R&I GENETICS

# SERVICE CHARTER

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## R&I GENETICS srl.

Genetic Diagnostic Laboratory

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## INTRODUCTION

With the Service Charter, R&I Genetics aims to present its principles, programs, and services that it commits to guarantee to all interested parties. The Service Charter is intended to provide a tool for participation and protection of rights for those who request its services. The Service Charter outlines the organization, programs, and commitments of R&I Genetics as a whole. Further information is available on the company's website www.rigenetics.online, where documents related to analyses can be downloaded or online reporting can be accessed.

R&I GENETICS

R&I GENETICS, a limited liability company (srl), is a certified clinical diagnostic laboratory that specializes in genetic testing, particularly in the area of rare diseases.

The laboratory, accredited within the Italian National Health Service (Servizio Sanitario Nazionale), provides comprehensive diagnostic genetic services ranging from single gene sequencing to whole exome or genome analysis for specialist diagnosis of patients with a suspected genetic disorder causative of a rare constitutive disease in different medical fields (e.g. neurology, ophthalmology, pediatrics etc.)

To this end, the laboratory also pursues research activities, primarily focused on improving current test methodologies and introducing new genetic tests within the laboratory, with a constant focus on the clinical needs and technical-scientific advancements in the field

The Laboratory *and its Cutting-edge Technologies*

R&I GENETICS is located in Padova in the 8$^{th}$ floor of the prestigious Pediatric Research Institute (IRP). The workspace, consisting of approximately 600 square meters, comprises fully equipped, state of the art, molecular diagnostic laboratories (wet and dry), in addition to research and office spaces. Available facilities, ensuring the most advanced diagnostic technologies, include high-throughput next-generation sequencing (NGS) technologies for exome and genome analysis, new cutting-edge bioinformatic computing techniques and unique, original, software programs and databases for data interpretation.

*Staff and Professionalism*

With over 20 years' experience in molecular research and diagnostics, the staff at R&I Genetics, has been at the forefront of genetic innovation, pioneering new technologies (e.g. microarray, NGS sequencing) into application for the diagnosis of genetic diseases.

A characteristic of R&I is its high degree of staff specialization, continuous updating and professional experience. This is, in addition to hard work and passion, promoted and supported through internal meetings and discussion, participation in international scientific congresses/ conferences/workshops and refresher courses.

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## Mission and Values

R&I GENETICS seeks to achieve excellence in the area of advanced diagnostic genetic testing in rare diseases so as to best support healthcare professionals in advancing precision medicine in genetically determined conditions in a timely and appropriate manner, with continuous attention devoted to the needs of the patients and quality of the services delivered.

The values and principles which inspire and guide R&I include:

- Clinical needs and Patient focus
- Continuous quality improvement
- Service excellence
- Multidisciplinary versatile approach to genetic testing
- Applied research development and continuous up-date of current methodologies

*Founding Principles and User/Patient Rights*

In perusal of the above, R&I GENETICS is committed to ensuring respect of the following *founding principles and patient rights:*

- *Equality*: all citizens/users are entitled to the most appropriate available services regardless of age, gender, ethnic origin, religious beliefs, nationality, culture, social status or political views;
- *IMPARTIALITY*: staff conduct towards all citizens/users is guided by criteria of objectivity, fairness, justice, impartiality and empathy;
- *CONTINUITY:* Each citizen/user is entitled to appropriate and continuous healthcare services, using the most advanced scientific knowledge along with the best technologies. In the event of malfunction or interruption of a service, measures are taken to provide users with as little discomfort as possible;
- *RIGHT TO CHOOSE*: each citizen/user has the right to choose their healthcare provider that best matches their needs. They are also free to request for second professional opinions or present suggestions/complaints without the fear of compromising the quality of the services provided;

- *INFORMATION AND PARTICIPATION*: consensus in the prevision of a service must be guaranteed in line with current legislation through accurate, clear and complete information. Users have the right to access information regarding the services provided and put forward suggestions or complaints on how to improve their quality.
- *QUALITY:* R&I GENETICS is committed to ensuring high quality services for its users/patients. It does this by adopting appropriate measures to guarantee their continuity, efficiency and effectiveness., in line with the latest national and international guidelines and up-to-date standards.

