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ARTICLE

Genetic testing in Italy, year 2004

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A comprehensive and long-range monitoring of genetic testing is ongoing in Italy starting from 1987. The data collected by the last survey of year 2004, on behalf of the Italian Society of Human Genetics, included the activities of 88 clinical centres and 160 cytogenetic and 183 molecular genetic laboratories, hosted by 256 structures. Only 42% of them fulfilled the requirements of current Italian legislation. Genetic tests included 283 601 cytogenetic analyses. There have been 120 238 invasive prenatal samplings, 84% of which were amniocenteses. A significant north-to-south decreasing gradient was evident for all activities. This study has also surveyed 190 610 molecular genetic tests. *CFTR* gene analysis accounted for 23% of prenatal and 29% of postnatal molecular tests. In total, 420 different genes have been investigated, 10 of which comprised three-quarters of the whole activity. More than 10% of molecular tests were performed on fetal samples, the analysis of *CFTR, DMD, FMR1, FMR2*, and *GJB2* genes accounting for 83% of all prenatal tests. In years 1997–2004, the demand of cytogenetic tests has increased two-fold and that of molecular tests has increased four-fold. Only 16% of cytogenetic and 12.5% of molecular tests have been followed by genetic counselling. This survey highlights the need for a major basic intervention in the general organisation of genetic structures in Italy, which should be rationalised in accordance with the national guidelines, and the necessity of constant training of general practitioners and education of consumers to the appropriate use of genetic testing.
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Introduction

Genetic testing is the major translational product of genetic research into practical medicine. The request for genetic tests has dramatically increased over the past 20 years, in parallel with the expanded knowledge on the biological mechanisms underlying human diseases. At present, in addition to chromosome anomalies, more than 1500 genetic disorders can be tested at the molecular level. Thus, the use of such tests reflects the advances of genetic research and the changes in medicine and in the human health market. To manage this impressive transformation, some countries, including Italy, have developed guidelines regulating the activities of clinical and laboratory genetic services. In particular, an agreement between the Ministry of Health and the 20 Italian Regions has been established on 15 July 2004, to set roles and functions of genetic departments and laboratories, with major emphasis on the autonomy of these structures within the National Health System.[1]

The Italian Societies of Human Cytogenetics (AICM) and Medical Genetics (AIGM), which merged into the Italian Society of Human Genetics (SIGU) in 1998, started monitoring genetic testing in Italy in 1987. The first four surveys (years 1987, 1989, 1991, 1994)[2–5] collected information

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concerning only cytogenetic tests, whereas surveys of years 1995–1996, 1997, 2000, 2002,[6–11] and 2004 gathered data on both cytogenetic and molecular tests. The last four surveys were carried out by rather homogeneous criteria, thus obtaining specific information on the transformation occurring in Italy from 1997 onwards, with respect to genetic testing availability, organisation, and utilisation.

This report summarises the genetic activities performed in Italy during the year 2004 and provides an overview of the changes that occurred over a 7-year period. Data were collected on a nationwide basis by the CSS-Mendel Institute in Rome, on behalf of the SIGU.

These results provide useful information to ponder on the availability and the use of these medical resources and to encourage a critical evaluation, which will benefit future genetic services planning and, in a more general perspective, genetic testing activities.

Methods

Data surveyed in 2004 were collected from the Italian genetic structures notified by universities, general and research hospitals, and private laboratories and listed in the SIGU database. Moreover, additional genetic testing services were identified through an Internet search and validated by qualified experts. Genetic structures were not required to fulfil any quality standard in order to take part in the survey.

Data were loaded online by each participating centre, which accessed the SIGU website through a private username and password assigned during the registration process. Each laboratory was asked to complete five forms, including personal data, cytogenetic, molecular genetic, immunogenetic, and clinical forms. Data collected included number and type of processed analyses, reason for referral, related clinical activities, and number of personnel employed.

