INTEGRATING A GENDER EQUALITY PERSPECTIVE

Expert report for the DH-BIO

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Summary

Women's groups have for decades addressed women's civil and political rights drawing attention to gender inequality and gender-based abuses in many areas; there exists a powerful international human rights framework, which lends legitimacy to political demands, since it is already accepted by most governments and brings with it established protocols. But substantive gender equity/equality is still something to fight for in many areas of women's (and other marginalised genders') daily lives; also within the field of biomedicine.

This report addresses a series of issues concerning gender equity/equality and human rights in biomedicine.

GENDER EQUITY/EQUALITY AND THE HUMAN RIGHTS PERSPECTIVE

- *Gender equality* is achieved when women and men and girls and boys have equal rights, responsibilities and opportunities and the power to shape their own lives and contribute to society. *Gender equity* is about social justice; it means fairness of treatment for women (and other marginalised genders) that have persistently experienced disadvantage or discrimination.
- While, historically, women have been systematically subject to exclusion and discrimination, achieving gender equity (and, ultimately, equality) also concerns men's health and how social constructions of masculinity may negatively affect the health of men.
- Gender minorities (adults as well as children and youth) have to be considered as particularly vulnerable and their special situation and needs have to be acknowledged. They are often exposed to stigma and social harms.
- Although human rights perspectives have proven useful in discussion of gender equity/equality in biomedicine, many issues concerning women's rights have been and to some extent still are considered marginal to the mainstream discourse on human rights.
- For gender equality to be achieved, the rights perspective has to be expanded: establishing gender equity/equality requires addressing structural problems and questions of economic justice that are at the core of inequality, poverty, and social policy cuts; and it has to be complemented by a focus on socially excluded groups and the dimension of collective action.
- There is a need for more research that builds on intersectionality - the insight that important social identities like gender, ethnicity, religion, sexual orientation, and social class 'mutually constitute, reinforce, and naturalize one another'.

EQUITABLE ACCESS TO BIOMEDICAL RESEARCH

- Women are still significantly underrepresented in biomedical research both as researchers and research participants, receive less research funding, and appear less frequently than men as authors on research publications. This underrepresentation, which in particular also concerns older women, is seen as one of the sources of gender bias.
- In spite of regulations and/or directives (internationally as well as at the European level) not nearly enough progress has been made with respect to the participation of women in clinical trials: bias against female participants in clinical studies persists despite legal and policy initiatives to increase female representation.
- Gender bias is at the roots of the dramatic underrepresentation of women in research on cardiovascular disease, hepatitis, HIV, chronic kidney disease, and digestive disease.
- One of the consequences of these and other forms of exclusion is the invisibility of women (and other marginalised genders); hence, there is a data gap because data about women have not been collected or they have not been separated from the male data.
- A gender bias in clinical trials leads to a situation in which 'the impact of science may not be equally beneficial for both men and women' (as well as gender minorities and other neglected social groups).
- There is some evidence that women's stronger presence in research may influence the selection of research topics and the design and analysis of clinical trials in favour of more gender equity/equality.

GENDER BIAS IN THE QUALITY OF HEALTH SERVICES

- While some of the identified issues are to do with 'numbers' – women's access to biomedical research as well as their participation in clinical trials, others point at the power of gender norms as determinants of how women's (and men's) health problems are interpreted and treated, often exposing the predominance of the 'male norm' in research and treatment.
- Some health disparities/inequalities result from a gender bias that leads to the unequal treatment of men and women based on preferences and prejudices. This gender bias may manifest in various ways, implicit and subtle or obvious.
- Particularly well-documented examples of gender bias concern the interpretation of women's and men's mental health problems. Examples are the expression and diagnosis of pain and its assessment by physicians or the diagnosis of borderline personality disorder and of autism; with the consequence that women/girls and men/boys may not be diagnosed adequately and treatment be delayed.
- Other studies demonstrate differences in symptom reporting by women and men and the reasons underlying these differences. However, these gender

differences are often disregarded in the clinical situation, with sometimes severe consequences for patients.

- Research suggest that health care personnel often act on an implicit (not always conscious) gender bias. However, the relationship between levels of implicit bias and clinical decision-making is complex. There is ample evidence that physicians are more likely to interpret men's symptoms as organic and women's symptoms as psychosocial or nonspecific.

AVOIDING THE PERPETUATION OF GENDER BIAS AND GENDER INEQUITY IN AI-BASED DECISION TOOLS

- Recent developments that use AI, 'big data' and machine learning in support of medical decision-making have prompted a discussion of how automated tools might introduce bias or entrench existing (gender) inequities.
- There is growing evidence of discriminatory bias in the diverse data sets used in algorithm-based analytics, in so far as these reflect the implicit gender (and racial) bias of medical practice.
- A broad discussion on *algorithmic fairness* and on the possibilities of making gender bias in data visible (e.g. through capturing metadata about how the dataset was collected and annotated) indicate how the perpetuation of gender inequity/inequality may be acted upon.

THE NEED TO PROTECT DIGNITY AND (GENDER) IDENTITY

- Issues concerning gender equality in neurotechnological research and interventions are difficult to address and there is little systematic reflection on the values underlying this research.
- Critical readings of contemporary functional MRI (Magnetic Resonance Imaging) research on sex/gender differences in the brain and in emotion processing suggest that neuroimaging technologies may encode social stereotypes about gender and culture.
- There is a discussion on how techniques of altering brain function with TMS (Transcranial magnetic stimulation), e.g. through cognitive and/or moral enhancement, might affect perceived personal identity, hence also a person's self-perception of gender. This raises questions concerning human dignity and personal identity.

TAKING ACTION TOWARDS GENDER EQUALITY IN BIOMEDICINE

In regard of the work of DH-BIO there are a number of lines of action to be considered that do not simply replicate the agenda of other institutions and bodies but complete and eventually reinforce them. Overall goals should be to a) strengthen equal access to health services and b) decrease the data gap for women (their 'invisibility') in biomedical research:

- Fill gaps in data;
- Action to encourage equal access and representation of women and men in biomedical research;

- Action to strengthen the inclusion of women (and other underrepresented groups) in clinical trials and drug development;
- Strengthen strategies of addressing gender bias in the diagnosis and treatment of mental health problems;
- Encourage drafting legislation on AI, big data and algorithmic fairness in biomedicine;
- Promote the provision of training for health care professionals in support of gender equity/equality;
- Carry out a survey of biomedicine textbooks to detect and address undue bias;
- Encourage public debate on gender equity/equality in biomedicine.

1 Aims and scope

1. The aim of this report is to provide an introduction to gender equity/equality issues and explain their relevance with regard to human rights protection in biomedicine. The report also responds to the current work plan of DH-BIO and offers a basis for discussing human rights and gender aspects of new technologies in biomedicine, namely neurotechnologies as well as artificial intelligence and big data.
2. The report's introductory part lays out key concepts in the debate on gender issues in biomedicine – the relationship between human rights and gender equity/equality, the distinction between sex and gender, the influence of gender norms - and sketches different approaches to achieving gender equity/equality in biomedicine.
3. The report takes up the distinction made between gender equality and gender equity:

> Gender equality, equality between men and women… does not mean that women and men have to become the same, but that their rights, responsibilities and opportunities will not depend on whether they were born male or female. Gender equity means fairness of treatment for men and women according to their respective needs. This may include equal treatment or treatment that is different but which is considered equivalent in terms of rights, benefits, obligations, and opportunities (United Nations Educational, Scientific and Cultural Organisation).

4. This distinction makes clear that many health disparities related to a person's gender are a question of social justice in the sense Margaret Whitehead (1992) formulated it in the early 1990s, defining inequity as differences in health that 'are not only unnecessary and avoidable but, in addition, are considered unfair and unjust' (p. 2016). On the other hand, equality is the principle which recognizes that the same rights apply to all citizens. Hence, while many issues concerning gender in biomedicine are to do with fairness and social justice (equity), it is important to maintain the perspective on equality as a human right, acknowledging that throughout history women have always struggled to gain equality, respect and the same rights as men.
5. Another key term in the debate about gender equity/equality is the notion of gender bias. Gender bias is a preference or prejudice toward one gender over the other. Gender bias is equated with discrimination:

> Gender bias or discrimination may be defined as differentiating people as male and female on the basis of gender or gender-based functions and treating them uniquely in the matter of social function, or treating them unjustly in the distribution of burdens and benefits in society (Mukherjee 2015).

6. Historically, the field of medicine has been dominated by a male perspective, which 'has been the standard view, not only on patients but also of patients. Not only was the doctor's gaze a male one, but also patients were conceived as standardly male' (Pot et al. 2020, p. 4). This had detrimental effects on women (and on people who do not identify as men or women) some of which still persist. However, achieving

gender equity in access to health care services also concerns men's health and gender bias may in certain cases result in men/boys not being diagnosed and treated adequately.

7. The following four sections go deeper into some key aspects of gender equity/equality under human rights aspects, addressing issues of access, autonomy, integrity, the right to a private life, the right to be informed etc., outlining possible action at the end of each chapter. The themes explored in these sections are:
    - Access to/representation in biomedical research /clinical trials;
    - Evidence of gender bias in medicine with special emphasis of mental health;
    - Related to this, gender aspects of neurotechnological research and interventions, problematising the notion of a 'female brain';
    - AI, machine learning and the gender bias in biomedical data.
8. The final part outlines a set of actions on different levels that have the potential to help achieve gender equity/equality in biomedicine.