  To this end, R&I GENETICS has implemented a QUALITY SYSTEM (UNI EN ISO 9001:2015) that establishes the standards and sets out the rules for verification of compliance by means of internal and external inspections regarding the quality of the services (genetic tests) delivered in accordance with the current ITALIAN legislation (D.L. 502/92 art. 12, comma 2, lett. a) and national (e.g. SIGU, Societa' Italiana di Genetica Medica,) and international (e.g. ACMG, American College of Medical Genetics) guidelines in the field.

- *EFFICIENCY AND EFFECTIVENESS*: the services are delivered in such a way as to ensure efficiency and effectiveness, employing the best optimal resources and modalities available to satisfy the healthcare need requested. The efficiency of the services also includes the safeguarding of resources, which are employed without wastage or unnecessary costs.

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# GENETIC TESTING SERVICES

Research over the last decades has resulted in the identification of genes responsible for over 50% of the estimated 7,000 rare monogenic diseases. This achievement is the result of dramatic improvements in DNA-testing methodologies, particularly next generation sequencing technologies and the associated analyses. As this has expanded, so have the types and numbers of genetic tests increased in the last years

Using molecular genetic diagnostics, R&I Genetics support the referring physician in making a diagnosis, and in many cases, can also make recommendations for treatments and therapies. We can also provide information on disease progression and prognosis. Family members may also receive a risk assessment on the basis of heredity.

*Information and Consent*

Given the peculiarity of genetic testing not only for the patient but also his/her family members, obtainment of informed consent is obligatory, following receival of appropriate information about the risks, benefits, efficacy, and alternatives to the testing. This usually occurs upon consultation with a geneticist or other medical specialist in a pre-testing setting.

For R&I GENETICS, receival of informed consent is mandatory for conduction of a genetic test. In addition, R&I GENETICS accepts referrals for genetic testing for clinical purposes within the Italian National Health Service solely from a clinical geneticist or other medical specialist operating within the healthcare system.

*Privacy Issues*

R&I GENETICS takes great precaution to protect patient's privacy very seriously.

Special measures are taken in place to anonymous samples and mandate that all staff members maintain the confidentiality of patients' personal health information, which includes both medical information and individually identifiable information about any patient, such as address, phone number or Social Security number that they may come in contact with that could reveal the person's identity. Data security measures and protocols have been implemented so that the personal and sensitive details of the patients concerned is processed in an appropriate manner in accordance with current legislation in the field.

Genetic test results are solely provided to the requesting medical specialist authorized by the patient. Otherwise, R&I GENETICS prohibits the unauthorized disclosure of any health or sensitive information except as required by law.

Patients have the possibility to exercise their rights in accordance with the current Italian legislation (GDPR 2016/679, art. 15-22)

*Genetic tests: types and characteristics*

The arrays of DNA based tests currently available at R&I GENETICS for diagnosis of human genetic diseases include:

- *Targeted mutation analysis*:

  These types of test search for a specific DNA variant in one gene. The selected variant is known to cause a disorder. It is often used to test family members of someone who is known to have a particular mutation, to determine whether the variant is inherited (family segregation studies) or whether other family members are affected.

- *Single gene sequencing*:

  These tests look for any genetic changes in one gene. These tests are typically used to confirm (or rule out) a specific diagnosis, particularly when there are many variants in the gene that can cause the suspected condition.

- *Gene Panels*

  These tests are designed to search for disease causing mutations (nucleotide and copy number variations) employing next generation sequencing technologies in any one of a number of genes that are known to be mutated in a specific type of disease. At difference with whole exome or genome sequencing (see below), gene panels are specifically used for the molecular diagnosis of diseases for which a small number of genes are causative of the pathological phenotype (i.e: hypercholesterolemia, Stargardt disease, neurofibromatosis, cystic fibrosis, etc…)

- *Whole exome /whole genome sequencing* and their analysis.

  These tests sequence the bulk of an individual's DNA to find genetic variations employing next generation sequencing technologies. While exome sequencing involves sequencing of all the

coding DNA regions, genome sequencing analyzes also the non-coding regions in one's genome.

