Returning Individual Research Results: What Role Should People's Preferences Play?

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INTRODUCTION: FACTS AND VALUES, PREFERENCES AND POLICY

Asking what role people's preferences should play in policies regarding the return of biobank research results is a specific case of asking what role facts should play in prescriptions governing action. Since Scottish Enlightenment philosopher David Hume articulated the point, it has been generally recognized that one cannot *derive* an "ought" from an "is."[1] Nevertheless, it is also generally and correctly assumed that facts matter for prescriptions. They *occasion* or *motivate* the development of policy as, for example, the revelation of Nazi atrocities committed in the name of research-motivated the development of the Nuremburg Code. They also *constrain* policies as prescriptive guides to action are constrained by what is actually, factually possible—"ought" implies or assumes "can," as philosophers say.[2] And, they *inform* policy as when facts about burdens of various research protocols, for example, are used to develop criteria for assessing an appropriate balance of burdens and potential benefits. Finally, a primary *point* of ethical, legal,

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1. DAVID HUME, A TREATISE OF HUMAN NATURE 302 (David Fate Norton & Mary J. Norton eds., 2007).

2. Robert Stern, *Does 'Ought' Imply 'Can'? And Did Kant Think It Does?*, 16 UTILITAS 42, 42 (2004).

and regulatory prescriptions is to protect and promote the interests of people and to fulfill their needs. Facts about those interests and needs are therefore fundamentally relevant to policy development. Moreover, if in fact no one actually embraced a particular prescriptive policy, there would be no will to follow or enforce it.

To determine what role people's preferences should play in policies regarding the return of biobank research results will involve examining how people's preferences regarding research results motivate development of a policy regarding their return; what is and can be known about people's relevant preferences; and the relationship between people's preferences and interests, including those served by research and the policies governing it. Put succinctly, I will examine what we mean when we talk about taking people's preferences seriously, as when an article about communicating results states: "Participants' desires do not necessarily determine policy, but respect for participants requires taking their preferences seriously."[3] In the first section, I discuss some generally agreed upon assumptions in the debate about returning results. In the second, I present an overview of the empirical research conducted to assess people's preferences about returning results. The third section focuses on people's preferences—what they are and whether they can be used to inform research policy. Here I also raise some problems with relying on people's preferences, but suggest the ways in which they must be taken seriously and a context in which they are decisive. In light of this analysis, in the final section, I examine some of the normative arguments employed to support return of individualized results of biorepository research.

I. UNCONTROVERSIAL ASSUMPTIONS

This inquiry begins by discussing some largely uncontroversial assumptions. First, the responsibility of investigators to publicize *aggregate* results of their research is well established. Investigators ought to publish their results in the professional literature so that other scientists may seek to replicate and build upon their findings. Moreover, they ought to make their findings available and intelligible to the public, and especially

3. David I. Shalowitz & Franklin G. Miller, *Communicating the Results of Clinical Research to Participants: Attitudes, Practices, and Future Directions*, 5 PLOS MED. 714, 717 (2008).

to the population that participated in or contributed to the research. Doing so contributes to general scientific literacy, increases awareness of the benefits and limits of scientific research, and recognizes the contribution made by subjects. This inquiry, therefore, focuses on the more controversial issue of disclosure of nonaggregate, *individual* results of research (IRRs).

Moreover, when speaking of the "disclosure" of IRRs, what is meant is the disclosure of IRRs to the individual him/herself, or alternatively to his/her physician or designee. Other disclosure of such personal information—on the nightly news, to a body concerned with presidential nominees' health, or to life insurance underwriters or other third parties—is obviously not contemplated, though the possible access of others to individuals' personal information following initial disclosure to them is worth consideration.

Second, in asking about the role of people's preferences in return of IRRs, it is really *the offer to return* individual results that is under consideration, although for ease and concision, the shorthand "return of" is sometimes substituted. It is agreed that in almost no case would it be appropriate to supply or impose information without first determining that an individual wants to receive it.[4] When an offer of a particular result is actually made, the individual's expressed preference (i.e., choice or decision) to receive it (or not) is generally decisive for reasons discussed at the end of Section three.

Third, the question here is what role people's preferences should play in policy development, specifically in policies regarding whether and how to offer return of IRRs. Because the nature of both the results and the research is relevant for such policy development, the inquiry here is restricted to the focus of this volume: genomic research using biobanked materials and associated data. Furthermore, the focus is on policies governing individual research results, not incidental findings, although admittedly the line between these is blurry in the case of genomic biobank research which is not hypothesis driven.[5] The

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4. One group of commentators states genetic information should never be given to a research participant who does not want it. *See* Laura M. Beskow et al., *Informed Consent for Population-Based Research Involving Genetics*, 286 JAMA 2315, 2320 (2001).

5. Where there are no specific aims, it is perhaps impossible to distinguish incidental findings (that are beyond the aims of the study) from individual research results. In such large-scale discovery research, perhaps the only

distinction is raised here primarily to acknowledge that for some types of biobank research, policies may differ with regard to offering individual research results versus incidental findings. Nevertheless, many of the considerations raised herein are relevant to considering policies governing return of IRRs from research with different designs, or where the finding is actually an incidental finding (i.e., a finding not responsive to the study's aims).

Fourth, to be a candidate for return, a genomic IRR must have analytic and clinical validity, i.e., both the genetic variation and the associated phenotype must be reliably identified. It is generally, though not uniformly, agreed that unreliable results ought not be offered back to individuals. Establishing clinical validity is more challenging than establishing analytic validity, because reported associations between genetic variation and phenotype are often not consistently replicated.[6] Moreover, when the mechanism of action or the functional relationship between genotype and phenotype remain largely unknown, that understanding cannot serve to bolster the clinical validity of a genomic finding. Thus determination of the reliability, and consequently the potential reportability, of a genomic IRR partly depends on the state of scientific understanding in particular domains (e.g., cancer versus psychiatric genetics), as well as the stability of the result through replication attempts. Some IRRs from research involving biorepositories, however, may be well-characterized polymorphisms.

Finally, the offer must comply with applicable laws. Specifically, the result must have been generated in—or verified in—a CLIA-certified laboratory, as per the Clinical Laboratory Improvements Amendments of 1988 (CLIA), in order to be offered back to individuals.[7] Although some commentators suggest there is uncertainty about how to handle an IRR when no test exists to enable replication of the result in a CLIA-certified laboratory prior to returning it to an individual,[8] the law seems

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findings that can be termed truly incidental are those identified upon baseline screening or determination of eligibility of biobanked material and data.

6. Joel N. Hirschhorn et al., *A Comprehensive Review of Genetic Association Studies*, 4 GENETICS MED. 45, 49–50 (2002).

7. *See* 42 C.F.R. § 493.3 (2011).

8. Richard R. Fabsitz et al., *Ethical and Practical Guidelines for Reporting Genetic Research Results to Study Participants: Updated Guidelines from a National Heart, Lung, and Blood Institute Working Group*, 3 CIRCULATION:

clear: only laboratories that "do not report patient specific results for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of individual patients" are exempt from CLIA requirements.[9]

II. RESEARCH ON PEOPLE'S PREFERENCES: FROM DIVERSITY COMES *APPARENT* CONSENSUS

For the past decade, findings from multiple studies of people's preferences regarding the return of research results have been used to motivate, inform, and justify policy recommendations regarding return of IRRs.[10] These studies vary across a number of dimensions.[11] Without attempting a comprehensive review, this section highlights some of the variation in these studies, as well as some of their major findings that are cited to suggest there is substantial consensus regarding return of IRRs. This section provides content and context for the analysis of preferences that follows.

In studies of people's preferences regarding return of results, participants were asked about receiving aggregate (or summary) results,[12] individualized results,[13] or both.[14] Receiv-

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CARDIOVASCULAR GENETICS 574, 576–77 (2010).

9. Ellen Wright Clayton, *Sharing Individual Research Results with Biospecimen Contributors: Counterpoint*, 21 CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION 260, 261 (2012) (quoting 42 C.F.R. § 493.3(b)(3) (2011)).

10. *See* Shalowitz & Miller, *supra* note 3, at 714 (presenting a narrative review of twenty-eight empirical studies and discussing the many dimensions of these studies).

11. *Id.*

12. *E.g.*, Ann H. Partridge et al., *Do Patients Participating in Clinical Trials Want to Know Study Results?*, 95 J. NAT'L CANCER INST. 491, 491 (2003) [hereinafter Partridge et al., *Do Patients Participating*]; Ann H. Partridge et al., *Offering Participants Results of a Clinical Trial: Sharing Results of a Negative Study*, 365 LANCET 963, 963–64 (2005) [hereinafter Partridge et al., *Offering Participants Results*]; Charlene J. Schulz et al., *Impact on Survivors of Retinoblastoma When Informed of Study Results on Risk of Second Cancers*, 41 MED. & PEDIATRIC ONCOLOGY 36, 38 (2003).