2 Introduction

9. Gender equity/equality in biomedicine is often associated with the question of access and representation. A great number of publications is dedicated to demonstrating that women are significantly underrepresented in biomedical research both as researchers and research participants, receive less research funding, and appear less frequently than men as authors on research publications. This underrepresentation is seen as a source of gender bias, as Ovseiko et al. (2016) argue: 'Historical gender biases may have created a path dependency that means that the research system and the impacts of research are biased towards male researchers and male beneficiaries, making it inherently difficult (though not impossible) to eliminate gender bias' (p. 1). While 'numbers' certainly matter, they only show part of the problem of gender inequity. The other part is to do with the power of gender norms as determinants of how women's (and men's) health problems are interpreted and treated, often exposing the predominance of the 'male' norm in research and treatment (Klinge and Bosch 2005).
10. The following sections outline the problem space of what has been identified as a continuing neglect of issues of gender equality in biomedicine. They
    - Provide a brief overview of the intellectual and activist roots of the movement towards gender equality;
    - Introduce key notions - the difference between sex and gender, gender norms, intersectionality;
    - Outline the relationship between human rights and gender equality;
    - Sketch out different approaches to achieving gender equality in biomedicine.

2.1 Intellectual and activist roots of the movement towards gender equality

11. Gender equity commitments for institutions and within policy agendas have a decades-long history. One important part of this history is the women's movement that was international from its beginnings, as women's groups in different parts of the world formed connections. Women maintained that 'biology is not women's destiny'; they introduced the notion of gender; they demonstrated that 'the private is public', bringing topics such as domestic violence, reproduction, abortion, and childcare into the realm of 'politics' (Tobias 1997).

12. Several conferences have shaped gender equality and women's rights as a global agenda. The most important and in many ways formative events were the Nairobi UN Conference on Women in 1985 and the Beijing women's conference in 1995, resulting in the *Beijing Declaration and Platform for Action*, which contains a strategic objective on 'increasing women's access throughout the life cycle to appropriate, affordable and quality health care, information and related services'. Also, the focus on gender issues in biomedicine is not recent. In 1993, based on feminist criticism of mainstream bioethics, the International Network on Feminist Approaches to Bioethics (FAB) was founded. In 2007 FAB established its own journal, the *International Journal of Feminist Approaches to Bioethics* (*IJFAB*). Although feminists were not the only ones that worked on gender issues in biomedicine, 'their contributions to the analysis of substantive bioethical issues, bioethical theory and methodology was significant' (Donchin and Scully 2015).

13. An important driving force for gender equality in biomedicine was the women's health movement and the feminist critique of science in the 1980s. Pioneering biologists such as Lynda Birke and Anne Fausto-Sterling started academic critiques of biomedicine (Birke and Vines 1987; Fausto-Sterling 1985). They argued that processes of gender have an influence on the production of biomedical knowledge. A prominent early example that gained widespread attention was cardiovascular disease that had long been defined as a 'male' disease. Evidence was found that 'heart attack symptoms differ by sex, that diagnostic tests, such as the exercise treadmill, differ in efficacy between men and women, and that aspirin is not a good primary preventive measure against heart attack in women' (Schiebinger 2012, p. 5). On the other hand, osteoporosis which had been understood as primarily affecting post-menopausal women, also affects men. In the 1990s research on osteoporosis in men started, based on evidence that at that time one third of osteoporosis-related hip fractures occurred in men, and men had twice the mortality rate of women with similar fractures (e.g. Schousboe et al. 2007).

14. These insights provided a strong motivation for initiatives to remove gender bias from biomedical research (Klinge 2010). Physicians in different countries promoted 'Gender Medicine' with the aim to address women's and men's health issues in research and clinical practice, the underlying ethical concern being justice - abolishing health inequities and fostering the quality of health care.

2.2 Sex, gender and the power of gender norms

15. Key to discussing gender equality in biomedicine is the distinction between sex and gender that has been widely taken up by researchers and institutions alike:

> Sex refers to biological differences between men and women such as chromosomes (XX or XY), internal and external sex organs (ovaries, testes) and hormonal profiles (of estrogens and androgens). Biological sex differences are often viewed as dichotomous, either male or female, although biological variability is substantial.
>
> Gender refers to the socially constructed roles and relations, personality traits, attitudes and behaviours and values that are ascribed to the two sexes in a differential manner. While sex is a biological fact that is the same in all cultures, the meaning of sex in terms of gender roles can be quite different across cultures (Klinge 2010, p. 18).

16. Sex and gender are not mutually exclusive – 'cultural expectations for women and men (gender) are not separable from observations about women's and men's physical bodies (sex)' (Lips 2017, p. 6) and we often don't know whether particular differences between men and women are due to biology or culture. But, in general, the term sex is reserved for discussions of anatomy. Gender is the more inclusive term when talking about differences between men and women and a much more complex concept than sex:

> Gendered behavior arises out of a dauntingly complex, reciprocally influencing interaction of multi-level factors, including structural-level factors (e.g., prevailing cultural gender norms, policies and inequalities), social-level factors (e.g., social status, role, social context, interpersonal dynamics) as well as individual-level factors such as biological characteristics […], gender identity, gendered traits, attitudes, self-concepts, experiences, and skills (Rippon et al. 2014, p. 3).

17. Gender is used as a label for the system of expectations held by societies with respect to feminine and masculine roles. Michel Foucault's notion of 'normalisation' addresses the power of these expectations that create an enormous pressure to conform to certain ways of behaving and presenting oneself (Foucault 1979). Foucault has described this pressure in particular with respect to the ways the body and sexuality are defined and experienced (Foucault 1973).

18. Achieving gender equity in access to health care services concerns also men's health and how social constructions of masculinity affect the health of men. Gupta et al. (2019) state: 'Due to the historical legacy of gender-based injustice, the health consequences of gender inequality fall most heavily on women, especially poor women, but restrictive gender norms undermine the health and wellbeing of women, men, and gender minorities' (p. 2551). Moreover, one of the reasons that impairs women's health and diminishes their agency is that they are more often exposed to abuse and violence than men (e.g. Donchin 2004). A recently much discussed form of abuse is the neglect, physical abuse and lack of respect during childbirth ('obstetric violence'; e.g. Sadler et al. 2016). This treatment is not only regarded as a violation of the women's rights; it also has the effect of preventing women from seeking pre-natal care and using other health care services.

19. Lately, the concerns of gender minorities are receiving more attention. For the US a study describes barriers to health care for transgender individuals and proposes 'research priorities to understand mechanisms of those barriers and interventions to overcome them' (Safer et al. 2016, p. 168). Littlejohn et al. (2019) point at an increased burden of depression and suicidality among transgender populations globally, arguing that 'such findings highlight the significance of differences attributable to social harms of discrimination and stigma' (p. 236). For example, Kosenko et al. (2013) reported mistreatment of transgender individuals in the form of 'gender insensitivity, displays of discomfort, denied services, substandard care, verbal abuse, and forced care' (p. 819). A study of a sample of female-to-male transgender individuals found that more than 40% experienced 'verbal harassment, physical assault, or denial of equal treatment in a doctor's office or hospital' (Shires and Jaffee 2015, p. 134).

20. Hence, gender minorities have to be considered as particularly vulnerable. This extends to children and youth who may behave in gender atypical ways and/or who may be subject to sex-normalising treatments that are not necessary for their physical health without their free and informed consent (Zillèn et al. 2017). Some progress has been made, when in 2018 the WHO announced that it no longer considers 'gender incongruence' a mental disorder, reclassifying what is also known as gender dysphoria as a sexual health condition.

21. Instances of gender bias in biomedical research, lack of access to innovative biomedical interventions or discrimination and stigma of gender minorities point to the power of gender norms. For example, in a literature survey Samulowitz et al. (2018) identified gender bias in pain treatment in both the patient-provider encounter and the professional's treatment decisions. Hamberg (2008) argued that even though 'huge efforts have been made by some researchers to counteract the neglect of women and support medical science with data on women', that in clinical situations identical narratives were often still interpreted differently depending on whether they came from a man or a woman, 'because of assumptions and preconceived ideas about women and men' (p. 241).

22. Many researchers today argue that addressing gender equity/equality requires examining complex relationships between biological and social dimensions. *Intersectionality* as an approach builds on the insight that important social identities like gender, ethnicity, and social class 'mutually constitute, reinforce, and naturalise one another' (Crenshaw, 1991, p. 302). It accounts for the fact that women (and men) may be affected differently by discrimination in the delivery of health care services, depending on where they are positioned within broader structures of power. For example, Hankivsky et al. (2017) demonstrate how an intersectional approach helps develop a better understanding 'in the areas of HIV, posttraumatic stress disorder, female genital circumcision/mutilation/cutting, and cardiovascular disease' (p. 73). These types of analysis are more common in the

context of developing countries where the health implications of poverty can be dramatic and girls are more likely to be neglected than boys (e.g. Borooah 2004).

2.3 Human rights and gender equality

23. For decades, women's groups have focused on addressing women's civil and political rights. They have fought to draw attention to gender inequality and gender-based abuses in many areas – 'education, employment, housing, credit, and health care; rape and domestic violence; reproductive freedom; the valuation of child care and domestic labor' (Peters and Wolper 1995 p. 2). At the same time, and for several decades, there has been a powerful international human rights framework, which lends legitimacy to political demands, since it is already accepted by most governments and brings with it established protocols (Friedman 1995, p. 19). Hence, the legitimate question why substantive gender equity/equality is still something to fight for in many areas of women's (and men's) daily lives. Although the human rights approach provides a potentially strong framework of accountability of governments, gender issues are still largely absent from the centre stages of global decision-making.

