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V. FRAMEWORK FOR ANALYSIS AND RECOMMENDATIONS

[to be completed after March discussion]

1 There are three basic premises underlying the framework of analysis used by the Commission in
2 the development of its recommendations:

- 3 • First, research use of human biological materials is essential to the advancement of science
4 and human health. Therefore, it is crucial that there be permissible conditions under which
5 such materials can be used.

- 6 • Second, the rapidly advancing Human Genome Project and the application of a molecular-
7 based approach to understanding human disease have raised the issues of autonomy and
8 medical privacy to a heightened level of public discourse. This discourse has relevancy to
9 all areas of medical research using human biological materials, not just genetic research.
10 An additional impetus is the interest by the public and private sector in the research use of
11 human biological materials.

- 12 • Third, there is disagreement within the scientific community about the nature of risks and
13 levels and types of protections needed to ensure that biological samples can be used in
14 research with minimal harms for those whose materials are used.

FRAMEWORK FOR ANALYSIS

16 The Commission relied extensively on a framework (see Figure 5-1) to organize its
17 assessment of the conditions under which research using human biological materials would be
18 permitted. This framework included five considerations, which are described in more detail
19 below: 1) whether the samples were already in storage or to be collected in the future; 2) the
20 conditions under which the samples were/are collected (e.g., clinical versus research setting); 3)
21 whether individuals who donate specimens can be identified by information linked to their
22 samples; 4) whether the research poses risks to individuals or communities; and 5) the types of
23 protections NBAC might consider recommending to protect against harms (specifically, coding
24 and encryption schemes, consent, Institutional Review Boards, community consultation).

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Samples Already in Storage versus Those to Be Collected in the Future

The issues concerning research use of biological samples already in storage are, in part, different than those that need to be considered when planning new and future collections. Thus, in devising policy recommendations NBAC found it useful to consider independently those samples already collected and stored versus those to be collected in the future, that is, after the release and presumed adoption of NBAC's recommendations.

In addition, within the category of samples already in storage, the Commission did not find it meaningful to distinguish between those stored as a result of a clinical procedure from those stored as a result of a research protocol for which there was no therapeutic intent or clinical association.

The primary reasons for considering all samples previously collected as distinct from those to be collected in the future is based, in part, on two primary considerations: 1) concern for the adequacy of the consent obtained for the research use of already stored samples; and 2) interpretation of the existing regulations protecting human research subjects (45 CFR Part 46).

The overwhelming majority of samples were collected from patients following diagnostic or therapeutic procedures (e.g., blood tests, biopsies, surgery). As part of the surgical consent procedure, for example, individuals are likely to have signed a general consent agreeing to have their biological sample stored for future diagnostic, educational, or research purposes.

Discussion at the mini-hearings convened by NBAC revealed that most people whose biological materials were obtained through clinical procedures have no recollection of consent to research use of their sample. Other studies of consent and participation in clinical trials have shown this phenomenon to be the norm, despite the appearance of a signature on the consent form. Individuals undergoing biopsy or surgery are likely to be distressed or anxious and therefore not as likely to understand or fully consider to what they are consenting. In addition, individuals might fear that failure to consent to research use of their tissue could in some way jeopardize their clinical care.

In comparison, in research studies that are designed to collect biological samples from individuals, the investigators generally will have the opportunity to communicate with potential

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1 subjects in advance and involve them as donors by obtaining informed consent. Consent is likely
2 to have been more robust for samples collected under these conditions than under those of clinical
3 care. *Therefore, for samples to be obtained in the future, a distinction is made between those*
4 *collected in research versus those collected during clinical care. [Note: this to be expanded*
5 *when NBAC decides on the levels of consent required.]*

6 In considering consent issues for samples already stored, the Commission chose to err on
7 the side of caution, that is to presume the worst case scenario, that there was no consent for
8 research use of the extant samples. If consent was given it is assumed to have been minimal.

