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## The Tension Between Policy and Practice in Returning Research Results and Incidental Findings in Genomic Biobank Research

Sharon F. Terry

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# The Tension Between Policy and Practice in Returning Research Results and Incidental Findings in Genomic Biobank Research

Sharon F. Terry\*

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## I. INTRODUCTION

The tensions between policy and practice in returning research results (RRs) and incidental findings (IFs) in genomic biobank research are readily apparent and potentially increasing as biobanks are built at a more frenzied pace. As a result, more policies are proffered and practices are ever more widely varied. Particularly for the Western mind, tension can have negative connotations, and in the face of it, one may consider reducing or eliminating it as a productive goal. However, tension is a force of balance, and allowing for a continuum, rather than a dichotomous world, is a generative role for tension. As the tension between policy and practice increases, it will lead to some novel and necessary solutions. In fact, tension can be a beacon that highlights the critical issues and even helps determine both policy and practice—a generative dialogue shareholders should be part of—as well as what processes will accelerate the balance.

This paper will consider the current tensions between policy and practice from a number of stakeholders' perspectives. It will also consider future tensions that might arise as data-sharing in general becomes more of a norm and contributors of biological samples and clinical data become more proactively engaged in biomedical research.<sup>1</sup>

Genomic biobank research means different things to many people. Further, the widely varying results coming from these biobank systems may lead to varying tensions.<sup>2</sup> There are several ways to approach this discussion, and for the sake of using the various stakeholders as spokespersons for the tensions, we will use a fairly simple—somewhat inclusive—model. I will consider the biobank to be the entire system as defined by the 2012 Wolf Consensus Document. Thus, the term biobank refers to the system of primary researcher, biobank, and secondary researcher.<sup>3</sup>

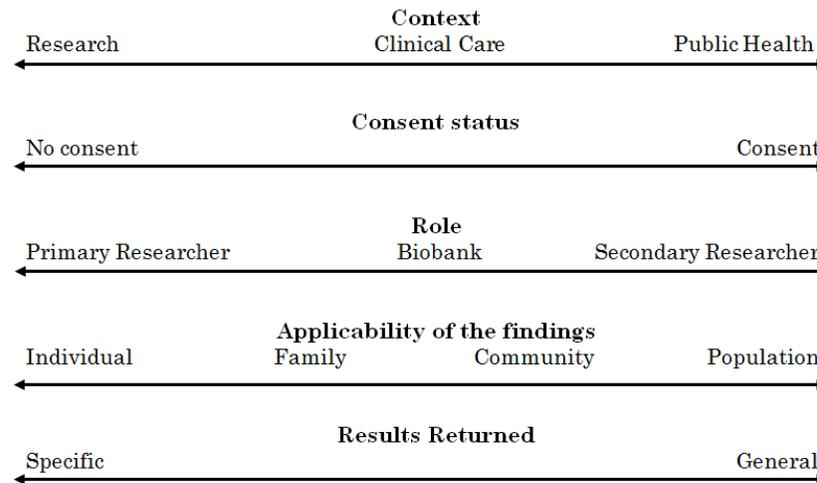
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1. See Sharon F. Terry & Patrick F. Terry, Commentary, *Power to the People: Participant Ownership of Clinical Trial Data*, 3 SCI. TRANSLATIONAL MED. 69cm3, at 2 (2011).

2. See generally Jasper Bovenberg et al., *Biobank Research: Reporting Results to Individual Participants*, 16 EUR. J. HEALTH L. 229 (2009) (discussing the results of a study on whether and how any results derived from research with large scale biobanks should be communicated to individual research participants).

3. Susan M. Wolf et al., Special Article, *Managing Incidental Findings and Research Results in Genomic Research Involving Biobanks and Archived*

This does not mean that I will simplify to such an extent as to ignore each of these dimensions. In fact, a complex matrix is needed to describe the intersection of various continuums. RRs and IFs can occur in various contexts from research to clinical care to public health (Figure 1). There are many roles in a biobank system and only the three delineated by the 2012 Wolf Consensus Document would be in a position to return RRs or IFs. Findings might be applicable to an individual, a family, a community, or to an aggregate population.<sup>4</sup> Finally, specific or general results can be returned.<sup>5</sup>



**Figure 1. Continuum in which RR and IFs occur.**

#### A. CURRENT POLICIES

I begin with a cursory review of policies and practices.<sup>6</sup> There are a relatively large number of policies and guidelines applicable to the governance of biobanks. In a 2008 review of policies, Haga reported fourteen international guidelines for biobanks and forty-four national and regional sets of guidelines.<sup>7</sup> Some of these guidelines impact the return of RRs and

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*Data Sets*, 14 GENETICS MED., 361 (2012).

4. *See id.* at 6–7.

5. *See id.* at 7–8.

6. For a more complete discussion, see Wolf et al., *supra* note 3.

7. Susanne B. Haga & Laura M. Beskow, *Ethical, Legal, and Social Implications of Biobanks for Genetics Research*, 60 ADV GENET 505, 509–11

some IFs, but not all address them explicitly.<sup>8</sup> In fact, the 2012 Wolf Consensus Document, in an extensive study, found that current biobank policies vary and U.S. biobanks are almost evenly divided on whether they address the return of IFs and RRs.<sup>9</sup>

i. To Return or Not to Return

Biobank policies range from returning no results at all to returning some results.<sup>10</sup> Vanderbilt University Medical Center's BioVU is "one of few biobanks" set up to conduct "non-human subjects research" and "the design explicitly precludes re-contact with any individual."<sup>11</sup> This policy rests on an Office for Human Research Protections (OHRP) guidance that stated studies with data or samples not collected for the specific research in question or not readily identifiable sources will not be considered human subjects research.<sup>12</sup>

Two recommendations put forth by a working group convened by the National Heart Lung and Blood Institute are also relevant as an example of a biobank policy:

Recommendation 1[:] Individual genetic results *should* be offered to study participants in a timely manner if they meet *all* of the following criteria:

- a. The genetic finding has important health implications for the participant, and the associated risks are established and substantial.
- b. The genetic finding is actionable, that is, there are established therapeutic or preventive interventions or other available actions that have the potential to change the clinical course of the disease.
- c. The test is analytically valid, and the disclosure plan complies with all applicable laws.
- d. During the informed consent process or subsequently, the study participant has opted to receive his or her individual genetic results.<sup>13</sup>

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(2008).

8. *See id.* at 508–12.

9. Wolf et al., *supra* note 3, at 365–66.

10. *Id.*

11. Jill Pulley et al., *Principles of Human Subjects Protections Applied in an Opt-Out, De-Identified Biobank*, 3 CLINICAL TRANSLATIONAL SCI. 42, 48 (2010).

12. *Guidance on Research Involving Coded Private Information or Biological Specimens*, OFF. HUM. RES. PROTECTIONS (Aug. 10, 2004), [www.hhs.gov/ohrp/archive/humansubjects/guidance/cdebiol04.htm](http://www.hhs.gov/ohrp/archive/humansubjects/guidance/cdebiol04.htm).

13. Richard R. Fabsitz et al., *Ethical and Practical Guidelines for Report-*

Recommendation 4[:] Investigators *may* choose to return individual genetic results to study participants if the criteria for an obligation to return results are not satisfied (see Recommendation 1) but all of the following apply:

- a. The investigator has concluded that the potential benefits of disclosure outweigh the risks from the participant's perspective.
- b. The investigator's I[nstitutional] R[eview ]B[oard] has approved the disclosure plan.
- c. The test is analytically valid and the disclosure plan complies with all applicable laws.
- d. During the informed consent process or subsequently, the study participant has opted to receive his/her individual genetic results.<sup>14</sup>

ii. More Recent Policy Recommendations

After considering these and many other recommendations, the recommendation made by the 2012 Wolf Consensus Document states what responsibilities biobanks should shoulder:

- (1) *clarifying* the criteria for evaluating findings (e.g., analytic validity, seriousness of condition, and actionability) and the roster of returnable IFs and [RRs];
- (2) *analyzing* a particular finding in light of those criteria and that roster to determine if it constitutes a returnable IF or [RR];
- (3) *re-identifying* the individual (or individuals) for potential return; and
- (4) *recontacting* the individual (or individuals) to offer the finding.<sup>15</sup>

Certainly these recommendations shift the onus for returning results from the primary researcher, previously the most common focus for this responsibility, to the entire biobank research system. The 2012 Wolf Consensus Document defines the system as including primary and secondary researchers and the biobank.<sup>16</sup> This suggests that the system should ensure that necessary IFs and RRs are offered to participants, with the biobank itself responsible for general oversight. The entire biobank system must have a procedure for evaluating findings, along with a list of returnable IFs and [RRs], and be responsible for determining which results are offered to participants.<sup>17</sup> Furthermore, the biobank research system must be able to

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*ing Genetic Research Results to Study Participants: Updated Guidelines from a National Heart, Lung, and Blood Institute Working Group*, 3 *CARDIOVASCULAR GENETICS* 574, 575 (2010).

14. *Id.* at 577.

15. Wolf et al., *supra* note 3, at 371.

16. *Id.* at 3–4.

17. *See id.* at 9.

identify and recontact the donor(s) relevant to the finding.<sup>18</sup> IFs and RRs with unlikely net benefit for donors should not be returned; however, there should be a distinction made between those results biobank systems must return and those that may be returned, based on net benefit.<sup>19</sup> Donors and potential donors should be involved throughout this process by providing input on their preferences regarding returning results, while biobanks learn from outcomes, and share experiences with other biobanks, in order to improve the system.<sup>20</sup>

Funders and regulators must also share some of the responsibility.<sup>21</sup> There should be processes for regulators to ensure that biobanks follow the standards set down for returning results and to support these biobanks in creating and updating these standards. The Advanced Notice of Proposed Rule Making on the Common Rule (ANPRM) published by the Office of Human Research Protections (OHRP) in July 2011 proposes that inclusion of a sample in a biobank will require explicit consent.<sup>22</sup> This proposed new rule arises from concerns that many biobanks obtain and archive samples without the participants' knowledge and may resolve some of the complexities inherent in returning results. If biobanks inform and even engage participants during this consent process by educating them about having identifying information stored in a way that enables RR, then many of the tensions dissipate. However, OHRP may have inadvertently disincentivized biobanks from engaging participants since the ANPRM indicates that research that doesn't return results is "excused": a new category that doesn't require the researchers go to an IRB to use the samples.<sup>23</sup> OHRP asked many questions related to this issue in their request for comments.<sup>24</sup>

Funders, be they public or private, must recognize the additional burden created by the necessity of having a system for returning results and must allocate funding accordingly.<sup>25</sup>

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18. *Id.* at 9–10.

19. *Id.* at 13.

20. *Id.* at 19.

21. *See id.*

22. Human Subject Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators, 76 Fed. Reg. 44512, 44515 (July 26, 2011).

23. *Id.* at 44518–19.

24. *Id.* at 44520–21.

25. *See* Wolf et al., *supra* note 3, at 364.

Funders can also require, through a variety of carrot and stick mechanisms, return of IFs and RRs. They will not be considered in this paper as distinct stakeholders, but are active players in the system and affect the level of tension in the system.

### iii. International Issues

Some authors have recommended that it is critical in a global age that international policies be considered.<sup>26</sup> To some extent, the international community has led policy development in this regard:

Indeed, the [incidental findings] issue was acknowledged by the international community in the mid-1990s in a statement by the international Human Genome Organization (HUGO), which declared that “choices to be informed or not with regard to results or incidental findings should . . . be respected.” In its “International Ethical Guidelines for Biomedical Research Involving Human Subjects,” the Council for International Organizations of Medical Sciences (CIOMS) has provided that “individual subjects will be informed of any finding that relates to their particular health status.” CIOMS also states that “subjects have the right of access to their data on demand, even if these data lack immediate clinical utility.”<sup>27</sup>

Zawati et al. argue that Spanish law implies that every person has the right to be informed of his or her genetic data and other data of a personal nature that are obtained in the course of a biomedical research.<sup>28</sup> Some of these international policies are worded more strongly than U.S. policies.<sup>29</sup> Many of these policies have their basis in human rights.<sup>30</sup> In general, U.S. policies present themselves as recommendations to the institutions holding the samples, rather than describing the rights of the participant.

