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<https://doi.org/10.1057/s41599-020-0416-5>

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# Gene editing and gender-specific medicine: a challenge for dementia research

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**ABSTRACT** Gender-specific medicine is a clinical discipline that studies the impact of sex and gender on physiology, pathophysiology, and diseases. Human genome modification of somatic cells could be useful for treating or preventing a range of diseases and for improving the safety and efficiency of existing gene therapy techniques currently in use or under development for clinical application. Sex and gender differences have been analysed in the incidence and prevalence of dementia. In fact, epidemiological studies have demonstrated that women are at a higher risk than men for developing dementia or Alzheimer's disease (AD); however, the reasons for these differences are not completely known, and the debate is still underway. In recent years, in the effort to clarify the risk of developing dementia or AD, increasing attention has been devoted to the differences between men and women in the causes and manifestations of neurological diseases, as well as to their response to treatment and to outcomes. Through a conceptual analysis we will argue that an emphasis on gender-specific medicine in gene-editing research can contribute to the progress of medicine by introducing a relevant value-driven perspective on health and diseases. This is something we will do on the basis of a gender-specific strategy. In fact, focusing on the effect of sex on dementias and in particular AD may be essential in advancing our understanding, treatment and prevention of these disorders, considering that AD and other dementias disproportionately affect women, and it underlined the relevance of empirical data relating to sex differences and emerging sex-specific findings in dementias in order to assess the scientific approach to these diseases for the improvement of quality of life for both women and men. It may be helpful and suitable to consider how the interventions that modify the genome should include sex and gender as a crucially important variable accounting for the differences between men and women in the causes and manifestations of diseases, as well as in the response to treatment and to outcomes. Of course, gene editing cannot remove biological differences, but its potential harmful effects, on one group relative to another, can be prevented with a research strategy that properly takes them into account with a view to equity between genders.

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## Introduction

**G**ender medicine, or most appropriately gender-specific medicine, is an emerging clinical discipline that studies the impact of sex and gender on physiology, pathophysiology, and diseases. It embraces differences between males and females pertaining to both psychological and social aspects and is important in improving our knowledge in all aspects of human health dealing with the differences between men and women: from public health perspectives to clinical practice, from basic research to the detection of diagnostic gender-specific markers (Legato et al., 2010; Baggio et al., 2013).

The difference in life expectancy of women and men is a worldwide phenomenon indicating that longevity seems strongly influenced by gender defined as the combination of biological sexual characteristics (anatomy, reproductive functions, sex hormones, expression of genes on the X or Y chromosome) and by aspects related to behaviour, social role, lifestyle, and life experiences.

The epidemiology of age-related diseases is substantially different between genders and changes dramatically in women after menopause. Women have a higher rate than men of chronic lower respiratory diseases, cerebrovascular diseases and Alzheimer's disease (AD). Influenza, pneumonia, septicemia, and hypertension—are also diseases with differences gender-related (Ostan et al., 2016).

Hawkes reports that differences between men and women have been reported relative to the structure and physiology of many organs, as well as to diagnosis and prognosis, response to treatment, and health outcomes. Furthermore, gender differences have been demonstrated to contribute to disparities in health behaviours, access to healthcare and medicines, and the response of the health system. These aspects therefore contribute to the burden of disease, which impacts women and men differently. An example is when women are not included in medical research studies on diseases that affect both sexes, where the assumption is that findings based on studies of men only will apply to men and women alike. But that assumption leads to misinterpretation when it comes to identifying sex-and-gender-specific determinants of health that affect men and women in different ways. The possibility of identifying sex and gender health determinants is an indispensable tool when looking to determine differences in pathophysiology, epidemiology, and response to therapies. This kind of knowledge could be of paramount importance for healthcare governance and policies, particularly when implementing health-related decision-making processes and designing appropriate clinical management for men and women (Hawkes and Buse, 2013).

