



FONDAZIONEISTUD

GENDER MEDICINE

A new approach for healthcare



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ABSTRACT

Gender Medicine is a fascinating newly emergent approach of medicine aimed at recognizing and analyzing the differences arising from gender in several aspects: anatomical, physiological, biological, functional, social and in the field of the response to pharmacological treatment. The term gender is to be intended as the definition issued by the World Health Organization (WHO), according to which gender refers to the socially constructed roles, behaviors, activities, and attributes that a given society considers appropriate for men and women. Therefore, Gender Medicine deals with a wider area than simply taking into account sex differences, which are merely the biological characteristics that define men and women.

Several studies have demonstrated that the physiology and the psychology of men and women are different and this diversity has a profound impact on the development, diagnosis and treatment of a disease and also on how the patient deals with that pathology. Gender Medicine applies these concepts in order to ensure everyone the best available treatment, with several benefits: it reduces the level of error in medical practice, promotes therapeutic appropriateness for both genders and improves personalized therapies, finally lowering the costs of the National Health Services (NHS), in a long term perspective.

The aim of this project is to drive awareness of this emergent topic. We firstly defined Gender Medicine, by analyzing the contents and by a historical overview, from its first steps to concrete applications, both in Italy and in the international context, thanks to interviews with national and international experts. We then moved to the analysis of clinical features: when, how and why the outcomes of drug therapies are different according to gender?

We also described the perceptions of the involved stakeholders (physicians, patients, institutions, etc.) and we finally asked people for their opinion on the topic, through an online questionnaire.

INTRODUCTION

Men and women, in sickness and in health... are different. Yet, since the dawn of medicine, it has been taken for granted that diagnosis and effective treatments for the male population were equally valid for the female gender. Discrimination of women has caused a bias as, too often, they have not been received a proper care. The Gender Medicine aims at finally paying attention to what makes men and women different, from biological, functional, psychological and cultural point of view. It is a major step forward in improving the adequacy of research and medical practice. Moreover the training of future physicians, and information in general, must take into account the reasons why giving weight to gender inequalities in medicine, means giving everyone an equal opportunity of health.

Gender medicine is the dimension of medicine that studies gender influences on pathophysiology, clinical signs, prevention and therapy of diseases. In the last 30 years, too many epidemiological and clinical studies reported results in only one sex.

The *New England Journal of Medicine* highlighted the discrimination of women in cardiology: women who were hospitalized for coronary heart diseases underwent fewer major diagnostic and therapeutic procedures than men. Those papers were a starting point for good work in the cardiology field. However, other fields of medicine did not improve in the same way, indeed, male research continues to dominate in both animal studies and human clinical trials, although the increasing recommendations as the one published in *Nature* in 2010: "Put gender in the agenda". Gender medicine is neither the medicine of gender-related diseases, nor the one of diseases that are prevalent in a gender. It is the study of how diseases differ between men and women in terms of prevention, clinical signs, therapeutic approach, prognosis, psychological and social impact.

Sex- and gender-dependent differences are a matter of fact in human health and disease. These gender-dependent differences exist from the cellular level to the level of human interactions within our societies. In fact, it could be postulated that each cell is characterised by, among other things, its gender. Incidence, causes, risk-factors, presentation of symptoms, diagnosis, treatment, response to treatment and prognosis, are all factors that differ significantly between women and men, and this for a large number of individual diseases and pathologies. Both women and men experience health and disease in a completely different way. Furthermore, we now know that each gender reacts to similar afflictions in completely different ways. These differences originate from the combination of biological, cultural and societal factors. Taking into account these differences and their origins when we treat our patients and take care of them, is possibly one of the biggest action that can lead to improved outcomes of treatment and care.

Women live longer than men, but they get sick more and use more health services. Moreover, women are more subjected to side effects, due to the fact that the female component is not

adequately represented in the experimental studies conducted to evaluate the efficacy and safety of drugs. Female population is an uncomfortable subject in clinical trials for several reasons. First of all, we have to consider biological factors: hormonal cyclical changes and possible interferences due to contraceptives make the female gender an extremely heterogeneous sample. It should be also evaluated the economic factor: to broaden its studies at the female population means to encounter a greater number of analysis and costs. But, actually, being excluded from clinical trials has been cause of several side effects in women: drugs found to be safe for the male gender indeed, have been in some cases extremely detrimental to the health of the mother or the foetus, resulting in their removal from the market and then also a serious waste statement. Moreover, cardiovascular diseases (CVDs) have been studied in the last decades mainly in men, but they are the first cause of mortality and disability in women. Risk factors for CVD have different impacts in men and women. Moreover, clinical manifestations and drug efficacy have lot of gender differences. Sex-related differences in pharmacokinetics and pharmacodynamics are also emerging, with obvious relevance to the efficacy and side effect profiles. This evidence should be considered for drug development as well as before starting any therapy.

One more example is gender disparity in cancer incidence, aggressiveness and prognosis, which has been observed for a variety of cancers and, even if partially known, is underestimated in clinical practice for the treatment of the major types of cancer. It is necessary to systematize and encode all the known data for each type of tumour on gender differences, to identify where this variable has to be considered for the purposes of prognosis, choice of treatment and evaluation of the possible toxicity.

Clinical data also suggest that men and women exhibit differences regarding the epidemiology and the progression of certain liver diseases, i.e. autoimmune conditions, genetic hemochromatosis, non-alcoholic steatohepatitis and chronic hepatitis C. Numerous hypotheses have been formulated to justify this sex imbalance including sex hormones, reproductive and genetic factors. Nevertheless, none of these hypothesis has thus far gathered enough convincing evidence and in most cases the evidence is conflicting. Osteoporosis is an important public health problem both in women and men. On the whole, far more epidemiologic, diagnostic and therapeutic studies have been carried out in women than in men.

The development of diagnostic and therapeutic approaches that evaluate gender differences between men and women could help to improve the outlook for women's health. The theme of inequality as a stimulus, the gender medicine as an area of intervention. Today, it is necessary an approach that implies a close cooperation between research centres, hospitals, universities and public institutions to promote the growth of knowledge, the increase of specific studies, a new style of doing research, but especially the construction of a public awareness.

A gender approach means taking into account men and women beyond the stereotypes and promoting, within the medical and pharmaceutical research attention to the biological, psychological and cultural factors that exist between the sexes.

Some private and public organizations are working on spreading the culture of gender: through series of informative articles, internet sites, books that describe the changes taking place in the way

we treat the patients and how, in Italy and worldwide, you can define new guidelines for the testing of drugs (1).

Gender differences are not limited to sexual and reproductive apparatus but affect also the heart, circulation, bone metabolism and the immune system. Autoimmune diseases, for example, tend to affect significantly women more than men, and cardiovascular diseases (occurring with greater frequency in women after menopause) present different symptoms depending on the gender. Gender inequality is observed also at cellular level: as a result of stress (such as drug-induced), female cells undergo different responses with respect to male cells. Men and women, not only respond differently to drugs, but also to natural substances taken with food or food supplements (as in the case of phytoestrogens contained in soy).

Gender-specific medicine is a new way of looking at the physiologic and pathological differences between men and women and great efforts need to be invested in research and education in order to re-write many chapters in modern medicine.

It is important to make stakeholders aware of the gender question through several approaches, for instance by stimulating the pre-clinical and clinical, by improving or establishing training courses within the major medical specialisations, at all the relevant educational levels.

Up to date, the awareness about the gender question is increasing. Gender medicine has been included as a course for medicine students in several universities and a growing number of agencies and associations have arisen in the last decade, so we can say that themes and dimensions of health, related to gender, are becoming information, knowledge and problems that the research and the practice of medicine, and even the choices of public health, can no longer ignore.

Moreover, Luca Pani, general director of AIFA¹, in the message sent on 10th October 2013, at the 3rd National Conference on Gender Medicine in Padua, said, “a more gender-oriented approach is ongoing and it is affecting the international regulatory agencies and the same AIFA. A renewal aimed at greater appropriateness of all stages of the care process, from drug trials, in which women, although numerically significant, are still under-represented, and that leads to develop trials in which the patient recruitment is consistent with the real subjects where the treatment is intended”. “The marketing of a medicinal necessarily passes through a proper evaluation of the study population, the objectives, other existing treatments and effects of the drug to be tested. Over the centuries, medicine has studied diseases, conducted research, tested drugs only with regards to the male world. Cultural reasons have excluded women from the medical and therapeutic practice and biological and physiological reasons have meant that female were considered difficult to enroll in clinical trials”, said also Pani.

As stated by the general director of AIFA, “compared to the past, current scientific knowledge have allowed us to identify, among men and women, differences in genetic, anatomical, physiological,

¹ AIFA: Italian Medicines Agency

hormonal features as well as in habits, lifestyles, sports, nutrition, social factors and cultural rights. In 2012 pharmacovigilance data of AIFA, also certify that most of the adverse reactions in women are caused by overdose or polypharmacy, events related to a drug dosage defined from a male model of 70 kg. So, these differences justify the importance of encouraging the development of the so-called gender medicine”.

He added, “researchers and doctors finally began to take into account what the Anglo-Saxons call gender bias. The gender-oriented publications are increasing dramatically, as well as activities and specific guidelines at international level preferred by the FDA and EMA”. On the position of AIFA he declared that “the Agency is strongly committed to the promotion of gender medicine. Examples are the introduction of gender equality among the criteria taken into account by the Commission for the evaluation of program agreements, the specific issues in the notices of independent research programs funded by AIFA, the contribution to the Green Paper on the health of woman, the establishment of a *gender-oriented Working Group*”. On the latter, Pani pointed out the functions: the evaluation of experimental clinical and pre-clinical models aimed at investigating gender differences, promotion of education and involvement of ethic committees in relation to the representation of women in clinical trials and in the provision of protocols analysis and evaluation of efficacy and safety in women, the definition of guidelines for the pharmacological testing of gender, gender research support for drug trials in relation to the different stages of the life cycle of women, with particular attention to pregnancy.

The fronts on which we could actually invest are, on one hand, those related to genomics research and its effects on the level of customization of treatments and preventive strategies, and on the other, the stimulation and integration of biomedical approaches and social health to improve the effectiveness and efficiency of the processes of training of physicians and health care professionals.

HISTORY

It was the mid '80s, just in the same period in which the supposed neutrality of science was challenged by historians, philosophers and sociologists, the United States gave birth to a new medical approach that correlates the health and the risk of diseases with the different social, cultural and economic roles determined by “gender”.

Indeed, only at the end of the eighties it was realized that, because of an erroneous belief concerning the perfect equivalence between the genders in the medical field, women were not receiving adequate therapies. Until that time the medicine was built on the paradigm of “young, adult, male, white”, that conditioned not only the diagnosis and treatment of diseases, but also the testing of new drugs.

Some researchers, including Marianne J. Legato, now director of the *Partnership for Gender-Specific Medicine* at Columbia University, made efforts to include women in clinical trials, and try to fill this gap in the medical and scientific knowledge. The idea was to go beyond women's health to consider other conditions beyond those affecting the reproductive system, and analyze all the different biological factors that make women and men different and also the influence of social, cultural and political factors on women's health.

The evidence basis of medicine may be fundamentally flawed because there is an ongoing failure of research tools to include sex differences in study design and analysis. The reporting bias which this methodology maintains creates a situation where guidelines based on the study of one sex may be generalized and applied to both. In fact, study design in the 1970s in response to sex discrimination legislation made efforts to mix gender within study groups since this was considered the best approach to equality.

In 1985 the U.S. National Institutes of Health (NIH) has made public the first report on the health of women, compiled on the basis of gender differences, stabbing at the cognitive delay in this important area of medicine.

During the mid-late 1990s, gender and social role became variables of social analysis that explain recurring social, institutional and structural disadvantages to women. It became clear that, unless structural adjustment and health service reform and social services development programs addressed gender inequity at all levels, they would continue to be ineffective. The outcome has been that mainstreaming of a gender perspective has become an integral part not only in United Nations and World Health Organization development programs but throughout the entire UN system and into government, non-government and other social institutions worldwide.

It was in 1991 when, for the first time, the “women question” was mentioned in medicine. The *New England Journal of Medicine* published *The Yentl syndrome*, by Bernadine Healy, director of the National Institute of Public Health. In this article the cardiologist commented on the results of two studies carried out on a group of women affected by coronary artery disease. The picture that came out was that of a persistent discriminatory attitude of doctors towards patients. Women, in fact, unlike men, received less care and were subjected to greater number of diagnostic errors and ineffective surgical procedures.

The "women question" in medicine was now opened, but it took 10 years to get a trial dedicated to women. Moreover, the first course of gender medicine "A new approach to health care based on insights into biological differences between women and men" was instituted at the Columbia University in New York only in 2002.

The Council of Europe played a crucial role in promoting gender equality in its member states, by defining common principles and standards to promote the full participation of women and men in society. With the idea that imbalances between women and men had influenced all walks of life, it became increasingly clear that new approaches, new strategies and new methods were needed to reach the goal of gender equality. One of these strategies was *Gender Mainstreaming*, meaning the organization, improvement, development and evaluation of policy processes, so that a gender equality perspective is incorporated in all policies at all levels and at all stages, by the actors normally involved in policy-making. In 1998² in a message of the Committee of Ministers to Steering Committees of the Council of Europe on *Gender Mainstreaming*, it was asserted that "The Committee of Ministers is convinced that gender mainstreaming is an important strategy, not only because it promotes equality and makes visible the gender dimension of each policy and activity, but also because it makes full use of all human resources and should lead to better informed and better targeted policy-making".

In 2000 WHO has included gender medicine in the *Equity Act* to highlight equity as a principle to be applied to access care as well as to pertinence in care, lending weight to the idea that non-discrimination should be promoted through the provision of appropriate medical care. The term "gender" was defined in 2002 by the WHO itself, as the "socially constructed roles, behaviors, activities, and attributes that a given society considers appropriate for men and women", and it must not be confused with "sex", that only refers to the genetic and biological characteristics of a person which indicate whether one is female or male.

In 2011, the European Parliament passed a resolution recommending that more attention be given to women's health and inviting member states to encourage and support medical and pharmacological research into the specific pathologies that affect women at all ages. The Key Messages of the policy brief are:

- Data on mortality, morbidity and use of health services reveal some important differences in health experiences between women and men.
- Health systems can make important contributions to gender equality and gender equity by addressing gender in a variety of ways.
- Identifying gender inequalities and addressing gender equity are also central to good stewardship of health systems.

Although significant social progress has been made, the application of the principles behind the legislation to women's health and gender-based research have not been so positive. Those who research gender issues in clinical and laboratory medicine are aware of significant barriers both for

² (Message of the Committee of Ministers to steering committees of the council of Europe on gender mainstreaming, appendix 2, 16 April 1998)

researchers and for subjects entering studies. For instance, in the UK, research funding for coronary artery disease in men is far greater than for women, yet the at risk population of women, which is an older age group, suffers more morbidity and mortality. It can also hinder research into gender medicine where significant advances in the diagnosis and management of coronary artery disease have built up from small differences into major gender medicine issues (2).

Clinical research exhibits gender bias in the recruitment into clinical trials (3) and also in the reporting of gender-related data (3).

For what concerns clinical trials, they've been conducted only on men for decades. The inclusion of women in trials is difficult for at least two reasons: the female body undergoes cyclic changes in hormonal balance, so it is not easy to have a homogeneous sample of female patients, and there is the fear of the consequences that such testing substances may have on fertility and health of children. The effects of this exclusion from clinical trials, however, are important: first, some women may have a different drug efficacy (6). Secondly, women have a higher frequency (1.5 to 1.7 times) of adverse reactions, those "side effects", often unpleasant and sometimes serious, that occur in the body every time you take a medical treatment. The management of adverse events is a cost that the health system could greatly reduce, if only drugs were also tested on women.

Moreover, some serious adverse reactions had slowed down the inclusion of women in clinical trials. It is the case of *Thalidomide* and *Diethylstilbestrol*, occurred in the '50s and '60s. Thalidomide was used against nausea and to alleviate morning sickness in pregnant women. It even became an over the counter drug in Germany around 1960. Shortly after the drug was sold, in Germany, between 5,000 and 7,000 infants were born with malformation of the limbs (*phocomelia*). Only 40% of these children survived. The statistic was given that 50% of the mothers with deformed children had taken thalidomide during the first trimester of pregnancy. Throughout Europe, Australia, and the United States, 10,000 cases were reported of infants with phocomelia, only 50% of the 10,000 survived. Diethylstilbestrol, a synthetic non-steroidal estrogen used as an anti-abortion drug, was found to be carcinogenic, especially for the children.

Making a change, in 1994 the US National Institutes of Health issued a policy for the study and evaluation of gender differences in clinical trials to ensure that the safety and efficacy of drugs would be adequately investigated in the full range of patients who would use the therapy (5).

This document set forth guidelines on the inclusion of women and members of minority groups and their subpopulations in clinical research, including clinical trials. For the purposes of this document, clinical research is defined as NIH-supported biomedical and behavioral research involving human subjects. These guidelines, implemented in accordance with section 492B of the Public Health Service Act, added by the NIH Revitalization Act of 1993, Public Law (PL) 103-43, supersede and strengthen the previous policies, NIH/ADAMHA Policy Concerning the Inclusion of Women in Study Populations, and ADAMHA/NIH Policy Concerning the Inclusion of Minorities in Study Populations, published in the NIH Guide for Grants and Contracts (Vol. 19, N° 31, August 24, 1990 and Vol. 19, N° 35, September 28, 1990).

The 1993 guidelines continued the 1990 guidelines with three major additions. The new policy requires that, in addition to the continuing inclusion of women and members of minority groups in all NIH-supported biomedical and behavioral research involving human subjects, the NIH must:

- ⤴ ensure that women and members of minorities and their subpopulations are included in all human subject research;
- ⤴ for Phase III clinical trials, ensure that women and minorities and their subpopulations must be included such that valid analyses of differences in intervention effect can be accomplished;
- ⤴ not allow cost as an acceptable reason for excluding these groups;
- ⤴ initiate programs and support for outreach efforts to recruit these groups into clinical studies.

The NIH was one of the first medical research institutions worldwide to put into funding policy that, where research is conducted in health issues that affect both men and women, than both male and female participants must be recruited for that research, and more importantly, that sex disaggregated data from those studies must be reported. Effectively this has meant that the amount of evidence of sex and gender differences being published has increased dramatically. This policy is being pursued by the more rigorous research institutions and funding bodies worldwide. The aims of the NIH guidance were to recruit enough women into studies to be able to allow valid analyses of differences in intervention effect, to evaluate the risks and benefits in women, and to provide opportunities for women to contribute to research through active participation in clinical trials, while preventing exposure of a fetus to a toxic drug.

Moreover, since 1997, the Food and Drug Administration (FDA), the U.S. agency for drug control, forced the inclusion, when possible, of a percentage of women in the sample to be studied. In Europe, there are not such stringent rules, but the national agencies are working to promote experimentation even on women as a good practice. (Federal Register/Vol. 58, N° 58 139/July 22, 1993).