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26. See generally Lynn G. Dressler, *Biobanking and Disclosure of Research Results: Addressing the Tension Between Professional Boundaries and Moral Intuition*, in *THE ETHICS OF RESEARCH BIOBANKING* 85 (Jan Helge Solbakk et al. eds., 2009) (discussing the emerging ethical imperative from international guidelines to communicate research results to the individual and questioning how that these duties can be implemented in practice).

27. Wolf et al., *supra* note 3, at 367 (citations omitted).

28. See Ma'n H. Zawati et al., *Incidental Findings in Genomic Research: A Review of International Norms*, 9 *GENEDIT* 1, 5 (2011) (“The Spanish Law confirms the existence of the participant’s right ‘not to know’ about incidental findings.”).

29. Wolf et al., *supra* note 3, at 367.

30. See *id.* at 7–8.

## B. CURRENT PRACTICES

There is significant variation, both within the United States and abroad, in the practice of how biobanks handle returning IFs and RRs.<sup>31</sup> Some biobanks, for instance, offer no results of any kind to research participants, while others only release aggregate data.<sup>32</sup>

Even within the subset of biobanks offering *some* form of returning IFs and RRs, there is still a wide deviation.<sup>33</sup> Certain biobanks offer only IFs to participants or only provide particular individualized RRs, whereas other biobanks consistently offer all IFs and RRs. The Coriell Personalized Medicine Collaborative, for example, is a multi-institutional study in the United States that periodically offers both IFs and RRs to research participants.<sup>34</sup> On the other end of the spectrum is the Icelandic Biobank, launched in 1998, which gave full ownership of health information to the state<sup>35</sup> and released no results—aggregate or individual. Most biobanks fall somewhere in the middle, like the UK Biobank, which offers IFs found during initial testing and grants access to the aggregate results, but it provides no other IFs or RRs.<sup>36</sup>

Thus, policy and practice are tightly coupled in a few instances, but for the most part policies regarding return of RRs or IFs have not yet been formulated and practice varies a great deal based on the individual researchers involved, the culture of the institution and the region, and the level of involvement of the participants.

A project called the Electronic Medical Records and Genomics Network (eMERGE) is potentially a good place to explore the tensions between policy and practice. This is a compilation of five major medical center sites, a data coordinating center, and National Institutes of Health, using a broad range

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31. *Id.*

32. *Id.* at 5.

33. *See, e.g., id.* at 5–6 (“Among those biobanks that do address [the issue of returning IFs and RRs], some return no findings at all, some return non-genetic IFs (such as abnormal blood pressure) discovered at enrollment, some return a subset of non-genetic or genetic IFs, and some return a subset of non-genetic or genetic [RRs].”).

34. Catharine B. Stack et al., *Genetic Risk Estimation in the Coriell Personalized Medicine Collaborative*, 13 GENETICS MED. 131, 131 (2011).

35. David E. Winickoff, *Partnership in U.K. Biobank: A Third Way for Genomic Property?*, 35 J.L., MED. & ETHICS 440, 441 (2007).

36. Haga & Beskow, *supra* note 7, at 533.

of community engagement—through surveys and focus groups—to assess *a priori* values and concerns.<sup>37</sup> In addition, some biobanks are engaging in deliberative democracy within the various communities and are also studying population attitudes toward biobanks.<sup>38</sup> These sites are involving communities in design and oversight and allowing these sites to explore participants' attitudes about policies and practice.<sup>39</sup>

### C. EMERGENCE OF PARTICIPANT-CENTRIC PERSPECTIVES

In the midst of these considerations of returning IFs and RRs, nonmedical data sharing—with return of results—has become more commonplace. In many areas in life, it is now easy to access and share data. Feedback is expected and ubiquitous. Consumers experience this in Netflix recommendations, iTunes Genius, and Facebook friends' likes and dislikes. Individuals share information and experiences in web applications such as Amazon, Angie's List, MapMyRide, FitBit, Daily Burn, and Nike and expect results back—how do I stack up against others and what do I need to change in my shopping, eating, or workout routine? Models are also emerging in clinical data sharing with various kinds of feedback and results shared. 23andMe gives individuals their genome sequence and some research results back.<sup>40</sup> Individuals can receive dozens of research results via a password-protected web platform.<sup>41</sup> Some argue that the “23andMe model promotes the idea that curiosity about one's genome on the one hand, and participation in research on the other, are not only compatible but complementary aspects of being an entrepreneurial subject of contemporary health and medicine framed by the technologies

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37. See Catherine A. McCarty et al., *The eMERGE Network: A Consortium of Biorepositories Linked to Electronic Medical Records Data for Conducting Genomic Studies*, 4 BMC MED. GENOMICS 13 (2011) (discussing the general set up and efficacy of the eMERGE Network).

38. See, e.g., Catherine A. McCarty et al., *Community Consultation and Communication for a Population-Based DNA Biobank: The Marshfield Clinic Personalized Medicine Research Project*, 146A AM. J. MED. GENETICS 3026, 3027–28 (2009).

39. *Id.*

40. Thomas Goetz, *23AndMe Will Decode Your DNA for \$1,000. Welcome to the Age of Genomics*, WIRED.COM (Nov. 17, 2007), [http://www.wired.com/medtech/genetics/magazine/15-12/ff\\_genomics](http://www.wired.com/medtech/genetics/magazine/15-12/ff_genomics).

41. *Id.*

of web 2.0.”<sup>42</sup> The return of these results is not based on clinical practice guidelines, instead the ‘results’ are based on correlations being established using common evidentiary standards, for example through genome-wide association studies that have led to associations with specific conditions.<sup>43</sup>

In another participatory web service, PatientsLikeMe collects information about individuals, at their own initiative, on hundreds of aspects of their lives.<sup>44</sup> This data, in an aggregated form, has proven useful to the research enterprise. PatientsLikeMe and 23andMe have shown through research conducted in their communities that participatory web services hold enough power to replicate traditional studies.<sup>45</sup>

An individual seeking associations relevant to his or her genome can use an add-on for the Firefox browser called SNPTips, created by 5 AM | Solutions.<sup>46</sup> A person can associate their 23andMe genome sequence data with SNPTips and webpages that include single-nucleotide polymorphisms (SNPs), from news articles to scientific papers, and reveal relevant SNPs.<sup>47</sup> This is certainly the tip of the iceberg in ‘network effect’ tools—tools that will augment the newly emerging data collections. In another example, Private Access gives individu-

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42. Richard Tutton & Barbara Prainsack, *Enterprising or Altruistic Selves? Making Up Research Subjects in Genetics Research*, 33 SOC. HEALTH & ILLNESS 1081, 1081 (2011).

43. See, e.g., Chuong B. Do et al., *Web-Based Genome-Wide Association Study Identifies Two Novel Loci and Substantial Genetic Component for Parkinson's Disease*, 7 PLOS GENETICS, no. 6, 2011, at 1, 2, <http://www.plosgenetics.org/article/info:doi/10.1371/journal.pgen.1002141>; Joyce Y. Tung et al., *Efficient Replication of Over 180 Genetic Associations with Self-Reported Medical Data*, 6 PLOS ONE, no. 8, 2011, at 1, 1–2, <http://www.plosone.org/article/info:doi%2F10.1371%2Fjournal.pone.0023473>.

44. See Paul Wicks et al., *Sharing Health Data for Better Outcomes on PatientsLikeMe*, 12 J. MED. INTERNET RES. e19, e21 (2010) [hereinafter *Sharing Health Data*] (“PatientsLikeMe is a Web-based application where members explicitly choose to share detailed computable data about symptoms, treatments and health in order to learn from the experience of others and improve their outcomes.”).

45. See, e.g., Nicholas Eriksson et al., *Web-Based, Participant-Driven Studies Yield Novel Genetic Associations for Common Traits*, 6 PLOS GENETICS, no. 6, 2010, at 1, 1–2, <http://www.plosgenetics.org/article/info:doi/10.1371/journal.pgen.1000993>; *Sharing Health Data*, *supra* note 44, at e19–e20; Paul Wicks et al., *Accelerated Clinical Discovery Using Self-Reported Patient Data Collected Online and a Patient-Matching Algorithm*, 29 NATURE BIOTECH. 411, 411–12 (2011) [hereinafter *Accelerated Clinical Discovery*].

46. SNPTIPS, <http://snptips.5amsolutions.com/> (last visited Feb. 8, 2012).

47. See *id.*

als a platform to enter their preferences for how their data will be handled, including who can see it, how it can be used, and what should be returned to the individual.<sup>48</sup> It provides technology solutions for researchers to communicate with participants in trials—including results and incidental finding reporting—all according to the individual's preferences. The individuals themselves, not the scientists, determine what is shared and what is returned.<sup>49</sup> Genomera, a small Silicon Valley company, provides a unique platform for individuals to share genomic and phenotypic information. It is unique because it allows individuals to set up the trials, and they are aided by the tools the company provides to run and analyze the trial.<sup>50</sup> This system allows on-the-fly return of results, either on an individual or a group level. None of these examples are traditional return of results or incidental findings. But all of them point to a growing trend for consumers to expect results—something that may very well carry over into the biomedical research arena.

#### D. RETURN OF RRS AND IF'S IN GENOMICS BIOBANKS: SOMETHING DIFFERENT THAN NON-GENOMIC STUDIES?

There has been much discussion about “genetic exceptionalism” over the years. This discussion has vacillated between the premise that there is nothing different about genetic or genomic information and the idea that it is different and requires different handling, guidance, regulations, and so on.<sup>51</sup> With respect to RRs, some studies show that individuals do consider genetic information to be different than other medical information, either because it reveals more information about health risks or because it may have meaning for the participant's family.<sup>52</sup> While familial importance can be implicated

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48. Robert H. Shelton, Commentary, *Electronic Consent Channels: Preserving Patient Privacy Without Handcuffing Researchers*, 3 SCI. TRANSLATIONAL MED. 69cm4, at 2 (2011).

49. *Id.*

50. See Ella Dolgin, *Personalized Investigation*, 16 NATURE MED. 953, 954 (2010); Terry & Terry, *supra* note 1, at 2.

51. Michael J. Green & Jeffrey R. Botkin, “Genetic Exceptionalism” in *Medicine: Clarifying the Differences Between Genetic and Nongenetic Tests*, 138 ANNALS INTERNAL MED. 571, 571 (2003).

52. See Miguel Ruiz-Canela et al., *What Research Participants Want to Know About Genetic Research Results: The Impact of “Genetic Exceptionalism,”*

in any data associated with indication of familial disease, it is especially obvious in genetic data.<sup>53</sup> Green and Botkin examined genetic exceptionalism and found “no clear, significant distinctions between genetic and nongenetic tests justify[ing] a different approach to testing by clinicians. Nevertheless, with many genetic tests, the results may cause stigmatization, family discord, and psychological distress.”<sup>54</sup>

It is true that genetic information may have consequences for the family, and genomic biobank policies should guide information exchange—even for the relatives of a contributor and even after the death of that contributor.<sup>55</sup> Vos et al. examined the impact on individuals who were told the results about unclassified variants and uninformative BRCA 1 & 2 testing for family members.<sup>56</sup> The way results were communicated was significant to family members’ perception of their own cancer risk.<sup>57</sup> Thus, despite some mixed evidence and conclusions, it is probably safe to say that genetic information at least gives individuals, families, and communities pause, and hence causes other stakeholders to at least ask if special considerations apply. For the sake of this paper we will restrict comments to IFs and RRs in genomic biobanks, but realize that many of these issues are inherent in IFs and RRs in non-genomic research as well.

#### E. THE RELATIVITY OF TIME AND CONTEXT

Differences between IFs and RRs are not always clear. For example, Bovenberg et al. use the term RR to encompass IFs.<sup>58</sup> They include results to individuals as well as aggregate results.<sup>59</sup> Others are more careful as to the specificity of the terms as is clearly laid out by Wolf et al.<sup>60</sup>

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6 J. EMPIRICAL RES. ON HUM. RES. ETHICS 39, 40 (2011).

53. See Laura M. Beskow et al., *Ethical Issues in Identifying and Recruiting Participants for Familial Genetic Research*, 130A AM. J. MED. GENETICS 424, 425 (2004) (explaining the importance of family-based research in a variety of diseases).

