Genetics inMedicine | SPECIAL ARTICLE

A closer look revisited: are we subjects or are we donors?

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The author offers personal reflections on the implications of the article "Managing Incidental Findings & Research Results in Genomic Research Involving Biobanks & Archived Datasets" in terms of how the article addresses serious knowledge disparities and differing expectations between participants and researchers.

Genet Med 2012:14(4):458–460

Key Words: biobanking; incidental findings; incidental research results; MeSH genetic testing; patient participant; physician–patient relations; physician's role; therapeutic misconception

I was diagnosed with breast cancer in 1992, 1 month shy of my 32nd birthday. Hallmarks of my cancer—early, aggressive, and multifocal—hinted at the cancer's familial nature, and I joined a long line of family members who had confronted their own breast, ovarian, pancreatic, and colon cancers—not to mention a few outliers such as lymphoma and parotid cancer. Two years after I was diagnosed, the *BRCA1* mutation was discovered. By that time my two sisters and mother and I had been enrolled in various linkage analyses and research studies designed to surface our family's risk in hopes that this information would shed light on possible interventions or increased surveillance that would help us survive. Three years into the most promising of these—a university study testing for the *BRCA1* gene mutation—our results remained "inconclusive." During that 3-year period, communication between the principal investigator and our family had been practically nonexistent, and on those occasions when it did occur, it was almost exclusively at our behest. We received no regular status updates and, when we called or wrote to learn of any developments, our inquiries were met with annoyance, treated as an imposition—as though, once we relinquished our blood to these researchers, we were entitled to lay no further claim upon it or what it might divulge about our particular genetic predispositions. At the end of that 3-year period, my two sisters, desperate to avoid meeting my fate and no longer willing to wait for results to come out of that particular study, underwent prophylactic mastectomies. We ultimately discovered neither of them possessed the *BRCA1* mutation. But the damage was done. My sisters' breasts were gone, and so was our family's faith in the willingness and ability of the Medical Establishment, writ large, to advocate for us-while nevertheless remaining willing and able to use our blood and tissue samples to further their own research ends. Ours was a case in which some sort of guidance around "return of results" would have been most helpful.

The disconnect between our expectations and the researchers' understanding of their obligations was, at its root, an illustration of the phenomenon known as therapeutic misconception: we expected our participation in the research to deliver actionable results specifically to us, whereas the principal investigators saw our family's contribution as only one set of data points among many. Informed consent materials failed (can they ever entirely succeed?) to unequivocally establish what responsibilities and expectations belonged to whom, exacerbating the mutual lack of understanding of the other's perspective. I remain unconvinced that any explanation or justification on the researchers' part would have disabused us of the notion that we "would get something back" in return for our participation. But we did not get anything back—just the sense that we were part of a machine that might ultimately churn out some useful information for someone, somewhere, but that cared little for us or our collective fate. Worse than the frustration and bitterness that resulted was a profound sense of betrayal that opened like a chasm between us and those we had viewed, rightly or wrongly, as guardians of our health. Also painful was the realization, over the ensuing years, that we often knew much more about our particular genetic situation and its impact than did most of our health-care providers—further eroding our confidence in what Paul Starr once aptly called the "sovereign profession" of American medicine.[1]

My experience is that this complex world of genetic and genomic research, where torrents of information have meaning that may or may not be established or widely accepted and that rotates on an axis of incomplete public policies and regulation, is not susceptible to easy, linear solutions—no matter how thoroughly researched or meticulously others' concerns have been anticipated and preemptively addressed. Out of this experience arise many misgivings over the ambitious and carefully considered but also narrowly scoped and perilously myopic Managing Incidental Findings & Research Results in Genomic Research Involving Biobanks & Archived Datasets[2]. I support the paper's central tenet that donors are entitled to know (if they wish to) of research results that may impact their medical decision-making;

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Submitted 01 September 2011; accepted 10 January 2012; advance online publication 23 February 2012. doi:10.1038/gim.2012.6

however, I have fundamental concerns about the paper's underlying assumptions and about the way in which the paper suggests this knowledge transfer should proceed.

My first concern has to do with the authorship of the guidelines: not the authors themselves, but rather their composition as a group. Of the 26 authors, there are only four physicians and just two genetic counselors. There is only one person who could be considered a patient or family advocate. Only one paragraph in the paper mentions, almost in passing, studies of how donors may feel about the return of results and what their expectations might entail. The voice of the research participant, individually or in the aggregate, is inadequately represented. Given that the donor population represents fully one-half of the interaction(s) that necessitate these guidelines to begin with, it is disconcerting that the paper fails to acknowledge this essential disequilibrium.

Equally disturbing is what this particular omission implies for the future of American medicine. Although affinity groups, social and professional networks, and even entire countries are democratizing and flattening all around us in ways never before seen, is American medicine destined to remain "sovereign"—and are donors (the cogs in its machine) doomed to remain its vassals? The paper leans in that direction by not making the case for a delivery model that makes possible an information or data "pull" rather than focusing solely on biobanks' responsibility to "push" it. A more distributive access model could become normative, generating greater inclusivity than what the Managing schema prescribes, by giving donors a mechanism for tracking the use of their own blood and tissue contributions. When interesting results surface, e-mail communication or newsletters could draw attention to them, giving participants the opportunity to learn more should they so choose. Greater inclusivity would mean donors, their physicians and genetic counselors, and researchers could all come together with this important information at the center, making it more likely that the space they share, however fleetingly, could fill with learning and relationship.