The FDA published a new guideline on FDA's expectations regarding the inclusion of patients of both genders in drug development, analysis of clinical data by gender, assessment of potential pharmacokinetic differences between genders and conduct of specific additional studies in women, where indicated. This guideline revised the 1977 guideline, entitled "*General considerations for the clinical evaluation in women*", that excluded women of childbearing potential from participation in early studies of drugs. The new guideline was the result of the growth, over the previous decade, of the concern that drug development process does not produce adequate information about the effect in women. This concern arose from a number of different sources. Analysis of published clinical trials in certain therapeutic areas, had indicated that there had been little or no participation of women in many of the studies. Certain studies of the role of aspirin in cardiovascular and cerebrovascular diseases, for example, did not include women, and this omission had left the scientific community with doubts about whether aspirin was, in fact, effective in women for these indications. Similarly, published studies of anti-angina drugs often had a few or no women in them. Moreover, FDA noted that there has been little study of the effects of such aspects of female physiology as the menstrual cycle and menopause, or of the effects of drugs widely used in women, such as oral contraceptives and systemic progestins and estrogens, on drug action and pharmacokinetics.

Since then, in the USA, women can enter phase one, two and three clinical trials. However there has not been a dramatic recruitment of women's data into trial results (7). Indeed, it was reported in 2005 that eight out of ten prescription drugs were withdrawn from the US market because of women's health issues (8).

Monitoring for gender in NIH research has been reported from the US Congress Office. In 1997, 94% of grant proposals included women as research subjects (9). This high figure, however, belies the underlying Society for Women's Health Research data that the richest charities were not progressing with the inclusion of women as researchers and subjects and that only 3% of grant proposals measured sex differences (7). One important methodological barrier appears to be that women using hormonal contraception must be considered as a separate group for purposes of analysis (10). However, even the basic concept of including women, whatever their hormonal status, has been brought into focus by recent studies that identified significant barriers to the inclusion of women in clinical trials.

Questions concerning contraceptive use in clinical trials were investigated by an Institutional Board survey. These trials were mainly government sponsored in the years after gender discrimination was outlawed. It was found that certification of contraceptive use was required in 42% of protocols without explanation and in 36% of protocols because of the study drug used (11). Almost 10% of protocols allowed no exclusions for contraceptive use (e.g. celibacy or sexual orientation). In addition, for the inclusion of women, up to four counter-signatures were required in some studies to confirm contraceptive use, whereas for men no signatures were required. The study concluded that access to studies by women created burdens that were disproportionate to men. Aspects of contraceptive requirements for studies that did not appear to have been considered by researchers or ethics committees included the risks of contraceptives, interference with drug metabolism by hormonal contraception (12), that partners may be sterile, that fetal harm may also affect men, that the risk of fetal exposure to one dose of a drug was minimal and that women could make their own decisions.

A similar study in Sweden from 1997-1999 investigated why researchers excluded women from clinical trials (3). The scientific reasons for excluding women were a lack of physiological data, repeat of studies that had previously used only men so as to obtain comparable data, and the economic costs of research in women. This latter problem has been highlighted in a publication by the Society for Women's Health Research, where the guidelines advise that for research into sex differences the best standards for women are to use different hormonal states (12). The economic costs of this '*gold standard*' methodology have the potential to quadruple medical research grant costs (13).

Following the idea that all the minorities should be included in the human clinical research, as stated years before by the NIH, and on the basis of the principle of drug development, according to which "patients entering clinical trials should be reasonably representative of the population that will be later treated by the drug", in 2005, the International Conference on Harmonization (ICH) has developed guidelines on the conduct of clinical trials in the geriatric and pediatric populations. Although the ICH has not developed specific guidelines also for women inclusion in clinical trials, the gender issue appears in a number of direct and indirect ICH guidelines, in particular M4E (*CTD1 - Efficacy*) and E3 (*Structure and Content of Clinical Study Reports*). These guidelines pay attention on

sex as a critical variable for the characterization of the patients population, on the importance of gender in the dose-response studies, on pregnancy as an exclusion criterion from clinical trials (with the exception of drugs intended for use in pregnancy), on the importance of the contraceptive therapy for women of childbearing age that are enrolled in clinical trials and on the stratification of important adverse events by gender. Moreover, the ICH guideline E8 requires that the study population should be representative of the target patient population, and also demands phase I pharmacokinetic information in women.

Another facet of gender bias in research is in the lack of incorporation of gender data into evidence-based medicine. If research lacks or excludes female subjects, then the guidelines should clearly state that the evidence has been obtained mainly from men. In addition, the context in which the evidence basis for medicine is drawn is also questionable because the factors that contribute to women's health, or lack of it, such as poverty and social deprivation will not be the same as for men. These differences need to be defined in order for guidance to reflect the social context of disease. In a NHS and Medical Research Council assessment of the causes and effects of socio-demographic exclusions of women from clinical trials, statins and non-steroidal anti-inflammatory drugs (NSAIDs) were investigated (14). The two drugs demonstrated a dramatic difference in the gender of subjects included in trials. Whereas studies of NSAIDs reflected the population in which they were used, those for statins did not and only 16% of women were included in trials compared with 45% who were using statins. The authors of this study identified the neglect of gender issues in UK research and recommended facilitators to be identified to remove barriers to researchers and women. Including women in clinical studies recognizes that the population is not homogenous, research should benefit all people, protective policies may exclude the people most at risk and exclusion accords a lower status to women.

One more example of gender bias is related to the study of the mechanisms of pain: this is a theme that better than others exemplifies what we mean when we talk about gender. The response to painful stimuli, in fact, depends very strongly not only on biology but also on education and culture. Just the way we've been educated on thinking of the diseases (for example, the fact that some diseases are traditionally considered more masculine or feminine), makes us underestimate some risks. This is the case of colorectal cancer: it is the second most common cancer in women, after breast cancer, but women are not afraid and aware of it as they are for other carcinomas and therefore they do not adequately follow the screening programs. Lung cancer is one more example: this disease is in strong growth in the female population due to the increasing habit of smoking by women.

With the advent of gender medicine as a specialty that is developing across the world, the research has confirmed that human health is closely linked to the aspects that constitute the "gender" and that men and women differ not only sexually, but also in factors such as weight, body fat percentage, liver enzymes, sex hormones and certain environmental variables, the type of society, education, culture and psychology of the individual.

As stated at the ERIH³: *Gender Expert panel Meeting*, which took place in Strasbourg in 2005, “*being a woman or a man is a health determinant that is as significant as social origin, economic situation and ethnic origin*”.

Because of gender differences, the course of diseases and the response to drug treatments vary significantly between men and women. Indeed, despite being subjected to the same pathologies, the different gender conditions symptoms, progression and course of pathologies and it may become significant in studying health, disease and pharmacology.

In 2004 a research project was carried out by the department of history, ethics and philosophy of medicine of Medical University in Hannover, with the aim of evaluating all the European medical curricula with respect to the extent and integration of gender specific teaching offered. It became clear, that across Europe, within the scope of medical education, practically no such teaching models exist.

Gender equality is a milestone of Italian legislation. In the Italian Constitution, the principles of gender equality (art. 3) and equal pay (art. 37) are upheld. This principle should be reflected in the priorities of State policies and of the laws that are being drafted in the country.

Several anti-discrimination laws have been issued since 1977. First, the law on equality (No. 903/77) and subsequently the law on affirmative action (No. 125/91), the law on maternity (No. 1204/71), the law on female entrepreneurship (No. 215/92) and the parental leave act (No. 53/2000). The European Directive (2006/54/CE), which was transposed into Italian law through a legislative Decree on 3 December 2009, aimed at ensuring equal treatment and opportunities for women and men in all field. In particular, everything started with health and safety in the workplace. Indeed, the European Parliament emphasized that women report a higher level of work-related health problems than men, irrespective of the type of work. Hence, in 2011, the European Parliament (EP) adopted a resolution on the mid-term review of the European strategy 2007-2012 on health and safety at work (Report 2011/2147(INI)). The text focused on the importance of a European health and safety strategy and sent a clear signal to the European Commission: the Parliament intends to maintain and develop this component of European social policies. With regard to the current strategy, the EP highlights certain weaknesses, for instance the lack of a systematic approach to long-term health effects. As a consequence, measures of health and safety surely need a gender-biased approach.

On the whole, we can say that, in Europe, gender awareness and approaches in healthcare sector were firstly fired between 2004 and 2006, although the literature on the topic dated back to several years before. Up to date, a lot of stakeholders such as academies, hospitals, associations are pushing on the application of the gender approach in medicine, as there is clear clinical evidence of the related benefits. The implementation of best practices for health care research across genders and the establishment of gender specific evidence based guidance, would be useful for effective health care satisfying both demands and needs, preventive and curative, and for increasing health and life expectancy as well as quality of life.

³ European Reference Index for the Humanities

THE INTERNATIONAL CONTEXT

There are several public and private institutions, as well as societies and universities that deal with gender medicine in the major Western countries, and many others are being developed in the rest of the world. In this work we present the most important and which marked a turning point in the development of the gender approach and its dissemination in the health culture.

WHO: World Health Organization

In 1998 the World Health Organization has issued a “*gender challenge*” to nations and international organizations, a call for: a better appreciation of risk factors involving women’s health; the development of preventive strategies to lessen the impact of diseases that disproportionately plague older women (e.g., coronary heart disease, osteoporosis, and dementia); and an increased emphasis on understanding why men die sooner than women (15).

Always the WHO, namely the Commission on Social Determinants of Health (CSDH) has released its final report in August 2008 “*Closing the gap in a generation. Health equity through action on the social determinants of health*”. The report expresses the three “strong ideas” against women: a) improve the conditions of everyday life or the circumstances in which people are born, grow, live, work and age, b) counter the inequitable distribution of power, money and resources (gender inequity), c) measure and understand the issues, assess and verify the impact of actions to increase the knowledge base (16).

In May 2007, the World Health Assembly (WHA) approved resolution WHA60.25 on the *Strategy for integrating gender analysis and actions into the work* of the World Health Organization and asked the Director-General to report on progress made in implementing the resolution every two years. WHO’s *Gender Strategy* promotes its broader objectives of health equity and gender equality as well as the Millennium Development Goals. The strategy builds on the WHO gender policy adopted by the Secretariat in 2002, and is grounded in various international agreements and commitments on gender equality and health. The WHO *Gender Strategy* is being implemented through six strategic directions (SD):

SD1: to include gender analysis and planning in joint strategic and operational planning, and budget planning as appropriate, including country cooperation strategies;

SD2: to formulate national strategies for addressing gender issues in health policies, programs and research, including in the area of reproductive and sexual health;

SD3: to lay emphasis on training, sensitization and promotion of gender, women and health;

SD4: to ensure that a gender-equality perspective is incorporated in all levels of health-care delivery and services, including those for adolescents and youth;

SD5: to collect and analyze sex-disaggregated data, conduct research on the factors underlying gender disparities and use the results to inform policies and programs;

SD6: to make progress towards gender equality in the health sector, in order to ensure that the contribution of women, men, girls and boys as providers of health care is considered in health policy and planning and training for the health-care workers.

In 2007, the Gender, Women and Health Network developed a monitoring and evaluation (M&E) framework built on actions and indicators identified in the *WHO Plan of Action* to support the implementation of the WHO Gender Strategy. Its first step was to conduct in 2008 a Baseline Assessment, followed in 2010 by a Midterm Review (MTR). This report presents the synthesis findings of the Midterm Review that was conducted to determine the progress towards achieving the six strategic directions set out in the Strategy.

FDA: Office of Women's Health

The Office of Women's Health (OWH) at the FDA was established in 1994 to protect and advance the health of women through policy, science and outreach, as well as to advocate for inclusion of women in clinical trials and analysis of sex/gender effects⁴. The OWH partners with several internal and external offices and participates in numerous activities including sex/gender research, health professional training, scientific workshops and health education and outreach. The Office was established following a report that women were not adequately represented in clinical studies and that data is often not analyzed for sex/gender differences. Overall, the Office aims to ensure that all research initiatives have a regulatory impact and are focused on understanding sex differences to drug response differences in men and women, inclusion of women and safety outcomes in clinical trials and data standards. The office is also making transformational changes in its approach to women's health through research efforts such as breast cancer imaging, product labeling changes; identification of sex differences in drug induced QT prolongation, an award-winning consumer education program and a comprehensive Pregnancy Registry Website.

PARTICIPATION OF FEMALES IN CLINICAL TRIALS AND GENDER ANALYSIS OF DATA IN BIOLOGIC PRODUCT APPLICATIONS

This research project examined the extent to which females have been included in clinical trials for biological products and to what extent the data from these studies have been analyzed and presented with respect to gender. This study was funded by the FDA Office of Women's Health, the "*FDA Scholarship in Women's Health Program*".

The project focused on currently marketed products, specifically biologics for which a new product or biologics license application was approved by the Center for Biologics Evaluation and Research (CBER) during calendar years 1995-1999.⁵

⁴ www.fda.gov/womens

⁵ CBER is the Center within FDA that regulates biological products for human use under applicable federal laws, including the Public Health Service Act and the Federal Food, Drug and Cosmetic Act. CBER protects and advances the public health by ensuring that

Data on enrollment, inclusion and exclusion criteria, study type and gender analyses were searched and recorded. The data were obtained from the Product license application/Biologics license application (PLA/BLA) review prepared by CBER reviewers, summary basis of approval (SBA), product label or clinical trial summaries contained in the PLA.

The results indicate that the inclusion of female subjects into clinical studies for biological products appeared to be similar to that for males. The population enrolled reflected the population that will receive the biological product. Documentation with regard to gender composition and gender analysis was not consistent. Clinical trials were not prospectively designed to evaluate potential gender differences. Gender analysis was by subgroup analysis using gender as demographic variable and occurred only for a small percentage of the total clinical trial summaries reviewed. Data on safety and effectiveness of the product were not presented according to gender. The female specific information included in the product label was generally limited to the pregnancy subsection of the label.

Historically, investigators have been reluctant to include female subjects in clinical trials due, in part, to concerns with potential birth defects. In addition, the 1977 FDA guideline entitled "*General considerations for the clinical evaluation of drugs*" excluded women of childbearing potential from early drug development studies. This may have further contributed to a general lack of females participating in drug development studies and thus, to a paucity of information about drug and biologic product effects in females.

In order to reverse this real or perceived regulatory barrier to the participation of women of childbearing potential in clinical trials the agency has taken a number of initiatives.

The 1988 document entitled "*Guideline for the format and content of the clinical and statistical sections of new drug applications*" emphasized the importance of including analyses of demographic data in NDA applications.

The 1993 "*Guideline for the study and evaluation of gender differences in clinical evaluation of drugs*" provides guidance regarding inclusion of both genders in drug development, analysis of clinical data by gender, and assessment of potential pharmacokinetic differences between genders.

In addition to these guidelines, FDA amended its regulations to require effectiveness and safety data for important demographic subgroups, specifically gender, age and racial subgroups (17). The final rule published in June 2000, permits the agency to place a clinical hold on one or more studies under an IND if men or women with reproductive potential are excluded from participation in an investigation only because of risk or potential risk of reproductive or developmental toxicity from use of the investigational drug (18).

The Food and Drug Administration Modernization Act of 1997 (FDAMA Sec. 115 Clinical Investigations Women and Minorities) amended the *Section 505* mandating the review and development of guidance, as appropriate, on the inclusion of women in clinical trials. In order to implement this section of the FDAMA the agency has formed the "*FDAMA women and minorities working group*" with representatives from the agency and the National Institutes of Health. One of

biological products are safe and effective and available to those who need them. CBER also provides the public with information to promote the safe and appropriate use of biological products.

the recommendations of this working group was that the agency continues to implement procedures that will enhance the ability to gather, search and evaluate demographic data.

The FDA Office of Women's Health has also developed a program to educate agency staff about women's health issues and to advance the women's health agenda within the centers. One critical objectives of this program is to gather information about past and current agency activities related to women's health. This research project was initiated with the objectives to determine:

- to what extent females have been included in clinical trials for biological products
- to what extent gender specific data have been submitted for review,
- to what extent gender specific data have been analyzed either by the sponsor or the FDA,
- whether there is a systematic documentation of results by gender either by the FDA or the sponsor,
- if biological product labeling includes female specific information and/or information specifically pertaining to women.

The inclusion of female and male subjects into clinical studies for biological products approved by the CBER during calendar years 1995-1999 appeared to be similar. In general, the population enrolled was reflective of the population for which the product is indicated. Documentation of gender composition was not consistent and information about gender analysis was available for only a small percentage of the total clinical trial summaries. Gender analyses was limited to exploratory analyses using gender as demographic variable. No statistically significant gender differences in terms of efficacy and safety of the products reviewed were found, however, trials were not prospectively designed to detect gender differences. There was no systematic documentation of results by gender. The female specific information included in the product label was mostly limited to the pregnancy subsection of the label.

The results suggest the implementation of procedures to ensure consistency in the documentation of information pertaining to gender composition, gender analysis and gender specific data. Further discussions may be needed to determine if and for what products and/or product indications gender analyses should be performed and during what stage in clinical development this information should be collected.

The Foundation of Gender-Specific Medicine

The Foundation for Gender Specific-Medicine is a non-profit collaboration between scientists throughout the world and the private sector established to investigate of the ways in which biological sex and gender affect normal human function and the experience of disease. One of the discipline's pioneers, Marianne J. Legato, FACP, MD established the Foundation in 2006 as a continuation of her work with The Partnership for Gender-Specific Medicine at Columbia University.

Create an evidence-based set of protocols to guide physicians:

The Foundation is working to assemble a critical mass of evidence-based criteria for optimal gender-specific treatment within each specialty of medicine. They have finished recommendations for gender-specific care of diabetics and are currently working on cardiovascular disease.

Educate of the lay public and the scientific/medical community:

The Foundation creates an open dialogue between patients and the medical community. In addition to the many books that Dr. Legato has written for the lay public, the Foundation promotes gender-specific medicine through lectures, symposia, and social media. Internationally, the Foundation works within a well-organized network of gender-specific scientists and institutions around the world, under the umbrella of the International Society for Gender Medicine.

Support original scientific research in gender-specific medicine:

Each year, the Foundation provides fellowships to untenured, young faculty members with the goal of fostering their interest in gender-specific medicine at the beginning of their investigative careers. Currently, they award two-year research grants at the Columbia University College of Physicians and Surgeons and one-year grants at the Johns Hopkins School of Medicine. The areas of particular interest include the impact of biological sex on gene expression, the mechanisms of the impact of experience/environment on male-female phenotype differences, and studies involving synthetic biology (i.e., applying concepts of engineering to biological systems through medicinal chemistry, genetic engineering, and other bioengineering approaches).

EU/US Gendered Innovation in Science, Health and Medicine, Engineering and Environment /Maastricht University

The current Gendered Innovations project was initiated in July 2009, by Londa Schiebinger, Professor of History of Science in the History Department at Stanford University, and Director of the EU/US *Gendered Innovations in Science, Medicine, and Engineering Project*, and since 2011 Prof. Ineke Klinge, from Maastricht University, is the co-director.