13. *E.g.*, Juli Bollinger, Joan Scott & David Kaufman, *Public Preferences Regarding the Return of Individual Genetic Research Results: Findings from a Qualitative Focus Group Study*, 14 GENETICS MED. (forthcoming 2012) (e-pub at 1); Kurt D. Christensen et al., *Disclosing Individual CDKN2A Research Results to Melanoma Survivors: Interest, Impact, and Demands on Researchers*, 20 CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION, 522, 522–23 (2011); Paul R. Helft & Christopher K. Daugherty, *Are We Taking Without Giving in Return? The Ethics of Research-Related Biopsies and the Benefits of Clinical Trial Participation*, 24 J. CLINICAL ONCOLOGY 4793, 4793–94 (2006); David Kaufman et al., *Subjects Matter: A Survey of Public Opinions About a Large*

ing aggregate results may have been conceived as involving receipt of a letter or newsletter,[15] having access to a study website,[16] or reporting results in public media.

The issue of receiving individualized results may have been conceptualized as being invited to request such results,[17] and/or being offered individualized findings, including those of unknown significance,[18] or only findings of apparent significance (usually clinical or health-related significance).[19] The offer and subsequent disclosure of IRRs could be envisioned as occurring in person;[20] by letter, email, or phone;[21] by the individual accessing a study website;[22] or by some combination of these methods (e.g., email notification that one may access an IRR available on a secure website); or the policy could be that IRRs

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Genetic Cohort Study, 10 GENETICS MED. 831, 835 (2008); Fiona Alice Miller, Robin Zoe Hayeems & Jessica Peace Bytautas, *What Is a Meaningful Result? Disclosing the Results of Genomic Research in Autism to Research Participants*, 18 EUR. J. HUM. GENETICS 867, 867–68 (2010); Juli Murphy et al., *Public Expectations for Return of Results from Large-Cohort Genetic Research*, AM. J. BIOETHICS, Nov. 2008, at 36, 38; M.P.M. Richards et al., *Issues of Consent and Feedback in a Genetic Epidemiological Study of Women with Breast Cancer*, 29 J. MED. ETHICS 93, 93 (2003); Dave Wendler & Ezekiel Emanuel, *The Debate over Research on Stored Biological Samples: What Do Sources Think?*, 162 ARCHIVES INTERNAL MED. 1457, 1457 (2002).

14. *E.g.*, Laura M. Beskow & Sondra J. Smolek, *Prospective Biorepository Participants' Perspectives on Access to Research Results*, 4 J. EMPIRICAL RES. ON HUM. RES. ETHICS, Sept. 2009, at 99, 100; Jasper Bovenberg et al., *Always Expect the Unexpected: Legal and Social Aspects of Reporting Biobank Research Results to Individual Research Participants*, CENTRE FOR SOC'Y & GENOMICS, Nov. 2009, at 1, 8–11.

15. *See, e.g.*, Partridge et al., *Offering Participants Results*, *supra* note 12, at 963; Schulz et al., *supra* note 12, at 36–38.

16. *E.g.*, Richards et al., *supra* note 13, at 96.

17. *Id.* at 93–94; Ellen J. Steinbart et al., *Impact of DNA Testing for Early-Onset Familial Alzheimer Disease and Frontotemporal Dementia*, 58 ARCHIVES NEUROLOGY 1828, 1828 (2001).

18. Miller, Hayeems, & Bytautas, *supra* note 13, at 868–69; Murphy et al., *supra* note 13, at 39; Wendler & Emanuel, *supra* note 13, at 1457–59.

19. Kaufman et al., *supra* note 13, at 837–38; Richards et al., *supra* note 13, at 94.

20. Richards et al., *supra* note 13, at 93; Steinbart et al., *supra* note 17, at 1829.

21. Christensen et al., *supra*, note 13, at 523; Partridge et al., *Offering Participants Results*, *supra* note 12, at 963.

22. Though not reporting an empirical study, this model is proposed under the Informed Cohort research regime. Isaac S. Kohane et al., *Reestablishing the Researcher-Patient Compact*, 316 SCI. 836, 836 (2007).

were not to be returned.[23] The results in question may have been (actually or hypothetically) from a clinical trial or intervention research (perhaps with a placebo control) where either aggregate or individualized results could have relevance for continued clinical care for the condition under study;[24] from a disease-specific epidemiological study;[25] from disease-specific genomic research;[26] from either hypothesis-driven or discovery research on materials from a disease-specific or population-based biorepository.[27]

The people whose preferences were sought may have been enrolled in a clinical trial or other clinical research,[28] disease-affected (or parents of disease-affected children),[29] at increased risk for a condition,[30] part of a non-disease specific patient population,[31] representative of "the public,"[32] or some combination of these populations. They may have been asked to make an actual choice about receiving results (aggregate or individual-

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23. Beskow & Smolek, *supra* note 14, at 101–04.

24. Partridge et al., *Do Patients Participating*, *supra* note 12, at 491; Partridge et al., *Offering Participants Results*, *supra* note 12, at 963–64.

25. Christensen et al., *supra*, note 13, at 522; Richards et al., *supra* note 13, at 93; Schulz et al., *supra* note 12, at 36.

26. Miller, Hayeems, & Bytautas, *supra* note 13, at 867–68; Steinbart et al., *supra* note 17, at 1828.

27. Beskow & Smolek, *supra* note 14, at 99; Bollinger, Scott & Kaufman, *supra* note 13, at 1–2; Bovenberg et al., *supra* note 14, at 8; Kaufman et al, *supra* note 13, at 831; Murphy et al., *supra* note 13, at 36–37; Wendler & Emanuel, *supra* note 13, at 1458. As Knoppers and Laberge note, there are important differences with regard to participants, their expectations, and the nature of findings between hypothesis-driven and discovery research, and across studies involving general or disease-specific biorepositories, or large-cohort studies. Bartha Maria Knoppers & Claude Laberge, *Return of "Accurate" and "Actionable" Results: Yes!*, AM. J. BIOETHICS, June–July 2009, at 107, 108.

28. Partridge et al., *Do Patients Participating*, *supra* note 12, at 491; Partridge et al., *Offering Patients Results*, *supra* note 12, at 963; Wendler & Emanuel, *supra* note 13, at 1457.

29. Christensen et al., *supra* note 13, at 523; Helft & Daugherty, *supra* note 13, at 4793; Miller, Hayeems & Bytautas, *supra* note 13, at 867; Richards et al., *supra* note 13, at 93; Schulz et al., *supra* note 12, at 37.

30. Murphy et al., *supra* note 13, at 37; Steinbart et al., *supra* note17, at 1828.

31. Bovenberg et al., *supra* note 14, at 9 (also surveyed biobank researchers regarding their preferences to communicate results or not); Wendler & Emanuel, *supra* note 13, at 1457.

32. Beskow & Smolek, *supra* note 14, at 100; Bollinger, Scott & Kaufman, *supra* note 13, at 1–2; Bovenberg et al., *supra* note 14, at 9; Kaufman et al., *supra* note 13, at 831; Murphy et al, *supra* note 13, at 38.

ized),[33] presented with a hypothetical vignette(s) or scenario(s),[34] or asked direct questions designed to elicit their preferences (e.g., about return of different types of results and/or method of doing so).[35] The study may have involved a survey,[36] interviews,[37] focus groups,[38] mixed methods research, or—relatively rarely—may have reported actual choices regarding offer of return and degrees of satisfaction with the choice.[39]

What appears rather consistent across most of these studies is the finding that a substantial proportion of people express a desire for receiving research results. In a summary of ten studies reporting participants' preferences regarding receipt of aggregate results, "a median of 90% (range 20–100%) wished to receive study results."[40] The same summary reported that 67–100% of participants from 9 studies would want to receive IRRs.[41] The number of participants in these studies, employing a range of qualitative and quantitative methods, ranged from 13 to 8491.[42] For example, in a genetic epidemiological study of women with breast cancer, 93% of 1484 participants indicated that they "would like to be informed if [the investigators] find something" that "may indicate that members of [their] family might have an increased risk of developing breast cancer."[43]

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33. Christensen et al., *supra* note 13, at 523; Partridge et al., *Offering Patients Results*, *supra* note 12, at 963; Richards et al., *supra* note 13, at 93; Steinbart et al., *supra* note 17, at 1828.

34. Bovenberg et al., *supra* note 14, at 24–25; Helft & Daugherty, *supra* note 13, at 4793; Murphy et al, *supra* note 13, at 38–39; Wendler & Emanuel, *supra* note 13, at 1458.

35. Beskow & Smolek, *supra* note 14, at 100; Kaufman et al, *supra* note 13, at 832; Miller, Hayeems & Bytautas, *supra* note 13, at 868; Partridge et al., *Do Patients Participating*, *supra* note 12, at 491.

36. Bovenberg et al., *supra* note 14, at 24-25; Helft & Daugherty, *supra* note 13, at 4793; Kaufman et al, *supra* note 13, at 832; Partridge et al., *Do Patients Participating*, *supra* note 12, at 491; Partridge et al., *Offering Patients Results*, *supra* note 12, at 963; Schulz et al., *supra* note12, at 37; Steinbart et al., *supra* note 17, at 1829; Wendler & Emanuel, *supra* note 13, at 1458.

37. Beskow & Smolek, *supra* note 14, at 100; Miller, Hayeems & Bytautas, *supra* note 13, at 867; Richards et al., *supra* note 13, at 93.

38. Bollinger, Scott & Kaufman, *supra* note 13, at 2; Miller, Hayeems & Bytautas, *supra* note 13, at 867; Murphy et al, *supra* note 13, at 38.

39. Christensen et al., *supra* note 13, at 523; Richards et al., *supra* note 13, at 93; Schulz et al., *supra* note 12, at 38.