So, on the one side, gender-specific medicine is revolutionary because it represents the demonstration that physiological and pathological differences between sexes go beyond the chromosomal differences and have been determined also because of different environmental factors and long-term adaptations, that have determined the psychological, social, political, and cultural differences between men and women that we face nowadays (Short et al., 2013; Caenazzo et al., 2015).

On the other side, scientific and technological progress in genomics are changing our approach to personalized therapy, screening, and prevention, towards a concrete realization of personalized medicine and genomics. Gender-specific genomics may influence different level of healthcare, from basic research to clinical decision-making relating to reproductive choices, of diagnostic and predictive testing, and of conditions that differentially affect the sexes, as well as on the level of wider societal implications (Krishan et al., 2016).

We know that the new CRISPR–Cas9 technology permits to identify specific DNA target sequences and, depending on the

purpose of the intervention, insert or delete new DNA sequences and illness-associated DNA traits. Unlike previous similar technologies, it is easy to use, given that various elements can be quickly and reliably assembled. The development of these new types of technologies has led to different applications in daily research and practice at the disposal of a wide range of scientists (Zhang et al., 2014). Therefore, what could change with the advent of technologies, like CRISPR–Cas9, that make it possible to modify somatic cells (Doudna and Charpentier, 2014; Liang et al., 2015)?<sup>1</sup>

It may be useful and suitable to consider how the interventions that modify the genome should include sex and gender as a crucially important variable. In particular sex which refers to gene expression and hormone function has undoubtedly an impact to gene expression itself. On the other hand, the differences between women and man are due also to other factors affecting gene expression, such as environmental/work exposure to toxics, nutrition and life style. In this context, it could be useful to refer to Sex- and Gender-Based Medicine, that is “An analytical approach that integrates a sex and gender perspective into the development of health research, policies and programmes, as well as health planning and decision-making processes. It helps to identify and clarify the differences between women and men and boys and girls and demonstrates how these differences affect health status, access to, and interaction with, the health care system” (Heidari et al., 2016).

More specifically, it will be necessary to test what transformations human gene editing brings in the future of the “gender research” agenda, this in order to consider the impact of the genomic era on gender-specific medicine where the mechanisms of genetic and hormonal factors combine with other factors in giving rise to a different approach to intervention on the expression of genetic vulnerabilities, as well as to explore the consequences of this new technology for men and for women in connection with this disease (Legato, 2015).

Gender-specific medicine, as a new medicine, has made significant progress in the last few decades, which has the potential to change and improve not only medicine but also global healthcare governance. At same time a new powerful gene-editing tool, such as CRISPR–Cas9 system, is now revolutionizing specific methods for editing the genomes of human cells, bringing benefits to human gene therapy. This advancement could arguably provide important changes in our concept of gender-specific medicine in the genomic era, in particular in implementing the core knowledge of gender-specific medicine in dementia disease research. This means arguing for the elimination of biases that negatively influence medical knowledge and clinical practice; for example, excluding female patients from medical research has obviously been a moral mistake, but also an epistemic one, as it created serious gaps in medical knowledge and clinical practice.

The issue of the role of gender-specific medicine in relation to gene editing does not seem to have received much attention from the bioethical specialist literature, nor to have much interest in the scientific literature. This paper deals with this topic in relation to dementia research, as an example of this kind of research, try to respond to a first fundamental question about the originality of the ethical dilemmas raised by this sector. The hope is that this may be of some use to the debate, which is expected to develop in the coming years in subsequent more specific or specialized studies.

## Somatic gene editing: latest advancements

It is important to mention the common distinction between somatic therapy and germlines, where the purpose in the first

case is to intervene only on the cells of an individual's body, whereas in the second case it is to intervene on the germline, with consequences on the individuals' descendants. While somatic gene therapy can be considered gender-neutral, germ therapy, insofar as it impacts on reproductive choices, can be gender-relevant. In this analysis only the use of somatic gene editing is considered, highlighting that gender issues are relevant in this field as well (Bauman, 2016; Bosley et al., 2015; Miller, 2015).