9 There are two consequences of this presumption, one moral and one practical. The
10 “moral” consequence is that the level of protection provided any given individual might be more
11 or less than is actually necessary (i.e., they actually provided full informed consent or they did not
12 consent at all). The practical consequence is that investigators are not required to go back to
13 determine the nature of the consent, that is, whether there was decisional impairment, whether in
14 fact there was a general consent, or whether there was no consent.

15 There is one notable exception to this standard. If someone explicitly refused to allow
16 research use of his or her biological materials, then that objection must be honored.

17 The second consideration, the applicability of 45 CFR Part 46 to research use of human
18 biological materials, was an additional factor to assess in making the distinction between tissues
19 already in storage versus those to be collected in the future. A more complete legal analysis of
20 this is provided in chapter 4.

21 **Research Using Samples from Deceased Individuals**

22 Under the federal regulations, people are subjects only during their lifetime. Research
23 involving tissues from individuals who are deceased at the time of the research is not subject to
24 the requirement of HHS regulations, regardless of whether or not prior informed consent was
25 obtained. Such research may, however, be subject to the requirements of applicable State law.
26 Of course, there may be ethical concerns regarding the use if such tissues beyond the scope of
27 current law or regulation. In addition, where research using samples from deceased individuals
28 involves identifiable private information about their living relatives, those relatives may themselves

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1 be “human subjects” under the HHS regulations and must be afforded all required protections.

2 Certain types of genetic research could pose risks for living relatives of the deceased.

3 *[Note: There should be some comment on research involving samples from the dead, including a*
4 *discussion of the adequacy and interpretation of the definition of “human subject” as defined in*
5 *the regulations at 46.102].*

6 **Can the Donor be Identified?**

7 Because the potential for benefit or harm is greater when the sample is directly linked to
8 the donor, this consideration was central to the Commission in its deliberations and in
9 development of guidance concerning protections.

10 As discussed in chapter 4, the language used to describe the identifiability of samples has
11 varied among organizations, which has resulted in some confusion. In a simple way, samples fall
12 into two categories: 1) those that are identifiable (more or less) which means they can be
13 connected, or linked, to the person from whom it came; and 2) those samples that are not
14 identifiable at all (which are anonymous). The reason one refers to the former as "more or less"
15 identifiable, is because the information content of the sample varies, from a very few data points
16 that, nevertheless could allow you to identify the sample with the person, to a sample that
17 contained an exhaustive number of data points allowing very easy identification with the person
18 from whom the sample was obtained.

19 Truly unidentifiable samples have no linking data and therefore no one (including the
20 pathologist) has the ability to track down the identity of the source of the specimen. As
21 mentioned previously, research using this type of sample, if already collected, is exempt from IRB
22 review and the investigator is not required to obtain informed consent. When research uses
23 unidentifiable samples, contact is impossible. NBAC chose to label this category of specimens as
24 “unidentifiable.”

25 Within the “identifiable” category are three subcategories: 1) *coded but untraceable*
26 *samples* include samples that have been stripped of all identifier before being turned over to the
27 investigator; 2) *coded but traceable samples* are encrypted so that the investigator cannot identify

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1 the donor but the entity holding the sample can, e.g., the pathologist, DNA bank); and 3)
2 *identified samples* are directly linked, such that a subject can be identified by the investigator by
3 name, patient number, or clear pedigree location. [Note: see definitions on figure 5-1 for
4 *agreement.*]

5 Previous guidelines and reports (see chapter 4) have categorized samples by the conditions
6 under which they are stored (with or without identifiers), although current federal regulations
7 permit investigators to take such samples without seeking consent, make them anonymous by
8 removing identifiers, and then use them in research.

9 NBAC chose to consider samples according to a different criterion as well, that is, how
10 the researcher will use the samples. In essence, if there is no way for the investigator to go back
11 and identify the donor based on information linked to the sample, then the biological material is
12 being used in an unidentifiable manner.