24. While the reasons for this are manifold, one key line of action to undertake is to start transforming human rights from a gender perspective. 'It is not possible fully to separate the struggle for women's human rights from the struggle for women's equal rights', Friedman (1995, p. 18) wrote arguing that it is no longer enough that existing human rights mechanisms 'merely be extended to women'. This statement has to be understood as a response to the experience that many issues concerning women's rights have been - and to some extent still are - considered marginal to international law's more 'serious' responsibility for human rights. Peters and Wolper (2018), among others, see this marginalisation as a result of the fact that 'traditional human rights formulations are based on a "normative" male model and applied to women as an afterthought, if at all' (p. 2). Already in the 1990s Charlotte Bunch criticised what she deemed a narrow definition of human rights, asking for specific women's rights to be elaborated:

> Starting with female life experiences as the point from which to examine human rights, certain questions become important: Who has been excluded from exercising the rights of citizenship and how have women been affected by limited forms of democracy? What has been the impact on women of narrow definitions of human rights? Why have so many degrading life experiences of women not been understood as human rights issues? (Bunch, 1995, p. 11)

25. Another line of arguments concerns the human rights perspective as such. It maintains that for gender equality to be achieved, the rights perspective has to be complemented, in two ways: firstly, establishing gender equity/equality requires addressing structural problems and questions of economic justice that are at the core of inequality, poverty, and social policy cuts. Second, the fact that the rights discourse emphasises individual rights at the expense of neglecting relational values tied to care and interpersonal connection (Donchin, 2004). This argument

goes back to an old debate that started with Carol Gilligan's (1982) seminal work on moral reasoning in which she formulated an ethics of care (which was later reformulated as an ethics of responsibility), contrasting it with modes of reasoning that privilege justice, rights, as well as personal autonomy. Critics of a rights approach maintain that it makes it difficult to uphold moral aims not expressible as matters of individual preference. Anne Donchin (2003) argues that addressing most of the needs of socially excluded groups requires well-functioning social ties and modes of collective action and 'even the right to self-determination requires considerable social cooperation […] it requires mastery of appropriate cognitive and emotional skills, opportunities to shape one's identity in non-oppressive ways, and social support to achieve personal agency' (p. 302).

26. An important source in this context is the 2005 Universal Declaration on Bioethics and Human Rights, which

> insists on the importance of developing 'new approaches to social responsibility to ensure that progress in science and technology contributes to justice, equity and to the interest of humanity' (Preamble); of taking into account 'the special needs of developing countries, indigenous communities and vulnerable populations' (idem); of promoting 'solidarity and cooperation' (Article 13); and of fostering the sharing of benefits resulting from scientific research within each society and between societies (Article 15) (Andorno 2014, p. 56).

27. While arguing that the human rights perspective has to be complemented by a focus on socially excluded groups and the dimension of collective action, feminist bioethicists find human rights principles useful, provided that 'the principles of autonomy, beneficence, and justice address gender-related issues in historical context' (Tong 1997, p. 3).

2.4 Approaches to achieving gender equity/equality in biomedicine

28. Taking the critique seriously that a human rights perspective does not 'automatically' enhance the rights of women and other marginalised genders, requires examining the set of human rights principles that have been defined in the Oviedo Convention from the perspective of gender equality; namely:

    - Protect 'the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine' (Article 1);
    - Equitable access to health care of appropriate quality (Article 3);
    - The right to information (Article 10).

29. Basic to these principles is Article 14 of the European Convention on Human Rights which articulates the prohibition of discrimination, stating:

> The enjoyment of the rights and freedoms set forth in the European Convention on Human Rights and the Human Rights Act shall be secured without discrimination on any ground such

as sex, race, colour, language, religion, political or other opinion, national or social origin, association with a national minority, property, birth or other status.

30. Achieving gender equity/equality in biomedicine can be done in a variety of ways.

THE PHILOSOPHICAL LEVEL

31. The foundational element of the human rights perspective is respect for persons, their integrity and rights. Snead and Mulder-Westrate (2014) see this as an enormous advantage as it 'subordinates autonomy' that has dominated bioethics for decades, 'to other goods such as human dignity, solidarity, and protection of the vulnerable' (p. 75). Indeed, a simplistic interpretation of autonomy as an individual right stands in the way of acknowledging the vulnerability of people (of different gender) with health problems and the need for an ethics of care and responsibility that has been claimed by researchers and women's groups all over the world. It also acknowledges that there are persons who lack the capacity to exercise autonomy, in general or in particular situations.

EQUAL ACCESS/REPRESENTATION

32. Many studies focus on 'numbers' – the underrepresentation of women in biomedical research as well as in the development of biomedical technologies. Issues of access/representation of women in biomedical research are discussed on two levels: a) the institutional level with regard to senior research positions and authorship; and b) the level of research funders and their policies. The representation of women in biomedical research on these two levels is not only a question of equal access and non-discrimination. There is some evidence that women's stronger presence in research may influence the selection of research topics and the design and analysis of clinical trials in favour of more gender equality.

33. A second stream of research looks into women's participation in clinical trials and their access to innovative medicines and interventions. Although the current EU guidelines concerning the clinical evidence required for a medicinal product benefit/risk assessment advise that both men and women are included in clinical trials, there continues to be a well-documented gap in the representation of women in clinical studies.

34. The *Oviedo Conference Rapporteur Report* (2017) also relates women's underrepresentation in biomedical research and clinical trials to failings of health systems 'in relation to certain disadvantaged persons or certain particularly vulnerable groups: Roma and travelers, migrants and especially children, pregnant women, transgender persons, the elderly, and prisoners' (p. 15).

EQUITABLE ACCESS TO HEALTH CARE

35. Much of the research literature deals with particular health conditions of women, men or gender minorities that have been either neglected or treated in problematic ways. Examples of such health conditions are:
    - Delays of sometimes years in the diagnosis of endometriosis, which is a painful condition affecting one in ten women of reproductive age (e.g. Agarwal et al. 2019);
    - PCOS (polycystic ovary syndrome) which is a chronic and serious health condition with a complex array of features and is also an example of how the ‘obesity stigma’ affects women (Satveit 2018*)*;
    - Gender differences in the neurobiology of Alzheimer’s disease that disadvantage women (e.g. Lin/ Doraiswamy 2015);
    - Gender differences in judgments of pain expression, diagnosis of depression, borderline personality disorder, and autism;
    - Control of women's reproductive capacities by limiting access to certain reproduction-assisting technologies (e.g., intrauterine insemination and in-vitro fertilization), as well as to certain reproduction-controlling technologies (e.g., abortion) (Tong 1997);
    - The medicalization of intersex (e.g. Feder 2014).

36. However, the concern about equitable access to healthcare reaches beyond the need to better account for gender-specific healthcare needs. Women have been found to be disproportionally affected by structural barriers, such as for example ‘out-of-pocket payments’ (in some countries), care responsibilities, limited access to transportation, and lack of workplace flexibility (Pot et al. 2020).

THE METHODOLOGICAL LEVEL

37. An important body of work addresses how to establish gender analysis as a methodology in biomedical research (Klinge and Bosch 2005, Klinge 2010, Schiebinger 2012). The European Union has prioritised gender equality issues in Horizon 2020. Article 15 promotes ‘gender equality and the gender dimension in research and innovation content’. Although an analysis of a number of EU FP7 projects that included the gender dimension shows promising results, its authors argue that much further work has to be done to develop tools for carrying out a gender analysis in biomedicine thereby helping to make it more common practice (Klinge 2013).

THE POLICY LEVEL

38. Important activities in regard to gender equity/equality in biomedicine on the European level are the Council of Europe’s commitment to gender mainstreaming (Objective 6 of Gender Equality Strategy 2018-2023) and Recommendation CM/Rec(2008)1 of the Committee of Ministers to member states on the inclusion of gender differences in health policy (adopted in 2008). The latter states that ‘gender inequalities can result in problems of access to health services, including

to information, and noting also the lack of resources to promote gender sensitivity in health care providers, which may all constitute structural barriers to quality of health care'. It recommends, among other measures, to 'develop and disseminate gender sensitive knowledge that allows evidence-based interventions through systematic collection of appropriate sex-disaggregated data, promotion of relevant research studies and gender analysis'. Another relevant initiative has been set by the Pompidou Group with regard to the non-medical use of prescription with women constituting a special risk group.