54. Green & Botkin, *supra* note 51, at 571.

55. Bovenberg et al., *supra* note 2, at 240.

56. Joël Vos et al., *Family Communication Matters: The Impact of Telling Relatives About Unclassified Variants and Uninformative DNA-Test Results*, 13 GENETICS MED. 333, 333 (2011).

57. *Id.* at 339.

58. Bovenberg et al., *supra* note 2, at 230.

59. *Id.*

60. Wolf et al., *supra* note 3, at 364.

Wolf et al.'s research discovered that many biobanks, studies, and policies recognize a difference between IFs and individual RRs.<sup>61</sup> For example, Yale University's institutional review boards (IRBs) have established policies recognizing that, in some studies, IFs may be returned but not individuals' RRs.<sup>62</sup> The UK Biobank is time dependent and will offer some IFs discovered during enrollment (such as elevated blood pressure) to participants but will not offer individual RRs from the ensuing genetic/genomic analysis. However, once into the research, the UK biobank does not provide individual RR for any reason.<sup>63</sup>

Wolf et al. acknowledge that “[s]ome commentators have questioned the utility of distinguishing between IFs and [RRs], especially in the context of whole-exome, whole-genome, or genome-wide association studies (GWAS)” and agrees that the distinction is “fuzziest” in these domains.<sup>64</sup> Whole-genome sequencing in clinics provides us an excellent example of the blurring of research and clinical settings and the distinction between what is an IF and what is an RR. As more systems like this are built to ascertain correlations in a hypothesis-generating environment, the differences between RR and IF will continue to blur. The term biobank will refer to the system and the stakeholders in it; the terms IF and RR will be used to describe a range of findings in keeping with Wolf's definition.

Typically, results are considered RRs, and not clinical results that should be disclosed to participants, because of a lack of evidence of clinical utility.<sup>65</sup> Over time, with the aggregation

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61. *Id.*

62. *Id.*

63. *Id.* at 4–5.

64. *Id.* at 4; see also Laura M. Beskow & Wylie Burke, Commentary, *Offering Individual Genetic Research Results: Context Matters*, 38 SCI. TRANSLATIONAL MED. 38cm20, 2 (2010) (explaining that the distinction between RRs and IFs based on “whether the information is related to the study” is problematic because “[e]ven when the initial study addresses a particular condition, consent is often requested to store materials for use in unspecified future research”); Mildred K. Cho, *Understanding Incidental Findings in the Context of Genetics and Genomics*, 36 J.L. MED. & ETHICS 280, 281–82 (2008) (noting that distinguishing IFs from other findings is difficult “because the nature of the genomic research question can be very open ended or descriptive”).

65. Susan M. Wolf et al., *Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations*, 36 J. L. MED. & ETHICS 219, 231–32 (2008) [hereinafter Wolf, *Analysis and Recommendations*].

of increasingly large datasets correlated with clinical information, RRs either become useful clinical results or become irrelevant because they are proven to be insubstantial.<sup>66</sup> The increasingly grey line between research and clinical care means that it is not always possible to determine if something is an RR or in fact has clinical attributes. Thus something may be an RR today, and as data is aggregated and analyzed, it may become more meaningful over time. This makes it difficult to create a definitive line before which to determine something is an RR, and after which something is a clinical result. The information itself can be independent of the system in which it was obtained, though some would point out that a result cannot be a clinical result unless it is obtained in a laboratory that is certified by the Clinical Laboratory Improvement Amendments (CLIA).<sup>67</sup> The issue then is one of appropriate infrastructure to deliver these results.

IFs may be considered such only because they were not the intent of the study. They can be considered incidental findings in one context and primary findings in another. Again, the system in which they are discovered may not allow contextualization to play a role, nor provide the infrastructure to deliver the results. But the results themselves are not the issue. In both RRs and IFs, what participants believe to be reportable and what is considered as having clinical utility may be different. We address this below.

Context and time play a significant role that is difficult to manage in the strict research context in the integration of genomics into clinical care. When systems exist that allow research and clinical care to cohabit (as in some emerging programs in research universities collaborating with their health centers), and information to be aggregated, correlated, and analyzed in real time—in the way that Amazon provides consumer feedback or TripAdvisor shares restaurant ratings and comments—then the issues that arise as a result of returning RRs and IFs will be less onerous.

Even when genomic biobanks establish, ahead of any recruiting, a roster of findings that will be reported back, this should be considered a starting point since ongoing research will continue to find associations in various populations and for some individuals. Further, though such advisory boards are

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66. *See id.* at 232–33.

67. *See id.* at 230.

recommended and useful, they cannot always determine what will be important to individuals in reproduction, life, death, or personal decisions.<sup>68</sup>

In addition to the meaning of various results changing over time due to research advances, personal preferences can change throughout the life course due to many circumstances.<sup>69</sup> Needs change for individuals depending on their personal and familial circumstances.<sup>70</sup> Reproductive planning, healthcare interactions, the diagnosis of oneself or someone in the family, deaths, and media reports about genetics, genomics and disease, are among the issues that could alter preferences as to receive research results and incidental findings.

Another aspect of context is related to culture. There are cultures in which biobanking represents an objectification of the community, an exploitation of the tribe, or simply part of something unthinkable, such as the removal, storage, and experimentation on blood or tissue.<sup>71</sup>

A final contextual aspect is the right not to know. Even when a biobank has decided certain results are important to share, an individual may not want to know about the result.<sup>72</sup> Though some would say that this right be exercised as long as it does not cause harm.<sup>73</sup> Not suprisingly, recent studies show that individuals fall in a contiuum of wanting to know, not wanting to know, and many in the middle want results at least when they are accurate and actionable.<sup>74</sup>

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68. Wolf et al., *supra* note 3, at 370.

69. Robert Klitzman, *Questions, Complexities, and Limitations in Disclosing Individual Genetic Research*, AM. J. BIOETHICS, Nov.–Dec. 2006, at 34, 34–35; see also Constance A. Griffin et al., *Patient Preferences Regarding Recontact by Cancer Genetics Clinicians*, 6 FAMILIAL CANCER 265, 269 (2007) (finding that patients wanted to be recontacted with new information regarding a genetic test for various reasons including information regarding cancer risk to the patient and relatives, cancer screening, and impacts on the patients' health).

70. *Id.*, at 35.

71. See, e.g., Michelle M. Mello & Leslie E. Wolf, *The Havasupai Indian Tribe Case—Lessons for Research Involving Stored Biologic Samples*, 363 NEW ENG. J. MED. 204, 204 (2010) (explaining that tribe members objected to use of their blood samples for various cultural reasons).

72. See Rebecca Bennett, *Antenatal Genetic Testing and the Right to Remain in Ignorance*, 22 THEORETICAL MED. & BIOETHICS 461, 462 (2001).

73. *Id.*

74. Bovenberg et al., *supra* note 2, at 232–33.

## II. TENSION FOR WHOM?

The tension in the system must be considered from numerous viewpoints since any tension is the result of several forces. These forces will be applied and perceived differently by various stakeholders. Thus, it is not possible to name tensions between practice and policy without examining those from the perspective of each stakeholder. The key stakeholders, though there are certainly others, are individual participants, communities, researchers, clinicians, institutions, and society. I write with a strong bias that all research be participant-centered, and will therefore call the donors, patients, and contributors of clinical data and/or samples, participants.

### A. PARTICIPANTS

The primary tensions for participants between current policies and practices can be described as arising from expectations, literacy, support, usefulness, and fears.

#### i. Expectations

When participants enter into a relationship with a genomic biobank system, they will have expectations.<sup>75</sup> In ethics considerations, “expectations are not just neutral facts.”<sup>76</sup> They indicate obligations on other individuals or entities to consider them.<sup>77</sup> This might suggest that participants consider the interaction with the biobank to be relational, rather than transactional. I do believe this is the case, given the desire of participants to trust the biobank system and to expect reciprocity from the whole and its parts.<sup>78</sup>

Participants’ expectations vary. Certainly the time and context issues raised above will color expectations. Thus some participants will expect results, and others will be indifferent. A fairly large, and increasing, body of research suggests that participants expect to receive some RRs back. For example, in one Dutch study, between 70% and 88% of what the researchers called “patients” and “citizens” “probably” or “definitely” wanted results to be communicated to them, dependent on the type

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75. *Id.* at 233.

76. *Id.* at 238.

77. *Id.*

78. Herbert Gottweis et al., *Connecting the Public with Biobank Research: Reciprocity Matters*, 12 NATURE REV. GENETICS 738, 739 (2011).

of results.<sup>79</sup> In this study, questionnaires were given to individuals with asthma, hay fever, or thrombosis (called patients) and to healthy volunteers (called citizens). Citizens preferred being informed of research results slightly more than patients.<sup>80</sup>

Although it sometimes appears that privacy concerns, and hence how a biobank manages the samples and data they acquire, are most critical when considering whether or not to contribute to a biobank, one study found willingness to contribute tied to the presence of a binding agreement between the parties including the return of results.<sup>81</sup> Focus group participants in this study conducted by the Genetics and Public Policy Center expressed an overwhelming desire for a “contract” with researchers.<sup>82</sup> This suggests that the public thinks there should be reciprocity between researchers and participants.<sup>83</sup> Indicative of the diversity in preferences, in the Dutch study referenced above, some participants did not want to be informed of results.<sup>84</sup>

As potential participants become increasingly involved and empowered in health and other aspects of their lives, there may be expectations that both policies and practices will be consumer focused.<sup>85</sup> These participants may expect that the research enterprise is there to benefit them, and they may not expect either a one-size-fits-all system or one that does not return any results. Participants may be surprised to find that the research enterprise doesn't have a culture of sharing information either between projects or with participants.<sup>86</sup> Participants may expect clear and well-articulated policies that serve the participant.<sup>87</sup> Some of the confusion in expectations may relate to an understanding of what is research and what is clinical care. Though there is certainly an element of literacy in this aspect,

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79. Bovenberg et al., *supra* note 2, at 233.

80. *Id.*

81. Juli Murphy et al., *Public Perspectives on Informed Consent for Biobanking*, 99 AM. J. PUB. HEALTH 2128, 2132–33 (2009).

82. *Id.*

83. *Id.*

84. Bovenberg et al., *supra* note 2, at 232.

85. See Amy Dockser Marcus, *Citizen Scientists*, WALL ST. J., Dec. 3, 2011, at C.1.

86. *See id.*

87. *See, e.g.*, Murphy et al., *supra* note 81, at 2132–33.

it is also probable that many biobank systems do not make the distinction clear in policy and practice. There is a tacit trust that the participant is being cared for, particularly in rare disease research.<sup>88</sup> And finally, some participants do not want researchers to have results that they themselves do not have.<sup>89</sup>

## ii. Literacy

Participant literacy, or lack thereof, causes a great deal of tension in the system. A biobank can have well-articulated policies, and then when it implements those policies it may find that the participants cannot comprehend the policy and/or the results as the biobank intended. In some genetic testing, participants are educated as to the range of possible findings before disclosure.<sup>90</sup> A number of studies have shown that participants can lack comprehension of the study in which they are participating.<sup>91</sup> Genetic literacy is based on health literacy, which, in turn, is built on science literacy.<sup>92</sup> A 1993 study, repeated with the same results in 2002, showed that forty-seven percent of U.S. adults “lack the literacy skills needed to meet the demands of twenty-first century society” defined as having “difficulty locating, matching, and integrating information in written texts with accuracy and consistency.”<sup>93</sup> Obviously, if individuals find it difficult to understand information, then RRs and IFs will also be difficult to understand.

## iii. Usefulness

Usefulness from the participant perspective differs from the technical definition of clinical utility, which is discussed below in Part II.C. Usefulness simply asks: is this information useful? For the participant, the answer to that is not a clinical answer—it takes into consideration all of the issues of time and

88. Henry S. Richardson & Leah Belsky, *The Ancillary-Care Responsibilities of Medical Researchers*, 34 HASTINGS CTR. REP. 25, 27 (2004).

89. David Wendler & Rebecca Pentz, *How Does the Collection of Genetic Test Results Affect Research Participants?*, 143A AM. J. MED. GENETICS 1733, 1736 (2007).

90. See Ellen Wright Clayton, *Incidental Findings in Genetic Research Using Archived DNA*, 36 J.L. MED. & ETHICS 286, 289 (2008).

