variants** associated to the disease will be identified by the analysis of patient's DNA and his/her parents as well in a strategy named "**family trios**" that ensures a robust mutation identification.

The whole exome sequencing (**WES**) will be performed on family trios using **up-to-date** next generation sequencing **(NGS) platforms**.

Fig. 1. Geographical distribution of participating centers.

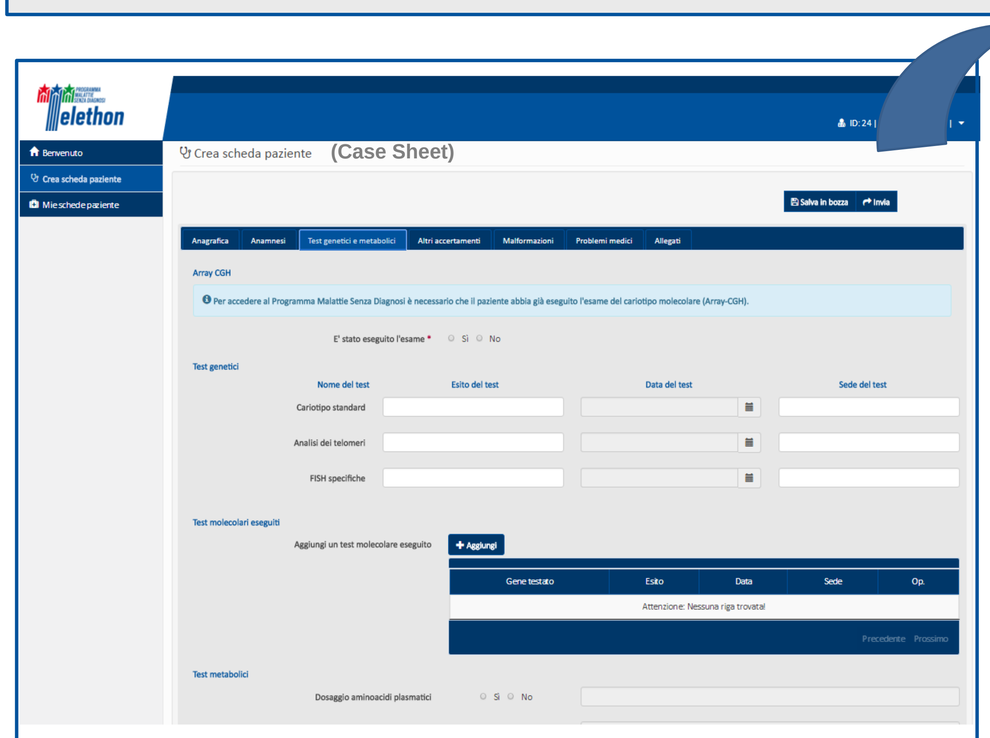

Fig. 2. The web-based platform. The "case sheet" page.