3 Issues concerning access/representation of women

3.1 Women in biomedical research

39. Although the representation of women researchers in biomedical research is a recurrent topic of studies, there are data gaps that make forming a coherent picture difficult. In general, most available studies describe the situation in North America (the US and Canada). In the United States, 'women are not underrepresented in biomedical research during training, but are underrepresented in independent research positions, providing additional evidence that advancement of women in the biomedical workforce is suboptimal' (Plank-Bazinet et al. 2017). According to a report by the US National Institutes of Health, women comprised half of the employees in the pharmaceutical and medical industries but they represent only about 17 percent of senior management positions. This applies also to the European context, where the lack of equal representation is most pronounced in decision-making positions. A recent article in *Nature Medicine* – 'A giant leap for women (2019) – mentions as a main source of concern from the point of view of the European Research Council's Gender Balance Working Group the disparity in funding between women and men researchers. This article also reports an increased hiring of women for group leader positions at several research institutions.
40. A gender gap is also visible in the representation of women as principal investigators and/or authors. For the field of biomedical engineering, Barabino et al. (2019) report that 'the success rate for male principal investigators and coordinators is still higher than that of women in 70% of the EU countries' (p. 2). Ovseiko et al. (2016) report for the US that female researchers in biomedicine receive less research funding and that in particular early career starters receive 'significantly less start-up support from their institutions' and are also less likely to apply for competitive grants for which they would be eligible. Also, data from the Netherlands suggest a gender bias in favour of male funding applicants (Van der Lee and Ellemers 2015). An automated literature mining study of scientific publications on genome editing in the period 2016-2017 found not only regional disparities but also an underrepresentation of women authors with 75% of the principal investigators being male (Siwo 2018). Asking why women are

underrepresented as researchers as well as board members of major medical journals, Fridner et al (2015) identify clinical workload, insufficient financial support for research, insufficient institutional support, and lack of mentoring as main reasons.

41. Women's representation in biomedical research seems to have improved over the years though, although currently available data do not permit to establish this across European countries and categories of participation (position, authorship, grants, etc.). It seems that considerable gender gaps persist in spite of efforts of the European Commission and of major European and national funding agencies to achieve equal representation of men and women in employment, decision-making, and as clinical research subjects and removing institutional barriers to gender equality. A report by Schiebinger et al. (2015) documents these efforts for the European Commission, Austria, France, Germany, Ireland, the Netherlands, Norway, Spain, and the UK.

42. Womens' equal representation as researchers in biomedicine does not only matter from the point of view of non-discrimination. In a paper entitled 'One and a half million medical papers reveal a link between author gender and attention to gender and sex analysis', Nielsen et al. (2017) suggest a connection between gender diversity and research outcomes. Their analysis provides 'global evidence linking the likelihood of a study involving GSA (gender and sex analysis) to the presence of women in the author group, especially in leading positions as first and last authors' (p. 793). Hence, increasing gender equity in biomedical research is likely to strengthen attention to issues of gender and sex helping eliminate gender bias in research. Ovseiko et al. (2016) use the notion of path dependency to explain why gender bias in health research persists in spite of the fact that in countries with strict non-discrimination laws women have reached 40% or more in admissions to medicine. Path dependency is an old concept that has been used, for example, by Wilsford (1994) in analysing health care reforms: 'In the path-dependent model, actors are hemmed in by existing institutions and structures that channel them along established policy paths'.

3.2 Women as participants in clinical trials

43. The WHO defines as a clinical trial,

> any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc. (https://www.who.int/topics/clinical_trials/en/).

44. Historically, clinical trials were done almost exclusively with male participants. This changed when first requirements to also include women in clinical trials were mandated. For the US this was the NIH Health Revitalization Act (1993), which, however, left women and minorities out of the discovery phases. In 2005, the

European Medicines Agency (EMEA) has asserted that matching the demographics of a study population to the demographics of patients eligible to receive a given treatment is ‘an underlying principle of drug development’ (EMEA, 2005). The new clinical trials regulation (Regulation EU No 536/2014) is considered a major step forward in increasing clinical trial data transparency in Europe (Maguire et al. 2018). It also mandates that ‘unless otherwise justified in the protocol, the subjects participating in a clinical trial should represent the population groups, for example gender and age groups, that are likely to use the medicinal product investigated in the clinical trial’.

45. The key message of much of the literature about the participation of women in clinical trials is that in spite of these regulations and/or directives not nearly enough progress has been made. To provide a few examples: Heidari et al. (2016) report: ‘A review of cardiovascular treatment trials included in Cochrane Reviews reveals that only 27% of the total trial participants in the 258 clinical trials were women. More importantly, among trials recruiting both men and women, only one third reported a gender-based analysis’ (p. 2). Tahhan et al. (2018) report that ‘in contemporary HF (contemporary heart failure) trials, older patients and women are consistently underrepresented. Race/ethnicity data are reported in less than half of trials; when reported, such data show that enrollment of nonwhite patients increased over time’ (p. 1011). The failure to include an adequate proportion of elderly people in the testing of drugs that are targeted at them or are contraindicated in them has been described by Reuter et al. (2019).

46. Citing work that analysed over 43,000 research studies in PubMed, a searchable database of biomedical science, and 13,000 clinical trials registered on clinicaltrials.gov. in the period 1966-2018, Feldman et al. (2019) identified a particularly dramatic underrepresentation of women in research on cardiovascular disease, hepatitis, HIV, chronic kidney disease, and digestive disease. Clinical research on diabetes, mental health, non sex-specific cancers, and respiratory disease had roughly equal representation. They found that ‘studies with more participants have greater female representation. However, sex bias against female participants in clinical studies persists despite legal and policy initiatives to increase female representation’ (p. 11). A study by Allotey et al. (2017) analysing the top five ranked journals in general and internal medicine from 2011 to 2016 showed a statistically significant gender bias against clinical case reports representing female patients. They also draw attention to the effects of an overall male bias of clinical medicine on the formation of young clinicians:

> Medicine in males may be regarded as more main stream, more interesting, more indicative of what is a normal disease process. Because the case reports have become an integral part of medical education, the risks of gender biased exposure to ‘interesting clinical medicine’ is potentially compounded, particularly in junior clinicians who are still laying down the matrix of expertise (p. 6).

47. A gender bias in clinical trials matters in two ways. First of all, it leads to a situation in which ‘the impact of science may not be equally beneficial for both men and

women' (as well as gender minorities and other neglected social groups) (Ovseiko et al. 2016, p. 2). More specifically with respect to clinical trials of drugs, Roth (2018) provides a number of reasons why including women in these trials (whenever practicable and appropriate) should be made mandatory: male and female bodies react to drugs differently; to fully include women in clinical trials 'may help stem the tide of prescription drug abuse'; it will allow 'to better treat major killers, like heart disease'; the drugs that will be released onto the market will be able to be used more safely. Roth (2018) adds that the consequences of not including women in drug studies 'may be severe'.

3.3 What can be done?

48. The research literature provides a whole array of recommendations of how to deal with issues of access/representation of women and gender bias in biomedical research, on different levels.

IMPROVE WOMEN'S RESEARCH OPPORTUNITIES

49. As concerns *access of women to research positions* improving their research opportunities (in terms of funding, authorship, etc.), the measures reach from providing role models and mentoring and increasing women's visibility in research to improving the workplace climate and changing the appointment criteria for scientific leadership, which are often based on 'male' characteristics. These measures to increase the gender balance in biomedicine mainly concern universities, the large academic health centers in Europe (see Kuhlmann et al. 2017), funding agencies, and scientific journals and have been partially taken up by institutions/organisations in European countries (for an overview see, for example Schrouff et al. 2018; Ovseiko et al. 2016; Barabino et al. 2019).

INCLUDE GENDER ANALYSIS IN BIOMEDICAL RESEARCH

50. Several reports and scientific papers point at the importance of making research, data collection, analyses, and reporting more gender equitable. The report of the European Commission's Expert Group 'Innovation through Gender' (Schiebinger et al. 2013) details methods of sex and gender analysis that were developed through European and international collaborations. The position paper of the Horizon 2020 Advisory Group for Gender (December 2016) emphasises that

> addressing the gender dimension in research and innovation entails accounting for sex and gender in the whole research process, when developing concepts and theories, formulating research questions, collecting and analysing data, and using the analytical tools that are specific to each scientific area.

51. In 2012, the Gender Policy Committee (GPC) of the European Association of Science Editors (EASE) published the so-called SAGER guidelines that 'accentuate needs to distinguish between research subjects by sex/gender, analyse

results according to sex/gender, and reveal meaningful differences whenever possible' (Lee 2018; for this point see also Clayton and Tannenbaum 2016).

52. An international consortium of authors (Morgan et al. 2016) outline how gender analysis can be incorporated into health research 'through sex disaggregation of data, and incorporation of gender analysis frameworks.' They propose to analyse whether and how gender power relations affect females and males in health systems, 'examining who has what (access to resources); who does what (the division of labour and everyday practices); how values are defined (social norms) and who decides (rules and decision-making)'. Their study also includes an extensive list of 'illustrative gender analysis research questions' (p. 1069).

53. A group of scholars and practitioners from Africa, America, Asia and Europe (Ovseiko et al. 2016) developed a set of recommendations directed at research funders, research institutions and research evaluators about how to strengthen analysis of gender equity in research impact assessment. They specify a set of methods to 'measure' and ultimately also assess and monitor gender equity.

INCREASE KNOWLEDGE AND AWARENESS OF THE GENDER BIAS IN BIOMEDICAL RESEARCH AND THE PRACTICE OF HEALTH CARE

54. Several authors stress the need to fill data gaps concerning gender bias and inequity/inequality. For example, Gupta et al. 2019 observe that

> global datasets are not amenable to studying how gender norms intersect with other social determinants of health (e.g., income, religion, ethnicity, race) and might be missing data for entire demographic groups, such as children aged 6–14 years and menopausal women. Linking gender norms and health outcomes using existing datasets is often not possible because datasets with rich health-related data do not measure attitudes, behaviours, or norms, and vice versa (p. 2554).

