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Broad Consent for Head and Neck Cancer Research

Thomas J. Ow, MD, MS¹, Kayte Spector-Bagdady, JD, MBE², Ethan Cowan, MD, MS, FACEP³, Andrew G. Shuman, MD⁴

¹Department of Otorhinolaryngology-Head and Neck Surgery, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY

²Center for Bioethics and Social Sciences in Medicine, and the Department of Obstetrics and Gynecology; University of Michigan Medical School, Ann Arbor, MI, USA

³Department of Emergency Medicine, Icahn School of Medicine at Mount Sinai

⁴Department of Otolaryngology – Head and Neck Surgery, and Center for Bioethics and Social Sciences in Medicine; University of Michigan Medical School, Ann Arbor, MI, USA

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Case

A 56-year-old gentleman has been diagnosed recently with locoregionally advanced left tonsil cancer. The patient has been offered participation in a clinical trial examining a new drug given in the neoadjuvant setting. The primary endpoint of the study is overall survival, but exploratory objectives will examine biomarkers that are potentially related to response to the new drug.

As part of the consent process for the study, subjects are asked to undergo tumor biopsy and blood samples before and after neoadjuvant therapy. They are also asked to provide a broad consent for genetic and molecular studies—specifically, the consent states that their tissues will be banked and will potentially remain available for genetic and/or molecular studies associated with head and neck cancer, but unrelated to the aims of the clinical trial.

Is this ethically appropriate?

Point: Yes, a broad consent allowing future studies on procured biospecimens is ethically appropriate.

Authors: Thomas J. Ow, MD, MS; Ethan Cowan, MD, MS, FACEP

CORRESPONDING AUTHOR: Andrew G. Shuman, MD, University of Michigan Health System, Department of Otolaryngology - Head & Neck Surgery, 1904 Taubman Center, 1500 E Medical Center Drive, Ann Arbor, MI 48109, UNITED STATES, 7348346930, FAX: 734-647-9691, andrewgshuman@gmail.com.

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The term “broad consent” can be used to describe a type of consent that allows investigators to use biospecimens from recruited subjects for a range of research endeavors, which can be narrow in scope or very broad. This differs from a specific informed consent, which only allows use of biospecimens for specific research, and differs from a “blanket consent,” where there are no limitations placed on potential uses. When subjects provide broad consent, there are constraints to the agreed upon use of their specimens. It should also be noted that there are certain pre-conditions that are often assumed when a broad consent is employed. These are listed in the guidelines for health-related research endorsed by The Council for International Organizations of Medical Sciences (CIOMS).¹ It is assumed that (1) data can be handled safely, (2) the donors can withdraw their consent for future studies and have their banked specimens discarded [which becomes complicated with shared specimens in biobanks], and (3) there will be review of future unspecified studies by an internal review board (IRB) or similar governance structure.

Broad consent can be considered ethical for several reasons. First, it can be argued that a broad consent does not violate the three basic ethical principles established in the Belmont Report.² The principle of “respect for persons” is perhaps the most difficult to justify, which states that a subject’s autonomy (decision-making) should be acknowledged and protected. Subjects should have the opportunity to deliberate about a research study, and decide to participate after weighing the risks and benefits of participating.³ One can argue that without knowledge of future studies, a recruited subject providing broad consent relinquishes the ability to consent to those studies, thus his or her autonomy is not upheld. However, broad consent does give a subject the right to choose to participate in the study (acknowledges autonomy) and provides the confines of potential research endeavors. In essence, a subject who agrees to a broad consent waives his or her liberty to choose what studies their specimens are used for, but he or she maintains autonomy because the choice to participate is upheld.

The second basic principle of “beneficence” obligates investigators to maximize potential benefits while minimizing potential harms. A broad consent places responsibility on the investigators and institutional research regulatory bodies to judge whether future studies might be harmful to recruited subjects. Additionally, one might argue that broad consent allows investigators to maximize the potential benefit of a research subject’s valuable contribution. In the current era of cancer ‘omics, big data, and precision medicine, broad consent allows the necessary flexibility to ensure that cancer research can keep pace with rapid scientific advances. One can argue that a broad consent enables investigators to maximize the benefits gleaned from research by expanding the breadth of information that can be potentially gained from the data and tissues obtained.

Finally, broad consent does not violate the third principle of “justice.” As long as subjects are recruited fairly, and future studies are not in some way designed to burden or benefit a specific group of people, a broad consent does not create injustice. So, it would seem broad consent does not violate core ethical standards in human subject research.

One can also argue that alternatives to broad consent are inferior. One alternative to broad consent is to forbid any deviation from specific research to which the subject consents. This

would necessitate re-contacting a subject in order to acquire a new consent for every secondary research study. This option is obviously cumbersome, requires increased resources and time, and in many cases would be impossible since subjects may be lost to follow-up. Another alternative that has been proposed is dynamic consent.⁴ This approach is a new concept, that uses modern information technology to allow investigators and subjects to engage in an active exchange while research is progressing. This approach allows the subject to continually assess ongoing research and therefore maintain an active decision to continue to participate. Though this approach has some intriguing benefits, establishing the resources and engagement by both the subject and the investigator remains challenging. Dynamic consent has not been easily adopted.