Generally, exome sequencing is currently employed and targeted analysis is carried out, in relation to the clinical phenotype. In these cases, the whole exome is sequenced and analysis initially focuses on a subset of genes (virtual panel) potentially causative of a particular condition. This approach is particularly useful in establishing a molecular diagnosis in many genetic disorders characterized by clinical, genetic and phenotypical variability (see below)

- *comparative genomic hybridization (CGH) at high resolution* (400 x)

  This test is a molecular cytogenetic method for analyzing gains or losses in DNA that are not detectable with routine chromosome analysis. CGH can detect small deletions and duplications, but not structural chromosomal changes such as balanced reciprocal translocations or inversions or changes in chromosomal copy number.

- *Testing for repeat expansions*

  These genetic variations, not easily detectable, are highly important in human disease, particularly in the field of neurology. Because of this, R&I GENETICS has developed a number of different tests specific for different disorders. This includes testing for repeats in suspected C9orf72-related disorders, myotonic dystrophy 1, FRAXA, etc. Others are in progress.

It is estimated that the number of rare diseases due to gene defect exceeds 7,000. Many families with children with rare diseases experience the diagnostic odyssey that involves multiple specialist visits, laboratory and imaging studies and in some cases surgical procedures. Despite extensive testing in many cases diagnoses are not made or solely suspected. In some cases, establishing a correct diagnosis was complicated by unusual clinical presentation. In others, genetic heterogeneity of the disorder where defects in a number of different genes can give rise to the same clinical or syndromic manifestations, complicates reaching a diagnosis. At times, defects in a specific gene may lead to presence of different subsets of clinical manifestations in a specific patient. Also, for many genetic disorders the most characteristic features of that disorder are not present in young infants. Furthermore, defects in a specific gene may lead to presence of different subsets of clinical manifestations in a specific patient.

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*Genetic Tests: availability in different medical specialties*

| Medical Specialty | Gene Panel | Includes |
|---|---|---|
| Ophthalmology | Non-syndromic Retinal Diseases | retinitis pigmentosa, Stargardt diseases, vitreoretinal diseases, macular dystrophies, congenital night blindness, cone rod dystrophies, fundus albipunctatus |
| | Usher syndrome | |
| | Albinism | |
| | Waardenburg syndrome | |
| | Optic Atrophy | Mitochondrial mutations |
| | Stickler Syndrome | |
| | Piebaldism | |
| | Congenital Cataract | |
| | Coloboma | |
| | Congenital Glaucoma | |
| | Congenital Nystagmus | |
| | Microphtalmia and Anophtalmia | |
| | Anterior segment dysgenesis | |
| Neurology | Neurodevelopmental disorders | Syndromic and non-syndromic, autism |
| | Brain Malformations | |
| | Microcephaly | |
| | Macrocephaly | |
| | Craniosynostosis | |

| | | |
|---|---|---|
| | Epilepsy | Syndromic and non-syndromic, developmental epilepsy, epileptic encephalopathy, focal epilepsy, neonatal benign epilepsy, temporal epilepsy, febrile epilepsy |
| | Motor-neuron diseases | ALS, spastic paraplegia, distal motor neuropathies, C9orf72 repeat expansion |
| | Neuropathies | Axonal, demyenilating, distal motor, autonomic |
| | Myopathies | Dystrophic, congenital, metabolic and mitochondrial limb-girdle |
| | Ataxia | |
| | Dystonia | DMPK repeat expansion |
| | Small Vessel Cerebral disease | Stroke, hemiplegic migraine |
| | Alzheimer | |
| | Parkinsonism | |
| | Dementia | C9orf72 repeat expansion |
| | Ciliopathies | Joubert syndrome, Meckel syndrome, Bardet-Biedl syndrome |
| | Leukoencephalopathy | |
| | Non syndromic hearing loss | Neurosensorial and conductive |
| Cardiology | Arrhythmias | Brugada syndrome, atrio-ventricular block, atrial fibrillation, LVNC, long and short QT |