91. E.g., Mary Dixon-Woods et al., *Beyond “Misunderstanding”: Written Information and Decisions About Taking Part in a Genetic Epidemiology Study*, 65 SOC. SCI. & MED. 2212, 2219 (2007).

92. See INST. OF THE NAT’L ACAD., HEALTH LITERACY: A PRESCRIPTION TO END CONFUSION 146 (Lynn Nielsen-Bohlman et al. eds., 2004).

93. *Id.* at 6.

context described in Part I.E above. Generally, participants consider: (1) how is this information relevant to me, (2) how do I act on it, and (3) who or what will support me through the actionable steps? Beyond clinical utility, usefulness denotes results that can be meaningful for families and individuals and communities. These can be related to family lineage, ethnic or cultural identity, and behavioral traits that could define personal identity for the individual.<sup>94</sup>

Botkin et al. describe a tension in the system when they consider that systematic evaluation is a challenge for traditional methods of evidence-based review when considering the broader impact of genetic tests on the individual, familial and societal levels, and psychosocial outcomes.<sup>95</sup> He describes the need to consider potential harms and benefits for the participant and the challenge of doing that in the Centers for Disease Control and Prevention initiated program called Evaluation of Genomic Applications in Practice and Prevention (EGAPP), which evaluates genetic tests.<sup>96</sup> The issues inherent in individual preferences, and a growing understanding that information impacts reproductive decision making,<sup>97</sup> offspring,<sup>98</sup> and eventually other uses, have garnered some attention and are considered by some authors.<sup>99</sup> Called “personal utility,” peer reviewed literature is beginning to highlight this participant-centric appraisal of genetic tests.<sup>100</sup> Several efforts to reconcile these tensions have been offered in the form of categorizing tests, using either a matrix that considers a test’s risk-benefit

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94. Vardit Ravitsky & Benjamin S. Wilfond, *Disclosing Individual Genetic Results to Research Participants*, AM. J. BIOETHICS, Nov.–Dec. 2006, at 8, 12.

95. Jeffrey R. Botkin et al., *Outcomes of Interest in Evidence-Based Evaluations of Genetic Testing*, 12 GENETICS MED. 228, 228 (2010).

96. *Id.* at 229–30.

97. Fabsitz et al., *supra* note 14, at 578; Wolf, *Analysis and Recommendations*, *supra* note 68, at 231.

98. See Susanne B. Haga & Sharon F. Terry, *Ensuring the Safe Use of Genomic Medicine in Children*, 48 CLINICAL PEDIATRICS 703, 703–05 (2009).

99. See, e.g., Conrad V. Fernandez & Charles Weijer, *Obligations in Offering to Disclose Genetic Research Results*, AM. J. BIOETHICS, Nov.–Dec. 2006, at 44, 45–46 (arguing for a broader participant-focused definition of utility).

100. See, e.g., Scott D. Grosse et al., *Evaluation of the Validity and Utility of Genetic Testing for Rare Diseases*, in RARE DISEASES EPIDEMIOLOGY 115, 121–27 (Manuel Posada de la Paz & Stephen C. Groft eds., 2010); Ilona M. Kopitz et al., *Willingness to Pay for Genetic Testing for Alzheimer’s Disease: A Measure of Personal Utility*, 15 GENETIC TESTING & MOLECULAR BIOMARKERS 871, 871 (2011).

profile against its clinical uncertainty,<sup>101</sup> or investigating which IF's specialists would recommend returning,<sup>102</sup> or using a formal risk-benefit framework for genomic tests that could take context into consideration.<sup>103</sup> A three-tier system has been recommended: Tier 1 "Implement in practice;" Tier 2a "Informed decision-making in practice;" and Tiers 2b and 3 "Do not use in practice" (for different reasons).<sup>104</sup> Though this doesn't take personal utility into consideration, it does begin to provide a basis for more complex decision making than just yay or nay. This may begin to resolve the tension in 'usefulness'. This system, combined with one that gives weight to the preferences of participants in the context of their lived experience and a vehicle for them to express their preferences, would provide a dynamic solution to the intersection of clinical and personal utility.

#### iv. Support

A critical tension in the system is support for participants as they receive, or do not receive, IFs and RRs. This is often considered from the clinicians' or the institutions' point of view. Discussions about the need for a larger workforce, licensure for genetic counselors, and/or cost to interpret genomic information—with no clear payment system for information sharing—are common.<sup>105</sup> It appears less common to consider this from the participant perspective. The lack of integration between research and clinical systems creates a gap in which the participant can fall as they try to navigate information. The support that participants need in learning of IFs and RRs is highly variable. Some studies have shown that how information

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101. See, e.g., David L. Veenstra et al., *A Formal Risk-Benefit Framework for Genomic Tests: Facilitating the Appropriate Translation of Genomics into Clinical Practice*, 12 GENETICS MED. 686, 691 (2010).

102. See Robert C. Green et al., *Exploring Concordance and Discordance for Return of Incidental Findings from Clinical Sequencing*, 14 GENETICS MED. 405, 406 (2012).

103. See, e.g., Muin J. Khoury et al., *Evidence-Based Classification of Recommendations on Use of Genomic Test in Clinical Practice: Dealing with Insufficient Evidence*, 12 GENETICS MED. 680, 682 (2010).

104. *Id.*

105. See, e.g., Wolf, *Analysis and Recommendations*, *supra* note 68, at 243 ("Research would be helpful to clarify the types of IFs generated by different kinds of research, the statistical prevalence of these IFs, the costs of evaluating them and clinical following-up, and the positive and negative impacts on research participants.").

is delivered and by whom is critical.<sup>106</sup> Some individuals will need written materials, some verbal communications, and others general community support with multimedia reinforcement. Particularly as the evidence develops for various findings, participants are going to need dynamic methods to stay apprised of the meaning of these findings and how they are relevant or not to their lives, for example, Private Access, 23andMe, and PatientsLikeMe.<sup>107</sup> This is like being given a very slowly developing Polaroid photograph and keeping it for years, watching more of the image appear over time. As information becomes more available, and more or less meaningful, the need for effective support for interpretation, application, and overall management of that information will change. This is a very challenging aspect of RRs and IFs for participants.

## v. Fears

### 1. Discrimination

Individuals could fear discrimination in employment or insurance, even though the Genetic Information Nondiscrimination Act of 2008 (GINA)<sup>108</sup> defends the rights of individuals in the United States in this regard, and comparable laws do this in other countries.<sup>109</sup> Individuals certainly could face discrimination in areas not covered by the law such as long-term care and disability insurance.<sup>110</sup> In one study, individuals who were worried that study results would be used against them were less inclined to participate in a hypothetical large-population study.<sup>111</sup> There is a need for further education about GINA for participants and providers if fear of discrimination is to be alleviated.<sup>112</sup>

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106. Johanna L. Schmidt et al., *The Impact of False-Positive Newborn Screening Results on Families*, 14 GENETICS MED. 76, 77–78 (2012).

107. See Terry & Terry, *supra* note 1, at 2.

108. Genetic Information Nondiscrimination Act of 2008, Pub. L. No. 110-233, 122 Stat. 881 (codified in scattered sections of 26, 29, and 42 U.S.C.).

109. Amy L. McGuire & Mary Anderlik Majumder, *Two Cheers for GINA?*, 1 GENOME MED. 6.1, 6.1–6.2 (2009), <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2651591/pdf/gm6.pdf>.

110. *Id.* at 6.2.

111. David J. Kaufman et al., *Public Opinion about the Importance of Privacy in Biobank Research*, 85 AM. GENETICS 643, 647–48 (2009).

112. Amanda L. Laedtke et al., *Family Physicians' Awareness and Knowledge of the Genetic Information Non-Discrimination Act (GINA)*, J.

## 2. Lack of Care

A related tension in the system is related to the fact that there will not only be little information for some IFs and RRs, but many times these findings are not actionable. Findings might predict a condition, convey risk, diagnose a condition, and so on, but across the board, there is a high chance that there is no treatment based on these findings. Even in the case of ending the diagnostic odyssey, it has been reported that individuals suffer a loss of confidence in the medical care system.<sup>113</sup> In an examination of expanded newborn screening in California, incidental findings related to diagnosing the mother appear to leave the family unsatisfied if the family is unable to act on the information. This may be because the newborn screening infrastructure is not set up to support treatment for the mother.<sup>114</sup>

## 3. Anxiety Associated with Risk

Early in the personal genomics movement, ethicists considered whether individuals would have increased anxiety as a result of genetic information and hypothesized that they might.<sup>115</sup> In recent years, some studies suggest that there is less anxiety over receiving results than previously thought, though most studies were based on cohorts that availed themselves of counseling.<sup>116</sup> Other studies emphasize that the differences in perceptions are based upon the level of counseling available to the individuals.<sup>117</sup> There is a need for more re-

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GENETIC COUNSELING (forthcoming 2012) (e-pub at 7), available at <http://www.springerlink.com/content/r355246172423511/fulltext.pdf>; McGuire & Majumder, *supra* note 109, at 6.2.

113. Milica Markovic et al., *Embodied Changes and the Search for Gynecological Cancer Diagnosis*, 18 MED. ANTHROPOLOGY Q. 376, 387 (2004).

114. Mara Buchbinder & Stefan Timmermans, *Newborn Screening and Maternal Diagnosis: Rethinking Family Benefit*, 73 SOC. SCI. & MED. 1014, 1017 (2011).

115. Amy McGuire et al., *The Future of Personal Genomics*, 317 SCIENCE 1687, 1687 (2007).

116. Katja Aktan-Collan et al., *Psychological Consequences of Predictive Genetic Testing for Hereditary Non-polyposis Colorectal Cancer (HNPCC): A Prospective Follow-up Study*, 93 INT. J. CANCER 608, 611 (2001); Chanita Hughes Halbert et al., *Long-Term Reactions to Genetic Testing for BRCA1 and BRCA2 Mutations: Does Time Heal Women's Concerns?*, 29 J. CLINICAL ONCOLOGY 4302, 4305–06 (2011); Kay Wilhelm et al., *Issues Concerning Feedback About Genetic Testing and Risk of Depression*, 194 BRIT. J. PSYCHIATRY 404, 409 (2009).

117. Sato Ashida et al., *The Role of Disease Perceptions and Results Shar-*

search in this area, particularly since there are no studies examining the psychological effects of RR and IF for individuals who did not chose to be tested. Meanwhile, disparities may be exacerbated as individuals who can afford testing, and perhaps unnecessary follow up tests, may 'raid the medical commons.'<sup>118</sup> This impacts communities, which is described in the next section.

## B. COMMUNITIES

The tension between policy and practice for communities is difficult to quantify and even difficult to describe succinctly. There appear to be a number of questions that need to be asked in this regard, and no ready answers.

### i. How Do IFs and RRs Challenge Community Identity or Norms?

One must ask if the IFs create some conflict in worldview *vis-à-vis* the community or if the identity of the community is challenged by the RRs or IFs? One can imagine that incidental findings or research results that are common to the community could challenge the community's sense of who it is. This could be true in an ethnic or geographic community as well as disease-based community. While most of the literature on this subject is about ancestry, there are also some indications that having a predisposition to a disease may also threaten a community's understanding of themselves.<sup>119</sup> Blogs and other postings from adolescents with cystic fibrosis (CF) indicate that 'disease legends,' akin to urban legends, may arise. For example, some in the CF community have created associations between mutations and classes of severity that do not reflect the

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*ing in Psychological Adaptation After Genetic Susceptibility Testing: The REVEAL Study*, 18 EUR. J. HUM. GENETICS 1296, 1300 (2010).

118. Amy L. McGuire & Wylie Burke, *An Unwelcome Side Effect of Direct-to-Consumer Personal Genome Testing: Raiding the Medical Commons*, 300 JAMA 2669, 2669–70 (2008).

