The Informed Cohort Oversight Board: From Values to Architecture

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I. THE CONCEPT OF THE ICOB

Current guidelines for return of research results in genomic studies focus on protecting the participant from harm using criteria including analytic validity, clinical validity,

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actionability, and severity of the outcome.[1] Historically, rules supporting or prohibiting disclosure of individual research results employed such variables.[2] However, the formulation of these rules was based on interpretive projections from the life experience of the rule-formulators and not on rigorously-collected empirical data concerning, for example, the prevalence and degree of harm, let alone data elucidating harm's dependence on other known or unknown variables that might be practically important in refining a practical ethical rule concerning results disclosure.[3] Thus communicating genomic research results has historically been opposed, by some, based on an assumption that therapeutic misconceptions are inevitable, that harm necessarily flows from a misconception and is unpreventable and incurable, and that such harm necessarily outweighs any potential benefit, regardless of how benefit might be conceived or measured.[4]

Such theorization omits a factor now widely accepted in clinical ethics: the personhood of patients and research participants, as reflected in respect for their autonomy and consideration of their own formulations of benefit, harm, and acceptable risk.[5] That one must "protect" research participants from "harm" by imposing on them the *ex cathedra* meanings that researchers or ethicists, without the benefit of empirical data concerning research participants themselves, attach to such terms has seemed to us to be an assumption worth identifying, examining and potentially reconsidering. This is especially necessary, since acceptance of the assumption seems to rest on a consequentialist or utilitarian analysis that is undefended theoretically and unsupported by research data from a well-constructed study of the sort we would demand in other con-

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1. *See*, *e.g.*, 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 CARDIOVASCULAR GENETICS 574, 575–78 (2010).

2. *See, e.g., id.*; Isaac S. Kohane & Patrick L. Taylor, *Multidimensional Results Reporting to Participants in Genomic Studies: Getting It Right* 2 SCI. TRANSLATIONAL MED. 1, 1–2 (2010).

3. *See, e.g.,* Fabsitz et al., *supra* note 1 at 575–58; Kohane & Taylor, *supra* note 2, at 1–2.

4. *See* Kohane & Taylor, *supra* note 2.

5. *See* Mark A. Rothstein, *Tiered Disclosure Options Promote the Autonomy and Well-Being of Research Subjects*, 6 AM. J. BIOETHICS 20, 20–21 (2006).

texts.

For this reason, we, among others, have argued that research should investigate whether the personal meaning of genomic information to participants,[6] participant preferences, and personal perspectives on utility[7] should inform ethical standards for return of research results. We have argued this not as a conclusion but as a hypothesis: entertaining the hypothesis is justified on theoretical grounds, and exploring it requires empirical testing of practically implemented, precisely stated ethical hypotheses. This suggested approach is in line with novel approaches in bioethics, which recognize the dependence of ethical conclusions on empirically verifiable data to the extent such data are made material by ethical theory, including examining the basic terms of traditional ethics in light of actual human potential and aggregate human experience.[8]

With respect to providing research participants with personal genomic data derived from genomic research, our group has embodied this participant-based approach in the "Informed Cohort" model, a novel concept for genomic studies that addresses the issues of collecting genotype and phenotype data, carrying out genomic studies, and returning research results to participants based on their preferences.[9] In an Informed Cohort, each participant provides clinical information and biospecimens when they enroll, and are then given a web-based Personally Controlled Health Record (PCHR).[10] The PCHR allows communication between researchers and participants

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6. *See*, *e.g.*, *id.*; Kohane & Taylor, *supra* note 2; Vardit Ravitsky & Benjamin S. Wilfond, *Disclosing Individual Genetic Results to Research Participants*, 6 AM. J. BIOETHICS 8 (2006).

7. *See* Morris W. Foster, John J. Mulvihill, & Richard R. Sharp, *Evaluating the Utility of Personal Genomic Information*, 11 GENETICS MEDICINE 570 (2009); Scott Grosse et al., *Personal Utility and Genomic Information: Look Before You Leap*, 11 GENETICS MEDICINE 57 (2009); Scott D. Grosse, Lisa Kalman & Muin J. Khoury, *Evaluation of the Validity and Utility of Genetic Testing for Rare Diseases*, in ADVANCES IN EXPERIMENTAL MED. & BIOLOGY: RARE DISEASES EPIDEMOIOLOGY (Manuel Posada De La Paz & Stephen C. Groft ed., v. 686, 2010) 115–31 (2010); Muin Khoury et al., *The Scientific Foundation for Personal Genomics: Recommendations from a National Institutes of Health-Centers for Disease Control and Prevention Multidisciplinary Workshop*, 11 GENETICS MEDICINE 559 (2009).

8. *See* KWAME A. APPIAH, EXPERIMENTS IN ETHICS (2008).