Genome editing is being developed to treat not only monogenic diseases but also infectious one and diseases that have both a genetic and an environmental component. As Doudna writes in *A Crack in Creation*: "Because CRISPR allows precise and relatively straightforward DNA editing, it has transformed every genetic disease—at least, every disease for which we know the underlying mutation(s)—into a potentially treatable target" (Doudna and Sternberg, 2017, XV).

Genome-editing technologies make it possible to genetically modify almost all types of cells and organisms, including those considered to be intractable with genetic modification. In addition, in conjunction with genome-wide association research, in vivo genome editing has shown potential for successful personalized clinical applications for genetic and brain disorders (Zang et al., 2014).

Current techniques for intervening on the genome using human-induced pluripotent stem cells (iPSCs), a type of pluripotent stem cells that can be produced by adult cells through genetic reprogramming, provide an opportunity to verify the contribution of alleles and pathogens to molecular and cellular phenotypes. However, the practical application of genome-editing approaches in iPSCs has been challenging. We know that the combination of this approach with recent advances in genome-editing techniques, such as the CRISPR–Cas9 system, has only made it possible to repair the alleles presumed to be causative in patient lines. As a result, isogenic cells that differ in a single genetic modification can be analysed so as to evaluate the molecular and cellular phenotypes that result from this abnormality. These isogenic cell lines can be used not only to understand the consequences of disease mutations but also to perform high-level genetic and pharmacological tests (Freude et al., 2014). So, using CRISPR–Cas9 technology, researchers believe it will be possible to introduce precise modifications into the genome of patient-derived iPSCs. When derived from the same patient, these cell lines will have an identical genetic background, differing only by the presence or absence of a specific risk allele.

The potential of iPSC cells looks promising because they could help us uncover novel mechanisms in these diseases: this could lead to the development of new treatments for patients, and in the case of known familial mutations, these cells could be targeted through the use of advanced gene-editing techniques to correct the mutation and be used for future cell transplantation therapies (Cox et al., 2015; Hotta and Yamanaka, 2015; Hockemeyer and Jaenisch, 2016).

But this kind of study needs to be developed and differentiated in relation to sex and gender differences in order to obtain valid results, providing better control cell lines for comparisons and potentially better phenotypes.

### **Gender-specific differences in dementia diseases as an example of a somatic gene-editing application**

In light of the foregoing remarks, we like to point out the case of dementia or AD, which is emblematic because the full impact of sex as a basic biologic variable on this neurodegenerative disease is still quite unclear.

The conceptual trends that underpin the gender-specific medicine are likely to transform the medical and research approach to identifying risk factors for dementia or AD. The societal impact of Dementia is of paramount interest nowadays, since it is a common age-related disease and population is ageing more and more in Western Countries. Epidemiological researches have demonstrated that women are at higher risk than men for developing dementia or AD: reasons of this differences are not completely known and it is still debated (Rocca et al., 2014). The recent analysis of Neu and collaborators has highlighted that there are not sex-related differences in risk of AD from 55 to 85 years of age: however, women have a greater risk than men between ages 65 and 75 (Neu et al., 2017).

It is well known in the literature that the strongest susceptibility variant for AD is the E4 allele of apolipoprotein E gene (APOE). APOE protein shows three major isoforms (APOE2, APOE3, and APOE4) that are, respectively, encoded by E2, E3, and E4 alleles. E4 allele is associated to a three to fourfold probability of developing AD and also an earlier onset age. Furthermore, carriers of two E4 alleles have an even higher risk of AD than carriers of one allele (Mielke et al., 2014). The E2 allele, by contrast, has been demonstrated to have protective effect that is associated with longevity and a lower risk of AD (Neu et al., 2017).

The allelic variant APOE E4 is not only associated with higher risk of developing sporadic AD, but also in developing age-related cognitive decline: this last association has not been so deeply characterized as the one to AD (Rusted and Carare, 2015).

