

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 **Chapter 2**
2 **Collection, Storage and Use of Human Biological Materials**
3 **In The United States**
4

5 As part of its analysis, the National Bioethics Advisory Commission sought to understand and
6 describe the magnitude, diversity, and use of human biological material collections in the United
7 States. To date, there has been a paucity of information concerning acquisition, use, and storage
8 of such materials; there is no central database that captures information about stored samples. To
9 assist in its review, NBAC commissioned a study to assess the size and characteristics of the
10 existing archives of tissues.¹ A second study was prepared for NBAC which reviewed the
11 contribution of human biological materials to biomedical research.² This chapter will provide
12 information about several aspects of stored human biological materials. The first section,
13 “Collections of Human Biological Materials,” provides information about the number of
14 specimens of human biological material stored in the United States, and the places these material
15 are stored. The second section, “Sources of Human Biological Materials,” provides information
16 about who the sources of these biological materials are, why the specimens were originally
17 collected, what identifying information is kept with the specimens, and what type of information is
18 passed on to the researcher. The last section of this chapter, “Uses of Human Biological

¹ These data were collected by Elisa Eiseman, Ph.D., RAND’s Critical Technologies Institute, in response to a request by the NBAC Genetics Subcommittee. The report, *Stored Tissue Samples: An Inventory of Sources in the United States* (available under separate cover), is not meant to be a comprehensive inventory, however it does identify the major sources of stored tissue.

² See David Korn, “Contributions of the Human Tissue Archive to the Advancement of Medical Knowledge and the Public Health” (A report prepared for the National Bioethics Advisory Commission), January 1, 1998.

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 Materials,” describes the various purposes for which human biological materials have been used in
2 the past and may be used in the future.

3

4 **Part I: Collections of Human Biological Materials**

5

6 NBAC estimates that there are over 282 million specimens from more than 176.5 million
7 cases of stored human biological materials in the United States, now accumulating at a rate of
8 over 20 million samples per year.³ The size and detail of collections varies considerably, ranging
9 from formal, highly organized repositories to the informal storage of blood or tissue specimens in
10 a researcher's laboratory freezer. Archives of human biological materials range in size from less
11 than 200 to more than 92 million specimens.

12

13 Large collections include archived pathology samples taken during diagnostic and surgical
14 procedures, or at autopsy, and stored cards containing blood spots from newborn screening tests
15 (Guthrie cards). These samples are stored at military facilities, forensic and other DNA banks,⁴

³ This estimate attempts to count both the numbers of cases from which stored tissues are derived as well as the number of specimens generated from each case. For example, when a patient enters the hospital for a biopsy, the resulting tissue is accessioned in the pathology department as a single case. However, that single biopsy may generate several specimens including a number of slides, a paraffin block, and a frozen sample.

⁴ The term “DNA bank” refers to a facility that stores extracted DNA, transformed cell lines, frozen blood or tissue, or biological samples for future DNA analysis. Specimens are usually stored with some form of individual identification for later retrieval. DNA data banks are repositories of genetic information obtained from the analysis of DNA samples, sometimes referred to as “DNA profiles” The genetic information is usually stored in computerized form with individual identifiers.

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 government laboratories, diagnostic pathology and cytology laboratories, university- and hospital-
2 based research laboratories, commercial enterprises, and non-profit organizations.

3

4 The collections of these materials generally fall into the following categories:

5

- 6 • large tissue banks, repositories and core facilities;
- 7 • samples collected as part of longitudinal studies;
- 8 • research studies requiring unique tissue collections;
- 9 • pathology specimens;
- 10 • newborn screening laboratories;
- 11 • forensic DNA banks;⁵
- 12 • umbilical cord blood banks;
- 13 • organ banks;
- 14 • blood banks; and
- 15 • sperm, ovum, and embryo banks.⁶

16

17 Two of the largest tissue repositories in the world, the National Pathology Repository and
18 the DNA Specimen Repository for Remains Identification, are housed within a single institution,

⁵ Only forensic DNA banks set up through state and federal legislation are discussed in this report. The use of human biological materials in other repositories for forensic purposes raises several ethical issues and is not addressed in this report.

⁶ Due to the unique and ethically complex nature of research on gametes and embryos, their use in research is not addressed in this report.

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 the Armed Forces Institute of Pathology (AFIP). These two repositories alone store more than
2 94 million specimens. State newborn screening laboratories collectively have archives totaling
3 more than 13 million. Finally, the pathology departments at Graduate Medical Education (GME)
4 teaching institutions collectively constitute the largest and oldest stores of tissue samples in the
5 United States, with some specimens over 100 years old.⁷ Three of these sources—the AFIP
6 National Pathology Repository, GME teaching institution pathology departments, and newborn
7 screening laboratories—represent more than 265.5 million diagnostic and therapeutic specimens
8 from over 176 million cases. Although the tissue repositories supported by the National Institutes
9 of Health (NIH) are not as large as those of AFIP, NIH is one of the largest funders of tissue
10 repositories, providing over \$53 million in Fiscal Year 1996.

11
12 The vast majority of samples currently in storage were originally collected for diagnostic
13 or therapeutic reasons. Although a small percentage of these samples may be used for research,
14 educational, and quality control purposes, the majority is not. These collections are generally
15 referred to as “pathology samples” and have been the primary source of specimens used to date in
16 research. However, samples collected specifically for research are increasingly in demand, as they
17 are more narrowly defined, are often provided with useful clinical data, and are more likely to
18 have been collected with explicit consent to use for research purposes.

⁷ Graduate Medical Education (GME) programs are the primary means of medical education beyond the four-year medical school training received by all physicians. Usually called residency programs, they are based in hospitals or other health care institutions, some of which do and some of which do not have formal relationships with medical schools. GME teaching institutions include medical schools, the Armed Forces hospitals, Veterans Affairs medical centers, the Public Health Service, state, county and city hospitals, non-profit institutions, and health

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 Several repositories have been established specifically for use in research. In addition,
2 several large longitudinal studies collect and bank samples from study participants. Likewise, a
3 fair amount of research simultaneously creates collections or contributes to existing banks.
4 Collectively, these special research collections contain more than 2.3 million specimens.

5
6 Other than for diagnostic, therapeutic (e.g., transplantation or transfusion), or research
7 purposes, samples are collected and stored for a variety of other reasons. Blood banks collect
8 approximately 12 million units of blood a year, but only about 20,000 to 40,000 units are stored
9 at any one time. Also, most of the blood collected is used for transfusions, and very little is used
10 for other purposes, such as research and quality control. Organ banks do not collect the same
11 volume of tissue as do blood banks, but are similar in that most of the organs and tissues collected
12 are used for transplants, and very little is available for research purposes. Forensic DNA banks
13 collect and store tissues for use in criminal investigations. The Department of Defense (DOD)
14 DNA Specimen Repository and some commercial DNA banks store DNA samples for remains
15 identification. Sperm, ovum and embryo banks store specimens for anonymous donation or for
16 later use by the individual storing the material. Umbilical cord blood banks also store blood for
17 anonymous donation and later use by families banking their newborn's cord blood. Table 1
18 summarizes sources of stored samples in the United States.

19

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 **Large Tissue Banks, Repositories, and Core Facilities**

2

3 Large tissue banks and repositories exist in almost every sector of the scientific and
4 medical communities, including the military, the Federal Government, universities and academic
5 medical centers, commercial enterprises, and non-profit organizations. In addition, several
6 universities have established core banking facilities to support both their own research as well as
7 collaborations with other universities. These large tissue banks, repositories, and core facilities
8 are a major source of human biological materials for biomedical research. Representative
9 collections of this type are described below.⁸

10

11 **Military Facilities**

12

13 The military maintains two of the largest tissue repositories in the world. As mentioned
14 previously, the National Pathology Repository and the DOD DNA Specimen Repository for
15 Remains Identification are housed in the AFIP⁹. The AFIP is responsible for maintaining a central
16 laboratory of pathology for consultation and diagnosis of pathologic tissue for DOD, other federal
17 agencies, and civilian pathologists. The AFIP also conducts research in pathology, trains enlisted
18 personnel in histopathology and related techniques, and offers over 50 pathology education
19 courses for medical, dental, and veterinary personnel.

⁸ The complete text of the inventory appears in the commissioned paper prepared by Elisa Eiseman.

⁹ Armed Forces Institute of Pathology (AFIP), <http://www.afip.mil/default.html>

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 The National Pathology Repository,¹⁰ located at AFIP, is the largest and most
2 comprehensive collection of pathology material in the world. Since 1917, the Pathology
3 Repository has collected over 2.5 million cases comprising over 50 million microscopic slides, 30
4 million paraffin tissue blocks, 12 million preserved wet tissue specimens, and associated written
5 records. The Pathology Repository currently logs in approximately 50,000 cases annually. In
6 addition, approximately 40,000 cytology cases are sent for primary diagnosis annually, but are not
7 deposited in the repository. Material is stored permanently unless there is a specific request by
8 the contributor or other authorized individual to return or release the material.

9
10 Cases are sent to AFIP for a variety of reasons. The majority of cases are submitted
11 because the contributor wants a second opinion on a diagnosis. Some are forwarded as part of
12 established peer-review and quality assurance programs. Some military cases are forwarded by
13 DOD regulation, such as forensic cases and those subject to litigation. Other cases are submitted
14 because they are unusual or rare and may be useful to AFIP in its research and education
15 missions. Pathologic specimens stored at the Pathology Repository can be used to study unusual
16 tumors, or as part of a public health surveillance system to study emerging infectious diseases or
17 trends in disease progression. For example, samples in the Repository have been used to identify
18 and date tissues harboring genomic material of the Human Immunodeficiency Virus (HIV) that
19 were obtained before the availability of HIV testing and before the spread of the HIV infection.
20 In addition, cases have been submitted over the years for specific purposes, such as to study a

¹⁰ National Pathology Repository , <http://www.afip.mil/repository/welcome.html>

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 particular disease, or to answer current and future research questions (for example, illnesses of
2 Gulf War veterans).

3

4 All submitted case material is coded by pathological diagnosis, and is identified by an
5 AFIP accession number. The source name, social security number, date of birth, age, sex, and
6 race are stored if provided by the contributing pathologist. Any medical history provided is stored
7 in the case folder and on an optical disk imaging system. The source address is not routinely
8 provided or stored but is obtained on occasion for follow-up studies. Likewise, the original
9 consent is a matter between the patient and the clinician and is not routinely provided to AFIP by
10 the contributing pathologist. The submitting pathologist's name and address, and the source's
11 surgical identification numbers are also stored.

