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A Philosophical Analysis of Informed Consent for Whole Genome Sequencing in Biobank Research by use of Beauchamp and Childress' Four Principles of Biomedical Ethics

Ebbesen M[1, 2, 3*], **Sundby A**[1, 2], **Pedersen FS**[4,5] **and Andersen S**[3]

[1]*iPSYCH (The Initiative for Integrative Psychiatric Research (financed by the Lundbeck Foundation))*

[2]*Department of Clinical Medicine, Aarhus University, Denmark*

[3]*Department of Culture and Society, Aarhus University, Denmark*

[4]*Department of Molecular Biology and Genetics, Aarhus University, Denmark*

[5]*Interdiscipinary Nanoscience Center (iNANO), Aarhus University, Denmark*

[*]**Corresponding author:** Ebbesen M, Department of Culture and Society, Aarhus University, Denmark, Tel: +45 28742924; E-mail: MEB@teo.au.dk

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Introduction

The use of Whole Genome Sequencing (WGS) in biobank research creates challenges because WGS produces fine, detailed genotype information at high resolution. The information from WGS is derived from DNA that is a powerful personal identifier and can provide a large quantity of complex and diverse information not just on the individual, but also on the individual's relatives. This implies that many known and unknown genetic variants in individual participants are generated.

Researchers point to the fact that the concept of "informed consent is not entirely attuned to the era of whole-genome sequencing" [1] and some write that a rethinking of the concept is demanded [2]. In this article, we present a philosophical analysis of dealing with informed consent in WGS in biobank research. Our intention is firstly, that this ethical framework establishes an appropriate balance between protection of the research subject and advancements in science and medical research. And secondary, our intention is to present the philosophical arguments justifying different types of informed consent to bioethicists and to biomedical researchers, so that they are informed when setting up studies within biomedicine involving WGS.

We think that the most plausible and justified way of reconsidering informed consent in this context is an analysis by use of the universal core of morality expressed in 'Principlism' outlined by the American ethicists Tom L. Beauchamp and James F. Childress. This approach is based on the four basic ethical principles of beneficence, nonmaleficence, justice, and respect for autonomy. The principle of respect for autonomy can be specified into the rule of obtaining informed consent. 'Principlism' is the leading method of bioethics and it has been developed, justified, and revised since 1979 [3].

In this article, we first present the ethical method of Beauchamp and Childress with focus on respect for autonomy, and specifically informed consent, as one principle among several. We show how this method can be used to analyse moral dilemmas of biomedicine. Second, we explore some of the various types of consent for research presented in the literature (e.g., specific, tiered, broad, dynamic, and presumed consents), third, we analyse the ethical principles that justify arguments for and against these different consent types. Lastly, we suggest an informed consent model which is useful and ethically justifiable to use in WGS in biobank research.

Analytical Method for Complex Cases of Biomedical Ethics

Beauchamp and Childress propose the framework of four ethical principles as a good starting point for analyzing complex cases of biomedical ethics [3]. These four principles serve as general guidelines for formulating more specific rules. Beauchamp and Childress defend four clusters of ethical principles:

- Nonmaleficence (an obligation of avoiding harm)
- Beneficence (an obligation of providing benefits)
- Justice (an obligation of the fair distribution of goods and burdens)
- Respect for autonomy (an obligation of respecting and promoting autonomous decision making)

The common morality

Beauchamp and Childress argue that 'principlism' is a good analytic tool dealing with ethically complex cases of biomedicine in a pluralistic society (figure 1). Placing themselves in the field of practical or applied ethics, Beauchamp and Childress investigate the formulation and use of norms to address particular ethical problems of biomedicine. They identified the four principles as the cornerstones of what they call 'common morality shared across cultures' [3]. They reached this conclusion that exactly these four principles rather than some other principles are central to biomedical ethics by examining "*considered moral judgments and the way moral beliefs cohere*" [3]. They write: "the common morality is a product of human experience and history and is a universally shared product" [3]. Hence, morality is a social product. Beauchamp believes that "human nature is similar enough throughout the world that we will make similar judgments when we experience limited resources, need to cooperate, etc." (personal communication with Beauchamp). The common morality's standards of right conduct apply to all persons living a moral life (morally serious persons), hence the common morality is "a set of universal norms shared by all persons committed to morality". "the common morality is applicable to all persons in all places, and we rightly judge all human conduct by its standard" so actions violating the standards of the common morality are rightly judged unethical. The following rules are examples of moral obligations contained in the common morality: Do not kill, do not cause pain or suffering to others, prevent evil or harm from occurring, rescue persons in danger, tell the truth [3].

The principle of beneficence

- Protect and defend the right of others
- Prevent harm from occurring to others
- Remove conditions that will cause harm to others
- Help persons with disabilities
- Rescue persons in danger (Beauchamp & Childress, 2013, p. 204)

The principle of nonmaleficence

"One ought not to inflict evil or harm", where harm is understood as "thwarting, defeating, or setting back of some party's interests" (Beauchamp & Childress, 2013, pp. 152-153).