Although the participation to this survey was voluntary, we estimate that the obtained data covered at least 95% of the national genetic testing activity, based on the high response rate, and all centres included in previous surveys also participated in the 2004 survey. Collected data were not subjected to verification; however, it is worth to note that two regions (Lombardia and Emilia Romagna), which independently performed similar surveys, gathered information comparable to our study.

The four past consecutive surveys (from 1997 to 2004) were performed adopting standardised criteria, thus allowing an accurate evaluation of the changes that occurred in the genetic testing services in Italy.

Results

The living Italian population in 2004 accounted for over 58 million individuals and the newborn population 562 000. The survey of year 2004 has monitored the activity of 88 clinical centres and 160 cytogenetic and 183 molecular genetic laboratories (including 10 immunogenetic laboratories), hosted by 256 structures. Only 42% of them fulfilled the requirements of the current Italian legislation, which commits genetic testing to specialised medical genetic laboratories. Therefore, 58% of genetic testing was performed by other service providers, including clinical chemistry, immunology, haematology, histopathology, and oncology departments. In addition, only 41% of the structures were certified according to the ISO 9000–9002 certification. Thirty per cent of the genetic structures were affiliated to universities, 27% belonged to general hospitals, 12% to research hospitals, 11% to local health services, 16% were private organisations, whereas 4% had a different affiliation. Concerning the territorial distribution of the genetic structures, there was a consistent north-to-south decreasing gradient, with about half of them being located in the eight northern regions and the remaining structures in the 12 central, southern, and islander regions (Table 1). This unbalanced distribution is supported by the lower figures of the average population served by each centre in northern Italy, compared to other regions.

There were 2372 genetic employees, of whom 56% were graduates (36% biologists, 16% medical doctors, and 6% with other degrees). Temporary employees made up 27% of personnel.

The total number of genetic tests performed in the year 2004 is summarised in Table 2.

Figure 1 provides a review of the different cytogenetic analyses. Out of 283 601 cytogenetic tests, 51.7% were prenatal. There had been 120 238 invasive prenatal samplings, of which 84% were amniocenteses, 15% chorionic villi sampling (CVS), and about 1% fetal blood samplings. Regarding postnatal chromosome analyses, 82% dealt with constitutional cytogenetic and 18% with cancer cytogenetic studies. More than 47 000 molecular cytogenetic tests had been performed, including 42% prenatal analyses. Overall, 93% were represented by FISH and 7% by subtelomeric rearrangement analyses.

About 34 and 31% of constitutional and cancer cytogenetic analyses were carried out in a single northen region (Lombardia). Likewise, 28% of cytogenetic analyses on amniocytes were performed in Lombardia, followed by Lazio (15%, central region), Emilia-Romagna (9%, northern region), and Sicily (9%, islander region). Up to 70% of CVS were performed in two northern regions (Lombardia, 48%; Emilia-Romagna, 22%). Similarly, 25% of fetal blood samples were collected in Emilia-Romagna and 23% in Lombardia. These figures are likely related to the specific technical skills of some obstetricians operating in these regions.

The survey of year 2004 has scrutinised 190 610 molecular genetic tests, of which 10.7% were prenatal

Table 1 Territorial distribution of medical genetic centres, living population, and average size of the population served by each centre in Italy

Area	*Region*	*Living population*	*Medical genetic centres*	*Population/no. centres ratio*
Northern	Emilia Romagna	4 151 369	20	207.568
	Friuli Venezia Giulia	1 204 718	7	172.103
	Liguria	1 592 309	11	144.755
	Lombardia	9 393 092	42	223.645
	Piemonte	4 330 172	14	309.298
	Trentino Alto Adige	974 613	3	324.871
	Valle D'Aosta	122 868	1	122.868
	Veneto	4 699 950	27	174.072
Total		26 469 091	125	211.753
Central	Lazio	5 269 972	27	195.184
	Marche	1 518 780	3	506.260
	Toscana	3 598 269	16	224.892
	Umbria	858 938	5	171.788
Total		11 245 959	51	220.509
Southern	Abruzzo	1 299 272	3	433.091
	Basilicata	596 546	3	198.849
	Calabria	2 009 268	5	401.854
	Campania	5 788 986	22	263.136
	Molise	321 953	2	160.977
	Puglia	4 068 167	18	226.009
Total		14 084 192	53	265.739
Islander	Sardegna	1 650 052	6	275.009
	Sicilia	5 013 081	21	238.718
Total		6 663 133	27	246.783
Total Italy		58 462 375	256	228.369