55. On an operational level, the Gender Working Group (GWG) that was set up by the Global Research Council (GRC) in 2017 proposes a set of knowledge and awareness-increasing measures; namely:

- Engage in national discussions of policy frameworks regarding equality, diversity and the status of women to ensure recognition of these issues.
- Collect and make available data (against consistent parameters) for comparative analysis […] The availability of disaggregated data on participation in research by different groups (for example by gender, by age, by discipline) would facilitate both benchmarking and a better understanding of the needs of different research systems. Currently data are often not available at a sufficiently disaggregated level.
- Incorporate the evaluation of progress towards gender-based goals.
- Provide training on equality and diversity policies, including the recognition of unconscious bias and how it can be addressed.

(Source:https://www.globalresearchcouncil.org/fileadmin/documents/GRC_Publications/Statement_of_Principles_and_Actions_Promoting_the_Equality_and_Status_of_Women_in_Research.pdf)

56. Few studies address issues of gender equity/equality and the gender bias in biomedicine in relation to medical education. An older study by Dijkstra et al. (2008) screened 11 medical textbooks, including four on internal medicine ⁄ cardiology, four on pharmacology and three on psychiatry. They found a lack of attention to gender in all textbooks. They also defined gender-related issues that should be present in medical textbooks concerning coronary heart disease, depressive disorders, alcohol abuse, and pharmacology. Ludwig et al. (2015) report on a curriculum development program at a large European medical faculty (Charité in Berlin, Germany) which resulted in an integration of sex and gender medicine–related content 'throughout all teaching and learning formats and from early basic science to later clinical modules (94 lectures, 33 seminars, and 16 practical courses)' (p. 996). Other examples are the Center for Gender Medicine (CfGM) at Karolinska Institutet (KI), the first in Europe to establish the web-based educational course 'Health and Disease from a Gender Perspective'; the University of Toronto's Collaborative Graduate Program in Women's Health; and the award-winning online interactive modules covering topics, such as osteoporosis, diabetes, cardiovascular disease developed at Texas Tech University Health Sciences Center (TTUHSC) (Miller et al. 2016).

57. Apart from these (and some other) initiatives, there is no overview of biomedicine textbooks with respect to issues of gender and health in use at the undergraduate and graduate level. Also, there is a lack of data on innovative curricula that include sex and gender aspects, their dissemination and impact.

4 Gender bias in biomedicine: the case of mental health problems

58. Ruiz and Verbrugge (1997) have argued that the gender bias in biomedicine is the result from two views –

> one assuming equality where there are genuine differences and the other assuming differences where none may exist. The views originate in a biomedical model that assumes equality for physical health problems and inequality for emotionally-toned ones and self-expressed health' (p. 107).

59. This section describes the production of gender bias in a) symptom reporting by women and men on the one hand, and b) the perception and interpretation of a patient's problems by physicians on the other hand. It focuses on mental health problems as one special problem area where gender norms seem to have a particularly strong influence on physicians' diagnosis and treatment.

4.1 Understanding gender bias in symptom reporting and its implications

60. In a recent book ‘Pain and Prejudice’ Gabrielle Jackson writes: ‘Diseases presenting differently in women are often missed or misdiagnosed, and those affecting mainly women remain largely a mystery: understudied, undertreated and frequently misdiagnosed or undiagnosed’. Evidence for this situation can on the one hand be found in studies of somatic symptom reporting (e.g. Barsky et al. 2001, Bardel et al. 2019) that show considerable gender differences and discuss some of the reasons behind these differences.

61. Why should these differences be considered a gender equity/equality problem and not just a result of biological differences? Barsky et al. (2001) consider several of potential explanations. One of the reasons may be women’s more frequent contact with doctors, based on the argument that ‘women are more interpersonally oriented, and more affiliative and relational, hence may find it easier to seek interpersonal help’. Women’s socialisation and social roles may reinforce this tendency – ‘men are socialised to be more stoical; women are encouraged to acknowledge distress; men resist assuming sick role more than women’ (p. 271). This has consequences for how women are treated by physicians:

> To the extent that women patients more openly express emotional difficulties and psychosocial distress, they may be more readily viewed as emotionally disturbed, histrionic, or somatising. Clinicians may then be quicker to conclude that diffuse or nonspecific symptoms have no medical explanation in women, more likely to ascribe such symptoms to psychosocial causes, and more ready to ascribe them to a somatoform disorder. This in turn could result in less vigorous attempts to ascertain a medical basis for the complaints, and less serious consideration of all possible medical etiologies (Barsky et al. 2001, p. 270).

62. Another reported reason for gender differences in symptom reporting is abuse and trauma – girls and women are more frequently victims of abuse, which is associated with greater symptom reporting (Barsky et al. 2001). Hence, symptom reporting is the result of a complex interaction of gendered socialisation, gender norms and psychosocial factors, such as ‘lack of social support, adverse life events, loneliness, depression, generalised anxiety, panic, social phobia’ (Beutel et al. 2019).

63. When the different experiences and conditions under which women and men report their health problems are systematically disregarded, this has consequences for diagnosis and treatment. Referring to Ruiz and Verbrugge’s (1997) ‘two-way view of gender bias’, Hamberg (2008) reports that physicians are more likely to interpret men’s symptoms as organic and women’s symptoms as psychosocial or nonspecific and that women are prescribed more psychoactive drugs than men. Using the treatment in psoriasis as an example, she also points out that although

> the number of patients and the severity of the disease did not differ between men and women, yet there were far more expenditures for clinic-based treatment for male patients than female patients who received emollients for self-care to a greater extent (Hamberg 2008, p. 238).

64. Another example of gender bias is endometriosis that is often interpreted by physicians as a sign of hysterical tendencies. Based on interviews conducted with general practitioners and gynecologists, Young et al. (2019) found: ‘The historical hysteria discourse was most often endorsed when discussing “difficult” women, referring to those for whom treatment was not helpful or who held a perception of their disease alternative to their clinician’ (p. 337).

65. These and other studies demonstrate that the differences in symptom reporting by men and women as well as the underlying reasons are often disregarded in the clinical situation with sometimes severe consequences for diagnosis and treatment.

4.2 Gender differences in physicians’ diagnosis and treatment of mental health problems

66. Gender bias in the diagnosis and treatment of women and men with mental health problems may have its roots either in research that does not account for the influence of gender and/or in an, often implicit, gender bias of health professionals. According to Chapman et al. (2013): ‘Cultural stereotypes may not be consciously endorsed, but their mere existence influences how information about an individual is processed and leads to unintended biases in decision-making, so called “implicit bias’(p. 1504).

67. Mental problems tend to have complex origins and they make people suffering from them particularly vulnerable. Moreover, patients with severe mental health problems, whether at home, in psychiatric care or in prison, may be more frequently subject to human rights violations than other people.

68. The following sections briefly present some well-documented examples of gender bias concerning mental health: the diagnosis of depression; the expression of pain and its assessment by physicians, the diagnosis of borderline personality disorder and of autism.

DIAGNOSIS OF DEPRESSION

69. Depression, a wide-spread condition, is regularly reported as being twice as common in women as in men. This higher prevalence of depression in women has been ascribed to social and cultural living conditions - for example, many women afflicted by depression have suffered sexual and physical abuse - as well as biological processes (Hamberg 2008). Moreover, psychiatric theory and diagnosis have changed over time. Studying the construction of the modern diagnosis of depression, Hirshbein (2016) demonstrates depression as having been framed in a gendered way. Between the 1950s and the 1980s researchers studied hospitalised patients whose symptoms were counted and used to define the category of depression. They were mostly women because there were more women than men with assumed depression in the hospital wards, while patients who abused drugs and alcohol (most of them men) were excluded from the studies:

> This means that the connection between women and depression has become a closed circle: researchers studied mainly women to establish the grounds for the diagnosis, thus more women fitted into the descriptions and received the diagnosis, which in turn supported conclusions that more women than men are depressed (Hirshbein 2016, p. 2).

70. Hence, historically the definition of depression as a diagnostic category is based on a sample of mostly women and on a gender bias – a series of assumptions about women. Does this mean that men that suffer from depression run the risk of not being diagnosed appropriately?

EXPRESSION OF PAIN

71. Many studies suggest that the expression of pain in women is taken less seriously by physicians than in men and that it is less adequately treated. The underlying reason is the persistence of strong gender norms that present men as 'braver' – more tolerant of pain – and women more sensitive to pain and more inclined to express and even exaggerate their pain (Schäfer et al. 2016). Research links pain perception and expression to early childhood socialisation of girls and boys (e.g. Myers et al. 2003). Samulowitz et al. (2018) use the concept of 'hegemonic masculinity' and 'andronormativity' (the extent to which masculinity and male values are considered as normal) to explain gender bias in the expression of pain and whether it is taken seriously. They also point to the fact that women's pain is often psychologised and suggest that

> symptoms in women-dominated conditions that do not fit the masculine norm actually seem to be invisible. The definitions of these conditions in the reviewed studies have focused on the absence of medically provable signs, for example, 'pain in the absence of diagnostic evidence' or 'pain without organic pathology' (Samulowitz et al. 2018, p. 9).

72. These findings suggest that being 'heard' and treated adequately for symptoms of pain is a problem that regards women and men, in a different way. Awareness about gendered norms is important for both, research and clinical care, in order to support health care professionals in providing equitably care.

