Time for physicians to be aware of molecular genetic testing

Report from the 3rd Viareggio Health Festival

È tempo per i medici di essere consapevoli delle possibilità della genetica molecolare

Resoconto dal III Festival della Salute di Viareggio

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In the last few years there has been growing excitement about the 'molecular revolution' that seems to offer both a promise and a threat at the same time. As more and more diseases are shown by research to be linked to a genetic cause, the field of prevention will potentially be revolutionized: genetic research has highlighted the fact that the conditions depending on the genetic makeup of a person are much more than the traditionally known Mendelian diseases, and range from metabolic disorders to susceptibility to certain types of cancer. In addition to this, it is well known that most of diseases causing disability and death in the western world are chronic diseases, best dealt with through prevention rather than treatment. There are few doubts that future medicine will move in the direction of "testing before" rather than "curing after". In this scenario, the healthcare system of the next decades will be able to dispense with most of the clinical activity as we know it today, as genetic knowledge will provide a "gateway" for referring patients to the form of treatment most adequate to each individual case. As a result, physicians will probably have to face the challenge of playing a completely new role.

However, so far, genetic knowledge has affected only marginally the everyday practice of medical professionals, who therefore run the risk of being "overcome" by their sudden impact in the near future. An opportunity to reflect upon genetic technologies and their impact on the medical profession was provided by the International Workshop held on September 22nd at the Ospedale della Versilia, within the 3rd edition of the Viareggio Health Festival. This year's Festival had the title "Genetic Testing and Hereditary Diseases: Between the Right not to Know and the Duty to Inform", and was aimed to investigate the ethical and legal aspects of medical genetic information, and the establishment of proper ways of handling it within the patient-clinician relationship.

The first form of genetic knowledge is the deterministic one that exists in the case of Mendelian diseases like cystic fibrosis or chromosomal abnormalities such as the Down syndrome. These diseases cannot be cured, but the presence of the chromosomal or genetic abnormality can be established before birth by performing a test on the pregnant woman. In Italy, the law (DM 10/10/98, D. lgs. 229-10/06/1999, "Decreto Bindi") has established that all pregnant women considered to be in a risk category - familial or age-related - have the right to free access to the test, leaving it to each region to set up specific screening programs. The tests in question are invasive and represent a risk for the pregnancy;

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therefore they are not suited for population-wide screening programs. In recent years, however, technical advances have made a non-invasive test possible, at least for the Down syndrome, by examining fetal proteins in maternal serum [1]. At present, non-invasive tests are not reliable on their own but they could be effective as a screening method (first step) for the pre-selection of candidates for the invasive tests, and for this reason they could be offered on a routine basis, as is already happening in some countries, namely the UK. A further reason why the management of prenatal genetic testing could move in this direction is that - at least in Italy - maternal age is no longer considered a satisfactory discriminator given the constant rise of the age of first pregnancy in Italian women [1].

Indeed, some of the presentations at the workshop dealt with the ethical consequences of prenatal testing. Matti Häyry and Tujia Takala from the University of Helsinki conducted a philosophic and historical analysis of the concept of parental rights and the form they have taken in different societal models. They argued that genetic screening empowers prospective parents, increasing their rights in reproductive matters. Societal interference upon the reproductive act is at the same time lessened, a result which is generally considered fair in liberal societies. On the other hand, Rebecca Bennett from the University of Manchester warned in her lecture that making prenatal tests routine might exert coercive pressure on those women who might not want to know their future child's makeup. Since the genetic condition cannot be cured, in most cases the information provided by the test only leaves the prospective parents with the painful choice of abortion or not. It is for this reason that prenatal genetic tests are criticized as "not preventing harm but preventing children". Bennett argued that, while testing does not actually bring any advantage to women or to their children, the routine setting causes the test to be perceived as something beneficial. Of course Bennett's point is not about advocating a 'blissful ignorance' about genetic conditions: what she contended is that routine prenatal genetic tests may not be the best possible use of public funds, given that they do not result in beneficial effects either for the mother or child while, at the same time, they might be infringing upon the woman's 'right not to know'.

It was to a close scrutiny - philosophical, ethical and legal - of this 'right *not* to know' that most of the meeting was devoted. Apart from the case mentioned above of a possible desire not to know genetic information about one's yet unborn child, this notion is classically applied to genetic information about one's own self regarding late onset diseases - Huntington's disease to name one – or conditions that imply only an increased risk or susceptibility for a disease. The best known instance of this latter case is probably represented by the pair of BRCA mutations that are involved in familiar breast cancer; however, BRCA mutations are just the leader of a pack of genetic alterations that have been identified so far and that have a widely variable degree of correlation with increased risk for many types of cancer. The level of increased susceptibility associated with BRCA mutations is high enough to push many women who test positive to BRCA to have prophylactic mastectomy. The problem is that at the moment medicine has not much more to offer in this field in terms of prevention, hence it is understandable that people may prefer not to have the information about their genetic alterations - particularly if the associated risk is low - in order to avoid the additional worries and anxieties posed by information which is in any case only probabilistic. On the other hand, some might want to have this information in order to better plan their life and to take informed decisions about their future. The problem, at this point, is that genetic information is shared between family members; therefore the information about one's genetic makeup generally brings with it information about the makeup of parents or siblings who may instead not want to know. How should physicians deal with the right not to know? Should they respect it, or are there over-ruling considerations? A well known challenge to the right of a person to remain in ignorance is the objection that knowledge is a form of empowerment; therefore ignorance about relevant aspects of one's health would undermine the person's autonomy and capability to plan their future life in an informed way. This in turn could be perceived as an additional burden on the shoulders of the practitioner, who may feel they are responsible for their patient's uninformed choices.

