

# Deidentification and Reidentification in Returning Individual Findings from Biobank and Secondary Research: Regulatory Challenges and Models for Management

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## I. INTRODUCTION

The consensus paper that anchors this Symposium breaks new ground contemplating the practicalities of returning incidental findings (IFs) and other individual research results (IRRs) to the contributors of specimens or DNA data stored in biobanks and used for genetic and genomic research.<sup>1</sup> Actors within the biobank system who conscientiously seek to address these issues will confront dizzying regulatory complexities at every turn. While acknowledged in the consensus paper, these complexities were too broad for detailed consideration in that paper. This Article fills in the compliance challenges connected to one key step in the return of IFs and IRRs: the reidentification of specimens or data.

The large majority of genetic and genomic research in the United States is subject to either the Department of Health and Human Services (DHHS) Common Rule<sup>2</sup> that governs human

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1. Susan M. Wolf et al., *Managing Research Results and Incidental Findings in Genomic Research Involving Biobanks & Archived Datasets*, 14 GENETICS MED. 361 (2012).

2. Multiple federal agencies have adopted the Common Rule. Each agency separately codifies the rule in the Code of Federal Regulations. The agency most relevant to this discussion is the Department of Health and Human Services, which has codified the Common Rule at Subpart A of 45

subjects research, the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule,<sup>3</sup> or both. Both of these regimes create huge incentives for biobanks to provide and for researchers to use specimens or data that have been deidentified according to specific definitions spelled out in the regulations or in guidance materials supplementing the regulations. The reasons for promoting deidentification are sound. By encouraging the stripping of identifying information from specimens or data used by researchers, these regulations and guidance materials aim to reduce threats to the personal privacy of contributors. But these rules do not accommodate emerging views, exemplified by the consensus paper, about the desirability of returning IFs and IRRs to contributors in at least some circumstances.<sup>4</sup> Indeed, a recent Advanced Notice of Proposed Rulemaking to amend the Common Rule,<sup>5</sup> while simplifying some aspects of the regulations, would further entrench deidentification as a fundamental attribute of most genetic and genomic research using specimens and data stored in biobanks. This reliance on deidentification creates obstacles for any attempt to return IFs or IRRs.

Following this Introduction, this Article proceeds in Part II to summarize the tangle of regulatory requirements implicated by the reidentification of specimens or data in order to return IFs and IRRs. Part III examines the recently issued Advance Notice of Proposed Rulemaking that contemplates changing the Common Rule in ways that would further complicate return of IFs and IRRs within biobank research systems. Part IV then describes the regulatory challenges that specimen or data collection sites, biobanks, and researchers face as a result of these current and proposed rules. Finally, Part V offers some models for biobank systems to address those challenges.

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C.F.R. § 46. 45 C.F.R. §§ 46.101–46.124 (2011). For more discussion of the Common Rule, see *infra* Part II.A.

3. 45 C.F.R. §§ 160.101–160.552, 162.100–162.1802, 164.102–164.534 (2011). For more discussion of HIPAA and the HIPAA Privacy Rule, see *infra* Part II.B.

4. Wolf et al., *supra* note 1, at 369.

5. Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44,512, 44,513–14 (July 26, 2011) (to be codified at 45 C.F.R. pts 46, 160, 164, and 21 C.F.R. pts 50, 56). For more discussion of these proposed amendments, see *infra* Part III.

## II. CURRENT REGULATORY REQUIREMENTS FOR BIOBANK RESEARCH UNDER THE COMMON RULE AND HIPAA

A biobank research system encompasses three roles: (1) initial collection sites feeding specimens or data into the system, (2) biobanks aggregating those specimens or data for downstream research use, and (3) secondary researchers obtaining and using specimens or data from biobanks.<sup>6</sup> In the simplest model, a collection site serves merely as the conduit between individuals who contribute specimens or related data and a biobank that, in turn, provides those specimens or data to secondary researchers who actually conduct the research and analysis. In reality, however, the design is often far more complex and differs significantly from one biobank system to the next. Research activities may take place anywhere within the system. Potential collection sites include both primary researchers conducting individual research studies and clinical sources such as hospitals that may or may not conduct research. Furthermore, biobanks may collect their own specimens or data, partly or entirely eliminating the distinct role of the collection site in that biobank system. Some biobanks, such as the Framingham Heart Study<sup>7</sup> and Coriell Personalized Medicine Collaborative,<sup>8</sup> conduct their own research in addition to aggregating and distributing specimens and data, while others, such as the Rhode Island BioBank,<sup>9</sup> serve only the latter function. Thus, a biobank may be a primary researcher if it is a collection site and it conducts research; a secondary researcher if it conducts research on pre-existing specimens or data obtained from primary collection sites; or not a researcher at all if it only aggregates and distributes pre-existing specimens and data.

Depending on the type of researching entity, the particular

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6. Wolf et al., *supra* note 1, at 362, fig. 1.

7. *About the Framingham Heart Study*, FRAMINGHAM HEART STUDY, <http://www.framinghamheartstudy.org/about/index.html> (last updated Apr. 5, 2012).

8. *About the Study*, CORIELL PERSONALIZED MED. COLLABORATIVE, <http://cpmc.coriell.org/Sections/About/?SID=9> (last visited Apr. 16, 2012).

9. Brown Univ., *Core Facilities, Research Facilities and Teaching Facilities*, CENTER FOR BIOMEDICAL ENGINEERING, [http://www.brown.edu/Departments/Center\\_for\\_Biomedical\\_Engineering/about/facilities\\_and\\_centers/facility\\_descriptions](http://www.brown.edu/Departments/Center_for_Biomedical_Engineering/about/facilities_and_centers/facility_descriptions) (last visited Apr. 16, 2012).

activities it conducts, and the level of identifiability of specimens or data used, research on specimens or data may be subject to multiple overlapping regulatory regimes. The most prominent of these are the Common Rule, which governs most federally funded research involving human subjects, and HIPAA's Privacy Rule, which limits the research use and disclosure of certain kinds of health information.<sup>10</sup> Generally speaking, the Common Rule and HIPAA provide oversight for most biobank-related research activities and require permission from contributors of specimens or data before researchers may take certain actions, including commencement of research and disclosure of contributor information.<sup>11</sup> Because both regulatory schemes depend on deidentification of specimens and data as crucial components of their privacy protections, both schemes also create obstacles to the reidentification necessary as a step for returning IFs and IRRs.<sup>12</sup>

In this Part we discuss what is required of a biobank research system under the Common Rule and HIPAA, and of whom it is required. We look at each of the primary regulatory regimes and consider the impact on collections sites, biobanks, and secondary researchers. We note that various players in the

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10. While other regulatory schemes may bind entities involved in biobank research, including the Food and Drug Administration (FDA) rules regulating investigations involving human subjects and the Privacy Act, detailed consideration of the incentives provided and challenges raised by those regulatory schemes are beyond the scope of this article. It suffices to say that the incentives and challenges imposed by the FDA regulations are likely to diverge significantly from those presented by the Common Rule and HIPAA for two reasons. First, the FDA rules do not encourage deidentification in the same way that the Common Rule and HIPAA do because FDA does not find that the regulatory requirements loosen when specimens and data are deidentified. See FDA, GUIDANCE ON IN VITRO DIAGNOSTIC DEVICE STUDIES USING LEFTOVER HUMAN SPECIMENS THAT ARE NOT INDIVIDUALLY IDENTIFIABLE 6 (Apr. 25, 2006), available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071265.pdf>. Second, to the extent that reidentification violates the rules, the FDA imposes penalties that are considerably more severe than those that accompany violations of the Common Rule and HIPAA. See, e.g., 21 U.S.C. § 333(a) (2006) (allowing for criminal charges). Similarly, the Privacy Act may have some application in this type of research; it requires Federal Agencies to provide protections for the collection, use, and dissemination of personally identifiable information that is maintained in systems of records under their control. It prohibits the disclosure of information that is retrieved by individual identifiers without prior consent or notice. 5 U.S.C. § 552a (2006).

11. See *id.*

12. See *infra* Parts A & B.

biobank system may take steps beyond what the Common Rule or HIPAA may require. For example, collection sites frequently require recipients of specimens or data to abide by the terms of a material transfer agreement (MTA).<sup>13</sup> Although MTAs were initially developed to clarify the allocation of intellectual property rights between the sender and recipient,<sup>14</sup> biobanks are increasingly using MTAs to address issues of research ethics including data privacy.<sup>15</sup>

#### A. REGULATORY REQUIREMENTS UNDER THE COMMON RULE

The Common Rule was established in 1991 to create uniform protection for human research subjects. The Rule reaches certain research “conducted, supported or otherwise subject to regulation” by fifteen federal agencies, including the National Institutes of Health,<sup>16</sup> as well as research by any institution claiming federal-wide assurance for the protection of human subjects by adopting the standards and rules articulated in the Common Rule.<sup>17</sup> The Common Rule only attaches when “research involv[es] human subjects.”<sup>18</sup> Both “research” and “human subject” have specific definitions under the Rule. “Research” is limited to “systematic investigation[s]... designed to develop or contribute to the generalizable

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13. See, e.g., MALARIA SPECIMEN BANK, WORLD HEALTH ORGANIZATION, MATERIAL REQUEST FORM & MATERIAL TRANSFER AGREEMENT 6–9, available at [http://www.who.int/tdr/research/malaria/rapid\\_diagnostics/malaria-material-request-form.pdf](http://www.who.int/tdr/research/malaria/rapid_diagnostics/malaria-material-request-form.pdf).

14. See *A Quick Guide to Material Transfer Agreements at UC Berkeley*, UNIV. CAL. BERKELEY, <http://www.spo.berkeley.edu/guide/mtaquick.html> (last visited Mar. 4, 2012).

15. See MALARIA SPECIMEN BANK, *supra* note 13, at 7–8.

16. 45 C.F.R. § 46.101 (2011); see Federal Policy for the Protection of Human Subjects (‘Common Rule’), U.S. DEP’T HEALTH & HUM. SERVS., <http://www.hhs.gov/ohrp/humansubjects/commonrule/index.html> (last visited Apr. 16, 2012) (listing agencies that have adopted the Common Rule). In addition to the fifteen agencies adhering to the Common Rule by regulation, an executive order applies the Common Rule to the Central Intelligence Agency, and the Department of Homeland Security voluntarily complies with the Rule. Exec. Order No. 12,333, 46 Fed. Reg. 59,941 (Dec. 4, 1981); *Regulations*, U.S. DEP’T HEALTH & HUM. SERVS., <http://www.hhs.gov/ohrp/humansubjects/index.html> (last visited Apr. 16, 2012).

17. *Federalwide Assurance (FWA) for the Protection of Human Subjects*, U.S. DEP’T HEALTH & HUM. SERVS., <http://www.hhs.gov/ohrp/assurances/assurances/filasurt.html> (last updated June 17, 2012).

18. 45 C.F.R. § 46.101(a) (2011).

knowledge.”<sup>19</sup> A “human subject” is defined as “a living individual about whom an investigator . . . conducting research obtains (1) [d]ata through intervention or interaction with the individual, or (2) [i]dentifiable private information.”<sup>20</sup> The Common Rule further stipulates that private information “must be individually identifiable,” meaning that “the identity of the subject is or may readily be ascertained by the investigator or associated with the information.”<sup>21</sup>

Because the Common Rule definition of research requires the researcher to acquire individually identifiable private information, the Common Rule does not typically regulate research involving deidentified information.<sup>22</sup> The Office for Human Research Protections (OHRP)<sup>23</sup> has explained that there are two situations in which research involving deidentified biospecimens or data does not qualify as human subjects research and thus lies outside the scope of the Common Rule entirely. These situations arise when the deidentified specimens or data were not collected for the purposes of that research<sup>24</sup> or when the deidentified specimens or data were obtained from another institution.<sup>25</sup> The Common Rule further provides a categorical exemption for “[r]esearch[] involving the collection or study of existing data . . . pathological specimens, or diagnostic specimens, if . . . the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through

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19. 45 C.F.R. § 46.102(d) (2011).

20. 45 C.F.R. § 46.102(f) (2011).

21. *Id.*

22. It is important to note that under the current regulations, HIPAA and the Common Rule use slightly different definitions of “deidentified.” Throughout this Article, we use “deidentified” to mean satisfying either the Common Rule or HIPAA standard. The mismatching definition may soon be irrelevant, as a recent Advanced Notice of Proposed Rulemaking from the Department of Health and Human Services proposed that the two standards be harmonized. *See infra* notes 104–110 and accompanying text.

23. OHRP is an office within the U.S. Department of Health and Human Services that provides clarification on regulatory requirements related to human subjects research, including extensive guidance interpreting the Common Rule. *See About OHRP*, OFF. FOR HUM. RES. PROTECTIONS, <http://www.hhs.gov/ohrp/about/index.html> (last visited Dec. 13, 2011).

24. *OHRP—Guidance on Research Involving Coded Private Information or Biological Specimens*, OFF. FOR HUM. RES. PROTECTIONS (Oct. 16, 2008), <http://www.hhs.gov/ohrp/policy/cdebiol.html>.

25. *Guidance on Engagement of Institutions in Human Subjects Research*, OFF. FOR HUM. RES. PROTECTIONS (Oct. 16, 2008), <http://www.hhs.gov/ohrp/policy/engage08.html>.

identifiers linked to the subjects.”<sup>26</sup> This exempt category of research is different from research identified by OHRP as non-human subjects research. In the latter case, the research is outside of the scope of the Common Rule entirely because it does not involve human subjects.<sup>27</sup> By contrast, in the former case, the research does involve human subjects, but is exempt from Common Rule requirements if the researcher refrains from recording information about the subjects in identifiable form.<sup>28</sup> This distinction is important because the DHHS and agency heads retain final authority for determining whether a particular human subjects research study does in fact qualify as exempt under the Common Rule,<sup>29</sup> but they have no such authority for research that does not involve human subjects.