40. Shalowitz & Miller, *supra* note 3, at 714.

41. *Id.* at 715.

42. *Id.*

43. Richards et al., *supra* note 13, at 93.

Beyond this summary, in a pilot study of offering IRRs to participants in a genetic epidemiology study of melanoma survivors, nineteen of twenty-seven (seventy percent) participants who were recontacted and offered their individual CDKN2A gene test result chose to receive it.[44] In contrast, only 21 of 251 (8.4%) of those at 50% risk for early-onset frontotemporal dementia requested individual testing (with return of results and counseling) following receipt of results reporting genetic findings in the family.[45] This difference in level of interest suggests a common theme: especially among those at increased risk for a specific condition, genomic results are most welcome when the condition is treatable or preventable.

Reporting on forty prospective contributors to a biorepository, another study found that "over 75% of interviewees thought researchers should provide access to at least some kinds of individual results. At the same time, almost 75% said they would not expect to get individual results, based on their understanding of the consent form. . . ."[46] Investigators in Amsterdam conducted a questionnaire study, using nine fictitious genetic risk results, to assess preferences for IRR return among two populations: patients who had consented to research involving banking of tissue and citizens.[47] For all nine fictitious IRRs, which varied as to associated condition and type of information (e.g., disease risk or pharmacogenomic), seventy to seventy-eight percent of citizens and patients would prefer to receive the results.[48] Citizens preferred receipt slightly more than patients.[49]

Though this is not a comprehensive analysis, it provides evidence that when people are asked about their preference, a substantial proportion express a desire or preference for receiving IRRs. As investigators in the Amsterdam study point out, however, a "sizeable minority" do not.[50] A focus group study found, in fact, a "small group remained adamantly opposed to the return of any IRRs, citing that returning IRRs was not the intent of the study and that the cost to do so could negatively

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44. Christensen et al., *supra* note 13, at 524.
45. Steinbart et al., *supra* note 17, at 1828.
46. Beskow & Smolek, *supra* note 14, at 108.
47. Bovenberg et al, *supra* note 14, at 231.
48. *Id*. at 232.
49. *Id.*
50. *Id.* at 232.

affect the research."[51]

Nevertheless, it is this apparent consensus of empirical findings that has fueled an "emerging consensus" that at least some IRRs should be returned.[52] That people's preferences warrant return of individual results of *biorepository research* (IRBRs) is a conclusion proffered as part of this empirically-driven normative trend. If it is so clear that at least the majority of people want to be offered IRRs, then why should there be any question about recommending and devising policies to do so? The problem is that there are problems with preferences.

III. PROBLEMS WITH EMPLOYING PEOPLE'S PREFERENCES IN POLICY DEVELOPMENT

Given that so many people apparently want to receive IRRs, why shouldn't that fact be decisive, or at least a primary factor, in developing a research policy? In an enterprise where the goal is preference satisfaction, people's individual preferences should play a huge role. In ethics, if our view of the Good were preference satisfaction—not, for example, a hedonistic view or a substantive view of the Good—then people's preferences would be supremely important. Their satisfaction would be valuable, indeed *the* value. On such a view, satisfying people's preferences would be the right thing to do *because* preference satisfaction is good, indeed the Good.

But the goal of research is not preference satisfaction; indeed that is not even the goal of public health or clinical care, which are sometimes blurred with or taken to be the overarching enterprises of which health research is a part.[53] Instead,

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51. Bollinger, Scott & Kaufman, *supra* note 13, at 6.

52. Anneline L. Bredenoord et al., *Disclosure of Individual Genetic Data to Research Participants: The Debate Reconsidered*, 27 TRENDS GENETICS 41, 45 (2011); Michelle N. Meyer, *The Kindness of Strangers: The Donative Contract Between Subjects and Researchers and the Non-Obligation to Return Individual Results of Genetic Research*, AM. J. BIOETHICS, Nov. 2008, at 44, 44. It might also be added that if the research context, type of results, and characteristics of study population matter for reliable assessment of people's preferences, relatively few studies have replicated preference results while employing the same set of study variables.

53. Christian Munthe, *The Goals of Public Health: An Integrated Multidimensional Model*, 1 PUB. HEALTH ETHICS 39, 40 (2008) (listing the goals of public health as the promotion of population health, addressing concerns with the distribution of health within a society, and promoting individual and autonomous health opportunities); Ann Nevin, Visiting Professor, Fla. Int'l Univ. & Professor Emerita, Ariz. State Univ., Keynote Address for Barry Univ. 2006

the increase of generalizable knowledge is the goal of research, though its activities are constrained and informed by the possibility of that knowledge having *social value*, which must itself be informed by some account of what is good/the Good.[54] The goal of public health and clinical medicine is health, which itself contributes to people's well-being.[55] Few people would embrace a preference satisfaction view of well-being, though arguing against it is well beyond the scope of this inquiry. It may be enough to recall an occasion when one's preference was based on mistaken beliefs and its satisfaction did not, therefore, make one better off.

Even if preference satisfaction is not the goal, however, there may be reasons to take people's preferences into account in developing policies regarding IRBRs.[56] Yet, there are also reasons militating against basing such policies on preferences.[57] To understand why people's preferences may not be the best motivation for development of policies to return IRBRs, or the best informational source for doing so, one must first examine what preferences are and their relationship to people's beliefs, decisions, behaviors, and interests in general.[58] Then one can specifically examine people's IRR-related preferences, beliefs, and behaviors to determine the proper role of preferences in policies regarding IRBRs.

A. WHAT PREFERENCES ARE

"Preference" can have at least three different meanings in

Research Conference: Why Do "We" "Do Research?"(Jan. 21, 2006) , *available at* http://www.eric.ed.gov/PDFS/ED492638.pdf (noting that to meet the needs of children, teachers, and classrooms; to fulfill personal needs because of other people; and to add to the knowledge base are common responses to "why do you do research?").

54. *See* Ezekiel J. Emanuel, David Wendler & Christine Grady, *What Makes Clinical Research Ethical?*, 283 JAMA 2701, 2701 (2000).

55. *See id.* at 2703.

56. *See, e.g.*, Daniel M. Hausman, *Valuing Health*, 34 PHIL. & PUB. AFF. 246, 257–59 (2006) (surveying arguments for and against relying on preferences to compare and value health states, and recognizing that reliance on preferences may be advocated "by arguing . . . that the variety of circumstances, aims, and values makes it impossible to construct a general theory of goodness of health states and . . . that it is offensive to disregard the evaluations of individuals, even though they may sometimes be badly off the mark.").

57. *Id.*

58. *Id.* For the account that follows, I am indebted to the work of Daniel Hausman, as well as to conversation with Marcus Adams, though I assume responsibility for any misunderstandings or errors in reasoning.

ordinary usage.[59] One can use "prefer" to refer to *choice* per se, as when one responds to the person scooping gelato, saying "I prefer the chocolate."[60] Perhaps this usage contributes to the belief that people's preferences can be "read off of" their choices. Yet, in a common way of understanding choices and preferences, that one chose chocolate may not reveal one's flavor preference. One may have preferred the *dulce de leche*, but chocolate was on sale and having left one's wallet at home, one can only scrape together coins to meet the sale price. In this case, one's preference for *dulce de leche* employs the second meaning of preference: *liking*.[61] Preference is not mere liking, however, but *comparative liking*.

In its third usage, preference reflects a *comparative evaluation* or judgment of which is the better choice, as when even though I prefer (i.e., more greatly like the taste of) *dulce de leche*, I judge the chocolate to be better to purchase and eat.[62] In my overall comparative evaluation, I may consider that I like both to some degree, though I like *dulce de leche* better; that I believe chocolate to have some health benefits lacking in *dulce de leche*; and that the chocolate in question is a Fair Trade product. The latter two considerations outweigh my greater liking of *dulce de leche*, leading to my preference for the chocolate. Still, if I have given up chocolate for Lent, this factor may compete with my preferences to influence my choice. Although this factor could be explained as influencing my choice by influencing my preferences—"she prefers to fulfill the obligations of her religion, rather than to eat chocolate"—this factor seems more naturally described as a constraint on my preferences or as competing with them.

It is this third meaning of preference as comparative evaluation that seems most relevant to considering research results. Such preferences are not mere "gut feeling" likings or desires, but are more cognitively complex in two ways. First, they are comparative.[63] Second, they are influenced by beliefs.[64] In the previous example, my beliefs about the health benefits and

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59. Daniel M. Hausman, *Mistakes About Preferences in the Social Sciences*, 41 PHIL. SOC. SCI. 3, 7 (2011).

60. *Cf. id.* at 5 (preferring tuna to salmon).

61. *See id.* at 5–6.

62. *Cf. id.* at 6 (comparing sorbet and cheesecake for dessert).

63. *See* Hausman, *supra* note 56, at 254.

64. *See id.* at 260.

the Fair Trade status of the chocolate influenced my preference for it. Preferences are comparative judgments that rank states of affairs about which people have preferences conditioned on beliefs. A person's preference that investigators inform her of clinically significant IRBRs might be conditioned on her belief that learning clinically significant genomic information will prompt her to engage in preventive health behaviors or to inform her offspring of increased health risks.