DIAGNOSIS OF BORDERLINE PERSONALITY DISORDER

73. There is a clear gender pattern in the diagnosis of borderline personality disorder (BPD), with substantially more women than men (3:1) being diagnosed borderline. BPD is a clinically complex and challenging condition which cannot be treated adequately in this report. Exploring the relationship between gender and the experience of psychological distress, Becker (2019) has described BPD as 'the most pejorative of personality labels' which is 'little more than a shorthand for a difficult, angry, female client certain to give the therapist countertransferential headaches' (p. 423). She also points out that there has not been sufficient work

> aimed specifically at addressing the 'woman question' in the borderline diagnosis. How does the fact of the preponderance of women in this diagnostic category relate to the vagueness of the diagnostic criteria? How does it relate to the tailoring of the criteria to fit women? Why do more women than men display so-called borderline symptoms? (Becker 2019)

74. BPD is one example of how difficult it may be to avoid gender norms in the diagnosis of mental illnesses, for both women and men.

75. A recent study of BPD in men shows that they ‘exhibit greater violence, self-harm and aggression’ compared to women suggesting a risk that men may be misdiagnosed (Bayes and Parker 2017). On the other hand, ASPD (antisocial personality disorder) is more often diagnosed in men. Moreover, the prevalence of BPD is significantly higher among prison inmates than among the general population (Sebastian et al. 2019). This makes providing proper treatment a challenge.

DIAGNOSIS OF AUTISM SPECTRUM DISORDER (ADS)

76. Men and boys are diagnosed considerably more often (4:1) with ADS than women and girls. Research suggests that this may have to do with the fact that screening or diagnostic tools have been developed and validated mostly in male subjects and that these tools, as a result, do not capture the female phenotype of ADS. Beggiato et al. (2017) have tested ADI-R, a frequently used diagnostic tool, concluding that ‘despite the existence of different norms for boys and girls with ASD on several major screening tests, the algorithm of the Autism Diagnosis Interview-Revised (ADI-R) has not been reformulated’ (p. 680). Adamou et al. (2018) have assessed the Autism Diagnostic Observation Schedule (ADOS) for gender bias, finding that it favours a ‘male-type’, being much less sensitive to symptoms of ADS in females.

77. This gender bias may be due to the fact that women might have developed more social skills than men, seem to be more ready to discuss emotions, make greater use of facial emotions and gestures and, in sum, might appear as better adapted. Men tend to show more restricted, repetitive, and stereotyped behaviour than women and are therefore more likely to receive a diagnosis.

78. In particular, young girls show ‘a great determination to learn social and societal norms and nuances’. Moreover, in young girls, sociocultural and familial influences can impact the way how they present themselves (Adamou et al. 2018). There is clearly the need to revise current diagnostic tools in order to take account of female ADS symptoms. Young et al. (2018) point at evidence of delayed diagnosis in females with ASDs arguing that such a delay is known to be related to more developmental difficulties in young girls.

4.3 What can be done?

79. There are considerably less recommendations to be found in the mental health literature than in studies dealing with issues of equal access/representation. This may be a result of the fact that the issues are complex and evidence from different studies not always conclusive. From a human rights perspective, the findings point at the importance of pursuing research on sex/gender differences concerning mental illnesses and also at the need for removing gender bias from diagnostic tools.

80. Another path of possible action concerns how to respond to the implicit gender bias of health care personnel; although the relationship between levels of implicit bias and clinical decision-making is complex and 'there is currently a lack of good evidence for a direct negative influence of biases' (FitzGerald and Hurst 2017, p. 14). It is also important to account for the fact that patients may have a gender bias, based on their previous interactions with physicians.

81. Chapman et al. (2013) conclude from a study of physicians' implicit bias that its contribution to health care disparities 'could decrease if all physicians acknowledged their susceptibility to it, and deliberately practiced perspective-taking and individuation when providing patient care' (p. 1508). They propose to provide clinicians with training in individuation which 'involves conscious effort to focus on specific information about an individual, making it more salient in decision making than that person's social category information' (p. 1508). They also suggest that increasing the number of women (and in their case African-American) physicians could be helpful. In a study in a Swedish teaching hospital Risberg et al. (2008) observed that physician teachers' approaches to gender was 'characterised by avoidance and simplification', strategies that could be indicative of resistance to gender issues.

82. These findings point at the critical role of educating health care personnel about gender norms and their implications for the doctor-patient relationship as well as for clinical decision-making. While 'the notion of gender is a construction and can be changed' (Samulowitz et al. 2018), experience shows that disrupting gender norms may take a long time.

5 Gender aspects of neurotechnological research and interventions

83. In a paper 'The ethics of neurotechnology: A discussion of the ethical issues associated with decoding and modulating brain function' a group of experts (Chang et al. 2019) describes some of the challenges associated with the emerging field of neurotechnologies:

- The right to a private life - how to protect the privacy, safety and consent of individuals using devices that introduce or record brain signals;
- Neuro-security - devices getting 'hacked' and, as a result, behaviour being unwilfully and unknowingly manipulated for reprehensible purposes;
- Dealing with the risks of direct-to-consumer devices that promise performance enhancement given that very little is known about the effects of brain stimulation;
- Dealing with the possibilities of manipulation - 'mining the mind' (Ienca/Andorno (2017) – that neuromarketing companies offer by using

Steady State Topography (SST) and physiological measurements (e.g. galvanic skin response) to study, analyse and predict consumer behavior;

- Access - people living in rural and remote areas are unlikely to ever have equal access to these technologies.

84. The latter concern applies to all expensive medical technologies and is potentially exacerbated by other sources of inequity, such as being poor, non-white or being a woman.

85. While gender equity/equality is not in the foreground of this debate, some issues stand out as relevant for avoiding the perpetuation of gender bias in this new emerging field: a) neuro-realism and the problematic notion of a 'female brain'; b) the danger of reifying gendered inscriptions in performance (or moral) enhancement and therapeutic techniques.

5.1 Problematising the notion of a 'female brain'

86. One of the foci of Neuroimaging (NI) research is to better understand mental health problems that show disparities between women and men. An article by Oster in the New York Times (Sep. 9, 2019) 'Do Men and Women Have Different Brains? How New Neuroscience Explodes the Myths of the Male and Female Minds' refers to the research of Gina Rippon, a British professor of cognitive neuroimaging, who is strongly critical of the ways, functional MRI (Magnetic Resonance Imaging) techniques seek to establish differences between the female and the male brain.

87. Rippon (2018) points to four key principles– 'overlap, mosaicism, contingency and entanglement' – that should guide all neuroimaging research. Firstly, she argues that individuals do not have a uniformly 'male' or 'female' brain but male and female forms in different areas of the brain in ways that differ among individuals. This mosaicism of gendered behavior and brains which has been recognised for decades is a critically important point. Moreover, Rippon describes research showing that new events, environmental change, and learning experiences, specific training activities or daily experiences (she mentions as vastly different experiences as 'sports involvement, hobbies, games, poverty and harassment') can alter brain functions throughout a person's life. All this shows the enormous plasticity of the brain and renders any evidence we might have about differences between male and female brains potentially 'suspect'; or: 'The answer may well be yes, brains appear systematically different across genders — but you'll never know if this reflects some underlying structural difference, or whether it's simply the result of different treatment' (Oster 2019).

88. Why do these ideas about male and female minds that some of neuroscience supports matter from a human rights perspective? Sex/gender differences exist; however, according to Jordan-Young and Rumiati (2012):

> The hardwiring paradigm erases the effect of the social world in producing sex/gender differences, so that sex/ gender hierarchies appear natural. Neuroscientific explanations of sex/gender differences have added a new allure to an old-fashioned sexism […]. The

> endorsement by neuroscientists of innate accounts of differences has inevitably reinforced the status quo and non-interventional policies (p. 311).

89. Investigating contemporary functional MRI research on sex/gender differences in emotion processing, Bluhm (2013) argues that some of this research not only uses problematic methods but that it reinforces gender stereotypes. She refers to the bestselling book by Louanne Brizendine 'The Female Brain' (2007) as well as to Simon Baron-Cohen (2004) who has stated that there is an 'essential' difference 'between men and women (and their brains); men's brains are built for systematising information, whereas women's are built for empathy' (Bluhm 2013, p. 321). Bluhm's argument is that we don't know enough about sex/gender differences in emotion and brain activity to reach such a conclusion that simply reinforces gender stereotypes: namely the link between women and emotionality which Shields (2002) has termed a 'master stereotype'.

90. *Neurorealism* is a term that Kempner (2018) and others use to refer to 'the ability of vibrant, colourful fMRI and PET (Positron-Emission Tomography) scan technologies to validate an argument or to create the impression that otherwise ephemeral phenomena are real' (p. 11). This term goes back to a study by Racine et al. (2005) that describes the portrayal of neuroimaging research in the media, showing

> how coverage of fMRI investigations can make a phenomenon uncritically real, objective or effective in the eyes of the public. This occurs most notably when qualifications about results are not brought to the reader's attention. For example, commenting on an fMRI study of fear, one article states, "Now scientists say the feeling is not only real, but they can show what happens in the brain to cause it" (p. 3).

91. *Neurosexism* is a term launched by Cordelia Fine (2010), and it 'stands for the (mis)use of neuroscientific facts and factoids […] to assert that women and men are categorical' (Dussauge/Kaiser 2012). The key question these researchers address is: in how far do neuroimaging technologies encode social stereotypes about gender and culture?

5.2 Neurotechnological enhancements

92. Clinical applications of brain imaging as well as other neurotechnologies are promising to improve the well-being of patients suffering from neurological disorders, offering new preventive, diagnostic and therapeutic tools. Without downplaying these potential benefits in the future, the emerging research field of 'neuroethics' has started a debate around concepts that are key to discussing ethical problems raised by our ability to understand, monitor and influence the human brain; namely: integrity, performance and/or moral enhancement, and 'freedom of mind'.