In January 2011 the European Commission set up an expert group on “*Innovation through Gender*” for two years with the aim of developing the gender dimension in EU research and innovation. The U.S. National Science Foundation joined the project in January 2012. Gendered Innovations has also collaborated in the development of the 2010 *genSET*⁶ Consensus Report and the United Nations Resolutions related to Gender, Science and Technology passed March 2011 (21).

⁶ genSET is an innovative project aiming to improve the excellence of European science through inclusion of the gender dimension in research and science knowledge making. It is a forum for sustainable dialogue between European science leaders, science stakeholder institutions, gender experts, and science strategy decision-makers, to help implement

The Gendered Innovations project was developed through a series of workshops: Stanford University (February 2011); Fraunhofer, Berlin (March 2011); Maastricht University (July 2011); Ministry for Higher Education and Research, Paris (March 2012).

The goal of the Gendered Innovations project is to provide scientists and engineers with practical methods for sex and gender analysis. To match the global reach of science and technology, methods of sex and gender analysis were developed through international collaborations. Gendered Innovations involves experts from across the U.S. and the EU 27 Member States.

Gendered Innovations employ sex and gender analysis as a resource to create new knowledge and technology. The peer-reviewed Gendered Innovations project:

- 1) develops practical methods of sex and gender analysis for scientists and engineers;
- 2) provides case studies as concrete illustrations of how sex and gender analysis leads to innovation.

Thirty years of research have revealed that sex and gender bias can be socially harmful and expensive. For example, between 1997 and 2000, 10 drugs were withdrawn from the U.S. market because of life-threatening health effects. Eight of these posed "greater health risks for women than for men" (20). It is crucially important to identify gender bias and understand how it operates in science and technology. But analysis cannot stop there: analyzing sex and gender from the start can serve as a resource to stimulate new knowledge and technologies. Sex and gender analysis work alongside other methodologies in a field to provide yet further "controls" (or filters for bias), enhancing excellence in science, medicine, and engineering research, policy, and practice. The methods of sex and gender analysis are one set of methods among many that a researcher will bring to a project.

These are the case studies which demonstrate, in very concrete ways, how methods of sex and gender analysis function to create gendered innovations.

In July, 2013 the Gendered Innovations project was presented to the European Parliament. As part of that session, it was published the paper "*Gendered Innovations: How Gender Analysis Contributes to Research*" with a foreword by European Commissioner Máire Geoghegan-Quinn.

CANADA:

A review of *Health Canada's Guidance Document on the Inclusion of Women in Clinical Trials* was identified as a key initiative in the report *Clinical Trials Regulatory Review: Targeted Measures for a Strengthened Framework, Health Products and Food Branch*.

The Guidance Document on the Inclusion of Women in Clinical Trials was released in 1997 to support inclusion of women in all phases of clinical trials research and provide guidance to sponsors on how to implement the policy objective.

effective overall gender strategies. The funding for genSET was initially from the European Commission, FP7 programme

Women constitute a large portion of the consumers of therapeutic products, including prescription drugs, medical devices and natural health products. Some of these products are used for conditions unique to women's physiology (e.g. menstruation, menopause and pregnancy), others for conditions that have greater prevalence in women (e.g. autoimmune diseases; osteoporosis) and others for conditions that tend to affect both women and men equally.

Accordingly, Health Canada recognizes that there is a need to develop the information base concerning differences between men and women in their response to therapeutic products and regarding therapeutic products used in pregnancy and while breastfeeding. Analysis of clinical trial data by sex can identify where there may be clinically relevant sex-related differences in therapeutic response in order to minimize the risks, maximize benefits and promote the optimal use of therapeutic products in women and men. Increased information on the safety and efficacy of products used in pregnancy or while breastfeeding can inform health care decisions.

This updated Health Canada guidance document supersedes the 1997 Guidance Document on the Inclusion of Women in Clinical Trials and has been developed in 2012 to address the following:

- To clarify the scope of the original guidance, including the populations to which it applies;
- To provide further guidance to sponsors on issues not addressed or minimally addressed in the 1997 guidance document. These include: inadvertent pregnancy in the course of a clinical trial and inclusion of pregnant and breastfeeding women in clinical studies/trials;
- To support and encourage good therapeutic product development practices, including new approaches and methodologies, to identify and analyze potential sex differences across the product life cycle;
- To provide guidance within the current regulatory environment.

This guidance encourages the generation and consideration of new scientific knowledge about sex differences, and about therapeutic products used in pregnancy and while breastfeeding. It also recognizes the importance of building the evidence base not only throughout the clinical trial process, but also throughout the product lifecycle - from non-clinical studies through to the post-marketing stage (22).

EMA

The European Medicine Agency (EMA) has undertaken a review of pivotal marketing application trials for evidence of gender bias⁷. The review, which involved marketing applications filed with agency between 2000 and 2003, was meant to assess whether the percentage of females in such trial populations is comparable to the target population. Ten randomly selected products have also

⁷ Pivotal trials are the main studies used in the benefit/risk assessment. The EMA study notes that such trials usually involve two large randomized, controlled (phase 3) studies, but that under certain circumstances one phase 3 or even phase 2 studies may suffice for marketing authorization.

been examined to assess whether the sponsor performed subgroup analyses by sex. Data from 240 pivotal clinical trials involving 84 products have been assessed. An additional 27 products were excluded as candidates, among them products meant to treat conditions specific to one sex. The review indicates that the percentage of females in study populations generally represents the expected percentage of females in the target populations. As expected, a high degree of variability was noted. Considerable variability was also sometimes seen within indications. The percentage of women was, as expected, lower in several indications and higher in others. While deviations were interpreted to be minor in nature, the report recommends that the apparent under representation of women in certain therapeutic categories (e.g. hypertension, diabetes and hepatitis B) and over representation in others (e.g. allergy and rheumatoid trials, arthritis and allergic conjunctivitis) warrants further assessment. At the same time, the review also notes the inherent difficulties in obtaining accurate estimates of the expected percentage of females in the target population. Findings from the randomized sample assessment reveal that some form of evaluation for gender effect was conducted in 8 of the 10 products, with Male/Female subgroup analysis for four products and PK/PD studies for an additional four. The study also notes that in two cases, subgroup analysis was probably not reasonable, owing to the size of individual trials and, additionally, the heterogeneity of clinical indications for one product (19).

Institute of Gender in Medicine, Berlin – GERMANY

The Institute of Gender in Medicine was founded as an interdisciplinary Center in the year 2003. In 2007 it has been converted into an independent Institute at Charité, University of Berlin, Germany.

Their labs for basic research are located in the *Center for Cardiovascular Research (CCR)* at Charité and they are part of a research group that studies the role of gender and sex differences on myocardial diseases to pressure load and maintain very close collaborations with several partners at the Center for Cardiovascular Research (CCR) and other European partners. Several project regarding these diseases have produced interesting information.

In the area of clinical research they conduct studies with primarily cardiologic focus and maintain intense collaboration with the German Heart Institute in Berlin. They also collaborate with the German Competence Network "Heart Failure" and were able to introduce their sex/gender-specific point of view. Several clinical and epidemiological studies have revealed sex/gender differences within the syndrome heart failure (HF). Women suffer more frequently from heart failure with preserved left ventricular function (diastolic HF), while men suffer more frequently from systolic HF. The diagnosis "ischemic heart disease" leads more frequently to heart transplantation in men. However, little data is available for the indication "idiopathic dilated cardiomyopathy". Aim of this project, funded by the Margarethe Ammon Stiftung (9/2007-2/2010), is the identification of possible sex/gender differences upon listing for heart transplantation in patients with idiopathic dilated cardiomyopathy and associated differences in outcomes in women and men.

Women worldwide are inadequately informed about their risk to come down with cardiovascular diseases or to die from. Some risk factors as well as protective factors differ between men and women. A planned representative study (*Berlin Women Risk Evaluation – BEFRI*) in a cohort of 1000 Berlin women will investigate the self-estimation of cardiovascular risks by women living in Berlin and compare the self-evaluated risk with objective data for a cardiovascular risk of the persons concerned. Additionally, new risk factors which are typical for women (e.g. rheumatic diseases, depression, complications during pregnancy) will be identified. The study should analyze and waken the awareness for the prevention of risk factors.

DEVELOPMENT OF SEX/GENDER-SPECIFIC LEARNING OBJECTIVES IN MEDICAL EDUCATION

Result of female and sex/gender-specific research have been integrated poorly and not systematically in the medical curriculum. However, the training of the next generation of researchers has to include solid information on the issue in order to translate the results into clinical practice and research. This information needs to be conveyed during medical education, as this represents the essential key for the systematic inclusion of the findings on women and gender research in medicine and will translate into better future care for women and men.

Aim of this project is the development of gender-specific learning objectives for teaching at Charite's based on international discussions on sex/gender-specific learning goals for medical curricula.

The Centre for Gender Medicine: The Karolinska Institutet, Sweden

The Centre for Gender Medicine at Karolinska Institutet was established in 2001 to promote public and medical professional awareness of the impact of gender and sex on health and disease by providing high-class education and funding frontline research in the field⁸. The Center addresses differences between men's and women's health and disease through research and education. Since its initiation the center has focused on educating physicians, scientists and health professionals in this promising field to help address challenges in this arena. Under Dr. Schenck-Gustafsson's direction, the Center for Gender Medicine has awarded 15 PhDs in gender medicine, published over 300 articles on the subject matter and released a textbook "Handbook on Clinical Gender Medicine"⁹ with outstanding editors and authors from across the globe. In addition, the Center has built a network of more than 500 persons throughout the world. The Center has focused on the following research areas: cardiovascular disease; steroid hormones and metabolism; neuropsychiatry and stress research; inflammation and autoimmune disease; and public health issues. Further, the center offers educational programs in Gender Medicine including a Master's in

⁸ Karolinska Institutet Center for Gender Medicine. <http://ki.se/cfg>

⁹ "Handbook of Clinical Gender Medicine" editors, Karin Schenck-Gustafsson, Paula de Cola, Donald Pfaff, David Pisetsky, Karger AG 2012, ISBN 978-3-8055-9929-0, e-ISBN 978-3-8055-9930-6

GM, a PhD course in GM, continuing education for teachers and post-graduate education and lectures for the public.

RESEARCH:

Their goals are:

- To support and encourage the development of gender-medical clinical and preclinical research with a focus on cardiovascular disease, endocrinology/metabolism, kidney disease, inflammation/rheumatology, neuropsychiatry and public health
- To further illustrate the role of gender in regenerative medicine, medical technology and pharmaceutical usage and identify other relevant areas that have no gender medical analysis

EDUCATION:

Center for Gender Medicine is actively involved various programs to introduce gender perspective as a core concept care and nursing. In the first place they turn to Karolinska Institutet, Karolinska University Hospital and Stockholm County Council but the center also has a well-documented participation in both national and international training meetings and programs.

Their goals are:

- To strengthen gender medical training at all levels of researchers, health professionals and other interested
- To raise awareness of gender medicine to the public and decision makers.
- To care to be equal requires medical knowledge, which also highlights the gender-medical aspects.

The International Society for Gender Medicine (IGM):

The IGM is an organization for national and professional societies dedicated to the study of gender and sex specific differences. The member societies and organizations are in Austria, Germany, Italy, Israel, Japan, Sweden and in the U.S. Together with individual members from countries without professional societies it counts now over 720 members and it is growing steadily. IGM member societies are sponsoring diversified educational programs and have organized until now 6 international congresses and many national workshops, scientific meetings and workshops.

Seven European universities from Germany, Italy, Austria, Hungary and the Netherlands will join forces to generate a flexible module "Gendermedicine (GM)" that teaches gender differences in wide-spread diseases, therapy and research methods at a European level. The project will generate internationally recognized experts for a gender-sensitive medicine and create an expandable European network from universitarian and non-universitarian partners.

It will combine the expertise of the partners in these disciplines to assemble scientific content and learning goals for a GM module. It can be flexibly integrated into bachelor or master programs or continuous medical education and will lead to an internationally recognized certificate. Network members will sensitize universities, medical professional organizations, health care politics, funding organizations and insurance companies for gender aspects.

Dissemination of gender aspects will improve the practical treatment of women and men and will reduce deaths and side effects from pharmaceutical management. Lay organizations are requiring

such knowledge, too. This will promote innovation in medical education and contribute to harmonization of biomedical study structures in Europe.

In the development of this curriculum, summer schools were held in Berlin 2010 (September 20-24) and in Sassari 2011 (September 19-22).



Picture 1. International societies of Gender Medicine

The Israel Society for Gender Medicine

In June 2008, an interest group for Gender Medicine was formed at the Rabin Medical Center in Israel by 27 chairs and vice chairs of different medical disciplines. This led to the foundation of the *Israel Society for Gender Medicine (IsraGeM)* in February 2009 at an inauguration congress which attracted more than 350 participants from most Israeli hospitals and most medical disciplines. The new society elected an executive board which is presided by Prof. Marek Glezerman, a gynaecologist and obstetrician. Current board members are Prof. Dov Feldberg, a gynecologist (secretary), Prof. Romelia Koren (pathologist), Dr. Tal Porter (Cardiologist), Dr. Zipora Dolev, Psychiatrist, and Prof. Hava Tabenkin (Family physician). IsraGeM has currently over 120 active members who represent 16 medical disciplines from 11 Universities and medical centers in Israel. Within the past year, members of IsraGeM have initiated dozens of research projects and starting in 2009, Tel Aviv University has for the first time introduced Gender Medicine in the post graduate program and has established a course for 6th year students. In December 2009 the first Workshop on Gender Medicine and Cardiology has been conducted by the IsraGeM and our society is proud to have hosted the 5th International Congress on Gender Medicine in Tel Aviv in 2010. In 2011 IsraGem has conducted a workshop on Gender Medicine and Nutrition, a workshop on gender aspects of pharmacokinetics and the next workshop in April 2012 will be dedicated to Gender aspects in psychology and

psychiatrics. IsraGem was also instrumental in the foundation of the first Israeli Research Center for Gender Medicine at the Rabin Medical Center in 2012.

The Swedish Society of Gender Medicine

The Swedish National Society is organized from the Center for Gender Medicine at Karolinska Institutet (KI) by Prof. Karin Schenck-Gustafsson. KI is one of the 6 European universities participating in the EUGIM Summerschool program “*Master in Gender Medicine*”. There is a national web- course in gender medicine according to the Bologna principles and a yearly national PhD-course and 2 national congresses. Ten national gender medicine seminars are organised every year and an international Handbook of Gender Medicine is under preparation. Close collaboration is ongoing with the NGO 1.6 million club, with 38.000 participants in Sweden working for gender issues in health also in, Norway, Germany, and Russia.

JAPAN:

The Ministry of Health, Labor and Welfare (MHLW), in collaboration with the Japan Pharmaceutical Manufacturers Association (JPMA), has collected data on the participation of women in marketing application trials based on 60 new molecular entities (NMEs) approved between 2001 and 2003. Through the use of a questionnaire, information was collected on the total number of men and women in the overall clinical package (including phase 1 trials) and on the stratification by therapeutic field, age, phase of clinical development and the origin of clinical evidence (i.e., Japanese versus foreign trials). Results from data collected indicate the following:

- Women represented 58 % of the total study population (involving 56 NMEs), including trials for 10 NMEs that are predominantly for use in women¹⁰. In the case of 44 NMEs with gender neutral indications, women constituted 42% of the overall trial population, a figure that was essentially the same for Japanese and for foreign conducted trials;
- In the case of gender neutral NMEs, women accounted for 44% of the subjects in phase 2 trials and 45% in phase 3 trials conducted in Japan, slightly higher than for foreign-run trials. However, results indicate that the participation of women in phase 1 - ½ studies is significantly higher in foreign trials (31%) than in Japanese trials (4%) due to the historical implementation of related guidelines;
- In the case of gender neutral NMEs, the percentage of women in the 16-30 age bracket in Japanese trials was lower (33%) than for other categories, but comparable in the 31- 45 age group (41%) to all other groups (42% - 46%) and to percentages seen across age groups in foreign trials (42% - 49%).

The study authors conclude that while the number of female subjects in trials involving gender neutral NMEs was somewhat lower than for men, the difference was not significantly large to

¹⁰ 10 NMEs were for predominately female diseases such as breast cancer, Sjogren's disease, osteoporosis and migraine.

prevent appropriate evaluation of gender effect, if any. The report also notes the rise in the use of foreign data since the implementation of the ICH-E5 guideline, with pivotal foreign trials now submitted in addition to Japanese trials in a significant proportion of recent new drug applications.

THE ITALIAN SITUATION

The European Society of Gender and Health Medicine (EUGHM)

The attention to the impact of the gender differences on the pathophysiology and, therefore, on the management of the most common social diseases – such as cardiovascular diseases, osteoporosis, diabetes, neurodegenerative disorders, anxiety and mood disorders, joints and rheumatic diseases, some tumors, to list a few – is both needed and lacking. In response to this challenge the Giovanni Lorenzini Medical Foundation is assisting in the establishment of the European Society of Gender Health and Medicine. The goal of the European and Italian Societies of Gender Health and Medicine, is not linked to the creation of a new specialty in gender medicine, but rather represents efforts to focus attention on gender differences and their impact on the individual in the diagnosis, prevention and treatment of disease, within the many medical specialties.

The aims of the Society, to mention a few, are:

- *to link* all the scientists and physicians who operate in the field of prevention, primary and secondary care, and rehabilitation by focusing on the biological, physiological and pathological differences between women and men;
- *to support* researchers, medical doctors, institutions, and individuals to identify healthcare issues and protect the health in both women and men;
- *to improve the cultural background*, professional updating, and the training of experts in Gender Medicine;
- *to promote the inclusion* of gender perspectives in the programs of both public and governmental institutions;
- *to develop alliances* with research centres, scientific societies, hospitals, academia;
- *to reach a more and more personalized medicine*; and
- *to educate the public* on the gender differences in healthcare needs.

These goals can only be reached through the collaboration and active participation of all the experts who work in the field of health prevention and care and are interested in the development of this new biomedical research area.