Table 2 Genetic testing in Italy in the year 2004

	Cytogenetic tests	*Molecular genetic tests*	*Total*
Postnatal	136 845	170 268	307 113
Prenatal	146 756	20 342	167 098
Total	283 601	190 610	474 211

diagnoses. About 53% of them were performed in northern regions, 23% in central regions, 12% each in southern and islander regions. Whereas the distribution of postnatal molecular tests confirmed a north-to-south decreasing gradient, prenatal tests were mostly located in a unique central region (Lazio, 71%). This result reflects the commercial promotion of a few private laboratories, advertising the analysis of *CFTR, DMD, FMR1, FMR2,* and *GJB2* genes on amniocytes and trophoblast cells in the absence of any specific parental risk. In fact, the analysis of these genes accounted for 83% of all prenatal molecular diagnoses. The list of the top 10 analysed genes, covering more than 97% of all prenatal molecular tests, is shown in Table 2. Table 3 summarises the 10 most requested postnatal molecular analyses, which represent about 70% of all tests. *CFTR* gene analysis accounted for 23% and was mostly connected with infertility screening, whereas the analysis of three genes involved in trombophilia (factor V Leiden, *FGA,* and *MTHFR*) accounted for 25%, and *HLA* for 9% of all tests. The major indication to *HLA* testing was disease-association studies. In total, 420 different genes have been investigated.

Interestingly, private laboratories performed 6.5% of postnatal cytogenetic tests and 5.5% of postnatal molecular tests (Table 4). These numbers well correspond to the territorial prevalence of such private structures. Conversely, the figures related to prenatal tests were consistently different, with 23% cytogenetic and 56.6% molecular genetic tests carried out by private organisations.

Figure 2 summarises the increase in the demand for cytogenetic and molecular genetic tests over the years 1997–2004 in Italy.

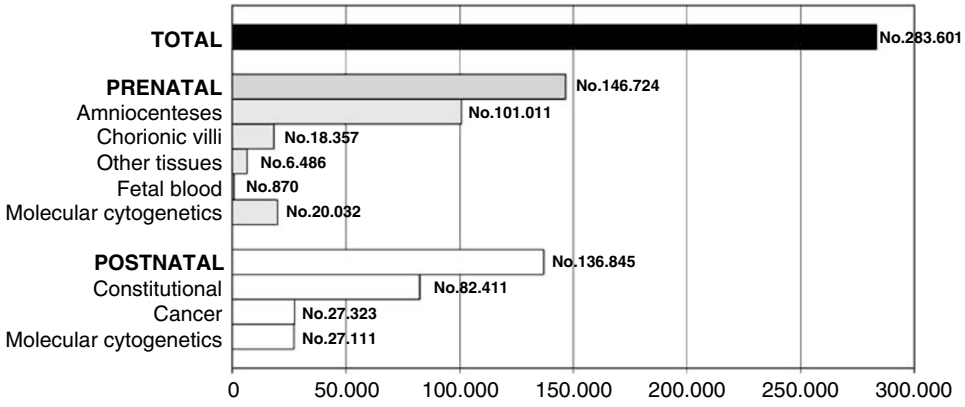

Figure 1 Cytogenetic tests in Italy in year 2004.