9. Isaac S. Kohane et al., *Reestablishing the Researcher-Patient Compact*, 316 SCI. 836, 836–37 (2007).

10. *Id.* at 837.

without identifying participants to researchers.[11] Through the PCHR participants are able to manage a secure copy of their medical data, update health information, refine phenotypic data, contribute additional biomaterials, and receive messages including general messages to some or all members of the cohort, as well as messages regarding individual research results.[12] This design allows participants to be contacted as necessary by researchers and as desired by each participant.[13]

Selecting and processing complex medical data for the full socioeconomic diversity of participant populations presents ethical, legal, and social challenges, and demands numerous forms of safety nets for the participants, ranging from ethical assessment by parties other than researchers, to structural mechanisms and sensors to detect harm and outreach to mitigate it. Because of the expertise required, and our belief that some degree of integration with researchers themselves is necessary to shape and implement structural safety nets, we have proposed a governing body outside of the Institutional Review Board (IRB), but nonetheless matrixed organizationally with it, to offer guidance regarding when genetic research results should be returned to study participants.[14] Kohane et al. proposed an Informed Cohort Oversight Board (ICOB) as a governance structure essential for the Informed Cohort to ethically return research results to participants while respecting autonomy.[15] The ICOB is envisioned as a body related to the IRB, but including expertise in risk communication and genetic counseling, that deals with what information is worthy of communication, how best to communicate it without confusing or overwhelming participants, and how to help participants choose what knowledge they want to receive and how they want to receive it.[16] In the Informed Cohort, individual research results are "broadcast" to participants based on the "subject's stated categorical preferences for information and the ICOB's study-specific determination about what information can be effectively communicated in

11. *Id.*
12. *Id.*
13. *Id.*
14. *See* Timothy Caulfield et al., *Research Ethics Recommendations for Whole-Genome Research: Consensus Statement*, 6 *PLOS BIOLOGY* 430, 431 (2008); Fabsitz et al., *supra* note 1 at 577; Ravitsky & Wilfond, *supra* note 6.
15. Kohane et al., *supra* note 9, at 836.
16. Id. at 836–37.

a manner sensitive to subjects' health literacy."[17] If "the characteristics, of the patient, genomic or clinical, match the characteristics of the patients described in the broadcast," that patient participant will receive the message.[18] In simplistic terms, ICOB-approved results are returned to participants in accordance with their preferences. The decision-making process for return of individual genomic information is consistent with the "multidimensional results" three-dimensional reporting model incorporating participant preferences, communicability, and the significance of the result suggested in Kohane & Taylor.[19]

Our group at Children's Hospital Boston has implemented the Informed Cohort and ICOB within the framework of a large-scale pediatric genomic study, The Gene Partnership (TGP).[20] TGP is a prospective longitudinal study at Children's Hospital Boston (CHB) designed to collect genetic information on a large number of children who have been phenotyped, facilitating the study of genetic and environmental contributions to childhood health and disease.[21] The term "Gene Partnership" reflects a partnership between researchers and participants.[22] The stakeholder TGP participants are allowed to exercise their autonomy by designating their preferences for what research results to receive on themselves and their children.[23] Key to this process was developing the ICOB, which was created in 2009 to ensure that research results are conveyed in a clear, accurate, and understandable manner, based in the first instance on enabled and educated participant choices, but with due regard for potential harm.[24] In this paper we describe the values, structure, and guidelines for the return of results that were developed by the TGP ICOB over the past two years. We believe this framework is ethical, sustainable, scaleable, and generalizable to large genomic research studies going forward.

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17. *Id.* at 837.

18. *Id.*

19. Kohane & Taylor, *supra* note 2, at 3.

20. *About TGP*, CHILDREN'S HOSP. BOSTON, http://www.genepartnership.org/about-tgp/ (last visited Feb. 10, 2012).

21. Erin D. Harris et al., *The Beliefs, Motivations, and Expectations of Parents Who Have Enrolled Their Children in a Genetic Biorepository*, GENETICS MEDICINE (Jan. 26, 2012), http://www.nature.com/gim/journal/vaop/ncurrent/index.html#16022012.

22. *About TGP*, *supra* note 20.

23. *See* Kohane et al., *supra* note 9, at 837.

24. *History*, CHILDREN'S HOSP. BOSTON, http://www.genepartnership.org/about-tgp/history/ (last visited Feb. 12, 2012).

A. THE ICOB-CREATION PROCESS

Policies arise from processes, not fully fledged or like Athena from the head of Zeus. We believe that honesty and respect for the opinions of others—especially where we are gently questioning the abstract policy-creation of non-empirically-based disclosure policies—requires that we frankly disclose what, in science papers, would be called our "methods." The ICOB's primary role in TGP, as we have seen it, is, through a combination of infrastructure demands, general ethical policies, and study-specific judgments, to act optimally to ascertain whether individual research results can be conveyed in a clear, accurate and understandable manner based primarily on enabled and educated participant choices, but with due regard for potential harm.[25] If results can be conveyed in such a way it is the ICOB's role to recommend such communication in a form that maximizes communicability in accordance with preferences; and, if results cannot be communicated, to recommend against communication.[26] The latter might occur, for example, because of a limitation on participant preferences, predicted and unremediable harm or the impossibility of appropriate communicability. It could also occur in the case of some pediatric results for adult-onset diseases, if an ethical conclusion sustainable without reference to empirical particulars is deemed to bar it on the ground that respect for the eventual autonomy of a child when she becomes adult is deemed to trump the parent's right to exercise the child's autonomy during the child's minority.