B. EPISTEMIC PROBLEMS LURKING BEHIND PREFERENCES

As comparative evaluations, preferences are plagued by particular epistemic problems. They may be based, in part, on false beliefs.[65] In the gelato example,[66] it may be the case that unbeknownst to me, the particular chocolate supplier has actually lost its Fair Trade certification for violating child labor standards, or the particular chocolate has been Dutch processed, which allegedly reduces its health benefits. Had I been better informed, I would have had different beliefs and, consequently, a different preference between the two gelato options.[67]

Several of the studies of people's preferences regarding return of IRRs—indeed, some studies reporting that a high proportion prefer receiving them[68]—also reported that people held various false beliefs.[69] Though people's beliefs relevant to return of IRRs have not been studied as extensively as their preferences, there is evidence that people do in fact frequently have several false beliefs.[70] Of prospective biorepository contributors

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65. Hausman, *supra* note 59, at 17–18.

66. *See supra* Part 3.A.

67. *See also* Hausman, *supra* note 59, at 18 (noting that there is never an exact one-to-one correlation between choices and preferences because of the different reasoning behind those choices).

68. *E.g.*, Kaufman et al., *supra* note 13, at 836–38 ("Public eagerness for genetic information is unsurprising in an environment where genetic research is widely believed to be beneficial . . . .").

69. Beskow & Smolek, *supra* note 14, at 99, 102–03; *see also* Conrad Fernandez, *Public Expectations for Return of Results—Time to Stop Being Paternalistic?*, AM. J. BIOETHICS, Nov. 2008, at 46, 47 (explaining the possible considerations of researchers); 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 5) (detailing the beliefs that underpin the medical philosophy of disease advocacy organizations).

70. Beskow & Smolek, *supra* note 14, at 102–03 (noting that patients did not understand the different obligations for researchers and physicians); *see*

drawn from a general, geographically-defined population, forty percent had somewhat mistaken views of differences in knowledge between investigators and their personal physicians:

> Some felt that their physician would already have discovered any problems with their health, expressing doubt that research results would represent information their physician did not already know. Others, however, thought researchers might have more or newer knowledge than their physician would have, and gave this as a reason they should get individual results.[71]

The first belief is largely mistaken given the types of research to be undertaken, and the disease susceptibility information that may be discovered using biobanked materials. The second belief may be false, given the relevance of examining family and personal medical history and environmental components in order to interpret the significance of many genomic findings, even though researchers are more likely than physicians to have a current understanding of particular genetic variations.[72] In addition, "many interviewees seemed to assume that individual research results would relate to a currently diagnosable, yet undetected condition," saying things such as:

> Give me any kind of information that would help me along. If I had cancer, I sure wouldn't want to go two or three years and they know it and I don't know it. Give it [the results] to me.
>
> Regardless of what they find out, whatever kind of diseases they find out that I have, I would want to know about it.. . .
>
> . . . [I]f they found out that, God forbid, I might have a tumor or cancer building up and I don't know it and I'm thinking I'm healthy, I think they should get in touch with somebody. Like send me a letter: . . . [W]e found some cancer on you or . . . you know, you might not be living that much longer.[73]

This apparent misunderstanding of biorepository research as discovering active, present disease conditions in individuals

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also Kaufman et al., *supra* note 13, at 836–38 (noting that potential clinical trial participants would like their data even if it was of little or no value, in part because of the perceived importance of genetic testing in modern medicine).

71. Beskow & Smolek, *supra* note 14, at 103.

72. *See* Brian H. Shirts & Lisa S. Parker, *Changing Interpretations, Stable Genes: Responsibilities of Patients, Professionals, and Policy Makers in the Clinical Interpretation of Complex Genetic Information,* 10 GENETICS MED. 778, 778 (2008) ("[C]omplex genetic traits usually involve [the] interaction of multiple genes and environmental factors. Understanding genetic risk for complex genetic traits has been much more challenging than expected.").

73. Beskow & Smolek, *supra* note 69, at 104.

linked to stored materials—rather than associations between genotype and (perhaps present) disease, or between genotype and increased risk for disease—perhaps explains why some participants believed their physicians would already have discovered any problems with their health that might be revealed through biorepository research.[74]

In one survey of individuals who had either contributed materials to biorepositories or were Medicare recipients, 88.8% said they would want to be "informed of results of uncertain clinical significance," prompting study investigators to comment: "Future research should assess whether respondents' desire for research results of uncertain clinical significance reflects a lack of appreciation for the difference between clinically validated tests and research assays with no proven reliability or validity."[75] The authors advise, however, that "[i]n the meantime, researchers should be aware that the common practice of not divulging results of uncertain significance may prove upsetting to many research participants."[76] Indeed in a paper summarizing findings from eighteen studies regarding participant preferences, the results of this study (88.8% desire receipt of IRRs of uncertain significance) are considered alongside affirmative responses regarding desire for reliable, clinically significant results as evidence supporting the growing consensus that people prefer to receive IRRs.[77]

Another study focused not on individuals' beliefs about receiving results, but on the effect of investigators generating individualized genetic results on individuals' desires for those results.[78] Here the problem with the preferences might be described as their being oddly influenced rather than their being based on false belief.[79] Study participants were either participating in a longitudinal study of Alzheimer disease (AD) or receiving clinical care for cancer (CA); all contributed biological

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74. *See id.* at 103 ("Some felt that their physician would already have discovered any problems with their health, expressing doubt that research results would represent information their physician did not already know.").

75. Wendler & Emanuel, *supra* note 13 at 1461.

76. *Id.*

77. Shalowitz & Miller, *supra* note 3, at 717 ("Available data consistently indicate that research participants want aggregate and clinically significant individual study results made available to them.").

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

79. *See id.*

samples for research purposes.[80] The participants were presented with a range of hypothetical opportunities to have genetic testing to determine their chances of developing Alzheimer's disease.[81] The first two opportunities involved testing saliva, either through a free home test kit or a test performed by a researcher.[82] After the first two options, participants were asked: "Suppose that as part of a study in which you were involved, a researcher had already done a test on your blood, and the researcher knew your chances of developing Alzheimer's disease. How likely is it that you would want to know the results?"[83]

Only thirty-six percent of AD and forty-two percent of CA participants reported being very likely to use the home test kit, and only forty-six percent of CA participants were very likely to ask a researcher to perform the test (the AD participants were not asked).[84] In contrast, sixty-four percent of AD and seventy-four percent of CA participants were "very likely" to want to know the result if the researcher knew it.[85] Combining those that answered "very likely" and "somewhat likely" to want to know if the researcher knew, the proportions rose to seventy-eight percent of AD and ninety percent of CA participants.[86] Asked directly "[h]ow would the fact that the researcher knew your results already affect your wish to know your results?," 40% of the CA cohort responded that it would greatly or somewhat increase their interest.[87] Asked as an open-ended question, members of the AD cohort indicated that the existence of the test result, or the fact that the researcher or another person knew their test result, would increase their desire to know the result as well.[88] These results do not, of course, indicate false

80. *Id.* at 1734 ("[P]atients were asked to contribute to research any remaining tissue that was not needed for their clinical care.").

81. *Id.*

82. *Id.* (explaining that participants were first asked about utilizing a home test kit before being asked about taking a test that involved a researcher).

83. *Id.*

84. *Id.* at 1734–35.

85. *Id.* at 1735. "Very likely" represented the highest level of enthusiasm to receive results. *Id.* at 1374–75.

86. *See id.*

87. *Id.* at 1734, 1736.

88. *Id.* at 1736.

beliefs.[89] They indicate reasons that, at least in the hypothetical context described, people would choose to learn a genomic result. These might be considered reasons that compete with the individuals' preferences to influence choice (I would prefer not to know, but since you do . . .), or they might be considered to influence the preferences directly. However they are thought to affect preferences, the fact that someone else knows the information appears to influence individuals' hypothetical choices regarding acquiring the information themselves.[90] Whether or not this is a good reason—and whether it is itself grounded in accurate or erroneous beliefs—it is not a health-related reason for learning the information, or even a reason related to personal or reproductive planning.

One health-related false belief did emerge from this study. "A small number of research participants indicated that the fact the researcher knew their test result would decrease their desire to know it: 'The investigator could keep me informed about what might help or affect me.'"[91] This false belief is a classic case of therapeutic misconception. A similar misconception was also evident in a study of beliefs and attitudes of those donating samples for genetic research, where a large percentage did not distinguish between research and diagnostic testing.[92] In yet another study, forty-two percent of clinical research participants agreed that results from a research biopsy would "influence their health and care," while another fifteen percent agreed that the biopsy may or may not do so.[93]

Clearly it is problematic to ground policy regarding offer of IRBRs in people's preferences if those preferences are often based on false beliefs.[94] Many of the studies assessing people's preferences have not examined the beliefs on which their preferences are based, so the prevalence of false beliefs is not currently known.

The obvious not-so-quick fix for those who believe prefer-

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89. *Id.* at 1737 ("Many respondents attributed this effect to the fact that they did not want investigators to possess genetic information about them that they did not possess.").

90. *Id.*

91. *Id.* at 1736.

92. Marsha Michie et al., *"If I Could in a Small Way Help": Motivations for and Beliefs About Sample Donation for Genetic Research*, 6 J. EMPIRICAL RES. ON HUM. RES. ETHICS, June 2011, at 57, 67.