12

13 The Pathology Repository loans pathologic material for patient treatment, research, or
14 litigation. Requests for loan of material or provision of data for research purposes requires
15 submission and approval of a research protocol. All research protocols using stored materials or
16 data are reviewed by the AFIP's IRB. Requests from individuals or organizations other than the
17 original contributor must be accompanied by a properly executed authorization signed by the
18 patient or designated representative. Research involving patient follow-up, and thus requiring
19 identifying information, is reviewed at a full meeting of the IRB prior to approval. Other than for
20 research involving follow-up, original sources of material are not notified of research results. If

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 an unexpected disease or abnormality is discovered, the contributing pathologist is notified, and it
2 is then up to the pathologist to contact the patient. Otherwise, current AFIP policy requires that
3 material be stripped of identifiers before release to outside investigators.

4
5 The DOD DNA Specimen Repository for Remains Identification¹¹ is the world's largest
6 DNA bank. As of September 1997, the DNA Repository has received approximately 2 million
7 DNA specimens. Specimens come into the DNA Repository at a rate of 10,000 per day, and the
8 tally is updated every seven seconds. It is estimated that by the year 2001 the DNA Repository
9 will contain approximately 3.5 million samples. All DNA specimens are maintained for 50 years
10 before being destroyed. However, donors may request that their specimens be destroyed
11 following the conclusion of their military service obligation or other applicable relationship to
12 DOD.

13
14 Since June 1992, DOD has required all military inductees, and all active duty and reserve
15 personnel to provide blood and saliva samples for its DNA Specimen Repository at the time of
16 enlistment, re-enlistment, annual physical, or preparation for operational deployment (McEwen,
17 1997). The DNA Repository also contains samples from civilians and foreign nationals who work
18 with the United States military in arenas of conflict. A total of three DNA specimens are
19 collected from each person: one bloodstain card is stored in a pouch in the service member's
20 medical record; another bloodstain card and a buccal swab are stored at the DNA Specimen

¹¹ Armed Forces DNA Identification Laboratory, <http://www.afip.mil/oafme/dna/afdil.html>

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 Repository. The blood is placed on special cards with the service member's Social Security
2 number, date of birth, and branch of service designated on the front side of the card, and a
3 fingerprint, a bar code, and signature attesting to the validity of the sample on the reverse side.
4 DNA will only be extracted from the specimens in the Repository when it is needed for the
5 purpose of remains identification.

6

7 **National Institutes of Health**

8

9 The National Institutes of Health¹² (NIH) is one of the highest funders of tissue and data
10 resources for basic, applied and clinical research. Some of the institutes at NIH that support
11 tissue banks include the National Cancer Institute (NCI), the National Institute of Allergy and
12 Infectious Disease (NIAID), the National Heart, Lung, and Blood Institute (NHLBI), the
13 National Institute of Mental Health (NIMH), and the National Institute on Aging (NIA).
14 Examples of tissue banking supported by NIH are described below.

15

16 The NCI Cooperative Human Tissue Network (CHTN),¹³ in existence since 1987,
17 provides biomedical researchers with access to fresh surgical or biopsy specimens of normal,
18 benign, pre-cancerous and cancerous human tissues. The CHTN is a tissue collection system and
19 not a tissue bank. Only rare specimens that are difficult to obtain are stored to anticipate future

¹² National Institutes of Health (NIH), <http://www.nih.gov/index.html>

¹³ NCI Cooperative Human Tissue Network (CHTN)

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 requests. Except for a collection of frozen tissue from rare pediatric tumors, banked specimens
2 are generally not stored for more than one year. Normally, the specimens are obtained
3 prospectively to fill specific researcher requests. Five member institutions coordinate the
4 collection and distribution of tissues across the United States and Canada. Tissues are provided
5 by the CHTN only for research purposes, and cannot be sold or used for commercial purposes.

6

7 During the first nine years of operation, the CHTN has supplied over 100,000 specimens
8 to approximately 600 investigators. Tissues obtained from the CHTN have been used in many
9 areas of cancer research including molecular biology, immunology, and genetics. Researchers
10 have used these tissues to study mutations of proto-oncogenes in human tumors, the role of
11 growth factors in cancer, and to isolate new cancer genes. Over 2,000 publications have resulted
12 from studies using tissues obtained from the CHTN.

13

14 CHTN obtains tissues from routine surgical resections and autopsies of adult and pediatric
15 patients, representing all organ systems, as well as blood and other body fluids. Specimens are
16 collected according to the individual investigator's protocol, and may be preserved as fresh, fixed
17 or frozen tissue, slides, or paraffin blocks. The CHTN was designed for basic research studies not
18 requiring clinical follow-up information. Each specimen is given a unique identifier. A link is
19 kept by the parent institution for quality control purposes. Only minimal demographic data is

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 provided with the specimen to researchers. Other information routinely provided with the
2 specimens includes pathology reports and histological characterization.

3
4 The NCI-National Action Plan on Breast Cancer (NAPBC) Specimen and Data
5 Information System¹⁴ contains information from 14 breast tissue banks. This database does not
6 represent an exhaustive national listing of all facilities holding breast cancer tissue. However, by
7 centralizing information on biological specimens, it provides access to breast tissue specimens and
8 facilitates collaboration among basic, clinical, and epidemiologic researchers. Cumulatively, the
9 14 breast tissue banks in the NCI-NAPBC database contain more than 130,000 cases of breast
10 cancer-related specimens and data, with banks ranging in size from 48 cases to approximately
11 101,000 cases. Three of the 14 banks are accruing as many as 200 new cases per year. A
12 specimen from a single case may generate several samples. For example, a specimen from a single
13 case may be split into 3 to 30 paraffin-embedded blocks, 10 slides, or matched frozen and
14 paraffin-embedded tissue blocks (i.e., one frozen and one paraffin-embedded sample from the
15 same case). A conservative estimate is that there are approximately 240,000 specimens in the
16 database. Samples available to the research and clinical communities include breast tissue, serum,
17 urine, cells, and DNA from patients diagnosed with breast cancer, those at high risk, and
18 unaffected individuals.

19

¹⁴ NCI-NAPBC Breast Cancer Specimen and Data Information System,
<http://cancernet.nci.nih.gov/breastdata/contents.htm>

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 The Transfusion Medicine Branch of NHLBI¹⁵ maintains a contractor-operated Blood
2 Specimen Repository available for use by the scientific community for research related to
3 transfusion-transmitted diseases, other blood disorders, or diseases of the cardiovascular system.
4 The repository, established in 1974, contains approximately 1.5 million well-characterized
5 specimens of serum, plasma, and cells from NHLBI-sponsored studies. Since 1991, the Blood
6 Specimen Repository has been storing an average of approximately 300,000 samples per year
7 (National Heart, Lung, and Blood Institute, 1996).

8

9 **Research Universities and Academic Medical Centers**

10

11 Research universities and academic medical centers maintain both formal human biological
12 material banks for distributing samples throughout the research community as well as core
13 facilities to support their own research. For example, the Harvard Brain Tissue Resource Center¹⁶
14 (The Brain Bank) is a centralized repository of post-mortem human brain specimens from both
15 diseased and normal donors. Samples from the bank are distributed for use in research on the
16 brain and nervous system. Since the majority of research requires a very small amount of tissue,
17 each donated brain provides a large number of samples for many researchers. Brain tissue
18 donations are accepted by the Brain Bank from individuals or the parents, siblings and offspring of
19 individuals with severe psychiatric or neurological disorders, as well as from unaffected
20 individuals for comparison.

¹⁵ National Heart, Lung, and Blood Institute (NHLBI), <http://www.nhlbi.nih.gov/nhlbi/nhlbi.htm>

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 Another example, the University of California-San Francisco (UCSF) AIDS Specimen
2 Bank, in existence since 1982, has banked over 76,000 specimens and sent out over 82,000
3 samples to researchers worldwide. Specimens include serum, tissue, saliva, cells, and
4 cerebrospinal fluid from HIV-infected individuals. Specimen data are archived on a computerized
5 database. The Bank provides investigators with specimens for basic, epidemiological, and clinical
6 research.

7

8 **Commercial Enterprises**

9

10 Some commercial enterprises maintain human biological material banks for their own
11 proprietary use, while others establish banks for storage and distribution purposes. OncorMed¹⁷
12 and LifeSpan Biosciences, Inc.,¹⁸ are examples of companies that maintain proprietary tissue
13 banks. For example, LifeSpan's Tissue and Disease Bank contains 250,000 normal and diseased
14 human samples. The tissue bank has over 175 different types of tissues from virtually every organ
15 in the body, covering all ages. The tissue bank also includes over 500 different pathologic disease
16 categories such as autoimmune diseases, infectious diseases, degenerative diseases, cancer and
17 benign proliferative diseases, and genetic diseases.

18

¹⁶ Harvard Brain Tissue Resource Center, <http://www.brainbank.mclean.org:8080/into.html>

¹⁷ OncorMed, <http://www.oncormed.com>

¹⁸ LifeSpan BioSciences, Inc., <http://www.lsbio.com>

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 In contrast, PathServe Human Tissue Bank ¹⁹ collects human tissues and organs for sale to
2 the research community. PathServe collects all types of organs and tissues including specimens
3 from placental and fetal origin. Tissues are obtained through post-mortem examinations, referrals
4 from transplant banks of nontransplantable organs, and donations by next of kin. PathServe
5 collects specimens from approximately 300 autopsies per year, and each autopsy yields
6 approximately 100 specimens. PathServe has approximately 300 specimens stored at any one
7 time, and distributed approximately 30,000 specimens in 1996. PathServe does not maintain a
8 centralized storage facility. Instead, specimens are stored in the morgues of different hospitals.

9

10 **Non-Profit, Non-Educational Organizations**

11

12 There are a variety of non-profit institutions that bank tissues for purposes of storage and
13 distribution. Non-profit institutions, such as the American Type Culture Collection (ATCC), the
14 Coriell Institute for Medical Research, the National Disease Research Institute (NDRI), the
15 Research Foundation for Mental Hygiene, the Rocky Mountain Multiple Sclerosis Center, the
16 National Psoriasis Tissue Bank, the Kaiser Permanente Center for Health Research, and the
17 Hereditary Disease Foundation, receive millions of dollars in federal funding to support their
18 human biological material collections. Examples of non-profit tissue banks are described below.

¹⁹ PathServe, <http://www.tissuebank.com/>

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 Since its establishment in 1925, ATCC²⁰ has served as an archive of living cultures and
2 genetic materials for researchers in the biological sciences. The mission of the ATCC is to
3 acquire, authenticate, and maintain reference cultures, related biological materials, and associated
4 data, and to distribute these to qualified scientists in government, industry, and education. The
5 ATCC maintains approximately 2,300 human cell lines as immortalized cultures. In addition,
6 cloned human genes are stored and supplied to the research community by ATCC.