From the beginning, it was clear that implementing a vision of optimizing ethical reporting of communicable results could not be reduced to editing messages any more than the role of an institutional review board (IRB) can be reduced to idiosyncratic revisions to research informed consent documents. To perform the function responsibly, the ICOB had to consider and advise on the infrastructural and decisional components of TGP that would ultimately affect participant experience, from the nature of studies selected and results anticipated to the characteristics of populations to be enrolled. It had to resolve tensions between the desire to minimize individual harm by

25. *See* Kohane et al., *supra* note 9, at 837, Kohane & Taylor, *supra* note 2, at 2–4.

26. *Id.*

maximizing individualized judgments and practical and ethical concerns arising from the fact that ideal clinical and information technology supports are themselves co-evolving. It had to address the probability that, within TGP, the primary results eligible for potential disclosure would not be known clinical variants incidentally discovered, but new and uncertain discoveries—novel variants, or novel understandings. The ICOB also had to identify and address diverse sources of uncertainty: an ethically divided field; IRBs skeptical of the value and communicability of genetic information or genetic research as a whole; uncertainty about how to assess harm and benefit in the context of our complete commitment to participants as people who should be aided to make beneficial choices they were happy they made; the level, diversity and effects of health literacy; evolving scientific interpretive standards for genetic information; and, indeed, the very organizational placement and functioning of an ICOB.

As reflected in the gradual, step-by-step generation of policy documents, the trajectory of the ICOB is most succinctly described as a path from values to architecture, through respectful and inclusive deliberation. The architecture is best described as a pyramid: on a foundation of values and principles of organizational placement is built an infrastructural policy which requires, for example, the TGP to establish mechanisms for educating participants concerning genetics and for educating the ICOB concerning participant cohorts based on surveys or other instruments; mechanisms of rapid impact assessment following messaging of validated results according to putative preferences; rules for the ICOB to choose among various sorts of written and oral messaging appropriate to results and sub-categorization of participants; and exceptions and "circuit-breakers" for situations of foreseeable harm. Essential to establishing such policies was close communication with geneticists, informaticians, clinicians, ethicists, independent thinkers brought in as advisers, and participants.[27] The ICOB deliberately invited the Director of Clinical Research Compliance (chief of the IRB staff) to join the committee, and always included the faculty and professional staff of TGP itself, to keep it grounded and well-informed, while deliberating independently.

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27. *For Experts*, THE GENE PARTNERSHIP, http://www.genepartnership.org/about-tgp/for-experts/ (last visited Feb. 13, 2012).

By intention, members of the ICOB have diverse views about how, when, and whether to communicate individual genetic results. Some, for example, disfavor results returned based on skepticism about whether preferences are actually durable, known by, and ascertainable from participants. Others have heightened concerns about therapeutic misconception.[28] Still others, including one of the authors of this paper, favor broad disclosure of analytically valid information regardless of whether its clinical significance is, in some views, certain.[29] However, they believe that disclosure must be coupled (except in rare cases) with disclosure of the radical uncertainty of genetic results generally when they stand alone without definitive analysis of the epigenetic, environmental, and behavioral co-factors in gene expression, and without the unknown effect of other genes that weak associations may reflect.[30]

Crucially, we have found these differences of perspective to be fruitful and productive *precisely because* we have agreed to set aside our theoretical, personal pet theories-as-certainties in favor of a mutual commitment by ICOB members, and to use our perspectives to fashion, test, and improve the optimal method and infrastructure as a basis for fair empirical testing and further conceptual scientific and ethical development and revision by ourselves and by others. In abandoning the desire to proclaim, enshrine, and defend indefeasible ethical certainties, we modeled our efforts on the more modest goal, daily pursued by both scientists and lawyers, of offering our work as a building block to the community of knowledge, no more and no less. Importantly, TGP is not merely a partnership between researchers and participants; it is a partnership between scientists, ethicists, scientific programs, and research ethics committees that is intended to benefit of participants by being informationally transparent and decisionally independent, and by building and improving an ethically responsive mechanism for results reporting. While this has some of the disadvantages of building and improving an airplane midflight, it also has some of the advantages: responsiveness, sensitivity, avoiding being marooned and ground-bound in a foggy airport, and an

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28. Kohane & Taylor, *supra* note 2, at 2; Leslie A. Meltzer, *Undesirable Implications of Disclosing Individual Genetic Results to Research Participants*, 6 AM. J. BIOETHICS 28 (2006).