The principle of respect for autonomy

- "As a negative obligation, this principle requires that autonomous actions not be subjected to controlling constraints by others" (Beauchamp & Childress, 2013, p. 107)

- As a positive obligation, the principle requires both respectful treatment in disclosing information and actions that foster autonomous decision making" (Beauchamp & Childress, 2013, p. 107). Furthermore, this principle obligates to "disclose information, to probe for and ensure understanding and voluntariness, and to foster adequate decision making" (Beauchamp & Childress, 2013, p. 107)

The principle of justice

No single principle can address all problems of distributive justice. A framework for allocation has to incorporate both utilitarian and egalitarian standards. However, specifically, Beauchamp and Childress defend the two egalitarian viewpoints:

- The so-called fair-opportunity rule (requires that each citizen "receive benefits that will ameliorate the unfortunate effects of life's lottery" (Beauchamp & Childress, 2013, p. 263)

- The principle that each citizen has a right to a decent minimum of health care (Beauchamp & Childress, 2013, pp. 272-274)

Figure 1: The four basic principles of the common morality. A brief formulation of the four ethical principles [3].

In contrast to the common morality, which is unchangeable in time and place, the particular moralities contain norms that bind only specific communities or specific groups, for instance of physicians or nurses. Hence, particular moralities are relative to cultures and groups and may change over time.

Two or more principles may conflict, then the person in question faces a moral dilemma: a circumstance "where moral obligations demand or appear to demand that a person adopt each of two (or more) alternative but incompatible actions, such that the person cannot perform all the required actions" [3].

Some philosophers hold that irresolvable moral dilemmas do not exist, because one supreme moral value or theory (for instance of utility) overrides all others. According to this view, there is only 'one ought', viz. the one demanded by the supreme theory. In contrast, Beauchamp and Childress hold that we may not be able to reach a reasoned resolution in many moral dilemmas [3]. This is because the four principles are not binding absolutely, but only 'prima facie': They are binding as long as they do not conflict with another principle. If two or more principles do conflict, first the obligations must be specified, next, the weight of each obligation must be determined, and lastly, the obligations must be balanced. Please, read Beauchamps article 'Methods and Principles in Biomedical Ethics' to get a detailed presentation and practical use of the concepts of specification and balancing [4].

Respect for Autonomy

In this section, we focus specifically on Beauchamp and Childress' formulation of the principle of respect for autonomy because the principle of respect for autonomy can be specified into the moral rule of informed consent, hence the principle of respect for autonomy justifies the rule of informed consent, which is the comcern of this article, therefore we have to go into detail with this principle to really understand the rule of informed consent.

In the following, we explore the following two concepts inherent in the principle: The concepts 'to respect' and 'autonomous choice/action'. The concept 'to respect' something or someone means 'to have regard for' or 'to consider' something or somebody worthy. This can be seen in contrast 'to disrespect' somebody, which means 'to insult somebody'. 'To respect' is not only an attitude, but also an action. This means that the principle of respect for autonomy is both formulated as a negative (passive) obligation and as a positive (active) obligation.

We focus on the concept of 'autonomous choice' or 'autonomous actions' rather than a characterization of the autonomous person. In line with Beauchamp and Childress, we argue that the concept of 'autonomous choice' most applicable to biomedical ethics is about 'normal choosers' and not about an ideal which cannot be reached. As Beauchamp and Childress formulate it "no theory of autonomy is acceptable if it presents an ideal beyond the reach of ordinary, competent agents and choosers". In line with this, we believe that three conditions should be fulfilled if an action should be autonomous, hence we understand autonomous action in order of ordinary choosers acting 1) intentionally, 2) with understanding, and 3) without controlling influences which can regulate their action [3]. According to the first condition, Beauchamp and Childress write: "Intentional actions require plans in the form of representations of the series of events proposed for the execution of an action. For an act to be intentional, as opposed to accidental, it must correspond to the actor's conception of the act in question" [3]. Regarding the second condition: because we focus on normal choosers, we also stress that 'understanding' is to be taken as inherent to ordinary people, who are thus equipped with a "substantial degree of understanding and freedom from constraint" in contrast to possessing full understanding and complete absence of limitations. People may experience temporary constraints such as disorders (like depression), however, generally, these persons are to be seen as normal autonomous choosers. The third condition of non-controlling influences refers to control exerted by either external or internal conditions that hinder the person to act autonomously, e.g. because of coercion or manipulation. Acts can be performed with various degrees of understanding and controlling influences, however, in contrast, actions are either intentional or not. Since understanding and controlling influences can be found in different degrees, a dynamic concept of autonomy seems most realistic (for instance incompetence can be temporarily). The principle of respect for autonomy does not apply to persons that cannot be rendered autonomous (because they for instance are immature, incapacitated, ignorant, coerced, or exploited), these persons are instead protected by the principles of beneficence and nonmaleficence. Examples could be infants, irrationally suicidal individuals, and drug dependent patients [3].

