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***Nature Biotechnology* replies:**

Expert advice from pathologists is sought on a case-by-case basis, particularly when phenotypic data from human tissues and/or genetically engineered mice is central to a paper's conclusions. We welcome the availability of this new resource for identifying relevant expertise.

Bypassing consent for research on biological material

To the Editor:

A thought-provoking correspondence in last September's issue by Gert Helgesson and coworkers[1] argues that previously collected identifiable biological material may be used for research without consent. In particular, these authors recommend that "when the study is not particularly sensitive, and on the condition that (i) strict coding procedures are maintained, (ii) secrecy laws apply to any handling of sensitive information and (iii) vital research interests are at stake …that genetic analyses of identifiable samples should be permitted without (new) consent." Their claim that this is in accordance with the *Convention on Human Rights and Biomedicine* and the Council of Europe's *Recommendation on Research on Biological Materials of Human Origin* has already been refuted in these pages[2]. I would argue, although it is highly questionable whether their recommendations apply to any real world research, if the principles they outline were ever generally accepted, they could become detrimental to the public's trust in the scientific enterprise.

The intention to minimize risks to the individual research subjects while ensuring optimal scientific value of research is highly praiseworthy. Although it is clear that the Helgesson group's recommendations ensure the latter, it is far from obvious that they maintain the former. The precondition that research "is not particularly sensitive" is so elusive it is meaningless. What is "not particularly sensitive"? And who is to decide? According to their ethical framework, this decision is left to "the researchers themselves and an ethical review board (ERB)". If it can be guaranteed that no harm can result from the research, it is easy to subscribe to their conclusion, but this bypasses the real problem: How can we know that there is no harm? The sensitivity of biological material will, among many other things, depend on future research results. Thus, to foresee sensitivity of research is at least as difficult as to predict future research results. The reason why broad consent, blanket consent or suspended consent has been suggested in biobank research is because it is extremely hard to predict future research. If we could predict relevant future research on a biological sample (or assess the sensitivity), there would be no reason to refrain from consent because we could easily use express informed consent. Moreover, the suggested framework leaves out those who are the only ones able to assess sensitivity (that is, the individual research subjects).

Thus, their framework is based on an odd kind of exceptionalism: biobank research is exceptionally harmless, which justifies that standard ethical requirement (that is, consent) can be omitted. This misses the nature and point of biobank research. The first and second conditions for suspending consent are on information safety, and miss the characteristics of biobank research where the most substantial risk is related to information. Although the results from biobank research may benefit the individual, a patient group or society at large, the informational risks relate to the research participants or their relatives. How are coding procedures and secrecy law applications to protect against future hazards?

The Swedish authors must be aware that, in the criminal case where the Swedish Minister for Foreign Affairs, Anna Lindh, was killed, the investigators used the biological material from a diagnostic biobank (PKU) to identify the killer (even though this was not strictly necessary for the investigation). There is no reason to believe that they would not have done so if it was a large-scale research biobank. Furthermore, the informational risk appears to increase with the development of other kinds of (nonmedical) biobanks, such as DNA-registers for criminals and suspects.

How can Helgesson and his coworkers present an ethical framework that is contrary to traditional research ethics and turns (well refuted) exceptionalism on its head? The answer is easy: it lies in their conception of autonomy. Their framework is built on the assumption that autonomy is a person's right to participate in research, and any restriction of this right has to be justified. Accordingly, informed consent is a restraint of people's autonomy, whereas broad and blanket consent, which comprises fewer restrictions, implies greater respect for autonomy[3]. In this, they are subject to the fallacy of confusing autonomy and liberty.

Thus, either the criterion for information safety does not address the core

characteristics of biobank research, where information is the risk, or it is overly strict, and does not promote biobank research, as it intends to. Therefore, Helgesson and coworkers do not only fall out with international conventions in research ethics, they fail to address pressing problems in biobank research.

Perhaps the most dangerous aspect of their framework lies in its potentially unintended consequences. If one applies a lax interpretation of "not particularly sensitive" research, any study can be justified as long as it serves research interests. Their lax interpretation of consent to "future cancer research" as being consent to any kind of future research endorses this. For the above reasons, instead of minimizing risk to research participants, the framework they suggest actually enhances the risk by not addressing basic challenges with biobank research.

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Gert Helgesson replies:

There is no risk of direct physical harm to research subjects once biobank samples have been collected. This does not make biobank research "exceptionally harmless," as Hofmann states; it simply makes it sufficiently different from much other research to motivate specific considerations[1,2]. As Hofmann points out, and as my colleagues and I stressed in our previous correspondence, a core characteristic of biobank research is that it is the inappropriate distribution of information that has a potential to harm research subjects[1]. This is why we stressed the importance of strict routines for coding, storage and use of biobank samples and related data as the first central feature of our ethical framework for research on previously collected samples.

The second central feature is that all biobank research should be reviewed by ethical review boards (ERBs). ERBs should decide what studies to approve and on what conditions. What studies are "particularly sensitive" should also be judged by ERBs, considering existing views in society. There is nothing lax about this. Note that in our framework sensitiveness concerns attitudes toward different kinds of research, not probabilities of future harm.

Abidance by strict routines for coding, storage and use and proper ethical review by ERBs protect research subjects against harm. Hofmann seems to require more, namely a guarantee against harm. There can be no such guarantee, especially not against misuses, unless all biobank research is stopped. Such an approach would indeed be contrary to traditional research ethics. For instance, the Declaration of Helsinki clearly underlines the importance of research[3]. Some risk to research subjects must be accepted, but it should be reduced to a minimum.

Our ethical framework balances relevant interests and values at stake by (i) respecting previous consent or dissent and (ii) allowing research to proceed without consent when no previous consent or dissent exists, when the study is not particularly sensitive, strict coding and storage procedures are maintained, secrecy laws apply and vital research interests are at stake. The main disadvantage of our framework is that it might not respect some individuals' (not yet communicated) preference not to have their samples included in research—opting out must therefore be a feasible option. The main advantage is that it promotes important research to the potential benefit of us all, while keeping risk of harm to a minimum.

As to Hofmann's insistence that our views on autonomy and informed consent seriously deviate from traditional research ethics, they do not. Recall that informed consent is defended as a means to respect autonomy and personal integrity[4]. Our framework includes important precautions considering these interests. We do argue, however, that strong research interests sometimes should have precedence over requirements for informed consent.

How serious is it that some people might be included in biobank research who would have said no if they had been informed and asked—if personal data are well protected, if they are not included against the owner's known will and if the study is not particularly sensitive? It seems fair to say that this is not very serious. It would still be important, out of respect for autonomy, to be able to exclude those who do not want to participate, but applying routines for informed consent might tip the overall ethical balance to the negative if they cause dropouts substantially reducing