93. The latter is a term that Bublitz (2006) uses in describing moral bio-enhancements (MBE). He refers to authors such as David DeGrazia (2014) who suggests that public policies should use MBE to help reduce or eliminate properties of persons

which he deems to be ‘moral defects’; or Thomas Douglas (2013) who ‘proposes that persons should be free to use moral enhancements, particularly those that reduce aggression and racism’. Bublitz points at the part of neuroscience that has emotions as a prime target for interventions with the aim ‘to improve morality, either by increasing pro-social or attenuating anti-social sentiments’ (p. 88). He argues that ‘whether emotions should be targeted by such interventions is one of the main contested ethical and legal issues’ (p. 88).

94. Referring to the notion of ‘the cerebral subject’ (Ortega and Vidal 2007), Schmitz (2012) adds the gender dimension to this debate. She explores some of the goals behind the ‘neurotechnological optimisation of the healthy subject’, arguing that these goals are based on gendered attributions

> that have been historically legitimised by apparently natural differences between women and men. With the help of neurotechnologies as instruments for optimisation the cerebral subject should become more efficient, more concentrated, more flexible and more self-confident. […] Some goals can be extracted from these approaches: enhancement of connectedness, operational readiness and flexibility, improvement of mobility and communication. These are optimizations for the ‘modern human’ who aims at effective self-marketing in modern information society (p. 262, 266).

95. Hence, inscribed in these notions of the ‘neurotechnologically upgraded’ human being are again traditional connotations of masculinity and femininity. The ability to enhance our essential traits and abilities runs not only the risk of commodifying them (Hamilton et al. 2001); it also may invite manipulations of the brain that conform with the myth of apparently masculine superior performance that is associated with high testosterone levels (see also Jordan-Young’s book ‘Brain Storm: The Flaws in the Science of Sex Differences’; 2010). Schmitz (2012) refers to the so-called ‘savant-skills’ – extraordinary perceptual abilities on tasks such as drawing, proofreading, numerosity judgment, and other cognitive processes that are more common in men diagnosed with high performance autism – as an example of ‘gendered inscriptions in the complex of cognitive enhancement with TMS (Transcranial Magnetic Stimulation) and autism’ (p. 267).

96. Another example of the hidden gendered aspects in neurotechnological research is neuroeconomics, with its focus on ‘rationality versus emotionality’. Some evidence is provided by studies suggesting that one of the impacts of TMS stimulation on brain materiality and functionality could be a decrease of empathic and moral judgement capabilities in favour of ‘egoistic’ cost-benefit judgements (Di Nuzzo et al. 2018).

97. A related question is how altering brain function with TMS might affect perceived personal identity, hence also a person’s self-perception of gender. Behind this is the idea of personal identity as malleable and open to ‘finetuning’ (Cheshire 2018). Hamilton et al. (2001) consider the potential of changing self-identity as one of the most salient neuroethical questions to address in the future:

> If the use of non-invasive brain stimulation for self-enhancement becomes widespread, it is likely that society will be forced to confront essential questions of self-identity and whether there

> are or should be limits on our ability to change our fundamental nature (Hamilton et al. 2001, p. 190).

98. Kempner (2018) makes an interesting argument about the potential of neuroscience to counterbalance inequalities in pain treatment, based on a person's gender and race, by using functional MRI to 'measure a neural signature or network of pain-related brain regions that could produce measures for use in clinical decision-making' (p. 12). On the other hand, she warns against tendencies to increase or reify these disparities, arguing: 'The neuroreduction of negative stereotypes associated with sex differences or racial categories into brain-based characteristics has profound implications for the future of equality' (p. 15).

99. A key concern that researchers express from the perspective of neuroethics is about gender (and race-related) stereotypes 'creeping' into emerging techniques of cognitive and moral enhancement. This not only raises questions concerning human dignity and personal identity. It also points at the importance of protecting the great diversity and 'collective appreciation of human gifts, talents, and achievements' that may be eroded by routinely enhancing neurologic function (cognitive skills, mood, social cognition) in particular selective ways.

5.3 What can be done?

100. Issues concerning gender equality in neurotechnological research and interventions are difficult to address and there is little systematic reflection on the values underlying this research.

101. As concerns sex/gender neuroimaging research, Rippon et al. (2014) formulate a set of recommendations that are based on the key principles she outlines: overlap, mosaicism, contingency and entanglement. These recommendations are directed at neuroimaging researchers. She also refers to the argument that the presentation of 'brain facts' through their popularisation may become part of gender socialisation, hence entangled with the mental phenomena under study. It is the responsibility of researchers and also the media to work against 'gender essentialist thinking'.

102. The other venue to be taken has been formulated by Kempner (2018) who observes that

> neuroethicists tend to be focused more on how new knowledge and technologies might transform the collective understanding and control of the human mind, than on the perhaps less glamorous questions of how these technologies will affect already unequal societies (p. 2).

103. This is also the approach suggested by Jourdan-Young and Rumiati (2012) who argue:

> Sex/ gender differences exist, but so do differences between groups that we might want to define on many other dimensions—social class, occupation, development index or global region, specific training experiences, to name just a few. And each of these categories are themselves heterogeneous; more research on the ways in which sex/gender patterns in brain and behaviour are specific to social class, ethnicity, and nation might provide much more illumination on the concrete mechanisms through which the social world shapes behavior, and even becomes embodied (brain) difference (p. 312).

104. Vidal (2012) also considers the role of the media in disseminating the results of dubious studies, and advocates deeper public information about the neuroscience of sex/gender understood through the lenses of brain plasticity.

6 AI, big data and the gender bias in biomedical data

105. In a recent book ‘Invisible Women: Exposing Data Bias in a World Designed for Men’, Caroline Criado Perez refers to the gender data gap in biomedicine and its consequences for ‘big data’ analyses:

> Invisible Women is a story about absence - and that sometimes makes it hard to write about. If there is a data gap for women overall (both because we don't collect the data in the first place and because when we do we usually don't separate it by sex), when it comes to women of colour, disabled women, working-class women, the data is practically non-existent. Not simply because it isn’t collected, but because it is not separated out from the male data — what is called ‘sex-disaggregated data‘(p. 2).

106. This is a timely observation, as Artificial Intelligence (AI) technologies based on ‘big data’ and machine learning are being developed, tested and also increasingly used for a range of purposes in the field of healthcare, including detection of disease, management of chronic conditions, delivery of health services, and drug discovery; with some success. So has *Google Health* developed an artificial intelligence application ‘that is better at spotting breast cancer in mammograms than expert radiologists’ (The Guardian, Jan 1, 2020). Other potentially successful examples of the use of AI technologies in medicine (most of them still being tested) are the diagnosis of neurogenerative diseases, such as Parkinson; dermoscopic melanoma recognition; applications in ophthalmology that support the early recognition of major eye diseases; and various applications that help improve accuracy in oncological treatment.

6.1 Algorithmic bias – data gaps

107. At the same time, well-documented alarming examples of algorithmic bias are being published and also discussed in the media. Tannenbaum et al. (2019) refer to the need to identify and reduce gender bias in AI:

> When translating gender-neutral language related to science, technology, engineering and mathematics (STEM) fields, Google Translate defaults to male pronouns. When photographs depict a man in the kitchen, automated image captioning algorithms systematically misidentify the individual as a woman. As AI becomes increasingly ubiquitous in everyday lives, such bias, if uncorrected, can amplify social inequities (p. 140).

108. Applications such as these use machine learning – the application of AI in providing systems with the ability to automatically learn and improve from experience without being explicitly programmed. Machine learning enables analysis of massive quantities of data - so-called ‘big data’. ‘Learning’ means that the computer program (an algorithm) is able to explore these big quantities of data,

identify patterns in them, discover errors, and modify the algorithm to produce accurate (and sometimes also unexpected and new) outcomes (e.g. a particular diagnosis). The accuracy and plausibility of the outcome of such a process depends on the quality of the data and the algorithm (the ‘model’).

109. In recent years, very large data sets and ever more complex models have prompted a discussion about how automated tools might introduce bias or entrench existing inequity — especially if they are being inserted into an already discriminatory social system. Nelson (2019) captures this concern in some provocative questions:

> Imagine an algorithm that selects nursing candidates for a multi-specialty practice - but it only selects white females. Consider a revolutionary test for skin cancer that does not work on African Americans. What about a model that directs poorer patients to a skilled nursing facility rather than their home as it does for wealthier patients? These are ways in which ungoverned artificial intelligence (AI) might perpetuate bias.

110. That bias exists in the ‘big’ databases that feed algorithm-based analytics in medicine is not surprising, as these data reflect medical practice, hence, also the implicit gender bias that has characterised this practice for decades. Sanchez-Martinez et al. (2019) speak of ‘inherited bias’:

> This inherited bias occurs because we ask ML (machine learning) solutions to predict which decisions the humans profiled in the training data would have made. Thus, we should not expect the ML method to be fair or impartial or to have the slightest idea about what the clinical goal is. The challenge is to find the way in which ML overcomes human bias, as this is crucial for successful decision-making applications that do not learn the mistakes that we have committed in the past (p. 19).