The autonomy-principle implies the concept of right: "respect autonomous agents are to acknowledge their right to hold views, make choices, and take actions based on their values and beliefs". This right is formulated as a negative (passive) obligation: "As a negative obligation, the principle requires that autonomous actions not be subjected to controlling constraints by others". As a positive (active) obligation "the principle requires both respectful treatment in disclosing information and actions that foster autonomous decision making". This obligates professionals to "disclose information, to probe for and ensure understanding and voluntariness, and to foster adequate decision making". Hence, Beauchamp and Childress specify the principle into rules which are part of informed consent: Respect the privacy of others, protect confidential information, obtain consent for interventions with patients, and when asked, help others making important decisions, and telling the truth [3].

Informed Consent or Refusal

We here consider informed consent for ordinary competent choosers. Competence is a dynamic concept, relative to context i.e. to the specific decision which has to be made and competence may vary over time. We subscribe to the definition that "Patients or prospective subjects are competent to make a decision if they have the capacity to understand the material information in light of their values, to intend a certain outcome, and to communicate freely their wishes to caregivers or investigators". Beauchamp and Childress stress that the demands to the degree of competence of a research subject or patient do not depend on the consequences of the decision. Hence, the levels of competence to decide do not increase as the risk of an outcome increases. We believe, the claim that making risky decisions requires more competence than making less risky ones is not ethically justified [3].

The act or the process of giving informed consent can be divided into two items:

1. "Informational exchanges and communication through which patients elect interventions, often based on medical advice"
2. "Acts of approving and authorizing those interventions"

Based on this distinction, the approaches of shared decision making or mutual decision making which have been considered in the literature is misleading as it: 1) Stresses item, 2) Ignores item and these approaches reduce informed consent to a bilateral transaction of informational exchange [3].

Put short and precisely an "informed consent is an individual's autonomous authorization of a medical intervention or of participation in research". In a way the family oriented approach also often stresses item 1) and ignores item 2). However, the family centered approach is morally acceptable if the research subject or the patient autonomously and informed delegates the right to make a choice to someone else for instance a family member, a doctor, or an ethical committee, because the very choice to delegate is itself autonomous and therefore morally defensible. Part 1) of the process of giving informed consent is culturally sensitive and takes cultural beliefs and values into account [3], however, the autonomous choice itself, part 2), is based on an autonomous choice and cannot be reduced.

Variations of Informed Consent

In the following we will present some of the various types of consent for research outlined in the pertinent literature e.g., specific/explicit, dynamic/flexible, broad, tiered/tailored, and presumed consent, and explore the ethical principles that justify arguments for and against these different consent types.

Specific consent

Specific consent is the cornerstone of the traditional concept of informed consent. A consent is considered specific, when it is provided for a specific purpose or research study. An example is the dynamic, also called flexible, consent type (described below), where individuals for instance specifically give consent to their genetic information being stored in a database for research use. There would be ongoing communication between participant and researchers to seek specific consent for follow-up medical treatment or research studies. This interpretation of informed consent has its roots in a liberalistic conception of the individual as more important than the society, and stresses self-governance or self-rule [5].

Dynamic consent

The dynamic consent type is proposed to provide research subjects a strong protection of their privacy and autonomy. Dynamic consent can be built on web based technology, a specific database contains genetic information of research subjects, allowing ongoing communication between investigators and subjects, updates on research findings, information on risks and benefits of research projects concerning the content of the database and new requests for providing specific consent or refusal for each new type of use of the data [6].

Broad consent

This type of consent is often used for biobank research, where participants give informed broad consent for research in general, which has been approved by a scientific ethical committee. It depends on the specific situation whether broad consent is sufficient or whether specific informed consent is morally necessary. Broad consent means that research participants consent for a range of unspecified research activities. If data are anonymous and completely de-linked (however, one could question if this is possible with genetic data since DNA is a personal identifier, which gives information not only on the individual, but also on relatives, related groups, and populations) [7,8].

Tiered or tailored consent

When giving tiered or tailored consent participants choose from a checklist of items including for example the type of research requiring consent. The checklist could also include the kind of feedback that the subject wants to get from a research project, for instance the findings of mutations in specific genes causing a higher risk of developing a specific disease.

Presumed Consent

Presumed consent is a kind of implied consent, however, subject to many different interpretations. Presumed consent was used in 1998 by deCODE Genetics under contract with the Islandic government to place the health records of all citizens, i.e. 270000 individuals, into a single database. Individuals were included without taking the following into consideration: Competence, information, disclosure, comprehension, and voluntariness. Individuals should specifically opt out if they did not want to participate. The data stored in the database was combined with Iceland's detailed genealogy and genetic data collected from volunteers [9]. According to presumed consent, persons consent to research or for instance organ donation unless they have explicitly opted out.