7
8 The Coriell Institute for Medical Research²¹ is a basic biomedical research institution that
9 conducts research on the causes of genetic diseases, including cancer. The Coriell Institute's three
10 missions are research, cell banking, and public education. The largest collection of human cells
11 for research is maintained at the Corriell Institute, and these cells are available to the general
12 scientific community. Seminal research on the genes associated with Huntington's disease, cystic
13 fibrosis, Alzheimer's disease, ataxia telangiectasia and manic depression have used cells from the
14 Coriell collection. Over 35,000 cell lines are currently stored representing approximately 1,000 of
15 the 4,000 known genetic diseases, and more than 60,000 cell lines have been distributed to over
16 40 nations, resulting in over 8,000 research publications. Cultures are established from both
17 blood and skin, and the cells are stored frozen at the Institute. There are approximately three
18 quarters of a million vials of cells in 37 storage tanks containing liquid nitrogen.

²⁰ American Type Culture Collection (ATCC), <http://www.atcc.org/>

²¹ Coriell Institute for Medical Research, <http://arginine.umdj.edu/info.html>

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 NDRI, founded in 1980, was initially established as a network to obtain human tissue for
2 diabetes research. Since then, it has grown into a center for retrieving and distributing a full range
3 of normal and diseased cells, tissues and organs for biomedical research. NDRI currently operates
4 three programs: 1) Human Tissues and Organs for Research (HTOR), NDRI's core program,
5 focuses on the retrieval and distribution of tissues and organs; 2) Human Biological Data
6 Interchange (HBDI) provides data, cell lines and DNA for genetic research of Type I diabetes,
7 thyroid disease and autism; and 3) Odyssey I coordinates the collection of rare tissues and organs
8 for research. NDRI currently provides 140 different types of human tissues obtained from
9 autopsies, eye banks, surgical procedures, and organ retrieval programs. More than 130,000
10 tissues have been retrieved and delivered to over 2000 scientists throughout the United States for
11 use in research on more than 100 different diseases including Alzheimer's disease, amyotrophic
12 lateral sclerosis (ALS), arthritis, asthma, cancer, cataracts, cerebral palsy, Crohn's disease, cystic
13 fibrosis, diabetes, glaucoma, hearing disorders, heart disease, malaria, multiple sclerosis, muscular
14 dystrophy and Parkinson's disease. Research using human biological materials supplied by NDRI
15 has resulted in more than 1000 publications.

16

17 **PATHOLOGY SPECIMENS**

18

19 A large number of human biological materials are collected for diagnostic or therapeutic
20 reasons. These samples are usually sent to a clinical, diagnostic, or pathology laboratory for
21 examination. These laboratories may be located at GME teaching institutions, physicians' offices,

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 community hospitals, or independent laboratories. Most patients sign a general consent stating
2 that after completion of any diagnostic tests, some of the sample may be saved for research
3 purposes. Although samples are made available for research, educational, and quality control
4 purposes, the vast majority is never used for these purposes.

5

6 To be accredited, laboratories are required to keep pathological specimens for a minimum
7 length of time. The Clinical Laboratory Improvement Amendments of 1988 (CLIA) set forth the
8 conditions that laboratories must meet to be certified to perform testing on human specimens.

9 CLIA stipulates that laboratories must retain cytology slides for a minimum of 5 years,

10 histopathology slides for a minimum of 10 years, and paraffin blocks for a minimum of 2 years

11 (Clinical Laboratory Improvement Amendments, 1996). In addition, some states have regulations

12 that require retention of pathology specimens for longer periods of time. Once the regulated

13 length of time for storage is met, institutions continue to store pathology specimens based on the

14 room they have for storage or specific policies of the institution.

15

16 **Pathology Departments at Graduate Medical Education Teaching Institutions**

17

18 Collectively, pathology departments at GME teaching institutions constitute the largest

19 and oldest stores of human biological materials in the United States. GME teaching institutions

20 include medical schools, Armed Forces hospitals, Veterans Affairs medical centers, the Public

21 Health Service, state, county and city hospitals, non-profit institutions, and health maintenance

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 organizations. In 1997, there were 1,687 accredited GME teaching institutions (i.e., sites for
2 clinical training) in the United States (American Medical Association, 1997). Of these 1687 GME
3 teaching institutions, 68 institutions had residency programs in cytopathology, 54 institutions had
4 programs in hematology, and 180 institutions had programs in clinical and anatomic pathology.
5 Combined, these pathology residency programs accessioned well over 8 million cases per year.
6 Most medical school pathology departments store samples indefinitely; some tissues have been
7 archived from 20 to over 100 years. In addition, pathology departments at GME Teaching
8 Institutions without pathology residency programs also accession pathology specimens, but most
9 likely not at the same rate as institutions with pathology residency programs. Since most GME
10 teaching institutions retain pathology specimens anywhere from 20 to 100 years, at a rate of 8
11 million cases a year for a minimum of 20 years, a conservative estimate is that there are more than
12 160 million cases stored at GME Teaching Institutions with pathology residency programs, and
13 with several million more stored at those without pathology residency programs.

14

15 **DNA Diagnostic Laboratories**

16

17 HELIX²² is a national directory of DNA diagnostic laboratories. It includes a
18 comprehensive listing of clinical service and research laboratories performing disease-specific
19 clinical molecular genetic testing for single-gene and contiguous-gene disorders. HELIX is
20 funded by the National Library of Medicine and administered through the National Network of

²² HELIX, <http://healthlinks.washington.edu/helix>

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 Libraries of Medicine. In January 1994, there were 148 laboratories listed in HELIX (McEwen
2 and Reilly, 1995).

3

4 In a 1994 survey of HELIX DNA diagnostic laboratories, 90 percent of the respondents
5 stated that they banked DNA. DNA banks ranged in size from having less than 100 to more than
6 1,000 samples in storage. Most laboratories banked DNA as a service to referring physicians or
7 for individuals and families at risk for a particular genetic disorder, for research purposes such as
8 gene mapping, and as a service to clinical, forensic or research laboratories. Over 50 percent of
9 the respondents stated that their laboratories had released samples to researchers after stripping
10 them of identifiers (McEwen and Reilly, 1995).

11

12 **Clinical Service and Diagnostic Laboratories**

13

14 The majority of clinical service and diagnostic laboratories are not associated with GME
15 teaching institutions. These include laboratories within physicians' offices or community
16 hospitals, and independent laboratories. In 1991, there were approximately 640,000 clinical
17 laboratories and other facilities that perform laboratory tests on human specimens (Department of
18 Health and Human Services, 1991). The number of tissues stored at these laboratories varies
19 greatly, but the minimum storage time is determined by CLIA and state regulations.

20

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 **NEWBORN SCREENING LABORATORIES**

2

3 Archives of newborn screening cards for inborn errors of metabolism (Guthrie Cards)
4 represent an enormous source of banked DNA. Guthrie cards are special filter paper that contain
5 dried blood spots from newborn babies, and contain identifying information, such as mother's
6 name and address, hospital of birth, baby's medical record number, baby's doctor's name and
7 address. Guthrie cards are used to test newborns for several different diseases, including
8 congenital hypothyroidism, phenylketonuria, galactosemia, hemoglobinopathies (e.g. sickle cell
9 anemia), biotinidase deficiency, homocystinuria, Maple Syrup Urine disease, and cystic fibrosis.
10 Interest in using Guthrie cards for population-wide genetic epidemiological studies has grown,
11 given the stability of DNA in dried blood, and the ability to analyze the DNA in these samples
12 (McEwen and Reilly, 1994).

13

14 A 1994 survey of all newborn-screening programs in all 50 states, the District of
15 Columbia, Puerto Rico, and the Virgin Islands revealed that the majority of laboratories have
16 accumulated less than 500,000 Guthrie Cards over the years. However, one laboratory reported a
17 collection of more than 6 million Guthrie cards. The number of cards collected over a 1-year
18 period ranged from less than 10,000 in 4 labs to more than 500,000 in 2 populous states
19 (McEwen and Reilly, 1994).

20

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 The trend in most states is to save Guthrie cards for longer and longer periods of time.
2 Forty of the state newborn screening laboratories retain—at least for a short period of time--all
3 the Guthrie cards that they receive through their newborn-screening programs, including those
4 cards that test negative (McEwen and Reilly, 1994). Twenty three laboratories indicated that they
5 keep their cards for a year or less, 10 plan to keep their cards for 1 to 5 years, 13 keep them for
6 longer than 5 years, three save all their cards for 20 to 25 years, and 4 plan to keep their cards
7 indefinitely (McEwen and Reilly, 1994). Thirteen other respondents discard their cards within
8 several weeks or months (McEwen and Reilly, 1994).

9

10 **FORENSIC DNA BANKS**

11

12 In 1989, the Virginia Division of Forensic Science²³ was the first state laboratory to offer
13 DNA analyses to law enforcement agencies, and the first to create a DNA databank of previously
14 convicted sex offenders. By November 1997, 48 states had established forensic DNA data banks
15 to maintain specimens from convicted criminals, especially violent sex offenders and other violent
16 felons (Finn, 1997). The two states without Forensic DNA banks, Vermont and Rhode Island,
17 are planning legislation to create them (Finn, 1997). In addition, the Federal Bureau of
18 Investigation²⁴ (FBI) is exploring ways to create a Forensic DNA bank for the District of
19 Columbia (Finn, 1997).

²³ Virginia Division of Forensic Science, <http://www.state.va.us/~dcjs/forensic/>

²⁴ Federal Bureau of Investigations (FBI), <http://www.fbi.gov/>

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20

In addition to collecting specimens from sex offenders and violent felons, a number of states also require samples from juvenile offenders, non-violent felons, such as drug or white collar offenders, and those convicted of misdemeanors (McEwen, 1997). South Dakota requires samples from people merely arrested (not convicted) for a sex offense (Finn, 1997), with several other states considering similar bills (McEwen, 1997). There is also a proposal to establish a federal DNA data bank that would include profiles of people convicted of offenses similar to those covered by most state laws in federal or military courts (McEwen, 1997).

Convicted offenders are required to provide blood, or in some cases, saliva, either at sentencing or before release from prison. Some states also require samples from people already incarcerated before the law's effective dates. The DNA from these samples is analyzed for its unique identification characteristics. Nationwide, samples from about 380,000 offenders have been collected, mostly in Virginia and California, and about 116,000 samples (30 percent) have been analyzed (McEwen, 1997). These DNA identification profiles are stored, along with the samples themselves, to help identify suspects by matching biological evidence found at crime scenes to state DNA databases.

UMBILICAL CORD BLOOD BANKS

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 Stem cells (progenitor cells that produce all other blood cells) are used to treat patients
2 with blood diseases, certain genetic disorders, and patients receiving chemotherapy and/or
3 radiation treatment for cancer. Until scientists discovered that umbilical cord blood contained
4 hematopoietic stem cells, the only known source of stem cells was from bone marrow. However,
5 retrieval of bone marrow is invasive, may be painful, requires general anesthesia, and is expensive
6 to harvest. In contrast, retrieval of umbilical cord blood is non-invasive, painless, and generally
7 only takes a few minutes to complete. After a baby is delivered and the umbilical cord is cut,
8 blood is withdrawn from the umbilical cord and placenta with a syringe and then cryogenically
9 stored.