The Notice of Proposed Rule Making (NPRM)⁵ released by the Department of Health and Human Services (HHS) in 2015 proposed several changes to the longstanding “Common Rule.”² The proposed changes recommended several restrictions to the use of biospecimens without obtaining informed consent for secondary studies. After the NPRM was opened to public comment, the responses against increased regulations for the secondary use of unidentified biospecimens were overwhelming; patients, the research community, and advisory and related groups were almost entirely opposed.⁶ An update to the Federal Policy for the Protection of Human Subjects (ie, the “Common Rule”) was released in January 2017.⁷ The new policy did not adopt the changes proposed in the NPRM mandating informed consent for secondary studies on human biospecimens. The update included options responsive to the NPRM and ensuing commentary to permit researchers to employ broad consent in order to promote the use of human biospecimens for future studies. Thus, it would seem that a broad consent format to allow ongoing research on human biospecimens is in line with the moral attitudes and desires of investigators and research subjects and has been supported by recent updates to federal regulations and policies. It seems, therefore, that broad consent as implemented in the case presented above is ethically appropriate.

Counterpoint: *While broad consent may be ethically appropriate, it is not the result of an equal balance of the principles of research ethics.*

Authors: Kayte Spector-Bagdady, JD MBE; Andrew G. Shuman, MD

We disagree that broad consent is an accurate reflection of the majority of participants’ autonomous preference or that the recent notice and comment period of the human subjects research regulations provided the opportunity for solidification of the “moral attitudes and desires” of the average research participant. While broad consent is ethically appropriate in many cases, we rest this analysis not on the equal balancing of all three of the principles of research ethics as our colleagues did, but the public beneficence and justice implications of enabling a larger breadth of future research from a more diverse patient population.

A major component of the legal framework governing human subjects research is whether a biospecimen is innately *identifiable* (ie, if there is a “reasonable basis” to believe that the information can be used to identify an individual). The federal government recently considered expanding the definition of human subjects research—and thus the scope of regulatory protections including IRB review and informed consent—from research with

identifiable biospecimens to *all* biospecimens (even if stripped of identifiers). Regulators in the final rule argued that to require consent for all biospecimen research was “consistent with the majority of the public’s wishes, which reflect legitimate autonomy interests.”⁷ But, the majority of commentators to the proposal disagreed with the assessment that autonomy interests (of the individuals from whom the biospecimens are derived) were the most important consideration. They argued that the *justice and public beneficence* implications of building scientific resources, reducing biases in biobank contributions, and helping future patients were more compelling.

In addition, the views of a majority of commentators are not necessarily representative of any given stakeholder. Those who comment on Federal Register notices do not represent the average research participant. And, in fact, when one analyzes comments on the NPRM from the public (as opposed to researchers and patient advocates), support for the proposal to require consent for all biospecimen research was divided.⁶

Second, empiric research of actual participants has found that many *do* expect informed consent for research—sometimes even that which is deidentified.⁸ For example in one study, while the majority (68%) of respondents stated they were willing to donate their specimens and information to a biobank for “any research study that it allows,” when given several actual controversial research protocols, the majority (70%) became unwilling to donate to at least one.⁹ Research has also demonstrated that it matters to participants with whom their specimens and data are shared. People are particularly suspicious of commercial uses; less than a quarter of participants were comfortable with a research university using biospecimens to generate income.¹⁰

And even if we can draft a broad consent form that appropriately conveys all of the information that we know that patients want to receive, many of these patients are facing life-altering diagnoses and treatment (as is clear from our case study). Providing informed consent for clinical care concurrently with research consent may strain even the most invested and educated patient. This may serve to discount research related risks in comparison to more pressing clinical concerns. The case study takes this further by requesting broad consent for biologic correlatives to a clinical research protocol. Thus, the patient is being asked to consent to three distinct interventions at the same time: his clinical treatment, a prospective research trial, and broad consent. Even the most astute patient may struggle to comprehend this all.

Broad consent was introduced into the new research regulations as a compromise: regulators still require informed consent to respect the autonomy interests of participants, but it also allows researchers the freedom to conduct any number of secondary protocols to advance the science as they see fit. We are not contending that broad consent is not an appropriate—or even the most appropriate—answer to the complex reconciliation of the autonomy of the individual participant and justice and beneficence interests of society and future patients. But, unlike our colleagues, we disagree that broad consent satisfies them uniformly. We agree that on balance, justice and public beneficence arguments in favor of facilitating research are more compelling, and that broad consent is an adequate compromise at this

time. But while it may be the *equitable* resolution of these principles, we disagree it is the *equal* one.

Research with human biospecimens has made it through the most recent debate largely unchanged: we must still secure some type of informed consent for research with identified specimens, and none for those without.¹¹ But neither legal nor ethical machinations have ended, and regulators reserved the right to consider all biospecimens identifiable in the future.¹² If this happens, honing our informed consent approach becomes even more critical as it will be the only way specimens enter the system. Trust will be our ultimate gatekeeper, and it is the key indicator of which patients choose to donate to research.¹³

It is important to be honest and pragmatic about both our research use of biospecimens and normative rationales for it. Certainly we should give patients notice, adequate information about general types of trials and process restrictions, and the opportunity to provide broad consent to enter their identifiable specimens into the research enterprise. But we should not pretend that the purpose of broad consent is robust fulfilment of participant autonomy interests. Empirical data has demonstrated it is not. Broad consent is a compromise between our current and our future patients—and our finger is justly on the scale for the future.

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