29. *Kohane & Taylor, supra* note 2.

30. *Id.*

engineering dedication to making sure the plane and passengers do not crash.

Having integrated education with policy development, the ICOB is currently in its last phase: inducing consensus "hypotheses" for results return, based on close examination of hard vignettes, involving starkly competing ethical and practical concerns, within the multidimensional space described in Kohane & Taylor.[31] Our objective is not to arrive at the abstractly "right" principle; it is to arrive at the most likely and beneficial hypotheses and subject them to testing.

In the future, the ICOB will be aided by three new inputs, each implementing the theory that "this is a system that will need to learn, as researchers and participants both learn from it and create it together."[32] First, the TGP website will include draft policy statements for participant comment, as well as information about the ICOB and its role.[33] Second, the ICOB will receive actual feedback on the consistency of its recommendations with participant preferences and resulting impact.[34] We believe this is a thoroughly novel approach for an ethics committee: neither IRBs nor conflict of interest committees, for example, learn of the correctness or consequences of their decisions. Third, the ICOB will be reviewed by a special advisory committee, whose function will be much like blue ribbon scientific program review committees.

B. TRANSLATING VALUES AND GUIDING PRINCIPLES

The ICOB is charged with evolving oversight that maximizes respect for participant preferences with respect to the scope and significance of results as a key variable in communication and is consistent with sound judgments about communicability of messages to recipients. To do so the ICOB must adequately identify and assess factors affecting communicability, from message substance to messaging methods and recipient characteristics. In an iterative manner the ICOB evaluates its own and TGP's judgments and modifies them based on experience and literature, identifying factors affecting the risks and benefits of TGP and the Informed Cohort model, as variously implemented. The ICOB strives for transparency, promotes col-

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31. *Id.*
32. *Id.* at 3.
33. *Id.* at 3–4.
34. *Id.*

laborative engagement with research participants and broader inclusiveness in policy-making, and fosters public engagement in genome-wide association studies—all are key to the ICOB's success.

C. ICOB STRUCTURE AND OVERSIGHT

The ICOB includes within its membership individuals with professional training or expertise in one or more of the following areas: bioethics, genetics, medicine, law, and interpretation and communication of probabilistic genetic results.[35] One of the ICOB members functions as chair. The ICOB shall also include at least one professional genetic counselor.[36] Additionally, the ICOB will include individuals who, by personal experience or profession, are able to represent or anticipate patient or participant perspectives.[37] It may draw on the expertise of consultants to provide specialized expertise in diseases or conditions, statistics, communications, or other matters as the ICOB deems necessary after a discussion and vote. ICOB decision-making will be by consensus after reasonable discussion where possible, and failing that, by formal vote.

In order to promote transparency and provide for input, an ICOB Advisory Group will be convened whose members are drawn from policy or program staff of the National Institutes of Health (NIH), foundations and advocates for gene-specific conditions, and the professions represented on the ICOB. The ICOB Advisory Group will review and provide feedback on proposed policies and pivotal decisions. Additionally, a web-based method of posting public comments regarding significant policy questions and proposed decisions will be developed in conjunction with TGP.

The ICOB has authority to make non-binding recommendations to TGP or its host hospital, Children's Hospital Boston (CHB). The ICOB is independent from TGP and from the CHB IRB. TGP members are included in its meetings and discus-

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35. *See Informed Cohort*, THE GENE PARTNERSHIP, http://www.genepartnership.org/about-tgp/informed-cohort/, (last visited Feb. 12, 2012) ("[W]e have developed . . . an Informed Cohort Oversight Board (ICOB) made up of ethicists, scientists, physicians, genetic counselors, and participant advocates to ensure safety and ethics throughout the partnership process").

36. *Id.*

37. *See id.* (the ICOB will include "participant advocates").

sions except in extraordinary circumstances where it convenes to discuss a matter of special concern where an inclusive approach would necessarily constrain discussion. The ICOB is also independent of the CHB IRB. The ICOB reports its recommendations and conclusions to the IRB if requested by the IRB or TGP, or at its own discretion. It is specifically recognized that by law the IRB is independent and authoritative on certain matters within the scope of ICOB functions.[38] However, the ICOB is uniquely placed to formulate sound and influential recommendations, and it is anticipated that TGP will be responsive to ICOB recommendations. The ICOB also retains the right to communicate concerns to the IRB, and the IRB is expected to pay serious attention to ICOB concerns, particularly with respect to participant harm or benefit. The ICOB is self-obligated over time to establish and modify policies addressing messaging, the form and content of information required from TGP and participating studies in order to perform ICOB functions, and evaluation of messaging and TGP vision in practice.