The current Common Rule provides three levels of independent review for research protocols based on the level of risk posed.<sup>30</sup> Research studies posing greater than a minimal risk<sup>31</sup> to subjects require review by a fully convened Institutional Review Board (IRB),<sup>32</sup> the highest level of independent review. Studies posing no more than minimal risk are eligible for expedited review,<sup>33</sup> which is typically performed by a single IRB reviewer who can either approve the protocol or find that the protocol poses more than minimal risk and requires full IRB review.<sup>34</sup> Studies exempt from or outside of

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26. 45 C.F.R. § 46.101(b)(4) (2011).

27. See generally Kyle Bertram Brothers & Ellen Wright Clayton, *Human Non-Subjects Research: Privacy and Compliance*, 10 AM. J. BIOETHICS 15–17 (2010).

28. OHRP—*Guidance on Research Involving Coded Private Information or Biological Specimens*, *supra* note 24.

29. 45 C.F.R. § 46.101(c) & (d) (2011).

30. Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44,514 (July 26, 2011) (to be codified at 45 C.F.R. pts 46, 160, 164, and 21 C.F.R. pts 50, 56).

31. 45 C.F.R. § 46.102(i) (2011) (“Minimal risk means that the probability and magnitude of harm and discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”).

32. See 45 C.F.R. § 46.109 (2011) (outlining the IRB’s responsibilities); 45 C.F.R. § 46.110 (2011) (allowing expedited review for studies posing no more than minimal risk to study subjects).

33. A list of categories of research eligible for expedited review is published by the Secretary of DHHS. 45 C.F.R. § 46.110(a).

34. 45 C.F.R. § 46.110.



the Common Rule's reach comprise the lowest risk category<sup>35</sup> and have no IRB requirements at all.<sup>36</sup>

When the Common Rule requires review by a fully-convened IRB, researchers proposing non-exempt human subjects research must obtain approval from the research site's IRB prior to commencing the study.<sup>37</sup> The IRB must evaluate ethical concerns posed by research protocols involving human subjects, approve protocols based on adequate handling of these concerns, and provide continuing review and record keeping for the duration of the approved research.<sup>38</sup> The Common Rule specifically directs the IRB to assess a number of factors, including: minimization of risks to human subjects; reasonability of risks in relation to anticipated benefits, if any; adequacy of informed consent; sufficiency of data monitoring; and protection of human subjects' privacy and the confidentiality of data.<sup>39</sup> The core of the IRB's charge is to oversee the ethical soundness of a research project from the initial submission of the protocol all the way through the completion of the project and, sometimes, even after completion if additional long-term concerns have been identified.<sup>40</sup> As noted above, when the study poses no more than minimal risks, a single IRB reviewer may conduct an expedited review of the study.<sup>41</sup>

When an institution conducting research that is regulated by the Common Rule "materially fail[s] to comply with the terms" of the rule, the "department or agency support for any project may be terminated or suspended."<sup>42</sup> Thus, the failure to obtain compliant informed consent and IRB approval, or failure to comply with requirements for an exemption, may result in the defunding of the project. Of particular significance for this Article, when deidentified information or specimens are reidentified, the research now involves human subjects and is

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35. Cf. OHRP—*Guidance on Research Involving Coded Private Information or Biological Specimens*, *supra* note 28 (instructing that research involving deidentified specimens and information does not involve human subjects and is therefore not bound by the Common Rule).

36. See *supra* notes 23–29 and accompanying text.

37. 45 C.F.R. § 46.109.

38. See *id.*

39. 45 C.F.R. § 46.111 (2011).

40. See *id.*

41. 45 C.F.R. § 46.110 (2011).

42. 45 C.F.R. § 46.123(a) (2011).

bound by the Common Rule.<sup>43</sup> If the researcher has not obtained IRB approval and informed consent from research participants, the material terms of the Common Rule have been violated and the project may lose its funding.<sup>44</sup>

Initial collection sites, biobanks, and downstream secondary researchers may be subject to the Common Rule, and potentially to IRB oversight, depending on a number of conditions, as depicted in Figure 1. Those conditions are: (1) whether the research involves newly collected or pre-existing specimens and data; (2) whether the entity is conducting research; (3) whether the specimens and data are recorded in a manner that is individually identifiable; and (4) whether the research involves deidentified specimens or data.

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43. OHRP—*Guidance on Research Involving Coded Private Information or Biological Specimens*, *supra* note 28.

44. See 45 C.F.R. § 46.123(a).

Biobank System Entity	Are the specimens/data new or pre-existing (collected for a different purpose or obtained from another institution)?	Are the specimens/data being used for research?	Are the specimens/data identifiable?	Will the investigator record information in a manner that subjects cannot be identified?
Primary Collection Site	New	No NOT HSR* Yes IC+IRB†	N/A	N/A
Biobank	New	No NOT HSR Yes IC+IRB	N/A	N/A
Secondary Researcher	Pre-Existing	No NOT HSR	No NOT HSR Yes	No IC+IRB Yes EXEMPT‡
		Yes	No NOT HSR Yes	No IC+IRB Yes EXEMPT

\* Not considered human subjects research (HSR); † Must satisfy Common Rule requirements for informed consent (IC) and IRB review; ‡ Exempt from Common Rule requirements for IC and IRB review

Figure 1. Applicability of the Common Rule to Biobank System Entities

The first locus where the Common Rule might attach is at the initial collection site obtaining new specimens or data.<sup>45</sup> The Common Rule requirements for IRB review and informed consent apply when new specimens or data are collected for research purposes.<sup>46</sup> In the context of a biobank research system, these primary collection sites may include typical academic or medical research institutions that obtain specimens or data for their own primary research studies prior to transmitting the specimens or data to a biobank. By contrast, clinical collection sites such as hospitals may contribute specimens and data to biobanks without ever conducting their own research and, thus, would not be regulated by the Common Rule.<sup>47</sup> As explained below, however, clinical sites are more likely than research sites to be covered by HIPAA.<sup>48</sup>

Downstream researchers using pre-existing collections of specimens or data from biobanks for secondary research also may be subject to the Common Rule in some circumstances. They are required to comply with informed consent and IRB review requirements whenever they use pre-existing specimens or data that are identified or that might be readily individually identified by the investigator under the Common Rule definition.<sup>49</sup> In some instances, informed consent requirements for such secondary studies on identifiable pre-existing specimens or data can be satisfied if the original collection site obtained general consent for future research, or if the secondary researchers' IRB finds the original consent is compatible with the secondary research use.<sup>50</sup> Although they

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45. 45 C.F.R. § 46.102(d) (2011).

46. See *OHRP—Guidance on Research Involving Coded Private Information or Biological Specimens*, *supra* note 24.

47. *Id.* at 5.

48. See *infra* notes 66–70 and accompanying text.

49. See 45 C.F.R. § 46.101 (2011).

50. Sec'y's Advisory Comm. on Human Research Prots., *FAQs, Terms and Recommendations on Informed Consent and Research Use of Biospecimens*, DEPT HEALTH & HUMAN SERVS. 4 (July 20, 2010), <http://www.hhs.gov/ohrp/sachrp/commsec/attachmentdfa%27stermsandrecommendations.pdf.pdf>.

("The determination of whether a proposed secondary research use is compatible with the original consent will be context-specific based on a range of considerations. If the original consent form specifically prohibited the proposed research activity, it is presumed the research is not allowable. If the

technically fall within the scope of the Common Rule, downstream researchers recording information in a manner that does not allow identification of contributors are exempt from the Rule and are not required to obtain informed consent and IRB review when using pre-existing specimens or data.<sup>51</sup>

On the other hand, secondary researchers are not engaged in human subjects research at all when they use pre-existing specimens or data that were already deidentified when the secondary researcher received them.<sup>52</sup> The current Common Rule regulations do not require initial collection sites or primary researchers to obtain informed consent or IRB review for downstream secondary research under any circumstances, though some may choose to obtain consent for future research as a matter of practice.<sup>53</sup> The obligation to obtain informed consent or IRB review, if it applies, rests with the secondary researcher.

Finally, biobanks may engage in research activities that trigger the Common Rule. Biobanks that collect their own specimens or data and conduct their own research are subject to the Common Rule in the same fashion as initial collection sites.<sup>54</sup> Biobanks that conduct their own research but only use pre-existing specimens or data are regulated in the same way as secondary researchers.<sup>55</sup> On the other hand, if they do not conduct research themselves and only collect and distribute specimens or data for the purpose of downstream research, biobanks are not engaged in human subjects research and are not subject to the Common Rule.<sup>56</sup>

## B. REGULATORY REQUIREMENTS UNDER HIPAA

HIPAA is a broad health care reform law enacted in 1996.<sup>57</sup>

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consent does not prohibit the proposed use, IRBs should consider several questions to determine compatibility.”).

51. See *supra* notes 26–29 and accompanying text.

52. See *OHRP—Guidance on Research Involving Coded Private Information or Biological Specimens*, *supra* note 24.

53. See 45 C.F.R. § 46.116 (2011) (omitting consent to future research from the list of required elements in an informed consent document).

54. See *supra* notes 46–47 and accompanying text.

55. See *supra* notes 49–53 and accompanying text.

56. See *Guidance on Engagement of Institutions in Human Subjects Research*, *supra* note 25.

57. Health Insurance Portability and Accountability Act of 1996, Pub. L. 104-191, 110 Stat. 1936 (1996) (codified as amended in scattered sections of the U.S. Code).

Among many provisions concerning the adoption of electronic medical records, the statute required DHHS to promulgate regulations concerning the privacy and security of individuals' personal medical information (provided Congress did not legislate further on the issue, which it did not).<sup>58</sup> The most significant of these rules for reidentification within the biobank system was the HIPAA Privacy Rule, finalized in 2002.<sup>59</sup> The Privacy Rule establishes HIPAA's requirements applicable to certain types of actors when handling certain medical information in order to ensure privacy. As discussed below, when applicable, HIPAA requires that certain medical information not be used or disclosed for research unless the researcher has obtained authorization from each potential research participant.<sup>60</sup>

Two important definitions limit the application of HIPAA. First, its requirements apply only to "covered entities," which include health care plans, health care clearinghouses, and health care providers—when they transmit health information in any electronic form.<sup>61</sup> Second, in order to qualify as "protected health information" (PHI) and fall within HIPAA regulations, health information must be electronically transmitted, must relate to an individual's past, present, or future health status or health care, and must individually identify a person or provide a reasonable basis for reidentification.<sup>62</sup> Even if an organization or individual is not a covered entity, it may still be bound by HIPAA as a business associate if the organization or individual uses or discloses PHI when performing certain functions, including data analysis,<sup>63</sup> on behalf of the covered entity.<sup>64</sup>

The HIPAA Privacy Rule, like the Common Rule, strongly discourages researchers from reidentifying data (or, by extension, any accompanying specimens).<sup>65</sup> HIPAA starkly

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58. *Id.* at § 264.

59. 45 C.F.R. §§ 160.101–160.552, 162.100–162.1802, 164.102–164.534 (2011).

60. 45 C.F.R. § 164.508(a)(1) (2011).

61. 45 C.F.R. § 164.104(a) (2011).

62. 45 C.F.R. § 160.103 (2011).

63. *Id.*

64. 45 C.F.R. § 164.504(e) (2011); 45 C.F.R. § 160.103 (2011).

65. *Cf.* Standards for Privacy of Individually Identifiable Health Information, 64 Fed. Reg. 59,918, 59,947 (to be codified at 45 C.F.R. pts 160–

differentiates deidentified information from personally identifiable information, although HIPAA's definition of deidentification departs from the Common Rule's definition.<sup>66</sup> Under HIPAA, deidentified health information falls outside of the definition of PHI entirely and so it is not entitled to the protections of the Privacy Rule.<sup>67</sup> Deidentification under HIPAA can be accomplished in one of two ways. If an expert using "generally accepted statistical and scientific principles and methods" determines there is a "very small" risk of data being reidentified, then the health information is not considered PHI.<sup>68</sup> Alternatively, health information stripped of eighteen specific identifiers listed in the regulation is not considered PHI.<sup>69</sup> HIPAA allows researchers to retain a code linking deidentified specimens or information to their original identified sources, but the Privacy Rule prohibits a covered entity from using or disclosing the code.<sup>70</sup> If a covered entity does use the code to reidentify specimens or information, the now-identifiable information becomes PHI and the covered entity is once again bound by HIPAA in its handling of the

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164) (noting the benefits of deidentification in research).

66. See *OHRP—Guidance on Research Involving Coded Private Information or Biological Specimens*, *supra* note 24; see also REPORT OF THE PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH (PRIM&R) HUMAN TISSUE/SPECIMEN WORKING GROUP: PART I ASSESSMENT AND RECOMMENDATIONS 22 (2007), available at [http://www.primr.org/uploadedFiles/PRIMR\\_Site\\_Home/Public\\_Policy/Recently\\_Files\\_Comments/Tissue%20Banking%20White%20Paper%203-7-07%20final%20combined.pdf](http://www.primr.org/uploadedFiles/PRIMR_Site_Home/Public_Policy/Recently_Files_Comments/Tissue%20Banking%20White%20Paper%203-7-07%20final%20combined.pdf).

