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COMMENTARY
Overcoming the obstacles to returning genomic research results

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On 11 October, 2012, the Presidential Commission for the Study of Bioethical Issues released a report concerning whole-genome sequencing and privacy (Presidential Commission for the Study of Bioethical Issues, 2012). The Commission's report, *Privacy and Progress in Whole Genome Sequencing*, correctly emphasizes that individual privacy must be respected – but we suggest that there remains one way in which genetic information is currently kept too private. As described in *Science Translational Medicine* in July (Hunter *et al*., 2012), our status quo often requires researchers to withhold genetic information not only from third parties such as insurers or employers, but also sometimes from patients and subjects themselves. A variety of obstacles prevent physicians and scientists from utilizing our most powerful technological advancements to benefit those very individuals who have trusted us with their bodies and their care.

As Dr Gholson Lyon reports heartbreakingly (Lyon, 2012), in 2009, he discovered the genes responsible for a devastating congenital illness – an aged appearance, facial abnormalities and developmental delay – and published a scientific manuscript in 2011 (Rope *et al*., 2011). However, when one of his subjects asked him what he knew, he was forced to withhold his knowledge because his results were generated in a research laboratory and not a clinical one. These family members – the very ones who had the most at stake – were excluded from the discussion.

Sometimes that heartbreak is unavoidable. In particular, there are four major obstacles to returning genomic findings to research subjects and their families. First, sometimes it is logistically impossible. Second, sometimes the results are too unreliable to be responsibly shared. Third, some commentators argue that results should be shared only when a medical therapy is available. Fourth, sometimes privacy concerns or previously signed informed consents prohibit the return of findings.

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We argue here that we must begin the reforms needed to overcome these four obstacles. The research community drafted informed consents, structured research laboratories, and wrote ethical guidelines about harms and benefits in the pre-genomic era. This often places genomics researchers in difficult situations in which they must choose between their research protocols and the well-being of their patients. The *New York Times*, among others, has reported several of these scenarios. One anonymous subject could not be told that he had HIV because no identification was kept with the samples, depriving him of an early start against his illness. Another research group found that 5% of colon cancers in a sample might respond to a medication called trastuzumab, but the protocol prohibited relaying that information to the participants and so that promising treatment will never be tried. In another case, a woman was planning on a prophylactic mastectomy, when researchers found that she did not in fact have the gene she feared predisposed her to breast cancer. They were barred by the study protocol from informing her, but fortunately in that case her institution's ethics committee intervened at the last minute. In contrast, a family being studied at another institution did carry the predisposing gene, but was never informed due to ethical concerns. They will find out only when the first diagnoses of breast cancer begin to occur in their mothers and daughters (Kolata, 2012).

Before genomics, research was often incapable of yielding helpful personal information. There was no benefit to returning results, and so the value of non-maleficence trumped beneficence and autonomy. After all, no beneficial options to return information were truly available and thus no meaningful choices existed for individuals to make. Thus, informed consents were drafted and information repositories were built on anonymity to protect privacy (Ries *et al*., 2010). Anonymous samples could not influence individual medical decisions (Cho, 2008), and so the careful controls used in clinical laboratories were reasonably deemed unnecessary in research projects.

However, we now live in an era with options, and those options properly belong to the autonomy of those who have the most at stake.

Some commentators argue that researchers have an obligation to return results to participants (Knoppers *et al.*, 2006) while others continue to maintain a non-disclosure position (Dressler, 2009); sometimes major working groups are unable to reach even internal consensus (Fabsitz *et al.*, 2010). Legitimate barriers remain, but we must place a priority on returning research results and even incidental findings, and we must commit to surmounting the four key obstacles to doing so. Below, we address each obstacle in turn, and describe ways in which the research community might overcome them.

1. Logistics

Many projects study a large number of subjects, and the range of potential findings in sequencing is nearly limitless (Cassa *et al.*, 2012). Often, searching for all known incidental findings and reporting them to participants will simply be impossible. However, many studies such as Dr Lyon's, are smaller, seeking out one genetic defect in a family with an obviously genetic but a yet undescribed syndrome (Lyon *et al.*, 2011). Returning findings to patients in small studies such as these would face minimal logistical barriers.