Table 3 Top 10 prenatal molecular genetic tests in Italy, year 2004

Disease/gene	*No. of tests*	*No. of centres*	*No. of regions*
Cystic fibrosis (CFTR)	5956	27	12
Duchenne muscular dystrophy (DMD)	3767	12	9
Genetic deafness (GJB2)	3659	10	6
Mental retardation (FMR1)	2417	16	11
Aneuploidy chromosomes 13,18,21,X,Y	1488	1	1
Mental retardation (FMR2)	1010	1	1
β-Thalassemia (HBB)	830	15	9
Uniparental disomy	386	12	7
Achondroplasia/Hypochondroplasia (FGFR3)	220	11	8
Spinal muscular athrophy (SMN1)	75	11	8

Table 4 Top 10 postnatal molecular genetic tests in Italy, year 2004

Disease/gene	*No. of tests*	*No. of centres*	*No. of regions*
Cystic Fibrosis (CFTR)	38 971	82	17
HLA	17 099	8	7
Coagulation factor V(Factor V Leiden)	15 366	46	14
Coagulation Factor II (F2)	13 968	43	14
Methylenetethrahydrofolate reductase(MTHFR)	13 667	47	14
Leukemia (different genes)	6093	10	8
Mental retardation (FMR1)	5166	47	14
Azoospermia Yq loci	4723	70	16
Haemochromatosis (HFE)	4302	45	15
Genetic deafness (GJB2)	3125	40	14

Finally, the clinical genetic structures performed 52 599 genetic consultations, including dysmorphisms (19%), Mendelian disorders (15%), prenatal chromosome anomalies (13%), and mental retardation (10%).

In agreement with the Italian legislation, it is expected that genetic testing should be accompanied by information and followed by genetic counselling, when indicated. However, only 16% of the total genetic tests and 12.5% of molecular tests have been followed by genetic counselling. This means that a large proportion of genetic testing in Italy is performed without proper information, mostly because of the lack of specialisation in human genetics of many services.

Discussion

The number of genetic structures providing clinical and laboratory services in Italy is impressive and, as far as we

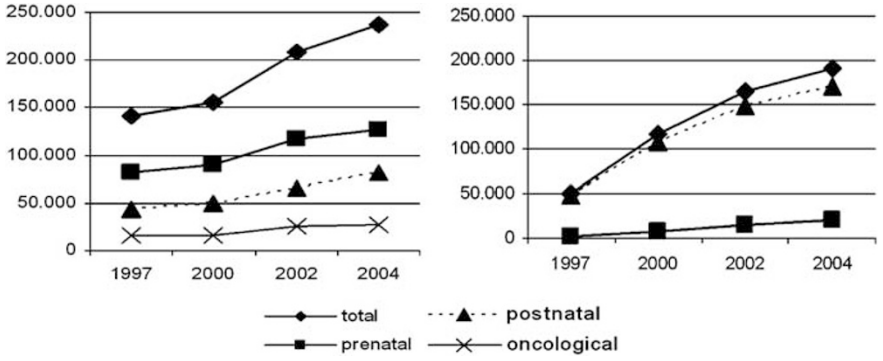

Figure 2 Prenatal and postnatal cytogenetic (left) and molecular genetic tests in Italy in years 1997–2004.

know, it has no equivalent in Europe. This anomaly reflects the historical absence of programmes related to the genetic activities in Italy, which has resulted both in an excessive number of diagnostic laboratories and a non-homogeneous territorial distribution. Nevertheless, it is difficult to understand why the number of genetic laboratories has continued to expand also in recent years (233 in 1997, 431 in 2004) despite the SIGU recommendation, which have urged health-care providers to review the network of structures and to reduce their number, in order to improve the quality, cut the costs, and expand the list of available services. It is likely that the lack of any interregional coordination has been a major drawback to delivering of this quite obvious action.

The number of cytogenetic tests has doubled from 1997 (141 046 analyses) to 2004 (283 601 analyses). Invasive prenatal tests have increased up to about 120 000, with a minor increase during the last 2 years, which suggests that this activity has probably reached a plateau, with about one in five newborns having had the pregnancy monitored. In this regard, the absolute number of prenatal tests would appear adequate to the current figure of 20–25% pregnant women aged 35 or more. However, about 23% of Italian women receiving prenatal tests are less than 35-year-old, meaning that, for some reason, a comparable number of aged mothers did not monitor their pregnancies using an invasive technique.