D. THE ICOB POLICY ON RETURN OF INDIVIDUAL RESEARCH RESULTS

Formulating optimal methods for informing participants in genetic and genomic research about individual research results consistent with the Informed Cohort proposal, if done well, upholds the values of reciprocity, partnership, joint interest in knowledge discovery that it seeks to translate into practice, participant welfare, and the potential motivating effect it may have on enrollment by subsequent participants. Historically, the issue of returning research results has raised numerous questions, many of which are focused on avoiding harm.[39] However, this encompasses a range of concerns, including the validity of the results and their meaning and communicability for any purpose in the context of studies of genes and conditions of unknown or partially known significance.[40] Additionally, uncer-

38. 45 C.F.R. § 46.109 (2010).

39. *See* Ebony B. Bookman et al., *Reporting Genetic Results in Research Studies: Summary and Recommendations of an NHLBI Working Group*, 140A AM. J. OF MED. GENETICS 1033, 1034 (2006) ("Psychological and social harm, as well as financial costs and risks, may result from providing information with significant implications for the health of the individual and his/her family members.").

40. *See* Ravitsky & Wilfond, *supra* note 6, at 11 ("An appropriate threshold of clinical validity is necessary to establish clinical utility because disclosure of results that have very uncertain meaning has little justification. Lim-

tainty remains about the ability of research participants to understand and integrate research-related information, particularly if it is conditional and is delivered apart from participants' clinical care history and providers.[41] There are also contextual differences from clinical genetic testing, in which patients are already known or suspected to have a given condition are tested following counseling, and often receive their results through personalized attention by highly trained professional genetic counselors or geneticists.[42] Thus, creating an optimal messaging policy necessarily implies creating mechanisms to address these concerns in an evidence-based way.

The desire to provide such information in accordance with participant personal preferences has added additional dimensions to the problem since the reliability and precision of stated preferences are open to question. It is not clear that participants, let alone researchers, really know the 'results' participants seek since participants tend to define results in terms of utility or pertinence, and there is significant evidence that stated choices and actual preferences do not necessarily match.[43] The skepticism over participants truly understanding the implications of their choice of which research results to receive suggests to some that it is unrealistic to incorporate participant preferences in return of research results and that doing so may in fact lead to harm. Alternatively, as with other aspects of medicine, we may resolve questions of benefit, up to a point, by acknowledging that it is the participant who is in the best position to assess personal benefit, and that providing information in accordance with participants' autonomous choices is therefore beneficial.[44] As required by law, the ICOB chose

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ited clinical validity can also result in unnecessary procedures or anxiety.").

41. *See* Conrad V. Fernandez, *The Return of Research Results to Participants: An Ongoing Debate Modeled in Cancer Research*, 8 HARV. HEALTH POL'Y REV. 16, 25 (2007) (recommending that results that are returned to participants be "understandable and accessible to the lay public").

42. *See How Does Genetic Testing in a Research Setting Differ From Clinical Genetic Testing?*, GENETICS HOME REFERENCE (Feb. 6, 2012), http://ghr.nlm.nih.gov/handbook/testing/researchtesting (highlighting the key differences between genetic testing in a research setting versus a clinical setting).

43. *See*, *e.g.*, Grosse, *supra* note 7, at 121 ("New metrics are needed to assess personal utility, including quantitative methods to assess people's preferences over various aspects of the genetic counseling and testing processes and both medical and non-medical outcomes.").

44. *See* Fabsitz et al., *supra* note 1, at 577–78 (recommending that inves-

to apply the same principle to parents' choices for their children, recognizing that the outside point at which the principle fails is marked by obligations to prevent abuse and neglect.[45]

The proper parental role is further obscured by the existence of bioethics literature that contrasts parents' involvement of their children in research with parents' clinical choices. Questions have been raised about the ethics of parental decision-making resulting in a life-long impact for their child, when such decisions could have been delayed until the child reached adulthood.[46] Such decisions may interfere with the child's "future autonomy."[47] Further complicating matters, the relevance of personal preferences for receiving negative information to resilience against negative information is also unknown. If there was a direct relationship, then there would be reasons for soliciting and understanding the preferences of children that go beyond the ethical and legal supports for minor assent in research, and minor consultation—or in narrow circumstances, consent—for clinical care. In that event, researchers could minimize harm by disclosing accordingly. The pediatric context raises additional issues involving who consents and who receives intended genetic results. These are matters for IRB resolution, not ICOB recommendation, but they directly affect the ICOB's key charge to help engineer optimal disclosure processes, create testable guidelines, and oversee and improve messaging based on experience.

The very concepts of harm and benefit are poorly defined to date. The genetic counseling profession has no established outcome measures, nor measures comparing personal counseling to alternative methods, let alone methods that allow one to control for whether genetic results are favorable or unfavorable. Established practice for delivering results is an intuitive art in which integration of certain professional values, including sensitivity in face-to-face communications, is the norm. Whether it is actually the most effective possible form of communication—

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tigators may choose to return genetic research results to participants if they indicate in the informed consent process their preference to receive such results).

45. 46 C.F.R. § 46.408 (2010).

