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MINI REVIEW

What is MAGI?

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Abstract
MAGI is concerned with research and diagnosis of rare genetic diseases. It has been operating since 2006 in Italy and abroad. Today it has three centers in Italy, including a medical genetics laboratory specialized in next generation sequencing in Bolzano, a medical genetics laboratory specialized in MLPA in Rovereto (Trento) and a genetic diseases information center at San Felice del Benaco (Brescia). MAGI has also invested outside Italy, setting up non-profit genetics laboratories in countries such as Albania, Russia and in the near future, Kazakhstan

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Introduction
MAGI is an organization for the diagnosis, research and therapy of genetic and especially rare genetic diseases. It consists of a medical genetic laboratory and a non-profit branch dedicated to scientific research and training. MAGI has been operating since 2006 from its headquarters in Rovereto, Trentino Alto-Adige/South Tyrol, Italy.

The Magi group now employs more than 30 persons, including young doctors, researchers and other highly qualified personnel. It has three centers in Italy, another in Tirana, Albania, and a laboratory in the Krasnoyarsk State Medical University, Siberia. The centers in Italy include a Research Institute and two molecular biology laboratories specialized in the diagnosis of genetic disorders and in research of autoimmune diseases by the latest human genetics technologies: state-of-the-art equipment allows analysis by different methods, such as diagnostic testing by next generation sequencing, direct sequencing (Sanger) and multiplex ligation-dependent probe amplification. For research, MAGI has a cell culture unit with a laminar-flow hood, a plate reader, a fluorescence microscope and western blot and immunoprecipitation equipment, and a molecular biology unit with various thermocyclers and an Agilent 2100 bioanalyzer.

MAGI is a member of the Alliance for Health Promotion and the FederazioneSanità Confcooperative, where Dr Bertelli is national consultant.

MAGI Charity Program
Testing for rare and hereditary diseases is now becoming a common diagnostic tool since the availability of better and more effective options for the treatment of certain diseases.

Most insurance covers genetic testing services, but each situation is unique. If a patient is uninsured or unable to cover the costs, MAGI offers genetic and biochemical testing free of charge on a research basis through its Charity Program (1).

MAGI'S mission
MAGI is committed to raising awareness and promoting knowledge. It organizes annual scientific congresses on genetic diseases. Invited speakers have included figures of great

Figure 1. Prof. Rita Levi Montalcini and Dr. Matteo Bertelli

prestige such as Nobel Laureates Rita Levi-Montalcini and Aaron Ciechanover, as well as Lucio Luzzatto (Nobel candidate), Luca Cavalli Sforza (Nobel candidate), Giorgio Brunelli (Nobel candidate) and Antonino Zichichi (President, World Federation of Scientists). MAGI laboratory's diagnostic work on several groups of rare genetic diseases has earned it recognition in Italy and the privilege of presenting its results to the Health Commission of the Italian Senate and the Chamber of Deputies.

Figure 2. Prof. Lucio Luzzatto and Dr. Matteo Bertelli

Some major events have been:

13 April 2012, Rome: "Presentation of clinical and genetic study of patients with inherited retinal dystrophies with Mendelian inheritance" before the Senate of the Italian Republic by:

- Prof. Giovanni Staurenghi, Department of Clinical Sciences and Hospital "Luigi Sacco", University of Milan;
- Dr. Chiara Olga Pierrottet, University Clinic of Ophthalmology, Hospital San Paolo, Milan;
- Prof. Benedetto Falsini, University Hospital "A. Gemelli", Rome

13 June 2013, Brussels: presentation of the *European Catholic Clinical Network against Genetic and Rare Diseases* at the Tyrol–South Tyrol–Trentino Euregio headquarters by:

- Prof. Sandro Michelini, Director, San Giovanni Battista Hospital of the Order of Malta, Rome
- Prof. Ettore Raul Mattassi, Angiology and Vascular Surgery Dept., Clinica Humanitas Mater Domini, Castellanza, Varese.