Even in larger studies, returning information may soon be logistically possible. Bioinformatics and information technology continue to proliferate, making search and communication easier. For example, large-scale genomics data repositories ('biobanks') already make it possible for multiple groups to study one genome in pursuit of varying projects, existing largely for the purpose of facilitating 'ancillary' research projects (Wolf *et al.*, 2012). Such biobanks could also include notification features, alerting researchers and physicians when clinically important findings were discovered.

Alternatively, one intriguing proposal suggests a 'cryptographic method' of keeping patient data confidential, in which each of several parties has a 'piece' of identifying information, and all pieces must be combined to share results with participants (Hunter *et al.*, 2012). This promising technique would combine the best of both worlds in preserving confidentiality while still keeping patients and their physicians – each of whom would likely hold a 'piece' – informed, so that they could make the best decisions for their health.

Most excitingly, participant-centric initiatives ('PCIs') use a variety of communications technology such as social media to create a 'user-centric' approach, providing an ongoing, interactive method for obtaining consent and maintaining communication among participants and between participants, physicians and researchers (Kaye *et al.*, 2012). These programmes vary considerably in their size and structure, and each would have to provide information to patient-subjects and their physicians in a slightly different way. However, this is precisely the point: adaptability allows the research sector to develop different tools, comparing them via the academic literature and accommodating the specific needs of their study's particular patient-subject population.

Furthermore, if harnessed correctly, each of these innovations could also help physicians and researchers share data quickly across research institutions. This would allow us to compare and thus better understand genomic trends among patients who share a certain phenotype – the very essence of modern genomics research (Editorial, 2012). There are currently almost no means of sharing such data (Editorial, 2012).

Modern communications technology has lowered logistical barriers in numerous other sectors, greatly facilitating the free flow of information. Such technology can also enable research to be shared from researchers to participants while still preserving privacy options. We strongly encourage genomics researchers to capitalize upon these tools.

2. Ensuring reliability

No data are ever fully reliable, but research findings are rarely subject to clinical-level regulation (Lyon, 2012). Most American research labs were not built to meet the requirements specified by the Clinical Laboratory Improvement Amendments ('CLIA'), and so in this country medically significant findings cannot be relayed to subjects suffering from illness or probable future illness. Ideally, subjects could be thoroughly informed and empowered even about radically uncertain findings. Just as physicians currently warn patients that no single laboratory test is fully reliable, so research subjects could be educated of the uncertainty in their data (Lindpainter, 2012) – especially in cases where research projects are highly exploratory and uncertain. This would allow them to plan their future and make their choices with the fullest knowledge possible.

We recognize, however, that this idealized vision will be difficult to execute in many situations (Ravitsky & Wilfond, 2006), and that many research institutions will therefore require that findings be subjected to clinical-level rigor before being disclosed to families. A second possibility is for researchers to coordinate partnerships with clinical laboratories (Lindpainter, 2012). This approach has had success where researchers have found genetic data pointing to a molecular deficiency, such as serotonin (Chan, 2012), that can be easily tested in a clinical laboratory.

It is also possible for new tests to be devised and certified (Lyon, 2012), although that process is painstaking and slow.

Dr Lyon suggests a third approach (Lyon, 2012): that the rigor of clinical laboratories be applied to research laboratories as well, particularly in small, family-centred studies. This is not a trivial task. It would require a formal protocol to decrease the odds of mistakes, probably including the use of technology such as bar codes, external verification of reagents used and accountability for any errors (Lyon, 2012). However, it also presents advantages. It would require fewer parties such as insurance companies or outside physicians; clinical-standard research labs can provide answers in a timely fashion from the researcher who best understands the implications of the data. Intriguingly, a recent proposal from the United States Department of Health and Human Services ('HHS') suggests that patients may soon have the right to obtain results directly from CLIA-certified laboratories (Letter from Genetics Alliance to the Honourable Kathleen Sebelius, 2012). This would greatly further the transparency and openness we advocate for patient-subjects.