119. Dena S. Davis, *Genetic Research & Communal Narratives*, 34 HASTINGS CENTER REP. 40, 42 (2004); Carl Elliot & Paul Brodwin, *Identity and Genetic Ancestry Tracing*, 325 BRIT. MED. J. 1469, 1471 (2002); Susan Parry & Carl Elliot, *Genetic Ancestry Tracing and American Indian Identity*, AM. PHIL. ASS'N NEWSL. ON PHIL. & MED., Spring 2002, at 12; Mee Lian Wong et al., *Concerns over Participation in Genetic Research Among Malay-Muslims, Chinese and Indians in Singapore: A Focus Group Study*, 7 COMMUNITY GENETICS 44, 45 (2004).

currently scientifically validated correlations. Anecdotes in the community abound trying to use these unfounded correlations to modulate behavior: “Can I ask ? Is there certain C[F] genes that are more sever [sic] than others or does it make any difference?”<sup>120</sup> This is an area that can use further research. If groups of people (cities, neighborhoods, affinity groups online, and church communities) are given IFs and RRs, will they build their own consensus around the results, determining behavior, and making recommendations? I certainly see individuals beginning to build their own conclusions, without scientific evidence, in the online Facebook community and in the Chat listserv I manage for PXE International, which serves the genetic disease pseudoxanthoma elasticum (PXE). One post on Facebook follows up many claims that fish oil is a good treatment for PXE, which is a disease caused by mutations in *ABCC6*—a gene that codes for a membrane transport protein. The Facebook user posted:

I havent tried [fish oil], but i am getting some tomorrow. Yes Karen, I am always in pain, my hip joints and knees, They are worse in the cold. If I walk for a long time too. My gp said my right kneecap is moving inward and will need an op eventually !!! I am sure it is pxe related. I also get leg pain all ove,r claudication, i dont like taking pills so use the ibuprofen gel when it is at its worse xxxx I also get sore wrists.<sup>121</sup>

There is no evidence of joint involvement in PXE<sup>122</sup> and certainly no research on fish oil that suggests it would alleviate any symptoms in the condition. However, the group makes its own determinations of such matters through reading a small number of posts from individuals. Even when we repeatedly point them to layman versions of peer-reviewed published literature, some group members chastise us for not allowing them to ‘learn from one another.’ This could create a set of communi-

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120. Ronnie Sharpe & Mandi Sharpe, *RUN, SICKBOY, RUN* (June 1, 2011), <http://runsickboyrun.blogspot.com/2011/06/question-from-reader-more-severe-genes.html>.

121. Karen McDougall & Maria Taggart, *PXE International Group*, FACEBOOK (Dec. 11, 2011, 12:52 PM), <https://www.facebook.com/groups/6236484169/> (errors in the original).

122. Nat’l Ass’n for Pseudoxanthoma Elasticum, *Frequently Asked Questions - Pain*, PXENAPE, <http://www.pxenape.org/faq.htm> (last visited Feb. 28, 2012) (responding to the question of whether a person’s joint aches and pains are a result of PXE, “[A]rthritic symptoms of any kind are not directly related to or caused by PXE. Mild to moderate joint aches and pains are very common among the general population . . . [, and] it cannot be said that the cause is PXE”).

ty beliefs. While the group members are not basing their treatments on specific mutations, one can imagine that the same groupthink would be applied to mutations discovered in PXE International research projects<sup>123</sup> if they were distributed to the group.

ii. Increased Data Sharing and Comparison Through Technology

The above examples lead to other questions about the difference between policy and practice in communities. Primarily one must ask if the sharing of results in online communities will create fodder for network effect systems to create ecosystems—i.e., can communities create their own data capture and share and reveal associations beyond what the original research intended? This has been shown to be the case in the PatientsLikeMe community and to some extent in 23andMe clients. In the PatientsLikeMe community, individuals reported changes in their behavior based on shared information.<sup>124</sup> This will create other tensions, such as what to do when the practice of sharing results leads to altered behavior not part of clinical practice guidelines. There are certainly pros and cons to this effect.

iii. Obligation to Share IFs and RRs that Are Meaningful for the Community

Policies about IFs and RRs usually refer to individuals. In some cases, those results might have meaning for the broader community, and perhaps should be shared proactively with the community, possibly in a generalized way. For example, founder effects, increased environmental risk, and strong correlations in a particular genotype would all be candidates for broad dissemination. A number of researchers recommend engaging the community in question to help determine return of results policies.<sup>125</sup>

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123. See, e.g. Ellen G. Pfendner et al., *Mutation Detection in the ABCC6 Gene and Genotype-Phenotype Analysis in a Large International Case Series Affected by Pseudoxanthoma Elasticum*, 44 J. MED. GENETICS 621 *passim* (2007).

124. See *Accelerated Clinical Discovery*, *supra* note 46, at 413.

125. See, e.g., Lainie Friedman Ross et al., *Human Subjects Protections in Community Engaged Research: A Research Ethics Framework*, 5 J. EMPIRICAL RES. HUM. RES. ETHICS 5, 7 (2010); Richard R. Sharp & Morris W. Foster,

## iv. Vulnerable Communities

## 1. Power Differential When Information Is Not Uniformly Available to All Parties

The local control of data access may be important to a community, and this may be difficult if the advisory body is removed from the community—as is done in some cases—particularly in large communities such as countries, cities, or even large university medical centers.<sup>126</sup> Further, RR can be seen as a necessary demonstration of respect and reciprocity for the community.

## 2. Potential Discrimination If RRs or IFs in a Group Are Aggregated

One could imagine that if a SNP purported to be associated with violence is highly prevalent in a cohort and research results are reported back to a community, that the community could suffer from aggregate results even if the association lacks validation. Communities could find results inconsistent with their beliefs and myths or fear stigmatism as has been reported by a number of authors.<sup>127</sup> Some communities have a difficult experience during the research process and then choose not to participate thus limiting the promise of translational medicine.<sup>128</sup> This has pros and cons for the community in question—

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*Grappling with Groups: Protecting Collective Interests in Biomedical Research*, 32 J. MED. & PHIL. 321, 325 (2007).

126. See Fabsitz et al., *supra* note 14, at 577.

127. See, e.g., Ibidapo Akinleye et al., *Differences Between African American and White Research Volunteers in Their Attitudes, Beliefs and Knowledge Regarding Genetic Testing for Alzheimer's Disease*, 20 J. GENETIC COUNSELING. 650, 656 (2011); Henry T. Greely, *Informed Consent and Other Ethical Issues in Human Population Genetics*, 35 ANN. REV. GENETICS 785, 798 (2001); Evaristus A. Nwulia et al., *Ethnic Disparities in the Perception of Ethical Risks from Psychiatric Genetic Studies*, 156 AM. J. MED. GENETICS PART B 569, 578 (2011); LorrieAnn Santos, *Genetic Research in Native Communities*, 2 PROGRESS COMMUNITY HEALTH PARTNERSHIPS 321, 322–23 (2008) (describing the objections of the Havasupai Indian tribe after blood samples taken from members of the tribe were used in a study of schizophrenia, which the Tribe felt risked stigmatization, and “inbreeding,” which implicated negative cultural beliefs).

128. See generally Ellen Wright Clayton & Lainie Friedman Ross, *Implications of Disclosing Individual Results of Clinical Research*, 295 JAMA 37, 37 (2006) (explaining that “respect for research participants requires minimizing harms so that they are not treated as mere means for scientific ends”); Stephanie M. Fullerton et al., *Commentary, Meeting the Governance Challenges of Next-Generation Biorepository Research*, 2 SCI. TRANSLATIONAL MED. 15cm3,

they will benefit from retaining power over their information and samples, but their community may be denied the benefits of research that may lead to diagnostics and therapies, particularly when those are community specific. In vulnerable communities, offering RRs and IFs could encourage a ‘therapeutic misconception’— the belief a clinical trial is primarily for therapeutic reasons.<sup>129</sup>

### C. RESEARCHERS

There are some who have written that showing respect to participants doesn’t necessarily mean giving back results.<sup>130</sup> Researchers must concern themselves with analytic validity, clinical validity, and clinical utility.<sup>131</sup> It is beyond the scope of this paper to discuss the current state of evidence generation to determine thresholds for each of these steps on the way to integration into clinical practice. As mentioned above, EGAPP and other efforts are trying to create a formal risk-benefit framework. It is thought that such a framework could offer guidelines for meaningful integration of genomic applications and avoid premature use of tests with little benefit or health significance.<sup>132</sup>

The tension in policy and practice is sometimes quite high for researchers, particularly those that receive samples that have been de-identified. This is in fact research that is not cov-

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at 3 (2010) (noting that “[r]esearch participants often cite a fear of having their genetic or personal health information used against them should it fall into the wrong hands”); Michelle M. Mello & Leslie E. Wolf, *The Havasupai Indian Tribe Case – Lessons for Research Involving Stored Biologic Samples*, 363 NEW ENG. J. MED. 204, 204–05 (reporting a legal settlement between the Havasupai Indian Tribe and Arizona State University after blood samples taken from members of the tribe by the University were used in studies that the tribe felt violated the scope of their consent); Santos, *supra* note 127, at 322–23 (describing two specific examples of abuse in genetic research of specific communities, one involving the Havasupai Indians and another multiple instances of abusive practices involving native Hawaiians).

129. Cho, *supra* note 67, at 284.

130. Clayton & Ross, *supra* note 128, at 37; Pilar N. Ossorio, *Letting the Gene Out of the Bottle: A Comment on Returning Individual Research Results to Participants*, AM. J. BIOETHICS, Nov.–Dec. 2006, at 24, 24.

131. Grosse et al., *supra* note 100, at 116–21.

132. David L. Veenstra et al., *A Formal Risk-Benefit Framework for Genomic Tests: Facilitating the Appropriate Translation of Genomics into Clinical Practice*, 12 GENETICS MED. 686, 691–92 (2010).

ered by the Common Rule.<sup>133</sup> For example, if policy dictates the return of IFs and RRs, then the researcher is in an untenable position with a difficult pathway to accessing enough information to comply with the policy. The Common Rule places secondary researchers, those using de-identified data or samples, outside of the biobank process, and Wolf et al. note that many biobanks exist for this purpose.<sup>134</sup>

Some researchers may well want to be part of the biobank system and wish to return results, and may in fact have an ancillary obligation toward participants. Others may enjoy the ‘absolution’ that consenting participants imply with agreeing to the typical terms of no return of research results.<sup>135</sup> Researchers, while in a gray area of interaction with participants, unlike clinicians, do not take a Hippocratic Oath and have no formal clinical professional codes of conduct.<sup>136</sup> In the Dutch study, as reported above, recall that the citizens and patients wished to receive findings eighty-five and seventy percent of the time respectively, and ninety-five percent of researchers disagreed with returning findings.<sup>137</sup> It is probable that researchers were not trained in genomic interpretation, nor did they anticipate the genomic era in which the line between research and clinical services would be so blurred. Some argue that withholding clinically important findings may be paternalistic on the part of researchers.<sup>138</sup> It is clearly best for both sides to be aware of the others expectations.

There are a number of considerations for researchers in the balance between policy and practice.

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133. HHS Common Rule, 45 C.F.R. § 46 (2011).

134. Wolf et al., *supra* note 3, at 364.

135. See generally Bartha Maria Knoppers et al., *The Emergence of an Ethical Duty to Disclose Genetic Research Results: International Perspectives*, 14 EUR. J. HUM. GENETICS 1170, 1174 (2006) (“[G]enetic information derived from research is of unknown or uncertain predictive value. Therefore, special care must be taken to prevent inadvertent release of immature data.”).

136. Dressler, *supra* note 24, at 87.

137. Bovenberg et al., *supra* note 2, at 232.

138. See Laura M. Beskow et al., *Informed Consent for Population-Based Research Involving Genetics*, 286 JAMA 2315, 2316 (2001); Conrad Fernandez, *Public Expectations for Return of Results—Time to Stop Being Paternalistic?*, 8 AM. J. BIOETHICS, no. 11, 2008, at 46, 48; Isaac S. Kohane et al., *Reestablishing the Researcher-Patient Compact*, 316 SCIENCE 836, 836 (2007).

i. Balancing Benefit and Risk: How to Assess and from What Perspective?