The APOE E4 allele effect in women by comparison with men represents a good example of a biological factor as a genetic variant that interacts with other biological factors, as hormones, or other genes hosted on chromosome X or Y, or with gender-related factors, such as education, physical activity, behavioural preferences, type of occupation (Rocca et al., 2014). When considering men and women carrying APOE E4 allele, it seems that women have a greater risk of developing AD than men with the same genotype. This sex-based and gender-based difference related to the presence of APOE E4 allele has relevant consequences in treatment trials, diagnostics, and therapeutics. Relatively to mild cognitive impairment (MCI), even if it is well known that APOE E4 allele is associated with a greater risk to develop this disease, it is debated in Literature if sex determinants influence the transition from MCI to AD or dementia in APOE E4 carriers. Some studies have shown that women expressing the APOE E3/E4 genotype have an increased risk of MCI between the ages 55 and 70 (Neu et al., 2017), between ages 70 and 80 (Mortensen and Høgh, 2001) and of AD between the ages of 65 and 75 (Neu et al., 2017). Lehmann et al. in 2006 described a correlation between gender and episodic memory impairment in E3/E4 carriers: women were affected by worse impairment than men in the ages of 70–74 (Lehmann et al., 2006). This means that carriers of APOE E4 alleles could benefit from early treatments for MCI and AD, taking into consideration the gender differences emerging from epidemiological studies (Neu et al., 2017).

As concerns these aspects, the Lancet Neurology Commission (Winblad et al., 2016) has just discussed the increasing costs of AD and associated dementias, suggesting action for a different research approach in developing prevention and treatment strategies. What is relevant in this analysis is the commission's emphasis on the need for new clinical approaches to AD patients' management in the context of new cost–benefit analysis models by which to optimize the use of resources. The commission also emphasized that focusing on the effect of sex on dementias and in particular AD may be essential in advancing our understanding, treatment and prevention of these disorders. The commission recognized that AD and other dementias disproportionately affect

women, and it underlined the relevance of empirical data relating to sex differences and emerging sex-specific findings in dementias in order to assess the scientific approach to these diseases for the improvement of quality of life for both women and men.

In the matter of treatment, the commission found that also clinical efficacy may be influenced by sex-specific genetic and hormonal factors. In addition, clinical outcomes in dementia seem to be also affected by gender-specific societal differences. A wide range of lifestyle behaviours also influence risk factors and the clinical outcomes and cognitive performance in individuals with dementia; an individual's brain is affected by behaviours and experiences during the life and these necessarily vary by sex and gender. Sex and gender differences, extending from genetic to psychosocial domains, are relevant to productive research, and they are crucial in defining priorities for public health planning. The Lancet Neurology Commission thus provides an opportunity to develop the research agenda for AD and other dementias where women remain underrepresented in biomedical research (Winblad et al., 2016).

In conclusion, in the case of APOE genes expression in dementias we have to consider that: the APOE2 is the allelic variant which seems to be more favourable, since it brings a lower-than-average risk of getting AD; APOE3 which is the most common form is associated with an average risk and APOE4 entails three to five times increase of the average risk of getting AD. CRISPR would ease genomic interventions in order to change one allelic form of the APOE gene into a more favourable allele, even if editing the germline to prevent such disorders seems highly complex, especially for genetic defects that present risks in combination with environmental factors or lifestyles, such as AD.

#### **"Editing" human DNA and gender-specific medicine: addressing the ethical gender issues**

As just noted, the research previously described cannot be advanced without taking account of the ethical concerns it raises, and these are also related to gender-specific medicine.

Somatic gene editing is developed on the basis of technical knowledge derived from traditional gene therapy and within the current system of regulatory framework that has facilitated research and the clinical development of gene therapy on somatic cells. These regulatory systems include a wide range of preclinical models and study designs to support the clinical development of therapies based on modified cells. The (bio)ethical standards to be complied with, as well as the regulatory procedures associated with clinical studies of somatic-cell genome modification, are similar to those associated with other medical therapies: all these standards and procedures call for minimizing risk, analyzing how reasonable risks are to participants in light of potential benefits, and making sure that participants with voluntary and informed consent are recruited and enrolled as appropriate. Approval of a gene therapy may depend on how carefully risks and benefits can be monitored once it moves into clinical use. The question of approval for clinical use hinges largely on identifying when benefits may be expected to outweigh risks when used as labelled and as intended (Califf, 2017).

