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OPEN PEER COMMENTARIES

The Fifth Face of Fair Subject Selection: Population Grouping

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The article by MacKay and Saylor (2020) claims that the principle of fair subject selection yields conflicting imperatives (e.g. in the case of pregnant women) and should be understood as "a bundle of four distinct sub-principles" (i.e. fair inclusion, burden sharing, opportunity, distribution of third-party risks), each having conflicting normative recommendations (MacKay and Saylor 2020). The authors also offer guidance as to how we should navigate between sub-principles that may conflict with each other. The problem is a crucial one since fair subject selection is one of the principles regulating clinical research that produces generalizable knowledge with the potential of improving people's health. Therefore, there may be cases where the way in which participants are selected directly influences the generalizability (or its lack) of the clinically relevant knowledge and its value (if any) to different groups. In my commentary article, written from the philosophical perspective, I notice a number of interrelated problems which I believe have not been discussed thoroughly in the target article: (1) the precise way in which health care priority setting should influence the content of health research priority setting and fair inclusion principles; (2) the distinction between group and individual benefits and burdens from clinical research; (3) the reference class problem in medical research.

The first problem stems from the authors' claim that "The precise content of fair inclusion will depend on answers to questions in the realm of health research priority setting." They add that sponsors of research ought to finance research that "fairly benefits

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people." If I understand this idea correctly, this is a compelling claim: the authors suggest that the rules of clinical research are a part of more general distributive principles for health care. But what are these last principles? Unfortunately, the authors neither provide, nor refer to, any theoretical framework of priority setting in healthcare, referring only to a very comprehensive legal document published in 1993 (the National Institutes of Health Revitalization Act) that requires the inclusion and sufficient representation of women and members of minority groups in clinical research. They also briefly mention three relatively marginal issues in this context: compensatory justice in research (mentioned in a footnote no. 3), the special duties of different types of founders, and the inclusiveness of research portfolios (rather than individual trials).

The lack of reference to any theoretical framework of priority setting in healthcare in general is a serious omission because the central claim of the paper is that clinical research fulfills the principle of fairness as far as it produces generalizable knowledge that "fairly benefits people." Thus one could expect that the authors explain their views on "fairness," which is a controversial subject in the health care contexts (Daniels and Sabin 2002). Moreover, the paper does not clarify how exactly we should understand "benefits" or "harms" (related to healthcare). They are value-loaded and theory-loaded terms, and philosophers and health care specialists have debated their precise content. Their meaning also depends on the level of individuation because benefits or harms may concern groups or individuals (see below). Since the paper accepts the very strong interconnection between fairness of research and fairness of health care, they must assume that different normative views on healthcare justice will imply different views of what is the precise content of the principles of fair research inclusion. If one accepts, for example, the Dworkinian approach to luck egalitarianism (e.g. inequalities are just "when they arise either from chosen risks or from risks against which agents would not have insured") then they will accept different principles of the selection of research participants than one who accepts the Cohenian approach (inequalities are just to "the extent that they eventuate from actual choices, including actual choices to take risks") (Hyams 2017). Let me use the example from the paper: the strength of reasons for the inclusion of "complex patients" in research depends on how exactly their situation arose. It also depends on the more general question about fairness: how much priority we should give to the most seriously ill patients; and where should we put these "complex patients" on this scale of priority.

Moreover, the next problem of how to delineate "minority groups" and how to understand the "sufficient representation" of a group in a clinical trial is also far from obvious. This leads us to the second issue, which stems from a surprising claim that "clinical research is a social practice from which all members of society benefit" (see also: "knowledge that fairly benefits all members of society"). It is surprising because the authors do not notice that many social practices may benefit (or harm) one group or another without benefiting (or harming) all members of these groups. This problem has been discussed in health care justice literature, with some authors (such as Daniel Hausman) opposed to defining inequalities in health across individuals, while others (like Kasper Lippert-Rasmussen) arguing that we should define health inequality across individuals (see their papers in Eyal et al. 2013). Again, let me demonstrate this by means of a very simple example: one could argue that affirmative action as a tool to promote racial diversity at universities benefits the group of African-Americans in the US (as a group). But this does not imply that it benefits "all members" of this group, e.g. it would be highly surprising that this policy would (directly) benefit President Obama's daughters.

The paper also mentions many different "groups" (women; pregnant women; racial minorities; populations that are not of European ancestry; the elderly; complex patients; children; people with limited education; people with language barriers; people with cognitive disabilities, among others), without noticing that the very process of grouping individuals are based on completely different biological or social features in these cases. Usually, people find some ways of categorizing people for research (e.g. being a pregnant woman) as more relevant in terms of inclusion in research than others (e.g. being a woman taller than 5 ft 8in). Obviously, it is not the case that the difference between these two groups is based on only some biological features which make pregnancy scientifically more precise (since defining women taller than 5 ft 8in is as well precise scientifically as "being pregnant"). Instead, a reason for this is our value judgment that it is much more likely that a pregnant woman is discriminated in clinical research qua being a pregnant woman than a tall woman for just being tall. We treat some biological features as more important than others because we suspect that they were reasons why some groups may have been previously excluded from research (or are still now). What is

more, we find that the group of pregnant women is much more important to the structure of social interactions than the group of tall women (on social salience see: Lippert-Rasmussen 2007). This is so even we learn that members of this second group (just because they are tall) may also suffer from specific illnesses (e.g. high women are twice as likely to fracture their hips as are women who are just 5 ft 2in, see: Hemenway, Feskanich, and Colditz 1995).

Additionally, in some cases, the authors suggest we should care about groups that cannot be categorized by means of any biologically relevant factor. For example, the authors do not explain how they understand the concept of "race", although they suggest that members of some populations defined by race do not benefit equally from research. But it is increasingly common to claim that human races do not exist in any meaningful biological sense, that is, there are no scientifically relevant physiological, genetic or biochemical natural differences between persons of different skin color (Perez-Rodriguez and de la Fuente 2017; cf. Malinowska and Żuradzki 2017). This absence of any relevant biological factor is even more vivid in the case of categorizing "people with limited education." And the authors seem not to recognize that risk stratification for health goals (in particular when based on social causation, as in the case of "limited education") may be harmful in the very similar way as racial profiling in law enforcement (Braithwaite, Stevens, and Caplan 2016).

Finally, any individual can be correctly classified as belonging to a number of groups that determine different probabilities of their possession of a specific trait. The fairness of inclusion in the research of a higher-educated, African American, pregnant female, aged 30 and living in Boston depends on which characteristic a decision-maker chooses to focus on, e.g. "pregnant," "higher-educated," "living in Boston," "African American," etc. Even calling upon the best available data regarding causal relevance might not be enough to fix a single class of reference for an individual (Hájek 2007). Therefore, we should distinguish an additional sub-principle of the "fair categorizing grouping research participants." However, this idea generates many problems which are well-known in the philosophy of science. First, even if we would like to treat all individual patients using fine-grained subgroup analyses, "most subgroup difference claims are spurious" (Djulbegovic and Ioannidis 2019). Why is this so? Because the epistemology of randomized controlled trials (RCTs) is such that the larger sample we have, the better evidence we get, so it is generally more useful to use larger samples than smaller ones from restricted groups. Second, there is a problem of the external validity of research on a particular group, in particular if it is small: how can we establish any conclusions that could also be true of a larger population? (Fuller 2019).

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