111. In the medical field, ‘big data’ analyses do not only use data from clinical trials but, increasingly, new kinds of data sources, including ‘DNA sequences, MRI scans, electronic health records (EHR) or social media posts’ (Pot el al. 2020). EHR data about a patient, for example, are generated in different clinical situations and settings and are therefore ‘inherently biased by the patient population structure, frequency of healthcare visits, diagnostic criteria, and care pathways’ (Prosperi et al. 2018, 10).

112. Such discriminatory bias is either due to the fact that the training data that are used for refining the algorithm do not represent the diversity of patient populations (‘bias of the sample’); or due to prejudice and stereotyping having influenced the collection of the data (‘prejudicial bias’). Although a biased database poses many largely unresolved problems, ‘a deeper dimension of unfairness lurks within algorithms’ (Courtland 2018). Using the example of depression, Rajkomar et al. (2018) argue:

> Biases may arise during the design of a model. For example, if the label is marred by health care disparities, such as predicting the onset of clinical depression in environments where protected groups have been systematically misdiagnosed, then the model will learn to perpetuate this disparity (p. 869).

113. We know that the very concept of depression has been framed in a gendered way. An algorithm for the diagnosis of depression that has been trained on a set of gender-biased data will replicate and perpetuate this bias.

114. A widely discussed example of gender bias is facial recognition systems. A study by Buolamwini and Gebru (2018) found that darker-skinned females were the most misclassified group with an error rate of up to 34.7% (lighter-skinned males had a maximum error rate of 0.8%). Facial recognition systems are widely used. As Keyes (2019) argues, through their 'reliance on fixed notions of gender and race as systems' they are 'inevitably discriminatory'. One of the solutions Keyes proses is to make performing an algorithmic audit that relies on data that are gender-diverse and racially diverse obligatory.

115. Based on examples such as these, there is a broad discussion on *algorithmic fairness* based on different definitions of fairness, some of which focus on groups/populations while others focus on individuals (e.g. Collett and Dillon 2019). Rajkomar et al. (2018) distinguish different types of fairness - equal patient outcomes, equal performance (accuracy) or equal allocation – emphasising that these types are not necessarily compatible with each other. They conclude from their analysis that

> Machine-learning fairness is not just for machine-learning specialists to understand; it requires clinical and ethical reasoning to determine which type of fairness is appropriate for a given application and what level of it is satisfactory (p. 872).

116. AI and machine learning are often thought of as opening the way to personalised or precision medicine, as big data 'comprehensively and objectively represent many different aspects of patients' lives and bodies' (Pot el a. 2020, p. 1). This should in the future help establish fairness/gender equity allowing tailoring medical practices to the particular conditions of individual patients. However, Pot et al. (2020) also point at the 'tensions between the desire for the abolishment of gender bias on the one hand, and the important critique of the invisibility of women and gender minorities in biomedicine on the other' (p. 11). The availability and use of more and more digital data do not necessarily reduce the invisibility of gender; on the contrary: 'The "data bodies" that digital medicine operates with often have no explicit gender attribution anymore' (p. 14).

6.2 What can be done?

117. AI, big data and machine learning do not 'automatically' help achieve greater gender equity/equality in biomedicine, as they tend to reproduce existing gender bias. While there are more and more examples of algorithmic bias being critically discussed when it comes to predictive policing or assessing credit risks, only few if any AI-based decision-support systems in biomedicine have been used in practice beyond testing.

118. Most of the recommendations are directed at the scientific community and deal with the need to identify and avoid bias in machine learning models. For example,

Tannenbaum et al. (2019) suggest, firstly, to evaluate when it is appropriate for an algorithm to use gender information – this may not be necessary in all cases. Pot et al. (2020) propose a set of questions that might help make gender bias in data visible. Secondly and as a general rule, when constructing databases to be used in machine learning, metadata about how the dataset was constructed should be produced. This should help understanding the contextuality of data, which is important when data that have been collected for a specific purpose are used in other contexts. The argument is that a 'lack of data empathy', as Ferryman and Pitcan (2018) call it, can limit the 'ability to recognise bias and optimise the analyses because they are too far "from the source" (p. 20).

119. On the institutional level, a newly proposed federal legislation for the United States, The Algorithmic Accountability Act of 2019, would, if ratified, 'require businesses to conduct an impact assessment that covers the risk associated with algorithms' accuracy, fairness, bias, discrimination, privacy, and security' (Nelson 2019).

7 Taking action towards gender equity/equality in biomedicine

120. This report has highlighted some key issues concerning gender equity/equality in biomedicine. The findings are of a rather different nature. While some are more 'straightforward' presenting gender bias concerning access, representation, as well as the influence of gender norms on how women's and men's health problems are treated, others are more difficult to identify and address directly. Some of these issues are at the core of ongoing debates within the various scientific communities and many recommendations to be found in the literature concern how to incorporate gender analysis in research through sex disaggregation of data and integrating gender analysis frameworks and questions.

121. Other lines of action, such as promoting women's research opportunities in biomedicine and addressing work climate in research in order to deal with issues of gender stereotypes, sexism, sexual harassment, and discrimination, are already on the agenda of European and international bodies, such as the Council of Europe, the European Commission, national funding agencies, as well as individual universities.

122. In regard of the work of DH-BIO, there are a number of lines of action to be considered that do not simply replicate the agenda of other institutions and bodies but complete and eventually reinforce them. Overall goals should be to a) strengthen equal access to health services and b) decrease the data gap for women (their 'invisibility') in biomedical research.

FILL GAPS IN DATA

123. Currently, there are significant data gaps concerning European countries with regard to many issues addressed in this report. These data are either not available

or not easy to retrieve. From the perspective of gender equality/gender bias particularly important data gaps concern:

- The representation of women researchers in biomedicine in the member states (with respect to type of positions, authorship, grants, etc.);
- Women's participation, respectively their underrepresentation in clinical trials and drug development studies, disaggregated by age (children of 10-14 years, old women) and type of disease.

124. DH-BIO could take action to have these data actively collected and shared to define and evaluate new policies.

ACTION TO ENCOURAGE EQUAL ACCESS AND REPRESENTATION OF WOMEN AND MEN IN BIOMEDICAL RESEARCH

125. Issues of equal access/representation are currently addressed by major universities, research centers and by national funding agencies in a number of European countries, with some success. However, measures to increase equal access/representation have not been implemented to the same extent in all European Council member states.

126. A line of action could be to provide a number of best practice examples to all member states in support of actions plans for gender equality in biomedicine on the level of institutions, hiring and promotion committees, funding agencies, etc.

ACTION TO STRENGTHEN THE INCLUSION OF WOMEN (AND OTHER UNDERREPRESENTED GROUPS) IN CLINICAL TRIALS AND DRUG DEVELOPMENT

127. As Maguire et al. (2018) argue, the new clinical trials regulation (Regulation EU No 536/2014) is a major step forward in increasing clinical trial data transparency. They also remark that 'the continued under representation of women in clinical trials needs to be urgently tackled, and the regulation must be enforced' (p. 285).

128. DH-BIO could add weight to this argument from a human rights perspective. It could also seek to ensure that more attention is given to older people (both women and men) in biomedical research.

STRENGTHEN STRATEGIES OF ADDRESSING GENDER BIAS IN THE DIAGNOSIS AND TREATMENT OF MENTAL HEALTH PROBLEMS

129. With respect to its task to carry out a study on 'good practices in mental health care'), the DH-BIO could incorporate measures to ensure the pursuit of research on sex/gender differences concerning mental illnesses and encourage increased effort at removing gender bias from diagnostic tools. The study should also account for the special mental health care needs of children/young people and gender minorities.

ENCOURAGE DRAFTING LEGISLATION ON AI, BIG DATA AND ALGORITHMIC FAIRNESS IN BIOMEDICINE

130. Several authors stress the need for AI governance - regulating the process of assigning and assuring organisational accountability, decision rights, risks, policies, and investment decisions for applying artificial intelligence. DH-BIO could support moves towards such regulation at the European level with a focus on

big data and machine learning in biomedicine. It could also initiate a public debate on the risks associated with the accuracy, fairness, bias, discrimination, privacy, and security of algorithms.

TRAINING OF HEALTH CARE PROFESSIONALS IN SUPPORT OF GENDER EQUITY/EQUALITY

131. The task of the DH-BIO to ensure the dissemination of the training course on essential principles for the protection of human rights in the biomedical field could be extended to include gender equity/equality issues. An important aspect would be to address physicians' implicit gender bias by providing 'perspective-taking and individuation when providing patient care' (see Chapman 2013); and increase awareness of gender norms and their implications for the doctor-patient relationship as well as for clinical decision-making.

CARRY OUT A SURVEY OF BIOMEDICINE TEXTBOOKS

132. Medical education has an important role in making future doctors aware of gender issues. DH-BIO could carry out a study of biomedicine textbooks in use at the undergraduate and graduate level in the member states. Such a study should provide an overview of how and to which extent textbooks and other major teaching material include sex and gender medicine-related content. In addition to that, data on innovative curricula that include sex and gender aspects should be collected and disseminated.

ENCOURAGE PUBLIC DEBATE ON GENDER IN BIOMEDICINE

133. The media have an important role in communicating scientific research. The emerging field of neurotechnologies has captured the attention of the media and the wider public arena. DH-BIO could launch a debate on the human rights aspects of these technologies that embraces gender aspects. This would include critical examination of the ways 'brain facts' and the emerging techniques of cognitive and moral enhancement are popularised and how functional MRI results may be used to promote political and personal agendas (neuro-policy).

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