93. Helft & Daugherty, *supra* note 13, at 4794.

94. *See* Hausman, *supra* note 56, at 261.

ences should motivate and inform policy development is to specify that when evaluating policy options in light of people's preferences, policy makers should attend to "*rational or informed* preferences," not those that are merely manifest.[95] But, "[s]hifting from actual to informed preference limits the significance of preference."[96] Relying on informed, or corrected preferences, shifts attention from people's actual preferences to the options or states of affairs that make their preferences appropriate or worth taking into account.[97] By introducing a notion of appropriate or corrected preferences, a direct normative evaluation of the options is smuggled in.[98]

Rather than assessing people's preferences, policy makers might better evaluate directly those options or states of affairs of which people's preferences are comparative evaluations.[99] In enquiring about people's preferences, researchers are asking people's opinions of matters of fact, when "they should instead be trying to find out what the facts are" and evaluating those facts directly.[100] After all, if people in general can form comparative evaluations of the options available regarding IRRs, policy makers can do so as well.[101] But if the options are more complex than preferring chocolate to vanilla,[102] even the majority that prefers one option will likely prefer it for a variety of different reasons, influenced by a variety of different beliefs.[103] Therefore, the majority's preference is frequently not a good guide to what is good about the preferred option.[104]

To develop policies regarding return of IRBRs, policy mak-

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95. *Id.* at 262.

96. *Id.* at 263.

97. *Id.*

98. *See id.* at 262 ("[L]et informed preferences rather than manifest preferences be the standard by which health states are compared. To measure informed preferences, provide survey respondents with information . . . . Give them time to reflect.").

99. *See* Hausman, *supra* note 59, at 23 ("But beneath the criticism lies a constructive thesis: that preferences in economics are subjective total evaluations that are both action-guiding and subject to rational criticism.").

100. Hausman, *supra* note 56, at 265.

101. *See generally id.* at 262–63 (noting that sophistication barriers can be removed by providing more information and using better questioning).

102. *See supra* Part 3.A.

103. Hausman, *supra* note 59, at 20.

104. *See id.* ("Choice could not by itself reveal preference, because, given the right set of beliefs, any set of choices is consistent with any set of preferences.").

ers—investigators, institutional review boards, or biorepository governing bodies—should evaluate different options, different possible states of affairs: for example, the option of offering individualized findings that meet criteria of validity and significance or offering no IRBRs that lack immediate life-saving potential. They should examine how well different options regarding return of IRBRs achieve the reasons for returning IRBRs—namely, whether (and to what degree) the different options regarding IRBRs further or impede important goals in research and health promotion.

C. MIGHT SATISFYING PEOPLE'S PREFERENCES NEVERTHELESS BE A GOOD THING TO DO, OR AT LEAST A BENIGN APPROACH TO MANAGING IRBRS?

Even if people's preferences do not themselves constitute a reason to offer IRBRs, might offering return of such results still be a good thing—a nice thing to do? If offering IRBRs were largely costless or did not have any substantial downsides, it would seem that providing people with what they say they want might be a *prima facie* good (though whether doing so actually enhances well-being is a different issue). But, developing the infrastructure to offer back results of biorepository research (and indeed other research) is not costless. It is not even cheap.

Few studies have attempted to establish the cost of returning a genomic research result. In one, $1,322 was the average cost per completed disclosure.[105] Of course, the details of a protocol to return results would significantly affect cost, especially with regard to personally tailoring or standardizing informational materials, the degree of personal contact and counseling provided, and the expense of confirming genotypes. Several commentators have indicated that additional funding will need to be built into research budgets—ranging from individual project budgets to those of funding agencies, foundations, and commercial entities—if the costs of result-return activities are not to encroach on funds for research activities themselves.[106] However, none has suggested sources of such additional fund-

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105. Christensen et al., *supra* note 13, at 527. A few other studies also report on the costs of offering back various types of individualized results. Shalowitz & Miller, *supra* note 3, at 716–17.

106. Lisa S. Parker, *Rethinking Respect for Persons Enrolled in Research*, AM. SOC'Y FOR BIOETHICS & HUMAN. EXCHANGE, Spring 2006, at 1; *see also* Fernandez, *supra* note 69, at 47–48 (acknowledging that returning research results will come with "financial and perhaps opportunity cost[s]").

ing at a time of rising costs in research and health care and constraints on overall state and national budgets. In addition, some commentators are beginning to raise the issue of downstream costs occasioned by return of IRBRs, particularly the cascade of interventions such information may occasion.[107] Anticipation of these costs prompts suggestions that the practice of returning research results should be subjected to comparative effectiveness analysis.[108]

Moreover, as a 2009 commentary advised, "if it is to be any benefit to health, genetic risk information needs to prompt individuals to pursue risk-reduction behaviors, yet early evidence suggests that genetic risk may not be an effective motivator of behavior change."[109] Variants discovered in gene-disease association studies have very small effect sizes, indicating that common diseases are complex (i.e., involve the interaction of multiple genes and the environment).[110] Therefore, genomic risk information may best serve as "an adjunct to current risk assessment, refining rather than replacing other methods of risk stratification."[111] Moreover, it is "unclear whether most behavioral interventions can or should be individualized for people at moderately increased risk of disease."[112] "Aggressive prevention measures, such as prophylactic surgery, would be ethically and socially unacceptable for people with moderately increased risk," while many less aggressive measures may be pursued as general healthy behaviors (e.g., diet, exercise, and smoking cessation), and their adoption may "have more to do with social circumstances than with genetic risk . . . ."[113] The

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107. *E.g.*, Clayton, *supra* note 9, at 261; Ellen Wright Clayton & Amy L. McGuire, *The Legal Risks of Returning Results of Genomics Research*, GENETICS MED. (forthcoming 2012) (manuscript at 3), *available at* http://www.nature.com/gim/journal/vaop/ncurrent/full/gim201210a.html; Amy L. McGuire et al., *Research Ethics and the Challenge of Whole-Genome Sequencing*, 9 NATURE REVS. GENETICS 152, 153 (2008).

108. *See, e.g.*, Clayton, *supra* note 9, at 261; Clayton & McGuire, *supra* note 107, at 1; Nora B. Henrikson, Deborah Bowen & Wylie Burke, *Does Genomic Risk Information Motivate People to Change Their Behavior?*, 1 GENOME MED. 37.1, 37.2 (2009).

109. Henrikson, Bowen & Burke, *supra* note 108, at 37.1.

110. *Id.* at 37.1–37.2.

111. *Id.* at 37.2.

112. *Id.*

113. *Id.* Indeed, even for individuals who are highly motivated to pursue such prevention behaviors (i.e., who have strong preferences for doing so), social circumstances may compete with their preference to influence their actual

commentators acknowledge that while receipt of risk information has been associated with little distress, of greatest concern "is the fact that we lack evidence that individualized risk information is an effective motivator of behavioral change."[114] They advocate holding provision of genomic risk information to a test of comparative effectiveness and state that "[h]ealth care providers and funders have a responsibility to use tests with proven health value—a standard not yet achieved for genetic risk information intended to motivate healthy behaviors."[115]

In comparison to studies of people's preferences regarding return of individualized genomic results, there has been little research showing how receipt of DNA-related IRRs affects recipients' health behaviors. In light of this paucity, studies of what people do with genomic information of the sort that could be reported back as IRBRs may be relevant. Unfortunately, the sort of information that would constitute IRBRs has not had a good track record of motivating health behaviors.

One study did report behavioral responses to return of genomic research results to melanoma survivors (a genomic IRR): "[f]ew health behavior changes were reported at the 3-month follow-up," though most participants were already engaging in prevention behaviors.[116] In eleven studies that assessed the impact of reporting a DNA-based increased risk for breast, ovarian, or colorectal cancer or for hypercholesterolemia, an increase in risk-reducing behaviors (e.g., increased screening, prophylactic surgery) was reported in five of them.[117] In a meta-analysis of twenty-one studies examining the impact of genetic counseling on those with familial cancer risk (though admittedly not DNA-based risk information), none of the four studies that examined behavioral impact found an increase in surveillance behavior.[118]

Explanatory models accounting for these disappointing behavioral outcomes are being devised and tested, including, for

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choice and behavior. This consideration thus fits with the model of preferences discussed above.

114. *Id.*

115. *Id.*

116. Christensen et al., *supra* note 13, at 526.

117. Theresa M. Marteau & John Weinman, *Self-Regulation and the Behavioural Response to DNA Risk Information: A Theoretical Analysis and Framework for Future Research*, 62 SOC. SCI. & MED. 1360, 1361 (2006).

118. *Id.*; *see* Dejana Braithwaite et al., *Psychological Impact of Genetic Counseling for Familial Cancer: A Systematic Review and Meta-analysis*, 96 J. NAT'L CANCER INST. 122, 129 (2004).

example, the hypothesis that "the provision of DNA based risk information may fail to activate behavio[]ral responses (e.g. adherence to treatment or dietary advice) that reduce a health threat either because a genetically based disease is perceived to be uncontrollable or amenable only to a biological treatment, or both."[119] This explanation moves beyond simple invocation of fatalism to suggest that perceptions of available interventions are also critical, as is the significance of risk reduction as a personally embraced goal.