10

11 In the last few years, privately owned companies have begun offering umbilical cord blood
12 banking services to individuals and families. When dealing with private storage companies, users
13 pay a one-time fee for the collection, testing and freezing of the blood. In addition, an annual fee
14 is charged for storing the blood in liquid nitrogen. The stored cord blood may be withdrawn if
15 illness occurs later in life. In contrast, when parents choose to donate their child's cord blood to a
16 public bank, they generally pay no fees, but they give up all rights to the sample to help build the
17 public supply of cord blood for use in transplantation and research. In general, expectant mothers
18 who choose to donate their baby's cord blood are asked to consent to providing medical, ethnic
19 and related information, donating the cord blood to the cord blood bank for transplantation and/or
20 research, allowing blood to be drawn from the mother for tests including HIV testing, and
21 granting permission to track the newborn's medical history for up to one year. Collectively,

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 private and public cord blood banks store more than 18,000 units of cryopreserved umbilical cord
2 blood. The majority of this stored cord blood is used for transplants. However, both private and
3 public banks do supply some cord blood for research purposes.

4

5 **ORGAN BANKS**

6

7 Organ and tissue banks recover, process, store and distribute for transplantation human
8 organs, bone, and tissue. Donations are from people who agree to donate upon their death and
9 families who consent on behalf of the deceased. Some organ and tissue banks may also have
10 tissue available for educational and research purposes. However, the demand for organs, bone
11 and tissue usually exceeds the current supply. Therefore, usually only organs and tissues not
12 suitable for transplantation are available for research.

13

14 **BLOOD BANKS**

15

16 The American Red Cross²⁵ collected approximately 5.8 million blood donations in 1996.
17 The Red Cross represents about half of all United States blood donations, so annually, about 12
18 million units of blood are donated in the United States. The American Red Cross usually
19 maintains about a 3-day supply of fresh blood as well as approximately 20,000 units of frozen
20 blood at any one time. The American Red Cross also maintains the world's largest registry of

²⁵ American Red Cross, [http:// www.redcross.blood](http://www.redcross.blood)

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 frozen rare blood. Approximately 1000 units of rare blood a year are supplied to recipients
2 around the globe.

3
4 Fresh red blood cells have a shelf life of 21 to 42 days depending on the preservative used,
5 and platelets have a shelf life of 5 days. Plasma can be stored frozen for 1 to 5 years, and frozen
6 whole blood can be stored for at least 10 years. Platelets and red cells that expire are sold for
7 research purposes. Researchers are informed that the samples have been found negative for all
8 FDA-required tests, and only by special request, may be provided with the donor's age and
9 gender. Plasma that can not be transfused is used for making blood derivatives, such as Factor
10 VIII for hemophiliacs, or for making diagnostic reagents. Nothing goes to waste.

11

12 **Part II: Sources of Human Biological Materials**

13

14 In this report, *human biological material* is defined as including everything from
15 subcellular structures like DNA, to cells, tissue (bone, muscle, connective tissue and skin), organs
16 (e.g., liver, bladder, heart, kidney), blood, gametes (sperm and ova), embryos, fetal tissue²⁶, and
17 waste (urine, feces, sweat, hair and nail clippings, shed epithelial cells, placenta). The most
18 common source of tissue is from patients undergoing diagnostic or therapeutic procedures.
19 Tissue specimens may also be taken during autopsies that are performed to establish the cause of

²⁶ Due to the unique and ethically complex nature of research on gametes, embryos and fetal tissue, their use in research is not addressed in this report.

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 death. In addition, volunteers may donate blood or other tissue for transplantation or research,
2 organs for transplantation, or their bodies for anatomical studies after death. Each specimen of
3 human tissue may be stored in multiple forms, such as slides, paraffin blocks, formalin fixed,
4 frozen, tissue culture, or extracted DNA.

5

6 **Identifiability of Sample Sources**

7

8 In the debate about research use of human biological materials, the language used to
9 describe the identifiability of research samples varies (see Appendix ___ for further discussion).
10 Previous guidelines and reports have categorized samples by the conditions under which they are
11 stored (with or without identifiers), although current federal regulations permit investigators to
12 obtain stored samples, make them anonymous by removing identifiers, and then use them in
13 research without seeking consent (see chapter 4 for further discussion).

14

15 Part of the confusion of terminology arises from the fact that people sometimes refer to
16 the state of the information attached to the biological material in the repository and sometimes
17 refer to the information that is sent forward to the researcher. For example, the material might be
18 identified in the repository but no identifying information is forwarded with the research sample
19 sent to the scientist. This distinction has considerable importance because the potential for benefit
20 or harm is greater when the sample is directly or easily linked to the donor, placing the burden of

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 protection in different places, depending on who has access to the information (e.g., the
2 researcher or the pathologist, or both).

3

4 In a simple way, research samples fall into two categories: 1) *identifiable samples* are
5 those for which the source can be identified (more or less), which means the sample can be
6 connected, or linked, to the person from whom it came; and 2) *unidentifiable samples* are those
7 for which the source cannot be identified at all. The reason one refers to the former as “more or
8 less” identifiable, is because the information content of the research sample varies, from a very
9 few data points that, nevertheless, could allow one (perhaps with some difficulty) to link the
10 sample to the person, to a sample that contains an exhaustive number of data points allowing very
11 easy identification of the person from whom the sample was obtained.

12

13 For purposes of clarity and to facilitate discussion, NBAC adopted the following
14 definitions of the diverse status of human biological materials, depending on whether they are
15 sitting in storage in a repository, or selected for research purposes.

16

17 Human biological materials stored in a repository are of two types:

18

19 *Unidentified materials* are those for which identifiable personal information was not
20 collected or, if once collected, is not maintained and cannot be retrieved by the repository.

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21

Identified materials are those linked to personal information, such that the person from whom the material was obtained could be identified by name, patient numbers, or clear pedigree location.

Most repositories contain identified materials by virtue of the fact that the vast majority of human biological materials in storage were originally collected with identifying information for diagnostic or therapeutic reasons. Examples of repositories containing identified materials include pathology laboratories and newborn screening laboratories where specimens are collected and stored with identifying information such as the patient's name, hospital identification number and/or social security number. In addition to identifying information, clinical and demographic information are often available with these specimens. In contrast, there are a few collections of human biological materials that contain unidentified materials. For example,

A repository might have collections of specific blood types such as O-positive (O⁺) or AB-negative (AB⁻). Donors are asked to contribute to the bank based on having these specific blood types, but no information about the donor is recorded when the sample is collected except for the blood type. Another example is a repository that collects human biological materials, such as brain, pancreas or kidney, that were originally collected by a hospital, but are submitted to the repository with no identifying information. These specimens may be contributed with corresponding clinical and demographic information,

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 *but any information provided with the specimen is not enough to identify the individual*
2 *from whom the specimen was originally collected.*

3

4 ***Research samples*** are the portions of human biological materials provided to investigators
5 by repositories. Such materials are of at least four types, which are differentiated by the amount
6 of information that is conveyed to the investigator about the person from whom the sample
7 comes:

8

9 ***Unidentified samples***—sometimes termed “anonymous” —are those supplied by
10 repositories from an unidentified collection of human biological materials.

11

12 ***Unlinked samples***—sometimes termed “anonymized”—are those supplied by repositories
13 from identified human biological materials without identifiers or codes such that the ability
14 to identify particular individuals via clinical or demographic information supplied with the
15 sample, or biological information derived from the research would be very difficult if not
16 impossible for the investigator, the repository, or a third party.

17

18 ***Coded samples***—sometimes termed “linked” or “identifiable” —are those supplied by
19 repositories from identified materials with a code rather than a name or any other personal
20 identifier such as a patient number, where the repository (or its agent) retains information

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 linking the code to particular human materials or where the extent of the clinical or
2 demographic information provided with the sample is sufficient that the investigator, the
3 repository, or a third party could link the biological information derived from the research
4 with material from a particular person or a very small group of identifiable persons.

5
6 *Identified samples* are those supplied by repositories from identified materials with a
7 personal identifier (such as a name or patient number) sufficient to allow the biological
8 information derived from the research to be linked directly, by the researcher, with the
9 particular person from whom the material was obtained.

10
11 By definition, unidentified samples can only come from collections of unidentified
12 materials. Because of the scarcity of truly anonymously collected human biological materials, few
13 research samples are unidentifiable. An example of a researcher's use of unidentified samples
14 follows:

15 *A researcher studying malaria needs O⁺ blood to grow the malaria parasite. The*
16 *researcher recruits donors with O⁺ blood to donate a unit of blood. The researcher only*
17 *needs to know the blood type of the donors and needs no identifying information from the*
18 *donors. When the blood is collected, the researcher gives each vial a number, but keeps*
19 *no record of which unit of blood came from each donor. The researcher places all of the*
20 *blood that is collected in storage until there is enough blood stored to perform the*
21 *planned experiments.*

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 Collections of identified materials may be provided to researchers as unlinked, coded, or
2 identified samples. The use of unlinked samples in research is a fairly common occurrence.
3 Unlinked samples are used when there is a one-time need for tissue and clinical/demographic
4 information. Because there is no link maintained between the sample and the individual from
5 whom it came, neither the researcher nor the repository knows which sample came from which
6 source. Therefore there is no way to go back to get more information about the source or to get
7 another piece of the same sample. For example:

8 *A researcher at a university is studying a mutation of a gene that may be associated with*
9 *prostate cancer. The researcher needs 100 samples of prostate tumors with*
10 *accompanying clinical information such as the size of the tumor. The researcher does*
11 *not need any other information about the individual from whom the tumor was removed.*
12 *The researcher contacts the pathology department at the university and requests the*
13 *samples. The pathologist pulls 100 samples from the pathology archives, records the*
14 *medical records number of the selected samples, removes any identifying information,*
15 *gives each sample a new unique identifier, and gives the samples to the researcher.*
16 *There is no link maintained between the sample and the individual from whom it came.*
17 *This means that neither the researcher nor the pathologist knows which sample came*
18 *from which patient.*

19
20 Another common category of samples used in research is coded samples. Coded samples
21 are used when a researcher anticipates the need to obtain additional medical information about the

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 source, to provide information to the source, or to get additional samples over time. For coded
2 samples, source identification is not provided. Instead, each sample is given a unique identifier,
3 and a link is kept by the repository for quality control purposes. The link also provides a one-way
4 flow of information from the repository to the researcher. Coded samples allow researchers to
5 obtain follow-up data on treatment, recurrence, and survival. An example of the use of coded
6 samples in research follows:

7
8 *A researcher studying systemic lupus erythematosus (SLE) wants to know if there is some*
9 *way to predict if a patient will go on to need a kidney transplant. The researcher uses*
10 *frozen serum from patients with SLE that have been stripped of identifiers and coded for*
11 *research purposes. During the course of this research, a unique serological marker is*
12 *found that may be predictive of rapidly progressive kidney disease. The researcher wants*
13 *to determine if there is a connection between the newly discovered marker and patients*
14 *requiring a kidney transplant. Therefore, the researcher wants to receive follow-up*
15 *information about each patient, particularly information relating to time to renal failure*
16 *and need for dialysis and/or kidney transplant.*

17
18 The last category of research samples is identified samples. Identified samples are used
19 when the research involves continual sample collection and/or clinical follow-up or when the
20 researcher has direct contact with the research subject. With identified research samples, the

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 investigator can go back directly to the source of the sample and request additional information.