9 July 2015, Rome: presentation of "Results of healthcare cooperation in the fight against rare genetic diseases" at the Italian Presidential Palace by:

- Dr. Natale Capodicasa, Director MAGI BALKAN, Albania
- Mr. Ilir Beqja, Minister of Health of Albania.

13 July 2017, Rome: presentation of "Networking centers for genetic and rare diseases: experience of MAGI" at the Library of the Italian Senate "Giovanni Spadolini", by:

- Dr. Leonardo Colombo, Ophthalmology Clinic, ASST Santi Paolo e Carlo, University of Milan.

23 September 2017 Tirana: presentation of "Course in Genetics and Biotechnology" at Tirana International Hotel by:

- Dr. Natale Capodicasa - Director of Magi Balkans
- Prof. Bruno Amato, Department of Clinical Medicine and Surgery, University of Naples "Federico II"
- Prof. Ettore Raul Mattassi, Head of Angiodysplasia Center, Mater Domini Clinical Institute, Castellanza, Varese
- Prof. Sandro Michelini, Department of Physical Medicine and Rehabilitation, St. John the Baptist Hospital of the

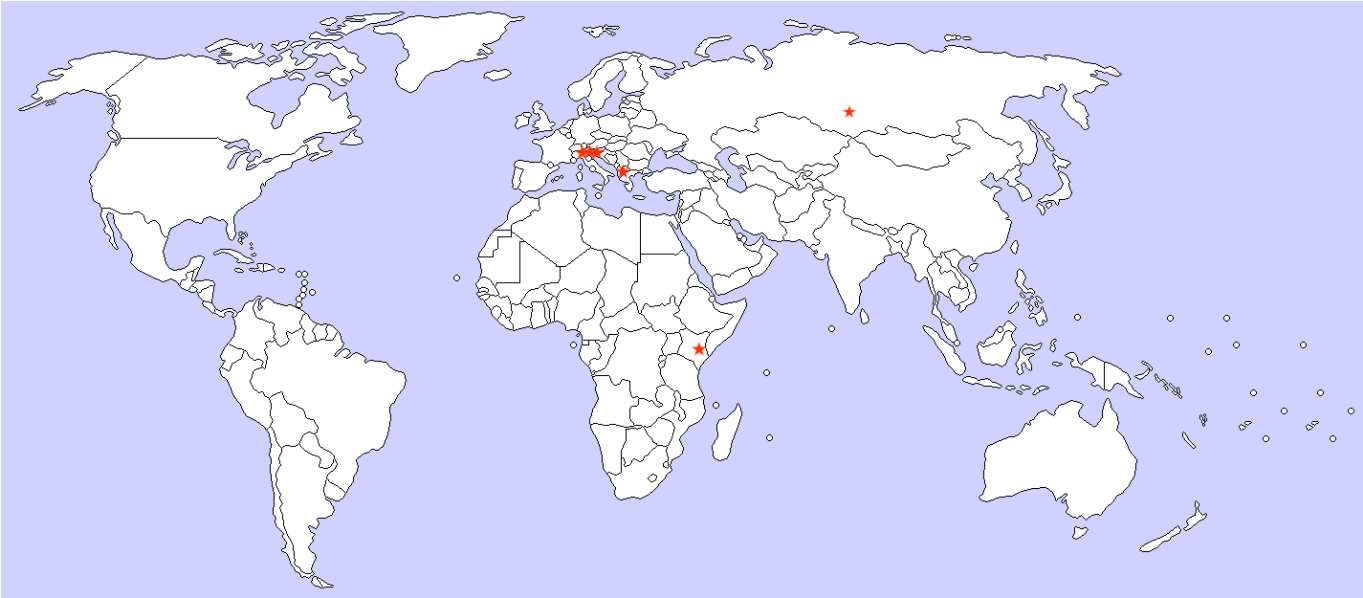

Figure 3. MAGI centers in Italy, Albania, Siberia and Africa

Knights of Malta, Rome
- Prof. Tommaso Beccari, Department of Pharmaceutical Sciences, University of Perugia
- Prof. Munis Dundar, President of the European Biotechnology Network Association.