67. See 45 C.F.R. § 164.500(a) (2011) (limiting the applicability of HIPAA to protected health information); Stacey A. Tovino, *The Use and Disclosure of Protected Health Information for Research Under the HIPAA Privacy Rule: Unrealized Patient Autonomy and Burdensome Government Regulation*, 49 S.D. L. REV. 447, 455–56 (2003) (“[C]overed entities always are free to use and disclose information that does not constitute PHI (i.e., information that is not individually identifiable) without regulation by the Privacy Rule.”).

68. 45 C.F.R. § 164.514(b)(1) (2011).

69. 45 C.F.R. § 164.514(b)(2). These include, for example: names, dates of birth and death, most geographic indicators below the state level, various forms of contact information, insurance numbers and other identification numbers, photos, and certain biometric information. *Id.*

70. 45 C.F.R. § 164.514(c). Under the Public Health Service Act, DHHS also has authority to issue certificates of confidentiality to any investigator conducting a study that requires IRB-approval under the Common Rule when the study involves the identifiable information. However, while HIPAA prohibits covered entities from disclosing identifying information, certificates of confidentiality only provide investigators the legal right to refuse disclosure. They do not prohibit investigators from making voluntary disclosures. 42 U.S.C. § 241(d) (2006).

data.<sup>71</sup>

The strongest disincentive to any such reidentification comes from HIPAA's more stringent consent requirements for studies involving PHI. Unlike the Common Rule which allows a participant to provide general consent to future research, HIPAA generally requires a covered entity using PHI to obtain individual authorization from each potential research participant before use or disclosure of that person's information for research in each research study.<sup>72</sup> A HIPAA authorization may be combined with the informed consent required by the Common Rule.<sup>73</sup> Although Common Rule informed consent must address a greater scope of potential harms and benefits to the human research subject, HIPAA authorizations must specifically address risks to an individual's privacy posed by the authorized use or disclosure.<sup>74</sup> Critics have argued that these requirements inject complex and detailed legalese into consent forms and hinder research.<sup>75</sup>

Two provisions of HIPAA allow researchers who are covered entities to avoid the required individualized authorization, even if the information they use qualifies as PHI and is not deidentified in accordance with the Privacy Rule.

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71. 45 C.F.R. § 164.502(d)(i)–(ii) (2011).

72. 45 C.F.R. § 164.508(b)(3) (2011); 45 C.F.R. § 164.508(a)(1); DEP'T HEALTH & HUMAN SERVS., PROTECTING PERSONAL HEALTH INFORMATION IN RESEARCH: UNDERSTANDING THE HIPAA PRIVACY RULE 11 (2003) [hereinafter PROTECTING PHI], available at [http://privacyruleandresearch.nih.gov/pdf/HIPAA\\_Booklet\\_4-14-2003.pdf](http://privacyruleandresearch.nih.gov/pdf/HIPAA_Booklet_4-14-2003.pdf); see also Secretary's Advisory Comm. on Human Research Protections, *FAQs, Terms and Recommendations on Informed Consent and Research Use of Biospecimens*, DEP'T HEALTH & HUM. SERVS, 4 (July 20, 2010), <http://www.hhs.gov/ohrp/sac/rp/commsec/attachmentdfac%27stermsandrecommendations.pdf.pdf>.

73. 45 C.F.R. § 164.508(b)(3)(i) (2011).

74. PROTECTING PHI, *supra* note 72, at 11 ("An Authorization differs from an informed consent in that an Authorization focuses on privacy risks and states how, why, and to whom the PHI will be used and/or disclosed for research. An informed consent, on the other hand, provides research subjects with a description of the study and of its anticipated risks and/or benefits, and a description of how the confidentiality of records will be protected, among other things.").

75. See *e.g.*, Norman Fost & Robert J. Levine, Editorial, *The Dysregulation of Human Subjects Research*, 298 J. AM. MED. ASS'N 2196, 2198 (2007) (noting that the major threat to the proper function of the regulatory scheme controlling human subjects research is "the increasing pressure to perform tasks that either do not require doing, could be done better by others, or could be done more efficiently using expedited review procedures").



First, HIPAA allows covered entities to use or disclose PHI for research when the covered entity obtains a waiver of authorization either from an IRB or from a similar oversight entity contemplated by HIPAA called a Privacy Board.<sup>76</sup> HIPAA directs IRBs and Privacy Boards to grant waivers only when three criteria are met: (1) the research poses “no more than a minimal risk to the privacy of individuals,” (2) “the research could not be practicably conducted without [a] waiver,” and (3) “the research could not be practicably conducted without . . . [the use of PHI].”<sup>77</sup> Second, the researcher need not obtain contributor authorization to use a “limited data set” instead of deidentified health information.<sup>78</sup> Unlike deidentified health information, a limited data set may retain information about the individual’s residence, including town, city, or zip code, and information about specific dates associated with the contributor, including birth date, admission date, and date of death.<sup>79</sup> A limited data set must be accompanied by a data use agreement which identifies “the permitted uses and disclosures” of the information contained in the limited data set.<sup>80</sup> The agreement may not permit the recipient of the limited data set to violate the requirements of HIPAA, and it must prohibit the recipient from identifying the information or contacting the contributor.<sup>81</sup>

A researcher entity’s failure to comply with HIPAA may have serious consequences. Federal statutes provide for both criminal and civil penalties if a covered entity violates HIPAA.<sup>82</sup> Researchers violate the HIPAA Privacy Rule if they disclose or obtain PHI without prior authorization, unless they fall into an exception under the Rule such as those discussed above.<sup>83</sup> Potential penalties are severe.<sup>84</sup> While historically the

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76. 45 C.F.R. § 164.512(i)(1)(i) (2011).

77. 45 C.F.R. § 164.512(i)(2)(ii) (2011).

78. 45 C.F.R. § 164.514(e) (2011).

79. *Compare* 45 C.F.R. § 164.514(e)(2)(ii) (2011) (setting up the requirements for a limited data set) *with* § 164.514(b)(2)(i)(C) (2011) (setting up the requirements for deidentification).

80. 45 C.F.R. § 164.514(e)(4)(ii)(A) (2011).

81. 45 C.F.R. § 164.514(e)(4)(ii)(C)(5).

82. 42 U.S.C. §§ 1320d-5, 1320d-6 (2006).

83. 42 U.S.C. § 1320d-6(a).

84. Civil penalties range from \$100 fines for unintentional violations to \$50,000 fines for those whose violation is the result of “willful neglect.” 42 U.S.C. § 1320d-5(a)(1)(C)(ii). Violations of HIPAA committed with “false pretenses” may be punished with criminal charges carrying a penalty of up to

number of criminal prosecutions and civil fines under HIPAA has been quite small, responsible institutions presumably ensure their compliance with these legal requirements regardless of the likelihood of sanctions.<sup>85</sup>

In general, players in the biobank research system are bound by HIPAA if they are (1) a covered entity or a business associate of a covered entity, and (2) using or disclosing information that meets the definition of PHI.<sup>86</sup> The original collection site is a covered entity if it provides health care at the time of the collection and transmits PHI in an electronic form.<sup>87</sup> Biobanks themselves may be housed within a covered entity such as an academic health center, clinic, or hospital; and if so they could be regulated by HIPAA when they use or disclose PHI.<sup>88</sup> Downstream researchers may be bound by HIPAA if they conduct research using PHI on behalf of a covered entity as a business associate.<sup>89</sup> Finally, downstream researchers, even if they are not directly regulated by HIPAA, may receive PHI from a covered entity that must comply with HIPAA and must ensure that recipients of certain information do likewise.<sup>90</sup>

Similarly, much of the information studied in genetic or

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five years in prison. 42 U.S.C. § 1320d-6(b)(2). Those committed with the intent to garner personal gain or commercial advantage may result in a penalty of up to ten years in prison. 42 U.S.C. § 1320d-6(b)(3).

85. See Al Franken, Sen., *Opening Statement from Hearing on Health Information Privacy* (Nov. 8, 2011), available at <http://www.franken.senate.gov/?p=news&id=1835> (indicating that the federal government has pursued sixteen criminal prosecutions, levied one civil monetary penalty, and reached six settlements involving monetary payments under HIPAA's privacy and security regulations).

86. See 45 C.F.R. § 164.500(a) (2011) (“[T]he standards, requirements, and implementation specifications of this subpart apply to covered entities with respect to protected health information.”).

87. DEP'T HEALTH & HUM. SERVS., RESEARCH REPOSITORIES, DATABASES, AND THE HIPAA PRIVACY RULE 1 (Jan. 12, 2004) [hereinafter DOH HIPAA], available at [http://privacyruleandresearch.nih.gov/pdf/research\\_repositories\\_final.pdf](http://privacyruleandresearch.nih.gov/pdf/research_repositories_final.pdf).

88. *Id.* (“Researchers are not themselves covered entities, unless they are also health care providers and engage in any of the covered electronic transactions. If, however, researchers are employees or other workforce members of a covered entity (e.g., a covered hospital or health insurer), they may have to comply with that entity's HIPAA privacy policies and procedures.”).

89. See 45 C.F.R. § 164.504(e) (2011).

90. *Id.*

genomic research will be PHI, assuming it was transmitted electronically. Although HIPAA does not directly attach to human biological specimens themselves, HIPAA does protect human research subjects against informational risks by limiting how covered entities may use or disclose PHI, including information attached to biological specimens.<sup>91</sup> When information attached to biological specimens is individually identifiable or provides a basis for reidentification, the information qualifies as PHI.<sup>92</sup> If a biobank or a downstream researcher is a covered entity or the business associate of a covered entity, and the research involves PHI, the biobank or downstream researcher must comply with HIPAA's privacy protections.<sup>93</sup>

Players in the biobank research system who are covered by HIPAA may relieve their regulatory burdens by availing themselves of Privacy Board waivers or limited data sets.<sup>94</sup> Because the informational risks generally associated with biobanking research are considered less serious than physical or psychological risks associated with interventional research studies, biobanks and downstream researchers are likely to seek, and qualify for, HIPAA authorization waivers.<sup>95</sup> Similarly, downstream researchers who would otherwise be bound by HIPAA's requirement of individualized authorization may use or disclose partially deidentified information included in limited data sets provided they agree to the limited data set's terms of use.

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91. 45 C.F.R. § 164.502(a) (2011); DOH HIPAA, *supra* note 90, at 11; *cf.* Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44,512, 44,513–14 (July 26, 2011) (to be codified at 45 C.F.R. pts 46, 160, 164, and 21 C.F.R. pts 50, 56) (“[I]ncreasing use of genetic information, existing (i.e., stored) biospecimens, medical records, and administrative claims data in research has changed the nature of the risks and benefits of research participation. Risks related to these types of research are not physical but informational (e.g., resulting from the unauthorized release of information about subjects).”).

92. *See* 45 C.F.R. § 160.103 (2011) (defining PHI).

93. *See* 45 C.F.R. §§ 164.500(a), 164.504(e) (2011).

94. 45 C.F.R. § 164.512(i)(1) (2011).

95. *See* Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. at 44,514, 44,516 (stating that the intensity of IRB review should be directly related to the severity of the risk posed by the research and proposing that studies posing only informational risks should undergo a standardized review process instead of being overseen by a fully convened IRB).

### III. REGULATORY REQUIREMENTS UNDER THE PROPOSED AMENDMENTS TO THE COMMON RULE

Given the complexity of requirements and exemptions under the Common Rule and HIPAA, DHHS has recently issued an advance notice of proposed rulemaking (ANPRM) seeking to improve protections for human subjects and to streamline regulations for researchers.<sup>96</sup> An ANPRM, of course, represents only a first step in the complex process for amending existing regulations, and the content of final rules may differ significantly from this initial proposal.<sup>97</sup> Nevertheless, an ANPRM reveals a great deal about an agency's thinking heading into a rulemaking. In this instance, many issues relevant to the return of individual research findings are not addressed in the ANPRM and others become even more complicated. Overall, an amended Common Rule along the lines of the ANPRM would create even greater disincentives for researchers interested in reidentifying data or specimens for the purpose of returning IFs or IRRs.

If adopted, the rules in the ANPRM would cover more research than the Common Rule and HIPAA now reach. Under current law, the Common Rule only applies to "research involving human subjects" that is conducted or supported by a federal agency that has adopted the Rule, or by an institution claiming a federal-wide assurance.<sup>98</sup> The ANPRM would extend the application of the rule to all research involving human subjects conducted at "domestic institutions that receive some Federal funding from a Common Rule agency."<sup>99</sup> Many entities within biobank research systems conduct at least some human

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96. *Id.* at 44,512.

97. Under the Administrative Procedure Act, an agency must provide notice of the content of a proposed rule before the rule is promulgated and goes into effect. 5 U.S.C. § 553(b) (2006). The Act requires only a notice of proposed rulemaking (NPRM), but if an agency particularly desires public input on a rule or additional time to ventilate an issue, the agency may opt to issue an ANPRM prior to publishing an NPRM. Bridget C.E. Dooling, *Legal Issues in E-Rulemaking*, 63 ADMIN. L. REV. 893, 897–98 (2011). The ANPRM is not binding and the agency retains the discretion to change the content of the proposed rule presented in the ANPRM. See 5 U.S.C. § 553(c)–(d) (requiring public opportunity to comment on proposed rules and requiring the agency to respond to those comments).

98. See 45 C.F.R. § 46.101 (2011).

99. Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. at 44,528.

subjects research funded by NIH or other federal agencies that adhere to the Common Rule; if this portion of the ANPRM survives to a final regulation, such entities would be required to adhere to the Common Rule in all of their human subjects research activities, however funded.