National Research Center for Gender Health and Medicine

The National Research Center for Gender Health and Medicine was founded in 2009 by renowned experts in basic and clinical sciences and management, together with the University Hospital of Padua and the Giovanni Lorenzini Medical Science Foundation (Milan - Houston). Gender Medicine

is an interdisciplinary approach to medicine to better evaluate and apply the influence of sex and gender on human physiology and pathophysiology and thus to optimize the approach on the person of the prevention and treatment of diseases. The objective of the National Research Center is to define promoting lines to join medical experts in motivating a growing knowledge towards information, education, research, and medical approach linked to the gender differences. This approach would be helped by a continuous and active exchange of promotional proposals where the Center represents an area of grouping and evaluation of the gender activities and of their advancement and results in favor of the subjects and of the health organization. The National Research Center for Gender Health and Medicine is following and evaluating the many gender approaches and activities developed not only in Italy in the last years, and is increasing its experience on the improvement of the primary and secondary medical results of the medical experiences in the years. Many attention is given to the promotional advances of the increasing number of experts who are taking care of the needs and of the not satisfying approaches to decrease the effect on the subjects of a not medical gender prepared and adequate commitment. The direct participation of the Center in many events follows the needs to recognize problems and opportunities linked to the direct approach to the diseased subjects throughout the active commitment of researchers and clinicians. For the mentioned reason the Center has been open to collaborate with the Italian National Institute of Health and many scientific societies to build and spread a common message that eventually will become the main approach of the modern medicine to the patient. From the *Third National Congress on Gender Medicine* held in Padua on October 10-12, 2013 the Center has been confirmed on the developing needs of the gender medicine not only in Italy. The gender medicine now needs to be included and articulated in the daily clinical practice and finally recognized by the organization of the National Health System, and is expected to contribute to the health development in several regions that have already included gender medicine in their regional socio-health plan (PSSR). Gender medicine is not a specialty on its own, but an extensive approach of every single specialty. Genders are not two but the many conditions in which subjects because of their medical needs are not properly approached and treated in relation to their sex, age, ethnic, social, economic, and lives conditions. The National Research Center for Gender Health and Medicine has the role of stimulating and facilitating the acceptance by all health professionals of gender medicine that, unfortunately, has been for too long forgotten and neglected not only in both basic and clinical research but also in the everyday clinical practice. And that is a new challenge.

The Center of National Health and Gender Medicine is a member of the International Society of Gender Medicine, and the President of the Center is sitting on the board of that organization. The Center is following with the due attention the development of the program of the new nominated Professorship on Gender Medicine in the University of Padua.

National Observatory for Women's Health (O.N.Da)

The National Observatory for Women's Health (O.N.Da) aims to study the main pathologies affecting women and to propose preventive strategies, promoting a gender-focused health culture. O.N.Da supports basic and clinical research on the main pathologies, it evaluates their social and economic impact, it informs Institutions, medical staff and public. Many studies show that women still result disadvantaged compared to men on the subject of health care, and confirm the importance of promoting a social and individual awareness about women's health risk factors.

These factors don't only refer to the reproductive aspects of women's life, but they are in general linked to women's social role. In fact women are today increasingly busy having an intense working life as well as an intense family life, with inevitable repercussions on their health. This comes from a women's natural attitude to satisfy first of all their families' needs, even before satisfying their own needs.

Another important matter is that the medical research and the health care system don't deal match with women's health problems because these issues are scarcely studied as is still scarce the participation of women to clinical studies. Gender differences and their implications on women's health have been just now reckoned.

O.N.Da aims to promote a gender-focused health culture by promoting the concept that the gender differences have different influences on health and on the way that health is perceived. Policies of disease prevention should take more into account these differences in order to gain equity and equal opportunities.

The National Observatory for Women's Health also aims to increase research on the main pathologies affecting women considering especially their economic, political and social implications. It contributes to diffuse medical information and to promote women's active social role in evaluating research and scientific knowledge.

In 2012, O.N.Da has appealed the Parliamentary Intergroup on Gender Medicine, chaired by the Hon. Sabrina De Camillis, to ensure a public commitment which considers that, because of longer working lives of women and by virtue of the recent reform of the labor market, the consequences of chronic diseases such as osteoporosis will become more apparent and impactful. It is important to closely monitor this condition to improve its prevention and its treatment (23).

The O.N.Da observatory considers essential actions to promote greater information and awareness about the disease, promote screening activities and remove some barriers to access of drugs to the women most at risk of fracture.

On August 2013, Pierpaolo Vargiu, President of the Social Affairs Committee, has presented the bill of law "*Legislation concerning Gender Medicine*", submitted to the Chamber of Deputies of the Italian Parliament, as first signatory with other colleagues. The proposal seeks to incorporate the gender medicine among the objectives of the National Health Plan, give practical effect to the

motion passed by the Chamber in March 2012 and spread accurate information on gender diversity, with the preparation of specific guidelines.

The Italian Group of Gender Health (GISEG)

The Italian Group Health Gender, founded in 2009 in Bari, aware of the need to medicine evidence will parallel the complexity of medicine, wants to enhance a careful medical bio-cultural issues related to gender, implement search paths, prevention, diagnosis, treatment and rehabilitation more oriented to promote access and reforms on gender equity. Their purposes are:

- centralization of "*gender approach*"
- construction of a gender perspective based on health of women and girls and men and children to overcome the "*gender blindness*"
- implementation of continuing professional training activities, with the aim to promote awareness of gender specific issues
- promotion of science and research, in collaboration with public and private entities, world production, sports and mass media
- definition of the paths preventive care and health education gender perspective
- correct and fair information to the men and women of the health issues and gender.

The Italian National Institute of Health (ISS):

Many aspects of gender medicine are been organically addressed by researchers from the Italian National Institute of Health (ISS), which since 2007 has set up an *ad hoc* structure that deals with the biological differences, and at the same time it coordinated the *Women's Health Strategic Project*¹¹ (2008-2012), funded by the Ministry of Health, which involved 25 operational units scattered throughout the country, studying five priority areas:

- metabolic and cardiovascular diseases,
- Immunity and endocrinology
- Work Environment
- iatrogenic diseases and adverse reactions
- Determinants of women's health



Picture 2. Women's Health Strategic Project

¹¹ "Women's Health Strategic Project, the gender medicine as a strategic objective for public health: the appropriateness of care for the protection of women's health"

Objectives of the project are to investigate areas of preclinical, clinical, sociological and economic in order to identify:

- the basis for design and development of health care that takes account of gender differences
- prevention protocols for gender-targeted
- specific guidelines
- environmental influences on health

⇒ PROJECT 1: *“Metabolic diseases and women health: studies on pathogenesis and innovative therapeutic approaches”*, coordinated by Dr. Stefano Vella from the Italian National Health Institute

⇒ PROJECT 2: *“Sex hormones as determinants of gender in the immune response and in the development of autoimmune and metabolic diseases”*, coordinated by Dr. Mauro Picardo from IRCCS-IFO¹²

⇒ PROJECT 3: *“Endocrine disrupting chemicals in the workplace and women's health”*, coordinated by Dr. Alessandra Pera from ISPESL-INAIL¹³

⇒ PROJECT 4: *“Iatrogenic diseases and adverse reactions: improve the safety of drug treatments in the female gender in order to reduce economic and social costs”*, coordinated by Dr. Angela De Sarro, Sicily Region

⇒ PROJECT 5: *“Determinants of women's health, preventive medicine and quality of care: production of guidelines, protocols and interventions aimed at improving women's health”*, coordinated by Prof. Flavia Franconi, Sardinia Region

¹² IRCCS-IFO: The National Cancer Institute Regina Elena, Rome

¹³ INAIL: Italian National Institut for insurance against accidents at work

GENDER AS A SOCIAL DETERMINANTS OF HEALTH

Social determinants of health are the economic and social conditions, and their distribution among the population, that influence individual and group differences in health status. They are risk factors found in one's living and working conditions (such as the distribution of income, wealth, influence, and power), rather than individual factors (such as behavioral risk factors or genetics) that influence the risk for a disease, or vulnerability to disease or injury. According to some viewpoints, these distributions of social determinants are shaped by public policies that reflect the influence of prevailing political ideologies of those governing a jurisdiction (29). The World Health Organization says that *"This unequal distribution of health-damaging experiences is not in any sense a 'natural' phenomenon but is the result of a toxic combination of poor social policies, unfair economic arrangements (where the already well-off and healthy become even richer and the poor who are already more likely to be ill become even poorer), and bad politics"* (30).

There is no single definition of the social determinants of health, but there are commonalities, and many governmental and non-governmental organizations recognize that there are social factors which impact the health of individuals. In 2003, the World Health Organization suggested that the social determinants of health included (31):

- *Social gradients* (life expectancy is shorter and disease is more common further down the social ladder)
- *Stress* (including stress in the workplace)
- *Early childhood development*
- *Social exclusion*
- *Unemployment*
- *Social support networks*
- *Addiction*
- *Availability of healthy food*
- *Availability of healthy transportation.*

The WHO later developed a Commission on Social Determinants of Health, which in 2008 published a report entitled *"Closing the Gap in a Generation"* (30). This report identified two broad areas of social determinants of health that needed to be addressed:

1. The first area was *daily living conditions*, which included healthy physical environments, fair employment and decent work, social protection across the lifespan, and access to health care.
2. The second major area was distribution of power, money, and resources, including equity in health programs, public financing of action on the social determinants, economic inequalities,

resource depletion, healthy working conditions, gender equity, political empowerment, and a balance of power and prosperity of nations (30).

The 2011 World Conference on Social Determinants of Health brought together delegations from 125 member states and resulted in the Rio Political Declaration on Social Determinants of Health. This declaration involved an affirmation that health inequities are unacceptable, and noted that these inequities arise from the societal conditions in which people are born, grow, live, work, and age, including early childhood development, education, economic status, employment and decent work, housing environment, and effective prevention and treatment of health problems (32).

Sex and gender are increasingly recognized as important determinants of health for women and men (33). Beyond the biological differences, gender roles, norms and behavior have an influence on how women, men, girls and boys access health services and how health systems respond to their different needs. The World Health Organization (34) recognizes that gender is an important determinant of health in two dimensions:

- gender inequality leads to health risks for women and girls globally
- addressing gender norms and roles leads to a better understanding of how the social construction of identity and unbalanced power relations between men and women affect the risks, health-seeking behavior and health outcomes of men and women in different age and social groups (35).

The usefulness of distinguishing between sex and gender, a common practice in the social sciences, has begun to percolate into the language of prevention, etiology and causation within health care. Sociologists describe sex as the relatively unchanging biology of being male or female, while gender refers to the roles and expectations attributed to men and women in a given society, roles which change over time, place, and life stage. Genetic makeup and hormone profile are both examples of sex, that is, of biologic characteristics, which tend to be constant across societies. Gender is a social, rather than a biological construct, and varies with the roles, norms and values of a given society or era. Being able to bear a child is, fundamentally, a function of biology, while expectations about the imperative to bear children, the nature of parenting, or the status associated with being a mother are more closely linked to gender roles and expectations (40).

Gender has an impact on health in a variety of ways. Powerlessness and lack of control underlie much of the exposure to HIV/AIDS amongst women in Africa, for example. Disproportionate barriers (that is, relative to men) in access to resources such as food, education, and medical care, disadvantage women throughout the developing world. Risk taking behavior is the norm amongst males throughout the world. Socially defined traits often stereotype men and women as having fixed and opposite characteristics such as active (male)/ passive (female), rational (male)/ emotional (female) (36; 37). The language of medicine and its underlying philosophy have, and may still equate male with normal, leaving female to be considered as "other" or, perhaps, abnormal (38). Both

women's and men's occupational and behavioral roles, constrained by social norms, can result in hazardous, though different exposures to dangers and illness (39). Any of these aspects of gender may intercede in the pathway from an individual to his or her health.

GENDER AND DRUGS

In recent years, many researches, conducted worldwide, have shown that there are significant differences between men and women. Indeed, the same disease may have different symptoms, course, prognosis and drug response, due to biological differences.

So far medicine has based the studies on a “neutral” body, which actually corresponds to that of an adult, white, average build and 35-year-old male.

Indeed, none of the drugs leaflet provides different doses for male and female individuals. An important practical aspect, which represents a challenge for the industry and for those who play a key role in the development of a drug, is in fact the setting of leaflets and data sheets with a gender approach.

In a conference held in Rome in 2012, dedicated to Gender Medicine, a change has been proposed for the leaflets: using pink color for women and blue for men. This would indicate that, in many cases, men and women should use different drugs, since different therapeutic responses are expected, as well as different adverse reactions. So, moving from theory to practice, the guidelines and the adjustments to the package inserts will be crucial in the coming years.

This adaptation of dosage of the same drug for different genders, in fact, it is not that difficult if you think about drugs marketed in Italy for children: if the drug is intended for the child, dose and pharmaceutical form change. The dose is reduced and the pharmaceutical form is made in order to facilitate the ingestion by children. Indeed, a child swallows hardly a tablet, but easily a palatable syrup. Trivial but effective example is the most widely used antipyretic, paracetamol: tablets for adults, syrup for children.

It's important, therefore, to evaluate a drug from a personalized perspective: also well-known medications, analyzed from a gender perspective, may reveal how their proper use is different for men or women.

The gender bias in pharmacology

The first description of a gender difference in drug research dates back to 1932, when Nicholas and Barrow (41) found that the sleep-inducing dose of barbiturates in female rats was 50% lower than the one of males. This important observation has not attracted the attention it deserved, and for many years, sex and gender variables have not been considered in pre-clinical and clinical research. This resulted in a drug therapy based primarily on the male body. This sounds as paradoxical, indeed drugs are less well studied just in the gender that uses them the most, the females. In addition, adverse reactions are more frequent and more severe in women (42).

Why do some drugs have been studied only in men and not in women?

Until 1991, it was believed that a woman's body was equal to the man's one, and this opinion has affected much of the clinical research. Surely the fear plays a fundamental role in the choice of not

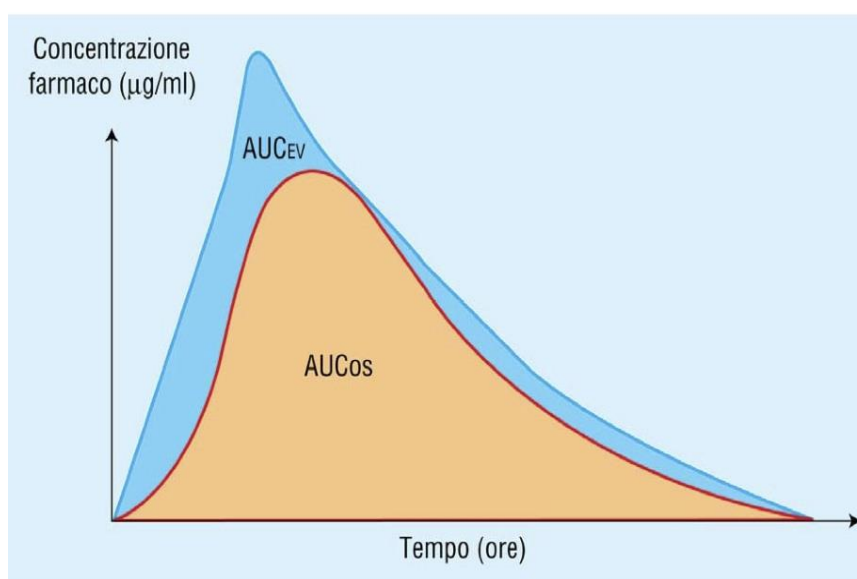
including women in clinical trials, in the light of two tragedies that have occurred: first of all, the thalidomide, which led to the birth of phocomelic children and, then, the one regarding the diethylstilbestrol, an estrogen that was administered during pregnancy and caused severe complications in female (cancer of the vulva, etc.). So, the fear of severe side effects was the factor that led to the lack of knowledge of drug effects on women.

Gender bias also affects men and this happens in high-prevalence female diseases, such as depression, migraine, osteoporosis. Therefore, the gender bias prevents both men and women from receiving the appropriate therapy.

Pharmacology

Men and women are different, not only for weight and body size, but also for a range of variables: the most known is related to hormonal changes but there are many other factors. Women, rather than men, have higher fat mass, different metabolism and different gastric acidity. Even the production of enzymes in the liver and gastro-intestinal transit times are different. This set of variables can significantly influence the processes of absorption, distribution and elimination of a drug, in other words its pharmacokinetics.

The differences in pharmacology concern both pharmacokinetics and pharmacodynamics. Bioequivalence studies, evaluated by the Food and Drug Administration (FDA), indicate that the lack of a dosage set up on the weight leads to an increase in the area under the curve (AUC) in women, ranging from 20 to 88% compared to man, which defines the extent of absorption of the drug (43).



Picture 3. Dosage of a drug in function of time.

Considering that the female body weighs less and has a higher amount of adipose tissue (25%) than men, the detection of pharmacokinetic differences is very frequent.

The fat varies according to age, from 33% in women of childbearing age to 48% in older women, while in men rise from 18% to 36% in the same age range.

These differences mean that in women, lipophilic drugs tend to accumulate in fatty tissue and then be subsequently released, as in the case of antipsychotics (44).

It is interesting to point out that the differences associated with differences in body weight and composition could be reduced by normalizing the dose for body weight or body surface area.

The metabolism of drugs is sexually dimorphic as regards the enzymes of phase 1 (functionalization reactions, implemented through oxidation, hydrolysis, reduction) and 2 (conjugation reactions or synthesis). For example, the activity of CYP3A4, which metabolizes approximately 50% of the drugs, is greater in the female sex, and it seems to be modulated by estrogens and progestins (42). Many women, are treated with a combination of estrogen-progesterone, so it becomes essential to know the interactions between these associations and other medicines. This is because the hormones can affect the metabolism of other drugs or, conversely, hormone metabolism may be affected by concomitant intake of other medicines.

Moreover, it must be also taken into account that cytochrome P450 enzymes are also present in other organs, and the metabolism of drugs may vary in individual organs by gender. In addition, gender differences in metabolism may depend on the ethnicity of the subject in question (46).

Pharmacokinetic differences also affect the renal excretion. The processes of glomerular filtration are in fact influenced by weight but, even after its correction, the filtration rate is a 10% lower in women than in men. Little is known about gender differences in the level of renal transporters and other organs, but some researches seem to suggest differences at this level.

Pharmacovigilance

It has been reported that women are about 1.7 times more vulnerable to adverse drug reactions than men.

In Italy, data from the National Network of Pharmacovigilance, show a great number (59% in 2011) of spontaneous reports of adverse drug reactions in female subjects (47).

Examples of adverse drug reactions in women are: severe arrhythmias, heart failure and drug-induced fractures of limbs.

Several theories have been proposed to explain this difference:

1) *because of differences in pharmacokinetics, women can be overdosed*: although gender differences in pharmacokinetics have been identified for several drugs, these differences usually do not result in changes in dosing because most drugs have a wide difference between efficacy and toxicity. For drugs with a wide therapeutic index, dose adjustment is not thought to be necessary. Although dose does seem to be an important factor in rare and serious adverse drug events, to date pharmacokinetic studies for predicting gender differences in these adverse events have been limited (47);

2) *because women take more medications than men, women are more likely to experience a drug-drug interaction that leads to an adverse event:* Women take drugs for contraception, and a women's reproductive function increases the need for medical treatment at an earlier age than men. Drug usage information shows that women use about 60% of all medications (48). Although taking multiple medications is known to increase the risk of an adverse event due to drug-drug interaction, to date we have no information denying what proportion of the adverse events seen in women is due to this reason. FDA Office of Women's Health (OWH) is gathering information on medication use in women, dietary supplement use in women, and the potential for drug-drug interaction and drug-dietary supplement interactions. The Office is currently funding studies to examine drug-drug and drug-dietary supplements interactions. Additional studies are needed to determine the role of these interactions in explaining the adverse drug reactions seen in women;

3) *gender difference is an artifact because women merely report adverse events more than men:* Although multiple studies have reported that women experience more adverse events during drug therapy, one population study on adverse events concluded that this was not due to report bias (49). Analysis of FDA adverse event database shows that the overall number of reports of adverse events reflects drug utilization by men and women.