The number of molecular genetic tests has increased about four-fold since 1997 (50 367, *versus* 190 610 in 2004). However, the total number of investigated genes remains rather low (420, compared to 290 in 2002), and three-quarters of all analyses refer to only 10 genes. Based on these data, the network of molecular diagnostic structures in Italy should be seriously reconsidered.

One of the most impressive results in the present survey refers to the astonishing number of prenatal molecular tests, which accounts for more than 10% of all molecular analyses. As anticipated, this figure reflects a commercial activity fostered by the private health market. There is no doubt that the direct search of some common mutations, like *CFTR* and *GJB2*, in amniocytes and trophoblast cells rather than in the parental blood is in disagreement with the good clinical genetic practice, and has some negative sequels in the parents of those 2–3% fetuses in which one of these common mutations is found.

To our knowledge, no other European country has settled a comprehensive and long-range monitoring of genetic testing at the national level, as Italy. However, there are several surveys that have provided snapshots on the state of these activities. Harris and Reid[12] have compared availability, access, and uptake of genetic testing across 31 European countries. Over 20 000 genetic tests had been carried out in the year 2000 in the Netherlands for about 250 different genetic disorders.[13] In the same year, the UK Clinical Molecular Genetic Society estimated that over 50 000 tests were carried out in that country.[14] A similar figure (45 000 tests) was reported in Spain in 2001, referring to the activity of 53 centres providing the analysis of 241 genetic conditions.[15] The European Directory of DNA Diagnostic Laboratories (EDDNAL) has listed 313 laboratories and 580 genetic conditions for which tests were available in the year 2003.[16] An EMQN European survey conducted in 2002 and involving only public centres estimated 381 000 genetic tests performed in 352 specialist clinical molecular genetic laboratories.[17] A subsequent survey of genetic testing in Europe estimated that more than 700 000 analyses had been performed in 2002, with a greater than 100% increase per year in some member states. At that time, there were 751 genetic testing laboratories and 936 additional clinical chemistry/haematology centres documenting similar activities.[17] A more recent comprehensive survey has measured the amount of genetic services in Germany between 1996 and 2002, by making use of the central database of the national health-care system, and by inquiring with private health insurances. A three-fold increase of DNA-based testing was documented (from about 60 000 to 175 000), whereas cytogenetic analyses and genetic counselling had remained

constant.[18] In general, most of these data indicate a substantial increase of genetic testing activities in the EU, along with an imbalance in the distribution of centres, reflecting the unplanned development of genetic testing in many countries. They also show that a large part of the activity is focused on diagnostic testing for a limited number of diseases, the most frequently performed tests correlating with traits and disorders with high incidence in the general population.

In conclusion, the Italian genetic testing survey addresses two major issues. Firstly, the need for some basic intervention in the general organisation of the genetic structures, which should be rationalised in accordance with the national guidelines, with the goals of providing tests of the highest quality, to link testing and genetic counselling, to cut the costs, and to widen the number of available services. These changes should be planned also in the perspective of an average 10–30% increase per year of the genetic testing demand, according to national and international expectancies.[18,19] Secondly, the need for constant training of the general practitioner and education of the consumer with regard to appropriate use of genetic tests, which should flank and sustain the good clinical practice. In this respect, a more sparing use of genetic tests, which should always follow specific clinical indications, must be recommended.

It is likely that the genetic testing surveys carried out in Italy during the last 20 years on behalf of the SIGU have now reached the end of the line. In fact, the EuroGentest programme, a European network of excellence aimed at harmonising genetic testing services,[20] in collaboration with Orphanet,[21] a free access European portal providing information on services dedicated to rare diseases and orphan drugs, is launching in 2006 the collection of cytogenetic, biochemical, and molecular genetic testing in the EU. The set of information and the experience gathered by the Italian census and similar surveys will possibly serve as a model to start this new comprehensive European laboratory database, and contribute to speed up the process of standardising the infrastructures, tools, resources, guidelines, and procedures, which are expected to raise, adjust, and improve the quality of genetic testing in our Continent.