The ANPRM identifies seven areas of concern with the existing Common Rule (see Table 1). While the scope of the ANPRM is broad, six of these seven areas of concern addressed by the proposed rule have a direct or indirect effect on biobank research entities. These proposed changes and their effects are discussed in the sections below.

Table 1	Seven Identified Areas of Concern with the Current Common Rule
1	Poor calibration between the level of review required and the level and type of risks posed by research studies;
2	Undue bureaucratic complexity, inefficiency, and delay resulting from multiple IRBs reviews for multi-site studies;
3	Ineffective protections for human subjects resulting from current informed consent requirements;
4	Insufficient harmonization between the Common Rule and HIPAA given the limited applicability of HIPAA;
5	Inadequate collection of information necessary for evaluating the effectiveness of the human subject research oversight system;
6	Under inclusive protection of all human research subjects resulting from the inapplicability of current human subject research regulations to non-federally funded research; and
7	Multiplicative, inconsistent, and unclear regulatory requirements resulting in problematic variations across institutions and IRBs.

#### A. HARMONIZATION BETWEEN THE COMMON RULE AND HIPAA

The ANPRM proposes that the limited applicability of HIPAA combined with the Common Rule's looser definitions of "identifiable" and "deidentified" inadequately protect data and, thus, do not minimize informational risks to subjects.<sup>100</sup> To address this gap, the ANPRM would have the Common Rule adopt HIPAA's standards regarding what constitutes individually identifiable information, limited data sets, and deidentified information.<sup>101</sup> The ANPRM also suggests a reevaluation of the particular identifiers that would have to be

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100. *Id.* at 44,525.

101. *Id.*

removed for information to be considered deidentified under both regulatory regimes.<sup>102</sup> The ANPRM points out that “[r]egardless of what information is removed, it is possible to extract DNA from a biospecimen itself and potentially link it to otherwise available data to identify individuals” and indicates that DHHS is “considering categorizing all research involving the primary collection of biospecimens as well as storage and secondary analysis of existing biospecimens as research involving identifiable information.”<sup>103</sup>

In addition to harmonizing these definitions, the ANPRM proposes that researchers using deidentified information or limited-data sets would be “strictly prohibited from attempting to reidentify the subjects of the information.”<sup>104</sup> Furthermore, because many investigators rely on third-party experts to remove identifiers instead of recording information in an unidentifiable manner themselves, the ANPRM would allow that “data could be considered deidentified or in limited data set form even if investigators see the identifiers but do not record them in the permanent research file.”<sup>105</sup> If promulgated, the ANPRM’s harmonization of definitions and requirements under HIPAA and the Common Rule would likely simplify compliance for those collection sites, biobanks, and downstream researchers that were already bound by both regulatory schemes. Because biobanks and downstream researchers are less likely to be covered entities or the business associates of covered entities than are collection sites, they are less likely to be subject to HIPAA in the first place. For these entities, the proposed harmonization of HIPAA and the Common Rule would introduce additional regulatory burdens because these entities would effectively be required to comply with both HIPAA and the Common Rule.

#### B. SHIFT FROM “EXEMPT” CATEGORIES OF RESEARCH TO “EXCUSED” CATEGORIES OF RESEARCH

As noted above, the existing Common Rule varies the degree of IRB oversight based on a tiered structure of assessed risk for research subjects. The ANPRM identifies several

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102. *Id.* at 44,525–26.

103. *Id.*

104. *Id.* at 44,526.

105. *Id.*

concerns about the poor alignment of these review categories with actual levels of risk posed by different types of studies. Among these concerns, the ANPRM contends, is the mismatch between IRB review and the informational risks associated with the inappropriate use or disclosure of subjects' information.<sup>106</sup> The ANPRM states that these informational risks are "correlated with . . . the degree of identifiability of the information" and are almost exclusively due to "inadequate data security."<sup>107</sup> The ANPRM further states that IRB review of research posing informational risks is both unnecessary and inadequate because IRB members may lack the necessary expertise regarding data security and "review of informational risks is an inefficient use of an IRB's time."<sup>108</sup> Instead, the ANPRM suggests that "[s]tandardized data protections . . . may be a more effective way to minimize informational risks."<sup>109</sup> The ANPRM would impose "mandatory standards for data security and information protection . . . calibrated to the level of identifiability"<sup>110</sup> of the information "whenever data are collected, generated, stored, or used."<sup>111</sup> These mandatory data security standards would be the basis for several subsidiary changes to when and how IRB review is required, many of which would affect biobank research entities.

The most significant changes proposed by the ANPRM would pertain to the types of research activities that are and are not exempt from Common Rule requirements. While the current Common Rule provides that research involving "existing data, documents, records, pathological specimens, or diagnostic specimens, . . . if the information is recorded by the investigator in such a manner that subjects cannot be identified" is exempt from all requirements,<sup>112</sup> the proposed rule would require these studies to comply with new mandatory data security standards.<sup>113</sup> The ANPRM frames this proposed change as "moving away from the concept of exempt [research

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106. *Id.* at 44,516.

107. *Id.*

108. *Id.*

109. *Id.*

110. *Id.*

111. *Id.*

112. 45 C.F.R. § 46.101(b)(4) (2011).

113. Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. at 44,518.

studies]” to a category of research studies “excused” from IRB review.<sup>114</sup>

Because this shift would increase protections for subjects, the ANPRM argues that the proposed “excused” category would include more types of studies than the current “exempt” category.<sup>115</sup> Thus, the ANPRM proposes that the current exemption for research on pre-existing specimens or data be expanded to include specimens and data that were “collected for purposes other than the proposed research” instead of being limited to data or specimens that existed at the time the study was commenced.<sup>116</sup> Furthermore, it proposes that the current limitation on investigators recording identifying information be eliminated “unless there are plans to provide individual results back to the subjects,” in which case the study would be ineligible for excused status altogether.<sup>117</sup>

If promulgated, the ANPRM would require fully convened IRBs to review research that does not qualify as excused under the proposed changes to the Common Rule.<sup>118</sup> However, with the adoption of mandatory data security standards, IRBs would only assess the ethical dimensions of these research protocols, and would no longer be responsible for assessing their information risks.<sup>119</sup> Furthermore, while the current Common Rule generally requires IRBs to provide ongoing review of such research studies,<sup>120</sup> the ANPRM proposes that continuing review would not be required “[w]here the remaining activities in a study are limited to . . . data analysis (even if identifiers are retained)” unless the IRB decides that ongoing review is necessary.<sup>121</sup> Research that qualifies as excused under the proposed Common Rule would be subject to several new requirements in addition to mandatory data security standards.<sup>122</sup> These requirements are discussed in the following

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114. *Id.*

115. *Id.*

116. *Id.* at 44,519.

117. *Id.*

118. *Id.* at 44,516.

119. *Id.*

120. 45 C.F.R. § 46.109(e) (2011).

121. Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. at 44,516.

122. 45 C.F.R. § 46.101(b) (2011).



section and provided in Table 2 reproduced from the ANPRM.

### C. INFORMED CONSENT AND IRB REGISTRATION

Under the current Common Rule, exempt categories of research are not subject to IRB review or informed consent requirements. Under the proposed amendments, IRB review still would not be required for excused categories of research.<sup>123</sup> However, to facilitate tracking and auditing of excused studies, researchers would be required to register these studies with an IRB using a brief form.<sup>124</sup> This form would allow institutions to identify those rare instances where an excused study might require expedited or full IRB review.

The proposed rules also change informed consent requirements, especially for secondary research. The Common Rule and HIPAA now do not require consent or authorization for secondary research involving deidentified specimens and data if they were obtained from another institution or were collected for purposes other than the proposed research.<sup>125</sup> Those same regimes do require secondary researchers to obtain informed consent for research on identifiable specimens and data.<sup>126</sup> Under the Common Rule, it may be possible for researchers to obtain informed consent for future research on identifiable specimens and data under certain circumstances, while HIPAA does not allow for such general authorizations.<sup>127</sup> The ANPRM proposes taking a middle ground on these issues and simplifying these requirements by requiring informed consent for a broader range of secondary research while allowing that consent to be obtained at the point of primary collection.<sup>128</sup> Under these proposed rules “the allowable current practice of telling the subjects, during the initial research consent, that the data they are providing will be used for one

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123. Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. at 44,516.

124. *Id.* at 44,515.

125. OHRP—*Guidance on Research Involving Coded Private Information or Biological Specimens*, *supra* note 24; *Guidance on Engagement of Institutions in Human Subjects Research*, *supra* note 25.

126. *See supra* text accompanying notes 18–21.

127. Secretary’s Advisory Comm. on Human Research Protections, *supra* note 50, at 6.

128. Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. at 44,519–20, 44,525.

purpose, and then after stripping identifiers, allowing it to be used for a new purpose to which the subjects never consented, would not be allowed.”<sup>129</sup> The ANPRM further provides that these consent requirements would be able to be satisfied in most cases at the time of the initial collection of specimens and data by having subjects consent to or reject participation in future research.<sup>130</sup> In instances requiring more specific consent, such as cell line or reproductive research, this initial consent form would provide check-boxes allowing subjects to opt in or out of particular types of research.<sup>131</sup>

Under these proposed amendments, some research currently “exempt” from the Common Rule would be “excused” from IRB review but potentially subject to new informed consent requirements.<sup>132</sup> Those new requirements would depend on the original purpose for which the specimens and data were collected and their level of identifiability.<sup>133</sup> Most significantly for our purposes, as explained above, the ANPRM potentially considers regarding all biospecimens as identifiable under the amended Common Rule regardless of whether identifiers are stripped.<sup>134</sup> The proposed rules might then require informed consent for all biospecimens and identifiable data regardless of whether they were originally collected for research or non-research purposes, but would allow for that consent to be acquired at the time of initial collection.<sup>135</sup> For research on limited data sets and deidentified data, informed consent would be required unless the data was originally collected for a non-research purpose.<sup>136</sup> The ANPRM states that these informed consent requirements would only apply prospectively to specimens and data collected after the potential adoption of new rules.<sup>137</sup>

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129. *Id.* at 44,519.

130. *Id.*

131. The ANPRM states that “[p]articipation in a research study (such as a clinical trial) could not be conditioned on agreeing to allow future open-ended research using a biospecimen.” *Id.* at 44,520.

132. *Id.* at 44,419.

133. *Id.* at 44,525.

134. *Id.*

135. *Id.* at 44,519.

136. *Id.*

137. *Id.* at 44,520.

## D. SUMMARY: THE POTENTIAL IMPACT OF THE ANPRM

<b>Table 2. Proposal for the Excused Category of Research Involving Pre-Existing Information or Biospecimens (reproduced from ANPRM)</b>			
	<b>Identifiable information and all biospecimens</b>	<b>Limited data set (as defined in the HIPAA Privacy Rule)</b>	<b>De-identified information (as defined in the HIPAA Privacy Rule)</b>
<b>Written consent required for future research with material collected for <i>non-research purposes</i>?</b>	Yes, which could be obtained in connection with the initial collection.	No consent required.	No consent required.
<b>Consent for future research with material collected for <i>research purposes</i>?</b>	Yes. Consent for future research typically obtained at the same time as consent for initial research (which, for data, could be oral when oral consent was permissible for the initial collection).	Yes. Same rules as for “Identifiable Information and All Biospecimens.”	Yes. Same rule as for “Identifiable Information and All Biospecimens.”
<b>Standardized Data Protections?*</b>	Yes. Protections would include encryption, use only by authorized personnel with audit tracing, prompt breach notification, and periodic retrospective random audits.	Yes. Same rules as for “Identifiable Information and All Biospecimens” plus a prohibition against re-identification.	Yes. Protection would include prohibition on re-identification.

<b>Table 2. Proposal for the Excused Category of Research Involving Pre-Existing Information or Biospecimens (reproduced from ANPRM)</b>			
<b>Registration of research with IRB or research office?</b>	Yes.	Yes.	No.
<b>Prior review by IRB or research office?</b>	No, unless investigators plan to re-contact subjects with their individual research results.	No.	No.
* These data protections are discussed in the context of secondary research uses of biospecimens and data which present mostly informational risks rather than physical risks to participants. However, as indicated elsewhere in this ANPRM, informational risks will always be present where data and biospecimens are collected, thus requiring these data protections to be applied to any such research.			

When crystallized, these proposed amendments would have varied effects on the level of regulation on primary collection sites, biobanks, and secondary researchers. In general, primary collection sites would face an increased regulatory burden because the proposed rule would require them to collect informed consent for any secondary research at the time they obtain informed consent for the initial research.<sup>138</sup> If they are not also primary collection sites, biobanks and secondary researchers would have mixed results: they would be less closely regulated in some respects and more closely regulated in others. Those using deidentified specimens and data initially collected for research purposes, a class which is currently entirely exempt, would face regulation under the proposed rule.<sup>139</sup> They would have to register their studies with an IRB and obtain informed consent from research participants.<sup>140</sup> However, the regulatory burdens would

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138. *See id.* at 44,519.

139. *See id.* at 44,518–19.

140. *See id.* at 45,419.

generally decrease for secondary researchers and biobanks conducting research on identifiable specimens and data. Under the current rules this category of researchers is required to submit to IRB review and approval;<sup>141</sup> under the proposed rules, they would merely be required to register studies with the IRB.<sup>142</sup> Taken together, these changes in regulatory coverage would further increase the already strong incentive to deidentify most specimens and data used in the biobank research system. As noted above, the expanded Common Rule would cover more research, and all Common Rule deidentification standards would shift to the generally more stringent HIPAA standards. The next Part delves into the challenges facing the biobank research system under both the existing and the potential revised regulations.