4) *there are pharmacodynamic differences that cause women to experience more adverse events* (50): The gender difference in *torsades de pointes*¹⁴ (*TdP*) and QT prolongation is the most dramatic example of a gender-based pharmacodynamic difference. It was first noted that cardiac drugs that prolonged the QT interval tended to induce *TdP* and that this arrhythmia usually occurred in women. FDA OWH funded several research projects to develop animal models to study the mechanisms of this drug-induced effect in vitro and to study the clinical outcomes of QT prolongation in human subjects. The results of these studies showed that drugs from many different therapeutic classes induce *TdP*, but these drugs all appear to cause this effect by prolonging cardiac repolarization and the QT interval. Studies in an isolated rabbit model system showed that androgen tend to speed cardiac repolarization, shorten the QT interval, and thus protect men from the adverse drug effect (51).

A major concern of the FDA OWH research program has been to determine why women experience more adverse events than men. Reporting bias does not seem to be a major factor in explaining this point. Pharmacokinetic differences exist between men and women and can influence dosing for drugs with a narrow therapeutic index. The role of altered pharmacokinetics in rare but serious adverse events requires further investigation. More information is also needed on medication use in women and how drug-drug interactions contribute to drug safety. To date, pharmacodynamic differences in drug safety have been less studied. The example of *TdP* demonstrates that pharmacodynamic differences in drug action may explain why women experience the adverse events.

Women consume at a greater extent the drugs that are not adequately tested on them, and the

¹⁴TdP: It is a polymorphic ventricular tachycardia that exhibits distinct characteristics on the electrocardiogram (ECG)

result is inevitably a greater frequency and severity of adverse reactions, often due to overdose or polypharmacy.

Gender Differences in Liver Failure

Acute liver failure is another rare but very serious adverse event that occurs more frequently in women. Acute liver failure occurs at a rate of about 2000 cases per year in the United States and over 50% of these cases are due to therapeutic drug use (49).

Improving Detection of Rare and Serious Events

Both clinical trials and pharmacokinetic studies are mainly designed to study drug effectiveness. Clinical trials also provide useful information on product safety in terms of common adverse events and toxicity. Inclusion of women in clinical trials helps in the evaluation of drug safety for common adverse events and drug toxicity. However, clinical trials cannot detect rare adverse events, even if these events are serious. In recent years, the detection of rare but serious adverse drug reactions has led to the removal of several drugs from the marketplace. In order to understand the role of gender in rare and serious adverse events, FDA OWH funded a research project to develop and utilize a Bayesian statistical model to analyze for gender difference in adverse events reported to the agency.

Women reaction to drug

The women's reactions to drugs are more difficult to monitor especially for the considerable variability: hormonal and enzymatic activity during menarche, menstrual cycle, pregnancy, lactation, menopause, and the possible use of hormonal contraceptives. Hormones such as estrogen and progestin female alter metabolism and consequently the pharmacokinetics and dynamics of a drug. Adverse reactions are more severe in women than men and therefore require more hospital admissions, increasing the costs of the national healthcare systems. So, apart from the aspects relating to women's health, we must also take into account the related problems of efficiency and management of health care resources.

Probably the higher frequency of adverse events is due to a series of factors, such as:

- particular susceptibility of females (as in the case of *TdP*, ventricular arrhythmias, that can be induced by numerous pharmacological agents, including drugs such as anti-arrhythmic, antibiotics, antihistamines, antipsychotics, azole antifungals etc.);
- polypharmacy, which is more frequent in women (it has been reported that a third of the female population of childbearing age is using estrogen-progesterone oral contraceptives);
- the dosage has been identified for male subjects of 70 kg;
- hormonal fluctuations characterize the reproductive life of women;
- the lack of clinical trials in women.

It is not possible, in fact, to determine whether a drug is effective and safe in women in the absence of studies. It is only in the post-marketing phase of the drug that any adverse events in women are discovered, with a great social cost of course.

Examples of gender difference in drug toxicity

As mentioned earlier, an example of gender differences in drug toxicity are *TdP*.

The FDA OWH has studied, in animals and human models, the mechanisms behind gender differences. These studies have shown that shortening the QT interval, increased the risk of *TdP*, and that androgens have a protective effect, slowing the cardiac repolarization and prolong the QT interval. Women appear to be more vulnerable to long QT syndrome and iatrogenic *TdP* because cardiac repolarization after puberty is longer in women than in men.

A number of drugs, such as anti-arrhythmic, antihistamines, antipsychotics and anti-infective, can cause arrhythmia. In addition to the increased susceptibility of women to develop the long QT syndrome, other adverse events, that predominantly affect women, are fractures of the limbs following treatment with *thiazolidinedione*. In other cases it has been observed, however, a higher incidence of these adverse events, such as fractures, during treatment with high-dose *corticosteroids* after liver transplant. Moreover, metabolic changes (weight gain, metabolic alterations) are more frequent in women (37%) than men during treatment with *valproic acid* and *antipsychotics*. This means that women may develop more easily insulin resistance, non-alcoholic steatosis, cardiovascular diseases and increased discontinuation of therapy.

One more example is related to HIV infection. HIV-positive women (in many countries, the number of women affected by HIV is higher than that of men), following a treatment with inhibitors of reverse transcriptase, undergo more easily adverse drug reactions, such as lactic acidosis and hepatic reactions.

Finally, since the risk of developing adverse drug reactions is associated with depression, a condition more prevalent in women, it is clear that depression becomes a major risk factor for adverse reactions in women.

In conclusion, despite literature suggests a higher frequency of adverse reactions in sex-female gender, it is evident that most of the available information is derived by post-hoc analysis, by meta-analysis of clinical studies and reports that have not considered the sex and the gender in all their complexity, including pharmacodynamics and hormonal changes.

We need therefore to overcome a knowledge gap. It must be filled with appropriate research, with the aim of reducing adverse drug reactions both in men and in women.

Drugs

We are not considering the description of specific drugs for women (such as those for the treatment of menopause or contraceptives) or for men (such as those for prostatitis), but we are giving some examples in which the same drug impacts differently in the two sexes.

Cyclosporine and “Gender attention” by Novartis

For the first time, a pharmaceutical company in Italy has launched an observational study of Gender Medicine, called “*Gender Attention*”, sponsored by Novartis, which will assess specifically the influence of gender on the different incidence of side effects in people with psoriasis and drug treatment as clinical practice with cyclosporine.

The influence of the gender factor, on the onset of side effects will be evaluated with respect to the drug that changed the history of immunology: cyclosporine, introduced in Italy in 1983, is the first immunosuppressant that has made possible to control the reaction of rejection in organ transplants and effective monitoring of the most common autoimmune diseases, such as psoriasis and rheumatoid arthritis. The safety profile and efficacy of this drug has been deepened over nearly 30 years.

In addition to detect any differences between men and women in the incidence of side effects, the study also aimed to explore the existence of any relationship between them and the changes in hormone levels in women, and then assess the patient's overall satisfaction to therapy with cyclosporine. The study, conducted on 1,200 patients, attended by about 50 outpatient dermatology centers affiliated with the National Health Service. The patient population will be composed of 800 women, of whom 400 and 400 of childbearing age at menopause, and 400 men.

Psoriasis is a chronic disease in which the gender appears to be a determining factor affects between 1, 5 and 2% of the population in Western countries, and social and psychological effects very heavy. The latter are particularly prevalent in females (54% vs. 40% in men) and cause limitations, often disabling, social life.

"For too long the medicine, as a tailor, was cut on the bodies of men", says Flavia Franconi, Professor of Pharmacology and Chairman of GISEG (*Italian Group for Health and Gender*), partner of Novartis in this project. "The study has a very significant and innovative: to investigate both the man and the woman in their differences and their similarities in response to drug treatments. Indeed, Gender Medicine is not a medicine that studies only “the feminine”, but it is the medicine that want to get fairness in the prevention and cure. It's the way to personalized treatments: to have individual care will take time, but this is an important first brick in the wall" (52).

The evidence shows that men and women get sick in a different way and that the same disease can have a different impact on them. In addition, compared to men, women are affected more frequently (1.5 to 1.7-fold) and more heavily by the side effects of therapies. This depends on many factors, including the fact that the drugs are poorly studied on women, even though they are the greatest consumers. In light of these findings, a greater involvement of women in clinical trials is now considered a priority by health care institutions.

"For several years now that the international health authorities such as WHO and FDA stress the importance of a fair representation of gender in clinical trials. Novartis, one of the first pharmaceutical companies, has decided to take up this challenge by initiating an observational gender study in Italy", says Maria Delia Colombo, Scientific Alignment Manager of Novartis Pharma

Italy, "the study *Gender Attention* reflects the strategic vision of Novartis, which translates into an ongoing commitment to research on molecules, including those established use as the cyclosporine, in order to know them better and to adapt them to the specific characteristics of patients, including those of gender" (53).

Zolpidem

Zolpidem is a non-benzodiazepine hypnotic belonging to the family of imidazopyridines, indicated in the short-term treatment of insomnia. At the beginning of 2013, the Food and Drug Administration (FDA) has recommended that the dose taken before bedtime should be reduced.

Indeed, clinical data showed that the blood levels of the drug in some patients could be high enough, in the morning after the assumption, to endanger those activities that require attention and alert, such as driving.

The announcement of security was referred to the formulation approved for use at night, which was marketed as an over-the-counter drug with different brands.

The FDA has also reminded the audience that all the drugs taken for insomnia can impair driving and activities that require attention, in the morning after use. The sleepiness is already listed as a common side effect in the labels of all medications for insomnia, in addition to the fact that patients may suffer drowsiness the next day of intake of these products.

FDA urged health professionals to warn all patients (men and women) who use these products based on Zolpidem about these risks. The data showed the risk reduction capacity of attention is higher for patients taking the extended-release forms of these drugs.

Women seem to be more susceptible to this risk because they eliminate Zolpidem from their bodies more slowly than men.

The FDA has informed the producers that the recommended dose of Zolpidem for women should be lowered from 10 mg to 5 mg, for immediate release products, and from 12.5 mg to 6.25 mg, for prolonged-release products. Moreover, the FDA has advised the producers that, for men, the labeling should recommend that healthcare providers consider the prescription of lower doses (54).

Aspirin (ASA)

Although aspirin is effective in the treatment of acute myocardial infarction and secondary prevention of cardiovascular disease in both men and women, its use in primary prevention is still controversial.

The available data for the use of aspirin in female subjects for primary prevention are based on limited evidence. But direct demonstrations that relate to the effects of aspirin in women are needed today because the cardio-vascular diseases are a major cause of death in both women and men. There are, as we know, the important differences according to sex for the metabolism of salicylates and there is still uncertainty about the effects of cardio-vascular therapy with hormones.

A study on this particular topic was conducted in 2005, with 39,876 healthy women over 45 years, and they were randomly assigned to receive 100 mg of aspirin every other day or a placebo. They

were checked after 10 years to see who had suffered a major cardiovascular event (non-fatal myocardial infarction, non-fatal stroke, death from cardiovascular causes).

During the 10 years of observation there were 477 cardiovascular events in the aspirin group and 522 in the placebo group, with a minimum risk reduction (9 %) in the aspirin group (relative risk 0.91, 95% confidence interval from 0.80 to 1.03, $P=0.13$). By limiting the observation to the stroke, it was observed a reduction of 17 % in the aspirin group, compared with the placebo group (relative risk 0.83, 95 % CI 0.69 to 0.99, $P=0.04$); only evaluating ischemic stroke, the reduction was of 24% (relative risk 0.76, 95% CI 0.63 to 0.93, $P=0.009$), whereas for hemorrhagic stroke, the reduction was not significant (55).

Intestinal bleeding that required a transfusion were more frequent in the group treated with aspirin of course that in the placebo group. Subgroup analyzes showed that aspirin significantly reduces the risk of cardiovascular events, ischemic stroke and myocardial infarction in women 65 years of age or above.

It was concluded that aspirin prevents the risk of stroke without affecting the risk of myocardial infarction. Every decision, as is done with men, about the use of aspirin in primary prevention should be made after a woman's participation in decision-making, to assess the net benefits and risks of treatment for the individual patient.

THE PERCEPTION OF PATIENTS

In 1946, the WHO has defined Health as *“a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”*. This definition is in line with the birth of a new approach to the issue, according to which health is to be intended as *“quality of life from a physical, psychological and social point of view”*.

Therefore, health is a concept that regards the body, but mainly the psyche of subjects, intended as being physically and psychologically interacting with the environment.

In this way, health becomes a complex matter, not only closely linked to healthcare but also to socio-cultural and economic factors that may determine it and to the perception of individuals. It becomes a sense of well-being, a way to feel and perceive our body and, ultimately, ourselves.

The transition from the concept of health, to that one of well-being, moves the focus from an objective to a subjective dimension.

Well-being is in fact a truly perceived condition because it is the way in which people evaluates their life: an assessment which may vary according to age, level of education, social class, psychological conditions, but especially to the gender.

Considering gender, implies keeping in mind how different the roles of men and women are in society. And it also means paying attention to the way in which women and men deal with diseases, to the ways they relate to the healthcare system, their body and its transformations. It becomes therefore interesting to address the issue of gender medicine from the patient point of view.

How can a man react when dealing with a disease, with the diagnosis and therapy? And how can a woman react to the same disease?

To understand how patients react differently to the disease, depending on their gender, we found some examples.

The psychological reaction of the patient in front of the oncological disease

Within the project aimed at psychological support to the users of the Medical Oncology Unit of Senigallia, Italy, in the period of February-May 2012, a study has been conducted on 50 patients undergoing chemotherapy treatments, in order to deepen the understanding of the psychological reaction to oncological disease.

The sample size did not allow to generalize the data, however, it provided a probable tendency of patients about the factors examined. To carry out this study, the researchers used a standardized questionnaire (Mini-Mac). The questions were focused on five types of psychological reaction and have been formulated to assess the quality of the reaction and not the quantity or the symptoms.

This means that if the patient shows, with their answers, a high index of depressive reaction, this does not mean that they are depressed, but that tend to react depressingly.

The five areas of interest, related to the types of psychological reaction, are the following:

- Fatalism: through this method of assessing and reacting to the events, the person lives day by day and relies on God or destiny to explain the reasons of their concern. There are no guilty or concatenating situations, nor chances to change the events, even if only little. The idea of the subject is that successes and failures are independent of their will and direct activities. There is a pattern of life already set to which we cannot escape.
- The fighting spirit: the individual believes in its ability to improve the situation of unease that is living and, therefore, they believe it can be optimized through the commitment and the right attitude. The main idea is related to the collaboration with health care staff to increase their well-being and decrease the discomfort, giving themselves an important part in the possibility of healing. The disease is seen as a challenge, as something to be fought right from the beginning even to ask for help themselves.
- Despair/Depression: this mode of psychological reaction to the disease involves the lack of confidence in the improvement of health. The subject refuses to evaluate alternatives and has a depressive approach towards the events. This type of perspective influences negatively the hope to healing or getting better.
- The anxious concern: the person who has this type of reaction feels strong emotions such as anger, fear, anxiety that tend to upset them and increase the concern about the therapy. The individual may have difficulty in believing what is happening and can feel a sense of upheaval.
- Avoidance / Minimization: having a reaction of avoidance/minimization means to escape from thinking about the disease and treatment, to try as much as possible to distract yourself not to face the situation. With this mode, you diminish the importance that the disease has on your everyday planning, by avoiding to pay attention to it.

The study on the psychological reaction to the disease in 50 patients undergoing chemotherapy has shown some relevant data, although it cannot be generalized due to the limited size of the sample. In particular, with regard to gender differences, women show higher values of depressive, avoidant and anxious reactions. They are a little less combative than men and a little more fatalistic.



“The bald Mona Lisa”

Another example that we thought important to mention, with regard to the different reaction to cancer of men and women, is the bald Mona Lisa.

It is the image that the Ant, an Italian no-profit foundation, has chosen for his campaign against cancer. The slogan: "A cancer changes your life. Not its value". The Mona Lisa, presented in this way, distorts the image carved in memory, explains the association. The same does a cancer. After having overcome the initial surprise, however, we realize that the work loses nothing of its value.

A strong image but certainly of big impact, chosen by Ant for the 2013 campaign in support of cancer treatments. The painting by Leonardo Da Vinci shows the physical upheaval that cancer brings. Especially for a woman, whose hair loss is a tragedy, a denial of her condition of being “female”.

Women as caregivers

The problem of the differences between men and women, goes far beyond even complex clinical aspects, invading the socio-health sector.

There is ample evidence that a socio-economic poverty reduces the probability to undergo Pap-test and mammography. Women are often disadvantaged in relation to the national health system: they often underestimate the early warning symptoms of disease. In other words, as caregivers, because this is often the role of women within the family, they do not receive as much attention towards their health status.

The higher psycho-social risk that affects women is not considered, and it is due to the double workload.

Women live longer but they get sick more and use more health services. It is the so-called women paradox: although women live longer than men, they have the burden of a greater number of years of life in poor health.

The toll that caregiving takes is not just financial. Higher levels of depression, anxiety, and other mental health challenges are common among women who care for an older relative or friend. Studies find that men respond to caregiving responsibilities in a fundamentally different way. Women tend to stay home to provide time-consuming care to one or more ill or disabled friends or

family members, while men respond to loved one's needs for support by delaying retirement, in part to shoulder the financial burden associated with long-term care (24).

One four-year study found that middle-aged and older women who provided care for an ill or disabled spouse were almost six times as likely to suffer depressive or anxious symptoms as were those who had no caregiving responsibilities (25). The same study found that women who cared for ill parents were twice as likely to suffer from depressive or anxious symptoms as non-caregivers (25). A particularly strong factor in determining the mental health impact of providing care is the amount of care per week that a woman provides. One study found a marked increase in risk among women who provided 36 or more hours per week of care to a spouse. Researchers concluded that there may be a threshold of time involvement beyond which the likelihood of mental health consequences rapidly escalates (25).

Despite the physical and emotional tolls of caregiving and risk factors for disease, women caregivers are less likely to have their own health needs met. One study found that women providing care to an ill/disabled spouse were more likely to report a personal history of hypertension, diabetes and hypercholesterolemia. These same caregivers were also slightly more likely to smoke and consume more saturated fat (26). Additionally, compared to non-caregiving women:

- 25% (vs. 17%) rated their own health as fair or poor
- 54% (vs. 41%) had one or more chronic health conditions
- 51% (vs. 38%) exhibited depressive symptoms
- 16% (vs. 8%) were twice as likely in the past year not to get needed medical care
- 25% (vs. 16%) had difficulty getting medical care (27).