2 For example:

3 *A researcher is investigating the genetic causes of psoriasis. The researcher identifies*
4 *patients with psoriasis or psoriatic arthritis through medical records and requests*
5 *samples of skin biopsies from the pathology laboratory. After the researcher completes*
6 *the experiments on the skin biopsies, the patients and their families are contacted to*
7 *further participate in the research by providing blood samples. This allows the*
8 *researcher to perform linkage analysis to try to localize genes that may play a role in*
9 *psoriasis.*

10

11 **Need to Identify Source for Research or Clinical Purposes**

12

13 For research samples that are identified or coded, there are several possible reasons for an
14 investigator to want to go back to the source either to gather additional clinical or phenotypic
15 information or to provide potentially therapeutic information.

16

17 Increasingly genetic research requires that there be sufficient phenotypic information
18 accompanying the genotypic information extractable from the biological material. Thus,
19 investigators stratify populations and then intensively investigate a smaller subset. As smaller
20 subpopulations of interest are identified, clinical investigators are likely to need more clinical
21 information about the population being studied. This will require some mechanism for

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 information retrieval. With coded research samples, the “trustee” of the sample has the ability to
2 gather more data for the investigator. With identified research samples, the investigator can go
3 back directly and request additional information. The possibility that the investigator, or an agent
4 of the investigator, will contact the source (or the source’s physician) for additional information
5 should be discussed in the consent process (see chapters 4 and 5).

6
7 There might also be circumstances in which an investigator wants to provide information
8 to the source, whether directly or indirectly. An example is an investigator who discovers new
9 information that leads to a better diagnosis of a clinical condition, an effect of a previously
10 administered therapy, or a misdiagnosis that might have important implications for the health of an
11 individual source. Another example is the discovery of an infectious agent and its public health
12 implications. In both of these examples, there have been compelling arguments made supporting
13 the investigator’s duty to contact the source. In cases where the implications of a finding are not
14 as clear, that is, where findings are preliminary or where there is no effective intervention
15 available, contact is less desirable because of the possibility that people could act on the findings
16 in a way that may result in harm.

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 **Part III: Uses of Human Biological Materials**

2

3 Once removed, human tissue may serve many beneficial purposes, including clinical care,
4 forensic determinations, identification of individuals, and research use. The most familiar and
5 widespread use of human tissues is in the diagnosis and treatment of illness. Another common use
6 of human tissues is for quality control purposes in diagnostic and pathologic laboratories. Human
7 tissue is also used for medical and biological research, and for medical education and training.
8 Other uses of human tissue include the identification of a person, such as in paternity testing and
9 cases of abduction or soldiers missing in action, and forensic purposes in crime cases where
10 biological evidence is available.

11

12 In the examples described below, there is tremendous variability in the identifiability of the
13 samples used depending on the research purpose. In some cases, such as the study of the
14 Hantavirus, it was not necessary to identify the individuals who served as the sources of the
15 stored samples. For other types of research, such as the studies of families with a high prevalence
16 of mental illness where extensive information on demographics, diagnosis, and family history was
17 crucial, the ability to identify the source of the sample may be necessary.

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 **Clinical Use of Human Biological Materials**

2

3 **Umbilical Cord Blood**

4

5 In 1988, the first successful human cord blood transplant was performed in a child with
6 Fanconi Anemia using cord blood from a sibling (Gluckman et al., 1989). Since then, over 500
7 autologous and allogeneic umbilical cord blood transplants have been performed worldwide, with
8 the majority done in the past two to three years (Perdahl-Wallace, 1997). Approximately two-
9 thirds of the cord blood transplants have been performed for malignant conditions including acute
10 lymphocytic leukemia, acute myelocytic leukemia, chronic myelogenous leukemia, and
11 neuroblastoma (Wagner et al., 1995). The other one-third have been for a variety of genetic
12 disorders including Hurler and Hunter syndromes, adrenoleukodystrophy, osteopetrosis, severe
13 aplastic anemia, severe combined immunodeficiency, and hemoglobinopathies, such as beta
14 thalassemia and sickle cell anemia (Wagner et al., 1995; Wagner et al., 1996). The majority of
15 transplants have been in children, although a small number of adults have been transplanted as
16 well. However, the Working Group on Ethical Issues in Umbilical Cord Blood recently
17 concluded that “until additional data are obtained regarding safety and efficacy, umbilical cord
18 blood banking and use ought to be considered an investigational technology rather than a proven
19 treatment” (Sugarman et al., 1997).

20

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 **Forensic Use of Human Biological Materials**

2
3 The DNA Identification Act of 1994 (Pub. L. No. 103-322, 1994 HR 3355, 108 Stat.
4 1796, 210304), a federal law enacted in 1994 as part of the Omnibus Crime Control Law, created
5 a national oversight committee to develop guidelines for DNA forensics and established a 5-year,
6 \$40 million grant program to assist state and local crime laboratories in developing or improving
7 forensic DNA testing capabilities. The DNA Identification Act also formally authorized the FBI
8 to establish the Combined DNA Index System²⁷ (CODIS) for law enforcement identification
9 purposes (TWGDAM, 1989). CODIS is a national computer network containing DNA profiles
10 of convicted offenders, unknown suspects, and population samples (which are used for statistical
11 purposes only). Using CODIS, federal, state, and local law enforcement agencies are able to
12 compare DNA profiles from crime scenes to DNA profiles of felons in the CODIS database.

13
14 DNA identification profiles prepared from samples from convicted criminals have already
15 proven to be a valuable resource for tracing biological material found at crime scenes to felons
16 with prior convictions. By February 1997, forensic DNA databanks had achieved over 200 cold
17 hits linking serial rape cases or identifying suspects by matching DNA extracted from biological
18 evidence found at a crime scene to that of a known offender whose DNA profile was in the
19 databank. The power of DNA testing lies not only in its ability to implicate an individual in a
20 crime, but also to exonerate innocent individuals by ruling them out as suspects.

²⁷ Forensic Science Research and Training Center, <http://www.fbi.gov/lab/report/research.htm>

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 **Use of Human Biological Materials for Identification**

2
3 Another use of human biological materials is the identification of a person, such as in the
4 case of paternity testing, and cases of abduction or soldiers missing in action. For example, the
5 DOD DNA Specimen Repository for Remains Identification, along with the Armed Forces DNA
6 Identification Laboratory (AFDIL), comprises the DOD DNA Registry. The purpose of the DNA
7 Registry is to identify the remains of soldiers killed in combat or missing in action. The military's
8 policy ensures that specimens can only be used for remains identification and routine quality
9 control except where subpoenaed for the investigation or prosecution of a felony. The specimens
10 cannot be used without consent for any other purpose, such as paternity suits or genetic testing.
11 In addition, the specimens are considered confidential medical information, and military
12 regulations and federal law exist to cover any privacy concerns.

13
14 Recently, the AFDIL performed mitochondrial DNA (mtDNA) analysis on samples taken
15 from the skeletal remains of the Vietnam Unknown, which had been exhumed from the Tomb of
16 the Unknown at Arlington National Cemetery. This mtDNA profile was then compared to
17 mtDNA samples from living relatives of those deceased service members thought to have been in
18 the area at the time of death. On June 30, 1998, the Pentagon announced that the remains of the
19 memorial's Vietnam War soldier belong to Air Force pilot Michael J. Blassie, bringing closure to a
20 26-year ordeal for the Blassie family.

21

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 **Research Use of Human Biological Materials**

2
3 Historically, the science of pathology has led the way in the investigation of the
4 mechanisms of disease causation by proceeding progressively from whole organs and tissues to
5 cells, and then from the subcellular to the supramolecular and molecular manifestations of disease
6 expression (Rosai, 1997).

7
8 The range of medical benefits already obtained through the use of stored biological
9 samples is impressive.²⁸ For example,

10
11 In 1953 autopsies of young American soldiers killed in the Korean conflict revealed that
12 atherosclerosis begins at a much earlier age than was previously thought and that blockage
13 of arteries can be far advanced in the absence of symptoms; this research contributed to
14 findings concerning diet and exercise which have had a major public health impact in this
15 country, evidenced by a significant reduction in coronary artery disease (Enos, 1953;1955;
16 Solberg,1983; Strong, 1986).

17
18 In the late 1960s the study of samples of tissue from an unusual tumor of the vagina led to
19 the discovery that a non-steroidal estrogen hormone diethylstilbestrol (DES), then

²⁸ For a survey of such benefits, see David Korn, "Contribution of the Human Tissue Archive to the Advancement of Medical Knowledge and the Public Health" (A report to the National Bioethics Advisory Commission), January 1, 1998.

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 commonly given to women during pregnancy, is carcinogenic (Herbst
2 1970;1971;1974;1981).

3
4 Thirty years ago a series of studies on tissue samples of precancerous lesions of the uterine
5 cervix led to the routine use of Pap smears, which have played an important role in the
6 early diagnosis and more successful treatment of cervical cancer. (Herbst
7 1970;1971;1974;1981; Younge, 1949).

8
9 Analysis of tissue from autopsies of persons in certain occupations, such as chemical
10 manufacturing and uranium mining, have established causal links between exposure to
11 environmental substances and certain diseases, including a cancer of the liver known as
12 hepatic angiosarcoma and cancer of the bronchial epithelium (Creech, 1974; Falk, 1981;
13 Dannaher, 1981; Popper, 1978; Regelson, 1968; Roth, 1957).

14
15 The analysis of autopsied lung tissue from smokers played a major role in establishing that
16 smoking causes lung cancer, that the risk of cancer increases with the duration of
17 exposure to the chemicals contained in cigarette smoke, and that precancerous changes in
18 the bronchial epithelium can be reversed by cessation of smoking (Auerbach, 1962; 1979;
19 Flehinger, 1984; Frost, 1984).