Since off-target events can be frequent and due to several factors (cell type, target genome sequence, etc.), it is not possible at this time to define a single standard for assessing the specificity of the somatic genome. The potential risks of negative consequences of gene modification, where a small number of modifications outside the control objectives may have negative effects, are extreme, and safety in clinical application is rightly one of the main concerns of researchers. It has been noted that most germline transmission tests have a low sensitivity, and it may therefore be necessary to manage a certain degree of uncertainty

in considering clinical development and regulation (Isasi et al., 2016). Concerning this aspect, it is crucial to communicate the relevance of risk information on genome editing for achieving the patient consent. Several guidelines have been published by regulatory authorities in the U.S. and Europe and by the International Conference on Harmonization (ICH) to illustrate the general principles for investigating and addressing the risks for inadvertent germline integration of gene therapy products in nonclinical studies, offering considerations about minimizing this potential risk in humans enrolled in clinical trials. These guidelines may be suitably adapted to design preclinical studies of somatic genome-editing strategies.

In an effort to speed up the development of regenerative medicine, including testing the transplantation of cells into live tissues and organs, research is moving forward with AD models of rodents, such as neural progenitor cells and mesenchymal stem cells, but it remains restricted because of ethical concerns in accepting this medical practice, and because of the safety issues that need to be addressed as part of this process (Cai et al., 2016).

As discussed, we believe that including gender analysis into research should be done in order to reinforce the research gene editing process, medicine and practice: when defining research aims, within the development of study designs and data collection, and in the interpretation and dissemination of results. By including gender in genomic somatic research, researchers can expand our understanding of the genome and the factors that modify its expression, ensuring that gender inequities are not perpetuated, collecting higher-quality and more accurate data, and actively engaging in positively changing gender relations and reducing inequities.

Gender differences have been considered significant variables with regard to the incidence of dementia. However, the reasons for these differences are not yet clearly understood, and it will be necessary to explore and advance gender-specific medicine in this field: this line of research will be useful in understanding gender differences, and it may well yield insights regarding the processes and circumstances that make genetic variation relevant for health. There is much to investigate in the field of sex and gender differences in AD, but a large amount of data is accumulating that is ready for meta-analysis and for improving early diagnosis and the quality of life, as well as for safer and more effective treatments. These differences in AD are relevant for each study, which should stratify and report data by sex and gender and carefully consider the impact of these differences in all aspects of the disease. We believe that the combination of gender-specific medicine and gene editing research contributes to the progress of medicine by introducing a relevant value-driven perspective on health and disease; in the field of dementia, this means that it will be relevant in

- analyzing how AD impacts health depending on sex,
- methodically comparing and evaluating data on gender-based differences,
- understanding how sex and gender ought to be integrated into experimental trials,
- defining standards for biomarkers and diagnosis, and
- incorporating sex differences in the development of AD treatment.

The question that comes into focus is whether gene editing can represent a new line of investigation to be explored in the development of gender-specific medicine that ensures gender equity in health policies. It follows that a better understanding of sex differences in cognitive functions can not only provide information on AD prevention but can also be an essential part of



such prevention. Of course, gene editing cannot remove biological differences, but its potential harmful effects, on one group relative to another, can be prevented with a research strategy that properly takes them into account with a view to equity between genders (Caenazzo et al., 2015). Sex refers to the biological differences between women and men, gender is rooted in biology, but it is primarily shaped by social, cultural, environmental influences, so we need to integrate these differences into a research ethics in the field of gene editing, in this terms of: what are the implications of concepts and theories about sex and gender for the way research is conducted on AD prevention by using CRISPR/Cas9 (by targeting specific genes including those that cause early-onset AD, as well as those that are significant risk factors)? What issues are being addressed or not (there are many factors by which sex and gender differences could affect the risk of AD. For example, depression and low education are associated with an increased risk of AD for both women and men, but they have a stronger effect in one sex or another)? (Mielke et al., 2014). This means that a better understanding of these sex and gender differences, by using gene editing tools for identifying where there are these differences, can contribute to improve the prevention and treatment of AD for both women and men.