As discussed above, the participant has a very different perspective from the researcher, whose primary goal is to do excellent science. In a climate of evolving technology, data aggregation, and societal interest in genetic information, it is difficult to determine the weight of benefits and risks. Participants have expectations, and these may not align with each other or with the researchers conducting the study. Vehicles for community engagement, coupled with mechanisms for participants to express their RR and IF preferences, would begin to create a new model for resolving this tension. Rather than reject the current paradigm, citizen scientists and those encouraging participants to have robust agency in the research enterprise, are advocating for a participant-centric system.<sup>139</sup> In this system, the participants' and researchers' needs and obligations are in dialogue with one another. One example of a system that will help participants have more power at least in one direction—enabling their data to be used beyond the initial project for which it has been collected—is the Portable Legal Consent<sup>140</sup> created by Sage Bionetworks, Creative Commons, Kaufman Foundation, Genetic Alliance, and other collaborators.<sup>141</sup> This falls short of providing participants mechanisms for deciding how their data should be used and what should be returned to them, as is essential in participant-centric research.<sup>142</sup>

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139. See Jane Kaye, *The Tension Between Data Sharing and the Protection of Privacy in Genomics Research*, 13 ANN. REV. GENOMICS & HUMAN GENETICS (forthcoming 2012) (manuscript at page 13) (advocating that researchers “consider new ways of engaging with research participants . . . [t]o do so respects the dignity of participants and protects fundamental human rights”).

140. *Draft Informed Consent Form*, CONSENT TO RES., <http://weconsent.us/consentform> (last visited April 10, 2012).

141. See *Your Data Are Not a Product*, 44 NATURE GENETICS 357, 357 (“[R]esearch participants can contribute their own data under a portable consent . . . [f]rom there, the de-identified data can be accessed by any researcher who agreed to protect the research subjects and their data under the terms of the consent.”).

142. See Jane Kaye et al., *From Patients to Partners: Participant-Centric Initiatives in Biomedical Research*, 13 NATURE REV. GENETICS (forthcoming 2012).

ii. Returning Findings Are Time and Resource Intensive: How to Pay for Such Activities?

It can be quite costly on many levels to disclose results, and some are concerned that those resources of time and money should be used for the research enterprise.<sup>143</sup> However, others simply ask the question of how it will be weighed in the assessments that need to be done both in creating policies and in determining practice.<sup>144</sup> Once the decision to return results has been made, the logistics of recontacting is not trivial in the current systems. If, as is thought by some, participants decide they want results returned, then systems will have to be built that will allow such preferences.<sup>145</sup> In addition, if there is a 'right not to know,' then these systems must allow sufficiently complex preferences and also allow them to change over time. It is not even easy to contact individuals with preliminary IF results that require verification, since that in itself reveals some result that may require genetic counseling or other follow-up.<sup>146</sup> Further follow-up for these individuals may burden the health care system with requests for diagnostic procedures that lack a sound basis.<sup>147</sup> Individuals with different levels of literacy will require different levels of support, which will require varying methods of education and a sundry of follow-up activities. It will be easy for individuals who do not have the right kind of support and follow-up to 'raid the medical commons.'

iii. Misconceptions Are Easy to Come by: How Can We Address Them to Allay Concerns?

There is a concern articulated by many authors that participants could suffer from 'therapeutic misconception' and researchers might be inclined to overstate the benefits of enrollment.<sup>148</sup> Are the researchers confused as well, or at least

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143. Paul Affleck, *Is It Ethical to Deny Genetic Research Participants Individualised Results?*, 35 J. MED. ETHICS 209, 212 (2009); Griffin et al., *supra* note 69, at 270.

144. See Fabsitz et al., *supra* note 13, at 577.

145. Affleck, *supra* note 143, at 212.

146. Cho, *supra* note 67, at 284.

147. Bovenberg et al., *supra* note 2, at 232.

148. Laura M. Beskow, *Considering the Nature of Individual Research Results*, AM. J. BIOETHICS, Nov.–Dec. 2006, at 38, 38 (2006); Clayton & Ross, *supra* note 128, at 37; Fernandez, *supra* note 138, at 47; Bartha Maria Knoppers & Claude Laberge, *Return of "Accurate" and "Actionable" Results: Yes!*, 9 AM. J. BIOETHICS, June–July 2009, at 107, 108; Ossorio, *supra* note 130, at 25.

perhaps lack the ability to communicate results to the participants?<sup>149</sup> It is not usually the activity of researchers to communicate results, and so miscommunication is highly probable.<sup>150</sup>

iv. Communicating with Participants Can Be Quite Complicated: How Can We Do This?

Clinicians can fall back on a defined relationship complete with a code of conduct, but researchers do not have this luxury. There is usually not an obvious or ready set of mores for this interaction. What if the participants require ancillary care—care beyond that required to carry out the research safely—how can this be done in a meaningful and utilitarian manner?<sup>151</sup> Though the relationship between researchers and participants is not meant to be therapeutic, or clinical,<sup>152</sup> one can ask of researchers: If they thought that there was no health benefit, then why subject the individuals to the research in the first place? Thus, even researchers may be entering into a compact with participants that, though not traditionally considered bilateral, are *a priori* also in a relational interest to the participant.

D. CLINICIANS

Clinicians, like researchers, are in the middle of the tension between policy and practice, since they will be among those who must administer the policy while following formal and informal practice guidelines. The clinician may raise several issues from his or her perspective.

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149. See Fiona A. Miller et al., *When Research Seems Like Clinical Care: A Qualitative Study of the Communication of Individual Cancer Genetic Research Results*, 9 BMC MED. ETHICS 1, 2 (2008), available at <http://www.biomedcentral.com/content/pdf/1472-6939-9-4.pdf>.

150. Lynn G. Dressler & Eric T. Juengst, *Thresholds and Boundaries in the Disclosure of Individual Genetic Research Results*, AM. J. BIOETHICS, Nov.–Dec. 2006, at 18, 19.

151. Henry S. Richardson, *Incidental Findings and Ancillary-Care Obligations*, 36 J.L. MED. & ETHICS 256, 268 (2008).

152. Teri A. Manolio, *Taking Our Obligations to Research Participants Seriously: Disclosing Individual Results of Genetic Research*, AM. J. BIOETHICS, Nov.–Dec. 2006, at 32, 33.

## i. I Lack the Resources to Educate the Participant

Clinicians may well ask: If I don't understand (or agree with) the implications of the finding myself, how will I describe it to my patients? Clinicians are challenged in interpreting genetic tests, which are becoming increasingly available through both clinical practice settings and through direct-to-consumer marketing.<sup>153</sup> Though they are becoming more ubiquitous, more often than not their clinical utility (for the clinician) or usefulness (for the participant) is not evident. Individuals troll the web and bring stacks of printed material from websites to office visits with clinicians, and clinicians are usually not as familiar with this material to even determine its appropriateness.<sup>154</sup> Adding the reporting of RRs and IFs to these challenges will create additional burden for clinicians. Clinicians will also be faced with either conflicting, or at least nuanced, policies for issues related to results for minors, which will have implications for other family members and the potential need for follow-up counseling.

## ii. I Have X Minutes per Visit. How Am I Going to Find Time to Deal with This?

With the burden of enormous numbers of tests becoming available, as well as the potential to be required to share RRs and IFs, already time-crunched clinicians will not be able to find the time to advise patients or participants. The current medical reimbursement system, particularly in the United States, does not generally pay for information exchange or counseling.

## iii. This Is My Patient, but I Have to Share Him/Her with a Researcher. How Do I Navigate This Complex Relationship?

If a biobank participant is recruited into a biobank by their clinician, and a researcher is using the data and samples, then there will be a complex set of relationships for the clinician to navigate. Deciding what should be reported, though potentially determined by policy at local institutions and the biobank, will be complex in practice. Determining how to report the findings and what to do about follow-up will require coordination that may not be present in the currently available infrastructure or

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153. Joshua L. Deignan & Wayne W. Grody, *Ordering Genetic Tests and Interpreting the Results*, 70 *ADVANCES OTO-RHINO-LARYNGOLGY* 18, 18 (2011).

154. Botkin et al., *supra* note 95, at 228–29.

protocols between clinicians and researchers. Some have suggested that these relationships can be sorted out effectively, for example, by allowing others in the team, not the principal researcher, give results to participants.<sup>155</sup>

#### E. INSTITUTIONS

When institutions put policies into practice the infrastructures' needs and necessary protocols may be onerous and/or costly. Kohane et al. recommend an electronic system that will take into account preapproved 'returnable findings' and participant preferences.<sup>156</sup> Most institutions require human interfaces, usually with genetic counselors. For example, the ClinSeq project at the National Human Genome Research Institute (NHGRI) uses healthcare professionals to report information back to participants when such information fits criteria they have determined for disease-causing variants.<sup>157</sup> Others have debated what and when to reveal to patients. The Coriell Personalized Medicine Cooperative returns findings to individuals, differentiating risk on genetic and non-genetic factors.<sup>158</sup> The REVEAL Study, which focused on reporting apolipoprotein E (APOE)<sup>159</sup> status to individuals, studied the psychological issues related to risk for Alzheimer's disease and the effects of results being reported to individuals.<sup>160</sup>

Institutions will need to consider how to conduct informed consent in a way that allows compliance with policies that require RRs and IFs to be returned. Wolf et al. recommend that biobanks (and therefore the institutions or organizations that determine policy for them) take several steps to assist in this process:

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155. Fernandez, *supra* note 138, at 47.

156. Kohane et al., *supra* note 138, at 836.

157. Leslie G. Biesecker et al., *The ClinSeq Project: Piloting Large-Scale Genome Sequencing for Research in Genomic Medicine*, 19 GENOME RES. 1665, 1671 (2009) ("ClinSeq is a pilot project to investigate the use of whole-genome sequencing as a tool for clinical research.").

158. Stack et al., *supra* note 34, at 134 ("[C]onsented participants provide saliva samples, which are genotyped . . . Using a secure web-based portal, the CPMC provides participants with . . . personalized results for potentially actionable health conditions.").

159. APOE is a susceptibility gene linked with Alzheimer's Disease. Ashida et al., *supra* note 117, at 1296-97.

160. *Id.* at 1297.

[B]iobanks should make sure that primary researchers (or collection sites) specify how they plan to handle the issue of IFs and [RRs], and indicate that they have consulted their IRB in erecting this plan. Biobanks will need to establish an agreement with primary researchers (or collection sites) on the respective roles the biobank and primary research (or collection site) will play in the CARR process. Together they will need to consider whether key codes will be housed not just at the primary research (or collecting) institution but also at the biobank or trusted intermediary . . . .<sup>161</sup>

Implementing this process will be easier for biobanks being built from the ground up than for those already in existence.<sup>162</sup>

It may be difficult for institutions to set institution-wide principles, particularly since different departments may view both the process of sharing RRs and IFs and the specific determinations of what is shared in different ways depending on their sensitivity to the information, sophistication about genetic and genomic information, culture of the disciplines they represent, and sensitivity to the vulnerabilities of their populations and/or clients.<sup>163</sup>

It will be important to educate the institutional review boards (IRBs) associated with the institution. A recent study showed that IRBs find oversight challenging as the terrain becomes more complex.<sup>164</sup> At the very least these entities need to consider whether results are from CLIA certified laboratories, since some research results are certainly not performed in these labs.<sup>165</sup> If not performed in an appropriate lab, the findings will need to be validated in a CLIA lab, and the institution will probably incur costs for this further testing.<sup>166</sup>

In 1999, the National Bioethics Advisory Commission (NBAC) put forth some recommendations on the subject:

IRBs should develop general guidelines for the disclosure of the results of research to subjects and require investigators to address the-

161. Wolf et al., *supra* note 3, at 379.

162. See Terry & Terry, *supra* note 1, at 1–2 (noting that there are several problems with the old system).

163. See generally Ashida et al., *supra* note 117, at 1299 (noting that reporting genetic problems can affect health).

164. Amy A. Lemke et al., *Broad Data Sharing in Genetic Research: Views of Institutional Review Board Professionals*, 33 IRB: ETHICS & HUM. RES. 1, 4 (2011).

165. See James O. Westgard, *Charts of Operational Process Specifications (“OPSspecs Charts”) for Assessing the Precision, Accuracy, and Quality Control Needed to Satisfy Proficiency Testing Performance Criteria*, 38 CLINICAL CHEM. 1226, 1226 (1992) (“These CLIA PT criteria describe limits for the ‘total error’ ascribable to the imprecision and inaccuracy of the testing process.”).