20

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 As the science and knowledge of human disease have progressed, researchers have
2 developed or co-opted in steady succession the newest in scientific tools and methodologies.
3 Novel insights and expanded knowledge of agents and mechanisms of disease causation have
4 attracted a broader representation of the biomedical research community, including
5 immunologists, virologists, and geneticists, to the vast and valuable resource of human biological
6 materials for investigating human disease.

7
8 The tools used to analyze biological specimens have evolved from studies of morphology,
9 to light and electron microscopy, to sophisticated histochemical approaches to probe the chemical
10 composition of tissues, to the development of antibodies and gene probes. These tools have
11 revolutionized diagnostic and experimental pathology, as well as biomedical research. For
12 example, with appropriately tagged antibodies, it is possible to identify with great precision the
13 presence, location, or absence of specific protein molecules, and thereby begin to understand the
14 differences between normal tissues and pathological lesions.

15
16 It is within the past 30 years that we have entered the era of molecular and genetic
17 medicine. To understand the chemistry and genetics of normal biological functions and their
18 pathological arrangements, molecular biologists and pathologists increasingly collaborate to define
19 disease entities and their patterns of expression on the basis of pathologic criteria. All new
20 methods for the study of disease, whether they be monoclonal antibodies, new molecular genetic
21 technologies, or others yet to come, ultimately must be interpreted and validated with reference to

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 known disease entities and appropriate controls. That process frequently requires that the
2 methods be developed and evaluated with authenticated pathologic materials.

3

4 **The Value of Human Biological Materials to Cancer Research**

5

6 Clearly, pathology specimens have been invaluable resources for much cancer research.
7 The availability of large archives of carefully documented and clinically correlated specimens
8 permits the direct, much more rapid and less expensive approach of applying new detection
9 technologies directly to existing specimens. To try to initiate new prospective studies for each
10 new promising candidate gene for each of the many varieties of human cancer would not only be
11 extraordinarily costly in dollars and human effort, but would require study periods of many years,
12 or even decades, before definitive endpoints could be reached. In contrast, being able to apply
13 such new technologies to archival materials, where clinical course, therapeutic response and
14 outcome are already known, can save time and money, to say nothing of human suffering.

15

16 Recent progress in elucidating the initiation and progression of cancer has been most
17 dramatic and gratifying in the area of colorectal cancer (Lenauer, 1997). During the past decade
18 at least five specific genetic changes have been found that seem to constitute a progressive
19 pathway from normal to neoplastic colon tissues. Some of these revelations have been derived in
20 subsets of patients with known hereditary forms of colorectal cancer, while others appear more
21 generally to be present in those without known patterns of familial inheritance. At least one of

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 these genetic changes, the inactivation of the p53 gene, is known to occur, at least at times, in the
2 germline, while the others appear to be exclusively of somatic origin (Kinzler, 1991a; 1991b;
3 1996).

4
5 Research on the role of the p53 gene was enabled by the availability of a large human
6 tissue repository containing various forms and stages of colorectal cancers, as well as blood
7 specimens from the same patients. The tissue archive consisted largely of typically fixed and
8 embedded specimens, but in addition the scientists benefited immensely from a large collection of
9 frozen samples (Fearon, 1987; 1990; Goelz, 1985; Vogelstein, 1988; 1989).

10

11 There are countless examples in which investigators have used archival collections of
12 human tissues to search for specific chromosomal and genetic abnormalities of pathogenetic
13 interest. For example, a recent effort is attempting to decipher the genetics of prostate cancers,
14 the most common cancer in American men and a significant cause of cancer morbidity and
15 mortality (Smith, 1996). The goal of this new multi-institutional project is to differentiate the
16 various forms of prostate cancer, determine the most effective methods of treatment for each, and
17 eventually find a cure. The research is dependent on the availability of carefully characterized
18 tissue samples of prostate cancers and close correlation with clinical data to establish the natural
19 history of the tumors and their responses to different therapeutic strategies.

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 **Screening Human Biological Materials Archives to Track Viruses**

2

3 Stored biological samples can be valuable resources during public health emergencies,
4 when investigators are trying to identify or track an emerging virus. For example, in 1993 healthy
5 young people began dying in the Four Corners area of the American Southwest from a form of
6 pneumonia. Within months the Hantavirus was identified as the culprit. The solution of this
7 public health mystery can be attributed to many sources, including a suspicious clinician, an
8 epidemiologist, observant Navajo elders, and two human tissue archives. One archive was that of
9 the Centers for Disease Control and Prevention (CDC), containing vast libraries of viruses, viral
10 proteins, and serum specimens from around the world. The second archive held pulmonary
11 tissues from the autopsied victims of this strange new disease. The CDC archive permitted initial
12 serological screening tests, from which arose the first suggestion that a Hantavirus might be
13 involved. The initial screens were followed by tests of autopsy tissue samples with specific
14 Hantavirus monoclonal antibodies, and ultimately, the tissue samples were exposed to Hantavirus
15 genetic probes that revealed the presence and tissue distribution of viral genetic material. These
16 molecular tools permitted identification of the local deer mouse as the host of the pathogenic
17 Hantavirus. Studies of older human autopsy tissue established that the virus was, in fact, not a
18 new variant but a fairly old virus with a well-established symbiotic relationship with the mice in
19 the region (Wrobel, 1995).

20

21

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 **Human Tissue as a Singular Research Resource in Brain Research**

2

3 Sometimes use of biological materials is the only way to study certain aspects of human
4 disease, for example, to study certain diseases of the brain and central nervous system. Currently
5 there are no accurate animal or tissue culture models for many common diseases of the human
6 brain, including brain tumors and most of the primary neurodegenerative diseases (e.g.,
7 Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis, or Multiple Sclerosis).
8 Moreover, neurological samples, particularly of the brain, are often inaccessible.

9

10 Until relatively recently, most brain tumor research was conducted with animal models, or
11 with cultured immortalized glioma cell lines. Over the last five years, several studies have
12 correlated genetic alterations in human brain tumors with the degree of malignancy and prognosis.
13 These studies relied on frozen samples and specially fixed samples of human brain cancers to
14 assess gene amplification, gene deletions, gene mutations, and cell cycle parameters. Many
15 insights into the pathobiology of brain tumors are emerging from these studies (Blessed, 1968;
16 Masliah, 1991; Masters, 1989; Raine, 1997; Will, 1996).

17

18 **Longitudinal Studies**

19

20 Longitudinal studies, in which the same group of individuals is studied at intervals over a
21 period of time, often collect large numbers of specimens that can be used for both retrospective

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 and prospective research. Several well-known longitudinal studies have been conducted over the
2 years, including the Physicians' Health Study, the Nurses' Health Study, and the Framingham
3 Heart Study. Other large longitudinal studies include the Health Professionals Follow-up Study,
4 Mr. Fit, and the Family Heart Study.

5
6 The National Institutes of Health Women's Health Initiative (WHI) is a 15-year research
7 program, concluding in the year 2005, which focuses on the major causes of death, disability and
8 impaired quality of life in postmenopausal women. The overall goal of WHI is to reduce coronary
9 heart disease, breast and colorectal cancer, and osteoporosis in postmenopausal women through
10 prevention, intervention, and risk factor identification. The study will involve over 164,500
11 women of all races and socioeconomic backgrounds ages 50 to 79. The women are enrolled in
12 either a clinical trial or an observational study and will be followed for 8 to 12 years, during which
13 they will provide multiple blood samples. Participants sign a consent form that states that the
14 collection of blood samples is for use in future research, which may include genetic research, and
15 participants will not be informed of any test results. Participants may opt out of having their
16 samples used for genetic research, if they so desire. Participants' charts contain identifying
17 information including name, Social Security number, address and telephone number, and are bar-
18 coded. Blood samples are labeled with matching barcodes to link them back to the charts. All
19 study records are kept indefinitely for analysis and follow-up.

20

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 The NIH-sponsored Bogalusa Heart Study,²⁹ at the Louisiana State University, has been
2 ongoing since 1972 and is the longest and most detailed study of children in the world. The
3 purpose of the study is to understand the environmental and hereditary aspects of early coronary
4 artery disease, essential hypertension, and cardiovascular risk factors in African American and
5 Caucasian children in the semi-rural community of Bogalusa, Louisiana. In addition, over 160
6 substudies have been conducted including special studies on socioeconomic evaluations, blood
7 pressure, lipid levels, genetics, exercise, heart murmurs, and pathology. Knowledge gained in the
8 study has been applied to develop, test and evaluate methods for cardiovascular risk intervention.
9 The research involves longitudinal observations of more than 14,000 children and young adults,
10 some of whom will be followed until 38 years of age.

11

12 **Relying on Stored Samples for Locating Genes**

13

14 The human genome is the complete set of genetic instructions for an individual. Though
15 the DNA of any two people is roughly 99.9 percent identical, the variation in this last tenth of a
16 percent is the source of human biological diversity. Inherited susceptibility to various diseases—
17 which occurs when a gene fails to give correct instructions for a trait or function—is one small
18 part of this diversity.³⁰ Researchers search for genes by constructing finer and finer maps of
19 known gene locations and functions or by comparing DNA of affected and unaffected individuals.

²⁹ Bogalusa Heart Study, <http://www.mcl.tulane.edu/cardiohealth/bog.htm>

³⁰ Some research aims specifically to document human genetic variation, such as the Human Genetic Diversity Project of the National Institutes of Health. This project relies on stored blood samples collected as part of the

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 The first phase of identifying a disease-related gene is the collection of diagnostic
2 information and blood samples from an appropriate set of affected individuals and their relatives.
3 Typically, blood samples are drawn from family members, and the blood cells are immortalized so
4 they can be grown continuously in the laboratory. These immortalized cells, called cell lines, can
5 then be used to make DNA in unlimited quantities, allowing many different researchers access to
6 this resource. The art of this collection phase is in identifying appropriate families. At this stage,
7 having valid and definitive criteria that accurately determine a particular diagnosis may make the
8 difference between success and failure. The actual research designs selected in molecular genetics
9 studies and the selected participants are closely allied.

10

11 Linkage studies are widely used to detect and locate genes that determine susceptibility to
12 certain disorders, and are often based on the identification of large, densely affected families so
13 that the inheritance patterns of known sections of DNA (called “markers”) can be compared to
14 the family’s transmission of the disorder. If a known marker can be correlated with the presence
15 or absence of the disorder, this finding narrows the location of the suspect gene. Great strides in
16 linkage analysis, including laboratory and statistical methods, are increasing the power of this
17 method and decreasing its cost.

18

19 Linkage-disequilibrium studies in isolated populations capitalize upon the likelihood that
20 the susceptibility genes for a particular disorder probably came from one or a few founding

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 members. Whether the isolation is geographic or cultural, there are fewer individuals in the
2 community's genealogies and therefore fewer variations of the disease genes within the
3 population. This limited variation makes the search easier. In addition, the groups of markers that
4 surround each of these susceptibility genes are likely to have the same limited variation, which
5 further simplifies identification.