Lastly, as with other innovation in healthcare, gene editing raises ethical questions as to whether benefits will be distributed equitably and in what ways the interests of people in vulnerable and minority groups may be affected. There may be risk of increasing inequity and tension between those who have access to the benefits of somatic genome editing applications and those who do not, between those who are included in research trials and those who do not for better understanding genomic and gender diversity. Innovation requires attending to ethical responsibility to engage with the public and to take account of public interests and values (Nuffield Council on Bioethics, 2015). It is necessary not only to produce more relevant research and clinical applications, but also to create a sense of inclusion and trust among participants in somatic gene therapy research, on a health systems level. The duty of balancing risks and ensuring informed consent cannot solely be fulfilled by adhering to the normal human subjects protections guidelines provided by institutional committee. Medical and research communities need to prove to the public that the inclusion of sex and gender differences in genetic AD research, the equal access to the benefits of this research, and that opinions and concerns of women and men are considered when designing protocols and developing new therapies are high priorities (National Institutes of Health, 2017).

## Conclusions

Although scientific literature and public debate have now become very sensitive to the importance of both sex and gender in health research, these concepts still seem to be largely ignored in health research. Thus, if we do not consider sex and gender differences, it will remain difficult, if not impossible, to achieve any improvement in reducing gender bias and its effect in developing prevention and treatment strategies; consequently, health policies at different decision-making levels can contribute to shifting gender differences in morbidity and mortality.

Among these fields are those where the aim is to improve our knowledge in all aspects of human health that deal with the differences between men and women: from public health perspectives to clinical practice, from research to the detection of diagnostic gender-specific markers, and in this direction gene editing could and should address those gender differences not to achieve equality but to meet the needs of persons of different genders. In fact, the development or improvement of cures could take advantage of the knowledge of sex and gender diversity in

order to ascertain and develop differential interventions between women and men.

If the potential and low cost of CRISPR–Cas9 will allow in the future to use it on a large scale, it is important to verify the possibility not only to eliminate single-gene disorders, insert protective genes, and potentially replace or modify genes to enhance physical and mental traits, but also to manipulate the genomic structure to test the impact of the intervention in both sexes to compare the impact on the phenotype in accordance with ethical recommendations. We think gene editing involving a *gender-specific strategy* and the relative finding and support for pursuing this strategy was provided by several environmental variables and scientific literature, so it would be a mistake to use CRISPR–Cas9 and gene-editing technology without paying attention to this factor.

Devoting attention to gender differences has to become standard practice in health policy, as by opening new perspectives in terms of the appropriateness, effectiveness, and equality of prevention and care initiatives. We believe that there are benefits to be gained from a greater emphasis on making the connection between sex-linked biological variation and gender differences in health outcomes, and that these benefits, in practical terms, also extend to the quality and sustainability of the national health service, improving its results and cutting its costs.

Received: 19 July 2019; Accepted: 3 February 2020;

Published online: 10 March 2020

## Note

1 In this article, we refer to somatic gene editing that involves modifying a patient's DNA to treat or cure a disease caused by a genetic mutation. In this case, gene editing is aimed at correcting the genetic mutation in patients without changing their sperm or eggs. We therefore do not consider germline human genome editing, which alters the genome of a human embryo at its earliest stages, and this may affect every cell, which means it has an impact not only on the person but also, potentially, on his or her descendants.

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### Competing interests

The authors declare no competing interests.

### Additional information

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