46. *See* Kyle Bertram Brothers, *Biobanking in Pediatrics: The Human Nonsubjects Approach*, 8 PERSONALIZED MED. 71, 77 (2011) ("[G]enetic testing in children to identify risk for an illness that does not develop until adulthood is controversial, since no medical harm will result from delaying testing until the child can decide about testing when he or she reaches adulthood.").

47. *Id.*

let alone the only effective form—for all kinds of cases is unknown.

The landscape is complex, and the analytic tools to manage some issues are in their infancy. The development of optimal principles and approaches to messaging in the context of so much uncertainty is therefore a process of discovery and refinement. TGP is an engineering work-in-progress, and its leaders, the IRB, and investigators conducting studies under its aegis, will need both immediate and long-term results about its impact to use those results for process improvement. TGP must be able to reassure itself and others, such as the IRB, that the mode and content of results communication is accurate and consistent with participant preferences and generally limited to emotional harms that a participant, on balance, has accepted as the price of desired knowledge. This means that an ethical messaging policy inevitably has infrastructural implications.

E. RETURN OF INDIVIDUAL RESEARCH RESULTS–THE REQUIRED INFRASTRUCTURE

Genetic associations are no stronger than the studies that yield them, and studies must be adequately powered and structured to support the associations they purportedly uncover. TGP needs to be assured, through the application process for proposed studies using TGP, of the quality of the study to yield anticipated findings. The results of that assurance and the nature of the study methods should be available to the ICOB in reviewing a proposed disclosure to participants. While it is not presently the standard to control the numerous variables that could affect gene expression, and thus the reported gene associations ranging from epigenetic to environmental factors, TGP should encourage studies that investigate these variables. Scientific reasons aside, understanding these factors may be as valuable to participants as whether a condition is medically treatable. Simple numerical probabilities that compare an individual's fate to a sampled population, without considering factors that could affect gene expression, may cloak ignorance about causation with an appearance of definite knowledge and inevitable randomness.

Identifying participant preferences, capabilities, and vulnerabilities will require new approaches to understanding participants that are better than genetic research has previously required. In an ideal world, investigators should be able to

characterize the health literacy, motivations, care experience, and vulnerabilities of the populations they seek to enroll. TGP has conducted general surveys and focus groups with parents of developmentally disabled children[48] that proved extremely useful, suggesting that surveys, focus groups, or some other effective mechanism for understanding the range of participant preferences, goals, and other characteristics should become a foundation for subsequent TGP studies as a tool to understand what parents who seek research results seek and what they fear most.

Of course, not all potential participants are the same. Ultimately, whether it is appropriate to send an electronic message versus direct oral contact with a participant may depend upon specific factors evident in the family's or child's history of clinical care and may be associated with additional resilience. Such information may help inform whether and how to message specific families. Furthermore, a comprehensive and reliable process for routinely obtaining and considering such information would provide a basis for an IRB to conclude that TGP had appropriately linked the methods of results disclosure with context-dependent potential harm. Without being prescriptive, more broadly pursuing the various methods by which electronic medical information could be available in useable or flagged form to investigators, TGP and the ICOB could distinguish categories and signals for distinct harm requiring distinct communication approaches. Currently, the pace of electronic records becoming accessible for use is outside the control of TGP. Other means to explore may include special inquiries through the PCHR or special inclusion or exclusion criteria that, in effect, identify those who may be expected to have special vulnerability to possible information anticipated from a study. Such data are too pertinent to results disclosure and its communicability to ignore, even if the infrastructure to extract it and interpret it is in development. Investigators proposing TGP studies will require a factual basis for assuring the IRB that risks to participants have been minimized; they will only be able to do so if TGP has assumed a more systematic responsibility of managing and understanding these risks.

Collecting and integrating impact information is crucial to the success of the ICOB and return of results. After returning any research result, participant written feedback should be

48. Harris et al., *supra* note 21, at 2.

immediately solicited, perhaps through an automated PCHR email process directed to the participant's understanding of the results and questions or concerns of any type. The process should also identify families in need of direct interventions given their responses, which may necessitate breaking the anonymity. Feedback data should be presented to the ICOB for oversight and quality improvement purposes. It will be important to understand whether a participant is unhappy solely because of the content but does not regret the message, its method, or seeking it, and whether the participant believes her or his preferences were misread. It is also important to assess whether additional participant questions should have been anticipated and addressed in a message and whether the message was mis-categorized with respect to form of delivery. Clusters of negative impact should trigger immediate review and action. In that case, the ICOB will work with TGP on methods of direct inquiry, including those participants who were, and were not, negatively affected.

The ICOB should have a program for periodic self-evaluation. Evaluating message impact is important and cannot be done thoroughly without evaluating the means by which message decision-making is made. Tools to determine the consistency of messages for given categories, if they address only genetic associations, will be useful for what they teach about the appropriateness of given categories. If the tools also address participant data, they will teach about the appropriateness of a message where impact data will be of primary importance. Rectifying messaging mistakes may require better data, better assessment algorithms, changes in infrastructure, and changes in enrollment and communication. The ICOB will bring any concerns and recommendations concerning human subject protections or the clinical research process for a study, such as the participant's misunderstanding of an informed consent document, to the attention of TGP and the IRB.