It is clear that caregiving can have negative health effects. It is important to note, however, that although caregiving can exact physical, emotional and financial tolls, it can also be rewarding. Some women caregivers:

- Reported a caregiver "gain": more purpose in life than their non-caregiving women peers (28)
- Reported beneficial effects including more autonomy, more personal growth and more self-acceptance when caring for friends (28).

WHAT PEOPLE THINK AND KNOW ABOUT GENDER MEDICINE: THE QUESTIONNAIRE

After a careful research on the historical, geographical and topical context of Gender Medicine, including those who are the stakeholders of this discipline, that is individuals or institutions, and also thanks to interviews with the Italian and international leading exponents, we wondered what is the knowledge and opinion of the common people in Italy about Gender Medicine, to understand also what are the needs of male and female population in relation to health, and from there we created a questionnaire, completely anonymous, which we first disclosed through some social networks (Facebook, Instagram, Twitter, Google+, LinkedIn) and emailed it, and then in collaboration with the online magazine IppocrateRosa, who posted the link of our questionnaire on its website. In two weeks we collected 293 responses. The questionnaire consists of two parts: one with questions about personal details and the other with questions relating to Gender Medicine.

The sample consisted of 69% of women and 31% of men (Table 1):

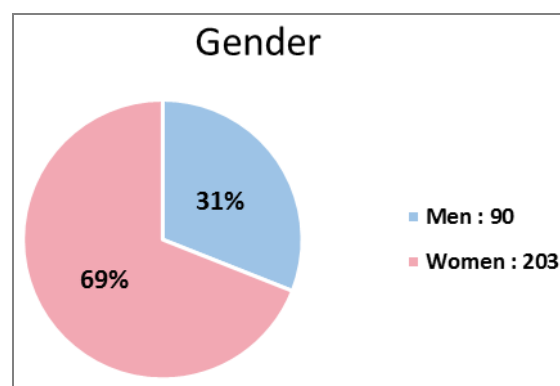


Table 1. Distribution by gender.

The highest percentage (64%) relates to the “18-29 years” segment, followed by the “30-45 years” segment (26%), and by the 46-59 years (6%) one. Both “<18 years” and “>60 years” segments amount to 2% (Table 2).

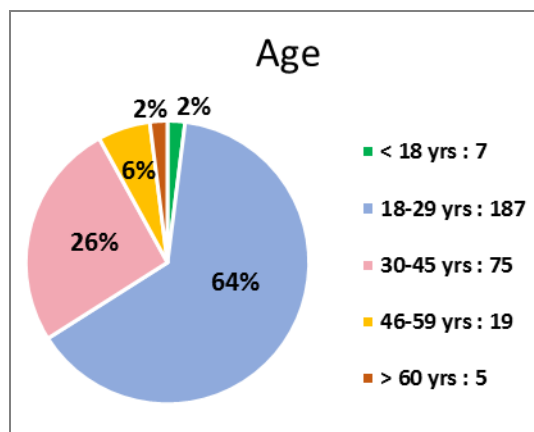


Table 2. Distribution by age.

The 44% of people who completed the questionnaire live in northern Italy, while the 18% in the central regions and the 39% in the south and in Sicily and Sardinia (Table 3).

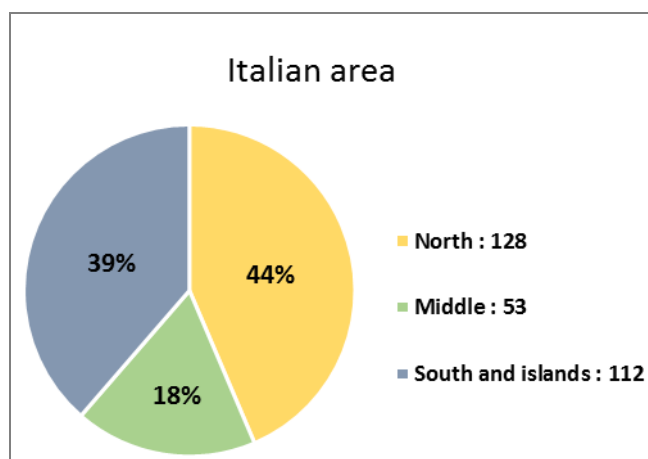


Table 3. Geographical distribution.

As regards the level of education, the highest percentage (53%) relates to people with an university degree, followed by post-graduate qualifications (23%), high school diplomas (21%); only few people has a low level of education (8%) (Table 4).

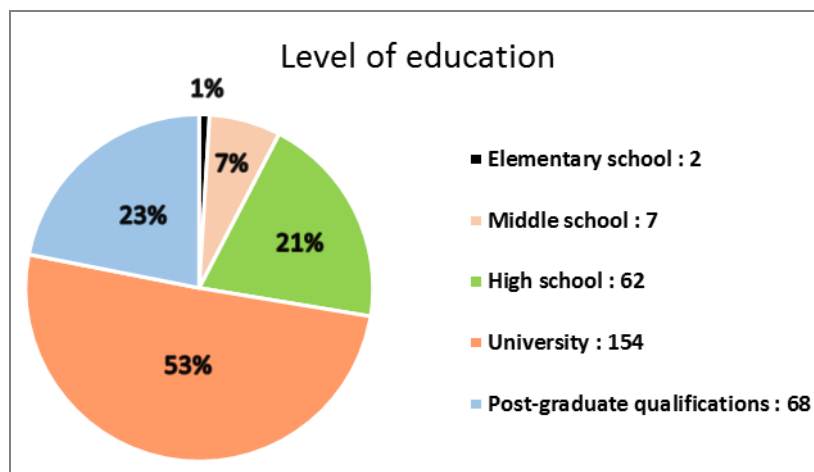


Table 4. Distribution by level of education.

Most of the people of our sample are employees (37%) and students (34%), followed by several self-employed (14%) and unemployed (13%). Very few housewives and retired people are present (2%) (Table 5).

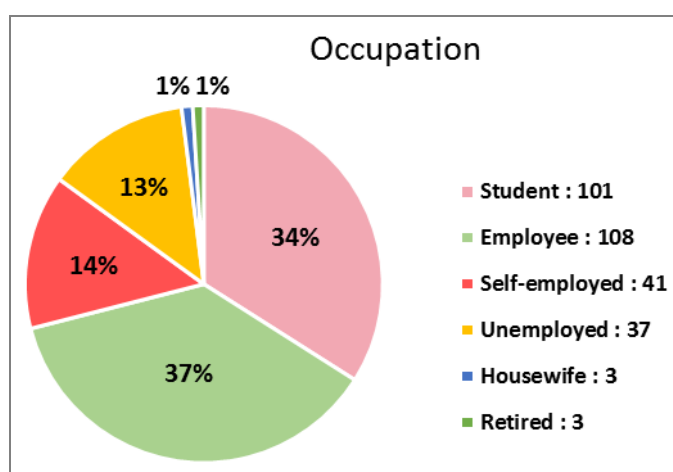


Table 5. Distribution by occupation.

The second part of the questionnaire starts with the obvious question about Gender Medicine:

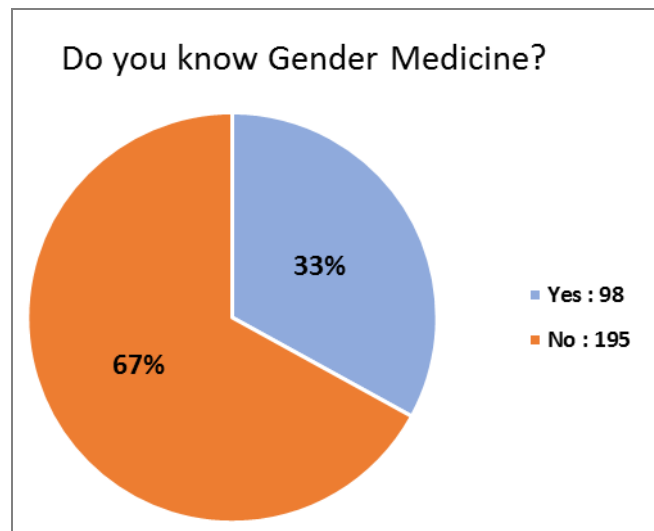


Table 6.

The 67% of responses indicates that people never heard about Gender Medicine, while the 33% knows it (Table 6).

After that, we asked what they think it may be (Table 7):

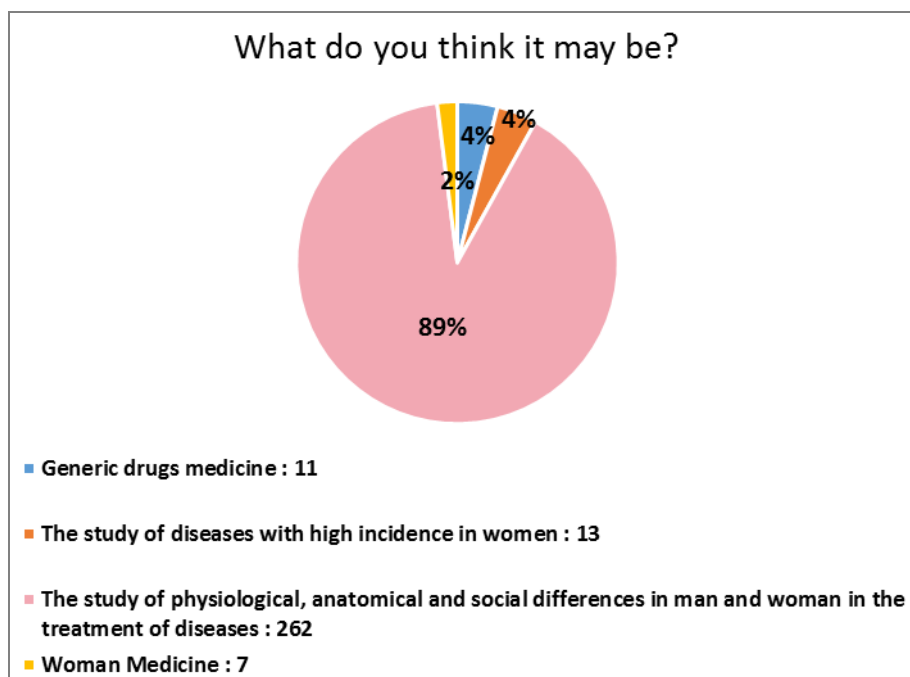


Table 7.

The vast majority has hit the correct answer (89%), mostly thanks to an intuition; next step, we asked where they heard about Gender Medicine: leaving out those who have not ever heard (44%), the means by which they are aware of Gender Medicine is first of all Internet (16%), to follow with university and health workers (both 10%), television, radio, newspaper and magazines (7%), and finally specialized magazines (6%) (Table 8).

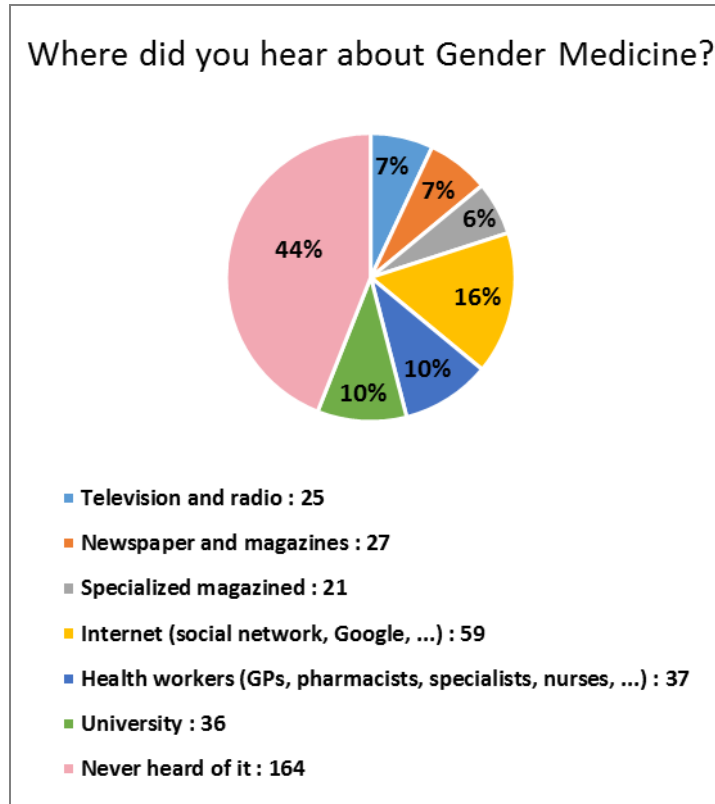


Table 8.

We then asked if they know that some diseases can affect differently men and women, and the 94% of the respondents chose yes, indicating that they are conscious about the differences between the two genders (Table 9).



Table 9.

As regarding the perception of the same disease in men and women, the 60% thinks it is rather true (Table 10).

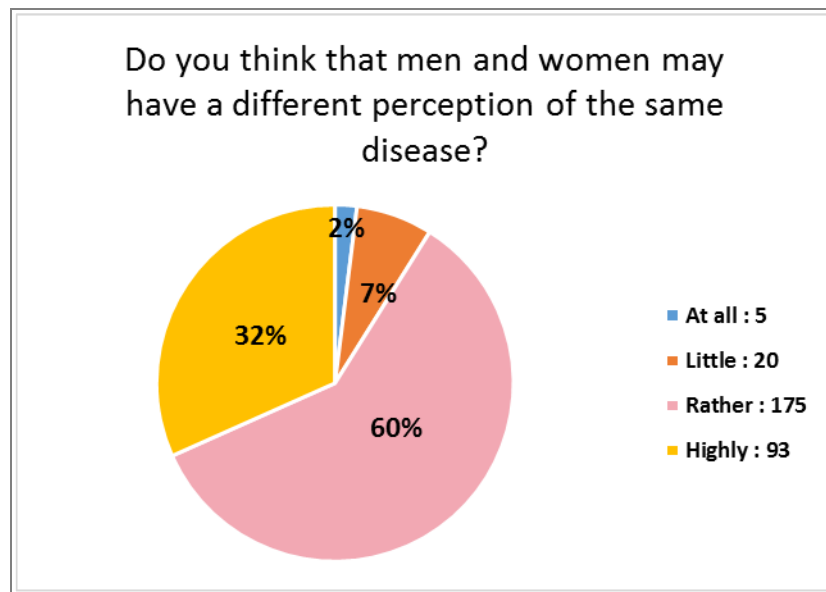


Table 10.

We then asked about the irrelevance of the sex of the patient in the diagnosis and treatment of the disease, and they answered that they partially (40%) or strongly (33%) disagree, showing that men and women want to be cured in a different way (Table 11).

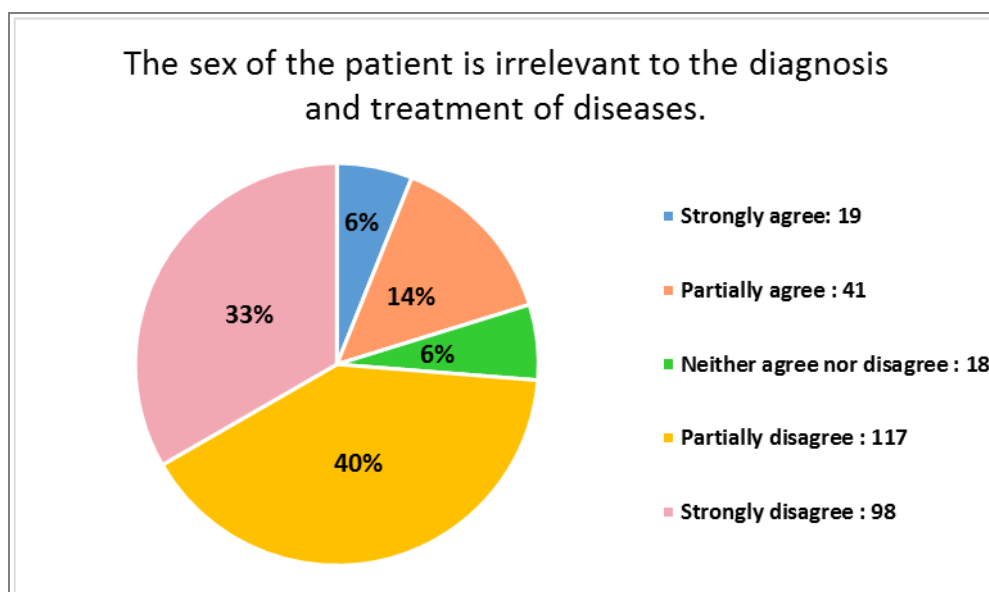


Table 11.

This concept is confirmed in the next question, where we wanted to emphasize it: so, the majority of people are partially (46%) or strongly (23%) agree with the statement that doctors should treat men and women differently (Table 12).

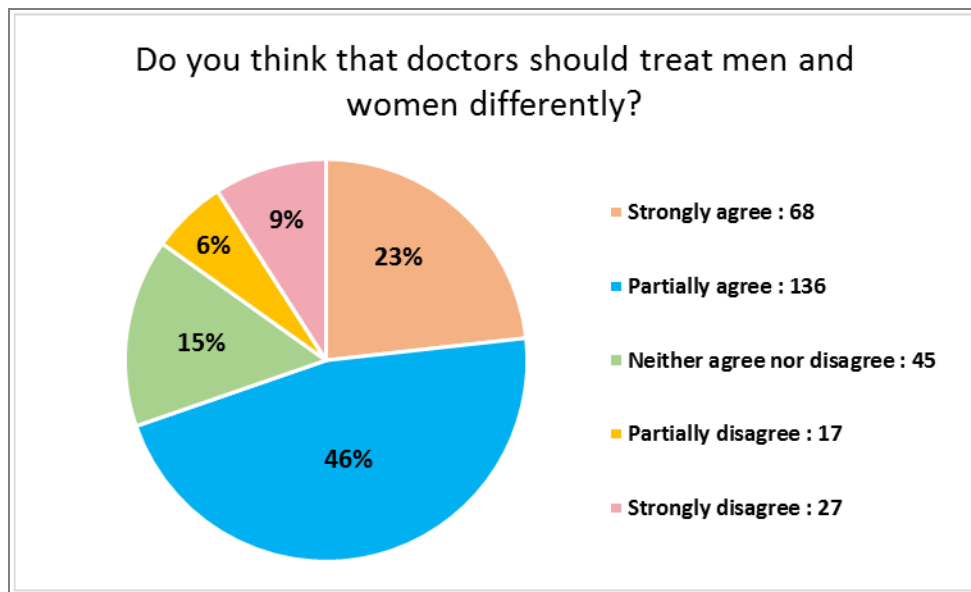


Table 12.

Considering the current economic crisis we are experiencing, we asked if this discipline could be considered as a waste of resources and time, the majority strongly disagree (47%), followed by who does not agree nor disagree (24%) and by who is partially disagreed (21%).

In general, we suppose that if applied, Gender Medicine could bring benefits to population and not be an useless discipline (Table 13).