These increased standards will not always be logistically or financially possible (Lindpainter, 2012) – but large research centres that accompany hospitals are often affiliated with CLIA-certified labs anyway. They should consider expanding those laboratories to make them available to human researchers – especially as whole-genome sequencing makes its way into clinical medicine (Kingsmore & Saunders, 2011; Gahl, 2012; Saunders *et al*., 2012). And researchers should, wherever financially possible, capitalize on those resources. The *status quo* catches patient-subjects between reliable but obsolete testing on the one hand and cutting-edge but unverified testing on the other hand. By merging the two, we can provide better care and, also, more reliable science.

3. Actionability

Organizations that have previously considered the issue of relaying genetic findings have placed great emphasis on the availability of medical treatment or cure for any findings. For example, the Public Population Project in Genomics and Society ('P^3G') emphasizes that researchers should consider returning findings to participants if those findings are analytically valid, reveal significant risk of a serious health condition, and are actionable – defined as having a recognized therapeutic or preventive intervention or other action with the potential to change the clinical course of a disease or condition (Knoppers *et al*., 2013). This is understandable; informing a patient of a predisposition towards a medically unactionable disease such as Alzheimer's, for example, may distress patients without providing any meaningful way to alter the course of their disease.

Nonetheless, we believe that the emphasis on *medical* actionability is misplaced. Physicians do not withhold prognostic information in other medical contexts. Magnetic resonance imaging scans can help families understand the severity of a child's neurological injury after a hypoxic-ischaemic event (McKinstry *et al*., 2002), cancer genotyping can point towards a more or less aggressive disease, and genetic counselling can help determine whether parents are carriers of recessive genes. Each of those tests help patients and families to make crucial financial or other life decisions. Genetic testing is no different – as just one example, returning results would allow families to work with genetic counsellors as they decide whether, or how many, or when, to have children (Hens *et al*., 2011). In fact, referral to professional, clinically trained genetic counsellors whenever possible can help mitigate any harm from disclosure as they help families to make decisions regarding their future.

Delivering research findings does not even require any additional testing. It requires only that we share the results of tests already performed with the individuals most affected by them.

A working group on the subject of 'biobanks' suggested as a guideline that researchers and biobanks may return results even in some situations where no medical treatment is available (Wolf *et al*., 2012). We take this recommendation one step further: in our view, these are properly decisions for patient-subjects to make, not their researchers and certainly not the aggregated bodies which regulate researchers en masse.

There are real concerns to delivering unactionable results, but participants themselves strongly urge us not to shield them from knowledge which we would deem distressing: 90% of surveyed participants would want to know all their individual results, even when entirely unactionable, and 75% state that they would be less likely to participate in research which withheld findings (Kohane & Taylor, 2010). This latter figure suggests that there are societal implications to withholding information even beyond the impact on patient-subjects themselves.

Accordingly, informed consents should be modified to offer options: patients could choose to be told only of findings which are medically actionable, or of any findings which offer a prognostic value and which therefore might be actionable in a broader sense.

Beyond this debate, however, we wish to emphasize that many findings from research laboratories do, in fact, have clear, immediate clinical utility (Hunter *et al*., 2012). Under those circumstances it is important for researchers to overcome the other obstacles to relaying information to patients.

In short: sometimes we will not be able to share data with subjects. Perhaps, it will be logistically impossible to return results, or prohibitively expensive to study the specimens in accordance with CLIA standards, or the binding laws in that laboratory's jurisdiction. And sometimes the research will be highly exploratory in nature or findings may be too uncertain to share (Miller *et al*., 2010). However, there will be times – there are already times – when all these standards can easily be met, and in those situations it is unconscionable to hide known information from research subjects after they have submitted to study for the benefit of others. We must ensure that the last barrier, the manner in which we draft our informed consent agreements, does not stand in the way when other factors permit.