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References

1 Conferenza Stato-Regioni. Atto n. 2045 – Seduta 15 luglio 2004.: Linee-guida per le attività di genetica medica. *Gazzetta Ufficiale*, no. 224, September 23, 2004.
2 Forabosco A, Dagna Bricarelli F: Laboratori di Diagnostica Citogenetica, I° indagine nazionale. *Analysis* 1987; **10**: 21–29.
3 Piombo G: Laboratori di Citogenetica, II° indagine nazionale anno 1989. *Analysis* 1990; **10**: 5–20.
4 Piombo G, Mantero M: Censimento dei Laboratori di Citogenetica – anno 1991, III° indagine nazionale. *Analysis* 1993; **2**: 41–57.
5 Dagna Bricarelli F, Dallapiccola B, Mantero M, Mingarelli R, Gavaciuto D, Martelli A: Malattie genetiche: guida dei servizi e delle associazioni. *Ministero della Sanità, Italsiel, Roma* 1994; **1**: 8–145.
6 Dallapiccola B, Mingarelli R, Miotti S, Novelli G: Indagine sulla diagnosi molecolare in Italia: anni 1995–1996. *Rapporti ISTISAN* 1998; **20**: 29–36.
7 Santucci S, Ranzi A, D'Ippolito C, Spagnolo A, Forabosco A: Indagine sulla diagnosi citogenetica prenatale in Italia: anni 1995–1996. *Rapporti ISTISAN* 1998; **20**: 37–57.
8 Dallapiccola B, Torrente I, Mingarelli R, Novelli G: Censimento della diagnosi genetica in Italia – 1997. *Tendenze Nuove* 2000; **16** (Suppl 3): 5–90.
9 Dallapiccola B, Torrente I, Mari A, Mingarelli R: Censimento dei test genetici in Italia – Anno 2000. *Analysis* 2002; **5/6**: 292–360.
10 Dallapiccola B, Torrente I, Morena A, Mingarelli R, Dagna Bricarelli F: Censimento delle strutture di genetica medica e dei test genetici in Italia – anno 2002. *Anaysis* 2004; **2/3**: 301–403.
11 Società Italiana di Genetica Umana. . URL: http://www.sigu.net.
12 Harris R, Reid M: Medical genetic eervices in 31 countries: an overview. *Eur J Hum Genet* 1997; **5** (Suppl 2): 3–21.
13 Health Council of the Netherlands: DNA Diagnostics publication num. 1998/11E Bezoekadres Parnassusplein 5, 2511 VX. Den-Haag, Netherlands 1998.
14 Patton S, Barton D, Elles R: Retaining the confidence of the public in molecular genetic testing – quality assurance. *Commun Genet* 2000; **3**: 164–169.
15 Rueda J, Briones E: Genetic testing services for hereditary diseases in spain: results from a survey; in: Ibarreta D, Bock AK, Rodriguez-Cerezo E (eds): *Report EUR 20516EN*, European Commission, Joint Research Center 2002.
16 European Directory of DNA Diagnostic Laboratories (EDDNAL), http://www.eddnal.com.
17 Ibarreta D, Elles R, Cassiman JJ, Rodriquez-Cerezo E, Dequeker E: Towards quality assurance and harmonization of genetic testing services in the European Union. *Nature Biotechnol* 2004; **22**: 1230–1235.
18 Schmidtke J, Pabst B, Nippert I: DNA-based genetic testing is rising steeply in a national health care system with open access to services: a survey of genetic test use in Germany, 1996–2002. *Genet Test* 2005; **9**: 80–84.
19 McGovern MM, Benach MO, Wallestein S, Desnick FJ, Keenlyside R: Quality assurance in molecular genetic testing laboratories. *J Am Med Assn* 1999; **281**: 835–840.
20 Cassiman JJ: EuroGentest – a European network of excellence aimed at harmonizing genetic testing services. *Eur J Hum Genet* 2005; **13**: 1103–1105.
21 Orphanet – Rare diseases – Orphan drugs. URL: http://www.orpha.net.