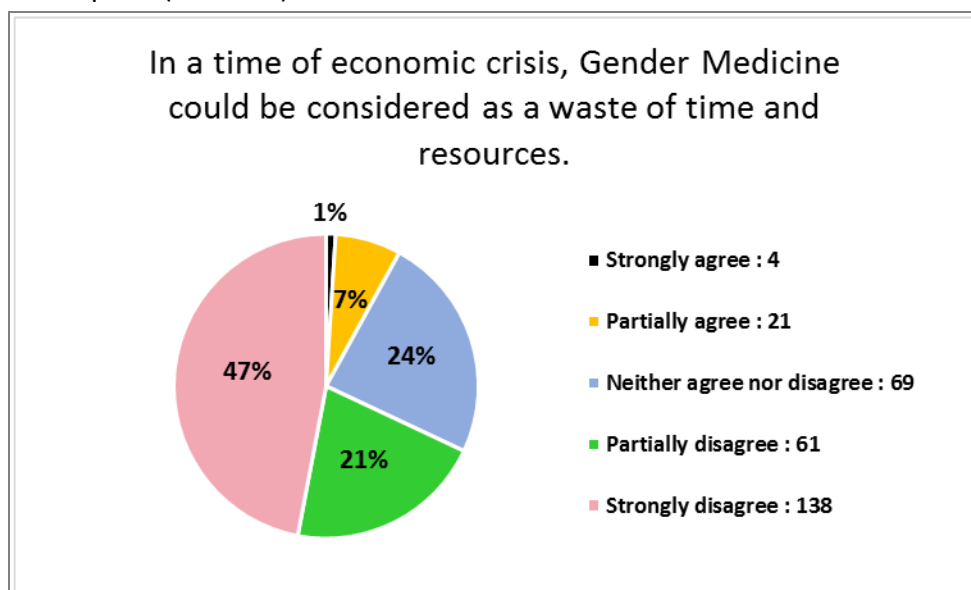


Table 13.

We then asked if they think that Gender Medicine may help to improve diagnosis and treatment of diseases, and the 74 % answered that it could be helpful, while the 25 % does not know (Table 14).

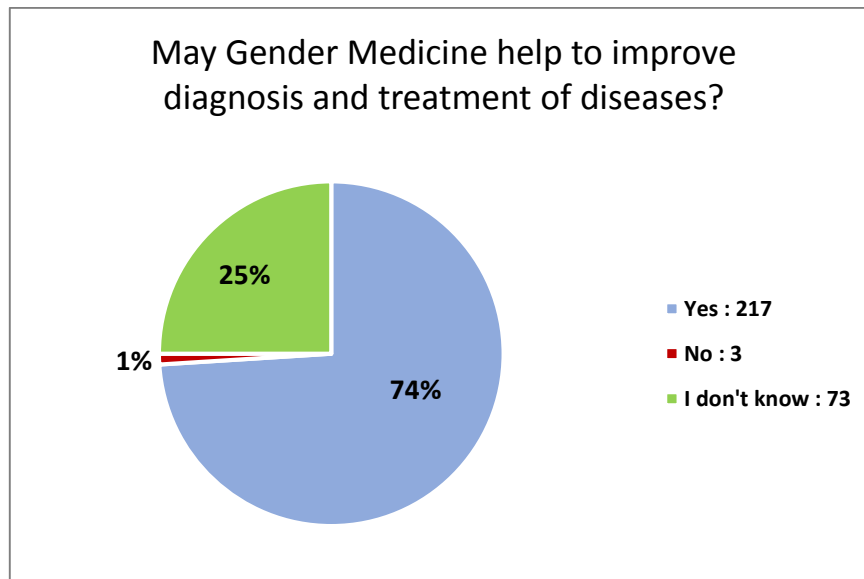


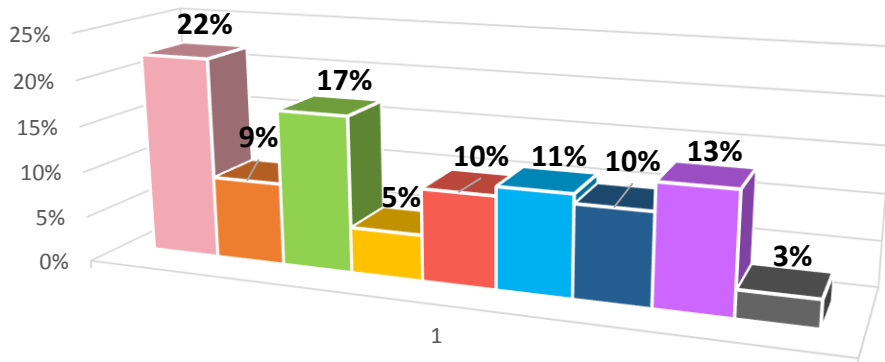
Table 14.

For this question we have provided the opportunity to argue their answer freely, without obligation, and we have collected several opinions that represent the needs of people. Here there are some:

- *“learn effectively the incidence and effects of a disease on a man or on a woman would help to administer the therapy promptly achieving positive results much more quickly”;*
- *“it could help in the prevention of certain diseases and in the diagnosis of those whose symptoms are manifested differently in men and women”;*
- *“The specialist medicine, considering also gender-specific medicine, can always work alongside to the generalist one. The important thing is the exchange of information between health workers with no expectation”;*
- *“It could make a more accurate and faster diagnosis, with more targeted treatments, this would not only make the shortest path to healing the patient, but also it would benefit the physical, psychological and economic aspects. Similar advantages there would be for the National Health system, which would incur lower costs for analysis unnecessary and ineffective medicines”;*
- *“A differentiated approach could make the patient feel more considered and followed, with a consequent benefits on his health”.*

The last question regards the healthcare and pharmaceutical areas which could be changed by Gender Medicine, and we find a good percentages for the Awareness and prevention of disease (22%), Research (17%) and Information (13%), followed by Primary care (11%), Health spending of families and Hospitals (both 10%), Pharmaceuticals companies (9%) and Home care (5%) (Table 15).

Which healthcare and pharmaceutical areas could be changed by Gender Medicine?



| | |
|---------------------------------------------------------------|-------|
| Awareness and prevention of diseases | : 208 |
| Pharmaceutical companies | : 83 |
| Research | : 158 |
| Home Care | : 51 |
| Hospitals | : 92 |
| Primary care (general practitioners, pediatricians,...) | : 108 |
| Health spending of families (drugs, medical examinations,...) | : 94 |
| Informations | : 120 |
| I don't know | : 30 |

Table 15.

Also for this question we asked to argue the answer without obligation, and these are some opinions:

- *“prevention and awareness, information and research are actions that tend to anticipate the onset of illness, rather than to cure it”;*
- *“we must do more sensitization talking about risks, causes and symptoms as opposed to the gender of the affected person. Search for possible specific therapies, trying to solve the fundamental problems for the female or the male. The doctor, often inept, should also lead to greater awareness and greater attention to the differences of his patients”;*
- *“prevention and awareness are more effective especially if we consider the socio-cultural and behavioral differences of the sexes”;*
- *“pharmaceutical companies could encourage clinical trials to assess the effect of different drugs and treatments in patients of different sex”;*

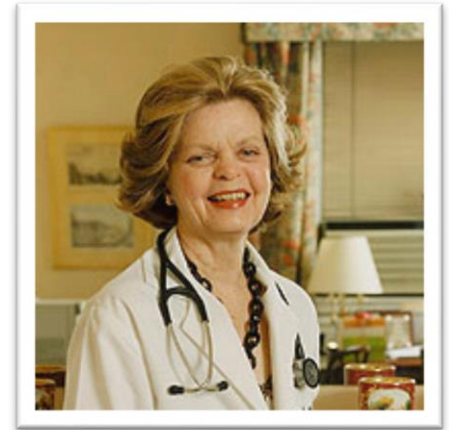
- *“a preparation in this way would make a the quicker diagnosis, patients would be more aware, pharmaceutical companies could produce targeted products, with cost reduction of unnecessary or ineffective products. Care centers may dispose of and manage the hospitalization and discharge of patients with further reduction in health care costs, already starting from the primary care, physicians could avoid unnecessary and expensive treatment and analysis, sometimes harmful. All this would reduce health care costs for the facilities and families”.*

From this data, we can resume that people want to know more about this discipline, especially when it concerns themselves and health. The knowlegde of informations and the awareness of differences between men and women is important for both healthy and sick people, to help them to live better and properly manage any situation of physical, psychological and social discomfort.

OUR INTERVIEWS

MARIANNE J. LEGATO

Marianne J. Legato, MD, FACP, is an internationally renowned academic, physician, author, lecturer, and pioneer in the field of gender-specific medicine. She is a Professor Emerita of Clinical Medicine at Columbia University College of Physicians & Surgeons and an Adjunct Professor of Medicine at Johns Hopkins Medical School. Dr. Legato is also the Director of the Foundation for Gender-Specific Medicine, which she founded in 2006 as a continuation of her work with The Partnership for Gender-Specific Medicine at Columbia University.



1. Can you give us a general definition of Gender Medicine?

Gender Medicine studies the differences in the normal function of men and women and in their experiences of the same diseases.

2. What triggered the interest in Gender Medicine in United States? Which were the first approaches to make stakeholders aware of this issue?

The interest in Gender Medicine in US was triggered in early 1990s, with the focus on the differences between men and women and their experience of coronary artery disease. I wrote, with a colleague that was a journalist, Carol Colman, a prize-winning book called *“The female heart: the truth about women and heart disease”*. And then it started a focus on gender specific medicine in this country. We developed this at Columbia University, to the point that we made an important alliance with the private sector, through a major affiliation with Procter & Gamble and we began the formal programme of the partnership for Gender Specific Medicine at Columbia, financed in a significant way by Procter & Gamble and smaller gifts from small foundations.

We have now founded the Foundation for gender specific medicine and we are continuing to support research and our scholars doing work and gender specific medicine throughout the world. We are currently finishing support for 5 young professors, 2 at Columbia and 3 at Johns Hopkins University.

3. Throughout your career, did you find more favorable or non-favorable receptions about Gender Medicine among practitioners and healthcare professionals?

I think that once professionals at all levels, are exposed to the astonishing and abundant data about the differences between men and women, they invariably became very interested in. They apply the new investigation with a gender perspective by implementing some of the practical points in their care of patients. So I find in general that once scientists and clinicians or anybody involved in the healthcare, really hear about and believe in the differences between the sexes, they find them fascinating and completely unexpected and I think their responses in general are almost invariably wonderful.

4. Can you tell us what are the strengths and the weaknesses of the gender approach?

There are no weaknesses in a gender approach. The more we understand about the reality of the differences between the sexes at all ages, the more obviously we need to know these differences and apply them to patient care and to the research that we do.

One of the most important area of investigation now is the study of the genome and the realization that the same genes are expressed differently as a function of the sex of the person or animal in which those genes reside. This is a very important and unexpected development and I think it is one of the most exciting.

5. Currently, what are the concrete applications of Gender Medicine in United States?

The concrete applications of Gender Medicine in the United States are largely in the research laboratories. People doing stem cell biology, for example, are becoming interested in the importance of cell sex and in the development of chimeric animals and in research that focuses on the therapeutic of stem cells.

We recently had a symposium about Gender Medicine implications in stem cells biology, chimeric animals, synthetic biology and artificial intelligence and robotics. We think that gender should be an important component of the development of these fields. And it is an opportunity to expose scientists working at this molecular level to the importance of gender in the research they are doing and in the models they are using.

6. Can you give us examples of how the different perception of the disease between men and women can affect the outcomes?

I think that if you read the history of the truth of diagnosis and treatment of coronary artery disease in men and women, you will find that before we understood the different experience of women with coronary disease, they were underdiagnosed, certainly undertreated, and died unnecessarily. That has changed remarkably, and the interesting to me is that although we have tried to change and successfully done so, the death rate has not been decreasing in women, but it has been decreasing in men. So we have to continue to vigorously try to understand what these differences, that make women vulnerable, are.

7. You have a gender specific private practice in New York. Can you tell us about it?

My gender specific practice in New York is composed of private patients, who come to me usually for complex issues and who appreciate the fact that me and my colleagues understand the different responses of the sexes, regarding therapeutic, interventions, interpretations of their symptoms and understanding what lifestyle and age has to do with the experience of illness.

8. As an international authority on Gender Medicine, you chaired several congresses worldwide. Which countries have already translated gender perspective into practice?

Sweden, at the Karolinska Institute, has an eleven-year story of studies of Gender Medicine. Israel, Austria, Italy, Japan, South Korea are other examples. Romania also showed recently interest in the topic.

9. Are you still a leading advocate for women inclusion in clinical trials?

I think that as a woman it is a matter of justice. Women should agree to be part of the subjects to be involved in clinical investigations. I think that women are very harmed by making the data that we get from men be applied to them, without individual testing.

10. Do you think that Gender Medicine could or should be the future of the medicine?

It should be the future of the medicine, in all the subspecialties. It is not a specialty, it is a point of view and a direction that all medicine and biomedical investigations must take. And to that end, we are beginning a project with Johns Hopkins to develop a curriculum for the practice of gender specific medicine and the application of gender specific medicine principles to clinical care for healthcare professionals.

INEKE KLINGE

Ineke Klinge is associate professor of Gender Medicine at Maastricht University. She combined her training in biomedical sciences with gender research. Since 2000, she has concentrated on EU grants for establishing sex and gender sensitive research throughout Europe. She is currently co-director of the Gendered Innovations project, financed by the European Commission, which aims to develop methods of sex and gender analysis for basic and applied research.



- 1. You started to deal with a gender approach since your PhD thesis in 1998 and then you've been appointed at Maastricht University as lecturer. Can you describe us what was the general situation about Gender Medicine at that time? Was there a gender perspective of medical evidence, patients, medical education, clinical practice?**

In 1998 the concept of Gender Medicine did not exist at all in The Netherlands. Many other faculties, such as social sciences and humanities, had gender studies in literature, but it was a pioneer position in gender studies in health sciences when I was appointed.

In our faculty there is the medical curriculum but there is also a curriculum for biomedical research and in that curriculum of biomedical sciences there is, I think, also an interest in GM.

- 2. Can you tell us what triggered the interest in Gender Medicine in your country? Which were the first approaches used to make stakeholders aware of this issue?**

In 2000, the European commission asked for a gender impact assessment of their research programs and then they wanted to know how much, how often or how good the address of sex and gender differences was in that program and that program covered a large part of health research and other parts of the life sciences. Then it turned out that in that research program there was indeed room for improvement, sex and gender were never really taken into account and no differences between women and men were made. And from that point I've been executing several projects for the European commission, building on the first state of the art that there was no attention and then we brought together the evidence from the literature and also about the negative effects of not paying attention to those differences. And over the time the European commission made more elaborate policy and regulations to stimulate excellence of research. All along the way, there were also centers for Gender Medicine in Berlin and in Stockholm and those people were meeting so in 2005-2006 in Europe but also in international collaborations. Then I think by that time the concept of the umbrella term of Gender Medicine was launched. It was a stepping up to new initiatives.

- 3. What about the inclusion of women in clinical trials in your country?**

There is no specific regulation. The Netherlands have to align the European Medicines Agency (EMA) which has no specific regulations for women inclusion.

4. Are you aware of any gendered study by a pharmaceutical company in your country?

In The Netherlands recently one pharmaceutical company has asked me for a master class in gender medicine. So I think this is a little point of awareness because they are asking for a kind of training or explanation.

5. How gender approach can help the research?

It is the aim of my recent project "Gendered Innovations". We have provided researchers of tools to understand the importance of sex and gender approach, because they do not get it in their traditional training. We developed really practical, easy-to-apply methods, which are illustrated in our website, and I think it can be really stimulating and appealing for young researchers. We have 30 years of literature but only 15 of practice, so this was done to give a positive message: just do it!

6. What about the patient point of view? How does the different perception of the disease affect the outcomes in men and women?

In patient perception and patient behavior you have to take into account the way how gender norms in society can influence behavior. It depends on what is considered as masculine or feminine in a certain society. For instance, at the time you go to the doctor, often men neglect their symptoms and go to the doctor far too late.

7. Would you add anything about the Gender Innovation Project? (aims, achievements...)

The aims are to provide researchers with the tools for sex and gender analysis and what we have achieved so far is this website and this materials will be used by the European commission in their new framework program *Horizon 2020*, there will be topics for instance in the health programs with an asterisk that means that for that topic sex and gender is relevant so will be directly linked to the website methods. So I think it can be used by researcher in the next *Horizon 2020* programs.

8. You've dedicated more than 10 years to Gender Medicine in biomedical and healthcare issues. What are your most important achievements?

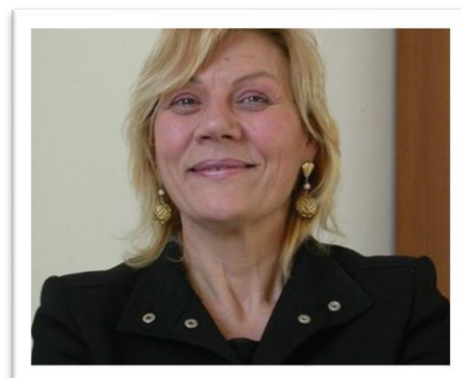
Of course the web site and the books and seeing that the issue is getting more support over the years. You start as a pioneer, and then you find colleagues and you feel that you are convincing people of the relevance of this issue. This support makes me happy!

9. Do you think that the Gender Medicine could or should become the future of the medicine?

I'm convinced that it would be the next direction of medicine. The ideas and the methods of Gender Medicine it would be great if they became the most natural thing to do, so integrated into traditional medicine in a way that the medicine became itself transformed into Gender Medicine.

FLAVIA FRANCONI

Flavia Franconi, MD, Professor of Molecular and Cellular Pharmacology at the University of Sassari, coordinator of the first PhD in Europe in Gender Pharmacology, along with four other European universities, has set up a master in Gender Medicine funded by the European Union; she has to her credit several international publications on the subject and she is a member of the editorial board of the journal Gender Medicine; she is responsible for the Gender Pharmacology Group in the Italian Pharmacology Society, vice president of the Society of Health and Gender Medicine, founder and president of the Italian Group of Gender Health (GISeG).



1. What is the Gender Medicine for you?

It is the study of the similarities and differences between different genders including men and women, at all ages of life, both in terms of the biological differences that social ones. It also means to arrive at a more appropriate and greater efficiency and equity in health.

2. What are the medical specialties that have developed a more gender "sensitivity"?

Worldwide, the specialties that have developed a greater ability to find a gender dimension in medicine are cardiology, where Gender Medicine is virtually born, and psychiatry. In Italy we find these specialties, but less than in the rest of the world.

3. In your opinion, what are the difficulties that might arise in adhering to Gender Medicine?

There are various difficulties. Meanwhile, with regard to the complete adherence to medicine generally many data of researches lack, because at the present time we know quite well the male physiology and almost totally lacking in the woman, then a first difficulty is still a lack of knowledge that exists about the differences or similarities between men and women. So we somehow encourage and stimulate research on this aspect. Second thing, there still remains a gender bias in society, and this prevents the application of Gender Medicine: there's still the custom to consider that women should be treated as men. So we have to bring this culture at all levels, including women, because women do not know for example of getting cardiovascular disease and therefore there is no prevention. So to overcome this gender bias. The differences are not only biological, but also social, we do not consider the different roles that can influence the development, epidemiology, natural history of disease. That is, women get sick of the same disease, but how these diseases evolve and their incidence and their prevalence depends on sex and gender; in other words, women carry the role of caregiver, and being a caregiver causes stress, increasing the risk of cardiovascular diseases, in addition to depression and anxiety. I am a supporter of the fact that the

social and biological differences are not dichotomous, but they must be studied together, adopting a range of intersectoriality and interdisciplinarity.