6

7 Association studies depend on the investigator hypothesizing that a specific gene or genes
8 may influence the disorder. In this type of study, the investigator examines whether those people
9 with the disorder have a different version of the gene than those without the disorder among
10 related or unrelated individuals.

11

12 Pinpointing the likely genetic anomaly in linkage and linkage-disequilibrium studies occurs
13 once an investigator narrows the search to a fairly small region in the genome. That "small"
14 region, however, may still be large enough to contain DNA that codes for dozens of traits, and
15 the investigator must now choose which parts of the region to study further. Because the Human
16 Genome Project is well on the way to identifying the location of all genes, this mapping of the
17 human genome will greatly simplify the identification of possible susceptibility genes. Once the
18 genes in a narrow DNA region are cataloged, they may each be tested and the susceptibility gene
19 identified.

blood samples used in the study.

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 An example of use of DNA repositories in linkage studies is the National Institute of
2 Mental Health's (NIMH) Genetics Initiative, begun in 1989.³¹ The goal of this special, large-scale
3 initiative in molecular genetics is to collect data from enough families to find the genes that
4 influence the onset of selected mental disorders. In addition, the Initiative enabled the
5 establishment of a national repository of demographic, clinical, diagnostic, and genetic data from
6 individuals with bipolar disorder, schizophrenia, or Alzheimer's disease to aid researchers in
7 identifying factors responsible for these disorders.

8
9 Diagnosis, family history, and DNA samples were collected using identical procedures
10 across multiple sites. The collecting researchers were given a 12-month proprietary period for
11 analyzing their data, at the end of which the data were made available to other qualified
12 investigators. The repository contains information on 862 individuals with Alzheimer's disease,
13 432 individuals with bipolar disorder, and 270 individuals with schizophrenia.

14
15 These researchers founded a resource that is in high demand. Requesting investigators
16 receive a file of demographic and diagnostic variables necessary for genetic analysis, with
17 accompanying documentation, access to DNA samples, a code manual listing additional clinical
18 and demographic data, and pedigree drawings.

19

³¹ See the National Institute of Mental Health at <http://www.nimh.nih.gov/>

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 Although there are numerous additional investigator-initiated studies, some have not been
2 able to recruit the necessary number of participants. Determining the necessary number is
3 problematic since such estimates are specific to the underlying mode of genetic transmission,
4 which is unknown. The more complex the transmission pattern, the larger the study must be.
5 Researchers who began collecting 10 years ago would have thought that 100 to 200 affected
6 individuals and relatives would have been adequate. Now that multiple susceptibility genes are
7 hypothesized, much larger samples than previously expected are necessary.

8

9 **Research Requiring Unique Tissue Collections**

10

11 Most researchers using human biological materials have relied on specimens from
12 pathology laboratories or existing tissue banks. However, some research studies require
13 specialized samples, i.e., with specific biological, clinical, or demographic characteristics, and
14 therefore must create a unique collection, which might have limited appeal to the broad research
15 community but high value to a small group of investigators.

16

17 For example, the University of Southern California AIDS-Malignancy Clinical Trials
18 Consortium (AM-CTC) helps design, develop, and conduct clinical trials of novel agents to be
19 used against AIDS-related malignancies. In addition, the AM-CTC stores tumor tissue and other
20 relevant biologic materials that have been obtained from patients participating in their trials. As
21 another example, Stanford University is investigating the role of environmental toxicants and

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 genetic susceptibility factors in the etiology of Amyotrophic Lateral Sclerosis (ALS). It has a
2 specialized collection of samples from patients with ALS.

3

4 Another example are the health examination surveys conducted by the Centers for Disease
5 Control and Prevention (CDC). Since 1960, the National Center for Health Statistics (NCHS) of
6 the CDC has conducted 7 health examination surveys of the population of the United States, the
7 National Health Examination Surveys (NHES) Cycles 1, 2 and 3, the National Health and
8 Nutrition Examination Surveys (NHANES) I, II and III, and the Hispanic Health and Nutrition
9 Examination Survey (HHANES). The surveys are designed to assess periodically the health and
10 nutritional status of children and adults in the United States through interviews and direct physical
11 examinations. The surveys employ interviews to answer questions about demographics,
12 socioeconomic status, dietary habits and health-related issues, and physical and dental
13 examinations, which include physiologic assessments and laboratory tests. Blood samples are
14 collected as part of the physiologic assessments, and placed in storage banks after laboratory tests
15 are completed.

16

17 Cumulatively, all of the health examination surveys have analyzed and banked samples
18 from more than 85,000 participants. The most recent survey, NHANES III³², conducted between
19 1988 and 1994, performed laboratory tests on approximately 29,314 people of all races aged one

³² National Health and Nutrition Examination Survey (NHANES),
<http://www.cdc.gov/nchswww/about/major/nhanes/nhanes.htm>

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 year and older from 81 counties in 26 states. Some of the 30 topics investigated in the NHANES
2 III included high blood pressure, high cholesterol, obesity, second-hand smoking, lung disease,
3 osteoporosis, HIV/AIDS, hepatitis, *helicobacter pylori*, immunization status, diabetes, allergies,
4 growth and development, anemia, dietary intake, antioxidants, and nutritional blood measures.
5 The NHANES I analyzed blood and urine samples from 23,808 study participants, and NHANES
6 II analyzed 20,322 samples. The HHANES was a one-time survey conducted from 1982 to 1984
7 that provided data on 11,653 people of Hispanic origin.

8

9 **Community-Based Studies to Determine Gene Frequency**

10

11 Certain diseases, particularly those with strong genetic components, are often found to be
12 more common in groups that share similar characteristics, whether they be genes, environmental
13 exposures, or lifestyles. For example, in the category of genetic disorders, Sickle Cell Anemia is
14 predominantly found in African Americans, Cystic Fibrosis in Caucasians, particularly of
15 European descent, Tay Sachs in individuals of Ashkenazi Jewish descent, and thalassemia in
16 Mediterranean populations. These are all autosomal recessive disorders, requiring two defective
17 genes for manifestation of the disorder, meaning otherwise healthy carriers (people with one
18 defective gene, and one normal gene) can only pass the disorder to their children by mating with
19 another carrier (and even then the odds in each pregnancy of passing on the disorder are 1 in 4).
20 The likelihood of two carriers producing offspring is greater in populations that are
21 geographically, politically, socially, or culturally isolated or segregated.

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 In the 1970s major Tay Sachs screening programs were begun in certain Jewish
2 communities in the United States. Because carrier status can be determined with a blood test,
3 some American Jewish community organizations urged persons of Ashkenazi descent to be tested
4 for carrier status. Tay Sachs is a lethal disease, severely affecting young children and resulting in
5 early and painful death. As a result of these large-scale screening programs, large quantities of
6 blood were stored after the carrier screening was completed. A collection of blood samples
7 stored at a Baltimore institution following a Tay-Sachs screening program in the 1970s became a
8 valuable resource to the investigators searching for clues to the genetic basis for *more to be*
9 *added here.*

10

11 In the 1980s there was growing evidence that there might be a genetic component to
12 breast cancer. In 1990, researchers had determined that mutations in a gene, labeled BRCA1, and
13 later another gene, BRCA2, cause inherited forms of breast and ovarian cancer. Knowing that
14 breast cancer runs in families, investigators collected data on women whose mothers,
15 grandmothers, or sisters had the disease (Easton, 1993; Tonin, 1995; add refs). Characteristic
16 mutations were found in Ashkenazi Jews. In one study, investigators aimed to estimate the risk of
17 breast and ovarian cancer in the Ashkenazi Jewish population through relatively simple assays to
18 determine the frequency of these mutations (Struewing, 1997). They enlisted the participation of
19 5,331 Jewish men and women over the age of 20 living in the Washington, D.C. area.
20 Participants provided family histories and blood samples. Participants were told at the beginning
21 of the study that they would not be informed of the results of the test. The scientists found that

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 over 2 percent of Ashkenazi Jews in the study population carried mutations in the BRCA1 or
2 BRCA2 gene, conferring increased risks of breast, ovarian, and prostate cancer (Struewing,
3 1997). In comparison, less than one percent of the non-Jewish population carry a mutated
4 BRCA1 and BRCA2 gene (Whittemore, 1997).

5

6 **CONCLUSIONS**

7

8 This chapter describes the large volume of pathology specimens that exist in the United
9 States at this time. It also provides examples of how samples of human biological materials have
10 been and continue to be invaluable resources for a wide variety of studies aimed at understanding
11 the etiology and progression of disease, the effects of viral and environmental impacts on health,
12 and for finding genes that might be responsible for the underlying mechanisms of disease.

13

14 Many of the specimens sitting in repositories of human biological materials will never be
15 used in research. Many research studies will rely on large numbers of unidentified research
16 samples to investigate the basic mechanisms of health and disease, or to screen samples for
17 evidence of disease, environmental insult, or responsiveness to potential therapeutic agents.
18 Other studies will rely on research samples that are at least somewhat identifiable. That is, an
19 investigator might initially request samples with no linking data and later request additional
20 clinical data linked to the sample. In still other cases, the research might require that the
21 investigator know who provided the sample, or the sample source might even be a patient, as well

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 as a research subject, of the scientist. How human biological materials are used in research and
2 the extent to which research samples can be linked to their sources are critical considerations
3 when trying to determine risks and necessary protections.