#### IV. THE MUTUAL AND CONCURRENT CHALLENGES OF RETURNING INDIVIDUAL FINDINGS FROM BIOBANK AND SECONDARY RESEARCH UNDER CURRENT AND PROPOSED REGULATIONS

Returning IFs and IRRs from the biobank research system to contributors of specimens and data poses a twofold challenge. First, the Common Rule and HIPAA explicitly address neither the return of individual findings from research nor the responsibilities of different biobank research entities and oversight bodies involved in such returns.<sup>143</sup> Consequently, biobank research entities—and the IRBs and Privacy Boards that oversee them—face considerable regulatory uncertainty when deciding whether to return findings.<sup>144</sup> In this atmosphere, it is likely that many will avoid legal risk and lean against returning results, notwithstanding any of the ethical arguments favoring return in some circumstances. The second and perhaps more significant challenge is that these regulations, and especially the proposed amendments to the Common Rule, in many ways do discourage the return of findings. In particular, the strong and increasing emphasis on

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141. *See supra* notes 18–21 and accompanying text.

142. *See* Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. at 44519.

143. Susan M. Wolf et al., *The Law of Incidental Findings in Human Subjects Research: Establishing Researchers' Duties*, 36 J. L. MED. & ETHICS 361, 362 (2008) [hereinafter *Law of Incidental Findings*].

144. *Id.* at 364.

robust deidentification standards generally deters return of results. More broadly, the principles and goals of the research oversight system diverge considerably from those of proponents of returning individual findings.

In this Part, we first discuss the sources and consequences of the emerging disparity between the philosophy of the regulations and the increased openness to returning individual research findings from biobank research. Second, we illustrate how current and proposed regulations under the Common Rule and HIPAA present practical challenges for biobank research entities contemplating returning results.

#### A. THE EMERGING DISPARITY IN THINKING ABOUT RETURN OF RESULTS

The Common Rule provides several criteria by which IRBs are to evaluate proposed research involving human subjects: minimization of risks to human subjects; reasonability of risks in relation to anticipated benefits, if any; adequacy of informed consent; sufficiency of data monitoring; and protection of human subjects' privacy and the confidentiality of data.<sup>145</sup> While risks can vary depending on the nature of the research and human subject group<sup>146</sup> (and while the Common Rule itself does not define "risks"), guidance for IRBs has typically identified potential risks to subjects as physical, psychological, economic, and social.<sup>147</sup> According to OHRP's predecessor, the Office for the Protection from Research Risks, concerns associated with subjects' privacy and confidentiality of data are "of a somewhat different character" than these other risks.<sup>148</sup>

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145. 45 C.F.R. § 46.111 (2011).

146. For example, children, prisoners, and pregnant women have been identified as human subject groups facing unique risks as human research subjects. Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research, 45 C.F.R. §§ 46.201–46.207 (2011); Additional Protections Pertaining to Biomedical and Behavior Research Involving Prisoners as Subjects, 45 C.F.R. §§ 46.301–306; Additional Protections for Children Involved as Subjects in Research, 45 C.F.R. §§ 46.401–46.409.

147. OFFICE FOR THE PROTECTION FROM RESEARCH RISKS, INSTITUTIONAL REVIEW BOARD GUIDEBOOK ch. III (1993), *available at* [http://www.hhs.gov/ohrp/archive/irb/irb\\_chapter3.htm#e1](http://www.hhs.gov/ohrp/archive/irb/irb_chapter3.htm#e1).

148. *Id.* Although this guidance is now considered an archived material and has not been updated since 1993, its analysis of risks to research subjects does not appear to be outdated and has been reiterated in subsequent DHHS publications, including the ANPRM.

Invasion of privacy typically involves “covert” research or “access to a person’s body or behavior without consent,” and confidentiality of data pertains to “safeguarding information that has been given voluntarily by one person to another.”<sup>149</sup> This distinction between risks to subjects and concerns about privacy and confidentiality may explain a corresponding division both in regulatory treatment and in commentary about related bioethical issues that arise in genetic and genomic research.

The first category of issues, which we will call the “return of results” category, has focused on the emerging challenges posed by rapid technological advancements that allow researchers to produce significant amounts of information, including IRRs and IFs, about contributors of specimens and data.<sup>150</sup> The advent of new capability, such as genomic microarrays enabling the sequencing of whole genomes, presents new ethical, legal, and regulatory challenges.<sup>151</sup> Commentary in this category has taken the form of debate about whether IRRs and IFs constitute any research benefits or risks to contributors, whether researchers have any ethical or legal duty to return IRRs and IFs to contributors,<sup>152</sup> and, if so, how returns of IRRs and IFs should be managed by researchers, IRBs, and oversight authorities such as OHRP.<sup>153</sup> Proponents of return of results have argued that IRRs and IFs of clinical significance to donors are a foreseeable outcome of research that presents both pertinent benefits and risks. As explained by Wolf et al.:

For a research participant recruited as a normal control, discovery of an IF suggesting pathology may trigger anxiety, burdens, and the costs of further evaluation to verify or rule out a clinical problem. Even research participants with known pathology risk discovery of an unrelated IF, triggering the same. . . . [S]ome IFs will lead to diagnoses of clinical importance. . . . For such a research participant, taking part in the study imposes both the risk of discovering an IF

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149. *Id.*

150. *E.g.*, Amy L. McGuire & James R. Lupski, *Personal Genome Research: What Should the Participant Be Told?*, 26 *TRENDS GENETICS* 199, 200 (2010) (arguing that in the direct-to-consumer genetic sequencing industry, results should only be returned “in a way . . . that the potential benefits of receiving the research results outweigh any potential harm”).

151. *See, e.g., id.*

152. *E.g.*, Law of Incidental Findings, *supra* note 151, at 362.

153. *E.g.*, Susan M. Wolf et al., Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations, 36 *J. L. MED. & ETHICS* 219, 230 tbl. 3 (2008) [hereinafter Analysis and Recommendations].

and potential benefit of discovering serious pathology in time to intervene.<sup>154</sup>

Proponents further argue that, in order to satisfy the regulatory mandates for minimizing risks and reasonably balancing risks and benefits, IRBs need to assess whether a research protocol has the potential to produce IFs of clinical significance to donors.<sup>155</sup> If so, the argument runs, then informed consent documents should provide adequate information to subjects about the benefits and risks of IFs and whether adequate procedures are proposed to address when and how returns of IFs will take place.<sup>156</sup> While the Common Rule does not explicitly address the issue of return of results, debate about the issue has resulted in recommendations for researchers, IRBs, and regulatory authorities like OHRP, from several groups including the National Bioethics Advisory Commission,<sup>157</sup> NIH's National Heart, Lung, and Blood Institute,<sup>158</sup> and the Centers for Disease Control and Prevention.<sup>159</sup> These recommendations have focused mostly on criteria for deciding whether IRRs and IFs ought to be returned.<sup>160</sup> The recommendations are oriented almost

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154. *Id.* at 227.

155. *See, e.g.*, Nat'l Human Genome Research Inst. (NHGRI), *Informed Consent Elements Tailored to Genomics Research*, <http://www.genome.gov/27026589> (last updated February 19, 2012) ("The decision on whether to return research results to participants . . . should be made by the study investigator in consultation with his/her IRB.").

156. *See, e.g.*, NIMH COUNCIL WORKGROUP ON MRI RESEARCH PRACTICES, MRI RESEARCH SAFETY AND ETHICS: POINTS TO CONSIDER (Sept. 14, 2005), available at <http://www.nimh.nih.gov/about/advisory-boards-and-groups/namhc/reports/mri-research-safety-ethics.pdf> (recommending that researchers "explicitly discuss[ ] the potential for incidental findings and associated risks, . . . inform[ ] the participant as to whether or not the scans will be reviewed by a clinician qualified to render a radiological interpretation, and . . . describe[ ] the path that will be taken in the event that an incidental finding occurs").

157. *E.g.*, NAT'L BIOETHICS ADVISORY COMM'N, RESEARCH INVOLVING HUMAN BIOLOGICAL MATERIALS: ETHICAL ISSUES AND POLICY GUIDANCE 71-72 (1999), available at <http://www.bioethics.georgetown.edu/nbac/hbm.pdf>.

158. *E.g.*, Richard R. Fabsitz et al., Special Reports, *Ethical and Practical Guidelines for Reporting Genetic Research Results to Study Participants: Updated Guidelines from an NHLBI Working Group*, 3 CIRCULATION: CARDIOVASCULAR GENETICS 574 (2010).

159. *E.g.*, Laura M. Beskow et al., *Informed Consent for Population-Based Research Involving Genetics*, 286 JAMA 2315, 2319 (2001).

160. *E.g.*, Fabsitz et. al, *supra* note 158.



exclusively toward primary researchers.<sup>161</sup> Despite this ongoing discussion, the recent ANPRM does not substantively address this category of issues.<sup>162</sup>

The second category of issues, which we will call the “biobank oversight” category, has focused on the regulatory challenges presented by the rise of large-scale biobanks that amass biospecimens and genetic data for future research use by secondary researchers. Commentators in this arena have been concerned not with physical and psychological risks to contributors, but with such issues as the limits of informed consent for future research using contributors’ stored specimens and data,<sup>163</sup> the data security and contributor privacy implications of transferring stored specimens and data through the biobank system,<sup>164</sup> and matters of ownership and custodianship of stored specimens and data.<sup>165</sup> As prior sections of this paper have shown, existing regulations including the Common Rule and HIPAA explicitly address many of these issues, as does the ANPRM.<sup>166</sup>

It is only very recently that these two categories of issues have begun to converge and commentators have started considering the complexity of issues surrounding IRRs and IFs arising within the complexity of the biobank research system. The consensus paper at the center of this symposium examines this point of convergence.<sup>167</sup> Even here, the recommendations are limited because the paper suggests only that contributors should be offered returns of clinically significant IRRs and IFs when feasible.<sup>168</sup> Yet the regulations discussed above, particularly as they relate to deidentification, profoundly affect

161. *E.g.*, NATIONAL BIOETHICS ADVISORY COMM’N *supra* note 157; Beskow et al., *supra* note 159; Fabsitz et. al, *supra* note 158.

162. *See generally* Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44,512 (July 26, 2011) (to be codified at 45 C.F.R. pts 46, 160, 164, and 21 C.F.R. pts 50, 56).

163. *See, e.g.*, David Wendler, *One-Time General Consent for Research on Biological Samples: Is it Compatible with the Health Insurance Portability and Accountability Act?*, 166 ARCHIVES INTERNAL MED. 1449, 1451 (2006).

164. *E.g.*, Mark A. Rothstein, *Is Deidentification Sufficient to Protect Health Privacy in Research?*, 10 AM. J. BIOETHICS 3, 6 (2010).

165. *E.g.*, R. Alta Charo, *Body of Research—Ownership and Use of Human Tissue*, 355 NEW ENG. J. MED. 1517, 1518–19 (2006).

166. For example, see notes 73–76 and accompanying text for an explanation of the limits of authorization under HIPAA.

167. *Id.* at 1–3.

168. *Id.* at 18.

the feasibility of any potential return. In order for return of results to take place, the IRB needs to evaluate the criteria for return, the adequacy of informed consent, and the procedures for re-contact.<sup>169</sup> Additionally, it must be possible to identify (or, more likely, reidentify) the contributors to whom returnable results are linked.

For example, Common Rule requirements for IRB review and informed consent typically will not apply to research on deidentified stored specimens and data; such studies either are not human subjects research or are exempt from Common Rule.<sup>170</sup> More fundamentally, reidentification negates researchers' exemptions under both the Common Rule and HIPAA.<sup>171</sup> Some biobanks like BioVu irretrievably deidentify specimens and data, making reidentification impossible.<sup>172</sup> Even in cases where collection sites and biobanks do retain the code for deidentified specimens and data, the terms of their agreements with secondary researchers may bar the latter from access to that code.

Quite noticeably, the proposed changes to the Common Rule are at odds with the emerging consensus view that favors return of IFs and IRRs from the biobank research system in some circumstances. This divergence occurs both at the level of principle and at the level of feasibility. While the consensus paper identifies both benefits and risks to contributors from individual findings,<sup>173</sup> the ANPRM states:

[I]ncreasing use of genetic information, existing (i.e., stored) biospecimens, medical records, and administrative claims data in research has changed the nature of the risks and benefits of research participation. Risks related to these types of research are not physical but informational (e.g., resulting from the unauthorized release of information about subjects).<sup>174</sup>

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169. See 45 C.F.R. § 46.111(a) (2012) (requiring IRBs to weigh the risks and benefits to study participants); 45 C.F.R. § 46.109(e) (2012) (requiring the IRB to continue to review the study over its course).

170. See *supra* notes 22–26 and accompanying text.

171. 45 C.F.R. § 164.514(d) (2012); OHRP—Guidance on Research Involving Coded Private Information or Biological Specimens, *supra* note 24.

172. *BioVu: Vanderbilt's DNA Databank*, VAND. UNIV., <http://dbmi.mc.vanderbilt.edu/research/dnadatabank.html> (last visited Apr. 19, 2012).