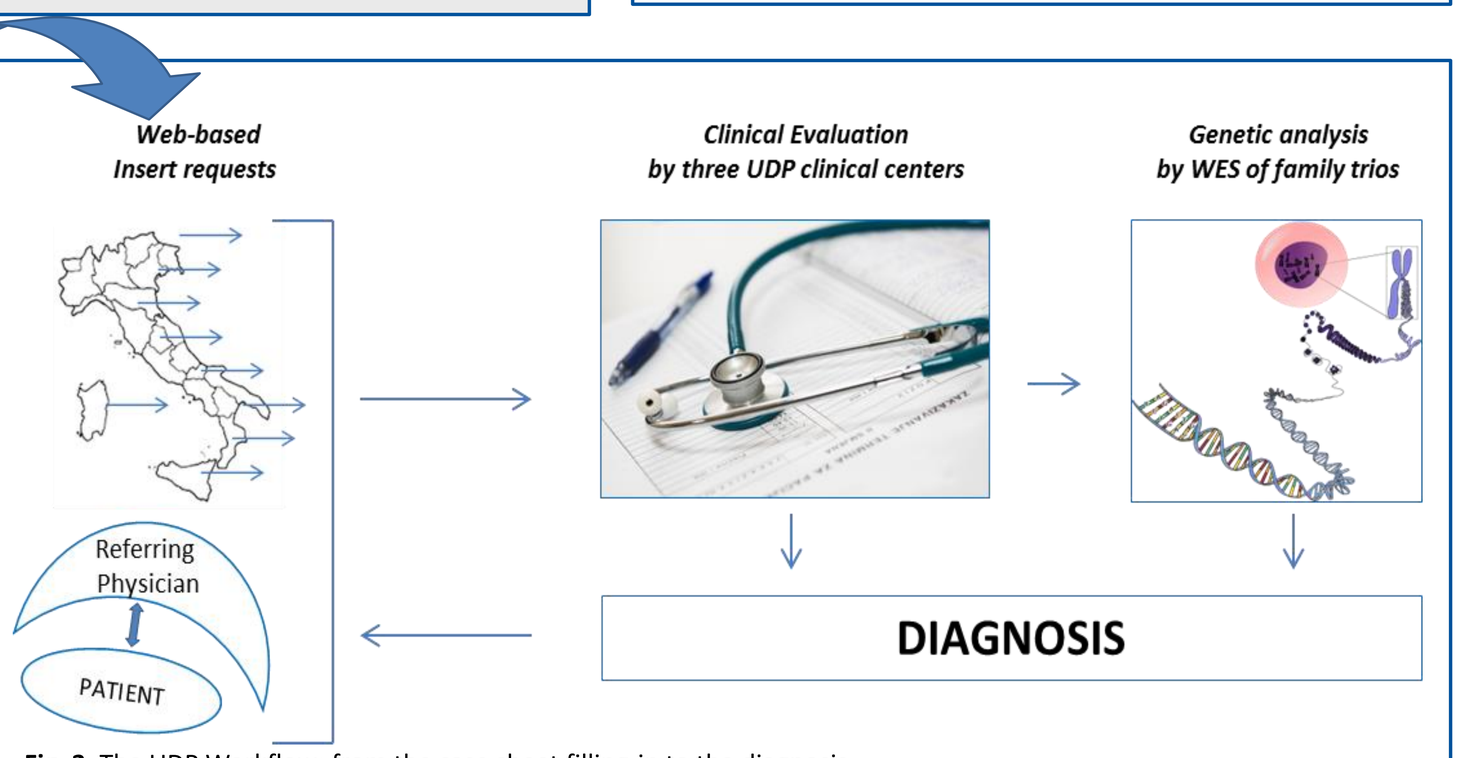

Fig. 3. The UDP Workflow: from the case sheet filling-in to the diagnosis.

Experimental Plan and Procedures

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** (100X on 80-90% of enriched target) using Illumina NexSeq 500 and HiSeq 3000 sequencers.
- DNA variants will be identified by a **bioinformatic pipeline analysis** and **shared/matched** with those of similar phenotypes throughout the world (Fig 4).
- Results will then be **returned to families**.

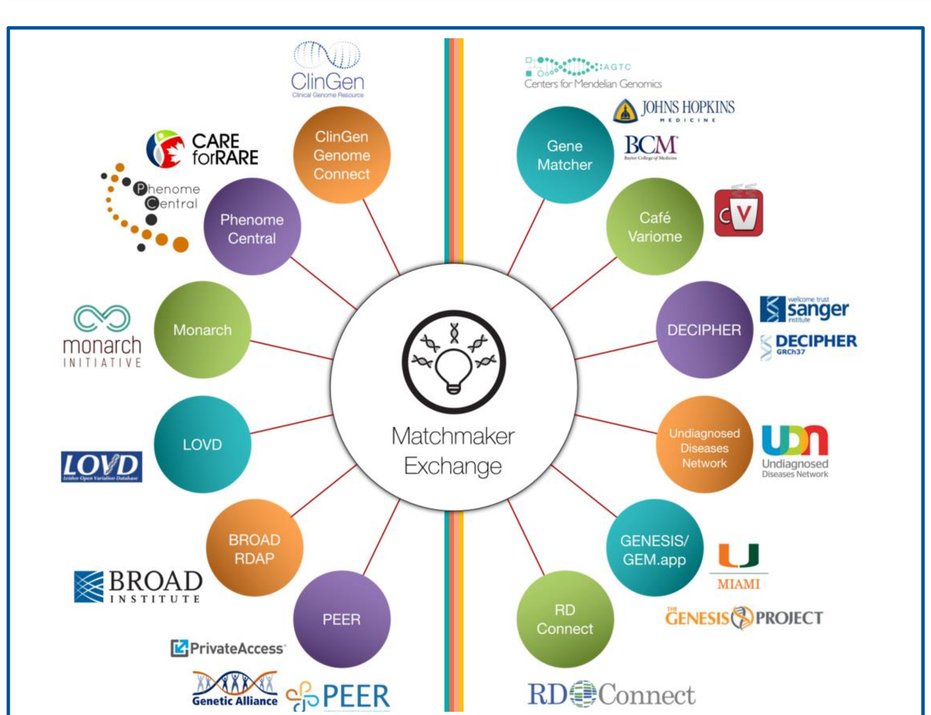

Fig. 4. Sharing data and looking for the "second case": **MatchMakerExchange**.

Scan me for more details!

Info

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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, and repositories) such as *Phenotips* and *MatchMakerExchange* (Fig. 4).

Impact

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