4 5 **REFERENCES**

- 6
7 1. American Medical Association. 1997. Graduate Medical Education Directory 1997-1998.
8 American Medical Association, Chicago.
9
10 2. Andrews LB. 1995. State laws and regulations governing newborn screening. American Bar
11 Foundation, Chicago.
12
13 3. Auerbach O., Hammond, E.C., Garfinkel, L., "Changes in bronchial epithelium in relation to
14 cigarette smoking, 1955-1960 vs 1970-1977," New England Journal of Medicine (300):381-
15 386, 1979.
16
17 4. Auerbach, O., Stout, A.P., Hammond, E.C., Garfinkel, L., "Changes in bronchial epithelium in
18 relation to sex, age, residence, smoking and pneumonia," New England Journal of Medicine
19 (67):111-119, 1962.
20
21 5. Blessed, G., Tomlinson, B.E., Roth, M., "The association between quantitative measures of
22 dementia and the senile change in the cerebral gray matter of elderly subjects," British Journal
23 of Psychiatry (114):797-811, 1968.
24
25 6. Clinical Laboratory Improvement Amendments. 1996. Clinical Laboratory Improvement
26 Amendments of 1988 (CLIA). 42 CFR 493 (10-1-96 Edition); pp. 796-921.
27
28 7. Creech, J.S., Johnson, M.N., "Angiosarcoma of liver in the manufacture of polyvinyl
29 chloride," Journal of Occupational Medicine (16):150-151, 1974.
30
31 8. Dannaher, C.L., Tamburro, C.H., Yam, L.T. "Occupational carcinogenesis: The Louisville
32 experience with vinyl chloride-associated hepatic angiosarcoma." American Journal of
33 Medicine (70):279-287, 1987.
34
35 9. Department of Health and Human Services. 1991. Clinical Laboratory Improvement
36 Amendments (CLIA). November 29, 1992. Press Release 1991.11.29.
37

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

- 1 10. Dunlop, M.G., Farrington, S.M., Carothers, A.D., et. al., "Cancer risk associated with
2 germline DNA mismatch repair gene mutations," *Hum Mol Genet* 1997 Jan; 6(1):105-110.
3
- 4 11. Enos WF, Holmes RH, Beyer J. Coronary disease among United States soldiers killed in
5 action in Korea. *JAMA* 1953; 152:1090-1093.
6
- 7 12. Enos WF, Beyer JC, Holmes RH. Pathogenesis of coronary disease in American soldiers killed
8 in Korea. *JAMA* 1955; 152:912-914.
9
- 10 13. Falk H, Herbert J, Crawley S, et. al: Epidemiology of hepatic angiosarcoma in the United
11 States: 1964-1974. *Environ Health Perspectives* 1981; 41:107-113.
12
- 13 14. Fearon ER, Hamilton SR, Vogelstein B. Clonal analysis of human colorectal tumors. *Science*
14 1987 oct 9; 238(4824):193-197.
15
- 16 15. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990 Jun 1;
17 61(5):759-767.
18
- 19 16. Finn P. 1997. Revolution Underway in Use of DNA Profiles. Bid to Link U.S. Databanks is
20 Crime-Solving Edge. *The Washington Post*. Sunday, November 16, 1997; B4.
21
- 22 17. Flehinger BJ, Melamed MD, Zaman MB, et. al: Early lung cancer detection: Results of the
23 initial (prevalence) radiologic and cytologic screening in the Memorial Sloan-Kettering study.
24 *Am Rev Resp Dis* 1984; 130:555-560.
25
- 26 18. Frost JK, Ball WCJr, Levin ML, et. al: Early lung cancer detection: results of the initial
27 (prevalence) radiologic and cytologic screening in the Johns Hopkins study. *Am Rev Respir*
28 *Dis* 1984; 130:549-554.
29
- 30 19. Gluckman E, Broxmeyer HE, Auerbach AD et al., 1989. Hematopoietic reconstitution in a
31 patient with Fanconi's anemia by means of umbilical cord blood from an HLA-identical sibling.
32 *New England Journal of Medicine* 321: 1174-1178.
33
- 34 20. Goetz SE, Vogelstein B, Hamilton SR, Feinberg AP. Hypomethylation of DNA from benign
35 and malignant human colon neoplasms. *Science* 1985 Apr 12; 228(4696):187-190.
36
- 37 21. Herbst AL, Scully, RE. Adenocarcinoma of the vagina in adolescence. *Cancer*, 1970; 25:745-
38 757.
39
- 40 22. Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina. *NEJM* 1971; 284:878-
41 881.
42

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

- 1 23. Herbst AL, Robboy SJ, Scully RE, Poskanzer DC. Clear-cell adenocarcinoma of the vagina
2 and cervix in girls: Analysis of 170 registry cases. *Am J Obstet Gynecol* 1974; 119:713-724.
3
- 4 24. Herbst AL. Clear cell adenocarcinoma and the current status of DES - exposed females.
5 *Cancer* 1981 July 15 Supplement; 48:484-4881.
6
- 7 25. Kinzler KW, Vogelstein B. Lessons from hereditary colorectal cancer. *Cell* 1996 Oct 18;
8 87(2):159-170.
9
- 10 26. Kinzler KW, Nilbert MC, Su LK, et. al: Identification of FAP locus genes from chromosome
11 5q21. *Science* 1991 Aug 9; 253(5020):661-665.
12
- 13 27. Kinzler HW, Nilbert MC, Vogelstein B, et. al: Identification of a gene located at chromosome
14 5q21 that is mutated in colorectal cancers. *Science* 1991 Mar 15; 251(4999):1366-1370.
15
- 16 28. Lengauer C, Kinzler KW, Vogelstein B. Genetic instability in colorectal cancers. *Nature* 1997
17 Apr 10; 386(6625):623-627.
18
- 19 29. Masliah E, Terry RD, Alford M, et. al: Cortical and subcortical patterns of synaptophysin-like
20 immunoreactivity in Alzheimer's disease. *Am J Pathol* 1991; 138:235-246.
21
- 22 30. McEwen JE and Reilly PR. 1994. Stored Guthrie Cards as DNA "Banks". *American*
23 *Journal of Human Genetics* 55: 196-200.
24
- 25 31. McEwen JE and Reilly PR. 1995. A survey of DNA diagnostic laboratories regarding DNA
26 banking. *American Journal of Human Genetics* 56(6): 1477-1486.
27
- 28 32. McEwen JE. 1997. DNA Data Banks. In Genetic Secrets: Protecting Privacy and
29 Confidentiality in the Genetic Era, MA Rothstein, ed., Chapter 11.
30
- 31 33. National Heart, Lung, and Blood Institute. 1996. Blood Specimen Repository: 1996
32 Catalog.
33
- 34 34. Perdahl-Wallace EB. 1997. Placental cord blood transplantation. *Transplant Forum* 4(2):
35 4-5.
36
- 37 35. Popper H, Thomas LB, Telles NC, et. al: Development of hepatic angiosarcoma in man
38 induced by vinyl chloride, thorotrast, and arsenic - comparison with cases of unknown
39 etiology. *Am J Pathol* 1978; 92:349-376.
40
- 41 36. Raine CS. The norton lecture: A review of the oligodendrocyte in the multiple sclerosis lesion.
42 *J Neuroimmunol* 1997; 77:135-152.

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

- 1
- 2 37. Regelson W, Kin U, Ospimam J, et. al: Hemangioendothelial sarcoma of liver from chronic
- 3 arsenic intoxication by Fowler's Solution. *Cancer* 1968; 21:514-522.
- 4
- 5 38. Rosai J. Pathology. A Historical Opportunity. *Am J Path* 1997; 151: 3-6.
- 6
- 7 39. Roth F. The sequelae of chronic arsenic poisoning in Moselle vintners. *German Med Monthly*
- 8 1957; 2:172-175.
- 9
- 10 40. Smith JR, Freije D, Carpten JD, et. al: Major susceptibility locus for prostate cancer on
- 11 chromosome 1 suggested by a genome-wide search. *Science* 1996; 274:1371-1374.
- 12
- 13 41. Solberg LA, Strong JP. Risk factors and atherosclerotic lesions. A review of autopsy studies.
- 14 *Arteriosclerosis* 1983; 3:187-198.
- 15
- 16 42. Strong JP. Coronary atherosclerosis in soldiers. A clue to the natural history of atherosclerosis
- 17 in the young. *JAMA* 1986; 256:2863-2866.
- 18
- 19 43. Struewing JP, Hargte P, Wacholder S, Baker SM, Berlin M, McAdams M, Timmerman MM,
- 20 Brody LC, and Tucker MA. 1997. The risk of cancer associated with specific mutations of
- 21 BRCA1 and BRCA2 among Ashkenazi Jews. *N Engl J Med* 336:1401-1408.
- 22
- 23 44. Sugarman J, Kaalund V, Kodish E, Marshall MF, Reisner EG, Wilfond BS, and Wolpe PR.
- 24 1997. Ethical issues in umbilical cord blood banking. *Journal of the American Medical*
- 25 *Association* 278(11): 938-943.
- 26
- 27 45. Technical Working Group on DNA Analysis Methods (TWGDAM). 1989. The Combined
- 28 DNA Index System (CODIS): A theoretical model. In DNA Fingerprinting: An Introduction,
- 29 LT Kirby, ed., New York: Stockton Press, pp. 279-317.
- 30
- 31 46. Vogelstein B, Fearon ER, Kern SE, et. al: Allelotype of colorectal carcinomas. *Science* 1989
- 32 Apr 14; 244(4901):207-211.
- 33
- 34 47. Vogelstein B, Fearon ER, Hamilton SR, et. al: Genetic alterations during colorectal-tumor
- 35 development. *N Engl J Med* 1988 Sep 1; 319(9):525-532.
- 36
- 37 48. Wagner JE, Kernan NA, Steinbuch M, Broxmeyer HE, and Gluckman E. 1995. Allogeneic
- 38 sibling umbilical cord blood transplantation in children with malignant and non-malignant
- 39 disease. *Lancet* 346: 214-219.
- 40

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

- 1 49. Wagner JE, Rosenthal J, Sweetman R et al. 1996. Successful transplantation of HLA-
2 matched and HLA-mismatched umbilical cord blood from unrelated donors: Analysis of
3 engraftment and acute graft-versus host disease. *Blood* 88: 795-802.
4
- 5 50. Will RG, Ironside JW, Zeidler M, et. al: A new variant of Creutzfeldt-Jakob disease in the
6 UK. *Lancet* 1996; 347:921-925.
7
- 8 51. Whittemore AS, Gong G, and Itnyre J. 1997. Prevalence and contribution of BRCA1
9 mutations in breast cancer and ovarian cancer: Results from three U.S. population-based
10 case-control studies of ovarian cancer. *Am J Hum Genet* 60:496-504.
11
- 12 52. Wrobel, S., "Serendipity, science and a new Hantavirus," *FASEB J* 1995; 9:1247-1254.
13
- 14 53. Younge PA, Hertig AT, Armstrong D. A study of 135 cases of carcinoma in situ of the cervix
15 at the Free Hospital for Women. *Am J Obstet Gynecol* 1949; 58:867-892.
16
- 17
- 18
- 19

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

1 **Table 1. Stored Human Biological Materials in the United States**

2

Type of Repository	# of cases	# of specimens	Cases/Year
Large Tissue Banks, Repositories, and Core Facilities	>2.6 million	>96 million	364,825
Longitudinal Studies	>263,500	>263,500	
Pathology Specimens	>160 million	>160 million	>8 million
Newborn Screening Laboratories	>13.5 million	>13.5 million	<10,000 to >50,000
Forensic DNA Banks	380,000	380,000	
Umbilical Cord Blood Banks	18,300	18,300	

July 2, 1998: This is a staff draft report developed for the National Bioethics Advisory Commission. It does not represent conclusions and should not be cited or referenced as such.

Organ Banks		>75,500	>75,500
Blood Banks		~12 million	~12 million
Grand Total	>>176.5 million	>>282 million	>20 million

1