Scientific production

MAGI group has collaborations with different institutes in Italy and abroad. Its many scientific articles can be viewed on our web site http://www.magi-group.eu/en/scientific-production. Areas of special interest include hereditary retinal dystrophies, lymphatic system anomalies and vascular malformations.

For retinal dystrophies we developed an NGS panel containing all the genes associated with retinal dystrophies. The test is useful for all genetic forms of eye disease. We contributed to the discovery of a new mutation related to cone rod dystrophy affecting the ciliary gene and KIZ protein (2). We also collected statistical data on electrophysiological aspects of Stargardt disease (3) and choroid thickness in patients with Usher syndrome (4). Our interest in retinal dystrophies also covers those with an autoimmune cause. We are currently working on a project to identify the autoantibody target that leads to blindness in autoimmune retinopathies for the purpose of developing an ELISA assay for its detection.

For lymphatic malformations with or without lymphedema we created an NGS panel for Mendelian forms and another for somatic forms (5). We have the biggest study cohort in Italy and one of the biggest in Europe. We contributed to a comprehensive clinical genetic description of the state of the art regarding lymphatic malformations and the techniques used for their diagnosis, defining guidelines for genetic testing. We also prompted the Italian parliament to recognise lymphedema as a rare disease. Our functional work on six variants in *FOXC2, a* gene associated with lymphedema-distichiasis, first reported in our case studies, led to the definition of their pathogenic potential: either complete loss or a significant gain in *FOXC2* function can disturb lymphatic vessel formation leading to lymphedema. Our molecular data therefore suggests a relation with epidemiological data indicating a higher frequency of tumors in patients with lymphedema (6).

For vascular malformations we created an NGS panel with the genes currently most prevalent identified in patients with vascular anomalies of Mendelian inheritance or somatic forms. We have analysed blood and tissues in more than 200 cases of primary MAV. Multigene panel sequencing by NGS facilitates identification of the disease-causing gene, allowing rapid molecular diagnosis and providing important data for defining genotype-phenotype correlations, determining segregation and establishing the risk of the disease in families. It may also help provide appropriate clinical management, monitoring and treatment of patients, especially those with complex syndromes (for example Loeys-Dietz). Defining the molecular diagnosis therefore paves the way for the development of new generation therapies that act specifically on the mutant gene or for adoption of therapies already developed for other purposes (7).

MAGI in the international network

MAGI has also been involved in various international projects, some with developing countries, offering study grants and hospitality to young graduates. Grant holders have been from the Czech Republic, Albania, Slovakia, India, Russian Federation, Argentina, Kenya, Belarus and Kazakhstan. Graduates are given the opportunity to work in top Italian research institutes and hospitals, directed by University teaching staff having long collaboration with MAGI. MAGI has also invested in setting up MAGI-model non-profit genetics laboratories in countries such as Albania (8), Russia(9, 10) and soon Kazakhstan.

ORPHANET, an organization to coordinate and manage services for diagnosis and therapy of rare genetic diseases, is helping spread knowledge in Europe and neighboring coun-

tries. Next year the European health service should be active, allowing patients to seek care in other countries and laboratories to exchange samples for genetic tests for very rare diseases. Indeed, for certain genetic diseases, there are only three laboratories in Europe (e.g. MAGI, London and Paris University labs for hereditary lymphedema).

In order to harmonize high quality standards of healthcare for citizens, MAGI wishes to create links in a European network that would enable patients with rare genetic diseases to overcome local absence of facilities for molecular diagnosis. It wishes to initiate a common effort to deliver services that can reach as many people as possible, improving the availability of genetic testing, improving links between labs for mutual benefit and favoring economic development of disadvantaged areas across Europe.

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