166. See Wolf et al., *supra* note 3, at 371.

se issues explicitly in their research plans. In general, these guidelines should reflect the presumption that the disclosure of research results to subjects represents an exceptional circumstance. Such disclosure should occur only when all of the following apply:

a) the findings are scientifically valid and confirmed, b) the findings have significant implications for the subject's health concerns, and c) a course of action to ameliorate or treat these concerns is readily available . . . . When research results are disclosed to a subject, appropriate medical advice or referral should be provided.<sup>167</sup> In 1999, these were appropriate guidelines for IRBs. I am not sure that in the past twelve years, IRBs have created the policies that were needed—in some ways these recommendations were very forward looking. The second sentence, however, belies the age in which these were written—they state that going forward, disclosing research results will be “an exceptional circumstance.”<sup>168</sup> Were these written today, they would be more direct and specific; particularly because the quality and relevance of the data generated by whole genome sequencing, which is now a much more common occurrence, requires clear disclosure policies.<sup>169</sup>

Perhaps the greatest tension for institutions will come from engaging participants as true participants in the process. Institutions and their IRBs—which are created to focus on protecting research participants—are not built on a relationship-based engagement model.<sup>170</sup> In my work on biobanks for both single diseases and multiple diseases, I have built a relational-trust model in which the biobank is steward for the participants in which the actual community owns and manages the biobank.<sup>171</sup> David E. Winickoff suggests that this is indicative

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167. NAT'L BIOETHICS ADVISORY COMM'N, RESEARCH INVOLVING HUMAN BIOLOGICAL MATERIALS: ETHICAL ISSUES AND POLICY GUIDANCE vi–vii (2000), available at [http://bioethics.georgetown.edu/nbac/hbm\\_exec.pdf](http://bioethics.georgetown.edu/nbac/hbm_exec.pdf).

168. *Id.*

169. Jane Kaye et al., *Ethical Implications of the Use of Whole Genome Methods in Medical Research*, 18 EUR. J. HUM. GENETICS 398, 402 (2010).

170. See Lemke et al., *supra* note 164, at 1 (outlining the IRB role of informing patients).

171. Sharon F. Terry et al., *Advocacy Groups as Research Organizations: The PXE International Example*, 8 NATURE REVS. GENETICS 157, 160 (2007) (noting the successes in information gathering and research of such partnerships); Sharon F. Terry & Charles D. Boyd, *Researching the Biology of PXE: Partnering in the Process*, 106 AM. J. MED. GENETICS 177, 180–81 (2001) (describing the formation and new model of a genetic disease organization); cf. David C. Landy et al., *How Disease Advocacy Organizations Participate in Clinical Research: A Survey of Genetic Organizations*, 14 GENETICS MED. (forthcoming 2012) (e-pub at 4–5) (discussing the potential pressures to participate that can stem from such organizations).

of a shift from benefit sharing, common in the biobanks created by research institutions, to power sharing:

[L]ooking at the situation prior to donation and the transfer of entitlement, the group of donors as a collective possesses a crucial form of material, informational and biological capital that could be used to demand a share of power. This is one of the insights to be drawn from the PXE International story, where disease group members formed and retained legal control of a biobank in order to help advance the particular research goals of the organization.<sup>172</sup>

Though the focus of this paper is not this paradigm shift, I believe it has implications for institutions that engage in biobanking. The idea that the individuals donating samples and data to biobanks might share in the power creates new mechanisms for decision making about what results are returned, how they are returned, and when they are returned.<sup>173</sup> This shift, since it will be part of what institutions need to consider, will be challenging, particularly for academic medical centers, which historically have tended toward a hierarchy that does not lend itself to such robust community engagement or participant-centered research.<sup>174</sup>

#### F. SOCIETY

There is some debate about whether biobanks serve society or serve the research community more.<sup>175</sup> If, in fact, they serve society, then society should have a role in the policy setting and execution of practice in RRs and IFs. There is no simple mechanism to increase participation, but the discussion about literacy above is relevant here for society as well. The engagement of society in biobanking in general could increase public interest in biomedical research, increase public literacy, and create

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172. David E. Winickoff, *From Benefit Sharing to Power Sharing: Partnership Governance in Population Genomics Research* 13 (Oct. 3, 2008) (working paper) (on file with Ctr. for the Study of L. & Soc'y Jurisprudence & Soc. Pol'y Program), available at <http://escholarship.org/uc/item/845393hh#>.

173. See Terry et al., *Advocacy*, *supra* note 171, at 160 (“The coordination of research by PXE International allowed the continued aggregation of both negative and positive findings, and dissemination of those results.”).

174. Kieran C. O’Doherty et al., *From Consent to Institutions: Designing Adaptive Governance for Genomic Biobanks*. 73 SOC. SCI. MED. 367, 367–68 (2011).

175. See Susan M.C. Gibbons et al., *Lessons from European Population Genetic Databases: Comparing the Law in Estonia, Iceland, Sweden and the United Kingdom*, 12 EUR. J. HEALTH L. 103, 122 (2005) (noting the distinct interests of informing participants and sharing research with the scientific community).

more active involvement overall.<sup>176</sup>

Questions about public health are inherent in societal perspectives on returning RRs and IFs because “[t]he central moral concern of public health ethics is to specify the conditions that warrant paternalistic interventions that override individual autonomy to prevent people from adopting unhealthy behaviors.”<sup>177</sup>

If society becomes more literate, more engaged, and has a role in determining the return of RRs and IFs reporting, then we must also consider what else might change.<sup>178</sup> For example, would the relatively paternalistic relationship of researchers and patients become more equal?<sup>179</sup> If participants feel more engaged in the research enterprise, would some of the power differential be reduced?<sup>180</sup> It is important to consider what would become of the clinical trial compact if society and communities were more involved in decision-making about research. Already, some of the social networking sites have altered the clinical trial compact.<sup>181</sup> Individuals can share information about the trial, potential treatments, and the pros and cons of placebos in such a way that trials are not truly blind, or worse, they are hard to recruit for.<sup>182</sup> Several years ago, when antiangiogenesis therapies for macular hemorrhaging became available for common condition macular degeneration, PXE International wanted to do a trial of the new therapy against the existing laser therapy. It was impossible to enroll in

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176. Richard R. Sharp & Morris W. Foster, *Clinical Utility and Full Disclosure of Genetic Results to Research Participants*, AM. J. BIOETHICS, Nov.–Dec. 2006, at 42, 43.

177. M. Sutrop, *Viewpoint: How to Avoid a Dichotomy Between Autonomy and Beneficence: From Liberalism to Communitarianism and Beyond*, 269 J. INTERNAL MED. 375, 375 (2011).

178. See Sharp & Foster, *supra* note 176, at 43.

179. See Terry & Boyd, *supra* note 171, at 179 (discussing an anecdote where researchers took a sample without an informed consent procedure).

180. See generally Sharp & Foster, *supra* note 176, at 43–44 (explaining that informing patients can empower them to make better choices for their health).

181. See *Accelerated Clinical Discovery*, *supra* note 45, at 411–12 (detailing research of drug effectiveness through the use of an online forum and a specialized control matching algorithm).

182. See generally A.D. Farmer et al., *Social Networking Sites: A Novel Portal for Communication*, 85 POSTGRADUATE MED. J. 455, 456–58 (2008) (discussing the sharing that occurs on social networks between people suffering from the same disease).

such a trial because, using mechanisms PXE International had built for community sharing, individuals experiencing hemorrhaging went to their retinologists and requested antiangiogenesis treatments. There were no participants left for a clinical trial. This could become more widespread, and the way clinical trials are conducted might have to be restructured.<sup>183</sup>

With the emergence of new technologies comes something termed “network effect.”<sup>184</sup> As the number of people who participate in technology increases, the benefit increases.<sup>185</sup> As participation increases, changes also occur in the industries, technologies, and communities around the new technology.<sup>186</sup> A veritable ecosystem of independent solutions and improvements on the original arise.<sup>187</sup> For returning RRs and IFs, it will be easier to offer society a role as new technologies arise.

We have witnessed similar increases in participation in numerous other “long tails” in other previously hierarchical industries.<sup>188</sup> Individuals share information via websites and apps such as Craigslist, Angie’s List, Amazon, Facebook, and iTunes, revolutionizing how consumers have interacted with markets and each other.<sup>189</sup> The Arab uprising was certainly

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183. See *Accelerated Clinical Discovery*, *supra* note 45, at 412 (describing one way that researchers conducted a clinical trial when presented with a community that was already participating in a treatment).

184. Garth Saloner & Andrea Shepard, *Adoption of Technologies with Network Effects: An Empirical Examination of the Adoption of Automated Teller Machines*, 26 RAND J. ECON. 479, 479–80 (1995).

185. *Id.* at 480 (“[A]s the number of people who make and receive calls increases, each individual can communicate with more people . . . [E]ach new user confers a benefit on all other users.”).

186. See Michael L. Katz & Carl Shapiro, *Network Externalities, Competition, and Compatibility*, 75 AM. ECON. REV. 424, 425 (1985) (noting that firms can make a choice about how to compliment the network effect).

187. See Venkatesh Shankar & Barry L. Bayus, *Network Effects and Competition: An Empirical Analysis of the Home Video Game Industry*, 24 STRATEGIC MGMT. J. 375, 376 (2003) (noting that there is still competition to improve and innovate in network effect markets).

188. See The Economist Online, *Blockbuster Files for Bankruptcy: From Blockbuster to Turkey*, ECONOMIST (Sept. 23, 2010), [http://www.economist.com/blogs/newsbook/2010/09/blockbuster\\_files\\_bankruptcy/print](http://www.economist.com/blogs/newsbook/2010/09/blockbuster_files_bankruptcy/print) (discussing how Blockbuster was pushed out in part due to the success of Netflix).

189. See John Seely Brown & Richard P. Adler, *Minds on Fire: Open Education, the Long Tail, and Learning 2.0*, EDUCASE REV. Jan.–Feb. 2008, at 17, 26–27 (noting that the internet offers an opportunity to change education by uniting people with interests in narrow disciplines).

aided by Twitter; traditional power structures cannot withstand the power of people.<sup>190</sup> Consider the example of Waze, a smartphone app that has the tagline “Outsmarting Traffic, Together.”<sup>191</sup> It allows travelers to input police presence, radar, disabled cars, traffic, and other notable activities along one’s travel route, thus giving other users warning about what to expect—even speed traps!<sup>192</sup> As noted above, crowdsourcing medical information with resources like 23andMe, Private Access, PatientsLikeMe, Genomera, and Althea’s Crowd Sourced Longitudinal Studies have the potential to change the paradigm of participation in biomedical research.

### III. CONCLUSION

#### A. POTENTIAL SOLUTIONS FOR KEY CHALLENGES

The tensions between policy and practice for biobanks RRs and IFs must, and can be, alleviated to some degree. The goal, as mentioned in the introduction, is not to exacerbate these tensions but instead to understand them from the perspectives of a variety of stakeholders in a variety of contexts.<sup>193</sup> Once understood, the applicable systems can be optimized to increase overall health and advance biomedical research. If the entire enterprise was built on a relational model rather than a transactional one, many of the disconnects would either be relieved or workable in the context of evolving relationships.<sup>194</sup> “[T]he lack of personal contact (visual, verbal, or otherwise) with a participant does not diminish the participant’s stake in the results or the researcher’s responsibility to consider the value of the research finding could have for the research participant.”<sup>195</sup> Certainly some of the processes must be codified protocols that

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190. Peter Beaumont, *The Truth about Twitter, Facebook and the Uprising in the Arab World*, GUARDIAN (Feb. 24, 2011), <http://www.guardian.co.uk/world/2011/feb/25/twitter-facebook-uprisings-arab-libya> (noting that social media had varying but important effects in the revolutions across the Arab world).

191. WAZE, <http://www.waze.com/> (last visited Feb. 9, 2012).

192. *About Us*, WAZE, [http://www.waze.com/about/about\\_us/](http://www.waze.com/about/about_us/) (last visited Feb. 9, 2012).