Individuals' own explanatory models, information-seeking/avoidance styles, and expectations are relevant to psychological impact of DNA-based results as well. In the first randomized study directly comparing the impact of Alzheimer's disease risk assessment, with and without the provision of genotype information, an unfavorable genetic test result had relatively little impact on risk perception.[120] Investigators explained this by hypothesizing that the majority of those tested may have expected the unfavorable result based on family history: "[t]est results that meet expectations regardless of whether they are favorable or unfavorable have a less negative impact than test results that confound expectations."[121] There are more studies that examine the psychological impact of receiving individualized genomic information than there are that examine the impact on behavior. A simplified but accurate summary of psychological impact studies to date may be: unfavorable results tend to cause less distress, and favorable results occasion less false reassurance than commentators have feared. It must be remembered that, because of the testing contexts generating results to date, most genomic results returned thus far were specifically sought, or at least the recipients expected their return. Among the contexts that matter for the effective return of genomic results is the context created by the recipient's expectations.[122]

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119. Marteau & Weinman, *supra* note 117, at 1364.

120. Theresa M. Marteau et al., *Predictive Genetic Testing for Alzheimer's Disease: Impact upon Risk Perception*, 25 RISK ANALYSIS 397, 400 (2005).

121. *Id.* at 402.

122. For a discussion of how context may affect the researcher's obligation to report IRBRs, see Laura M. Beskow & Wylie Burke, Commentary, *Offering Individual Genetic Research Results: Context Matters*, 2 SCI. TRANSLATIONAL MED., June 30, 2010, at 1.

D. MIGHT ACCEDING TO PEOPLE'S PREFERENCES WITH REGARD TO IRBRS BE PRUDENT FOR THE SAKE OF THE RESEARCH ENTERPRISE ITSELF?

Strong preferences about policies can affect their practicability. If, for example, people so dislike a policy regarding the return of IRBRs that no one followed it, or if their dislike prompted actions with negative social consequences, then practicality would require that the policy be changed. Assume for the moment that a policy was developed that sought to curtail any return of IRBRs, and no one preferred the policy; indeed, everyone strongly disliked it. (Ignore issues of how it could even come to be.) If investigators and those regulating research at all levels strongly disliked the policy and thus refused to adhere to or enforce it, the policy would be ineffective. More likely, given the preferences reported, prospective contributors would refuse to donate samples to biobanks. The policy would undermine or render impossible biorepository research. Even if the percentage of prospective contributors who refused to participate was less than 100%, a somewhat more realistic assumption, the number would likely be so high that biorepository research would be substantially slowed (because of substantially slower recruitment), or there would be increased risk of research bias (particularly if participation refusal were not consistent across all relevant populations). To be enforceable and socially beneficial, policies must serve the needs and interests of people, and must be *seen* to do so—or at least cannot be viewed as doing the opposite. Policies need "buy in."

It is true that when specifically asked about the importance of the possibility of receiving IRBRs, a large proportion of people surveyed and interviewed indicate that this possibility serves as an incentive to their consent to participate and/or that not being able to receive IRBRs would make them less inclined to do so.[123] Thus it may be thought that the goals of biorepository research cannot be accomplished without satisfying the IRBR-related preferences of prospective biorepository contributors. Indeed, commentators imply that acceding to people's stated preference for return is warranted for the sake of the research enterprise itself,[124] even though incentives to en-

123. Murphy et al., *supra* note 13, at 41.

124. Ann H. Partridge & Eric P. Winer, *Informing Clinical Trial Participants About Study Results*, 288 JAMA 363, 363–64 (2002) (suggesting that

courage participation in research that participants would otherwise not consent to are frequently discouraged, if not prohibited as undue inducements.[125]

Findings from four studies illustrate the nature and strength of the IRBR-related preferences, as well as normative conclusions being drawn from them. In the first study, researchers conducted an on-line survey to gage public willingness to participate in a large -cohort study. The most influential factor affecting the respondent's willingness to participate in the study seemed to be the offer of individualized results (associated with a six percent increase in the willingness to participate), as opposed to an offer of monetary compensation (an offer of $200 resulted in only a five percent increase in the willingness to participate).[126]

In a second study, a genetic epidemiology study involving melanoma survivors, of participants who were re-contacted and offered their genetic IRRs, fifty-nine percent reported that disclosure increased the likelihood of their future participation in research.[127]

In a third study, prospective biorepository contributors were presented with the informed consent template that had been developed for the biorepository.[128] The template specified: "You should not expect to get individual results from research done with your blood."[129] When asked whether this statement affected their willingness to participate, ten percent said 'yes'.[130] Over seventy-five percent of those interviewed thought investigators should return at least some IRRs, while almost seventy-five percent stated they understood they would not receive them based on the consent template; and, approximately ninety percent said this fact would not affect their opinion about participating.[131]

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sharing results might motivate individuals to participate in clinical trials and bolster accruals).

125. *E.g.*, General requirements for informed consent, 45 C.F.R. § 46.116 (2010) ("An investigator shall seek such consent only under circumstances . . . that minimize the possibility of coercion or undue influence.").

126. *See* Kaufman, *supra* note 13, at 832.

127. Christensen et al., *supra* note 13, at 526.

128. Beskow & Smolek, *supra* note 14, at 99.

129. *Id.* at 100.

130. *Id.* at 104–05.

131. *Id.* at 108.

In a fourth study, investigators reported and reflected on their focus group results:

> [A]ccess to individual research results was viewed as a valuable incentive for participating in the proposed study. Because large cohort gene-environment studies require long-term commitments from study volunteers with few incentives in the way of direct medical benefits, offering participants access to their personal research results may be useful in recruiting and retaining research participants.[132]

They seem simultaneously to recognize the unlikelihood of individual benefit from the return of results and to advocate encouraging prospective repository participants to view results as benefits for the sake of study recruitment and retention.

As if in direct response to such studies' findings that the possibility of learning IRBRs serves as an incentive to enrollment, other commentators note that "[t]o hold out access to undefined research results as a benefit would be a 'dangerous move toward encouraging the therapeutic misconception if the results are preliminary and not validated, or their predictive value is not well understood'."[133] Moreover, offering participants information lacking health-related value when they mistakenly believe it to be valuable should be discouraged on grounds that is disingenuous to do so. This is especially true in light of findings from the investigators' focus groups that the possibility of direct medical or at least health-related benefit is frequently cited as a primary reason that people prefer to receive results[134] and that the most preferred option would be return of results that are accurate and actionable.[135]

Although people report a preference for receiving IRRs (including genomic IRRs) and indicate that the possibility of receiving them increases their willingness to participate in research, when there has been no plan or promise to return results, there is no evidence of actual widespread research participation refusal, and especially no evidence of any systematic trends in refusals, that would raise concern about introducing bias into biorepository research.[136] Both whether and how not

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132. Murphy et al., *supra* note 13, at 41.

133. Knoppers & Laberge, *supra* note 27, at 108 (quoting Mildred K. Cho, *Understanding Incidental Findings in the Context of Genetics and Genomics*, 36 J.L. MED. & ETHICS 280, 284–85 (2008)).

134. *E.g.*, Murphy et al., *supra* note 13, at 39–40.

135. *See, e.g.*, *id.*, at 39.

136. The concern about such bias is similar to the concern expressed that relying on "information altruists," those "who are most willing to have their health data publicly shared," could create subject bias and impede the ability

receiving IRBRs would affect recruitment for biorepository research are empirical questions that warrant further study. In light of problems with people's preferences identified herein, as well as evidence—admittedly from other contexts—that preferences do not predict behavior, it would be a mistake to accede to people's manifest preferences for return for the sake of recruitment to biorepository research, especially without evidence that doing so is necessary.

E. ADDITIONAL PROBLEMS WITH BASING POLICIES ABOUT OFFERING IRBRS ON PEOPLE'S PREFERENCES

In addition to the possibility that people's preferences may be influenced by false beliefs, and the fact that asking about people's preferences is a poor way to evaluate the relationship of those options to the goals of research, public health, and health care, there are additional problems with trying to use people's preferences to inform research policy.

First, the idea of "people's preferences" is incoherent. Individuals have preferences, but "the people" do not. We can determine what the majority of a specific population prefers, but unless that *majority* is instead *unanimity*, we cannot infer an individual's preference from the majority's preference.[137] Except perhaps for a few rare cases, there is no uniform preference, unified view, or social consensus about the value or desirability of being offered IRBRs.[138]

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of genomic research to identify genetic variation relevant to the general population. Amy L. McGuire & Richard A. Gibbs, Policy Forum, *No Longer De-Identified*, 312 SCI. 370, 371 (2006).

137. Even in a case of unanimity, if the states of affairs over which comparative evaluations are being made are themselves at all complex, individuals are likely to prefer the same option for different reasons based on different beliefs. So again, analyzing even a unanimous preference may not reveal much about the value of the option itself, and the unanimity of preference may be quite unstable.

138. The strongest candidate for attracting such social consensus is, I argue, information meeting the criteria for a duty to warn articulated in *Tarasoff v. Regents of University of California*, where such a duty was found to hold for the individual having privileged access to credible information regarding risk of a serious, preventable harm to another. *See* Parker, *supra* note 106, at 6 (comparing the duty to warn established in Tarasoff v. Regents of Univ. of Cal., 551 P.2d 334, 340 (1976), with the duty of a researcher in possession of life-saving information). Indeed, in this case it is the likelihood of being able to prevent a serious harm (murder) that justifies warning the potential victim, not data showing that most people would prefer to be warned.

In practice, we are stuck with the problem of moving from knowing data about "people's IBRR preferences," or the majority of people's preferences, to learning about a specific individual's personal preference. Facts about the majority's preferences do not straightforwardly reveal the preference of the particular person who is the subject of a specific IRBR.