173. Wolf et al., *supra* note 1, at 1, 366–68.

174. Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44,512, 44,513–14 (July 26, 2011) (to be codified at

The ANPRM further argues that these informational risks are best mitigated through mandatory data security provisions that adopt HIPAA's more stringent definitions for levels of identifiability and that include a prohibition on reidentification as a replacement for IRB review.<sup>175</sup>

Instead of providing any mechanisms to facilitate the return of results where it is otherwise justified, the ANPRM treats reidentification as categorically undesirable.<sup>176</sup> It recommends that standard data protection requirements under the Common Rule for secondary research involving deidentified data and limited data sets include a prohibition on reidentification.<sup>177</sup> The proposed changes would also expand the categories of research activities excused from IRB review altogether based on these prohibitions against reidentification.<sup>178</sup> In these situations, there might be no IRB to consult when contemplating a return of results. Regulators' exclusive focus on informational risks ignores other risks and benefits of reidentification, including those that might arise in a well-considered return of results. The existing and proposed rules recognize the regulatory delays and difficulties that could result from reidentification<sup>179</sup> and the potential to further burden overtaxed IRBs.<sup>180</sup> But, the existing and proposed rules leave little space for legitimate reidentification in situations such as those envisioned by the consensus paper. This philosophical divergence leads to practical challenges for the biobank research system, which we discuss in the following Section.

## B. PRACTICAL CHALLENGES

To demonstrate the practical challenges of returning individual findings from the biobank research system, we offer the following narrative descriptions of an extremely ordinary chain of events within the biobank research system. We use this narrative to illustrate the dilemmas facing primary

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45 C.F.R. pts 46, 160, 164, and 21 C.F.R. pts 50, 56).

175. *Id.* at 44,515–16.

176. *See id.* at 44,525 (noting that current privacy protections are not strong enough because they did not anticipate how genetic technology would “make . . . reidentification . . . easier”).

177. *Id.*

178. *Id.* at 44,519.

179. *See id.* at 44,525.

180. *See id.* at 44,518.

collection sites and researchers, biobanks, and downstream secondary researchers. We first describe the situation as it arises under current law and then describe how proposed changes to the law under DHHS' recent ANPRM may affect these outcomes.

First, the hypothetical story: A primary researcher obtained IRB approval to conduct a research study on human specimens. The IRB evaluated the proposed research with respect to all the criteria provided under the Common Rule. Because the research study did not present any benefits or risks associated with the return of IRRs or IFs, the IRB did not require the researcher to include information about such returns in her informed consent documents or to present procedures for return of results as part of the research design. After commencing the study, the primary researcher decided to send the specimens to a biobank. The biobank, in turn, sent the specimens to a secondary researcher conducting a large-scale genetic study. In the course of this research, the secondary researcher now discovers an IF of potential clinical significance to a contributor. What are the challenges that may arise if attempts are made to return this IF back to the contributor in question?

Initially, it is important to recognize that the contributor likely has no idea that his specimen has been used for secondary research. Furthermore, the contributor likely is not aware of any possibility that an IF of clinical significance might arise or the possibility that he may be re-contacted with such an IF. Keeping this mind, we consider the challenges faced by the secondary researcher, biobank, and primary researcher as they consider what to do with this IF.

It is possible that this secondary researcher received the information necessary to identify the contributor himself. However, if he received the specimens from the biobank in identifiable form, he most likely recorded all information in a manner that prevents him from identifying the contributor, thereby exempting him from Common Rule requirements for IRB review and informed consent.<sup>181</sup> Even if the secondary researcher retained the code for reidentification, there are several reasons he almost certainly would not dare to reidentify the specimen himself. First, the secondary researcher's MTA

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181. See 45 C.F.R. § 46.101(b)(4) (2012).

with the biobank may well include a prohibition on reidentification. Second, an attempt by the secondary researcher to reidentify the specimen would trigger regulatory obligations for him and his institution under the Common Rule.<sup>182</sup> In that situation, how can the secondary research institution handle the fact that the researcher is now engaging in activities that required IRB approval and authorization from the contributor or a waiver prior to the research commencing the first place? The institution would likely be concerned that reidentification would render it materially non-compliant with the terms of the Common Rule and jeopardize the project's funding.<sup>183</sup>

It is more likely that the secondary researcher is unable to reidentify the contributor himself because he obtained the specimens in deidentified form from the biobank. In this instance, the secondary researcher is not engaged in human subjects research at all.<sup>184</sup> If he contacts the biobank, is it able to provide him with the code to reidentify the specimen? Again, the biobank may be barred from doing so under the terms of its MTAs with the primary collection site, the secondary researcher, or both. Even if all applicable MTAs allow the biobank to provide the secondary researcher with the code, doing so would change the secondary researcher's work from non-human subjects research to human subjects research and raise the regulatory complications described above.<sup>185</sup>

Can the secondary researcher ask the biobank to perform the reidentification itself? If the biobank has the code to reidentify, it may be barred from doing so under its MTA with the primary researcher. The biobank may also face a regulatory compliance quandary if it decides to reidentify the specimen. If the biobank only aggregates and distributes specimens without conducting its own research, these activities are not considered human subjects research and the biobank never had to comply with the Common Rule in the first place.<sup>186</sup> Since the biobank is not engaged in research, reidentification would not per se

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182. See *OHRP—Guidance on Research Involving Coded Private Information or Biological Specimens*, *supra* note 24.

183. See 45 C.F.R. § 46.123(a) (2011).

184. *OHRP—Guidance on Research Involving Coded Private Information or Biological Specimens*, *supra* note 24.

185. See note 191 and accompanying text.

186. *Guidance on Engagement of Institutions in Human Subjects Research*, *supra* note 25.

trigger the Common Rule.<sup>187</sup> However, the biobank would be left with the complicated dilemma of how to contact and return results to a contributor who is not even aware that his specimen was being used for secondary research. If the biobank conducted research in addition to aggregating and distributing specimens, then reidentification would create similar regulatory complications to those facing the secondary researcher.<sup>188</sup> Under any of these situations, reidentification could also place the biobank, if it is a covered entity under HIPAA, at risk of civil and criminal penalties.<sup>189</sup>

If neither the secondary researcher nor the biobank can or will reidentify the specimen, can the primary collection site do so? Certain practical obstacles are most likely for the primary collection site, especially if it gathered specimens or data while engaged in a particular research project and most especially if (as is usually the case) that research did not contemplate any grounds for recontact. Grants expire, employees go to other institutions or projects, files get archived, and memories fade.<sup>190</sup> These obstacles may be less likely to occur in a long-term research project or at a clinically-oriented collection site,<sup>191</sup> but they are still important considerations.

Even if these practical obstacles do not arise, legal ones may. The primary researcher may, again, be barred from performing the reidentification under the terms of her MTA

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187. See notes 48–50 and accompanying text.

188. See notes 189–195 and accompanying text.

189. See 42 U.S.C. § 1320d-5 (2006) (establishing civil penalties); § 1320d-6 (establishing criminal penalties); 45 C.F.R. § 164.502(d)(i)–(ii) (2012) (bringing reidentified information back into HIPAA's scope).

190. Wolf et al., *supra* note 1, at 373 (discussing the difficulty of relocating and recontacting a contributor).

191. Long-term projects may encounter less difficulty reidentifying contributors because they frequently have continuous funding and record-keeping. See, e.g., Dellara F. Terry et. al, *Cardiovascular Risk Factors Predictive for Survival and Morbidity-Free Survival in the Oldest-Old Framingham Heart Study Participants*, 53 J. AM. GERIATRICS SOC. 1944 (2005) (including Framingham Heart Study participants, aged 85 and older, who died since 1948 and noting that only fifty-six of 2,531 participants were lost to follow-up). In the case of clinical collection sites, an individual's records are less likely to get lost in the shuffle because state law typically requires clinics to retain medical records. E.g., MINN. STAT. § 145.32 subd. 1 (2011) (requiring the retention of the “[p]ortions of hospital medical records that comprise an individual permanent medical record”).

with the biobank.<sup>192</sup> Even if no such bar exists, or if the parties agree to modify the MTA's terms, the primary researcher probably will not want to perform the reidentification. If the primary researcher's institution is a covered entity under HIPAA and the relevant information is PHI, reidentifying the specimen would trigger HIPAA requirements for individual authorization or waiver from a Privacy Board.<sup>193</sup> Any such authorization or waiver that the primary researcher obtained would have been limited only to the scope of the primary research project and would not include provisions for reidentification resulting from secondary research on the specimen.<sup>194</sup>

Furthermore, the primary researcher's IRB never required her to obtain informed consent for secondary research from the contributor, nor did it require her to disclose any information about return of results in her informed consent agreements. Thus, the contributor has no knowledge that his specimen was used for secondary research nor did he consent to having the IF returned to him. Consequently, the primary researcher has significant incentive to refuse to reidentify the specimen.

If the changes contemplated in the ANPRM come into effect, some of these conclusions might change. First, the ANPRM would require informed consent for future research, which typically could be obtained at the same time as consent for the initial research.<sup>195</sup> Thus, under the proposed rules, the contributor theoretically would be made aware that a secondary researcher might get access to his specimens or related data (although the contributor still may not be informed about any risks associated with IFs arising from that secondary research).

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192. See OFFICE OF BIOREPOSITORIES & BIOSPECIMEN RESEARCH, NAT'L CANCER INST., NCI BEST PRACTICES FOR BIOSPECIMEN RESOURCES 78 (2011), available at <http://biospecimens.cancer.gov/bestpractices/2011-NCIBestPractices.pdf> (providing model MTA language that includes requiring the recipient of biospecimens to "agree[ ] not to identify or contact any donor . . . who may have provided" specimens or data).

193. See 45 C.F.R. § 164.502(d)(2)(i)–(ii).

194. See Sec'y's Advisory Comm. on Human Research Prots., *supra* note 50, at 6–7 (interpreting the Privacy Rule to require study-specific HIPAA authorizations).

195. Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44,512, 44,519–20 (July 26, 2011) (to be codified at 45 C.F.R. pts 46, 160, 164, and 21 C.F.R. pts 50, 56).

More significantly, the ANPRM's new IRB requirements strongly encourage secondary researchers who work with deidentified data to promise, in advance, that they will make no attempt to reidentify.<sup>196</sup> If the secondary researcher had any plans to potentially re-contact contributors with individual findings, he would have had to obtain prior review by an IRB. It is likely that many secondary researchers would forswear any such plans to re-contact contributors in order to avoid such IRB review and its associated administrative costs and delay to research. Consequently, the proposed rules would further and more directly disincentivize return of results from secondary research.

Finally, it is important to note that, under the ANPRM, biospecimens would be regarded as identifiable under all circumstances.<sup>197</sup> Thus, we ask: would the outcome be different under the proposed rules had the secondary researcher been working with pre-existing data rather than pre-existing specimens? We find that the outcome would even more certainly prevent reidentification as the standardized data protections for limited data sets and deidentified information under the proposed rules explicitly include a prohibition against reidentification.

#### V. MANAGEMENT MODELS FOR REIDENTIFICATION AND RETURNING INDIVIDUAL FINDINGS

Entities in every part of the biobank system now must confront the regulatory and ethical dilemmas discussed above.<sup>198</sup> As we have described, existing regulatory structures that encourage robust deidentification create tension with a growing belief that researchers should return individual findings in at least some situations.<sup>199</sup> The future direction of policy exemplified by the recent ANPRM may increase this tension by creating additional barriers to the reidentification necessary for return of results.<sup>200</sup>

Yet ignoring this conflict will not make it go away. Debate

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196. *See id.* (proposing a consent requirement at the outset for all future research).

197. *Id.* at 44,519.

198. *See supra* Part IV.

199. *See supra* Part IV.A.

200. *See supra* text accompanying notes 165–71.



continues about the proper scope of any duty to return results, but as long as participants in the biobank system contemplate at least some possible return of results—even in a narrow subset of cases—then they must plan for that eventuality. This imperative unites all viewpoints except for those who believe researchers should never return results.<sup>201</sup> Whatever decision researchers and institutions make about which results to return, they must plan in advance how to return those results. That second challenge is the focus of Part V.

We offer two strong recommendations followed by a range of three possible management models to implement those recommendations. First, it is vital that actors in the biobank system make some plan for possible reidentification and subsequent return of individual findings. Second, it is important that regulators accommodate reidentification for the purpose of returning results, in contrast with their current posture. As to the management models, the particular details of the plan and its regulatory treatment will vary based on many individual circumstances, so we offer alternative approaches and leave it to individual actors within the biobank research system to choose those arrangements most suitable for their situation. Regulators ought to maintain a similar agnosticism about precise implementation.

#### A. ACTORS IN THE BIOBANK SYSTEM MUST PLAN FOR REIDENTIFICATION AND RETURN OF RESULTS

The consensus paper discusses at length the importance of advance planning and agreement in managing all the complexities of returning individual research findings.<sup>202</sup> The same is true for reidentification.<sup>203</sup> Right now, each biobank system is defined primarily by its flow of information from an individual who contributes specimens or data through various entities including collection sites, biobanks, and secondary researchers. This information flow yields scientific knowledge, the very purpose for which the entire system exists, so it properly remains the primary focus of internal management and external regulation of biobank systems. It is not the only

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201. See, e.g., *Biobank Frequently Asked Questions*, NAT'L PSORIASIS FOUND., [http://www.psoriasis.org/biobank\\_faqs](http://www.psoriasis.org/biobank_faqs) (last visited Apr. 19, 2012) (“You will not receive any information from your donated samples. You will not receive results on the research performed using your samples.”).

202. See Wolf et al., *supra* note 1, at 368–69.

203. *Id.* at 18–19 (offering “Recommendation 6”).

important information flow, however.