II. RETURN OF INDIVIDUAL RESEARCH RESULTS – PRINCIPLES

A. ACCURACY IN CONTEXT

Genetic associations must be communicated in context and be appropriately conditional. Meaning, rather than presenting an abstract association or probability, the association will be

presented in the context of the methods of the study that produced it, any corroborative studies, consistency or inconsistency with other studies, and its limitations (e.g., study basis, available family genetic information, degree of peer reviewed confirmation, possible influence of other genes, degree to which environmental influences are identified, etc.).

B. A PROGRAM OF EDUCATION

CHB's web-based program for parents on pediatric research shows that well-executed educational materials can enable parents to understand many complex issues, and therefore make more informed and satisfactory choices when considering participation in research. Two such programs should be created by, and for, TGP. The first should be used during enrollment and specifically focus on TGP and issues involved in receiving individual research results, including how to approach making key choices—from the choice to enroll to choosing the sorts of results desired. The second should always be available to enrollees on a TGP web site, should be linked to each message, and should explain how to interpret the results they receive. Substantive updates about research results overall, new forms of research, and the status of particular studies should also be communicated to the general participant population. But most important is teaching both the basis and limitations of genetic interpretation.

C. SHARED RESPONSIBILITY FOR PROCESS AND RESULTS:

The investigator: Potentially reportable content should originate with the investigator, who will present a detailed description of the research result to TGP, explaining its basis and including a judgment of its significance to a participant or a subset of participants. The investigator is expected to provide supporting evidence for the reported finding, including: a) a clear description of phenotypic effect and personal impact of finding; b) the study design, methods, and analysis; c) the strength of the association and degree to which condition emergence depends upon other genetic, environmental, or other modifying factors; d) the strength of the evidence for association in light of peer-reviewed literature; e) numerical risk estimate(s); and f) references to scientific publications and resources relevant to the finding. The investigator may also propose a draft message but is not required to.

TGP: Investigator-reported findings will be evaluated by

TGP and used as the basis for the proposed message. In a written report to the ICOB, TGP should communicate its agreement or disagreement with each of the elements reported by the investigator, and also address the: a) degree of risk, b) certainty of the findings, c) known impact on persons affected and any variability in such impacts, and d) specific actionability (including the form, availability, and effectiveness of preventive and/or therapeutic methods). The TGP report should also propose classifications, as described below, and draft messages consistent with the classifications. TGP draft messages should be consistent with any applicable ICOB policies and with identifying information about the participants that is pertinent to preferences and vulnerabilities gathered from data provided from, or about, participants through the research-associated PCHR, surveys, focus groups, and other sources available. The proposed message or messages should be accompanied by educational or other materials designed to ensure that the message will be understood by the intended recipients.

ICOB: The ICOB should evaluate the recommendation and concur or disagree, stating its reasons for doing so in writing or in the minutes and communicating accordingly with TGP. The ICOB may also approve messages conditioned on modifications to proposed messages.

D. PROMPT REVIEW OF PARTICIPANT FEEDBACK

Feedback should be collected by TGP and concerns should be immediately conveyed to ICOB members and the investigator. The ICOB may recommend certain steps to the investigator and TGP, and may withdraw or modify approval previously given. It remains the investigators' primary responsibility, consistent with applicable regulations and IRB directives, to take appropriate action to address participant harms. The role of the ICOB shall not dilute that responsibility. The ICOB shall communicate to the IRB on whatever issues the IRB designates.

E. MESSAGE CATEGORIES

Until new categories are created through experience, messages should be categorized at each stage (by the investigator, TGP, and the ICOB) as follows: 1) In the case of messages of extraordinary importance, the results will be provided regardless of the participants' stated preferences. This requires that the participants be proactively identified, and that genetic

counselors or clinicians reach out to them regardless of participant preferences. 2) Most messages are expected to be congruent with preferences, in which case they are returned in accordance with the participants' preferences. 3) There may be cases in which participants' preferences are followed but a cautionary note is sent to the participant asking "are you sure" with some context to enable participants to make a situation-specific choice.

Different forms of communication may be required depending on the message. For some messages, personal oral communication of results will be deemed unnecessary and an appropriate written message will be adequate. On the other hand, there will be messages in which personal oral communication of results is always necessary for first disclosure, and the need for personal oral communication may depend on participant characteristics. For all written disclosures, personal oral communication with genetic counseling must be available on request following the disclosure.