| | | |
|---|---|---|
| | Cardiomyopathies | Hypertrophic, dilatative, restrictive, LVNC |
| | Congenital heart defects | |
| | Rasopathies | Noonan disease, neurofibromatosis |
| Endocrinology - Metabolism | MODY | |
| | Diabetes | Neonatal diabetes, infancy diabetes, insulin resistence, hyperinsulinism |
| | Glycogen diseases | |
| | Glycosylation diseases | |
| | Hypercholesterolemia | |
| | Mitochondrial diseases | Nuclear genes affecting mitochondrial metabolism |
| | Hypogonadism | |
| | Disorders of sex differentiation | |
| Dermatology | Epidermolysis Bullosa | |
| | Congenital Ichthyosis | |
| | Peeling skin syndrome | |
| | Palmoplantar keratosis | |
| | Rasopathies | Noonan disease, neurofibromatosis |
| | Monilethrix | |
| Nephrology | Nephronophthisis | |
| | Autosomal Dominant Polycystic Renal disease | PKD1 |
| | Polycystic hepato-renal disease | |
| | Nephrotic syndrome | |
| | Tubulo-interstitial diseases | |

| | | |
|---|---|---|
| | Tubulopathies | |
| | Proteinuria | Nephrotic syndrome, Alport Syndrome, syndromic syndromes |
| | Alport Syndrome | |
| | Uremic hemolytic anemia | |
| Gastroenterology | Cholestasis | |
| | Metabolic liver diseases | |
| | Glycogenosis | |
| | Alagille syndrome | |
| | Liver fibrosis | |
| | Polycystic hepato-renal disease | |
| | Pancreatitis | CFTR |
| | Very early onset inflammatory bowel disease | |
| | Congenital diarrhea | |
| Skeletal | Congenital Short Stature | |
| | Skeletal Malformations | |
| | Jeune disease | |
| | Craniosynostosis | |
| | Ospetopetrosis | |
| | Osteogenesis imperfecta | |
| | Arthrogryposis | |
| Immunology | Autoinflammation and Autoimmunity | Periodic fevers |
| | Immunodeficit | SCID and CVID |
| | Hypogammaglobulinemia | |
| | Deficit of the complement system | |

*Test Reports*

According to the Italian law and the recommendations of the Italian society of human genetics (SIGU), genetic reports are delivered to the requesting physician.

The report contain:

- Patient informations
- Genetic results summary
- Detailed information concerning the genetic variations found in the patient
- Comments and interpretation in which we summarize the current state of scientific literature for the variants found and discuss them in relation to the patient.
- Additional information: at the end of the report, we present technical information. This includes information such as technology used, limits and bioinformatic parameters.

Reports are available within 8-12 weeks after receiving the sample for multigene panels constituted of less than 200 genes, for genetic tests requiring > 200 genes referral times are 24-32 weeks.

## COMPLAINTS

If you have a concern or complaint about our work, we want to hear from you. We continuously try to improve the work we do and we value any feedback that will help us to do this. We take all feedback seriously and we will take action when appropriate to do so. All complaints will be dealt with in a timely and professional manner.

If you would like to formally raise a concern or complaint please write to:

R&I Genetics Srl
C.so Stati Uniti 4, int. F
35127 Padova (IT)
or e-mail us:
info@rigenetics.com
genmed@rigenetics.com

Including the following details will help us to effectively and quickly investigate your complaint:

- Your name and contact details: this is essential as we will not investigate anonymous complaints.
- The specific area, service or resource to which the complaint applies.

## COMMITMENTS AND PROGRAMS

Striving for excellence

Continuous improvement of the quality of services is one of the main objectives of R&I GENETICS. To achieve and maintain its standards of excellence, at R&I GENETICS has developed an improvement process based on a rigorous quality plan modelled on some of the top national and international benchmarks (latest ISO standards, European guidelines etc.) now extended to all activities

Users/Patients may also actively contribute to our improvement process, by submitting suggestions (or reporting malfunctions), or participating in our patient satisfaction surveys.

## ACCESS TO THE SERVICES

According to the Italian law, genetic test can be requested only by medical specialists and genetic counsellor.

Blood or DNA samples must be accompanied by the compiled and signed consent form and request form available at www.rigenetics.online.

Administrative and payment information are available upon request (see contact information)

## CONTACTS

R&I Genetics laboratories are in Padova, Corso Stati Uniti 4, int. F.

Opening hours: Monday to Friday from 8:30 a.m. to 5:30 p.m

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