193. See *supra* Figure 1.

194. See Sharp & Foster, *supra* note 176, at 43.

195. Lynn G. Dressler & Eric T. Juengst, *Thresholds and Boundaries in the Disclosure of Individual Genetic Research Results*, AM. J. BIOETHICS, Nov.–Dec. 2006, at 18, 18–19.

are immutable, and all processes must be based in carefully thought out policies; however, the execution of these policies and procedures should be relationally based. This has been said quite well by Lynn G. Dressler:

DNA and other human specimen banking coupled with studies in genetic and genomic research highlight the need to transition to a more socially responsible standard of research conduct in biomedicine. We need a deliberative process to address the roles and responsibilities of biobankers and researchers to inform the development of “codes of conduct.” This process must address the tensions between moral intuition and professional boundaries so the resulting codes are broad enough to allow for moral analysis and yet narrow enough to provide some boundary for decision-making. This would require moving toward a collaborative process for decision-making, with a strong involvement by the community and contributors to the biobank, not just the professional or regulatory groups.<sup>196</sup>

The current provider-patient relationship is built on paternalism.<sup>197</sup> Moving to a partnership will allow relationships built on beneficence rather than rights. Unlike paternalism, beneficence is not in conflict with the autonomy called for by various bioethics policies.<sup>198</sup> In closing, there are a number of areas where careful consideration would alleviate some of the challenges described above.

#### i. Reidentification

Wolf et al. note three different solutions to alleviate the challenges associated with reidentification: (1) primary researchers could reidentify participants when needed; (2) the biobank itself could hold the key to reidentification; or (3) they could rely on a “trusted intermediary” or “honest broker” to hold the key and reidentify.<sup>199</sup> It is possible, as is the case for

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196. Dressler, *supra* note 24, at 96–97.

197. Fernandez, *supra* note 138, at 46–47.

198. O’Doherty et al., *supra* note 174, at 372 (noting that increased participation by disease communities actually does not have a negative effect on the formation of biobank despite widespread knowledge of related concerns).

199. Wolf et al., *supra* note 3, at 375–76. The disclosure process is best served if a strategy is decided at the onset of the project instead of when problems emerge. Mark A. Rothstein, *Tiered Disclosure Options Promote the Autonomy and Well-Being of Research Subjects*, AM. J. BIOETHICS, Nov.–Dec. 2006, at 20, 21 (advocating for patients to be given a range of disclosure options); Rihab Yassin et al., *Custodianship as an Ethical Framework for Biospecimen-Based Research*, 2010 CANCER EPIDEMIOLOGY BIOMARKERS & PREVENTION 1012, 1012 (emphasizing that transparency can positively affect the relationship between researchers and patients).

the Genetic Alliance Registry and BioBank,<sup>200</sup> for the biobank to be the trusted intermediary.<sup>201</sup> There are electronic solutions being considered to alleviate the burden and complex challenges of varied preferences in different contexts.<sup>202</sup>

## ii. Participant-Centricity

Partnerships between researchers and participants could be a core around which robust biomedical research could be developed, and offering participants the results from research could cement that relationship.<sup>203</sup> A more participant-centric engagement will alleviate some of the tensions and help to define the solutions that are required.<sup>204</sup>

A major attribute of biobanks becoming participant-centric is recognition of the context in which people make decisions and the dynamic nature of contextual decision-making.<sup>205</sup> For this reason, biobanks must make it easy for participants to modify their preferences.<sup>206</sup> Technology solutions can offer flexibility and the opportunity to customize one's preferences to the state of one's life, including the immediate needs of the participant and their family.<sup>207</sup>

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200. *About BioBank*, GENETIC ALLIANCE REGISTRY & BIOBANK, <http://www.biobank.org/english/View.asp?x=1360> (last visited Feb. 9, 2012).

201. Wolf et al., *supra* note 3, at 80; *see also* Jimmie Vaught et al., *An NCI Perspective on Creating Sustainable Biospecimen Resources*, 2011 J. NAT'L CANCER INST. MONOGRAPHS 1, 2 (2011) (noting that the National Cancer Institute has identified ethical and legal requirements in addition to other best practices).

202. Kohane et al., *supra* note 138, at 836–37.

203. *See* Grégoire Moutel et al., *Communication of Pharmacogenetic Research Results to HIV-Infected Treated Patients: Standpoints of Professionals and Patients*, 13 EUR. J. HUM. GENETICS 1055, 1059 (2005) (identifying the potential positive effects of informing patients participating in long-term studies).

204. *Id.* (noting that withholding information can lead to anxiety).

205. *See* Wolf et al., *supra* note 3, at 380 (explaining that biobanks could participate in the disclosure process).

206. Bovenberg, *supra* note 2, at 234 (explaining that biobanks can ease the process by regularizing meeting with participants and using the internet to communicate changes); *see also* Knoppers et al., *supra* note 135, at 1173 (“[P]ublishing clinical research results in a scientific journal or in a regulatory database is no longer ethically sufficient. The ethical principles of respect for the person, beneficence and justice obligate the researcher to offer results in a manner that is clear and understandable to the research participants.”).

207. *See* Bovenberg, *supra* note 2, at 234 (noting that the internet can help people make changes to disclosures); Kaye, *supra* note 142.

If biobanks were established primarily in the service of participants, then decision-making would be easier.<sup>208</sup> It might also be said that it would be harder to conduct objective research in the service of science—science that will lead to the solutions the participants may desperately need.<sup>209</sup> This is probably true but not a reason to move participant interests to the side or to demote them. It is also true that a sophisticated system can offer participants the choice to donate their sample to be used for any and all research with no strings attached, expressing no desire for the return of RRs and IFs.<sup>210</sup>

### iii. Expense/Cost

There is great concern that there is no reasonable way to pay for complex consenting systems that would allow participant preferences to determine the return of research results and incidental findings.<sup>211</sup> One need only consider the current social network systems, including the inexpensive nature of such systems, to imagine comparable systems for the research world. Facebook, with a network of around 800 million individuals, representing the third largest country on the planet (only smaller than China and India), started on a couple of computers in a dorm room.<sup>212</sup> Craigslist, with more than 20 billion page views per month, began as a listserv by Craig Newmark when he was new to San Francisco and trying to find events in the city.<sup>213</sup> Of course, these systems now have whole economies, largely based on advertising or subscriptions, connected to them to enable the build outs, expansions, and improvements we all have come to expect. While there is a great fear of what

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208. See Wolf et al., *supra* note 3, at 378.

209. Landy, *supra* note 171, at 4–5 (noting that there are problems with disease advocacy organizations, the parent groups that run some biobanks); see *supra* Part II.F. (explaining the problem with antiangiogenesis therapies on conducting clinical trials for a small disease community).

210. See Rothstein, *supra* note 199, at 21 (advocating a tiered approach that lets patients make a choice about disclosure and the length of the term of use of genetic samples).

211. See Moutel, *supra* note 203, at 1059.

212. See Don Reisinger, *Facebook Six Years Later: From a Dorm Room Experiment to a Household Name*, L.A. TIMES, Feb. 4, 2010, <http://latimesblogs.latimes.com/technology/2010/02/facebook-six-years-later-from-a-dorm-room-to-a-household-name.html>.

213. See *On the Record: Craig Newmark*, S.F. CHRON. (Aug. 15, 2004), <http://www.sfgate.com/cgi-bin/article.cgi?f=/c/a/2004/08/15/NEWMARK.TMP&ao=all>.

advertising might do to biobanking, clinical trials, and biomedical research in general, it is possible to maintain authentic and transparent systems without endangering the core mission.<sup>214</sup> The public can distinguish to some extent between authentic and inauthentic network tools.<sup>215</sup> In addition, because most of these interactions are virtual, new tools will be needed to supplement the ones people already use to discover inauthenticity. Currently, there are researchers working on algorithms to detect fake reviews; for example, a team at Cornell has published a possible method for such screenings.<sup>216</sup>

It is possible that the costs for creating and maintaining systems that allow individuals to detail how and when they want results to be reported back to them can be built into grants.<sup>217</sup> It is also a certainty that the cost of such systems will decrease over time.<sup>218</sup> In an analogous information technology example, when I built a shopping cart to take donations on the PXE International website in 1997, it cost me hundreds of hours of coding work. Now I can add a robust shopping cart free, with no design, build, installation, or transaction fees. This was unthinkable a few years ago. A whole ecosystem has been built around these tools, and the tools themselves cost very little to nothing now. The same can happen with emerging software such as Private Access;<sup>219</sup> Bio-PIN;<sup>220</sup> an ‘intelligent’

214. Rothstein, *supra* note 199, at 21.

215. *Cf.* Moutel, *supra* note 203, at 1059 (noting that patients wanted to view results even if they did not have the technical science background to accurately interpret the results).

216. Myle Ott et al., *Finding Deceptive Opinion Spam by Any Stretch of the Imagination*, in PROCEEDINGS OF THE 49TH ANNUAL MEETING OF THE ASSOCIATION FOR COMPUTATIONAL LINGUISTICS: HUMAN LANGUAGE TECHNOLOGIES 309, 309 (2011) (researching filtering of opinion spam for websites such as Yelp and TripAdvisor).

217. Fernandez, *supra* note 138, at 48.

218. See William E. Evans & Mary V. Relling, *Moving Toward Individualized Medicine with Pharmacogenomics*, 429 NATURE 464, 468 (2004) (“[A]dvances in technology will drive down the cost of genotyping sooner than science and medicine will be able to establish definitive polygenic models for optimizing drug therapy.”).

219. About Us, PRIVATE ACCESS, INC., <https://www.privateaccess.info/about-us/> (last visited Feb. 9, 2011) (“Private Access, Inc. has developed a transformative consumer-centric technology platform that permits internet search for private information.”).

220. J.J. Nietfeld et al., *The Bio-PIN: A Concept to Improve Biobanking*, 11 NATURE REVS. CANCER 303, 304 (2011) (“The Bio-PIN concept is based on the

cancer risk protocol;<sup>221</sup> the UK BioBank,<sup>222</sup> which considers consent as an ongoing process; and others. As Fullerton et al. put it: “It is time to acknowledge that first-generation technical and regulatory solutions are not up to the task of addressing the ethical and scientific challenges of next-generation biorepository research.”<sup>223</sup>

#### B. THE MOVEMENT TOWARD OPEN DATA SHARING

Some have called for a new ethical framework on collective values.<sup>224</sup> There is a broad movement towards data sharing that is changing our values. The current biomedical research culture was built on a 19th century model of win, lose, and completion.<sup>225</sup> As this culture evolves, impacted by the current cultural mores of open access and data sharing, it will enable relational, partnership-based, solutions. Until it evolves (and it may do so kicking and screaming in some quarters), there will be some enormous tensions in the system. At the same time, as some suggest, academic medical centers can take a lead in this regard.<sup>226</sup> It is critical that all of the stakeholders are engaged in this culture shift.<sup>227</sup> Participants must take a proactive role in partnering, with all of the inherent and concurrent responsibilities and benefits. The tension in the system is a beacon of light that allows great clarity if all stakeholders are empowered to look carefully at the land between policy and practice in returning results. This tension can spur innovation if all stakeholders work for the benefit of the ultimate goal: better health. There will be risks for all entities involved, but the benefits will

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principle that from each individual a unique distinguishing biological characteristic (DBC) can be derived that is present in every sample of biological material from that individual.”); J.J. Nietfeld et al., *The Flexibility of Biobanking with the Bio-PIN System*, 11 NATURE REVS. CANCER 895, 895 (2011) (“The Bio-PIN system is flexible. It enables donors and biobanks to communicate in a secure way . . .”).

221. See J. Scott Roberts et al., *Returning Individual Research Results: Development of a Cancer Genetics Education and Risk Communication Protocol*, 5 J. EMPIRICAL RES. ON HUM. RES. ETHICS, Sept. 2011, at 17, 23.

222. See Tutton & Prainsack, *supra* note 42, at 1082–83.

223. Fullerton et al., *supra* note 128, at 3.

224. Bartha Maria Knoppers & Ruth Chadwick, *Human Genetic Research: Emerging Trends in Ethics*, 6 NATURE REVS. GENETICS 75, 79 (2005).

225. See Terry & Terry, *supra* note 1, at 1–2.

226. Heather A. Piwowar et al., *Towards a Data Sharing Culture: Recommendations for Leadership from Academic Health Centers*, 5 PLOS MED. 1315, 1315 (2008).

227. See *id.*

exceed the risk. The real risk in not creating a dynamic, participant-centric system is too great—translation science and those awaiting diagnostics and treatments cannot afford that loss.