Every biobank system also should identify explicitly the appropriate “return path” for individual research findings through the system in cases where their return is warranted. This path points in the opposite direction from the flow that dominates discussion about biobank structures, instead leading back to the person whose specimen or data became the subject of research and gave rise to an individual research finding. Somewhere along that return path, some entity within the biobank system must reidentify the data or specimen, possibly acting in tension with the applicable regulations.<sup>204</sup> On balance, as elaborated below, biobanks themselves will do the best job of taking on the bulk of responsibility to oversee both the necessary planning for a return path and the actual reidentification of data or specimens. But all actors within the biobank system, and perhaps some additional trusted intermediaries, will have roles to play.

The shared understanding about entities’ responsibilities for any reidentification and return of results should be memorialized explicitly in agreements between the parties, presumably as part of the MTAs that already govern those relationships.<sup>205</sup> Two key variables must be specified in such agreements. First, they should spell out the sequence of actions from the first realization that an IF or IRR exists through recontact. This description of the return path allows each actor to understand its role in any return of results. Second, they ought to impose an obligation on one of the entities to perform the reidentification. The document should clearly indicate where consultation with an IRB would be necessary and which entity (and which entity’s IRB) would take on any regulatory burden associated with reidentification.

Newly created biobanks will have an easier time identifying and maintaining this return path than will biobanks already in existence. A new biobank will have the freedom to arrange its relationships with collection sites and secondary researchers in accordance with its decisions about the return path. Older biobanks will have to retrofit existing agreements to accommodate a return path as well as they are able. This may lead to considerable complexity, especially in

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204. See *supra* note 164 and accompanying text.

205. See *supra* notes 10–12 and accompanying text.

light of the wide variety of collection sites' informed consent procedures regarding biobanking and subsequent deidentified research.<sup>206</sup> This difference between future and preexisting biobanks is just one of the many individual features that require flexibility in determining the best return path for each biobank structure. The alternative management models discussed below present that range of choices.

Overall, the existence of some explicit agreement acceptable to all parties in the biobank system matters more than its precise content, for two reasons. First, if actors in the biobank system do not plan deliberately for the return path, it may never exist or it may disappear with time. Of course, some biobank systems maintain the identifiability of specimens and data throughout the research process, notwithstanding the increased regulatory burdens that result. They generally make this choice for research-related reasons such as a desire to study correlations between genetic results and certain demographic or lifestyle factors.<sup>207</sup> For example, a researcher attempting to connect area of residence to health outcomes likely needs to know where study participants lived in geographic subdivisions smaller than a state.<sup>208</sup> Under HIPAA, and potentially under the Common Rule, such information is identifiable and, consequently, the researcher must comply with these regulatory schemes and obtain IRB approval, informed consent, and individual authorization or a waiver of authorization.<sup>209</sup> In these cases, reidentification obviously

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206. See Wolf et al., *supra* note 1, at 380.

207. See Susanne B. Haga & Laura Beskow, *Ethical, Legal and Social Implications of Biobanks for Genetics Research*, 60 *ADVANCES GENETICS* 505, 522 (2008); David Wendler, *supra* note 171, at 1449–50 (“[R]emoval of personal identifiers diminishes the scientific value of biological samples, making it impossible to conduct some epidemiological research and preventing investigators from following up on unexpected findings.”).

208. See, e.g., Sam Harper et al., *An Overview of Methods for Monitoring Social Disparities in Cancer with an Example Using Trends in Lung Cancer Incidence by Area-Socioeconomic Position and Race-Ethnicity, 1992–2004*, 167 *AM. J. EPIDEMIOLOGY* 889, 890–92 (2008) (using banked data from a national cancer registry to connect race, ethnicity, and average income in geographical unit to incidence of lung cancer).

209. Under HIPAA, “geographic subdivisions smaller than a state” must be removed in order for information to qualify as deidentified. 45 C.F.R. § 164.514(b)(2)(i)(B) (2012). Under the Common Rule, such information is identifiable if the researcher could readily ascertain the identity of the individual. OHRP—Guidance on Research Involving Coded Private Information or Biological Specimens, *supra* note 24, at 3. As discussed above, the ANPRM would harmonize these standards and would define such

presents no obstacle to returning results. At the other extreme, a few biobank systems eradicate the return path intentionally, based in part on their assessment that risks associated with reidentification outweigh any potential benefits.<sup>210</sup>

In a significant number of cases, however, biobanks or other entities deidentify specimens or data, in satisfaction of the regulatory incentives now in place, without sufficiently careful protocols for potential reidentification. Often they have given little consideration to the possibility. For example, if the ANPRM takes effect, conscientious primary collection sites would likely routinely strip identifiers in compliance with the existing HIPAA definition before ever transferring specimens or data to a biobank for use in subsequent downstream research. Without any incentive to plan for potential reidentification—and often with agreements in place that positively forbid reidentification—any notions a secondary researcher might entertain of returning individual research findings in a particular case could be mooted by the practical difficulty of doing so. Alternatively, even where biobanks or researchers do anticipate the existence of a return path, it can fade with time when no one recognizes the importance of maintaining it.<sup>211</sup> Files are purged, protocols are misplaced or forgotten, key personnel depart, or research projects and even whole institutions go out of existence. Planning in advance for the continued existence of a return path can help prevent this entropy.

Second, working out the practicalities of reidentification in the abstract in advance will permit actors in the biobank system to choose best practices across the board, apart from the

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information identifiable. *See supra* Part III.A.

210. *BioVu: Vanderbilt's DNA Databank*, *supra* note 180.

211. This is a recognized problem in information security. For example, programmers frequently write customized computer code in legacy systems, intended to solve a particular problem quickly. Over time, those programmers leave the institution, or they forget about the patch they wrote, and unintended difficulties arise in other contexts. *Cf.* Edward H. Freeman, *Source Code Escrow*, 13 INFO. SYS. SECURITY 8, 10 (2004) (describing how purchasers might protect against software vendors' instability by placing the program's source code in escrow, only to be released in certain circumstances). This problem occurred on a large scale as the year 2000 approached and programmers needed to examine old code line by line for instances of dates that were presumed to be in the twentieth century. *See Five Months and Counting*, PBS ONLINE NEWSHOUR, July 27, 1999, [http://www.pbs.org/newshour/bb/cyberspace/july-dec99/y2k\\_7-27.html](http://www.pbs.org/newshour/bb/cyberspace/july-dec99/y2k_7-27.html).

circumstances of an individual case. A decision to return results necessarily involves fact-specific inquiry into a particular case. Judgments about the best method of recontact may turn on such details as the nature of the finding,<sup>212</sup> the informed consent in force,<sup>213</sup> the availability of a clinician who has a relationship with the individual,<sup>214</sup> and even the individual's age.<sup>215</sup> Reidentification and the return path, in contrast, are systematic issues that can be resolved once for all research within a particular biobank system. These types of issues, independent from individualized factual considerations, are more amenable to an advance plan that sets up clear rules rather than situation-specific standards.<sup>216</sup> Furthermore, keeping a clear return path open eliminates one of the many variables that add so much potential complexity to decisions about return of results. Even as conscientious biobanks and their partners are struggling in some particular situation to determine whether to return results and how to recontact, the issue of reidentification can be made simple with an advance plan.

#### B. THE COMMON RULE AND HIPAA PRIVACY RULE SHOULD ADDRESS REIDENTIFICATION FOR RETURN OF RESULTS

The Common Rule and HIPAA generally impede rather than promote the practices we recommend to entities within biobank research systems in the previous section. Both regimes encourage early and robust deidentification of specimens and data used for research purposes. Neither promotes planning to reidentify those same specimens or data. If the ANPRM informs the future of the Common Rule, deidentification will be further enshrined and IRBs will reduce their already minimal oversight of the movement of specimens or data through the biobank research system.

Especially as DHHS appears poised to reengineer the Common Rule based on the ANPRM, we would recommend two types of alterations in the regulatory regime.

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212. See, e.g., Fabsitz et al., *supra* note 166, at 575 (suggesting criteria for determining if a result ought to be returned).

213. See, e.g., *id.*

214. See, e.g., Henry S. Richardson, *Incidental Findings and Ancillary-Care Obligations*, 36 J.L. MED. & ETHICS 256, 265 (2008).

215. *Analysis and Recommendations*, *supra* note 151, at 241–42.

216. See Louis Kaplow, *Rules Versus Standards: An Economic Analysis*, 42 DUKE L.J. 557, 621 (1992).

First, the Common Rule and related HIPAA-based rules could and should specifically stipulate that return of individual research findings can be an ethically appropriate reason to reidentify specimens or data. At present, neither regime contemplates any acceptable non-research reason to engage in reidentification.<sup>217</sup> The rules could base any authorization for reidentification on the sorts of principles identified in the consensus paper, such as the clinical actionability of findings.<sup>218</sup> Because views about return of individual research findings remain unsettled and fluid, however, regulators might be better off limiting the requirements to ensuring satisfactory institutional oversight. For example, the rules could allow reidentification for the purpose of returning individual research findings contingent on approval of the plan for reidentification and recontact by a relevant IRB or Privacy Board (as we discuss below, the existence and availability of these oversight bodies is one consideration in designing an appropriate the return path). Under administrative guidance interpreting the Common Rule, an investigator's reidentification of deidentified specimens or data brings the investigator's research within the scope of the Rule.<sup>219</sup> No matter what changes DHHS opts to make to the Common Rule, administrative guidance or regulatory text ought to make clear that reidentification of data or specimens, if done for the narrow purpose of returning an IF or IRR under the supervision of an IRB, does not trigger the application of the Common Rule.

Our second and related recommendation is that the regulatory regime should reinforce our previous points about the importance of articulating a plan for the return path. The Common Rule could require institutions to have such a plan as a condition for the deidentification-based exemptions and exceptions discussed above. Plans need not be unique to every

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217. Cf. *OHRP—Guidance on Research Involving Coded Private Information or Biological Specimens*, *supra* note 24, at 4 (advising that if deidentified information is reidentified, the research involves human subjects and is within the purview of the Common Rule).

218. Wolf et al., *supra* note 1, at 373.

219. *OHRP—Guidance on Research Involving Coded Private Information or Biological Specimens*, *supra* note 24. The ANPRM anticipates codifying this position. See *Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators*, 76 Fed. Reg. 44,526 (July 26, 2011) (to be codified at 45 C.F.R. pts. 46, 160, 164, and 21 C.F.R. pts. 50, 56).

research project because they could be the same for each biobank research system. This would create further incentives for biobanks, as the central repository in most systems, to have established reidentification and recontact plans that could be used by downstream researchers for compliance with this condition. The management models described below represent various possible forms these plans could take.

### C. THREE MANAGEMENT MODELS FOR RETURN OF RESULTS WITHIN BIOBANK STRUCTURES

As biobanks and their partners in collection sites and secondary research sites consider ways to design and implement a return path for individual findings and results, their most important decision will be their respective roles in that process.<sup>220</sup> In short: who will do what? These assignments may come with regulatory burdens, particularly if the Common Rule and HIPAA Privacy Rule do not change as we recommended in the previous section. In this final section we present three management models, each centered on a different entity as the primary “keeper of the key” who has the capacity to reidentify specimens and data, and we suggest some of the advantages and disadvantages of each. We look first at a model giving the collection site principal responsibility, then at one giving that role to the biobank, and finally at a model relying on a third-party intermediary to hold the code.

We do not consider a model giving the job to the secondary researcher, for several reasons. Most obviously, by the time specimens or data reach that point, they are highly likely to be deidentified already because of all the regulatory incentives to do so.<sup>221</sup> The secondary researcher comes too late in the process to meaningfully safeguard the integrity of a return path. And finally, secondary researchers have neither the collection site’s proximity to the contributors of specimens or data nor the archival role of the biobank.

#### 1. The Collection Site

Under one management model, the initial collection site

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220. There are, of course, myriad narrower but very important issues which follow that first one, all of them beyond the scope of this Article, including the design of informatics, management of data privacy and security to prevent unauthorized reidentification, and financial support for these functions, to name a few.

221. See *supra* Part IV.A.

would deidentify specimens and data before entrusting them to a biobank. In the event of a potentially returnable result a secondary researcher would notify the biobank, which would in turn notify the collection site, which would take responsibility for reidentification and presumably recontact. Ideally, the collection site would ensure the existence of explicit agreements about return of results and the associated return path (presumably as part of MTAs or similar contracts) with both the biobank and all subsequent secondary researchers, spelling out the duties of each.

This management model imposes regulatory burdens on the fewest actors within the biobank research system. Neither the biobank nor the secondary researcher would take on additional regulation-based duties, because they would only handle specimens and data that have been properly deidentified. Thus, their activities would not constitute human subjects research and the data would not qualify as protected health information.<sup>222</sup>

The collection site, however, undertakes greater regulatory responsibility in this model. First, the regulatory change we advocated above in Section B of this Part would require the collection site's IRB (or possibly a separate privacy board if applicable) to scrutinize the plan for the return path before any transfer of data or specimens to a biobank.<sup>223</sup> This review would add to the burden on the IRB, which currently has no obligation to inquire into the terms of transfers of deidentified data to biobanks.<sup>224</sup> On the other hand, we would also argue that it should be best practice for a collection site to engage in a formal examination of such transfers to ensure that they incorporate a viable plan for the return path, even if the regulations do not require this review.

Furthermore, if a collection site received a returned individual result from a biobank under this model, it probably would create additional regulatory complications for the collection site. Once reidentified, specimens or data could be subject to the Common Rule, even if the collection site had never itself conducted any research on them.<sup>225</sup> This might

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222. See *supra* text accompanying notes 23–25.