Lisa Bortolotti from the University of Birmingham took up precisely this point in her lecture. Drawing an analogy between the form of self-knowledge represented by genetic information and that associated with psychological features, she concluded that not knowing does not imply by necessity an impairment of personal autonomy. But can a guideline, or a default state, be chosen regarding whether information should be given to patients? Matteo Mameli from King's College, London, confronted this in his lecture. Clearly, the default cannot be withholding the information, since this attitude would be unacceptably paternalistic and patently harming the interest of the patient. However, the option cannot be to inform by default either, since in this case the interest of those who do not want to know would be infringed. The right not to know indeed configures itself more as an interest, or a *prima facie* right that can be overridden by other considerations and particularly other people's rights and interests. It is ultimately a legal matter to define the boundaries and the most appropriate forms of realization of this right: this legal analysis was undertaken by Roberto Andorno from the University of Zurich. At the EU level, the right not to know is outlined in the framework of the Oviedo convention, within Art. 10.2 "Everyone is entitled to know any information collected about his or her health. However, the wishes of individuals not to be so informed shall be observed" and in Art. 10.3 "In exceptional cases, restrictions might be placed by law

on the exercise of the rights contained in paragraph 2 in the interest of the patient".

As we see, the Convention states the right not to know in the same terms that emerged from the discussion reported above: as an interest of people that ought to be respected, but that can be overridden in consideration of other factors. In general in almost all legal settings the right or, better, interest of a person not to know is honoured under the condition that no harm results to others, and that such interest has been made explicit.

There is an additional facet of genetic information, one that is probably not so familiar to the Italian public. It is the case of Direct-to-consumer genetic tests (DTCs) that are offered in the US by private companies, which advertise and market them generally online, completely outside the clinical setting. What these companies offer is the possibility to send a biological sample and have it analyzed, obtaining at the end of the process a personal table with the risk factors determined from genetic data for a number of diseases. The main problem is that, contrary to what happens for pharmaceutical products, there is at the moment very little supervision of the marketing of genetic tests. The need for regulation was perceived only recently, when one of the companies offering this service, Pathway Genomics, announced its intention to make its test kit available in a big retail chain. Concerns voiced by many parts upon this announcement prompted the FDA to make a concrete plan for the regulation of genetic-testing companies [2]. What is at issue is the clinical utility of these tests, i.e. the fact that the benefits they provide may not be enough to outweigh the risks. The risk in this case is to have patients left to make complex medical decisions without counselling and support from healthcare professionals. In fact, even if the tests offered are totally reliable and the results presented are aligned to state-of-the-art genomic knowledge, there is still the problem that the information that the test client receives is probabilistic. The data that are given are in fact percentages of an increase/decrease of risk with respect to a reference population, information which is admittedly difficult to interpret, particularly so for the non-specialist. And yet genetic testing companies do not offer any kind of counselling on the results: patients have to seek healthcare professionals for help with the interpretation.

In the latest issue of the *New England Journal of Medicine*, two comments dealt with the possibilities and risks posed by the so-called "Consumer-driven Genomic Age" [3-4]. In the scenario in which genetic medicine would be fuelled by the individual patient's private initiative, the role of healthcare professionals in this field would be likewise reduced to counselling and follow up on the results of the genetic test. DTCs have recently appeared in Italy in a context that is cosmetic rather than strictly medical. An international company does in fact offer through chemist's shops the possibility to be tested for one's 'metabolic profile', in order to get personalized dietary advice based on genetic information on metabolism. It is still open to development whether DTC in Italy will remain at this level of cosmetic application or if it will be extended to more comprehensive health aspects like the situation is in the US.

A further impulse in this direction is the fact that, under the current trend, the cost of sequencing technology is continuously shrinking and it is possible to foresee that in the not too distant future full access to one's own genetic information will be within the possibilities of a sizeable portion of the population in wealthy industrialized countries. On this aspect the last speaker, Søren Holm from the University of Manchester, focused attention in his lecture entitled 'The 1000$ genome and the duty not to worry (too much)'. He stressed the fact that virtually every person carries in their own genome at least one allele that is a putative risk factor for common diseases: there is an effective problem about how this information could negatively affect people's lives if not properly managed. Actually, genetic information is less relevant than other factors for people's health: however, this message has to be passed on to the public and to physicians. Genetic counselling is likely to cost more than genome sequencing in the future, and it is equally likely that the onus to provide it will be on the traditional healthcare providers' shoulders.

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