Ironically, those who draw the strongest connection between subjects' preferences and researchers' duties—by claiming that the former entail the latter—render empirical data about preferences of minimal use. Whatever else it requires, respect for persons demands that we attend to the unique preferences of each individual. Regardless of whether empirical data show that *most* subjects want results or not, as long as we know that even one may, researchers would be obligated to offer results to all in search of that one.[139]

This comment both points to the incoherence and suggests a possible way out. The suggestion is made that every individual be offered return of every IRBR, in order to ensure that those wanting IRBRs have access.[140] But, this solution will not work, and it suggests the next set of problems.

There is a second incoherence in the case of trying to return an IRBR according to the preferences of the individual to whom it is linked. There is no way for that individual to make an informed decision about whether she wants to receive the result unless she is substantially informed of the result. This problem arises at two decision stages: during informed consent to biobank participation and when an offer to receive an actual IRBR is made. An individual cannot be offered the options (to be offered/receive an IRBR or not) and make an adequately informed comparative evaluation of her options without knowing important facts about the IRBRs that she might receive. But, informing her of those facts risks imposing on her information that she prefers not to receive.

Choice of an option regarding IRBR return, even in the context of informed consent to biorepository participation, is choice in a hypothetical context. The informed consent context regarding IRBR management is similar to the hypothetical scenarios used in research on likely uptake of genetic susceptibility testing.[141] Indeed, the second decisional context—when

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139. Meyer, *supra* note 52, at 45.

140. *Id.*

141. *See* Susan Persky et al., *Assessing Hypothetical Scenario Methodology*

one receives an offer of a specific (but as yet unrevealed/unreturned) IRBR and must make a decision—is also essentially a hypothetical situation.

Research on people's preferences regarding genetic susceptibility testing frequently employs hypothetical scenarios, and there is often a substantial gap between anticipated (based on such research) and actual uptake of testing.[142] Research on hypothetical scenario methodology suggests that, for example, "higher intention-behavior congruence might be achieved via consideration of temporal proximity . . ." (i.e., "the extent to which a decision is portrayed as being immediate or having immediate consequences").[143] While such a change in research methodology might improve congruence between individuals' actual behavior and the investigator-prompted expressions of their preference, it is not clear that this amendment could improve the informed consent process regarding offers of IRBRs.[144] It would be disingenuous to suggest to a biobank contributor that the opportunity to receive an individual result is likely to be temporally proximate, or that if eventually found and reported, the result would have immediate consequences.

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in Genetic Susceptibility Testing Analog Studies: A Quantitative Review, 9 GENETICS MED. 727, 727 (2007) ("Because GST is generally not yet available for many common diseases, hypothetical scenario methodology has often been used to assess testing interest and estimate upcoming need for services. This methodology has the benefit of allowing investigators to manipulate important test characteristics and contextual variables to understand better how these factors influence reported interest levels and intentions to test."). This framework also applies to IRBR informed consent because in "the context of a biorepository . . . participants may be enrolled based simply on their membership in a particular population . . . and not because they have a particular condition of interest." Beskow & Smolek, *supra* note 14, at 99. "Specimens and data are stored for future, unspecified use in a variety of studies that typically take place without the subject's direct knowledge or consent." *Id.* Thus, when researchers are providing informed consent in contexts that may generate IRBRs, they often must use the equivalent of hypothetical scenarios what the research may reveal and the very tests the specimen will be used for are unknown.

142. *See* Persky, *supra* note 141, at 727 ("Hypothetical scenario methodology is commonly employed in the study of genetic susceptibility testing uptake estimation. The methodology, however, has not been rigorously assessed and sizeable gaps exist between estimated and actual uptake for tests that have recently become available.").

143. *Id.* at 728.

144. *See generally id.* (discussing only generally how hypothetical scenario methodology could be improved without discussing any implication these improvements could have for the informed consent process).

Nearly two decades ago, the proposal of generic consent for genetic screening anticipated this problem of needing to make a decision about whether to receive genomic information in a context of substantial uncertainty about the nature of the information and implications of receiving it.[145] Unfortunately, generic consent does not provide a good solution.[146] Selection of the results or the type of results one would want to receive from research with biorepositories is daunting and probably not a good bargain to make with the future. Pleiotropy makes it impossible, for example, to elect to learn about risks for cardiovascular conditions, but to refuse risk information regarding future cognitive impairment, because already the pleiotropy of the APOε4 allele is known. But many similar associations of a specific genetic variation with multiple conditions remain to be discovered and reported, or not. How can one meaningfully choose? How should one factor into the decision that additional associated conditions may be discovered in the future? Of course, in clinical care informed consent decisions are at best substantially informed and never fully so. Yet, most clinical interventions are more immediate and time limited.[147] Consent to clinical interventions is less of a blank check. Most importantly, the potential benefits of a clinical intervention are often well-characterized, even if they do not all eventuate. Admittedly, the risks of actual clinical interventions are frequently greater than those of merely receiving genomic information.[148] If, how-

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145. *E.g.*, Sherman Elias & George J. Annas, *Generic Consent for Genetic Screening*, 330 NEW ENG. J. MED. 1611, 1611 (1994).

146. *E.g.*, Leslie G. Biesecker & Benjamin S. Wilfond, Letter to the Editor, 331 NEW ENG. J. MED., 1024 (1994) ("A generic-consent model would draw patients into the prenatal testing process with an incomplete understanding of what is involved. This policy would have the undesirable effect of diminishing the opportunity to decline testing, which may be the best option for some patients.").

147. *See also* Beskow & Smolek, *supra* note 14, at 101 ("Approximately 30% of interviewees made comments about research relative to medical care. . . . Almost all described differences between the two, noting for example that research was 'not like a regular doctor visit' where one would expect diagnosis, treatment, and followup. Some specifically noted a difference between a biological sample that could 'sit on a shelf with a million others' and individual medical care, although a few felt that a personal connection remained between a biospecimen and the individual from whom it came.") (internal reference omitted) (emphasis omitted).

148. *See, e.g.*, Henrikson, Bowen & Burke, *supra* note 108, at 37.2 ("It is also unclear whether most behavioral interventions can or should be individualized for people at moderately increased risk of disease. Aggressive prevention measures, such as prophylactic surgery, would be ethically and socially

ever, one considers that undertaking health behaviors or clinical interventions in light of the genomic information is part of a package deal of receiving genomic information, then the ratio of risks and potential benefits shifts once again.

A third problem with trying to use an individual's preferences to manage any IRBRs discovered about her is that an individual's preferences are frequently inconsistent and change over time.[149] Moreover, the circumstances that influenced or competed with those earlier preferences change over time, as do the beliefs that influenced them.[150] The person who expressed a preference for learning an IRBR because she would want to inform her offspring of any significant health risk may find herself without children. A person who wanted to learn his/her health-related IRBRs to motivate preventive health behaviors may still highly value health and prevention, but be preoccupied with a health concern unrelated to the IRBR. It may be said that these are simply reasons for embracing a policy that establishes a two-step process: first asking (during informed consent) whether one would want to be offered an IRBR upon its discovery, and then later asking whether one, in fact, wants to receive the IRBR that is discovered. But this two-step process does not address the problem of an individual's lacking adequate information to make an informed decision about whether she wants to know what she does not yet know.[151]

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unacceptable for people with moderately increased risk, whereas many behaviors, such as smoking cessation and regular exercise, reduce risk for many diseases at all levels of risk.").

149. *See, e.g.*, Hausman, *supra* note 59, at 9 ("As comparative evaluations, preferences are subject to criticism and discussion. Even preferences that seem like mere comparative likings can be criticized and rationally reconsidered. For example, even though Jack likes cheesecake a great deal more than he likes sorbet, his preferences among those desserts may change radically after a mild stroke coupled with a stern warning from his doctor about his cholesterol level.").

150. *See, e.g.*, *id.* at 16 ("The most fundamental difficulty with actual revealed-preference theory (which also bears on hypothetical revealed-preference theory) is that an agent's preferences influence her choices only via the agent's beliefs. Keep her preferences constant and change her beliefs, and her choices may change. There is no one-to-one relation between preference and choice. Preferences can be inferred from choices only given knowledge of beliefs.").

151. *See* McGuire & Gibbs, *supra* note 136, at 371 ("Some of the practical challenges [with stratified consent procedures] include providing adequate disclosure and education about a complex risk calculus, ensuring subject comprehension, coordinating a system of restricted access, and managing a com-

F. SHOULD PREFERENCES PLAY ANY ROLE IN OFFERING AND RETURNING IRBRS?

In short, yes. Abiding by the enrollee's manifest preference—the choice made during the informed consent process for biobank participation—is ethically appropriate, but not as a matter of fact about preferences with the goal of their satisfaction. It is ethically appropriate as a matter of respecting the right of a competent person to make a research or health-related decision to refuse or accept options being offered. Respecting an enrollee's choice is warranted by the norms governing research, informed consent, and health-related decision making, not by alleged facts about people's preferences or the effect of preference satisfaction on research enrollment.[152]

If an individual has been asked, as part of the informed consent process, and has responded that she wants to be offered IRBRs, her choice should be respected. Whatever her preference (*qua* comparative evaluation) with respect to receiving the results may be, she has made it known that she wishes to be offered the opportunity to make such a choice. In like manner, if upon being offered a specific IRBR, an individual chooses to receive it, again that choice should be honored. Why should investigators honor it? First, although the consent context suffers from the problems plaguing choice in hypothetical contexts, at least the notion of preference is coherent: an individual can form and express her own preference *qua* comparative evaluation. Second, the informed consent decisions of putatively competent individuals are to be respected, as are their other decisions made in response to provisions of an ethically approved research protocol. Third, the individual's preference *qua* choice should be respected, in short, because she was asked. The investigator or biorepository created the context in which the contributor was asked to make a comparative evaluation and to express a decision. The investigator or biorepository created expectations on the part of the participant that it would be disrespectful not to endeavor to fulfill. If outside of the context of informed consent, the participant were asked—by the investigator, not just in casual conversation with her friends—her preference about being offered IRBRs, this reason for respecting her preference might still apply. The creation of justified

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plex database that accounts for subjects' informed disclosure preferences.").