13 **Use of Unidentifiable and Coded, but Untraceable Samples**

14 If the sample is already stored, and there is no way for the researcher to identify the source
15 of the sample, then NBAC concurs with the existing regulations, which state that there is no need
16 to obtain consent. However, NBAC differs with the regulations in that it recommends that the
17 protocol be submitted to an IRB for administrative review, to ascertain that it indeed belongs in
18 this category, that individual privacy is appropriately protected, and there is no implication of a
19 particular group or community (to be discussed later)

20 The basis of this recommendation is NBAC's belief that it is ethically acceptable to use
21 unidentifiable or coded, but untraceable samples without the source's consent because there is no
22 possibility for stigmatization or harm once the identifiers are gone. In addition, going back to seek
23 consent would be costly and time consuming. The Commission also considered input it received
24 during its mini-hearings, in which most people emphasized that they did not view their donated
25 biological material as something that belonged to them, rather it is a gift to be used by the
26 scientific community subject to the standard review for quality and ethical acceptability.

27 The tenet that anonymizing samples reduces or removes harms depends on a secure, non-
28 conflicted guardian, whether it be an encryption system, a pathologist, or an oversight board.

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1 *[The attributes of this “wall” or “barrier” have to be discussed and defined.]*

2 Some have argued, however, that using coded, but untraceable samples without consent is
3 problematic because researchers had the opportunity to seek consent but did not exercise it.
4 Undertaking research using identifiable samples without the consent of the sources can wrong
5 them even if no direct harms occur. For example, the research might be objectionable to the
6 source. *[This issue is raised in the paper by Buchanan and should be discussed. In addition,*
7 *the impracticality of seeking consent has been discussed but not defined].*

8
9 NBAC recommends that, in the future, consent always be obtained for use of samples. In
10 some cases, the consent can be general because it is likely that intended uses cannot be
11 anticipated. In cases where the nature of the research is known full consent should be obtained. A
12 donor might want to restrict the types of research that can be done with his or her sample (e.g.,
13 research pertaining to behavior, conduct, socioeconomic or religious status). Or an individual
14 might want to contribute only to research relevant to his or her own medical condition. These
15 contingencies have raised discussions about the appropriateness and feasibility of “tiered” or
16 “layered” consent. *[The Commission must resolve differences in the consent it is recommending*
17 *for future samples, see figure 5-1. There also must be more discussion regarding the nature of*
18 *the consent when the specimen is obtained in a clinical care versus a research setting, because of*
19 *the need to address therapeutic expectations.]*

20 **Use of Coded, but Traceable Samples**

21
22 The ease with which the investigator or another third party can identify the person from
23 whom the sample was obtained, the greater the possibility of harm or benefit.

24 *[Questions to be answered: How will coded but traceable samples differ from*
25 *unidentified, coded but untraceable, and identified? See figure 5-1]*

26 **Use of Samples that are Identified**

27 NBAC concludes that for research conducted in which the sample is linked to an
28 individual (that is, their identity is not concealed from the researcher), regardless of whether the
29 sample is already stored or yet to be collected, and regardless of whether it is collected initially for

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1 clinical or research purposes, there must be full consent (in the usual sense) in advance of that
2 research. In addition, there must be review by an Institutional Review Board, as specified in 45
3 CFR 46.

4 The nature of the consent required would depend on whether the specimen is being
5 obtained for a specific protocol. If there is no known protocol then the consent must
6 acknowledge the ambiguity. As with research conducted in an anonymized manner on
7 prospectively obtained samples the nature of the consent might be tiered, or restricted if there is a
8 specific protocol for which consent is sought. NBAC wants to avoid requiring that an
9 investigator go back and re-consent for every procedure, particularly if there are a related series
10 of protocols. In future collection of biological materials, an individual retains the right to opt out
11 of any study at any time. [*Note: This is also true for individuals who are identified with*
12 *previously collected samples, but not true for retrospective, anonymized samples, correct?*]

13 Because IRB review is required for this research use of tissue, the burden of proof is
14 placed on the investigator to show that consent remains appropriate and adequate for
15 subsequent studies. If consent was not general, and the nature of subsequent studies differs from
16 those for which consent was originally obtained, then there are two courses of action. First, if the
17 samples are being used in a coded manner, and consent was not general, the investigator must
18 submit the new protocol to an IRB for review. If the samples are identifiable, then the
19 investigator must contact individuals for re-consent. If the investigator is unsure whether the new
20 protocol under consideration has a similar mix of benefits and burdens as was contemplated by the
21 subject when they signed the original consent, then the investigator should err on the side of
22 caution and submit the protocol to an IRB for review.