III. ICOB GUIDELINES FOR RETURN OF RESULTS

The guiding principles for the ICOB in the disclosure of individual research results to TGP participants are: 1) to protect participants from disclosure of results that may lead to harms, and 2) to return results that are consistent with the participants' preferences. Potential harms in return of results include returning results that are not scientifically "sound" (i.e., lack of analytic validity) or are not clinically "meaningful" (i.e., lack of clinical validity), loss of the future autonomy of a child (vulnerable population), discoveries that pose imminent risks of severe harm to families that can be prevented by nondisclosure (e.g., mis-identified paternity), lack of communicability, and returning results that are inconsistent with participant preferences.

The ICOB has identified strategies to return individual research results that reduce or eliminate these harms. Careful advance review of studies proposed for inclusion in TGP is especially important to guarantee the validity and precision of potential results. A commitment to analytic validity requires that studies are performed in a CLIA-certified laboratory before returned to participants. The ICOB will specifically consider the mode of communication, including considering the role of genetic counselors throughout the entire return of results process. The contextualization of results will be important (e.g., limitations on conclusions given lack of knowledge about envi-

ronmental influences). A process of immediate follow-up and querying, combined with an offer of genetic counselor involvement for further questions or concerns and maintaining a philosophy of working incrementally and iteratively in response to feedback, will be critical to assure that no harm is done, and, if there is harm, to detect it.

The issue of the child's future autonomy deserves special consideration, in particular as TGP is a study of childhood health and disease. Capable adult participants make preference choices for themselves, but parents make preference choices for their children. However, as children grow towards being fully independent at eighteen years of age, this developing autonomy must be considered. To this end, the ICOB and TGP have adopted the policy that capable adolescent participants and their parents make preference choices for children thirteen to eighteen years of age. But what if the parental and adolescent preference choices are not congruent? In these cases the adolescent participants' disclosure choices trump parental choices, thus acknowledging the adolescent's right to his or her future autonomy. It should be noted that there are exceptions to adhering strictly to parent and/or adolescent preferences. Discoveries that implicate the child's future "sphere of privacy" life planning (adult onset conditions that are not treatable, nonmedical traits, etc.), and discoveries that implicate the child's future reproductive risks, are not disclosed until the child participant is eighteen years of age (or is an emancipated minor in the case of reproductive risks) and only if the participant chooses disclosure.

Using these principles, individual research results must be analytically valid and meet a threshold of clinical validity for return. Individual research results that are not analytically or clinically valid—as determined by a Scientific Review Group assessment—will not count as "discoveries" which TGP participants can elect to learn about themselves. Individual research results must be communicable—able to be contextualized in adequate education and counseling. Results that are not communicable to patients in a clear way will not count as "discoveries" which TGP participants can elect to learn about themselves based on a genetic counseling assessment.

There may be times when participant preferences are overridden. Although this situation is likely to be rare, some consideration must be taken for this possibility. Discoveries that

predict imminent risks of severe harm that can only be *prevented by disclosure* (juvenile leukemia) may be disclosed regardless of participant preferences. If adult participants decline disclosure of discoveries that predict risks of preventable harm to children, the discoveries may be disclosed to third parties (treating physicians). On the flip side, discoveries that pose imminent risks of severe harm to families that can be *prevented by nondisclosure* (e.g., mis-identified paternity) may *not* be disclosed, regardless of participant preferences. Finally, discoveries that pose risks of harm may be disclosed to some of those families implicated, but not others, and only to some family members (parents/child/spouse), but not others, depending on the nature of the discovery and what screening metrics of "resilience" or "vulnerability" are available.

CONCLUSION

In daily life, we learn that there is often more than one potential "right" answer. What is "right" may depend upon known or unknown factors, not simply because utilities depend on circumstances, but because the genuine applicability of nonconsequential ethical theories will depend upon practical realities. Just so, we argue, when it comes to considerations of the harms and benefits that come from disclosing research results. Just so also when one argues that the burdens of disclosure will be unmanageable or that therapeutic misconceptions are inevitable and outweigh any possible benefit. Such assertions necessarily depend upon unstated assumptions that these challenges are invariable, change is impossible, and we live in, if not the best of all possible worlds, one of fixed and necessary limitations that foreclose any alternative universe. In offering a model of ICOB policies and processes, we do not claim that we have offered the only "right" ones. Instead, we claim only that limiting assumptions calls out for identification and testing; that testable ethical hypotheses—beginning with classical ethical thinking but not ending there—can be formulated, and that formulating and testing such hypotheses about what is right or wrong with respect to individual results disclosure reflects devotion to the personhood of research participants, translating values into testable behaviors.

The ICOB is a governance mechanism, and a particularly influential one in part because of, not despite, its communicative integration with scientists, the IRB, and research partici-

pants who are, through its means, empowered to speak for themselves about preferences, benefits, and harm. Governance over return of individual research results is complex with a multitude of ethical, legal, and social challenges to face. Over a two-year period, the ICOB for TGP has wrestled with many of these challenges and derived a framework from which to address the challenges. As individual research results are generated in TGP, the framework will be tested and modified, as there is no better test than putting the framework into practice.