Discussion

Arguments for and against specific, tiered, broad, dynamic, and presumed consents

In the following we will analyze and discuss the various arguments for and against different forms of informed consent in light of the four principles of biomedical ethics.

Arguments based on the principle of respect for autonomy favoring broad consent

An argument favoring broad informed consent is based on the principle of respect for autonomy. The participant delegates the consent to a trusted intermediary who consents on behalf of the participant, for instance a scientific ethical committee. This decision is justified by respect for autonomy, since it is an informed autonomous choice to delegate consent to a third party [10,11]. However, a critical voice argues that broad consent results in passive participation, and in reality subjects should actively opt out, which as an empirical fact they seldom do [11]. However, a critical comment to these premises is that DNA samples are re-identifiable and donors should actually be informed that they are enrolled in research [12].

Arguments based on the principle of nonmaleficence favoring broad consent and being opposed to specific consent

Literature presents an instrumental or material argument based on the principle of nonmaleficence. Because of the large number of participants and the long term nature of biobanking a specific consent approach presents a substantial challenge. It is impossible and impractical to obtain specific consent from thousands of participants for each future study, however it is argued that cohorde studies represent minimal risks of harm to participants and are therefore justified [5,10,13].

Arguments based on the principle of justice favoring broad consent and being opposed to specific consent

An argument based on the principle of justice could be that it would cost a lot of resources obtaining specific consent from the large number of research subjects in population-based studies. These resources could instead be used for research and therefore broad consent and not specific consent is preferable. This argument against specific informed consent favoring broad consent is based on a communitarian conception of the individual, where society is more important than the individual, and which stresses the common good [5,10,13]. However, an interesting approach opposed to broad cosent is given by Howard et al. writing: "As opposed to individual risks to participants, collective risks posed by research studies to all members of a specific ethnic, racial, geographic or religious community have not been regularly addressed in the evaluation of a human subject's protection" [14]. As examples these harms could include employment or insurance discrimination, or these communities or groups may be stigmatized in different ways [14,15].

By using a broad consent model we stress ethical principles of justice specified into obligations of solidarity and equity. At least according to Chadwick, who writes that we have to stress solidarity in genetic research. Therefore, we should share information and we should participate in research since this is a contribution to the common good and to society. This may be a way to reduce health inequalities between different populations and move towards equal access to health care (defending an egalitarian principle of justice like Beauchamp and Childress) [8].

Arguments against tiered consent

Based on the principle of justice, one could respond that in comparison with broad consent, it would cost a lot of resources obtaining tiered or tailored consent from a large number of participants, and that these resources could instead be used for health care or research. If this kind of consent is used, considerable resources may be used and may limit the use of samples for some specific types of research.

Arguments for and against dynamic consent

One argument in favor of dynamic consent could be that it is a participant-centered initiative, which respects autonomy and privacy, provides a large amount of information, increases engagement and control. This may shift the motivation of participation from favoring the common good and altruism to personal interests. Dynamic consent shifts the control and responsibility from research ethics committees to research participants. However, this and the increased level of choices may become a burden of autonomy and put stress on research subjects (harm them) [6,11]. Since dynamic consent is web based it might result in unfair (unjust) exclusion of persons not familiar with IT [11].

Arguments for and against presumed consent

To be morally justified, we believe that consent should be based on what is actually known about a person's choices and not on what is desirable or what a rational will would choose. As described earlier Beauchamp and Childress divide the process of informed consent into two parts: 1) informational exchanges and communication and 2) acts of approving and authorizing [3]. We believe that to be morally justifiable consent should include the second part of the process of informed consent, it "should refer to an individual's actual choices or known preferences, not to presumptions about the choices the individual would or should make" [3]. Presumed consent assumes that the person consents to biobanking research unless that person has explicitly actively opted out, hence it is not morally justified.

Conclusion

In this article, we have performed a philosophical analysis of informed consent for WGS studies by use of the four principles of biomedical ethics. We have presented and discussed some of the different types of consent types presented in the literature and we have argued by use of Beauchamp and Childress' method which principles justifie the different types of consent. We reach the conclusion that based on the principle of nonmaleficence, the research of these studies involves populations (in contrast to individuals) and are anonymized and therefore there will be no feedback to research subjects, therefore these studies involve minimal risk to individuals and no physical or mental interventions, therefore, specific informed consent is not necessary and a broad consent is ethically justified [5,10,13]. Furthermore, based on the principle of respect for autonomy when providing broad informed consent the research subjects have autonomously delegated their consent to an ethical commitee which approves the research studies.

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