23 **“WALKING BACK”**

24 For samples that are identified or coded but traceable, there are several possible reasons
25 for an investigator wanting to go back to the source either to gather additional clinical or
26 phenotypic information or to provide potentially therapeutic information.

27 Increasingly genetic research requires that there be sufficient phenotypic information
28 accompanying the genotypic information extractable from the biological material (see chapter 2).
29 Thus, investigators stratify populations and then intensively investigate a smaller subset. As

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1 smaller subpopulations of interest are identified, clinical investigators are likely to need more
2 clinical information about the population being studied. This will require some mechanism for
3 information retrieval. With coded but traceable samples, the “trustee” of the sample has the
4 ability to gather more data for the investigator. With identified samples, the investigator can go
5 back directly and request additional information. The possibility that the investigator, or an agent
6 of the investigator, will contact the source (or the source’s physician) for additional information
7 should be discussed in the consent process. *[Note: are there differences here between stored
8 and to be collected samples?]*

9 There might also be circumstances for which an investigator is compelled to provide
10 information to the source, whether directly or indirectly. An example is an investigator who
11 discovers new information that leads to a better diagnosis of a clinical condition, an effect of a
12 previously administered therapy, or a misdiagnosis that might have important implications for the
13 health of the source. Another example is the discovery of an infectious agent with public health
14 implications. In both of these examples, there have been compelling arguments made for the duty
15 of the investigator to contact the source. In cases where the implications of a finding are not as
16 clear, that is, findings are preliminary or for which there is no effective intervention available,
17 contact is less desirable because of the possibility that people will act on the findings in a way that
18 may result in harm. *[Note: The Commission has to discuss these issues both in ethical and legal
19 terms, such as the duty to inform or what has been called “look-back liability.”]*

20 The likelihood that a donor will be contacted with information relevant to his or her own
21 medical status is small but should be discussed in the consent process. Participants must
22 understand that they are agreeing to participate in research for which there may be no direct
23 benefit.

24 **COMMUNITY CONSULTATION**

25 NBAC is considering a community consultation model for research conducted in such a
26 manner that communities are identified. While the concept of community is by no means unique
27 to genetic research, genetics has a long history of studying kindreds with unique or distinctive
28 characteristics. Techniques such as linkage analysis, linkage disequilibrium, DNA pooling, and
29 homozygosity mapping can be used to identify genes for disease susceptibility. Recent studies
30 have identified genes for breast cancer, prostate cancer and cystic fibrosis that vary by

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1 subpopulation. Subpopulations of interest to investigators are often ethnically or geographically
2 identifiable and may be the target of screening or research programs for cost-effective reasons
3 (the likelihood of positive findings is greater). The risks of being identified by health status
4 include stigmatization and discrimination. Thus, even those who are not research subjects
5 themselves are subject to discrimination if research results reveal something about the community
6 to which they belong. Even for research conducted in an unidentifiable manner with respect to
7 the individual, there is a possibility that research results could result in identification of the
8 individual or the community to which he or she belongs.

9 Current federal regulations do not address the concept of community. Formal
10 consideration of collective risks is not standard practice.

- 11 • *NBAC must address the following issues concerning community:*
- 12 • *Define community (e.g., social, ethnic, racial, geographic, disease groups, and families).*
- 13 • *How do you identify the actual social units through which communities address issues*
14 *that affect its members?*
- 15 • *What are the implications for the community consultation model applied to stored versus*
16 *yet to be collected tissues?*
- 17 • *What should be the requirements or considerations for community consultation?*

18 **TYPES OF PROTECTIONS AND LEVELS OF RISK**

19 The Commission has discussed the various protections required depending on the status of
20 the research (retrospective v. prospective, identifiable v. unidentifiable, individual v. community).
21 The protections include IRB review, individual consent, and community consultation. Other
22 considerations include a national review body and a review board for the tissue or DNA bank.
23 There are gradations within each of these categories, such as administrative versus full IRB
24 review, and general versus full consent.