By underemphasizing the important (although, some have asserted, still developing) role of the physician and the long-established expertise of genetic counselors in the delicate task of delivering potentially life-changing information, the paper gives the impression that its authors consider it more important for primary researchers and biobanks to fulfill a contractual duty, however perfunctory, than for them to enter into a covenantal relationship with the donor. I do not disagree that fulfillment of donors' right to know about incidental findings and individual research results that affect them must and should occur; I simply think this approach falls short. Suggesting that donors seek additional help and guidance from physicians or genetic counselors on the assumption they will do so is shortsighted and does not take into account the realities of the situation: there is evidence that many physicians still do not possess sufficient understanding of the implications of genetic tests. A recent Lancet editorial states, "A 2009 survey of more than 10,000 US physicians by the American Medical Association showed that only 26% had any type of education in the use of genetic testing to guide treatment decisions (and) only 10% felt they had the necessary training and knowledge to put pharmacogenetic testing to good use when treating patients."[3] If a donor seeks the help of a genetic counselor, that help can be hard to find. "Reimbursement for genetic counselors is low and often not reimbursed commensurate with the amount of time it takes,"[4] creating a disincentive for oncologists to have a genetic counselor in their practice because they cannot generate enough income to justify their salaries. (I once had a breast surgeon tell me he would never introduce genetic testing into his practice because "there wasn't any money in it.") When my family was trying to find a way through a morass of confusing new words and concepts, struggling to decipher what they could possibly mean for our survival, we felt very much alone. Often, we found ourselves in the unusual predicament of knowing more than our physicians but less than the remote and anonymous researchers who were busy poring over our cells at some laboratory workbench. This led to a painful communication gap that opened not only between us and these important others, but also among these important others themselves, whose work—we felt—was to advocate for us and our continued health, either directly (by communication with us) or indirectly (by communicating with our health-care providers). I fear this communication gap is far larger and far deeper than the paper's authors anticipate.

Another of my concerns has to do with the tone of the guidelines. In an authoritative and definitive manner, the paper places unwarranted confidence in the ability of primary researchers and biobanks to act as custodians of the innumerable evaluative and administrative tasks involved in making sure "actionable" test results (the word "actionable" is problematic; more in the following) are delivered back to donors. But the fact is that there are thousands of biobanks, most of which are not part of any national or institutional laboratory system.[5] The paper recommends the formation of a "central advisory body" to advise on the roster of results to consider for return. Attempting to legislate or otherwise establish standards around the activities of biobanks concerning how, when, and whether to disseminate research results to participants—an activity not typically associated with biobanks, even with a central advisory body in place—may have the often-voiced undesirable effect of thwarting research.

Finally, the word "actionable" in the paper is quite troubling. In my family's case, our *BRCA1* mutation is located on an intron at 17q21.31. Just down the road at 17q21.32 is the marker for Glanzmann thrombasthenia type B, which is implicated in the life-threatening bleeding disorder that affects two of my *BRCA1*$^{+}$ cousins, one of whom nearly hemorrhaged to death during childbirth. The relationship between *BRCA1* and Glanzmann's is established in the medical literature, but the number of cases that have been written up to document the correlation are few. That paucity of correlative data means this particular result might never appear on the "roster" of actionable results, but does that make it

any less important to these relatives of mine? My point is that the paper's parametric approach that begins, "(researchers in the biobank system should return results if) the findings reveal an established and substantial risk of a serious health condition" fails to account for outliers such as this. And it is not as though the authors are unaware that these types of significant outliers exist and can be critical, although the populations they affect may be small. I articulated this *BRCA1*–Glanzmann matter to many of these authors twice previously, both when I participated as one of the 28-member multidisciplinary Working Group charged in January 2009 with updating the National Heart, Lung, and Blood Institute's 2004 recommendations to produce new Guidelines for Reporting Genetic Research Results[6] and again, more recently, as part of my remarks at the May 2011 National Human Genome Research Institute–funded conference producing this symposium.[7] It is concerning that the guidelines do not see this particular example and others like it as proof that trying to manage the space between genomic discovery and the human beings who rely upon it by using a roster of "actionable" findings is inadequate.

In closing, I offer for further consideration five of the points I raised at the January 2009 National Heart, Lung, and Blood Institute meeting. I believe they remain valid and applicable, but I reiterate them here because I believe they represent a perspective largely missing from the Managing guidelines:

- When my family embraced the research community with—literally—open arms, we began a journey alongside researchers and "we learned as they learned." As author James Carroll put it, "…the perennially contingent nature of our knowing leaves us no choice but to try to refine" what it is that we know.[8] The process of refinement *must include us*.
- Donors' aspirations toward health and life are larger than any language or "informed consent legalese" that can be developed to contain or quell them.
- Never underestimate the power of the donor's desperation to overcome any number of constraints—of access, of understanding, or the ability to learn—in getting to knowledge that he or she believes (rightly or wrongly) will extend his or her prospects for survival.
- Human beings are not only capable of but built for altruism; when we gave our blood, we did so as an almost sacred act. We entered a covenant, not a contract.[9]
- The only logical solution is movement toward a more distributive model that spreads responsibility across a wider swath of stakeholders, including the donors themselves. The Web provides innumerable opportunities for facilitating just this type of communication, such that donors could track the journey of their own tissue samples and make the decision for themselves to reach back for additional information or professional guidance in the event clinically interesting information arises.

ACKNOWLEDGMENTS

The author gratefully acknowledges National Institutes of Health/National Human Genome Research Institute grant no. 2-R01-HG003178 for support in participating in the May 2011 conference and in the writing of this article.

DISCLOSURE

The author declares no conflict of interest.

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