4. Do differences in pharmacology concern pharmacokinetics and pharmacodynamics?

Yes, with regard to the pharmacokinetics we are one step ahead, because we know better and it is fast to study, while pharmacodynamics is more difficult to study and it is still a bit unknown, now it's beginning to emerge, but what I would like to point out is that the pharmacological response is complex, which not only affects the pharmacokinetics or pharmacodynamics, but also about the role of the patient, for example the adherence to therapy is an important component. Adherence means how well the patient follows the treatment, if he respects what the doctor has told about the therapy. Contrary to what one might think that women are more adherent, in fact, the few data in the international literature indicate that males are more adherent than women, because I suppose there's the wife behind...and women have no one behind that tells them to take the pill. There could be also other reasons. Another thing is that in the pharmacological response it's important the "bond" between doctor and patients: with regard to some data in the international literature shows that women with diabetes treated by female physicians more easily reach the therapeutic targets, and it means that a "collaboration" woman-woman (doctor-patient) increases the response to treatment, that is not that medication has changed, but the aim of counseling, let's say the doctor-patient relationship is best when the doctor is a woman.

5. The "skeptics" claim that would be enough to change the dosage for a drug, and we would have the appropriate amount for women: why can be difficult to understand that there are more important issues to be evaluated rather than the "simple" dosage and administration?

Reduction of the dosage based on body weight is a mistake because the woman body, with equal weight to man's, is not the same: the woman in fact contains much more fat than men, so the distribution of drugs is carried out in a different manner. For example, there is a greater distribution of drugs that dissolve in fat tissue in women, while in men drugs dissolve more in water. But then is not just a matter of size and composition of the body, but is also a function of the metabolism of a drug, rather than its renal elimination. Another thing to consider is the pharmacokinetics, but also pharmacodynamics... who tells us that pharmacodynamics is not equal between men and women? So we are going to study these things, and every single drug and every single molecule should be restudied in male and female, and considering the fact that pre-clinical studies in animals or in the cells are made predominantly, as regards the animals are male animals, and so there is an apparent knowledge of women at all levels; cells are considered asexual and it is never mentioned, in any case, the sex of the cell.

6. Can you give us some examples of significant "gender" drugs in Italy?

At the present time we do not have "gender" drugs in Italy except those dedicated specifically to the prostate gland or the ovary. However, there are reports, and this is the first report important, as I call it, the "clearance" of the gender pharmacology, there was a warning from the Food and

Drug Administration (FDA), where a sleep-inducing drug (*Zolpidem*), should be administered in lower doses in women than in men. This is a drug that has 15 years of life, induces in women hypersomnia in the morning when administered at the same dosage of men. This means that women who go to accompany their children to school, have a greater risk of having an accident.

7. How has the subjective perception of health changed over time and which gender differences can be detected?

Slowly women are learning to be different, women are carrying out these things, and this is normal because they are the most disadvantaged. Some men are becoming aware of the benefits that can come to them with gender medicine, because men are significantly disadvantaged in some areas, nobody knows for example that in Italy, next to 4 million of osteoporotic women, there are about 800,000 men with osteoporosis, and are not entitled to reimbursement of medical examinations. The men are becoming aware of this and therefore are adhering to gender medicine for this reason. I will say one thing, and it may seem trivial, that during some meetings men were very rare in an auditorium full of women. I have to say that at the last meeting that I made on 15 November in Florence, about 130 people, 51% were men. So let's say there is an increased interest of men towards gender medicine, especially when they realized that they too can benefit.

8. Giving voice to patients, and people in general, could make a contribution towards the improvement of the quality of life, therapeutic treatments, as well as give a boost to certain research or experimentation?

Yes and no. I believe that the more you inform the patient, and it's so much better, because the patient should even have a say in the choice of subjects, indicating what the needs are. On the other hand, we can come to terms with a lack of knowledge that a citizen may have, then the problem is that people is very important because the information is essential to the population, but very often it is not guided by rationality and sometimes can be driven by emotion. Who is the craft must use rationality otherwise nothing is done in this world, there must be a methodology, a methodology of science, and so you have to explain to people that sometimes there are no drugs, sometimes we cannot do nothing, they should be informed in a fair and adequate way, and people know despite what the press says that there are still some diseases that cannot be treated. So citizens should be aware that to get to a scientific discovery to defeat diseases you have to use a methodology, and the scientific method should be applied to biomedical research. On the other hand we are in the land of Galileo, who was the first who made the scientific method. Then yes to the citizens, but without emotion.

9. Can Gender Medicine be a strategic goal for public health and for pharmaceutical companies?

Absolutely yes. In healthcare, Gender Medicine is a priority of the WHO. In July this year a document was created, so at this point Gender Medicine should be a priority for national health systems; on the other hand, pharmaceutical companies have interpreted Gender Medicine far as a cost, because they need to increase the number of subjects in research before placing the drug on the market. Whereas before they put men and a 10% of women, according to the FDA now they must increase

the number of women similar to the incidence of the disease in the real world, and then of course the cost increases. It's different when there are 500 people, and when there are 1000. In fact we have to explain to pharmaceutical companies not only that there is a cost, but there may even be a gain, because they might have a drug thrown away because it is not effective in the male and it could be effective in females. So the higher costs could be reduced considering that there may be drugs that have been thrown away, and second, there could be marketed drugs that cause fewer side effects in women, and therefore less risk after the marketing. You can save a lot of money if the drugs were studied in men and women for whom the side effects are known prior to marketing.

10. The project "Gender Attention" is the first study that highlights the Italian Gender Medicine and women in clinical trials. Were others born or are planning their design in Italy?

Similar to Gender Attention no, but I know that other pharmaceutical companies are analyzing old clinical studies that were previously analyzed without dividing males and females, that is the analysis of the clinical trials, that is how can we get information on what you already have, this is the plan. These studies have resulted in registration and marketing of drugs. So, in these studies there were a number of women, if this number is enough to give a statistical value, the results of these studies can be divided by gender, because so far the results were all put together. Being that men were 80% and women 20%, the overall result was the male. If we separate, when the number is enough to make a good statistic, we can learn some specific issues for women, and these results must be done only on the statistical analysis, and with a relatively low cost. There is another problem: several drugs have become generic, so who does more studies? So we have to get the information from the old ones.

11. Do you think that the gender approach will become the future of medicine?

Definitely, because the gender approach considers the person as a whole, considering psychology, social, role, together with the biological differences you go to a medicine I can say "holistic", and in this case we consider the individual as a whole, in its environment, ranging from the geographical environment, the society that is never the same, and this is definitely the future of medicine. And then we say that the gender approach is also a way to move towards personalized medicine.

ANTONIO SASSU

Antonio Sassu, Professor of Political Economy at the Faculty of Political Sciences in Cagliari, he devotes importance to research topics concerning the determinants of women's health in relation to gender and the organization of economic-working life, within the framework of the Women's Health Strategic Project, whose leader is the Italian Institute of Health and they are involved in many Italian and some foreign universities.



1. What is the Gender Medicine for you?

It's the medicine that at the same time takes into account sex and social role built by people. Humans differ in biological and "environmental" aspects. For this reason, we should talk about, accurately, sex-gender medicine. Medicine must take into account all these differences and then give an evaluation.

2. How has the subjective perception of health changed over time and which gender differences can be detected?

Until recently, medicine was essentially practiced on the male body of 70 kg. The experiments were performed on it and drugs were tested. Subsequently, the findings were extended to the female body. A demonstration of this is the fact that women were not enrolled or were in very limited number in clinical trials. Over time, even for the feminist world pressures, we have realized that there are biological differences between men and women (regardless of the specific functions of the sexes, for example, maternity) which must be taken into account in the therapy. For example, the circulatory system, the immune and nervous systems show significant differences between men and women. Today, many women, at least of 30%, are enrolled in clinical trials. Obviously this is not enough, but it is a step in the right direction.

Nothing is done, however, regarding the "environmental" factors that can affect the health. Income, education, lifestyle exert a great impact on the health of individuals and they are normally not considered in diagnosis and therapy. There are huge differences between rich and poor, educated and illiterate. I do not want to say that rich people do not die, but they get less sick than poor people and die at a later age. These differences, which are essentially gender differences that affect both men and women, are generally neglected. The medicine has certainly changed, as well as health care and health perception that citizens have, but much remains to be done.

3. What are the socio-economic determinant factors that can impact in both men and women and in their access to health care?

Surely the income, education, employment, lifestyle (in which we include many factors), cognitive problems and pollutants (which are often derived from the workplace) play a great role. A trivial

example is given by the criterion by which the suggested therapy is applied: it is different depending on the education of the patient. The income has influence in the purchase of medicines, access to care, choice of doctor, especially specialist. The efficacy of the drug is different if you are taking substances (alcohol, smoking, birth control pills). All these factors that are not normally considered in the diagnosis and treatment are very important. The statistics are illuminating in this regard and documenting the differences between men and women and people of different social class.

4. Professor Flavia Franconi believes that Gender Medicine is an interdisciplinary and cross-sectoral field, and that the biological and social differences should not be considered separately. Do you agree with this statement?

If you intend that the medicine explains better the functioning of the human body considering genetic and "environmental" aspects, I totally agree. The experience and knowledge allow us to say that both aspects, although with evolution and with time, have an impact on the health of organisms. The medical science is very clear in this regard and discovers more and more the correctness of this position.

5. In your opinion, what are the difficulties that might arise in adhering to the Gender Medicine in the Health System in Italy?

The main difficulty is cultural, and then comes the professional one. Cultural change takes time because the inertia is a typical phenomenon of human beings, starting with the politicians. Secondly, professionalism *ad hoc* (often linked to knowledge) requires a modification of the physical facilities too. Think of the degree programs that do not provide a gender medicine.

6. In this scenario of economic crisis and spending review, do you believe that Gender Medicine could be beneficial for the National Health System and the pharmaceutical companies, of course not immediately?

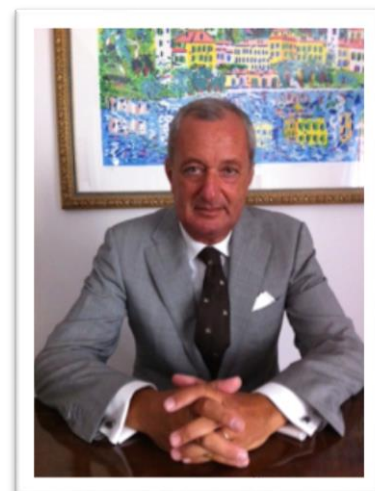
As for the SSN (i.e. in a context of health as a universal right) I would say yes: there will a better knowledge of the human body and therefore a better prevention. Just think of the adverse drug reactions. If women were recruited to a greater extent in clinical trials, there would be a lower percentage of adverse reactions (and access to hospitals, including hospitalizations), and lower costs. If the suggested therapy was effective and did not create any negative reaction would have better health and cost savings. It would increase the knowledge and there would be major economies to society. Unlike the speech against pharmaceutical companies that have as their goal the profit, if the market decreases (and with Gender Medicine will differ by sex, social categories, until a personalized medicine) pharmaceutical companies are less profitable to invest. However, they have more convenience to concentrate in the areas of elongation of life cycle and the conditions of well-being, to which we are increasingly going.

7. Giving voice to patients, and people in general, could make a contribution towards the improvement of the quality of life, therapeutic treatments, as well as a help in health care spending?

The answer is yes. In general, the consideration of the needs of patients improves the quality of treatment and of life.

GIUSEPPE ASSOIGNA

Giuseppe Assogna, MD, specialized in Diseases of the Liver and Metabolism at the University La Sapienza in Rome, after a brief period of medical practice, he has gained extensive experience in multinational pharmaceutical companies, as Director of Clinical Research, Medical and Regulatory Affairs, in the areas of clinical research, medical affairs, product registration and reimbursement, pharmaco-economics and market access, he has also made important educational projects, launch, support and defense of numerous products, including crisis management; he has been involved in governance and corporate management, scientific advice and management for pharmaceutical companies and scientific societies. At the moment, he is the president of SIFEIT (Italian Society for the study of economics and ethics on medication and on therapeutic interventions).



1. What is in your opinion Gender Medicine?

In my opinion, Gender Medicine is the kind of medicine that assesses the relationships between genders and the effectiveness of therapy in certain areas or diseases.

2. Did you find interest in this topic during your career?

My testimony as a clinician is indirect, because I've been working for a few years in the clinical field (hospital and clinic) and for about 30 years in pharmaceutical companies and now as a consultant. Gender Medicine today is intended especially with regard to women. As the medical director of Organon, for years I have been dealing with oral contraceptives, hormone replacement therapy, cancer or breast cancer: therefore my approach has been indirect.

3. What are the main strenghts and weaknesses of Gender Medicine?

The main strength appears in the moment when you decide to consider the gender to test the efficacy of a therapy. This means that the real goal is therapeutic appropriateness, that is, if you know the target, then you can better treat the pathology. An example may be the fact that women have a stronger immune system than men. And this is an advantage. But there are also the "cons": the weakness is the fact that having a stronger immune system, at some point, causes a sort of "biological and physiological exhaustion", that leads women to getting sick more than men.

Another advantage of Gender Medicine is to focus on some particular pathologies to which women respond in a different way than men.

The advantages of Gender Medicine are linked, in theory, also to some oncological diseases with biological markers: if we know that a certain type of cancer responds to treatment in a certain way,

the more we go on, the more there is an appropriate therapy for the disease. This is also true for the side effects of some treatments: some women are more sensitive than men.

In my opinion, the big weakness of Gender Medicine is the lack of awareness in Italy: both in Australia and in the United States there is more knowledge. In Europe, and much less in Italy, this approach has not yet fully taken off. This is a demerit that must be filled as soon as possible.

4. According to the AIFA director Luca Pani, “Gender Medicine is not a craze but a necessity”. What do you think about? Do you agree with this statement?

Definitely. I agree with Luca Pani. Gender Medicine is a necessity because, the more we go on, the more we can identify the most appropriate therapy for each patient. And this is better for everyone: healthcare system, costs, resources, and mainly patients.

5. Can the knowledge of gender differences lead to an increased appropriateness of therapies? Which kind of strategies can we adopt to ameliorate the therapeutic appropriateness by taking advantage of Gender Medicine?

Absolutely yes. The knowledge of gender differences between male and female definitely helps. For instance, knowing that prolactin levels are different between women and men, unless the case of men with a pituitary adenoma, it is certainly useful. And it is helpful to know the hormonal fluctuations in women that the man does not have. It is also useful to know that testosterone levels in men are at a certain level. On the second point of the question, I have already answered in part: it is a matter of prescription appropriateness. So far, in Italy there was an “indiscriminate prescription”, not in a bad way but because until now most studies have been conducted in men and women without man/woman distinction and it would instead necessary to understand the different impact. So, for me, Gender Medicine is needed.

6. Women are at the top for the consumption of drugs but, so far, they have been underrepresented in clinical trials. Soon, there will be trials according to sex and clinical trials of marketed drugs to evaluate the different responses of men and women. What do you think? Do you think it is right to consider gender equality in the recruitment of patients in clinical trials?

I would make a distinction. Some time ago, it is true that only males were involved in the pre-authorization clinical studies (up to phase 3). Today also women participate in these studies and, moreover, I think that we should get to a point where certain diseases should be studied exclusively in women. An example: women generally live longer than men and do not have a whole series of diseases up to 60 years or so. After a certain age, however, women get sick, more than before, to cardiovascular diseases. This is an aspect that should be studied and deepened both to give greater therapeutic appropriateness and to avoid large costs.

7. From your clinical experience, what do you think are the pathologies, and therefore the drugs, that are most in need of Gender Medicine? And why?

Surely cardiovascular diseases, taking into account the age. The inflammatory and/or autoimmune diseases, those involving reactive elements of the body (cytokines, etc.), for instance some connective tissue diseases. Another pathology is psoriasis, which has been studied by Novartis. Obvious, but not to forget, breast cancer. The list is longer when the woman goes through menopause: bone, cardiovascular, neurodegenerative diseases etc.

8. Why we should invest in Gender Medicine? Do you think it could reduce costs of health care systems?

Yes, it is worthwhile. An investment does not mean to have a return in a few hours, but in a few years. Let me explain: if you invest in Gender Medicine, it does not mean that in a short time you will manage to optimize not only the disease but also the therapy. It takes time to understand how the therapy, according to those parameters and those features, could be efficient and appropriate. Gender Medicine also reduces health care costs because, although initially you spend more, then, in a time span that can be 4 or 5 years, you spend actually less because you treat only patients who really need that treatment.

We have a national health service that is one of the best in the world, and this is good for emergency treatment but, for chronic conditions, what future do we have? In 2020, chronic obstructive pulmonary disease, probably, will be the third most frequent pathology in the world, as well as in Italy and Lazio. The difference is therefore essential for a discourse of preventive health care. In Italy, unfortunately we tend to solve the problem rather than to anticipate it. But it is also true that our national health system is accessible to everyone, unlike other countries.

9. How we can spread the gender culture in the regulatory field?

The AIFA has shown, through its director, a range of intentions. At corporate level, Novartis, for example, has conducted the psoriasis project. As I know, some pharmaceutical companies are moving towards Gender Medicine. This does not mean that they have already defined protocols or areas of intervention, but it means that for some diseases, which I mentioned before, they are quickly increasing their awareness.

If we give a value of importance from 1 to 10 to Gender Medicine, in Italy and in Europe, certainly, at this time, we can represent it with a 5 because there is still much to do.

10. We want to deal with the issue of Gender Medicine also from the point of view of the different perceptions of patients: depending on gender and age, the patient reacts differently to the disease, diagnosis and consequently treatment. For example, in oncology, hair loss due to

chemotherapy causes more problems in women than in men. Do you agree? From your experience as a clinician, can you give us some examples?

I've worked in the field of antipsychotics and seeing a patient that, after taking two tablets of a certain drug, begins to play table tennis has an impact in a positive sense: explosive, on him, on the family, on everyone. Another example, referring to women, is that of emergency contraception or fertility. In order to have a baby, a couple could be willing to do anything. I understand and agree that there may be, from the point of view of patients, a need to express their opinion.

Patients are in need of expressing their opinion and this is sacrosanct, but we should also, in my opinion, "rationalize the emotionality": you cannot always pay heed to everyone and everything. The patient should also consider the point of view of the AIFA and of the Italian state, which is in a difficult situation. So, yes to all, but then you have to be rational and understand that there must be an address of these things by the Italian Government and AIFA.

A little healthy "scientific rationality" is needed by people that make decisions.

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