152. *See, e.g.*, Moore v. Regents of Univ. of Cal., 793 P.2d 479, 483 (Cal. 1990).

expectations through the interaction, not her having and expressing the preference, is ethically critical.

IV. THREE NORMATIVE ARGUMENTS INFORMED BY THE FACTS

In the preceding pages, this inquiry has provided reasons to be at least skeptical and cautious about turning to people's preferences regarding return of IRBRs to motivate, justify, or inform policies to manage IRBRs. In this final section I want to turn from alleged facts about people's preferences to some normative considerations about returning results. The literature in this regard is large and growing, as is this paper.[153] For those reasons, I limit myself to three points.

First, let us begin with interests and well-being, as research regulations concerning human subjects are designed to protect participants' well-being, though not to promote individual interests.[154] Instead, research promotes social interests, adequately constrained by protecting individuals' welfare and respecting persons.[155] I believe one reason that the assessment and incorporation of people's preferences into policies regarding IRBRs has seemed so attractive is that we tend to believe that people's preferences guide us toward what people value, which in turn provides guidance toward at least their own conceptions of their well-being. If only we could rely on peoples' preferences, we would not need to inquire directly, and perhaps paternalistically, into their interests. But, paternalistic understanding of individuals' well-being can be justified in the context of research, even genomic research.[156]

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153. Within this literature I find myself in greatest sympathy with the normative arguments of Laura Beskow, Ellen Wright Clayton, and Pilar Ossorio. *See, e.g.*, Beskow & Smolek, *supra* note 14, at 108–09; Clayton & McGuire, *supra* note 107, at 1–2; 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, 24–25. On empirical points relevant to these normative arguments, I am persuaded by considerations raised by Fiona Miller and her co-authors. *See, e.g.*, F. A. Miller et al., *Duty to Disclose What? Querying the Putative Obligation to Return Research Results to Participants*, 34 J. MED. ETHICS 210, 210–11 (2008).

154. *E.g.*, Franklin G. Miller & Alan Wertheimer, *Facing Up to Paternalism in Research Ethics*, HASTINGS CENTER REP., May–June 2007, at 24, 24 ("The reigning regulatory and ethical frameworks for human research emphasize the *protection* of research subjects.").

155. *See id.* at 28–30.

156. *Id.*

Perhaps even more important in this case, research is a context in which we can justify promoting social interests (e.g., by demanding the comparative effectiveness of health-related—and frequently, publicly funded—interventions and reserving research funds for the pursuit of research) even when this involves limiting individuals' access to what they want.[157] Such limitation seems especially justified when what people want is not clearly in their interests, or is occasioned by an apparent psychological disposition that leads people to want their personal genomic information largely because someone else knows it.[158] Social interest in the progress of research may justify not supplying individual benefit (e.g., information that would actually contribute to an individual's well-being).[159] It may justify granting less weight to individuals' interests in control per se than in their interest in protecting their person or various material interests they have.[160] Eventually, if all goes well, the information that is now the content of genomic research results, aggregate and individual, will inform individuals' clinical care. The topic of returning IRBRs of biorepository research will become an issue of the past, because the reliable and significant results will not only inform clinical care, but also individuals' access to that personal information will be part of a health care infrastructure grounded in science and guided by results of comparative effectiveness research.

Second, two related reasons frequently offered in support of offering IRBRs back to biorepository contributors are respect for persons and reciprocity.[161] Respect for persons demands not treating contributors to research solely as means to an end.[162]

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157. *Id.* at 29 ("Because prospective subjects are rarely in a position to assess either the social or scientific value of a research protocol or the validity of its research methods, IRBs are given that charge in their stead.").

158. *See id.* at 24.

159. Failure to benefit research participants is not the same as harming them. If failure to benefit were to become a prevalent understanding of "harm," then IRBs' assessment of probable harm-to-benefit ratios and the appropriateness of various research designs would need to be revised in myriad contexts.

160. *Id.* at 33 ("There is a tendency to see informed consent as being motivated solely by the value of the agent's autonomy, as contrasted with the agent's welfare or interests. This is a mistake. After all, people want to be in control of their lives not just to protect some abstract value of noninterference or to keep themselves from being treated merely as a means, but also to protect their interests from those who would harm them.").

161. F. A. Miller et al., *supra* note 153, at 210.

162. *Id.*

The duty to respect participants as persons requires respecting their informed refusal of participation and honoring their other choices during informed consent (and throughout the research). It involves treating them with respect, not satisfying their preferences. Failure to offer individualized results does not treat subjects solely as a means to the scientific end of obtaining generalizable data. Further, treating participants with respect may involve recognizing their contributions (where doing so would not violate confidentiality or impose group harms) and providing them with aggregate study results in terms they can understand; it certainly involves interacting with them respectfully.[163]

Giving participants the IRRs they want is advocated as a matter of reciprocity.[164] The results are regarded as a "thank you" gift or compensation for study participation, or a reward for altruism.[165] I disagree with this approach. If study participants and biorepository contributors are to be compensated, that compensation should be given to all of them. Being compensated or thanked for participation should not depend on one's particular genome (giving rise to an IRR/IRBR). If offering a benefit is necessary to compensate, evidence respect, or avoid exploiting subjects, then the benefit should not be of uncertain scientific or personal value; it should not depend on the individuals' social circumstances and personal ability to translate it into something of value (e.g., clinical interventions or positive behavioral change). Out of fairness, the benefit should be of established and of relatively uniform value to all subjects (e.g., money in exchange for inconvenience or a gift certificate for something everyone uses).

A final point about fairness is the third normative consideration I want to raise. Fairness dictates that individual benefit from research participation should not depend on one's genome or other individual characteristics, but should be given to all who contribute. Obviously, the possibility of receiving an IRBR depends partly on one's own genome. It also depends partly on the research questions and procedures pursued, as well as on the other people and genomes accrued into in the biorepository or genomic study, because discovery of patterns of genetic vari-

163. Ossorio, *supra* note 153, at 24.
164. *See id.*
165. *See id.*

ation is critical to discovering genotype-phenotype associations.[166] Currently, a substantial amount of pharmacogenomic research, for example, relies upon the fact that genetic variations associated with different drug responses occur in varying frequencies in different continental ancestry groups.[167] Substantially unequal representation from different continental ancestry groups, inadequate representation from some groups, or the failure to ask research questions relevant to particular groups or individuals with particular patterns of genetic variation can all limit the likelihood of identifying a reliable finding relevant to particular continental ancestry groups. Genetic variations common to particular ancestry groups must be sufficiently well-characterized to ground accurate and clinically meaningful interpretation. Such characterization must be undertaken through initiation of studies. However, to cite a prominent pharmacogenomic example, to date, fewer studies of drug response associated with the CYP2D6 and CYP2C19 genes, which are associated with the metabolism of at least fifty drugs, have been undertaken in African Americans and Hispanics than in Whites and Asians.[168] The potential for such disparities in the likelihood of research participation revealing an individual genomic result of some value suggests that return of IRBRs is not a suitable form of compensation or gratitude for research participation.

CONCLUSION

Factual information is obviously relevant to normative considerations of fairness, what is respectful, what is a suitable "than you" gift, and what contributes to individuals' well-being. As a whole, this inquiry has sought to shift attention away from facts about preferences—especially the incoherent notion of "people's preferences," but also individual's preferences. It

166. *See* Cho, *supra* note 133, at 282.

167. Geography has influenced mating and migration patterns across centuries, with the result that people who have a specific continental ancestry (e.g., Asian or African) exhibit frequencies of genetic variation that differ from those with a different continental ancestry. Members of different ancestry groups exhibit slightly more genetic difference from each other than from other members of the same continental ancestry population. *E.g.*, Morris W. Foster & Richard R. Sharp, *Beyond Race: Towards a Whole-Genome Perspective on Human Populations and Genetic Variations*, 5 NATURE REV. GENETICS 790, *passim* (2004).

168. N. Poolsup et al., *Pharmacogenetics and Psychopharmacotherapy,* 25 J. CLINICAL PHARMACY & THERAPEUTICS 197, 201, 206 (2000).

has instead advocated direct examination of what can improve individuals' health, which social circumstances impede adoption of disease prevention behaviors, and which false beliefs and expectations need to be corrected to enable incorporation of genomic information into clinical care. It has suggested that facts regarding the comparative effectiveness of various interventions inform normative arguments regarding fairness, harm avoidance, and benefit in health and research policies. Facts have important roles to play in policies, though facts about people's preferences do not.