4. Privacy and informed consent

The Presidential Commission properly stresses the importance of informed consent and privacy and recommends that the Office for Human Research Protection (OHRP) institute minimum requirements for such documents (Presidential Commission for the Study of Bioethical Issues, 2012). These protections are indeed absolutely critical (Trinidad *et al*., 2011). Further, we strongly urge that OHRP permit researchers to disclose findings to research participants. This will not only permit crucial clinical decisions to be made, but will also give subjects a greater degree of ownership in the studies themselves, a critical feature of past breaches of trust (Miller *et al*., 2010).

Many informed consent documents, based on agreements drafted in the pre-genomics era, prohibit researchers from contacting patients or family members with potentially relevant information (Cho, 2008). Informed consents that keep data entirely anonymous and which prevent re-contact with subjects are of questionable effectiveness anyway (McGuire & Gibbs, 2006; Ohm, 2010), especially when it comes to whole-genome sequencing (Homer *et al*., 2008; Jacobs *et al*., 2009). Regardless, anonymity comes at too high a cost. In our efforts to keep private information from falling into the hands of third parties, we destroy it entirely or hide it even from subjects themselves. We can protect privacy without hiding information from research subjects themselves, and the cryptographic approach cited above (Hunter *et al*., 2012) serves as just one means by which we could accomplish that. We recognize that this will be a significant cultural shift compared with past research efforts. Nonetheless, when returning results are logistically possible, when those results are clinically reliable and when the results would be actionable in some way, we must draft informed consent documents to allow individuals access to their research findings.

Informed consents must, of course, continue to stress privacy, and clinically relevant patient and research information will continue to be subject to the protections of both the Health Insurance Privacy and Accountability Act ('HIPAA') (1996) and the Genetic Information Nondiscrimination Act ('GINA') (2008). The Presidential Commission rightly recommends that all genetic information – for example, samples obtained by a third party from a coffee cup – be subject to the same laws. However, research participants themselves should have as much access as we can reasonably grant them. The Commission worries reasonably that privacy concerns may deter individuals from participating, but we can preserve privacy while allowing subjects themselves to benefit, thus encouraging individuals to proactively seek out such research projects (Hens *et al*., 2011; Terry & Terry, 2011).

Above all, we must provide subjects with choices. They should be given the option of retaining our current, standard privacy protections: anonymous samples and/or prevention of re-contact (Hunter *et al*., 2012; Kolata, 2012; Lyon, 2012). However, these should merely be options, and we suspect that few patients would choose them. A 2002 phone survey suggested that 89% of respondents would want to be informed of results even when clinical significance was unclear (Wendler & Emanuel, 2002). In addition, subjects may wish that their family be notified, or not (Offit *et al*., 2004); and that they be informed even if no medical treatment is available, or not. The Presidential Commission suggests that subjects should be told whether or not incidental findings will be disclosed; we recommend further that they should be given the option if at all possible. These options would complicate informed consent documents, but the autonomy which they grant patients outweighs that marginal increase in complexity.

For legal reasons, findings from past and current studies ought to remain bound by the informed consents that subjects have signed. In some severe situations – medical exigency, or with permission of ethics boards (Kolata, 2012) – such agreements may be overruled, but in general existing agreements must be honoured, no matter how heartbreaking. This emphasizes the urgency of our much-needed cultural shift: we must begin drafting and implementing new informed consents immediately in order to prevent subjects and researchers from being placed in such situations in the future.

Sequencing promises the ability to unravel many of the puzzles that lie at the heart of modern medicine: why certain medications work in some individuals but not others; how some diseases originate; what we can expect in our own future. These are crucial benefits, and they hold great promise for our world at large,

and especially for our future. Yet, too often, subjects themselves are kept in the dark.

In its 12th and final recommendation, the Presidential Commission rightly stresses that the benefits of whole-genome sequencing should accrue to as large a segment of society as possible. We agree fully – but we urge the Commission and researchers worldwide to go one step further: to include the very individuals who have contributed their very selves in pursuit of this research, and who have the most at stake in its success.

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