223. See *supra* Part V.B.

224. See *supra* text accompanying note 53.

225. See *supra* text accompanying notes 18–19.



often be the case, for example, when the collection site is a clinical facility that merely passed on specimens or data to a biobank based on the applicability of the exemption for deidentified specimens used for diagnosis or treatment.

The regulatory change we recommended above would require the collection site's IRB to review such transfers in the future to ensure adequate planning for the return path. The collection site is the one place where informed consent and IRB approval is required, especially under the proposed amendments to the Common Rule.<sup>226</sup> The initial collection site is also the locus of direct interaction between donors and the biobank research system.<sup>227</sup> As the origin point for the rest of the biobank system, collection sites could ensure that material transfer agreements contain provisions binding all downstream biobanks and secondary researchers to the IRB-approved plan for reidentification. This approach may also be best for mitigating privacy and data confidentiality concerns, as there would be no need for the code to ever be moved. Consequently, the risk of unauthorized access would be lowered.

However, this approach has several potential limitations. First, collection sites are often established for the purposes of a particular research project and, once that project is complete, the collection site no longer has funding or staff and ceases to operate. Collection sites with primarily clinical functions may lack research-oriented institutional structures such as highly developed IRBs. Because many collection sites pass along specimens and data to biobanks without receiving significant direct benefit in return, imposing extra duties on them may discourage their participation in biobank research, eliminating potential sources for medical research. Finally, collection sites may lack the financial resources, staffing, or expertise to manage the code.

## 2. The Biobank

In the second management model, the biobank would take on the central role of ensuring a return path and probably of performing any necessary reidentification. The biobank could receive specimens or data from primary collection sites in identifiable form and could itself deidentify them.

There are several obvious advantages to this approach.

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226. *See supra* Part III.B.

227. *See supra* text accompanying notes 19–21.

Biobanks already perform an intermediary role as archives and brokers within the larger system. The functions of managing the flow of information through the return path and of retaining the codes needed for reidentification would mesh better with the primary mission of the biobank than with that of many collection sites. In addition, biobanks are less likely than collection sites to be short-term institutional actors associated with particular projects. By their nature, these repositories are designed for a long and stable existence. Finally, economies of scale would result because most biobanks aggregate data and specimens from a large number of primary sources. Each biobank, without reinventing the proverbial wheel, could develop a careful advance plan for the return path, robust security and other procedures for maintaining reidentification data without compromising privacy, and a large pool of experience in handling any returns of results that might transpire.

This model might cause difficulty in situations where a biobank also conducts its own research (or is housed in an institution that conducts research).<sup>228</sup> Handling specimens or data that remain identifiable could trigger regulatory obligations. While these problems would only arise where a biobank's research used the specimens or data at issue, that might be the case for a significant proportion of the overall pool. Thus, this model might prove most attractive to biobanks that serve solely as clearinghouses and do not engage in research themselves.

Conversely, where biobanks do not conduct research or handle PHI, they may operate largely outside the purview of both the Common Rule and HIPAA.<sup>229</sup> In these situations, mechanisms for evaluating the plans as we recommend could be absent because of this regulatory lacuna. One potential regulatory response would be the development of guidance. Such guidance could extend to standards that allowed a biobank to certify its adherence to specific data security and related practices, and perhaps even to a structure as elaborate as the Clinical Laboratory Improvement Amendments

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228. See *supra* note 48 and accompanying text.

229. See *Guidance on Engagement of Institutions in Human Subjects Research*, *supra* note 25 (advising that merely releasing information or specimens to investigators is not, by itself, considered engaging in research and so the Common Rule does not apply).

(CLIA).<sup>230</sup> Preferably, guidance would be simpler, more in keeping with the specific HIPAA deidentification rules. By establishing a set of best practices to help guide biobanks' activities in maintaining reidentification codes and planning for a return path, regulators could protect privacy, allow for return of results when warranted, and avoid undue interference with biobanks' important activities.

Finally, biobanks that perform reidentification and take responsibility for planning and maintaining a return path would need to work with primary collection sites and secondary researchers to ensure that they acted in concert with the biobank's efforts. There may be some educational efforts required, for example, to make primary collection sites comfortable with transferring identifiable specimens or data to the biobank, particularly if they qualified as PHI but even if they did not. The biobank probably would need to develop standardized language for incorporation into agreements like MTAs that would spell out each party's role and obligations. While this could mean more paperwork, we also see it as a positive step to ensure advance planning. The consensus paper emphasized the importance of such forethought, and we also have highlighted the need to plan for the maintenance of a return path.

### 3. A Trusted Intermediary

A third possibility is to have collection sites and biobanks transfer the code to a trusted third-party intermediary, also referred to as a "tissue trustee,"<sup>231</sup> or "honest broker."<sup>232</sup> The potential role of trusted intermediaries in the proper functioning of interlinked health care records has recently

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230. Federal law requires laboratories that test "materials derived from the human body for the purposes of providing information for the diagnosis, prevention, or treatment of any disease or impairment, or the assessment of the health of human beings" to meet certain standards established by the Secretary of Health and Human Services. 42 U.S.C.A § 263a(a) (2006). These standards are provided in regulation at chapter 42, part 493 of the Code of Federal Regulations.

231. Rihab Yassin et al. *Custodianship as an Ethical Framework for Biospecimen-Based Research*, 19 *CANCER EPIDEMIOLOGY & BIOMARKERS PREVENTION* 1012, 1013 (2010).

232. *Id.*; Andrew D. Boyd et al., *An 'Honest Broker' Mechanism to Maintain Privacy for Patient Care and Academic Medical Research*, 76 *INT'L J. MED. INFORMATICS* 407, 408 (2007).

become an issue of considerable discussion.<sup>233</sup> Some observers argue that an intermediary model is especially well-suited for situations where there is the potential for significant growth in the volume of data that needs handling, where data is especially complex, and where data is sought by multiple users for different purposes.<sup>234</sup> Meanwhile, scholars in areas beyond health care have long contemplated various forms of trusted intermediaries as mechanisms for facilitating data transfers, filtering and organizing information, and protecting information privacy.<sup>235</sup> Understandably, discussion of such intermediaries focuses on more typical information flows—in the case of the biobank research system, the movement of information from a collection site to a downstream researcher. There is great potential for trusted intermediaries to improve privacy and security in those ordinary flows, but our discussion focuses on an additional benefit they might provide in managing the reverse information flow required for return of results.

Under this model, a secondary researcher who encountered an IRR or IF would communicate that finding to the trusted intermediary in whom the deidentification key had been entrusted. The intermediary would then bear primary responsibility for reidentifying the specimen or data and arranging subsequent recontact, presumably in concert with the collection site. The intermediary might be charged with the decision about whether to proceed in returning a particular result, but that decision also could be assigned to other actors such as the secondary researcher or the biobank while leaving

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233. See, e.g., David Budgen et al., *A Data Integration Broker for Healthcare Systems*, 40 *COMPUTER* 34, 35 (2007); Barbara J. Evans, *Much Ado About Data Ownership*, 25 *HARV. J. LAW & TECH.* 69, 100 (2011); Mark A. Hall, *Property, Privacy, and the Pursuit of Interconnected Electronic Medical Records*, 95 *IOWA L. REV.* 631, 661–63 (2010).

234. Budgen, *supra* note 238 (citing D. KRAFZIG, ET AL., *ENTERPRISE SOA: SERVICE-ORIENTED ARCHITECTURE BEST PRACTICES* (2004)).

235. See, e.g., Frank Pasquale, *Copyright in an Era of Information Overload: Toward the Privileging of Categorizers*, 60 *VAND. L. REV.* 135, 187–88 (2007) (discussing Google Library as an intermediary for copyrighted works); Kenneth C. Laudon, *Markets and Privacy*, 39 *COMM. ACM*, Sept. 1996, at 99–101 (1996) (discussing a possible intermediary for privacy information); Kim Cameron, *The Laws of Identity*, *KIM CAMERON'S IDENTITY WEBLOG* (Jan. 8, 2006), <http://www.identityblog.com/?p=352> (discussing how a “unifying identify metasystem” could be employed to protect Internet privacy and safety).

the actual management of the reidentification and recontact to the intermediary.

Third-party intermediaries are even more likely to lie outside the coverage of the Common Rule and HIPAA than are biobanks. Presumably they are not engaged in their own research. They rarely would fall within HIPAA's definition of covered entities. As a result, some form of regulatory coverage may be desirable for an institution that could play a sensitive role both in the traditional activities of a biobank research system and in the potential return of results. As noted above in reference to biobanks, oversight of trusted intermediaries could be provided through a certification program, perhaps modeled on CLIA. (Indeed, one set of standards could apply to both biobanks and intermediaries, reducing complexity and allowing institutions to choose the best management model without regard to unjustified regulatory distinctions.) One example of such a trusted intermediary model and certification system has been implemented and evaluated by the University of Pittsburgh. In 2003, the University obtained IRB approval for an "honest broker" entity serving as a "firewall" between the University's stored tissue bank and its clinical and research functions.<sup>236</sup> In 2003, the University obtained IRB approval to develop an Honest Broker Facility.<sup>237</sup> Prior to commencing any brokering activities, personnel from this facility were required to obtain an honest broker certification by completing an IRB-mandated educational program on research integrity, human subjects research protections, and HIPAA requirements.<sup>238</sup> The Honest Broker Facility also provides biannual updates to the IRB as part of on-going auditing and monitoring.<sup>239</sup> Certified honest brokers from the Honest Broker Facility are the only individuals with access to information linking stored tissues with donors' identifying information.<sup>240</sup> New information about donors from upstream clinical sources and research findings from downstream researchers both flow to the honest broker, allowing the broker to maintain an accurate database of current information and a means to reidentify donors in the

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236. Rajiv Dhir et al., *A Multidisciplinary Approach to Honest Broker Services for Tissue Banks and Clinical Data: A Pragmatic and Practical Model*, 113 *CANCER* 1705, 1711 (2008).

237. *Id.* at 1711–12.

238. *Id.* at 1709.

239. *Id.*

240. *Id.* at 1708–09.

event of an IRB-approved returnable result.<sup>241</sup>

A variation on the trusted intermediary is the “charitable trust” model. This model is similar to the trusted intermediary model in that a third-party charitable trust assumes the responsibility for holding codes for reidentifying contributors. The charitable trust model goes one step further, however, by establishing a fiduciary duty to donors to use specimens only as approved by donors.<sup>242</sup> Under this model, donors must provide informed consent to future research on specimens or data collected for primary research or non-research purposes.<sup>243</sup> The trust is responsible for encrypting identifying information before sharing specimens or data with secondary researchers and biobanks and for maintaining the encryption key.<sup>244</sup> If contributors requested during the informed consent process that they receive information about the research findings facilitated by their participation, the trust is also responsible for communicating that information from secondary researchers back to donors.<sup>245</sup> The trust is governed by a board of trustees composed of members from the trust’s IRB and donor advocacy groups.<sup>246</sup> Needless to say, because such a model already anticipates an information flow from secondary researchers back to donors, it would be especially easy for it to accommodate a return path for individual findings where warranted.

These various intermediary models have several advantages in common. First, they can serve the role of broker and steward. Second, they can be designed with structures such as boards of trustees that enable donor groups to have a direct voice in governance. Third, they have the benefit of longevity where collection sites and even biobanks may be forced to shut down due to lack of funding or completion of purpose. Finally, and perhaps most significantly for the purposes of this article, trusted intermediaries generally stand outside the existing complex tangle of regulatory requirements we have described.

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241. *See id.*

242. David E. Winickoff & Richard N. Winickoff, *The Charitable Trust as a Model for Genomic Biobanks*, 349 NEW ENG. J. MED. 1180, 1182 (2003).

243. *Id.* at 1182–83.

244. *Id.* at 1182.

245. *See id.* at 1183 (proposing that the charitable trust could recontact donors to gather more information if needed).

246. *Id.* at 1182–83.

This model allows for a clean slate and minimizes the awkward process of fitting new practices such as return of results into existing regulation designed for different purposes.

The principal disadvantage we see is the addition of another actor to the already complicated structure of biobank research systems. In some relatively simple arrangements, the addition of another player would not be worthwhile. As large-scale collection and transfer of specimens and data increase, however, we expect to see greater reliance on various types of intermediaries, driven in part by considerations completely separate from our concerns about return of results, legitimate reidentification, and a return path. In those situations, we hope they will be designed to accommodate return of results as well.

### CONCLUSION

As biobank research systems contemplate the possibility of returning individual research results and incidental findings to contributors of specimens and data, they face a host of regulatory complexities. Many of these arise from the difficult ethical issues connected to the initial decision to return such results. This article has emphasized regulatory obstacles that occur later, but may render meaningless any previous decision to return results. Without a legally sound basis for reidentifying specimens and data, and an agreed-upon distribution of responsibilities for the return path of information back to the original contributor, it will never be delivered.

The current regulatory regimes of the Common Rule and HIPAA create strong incentives for deidentification of specimens and data. They do not contemplate any legitimate reasons for reidentification. Moreover, the regulators have signaled, in a recent ANPRM, a desire to increase their emphasis on deidentification even further in future regulatory amendments. We have demonstrated the poor fit between these regulatory structures and the growing view that return of results should be considered in at least some circumstances. We also have suggested some regulatory changes that would better accommodate that view and some management models for biobank research systems interested in preparing for the possible return of results. Clearly, there needs to be more deliberation about these complex issues, but we hope the consensus paper, this symposium, and this article help to start the conversation.