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1 **IRB Review**
2 need to discuss

3 **Consent Process**
4 need to discuss

5 **Other Review Mechanisms**
6 need to discuss

7 *It would be useful to have a fuller discussion about the risks or harms that might result*
8 *from various types of research and whether the risks serve as a useful measure by which to*
9 *recommend protections. This discussion will be aided by consideration of particular cases and*
10 *by receipt of the paper on ethical/moral issues. Having this discussion will allow NBAC to*
11 *arrive at principles it wishes to communicate to investigators and IRBs.*

12 **SAMPLE RECOMMENDATIONS**

- 13 ● For any study undertaken using human biological samples, the investigator should obtain,
14 at a minimum, administrative review by an IRB to determine the consent requirements.
- 15 ● NBAC concludes that for research conducted in which the sample is linked to an
16 individual (that is, their identity is not concealed from the researcher), regardless of
17 whether the sample is already stored or yet to be collected, and regardless of whether it is
18 collected initially for clinical or research purposes, there must be full consent (in the usual
19 sense) in advance of that research. In addition, there must be review by an Institutional
20 Review Board, as specified in 45 CFR 46.
- 21 ● In the future, consent should always be obtained for research use of samples. The consent
22 might vary from presumed, to general, to full, depending on the circumstances under
23 which the sample was collected, the predictability of the research use to which the samples
24 will be put, and the anticipated risks and benefits.
- 25 ● Any time a community might be implicated in research involving human biological
26 samples, and the source of the samples is identifiable, the investigator should seek

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1 community consultation regarding risks and potential benefits.

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**Figure 5-1: RECOMMENDED PROTECTIONS FOR INDIVIDUALS
(NO APPARENT COMMUNITY LINKAGE)**

[redlined text indicates areas in need of discussion]

		COLLECTION CIRCUMSTANCES		
IDENTIFIABILITY OF SAMPLE	Existing Samples Collected in Clinical Care or Research Studies	Samples Collected in the Future in Clinical Care	Samples Collected in the Future in Research Studies	
Unidentifiable sample	administrative review by IRB, consent not required	administrative review by IRB, <i>presumed consent with opt out or general consent required?</i>	administrative review by IRB, general consent required	
Coded but untraceable sample	administrative review by IRB, consent not required	administrative review by IRB, <i>presumed consent with opt out, or general consent required?</i>	administrative review by IRB, general consent required	
Coded but traceable sample	administrative review by IRB, consent might be required	administrative review by IRB, general consent required	<i>administrative or full review by IRB, general or full consent required?</i>	
Identified sample	full review by IRB, full consent required	full review by IRB, full consent required	full review by IRB, full consent required	

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DEFINITIONS

Unidentifiable sample means the samples were collected without identifiers and are impossible to link to their sources. There can be no flow of information in either direction.

Coded but untraceable samples are unidentified for research purposes but retain identifiers in the originating repository. There can be limited flow of additional medical or scientific information from the repository to the investigator (one-way).

Coded but traceable samples are unidentified for research purposes, but can be linked to their sources through the use of a code. There can be two-way flow of information, from the pathologist to the investigator and vice versa.

Identifiable samples are directly identified, such that a subject can be identified by the investigator by name, patient number, or clear pedigree location. There can be two-way flow of information.

Administrative review by the IRB means the IRB chair must determine whether the “identifiability” status of the sample has been correctly determined by the investigator.

Full review by the IRB means the entire committee must consider the protocol and vote on its acceptability.

Full consent means consent to objectives, benefits, and risks specific to the protocol or category of research studies.

General consent means consent to future, unspecified research uses of the sample. Benefits and risks are specified regarding future research use but not regarding any specific protocol.