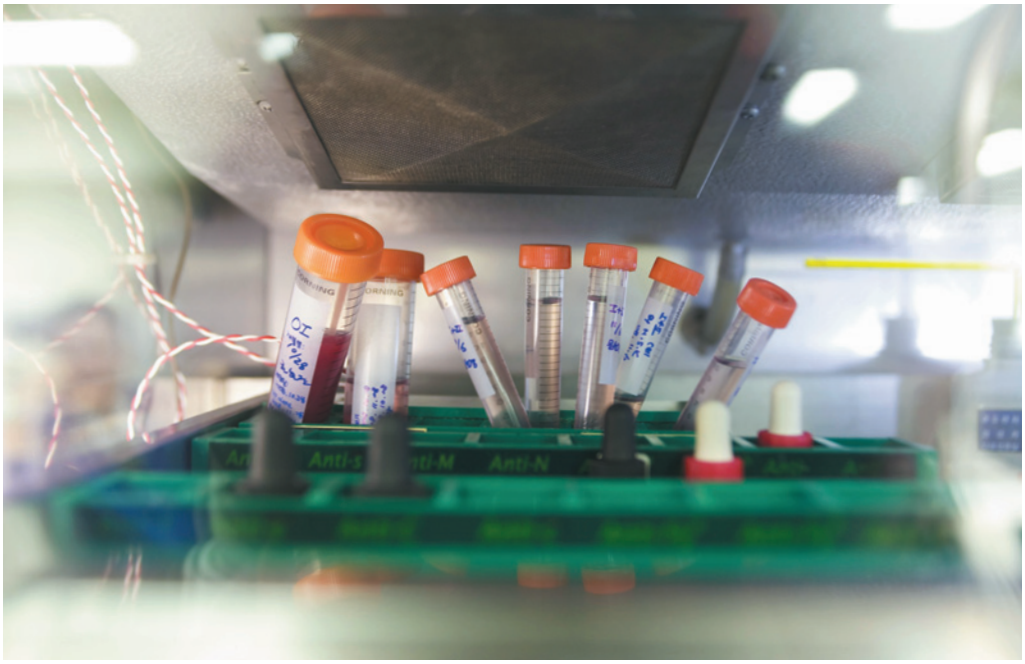

Scientists are generating a wealth of human-DNA data, but no system exists for informing volunteers of their results.

Bring clinical standards to human-genetics research

Study protocols need to be rigorous, because more than science is at stake. Sometimes participants' lives depend on the results, writes **Gholson J. Lyon**.

In November 2009, I met a family in Ogden, Utah, in which three boys over two generations had died from an unknown disease with a distinct combination of symptoms, including an aged appearance, facial abnormalities and developmental delay. At the time, a fourth boy was affected; he died a few months later.

Like any researcher in human genetics and biomedicine, I wanted to identify the genes behind this disease. As a medical doctor, I heard their tragic story and drew blood from several family members in their home. Using those samples, my colleagues and I identified the genetic basis of this disease[1], which we named Ogden Syndrome after the town in which the family lives.

Then, in November 2010, another family member told me that she was four months pregnant — and she was having a boy.

She was, understandably, very worried that she might be a carrier of the mutation — two of her sisters had already lost one boy each to this heartbreaking disease. My colleagues and I had sequenced her DNA for our research, and the data suggested that she was a carrier, implying a 50% chance that her son would be born with Ogden Syndrome. But when she asked me what I knew, I hesitated.

I was not her physician; I was a researcher, and I had done this work on a research basis, not following the specific protocol required for performing validated clinical or diagnostic tests. I couldn't be totally sure that her individual results were accurate. Should I share them with her anyway, knowing the devastation they could cause? What if I was wrong, and she terminated the pregnancy?

Now is perhaps one of the most exciting periods in human genetics and medicine — it is possible to sequence most of an entire human genome for less than the cost of many tests and procedures done routinely in clinical medicine, including magnetic resonance imaging scans and many types of surgery.

But this rapid expansion is shining a spotlight on the problems with how that information is handled and processed. Specifically, researchers are largely unable to share their findings with the people who make that research possible: study participants. At the moment, human-genetics researchers operate in a totally unregulated environment, following their own protocols to obtain, store, track and analyse DNA — creating many opportunities for error. Researchers take shortcuts to save time and money, given that most never expect (as I did not) that their results might have a direct effect on the life of another human being. But when the result can mean the difference between life and death, mistakes are not an option.

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I suggest that we change the way we collect and process samples for human-genetics research. We should create a formalized protocol akin to the rigorous process that doctors and other health-care workers go through during any clinical lab test, which practically eliminates the chances of mistakes and mix-ups. In this way, when participants want to know what we know, we will feel confident that what we tell them is correct.

In 2009, after finishing my clinical training, I moved to one of the best places in the United States for the genetic study of large pedigrees: Utah. I began to collect DNA samples from families with neuropsychiatric disorders, including individuals with severe

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developmental delay, mental retardation and autism. I also began to understand the problems with how human-genetics research is conducted.

WHEN THE UNEXPECTED OCCURS

Towards the end of my first year in Utah, I began sequencing DNA from a family in which a father and two sons were affected by severe attention-deficit and hyperactivity disorder (ADHD). Before I had finished my analysis[2] of the sequencing data, one of the sons revealed to me that he had a severe case of anaemia. Even though I was searching for the genetic cause of ADHD, as a physician and a human being, I felt an ethical and moral obligation to try to figure out whether he had any mutations that could have led to his anaemia. It turns out that he did.

But I was not able to return any results to him, because this research was not performed in a clinical environment. Wouldn't it help him to know that the jaundice and other problems he had battled for the past 20-plus years of his life were caused by two rare recessive mutations? Most importantly, as he moved forward in his life, wouldn't this information help him to decide with a future partner whether to undergo genetic counselling, and perhaps even genetic testing, before conceiving any children?

In the United States, all clinical laboratory testing performed on humans is regulated by the US Centers for Medicare & Medicaid Services in Baltimore, Maryland, through the Clinical Laboratory Improvement Amendments (CLIA).

When a clinician orders a blood test for anaemia, that blood is drawn by a licensed phlebotomist in an accredited laboratory setting, and the sample tube is barcoded immediately, thus reducing to about zero the chances of mix-up. The blood sample is then processed in an accredited laboratory with reagents that are carefully documented and maintained, so that haemoglobin and haematocrit are assessed and calculated in the same way for that sample as for all other samples in that laboratory, each and every time.

Even companies that perform direct-to-consumer genetic testing, such as 23andMe based in Mountain View, California, track the saliva samples quite carefully from the moment the tube is closed, so that the results can be returned to the consumer.

Now, how do most scientists in the United States conduct human-genetics research? Not in the manner described above, and not under regulation by CLIA. Instead, blood is drawn by just about anyone who is able, and there is certainly no "treating physician" ordering the blood draw (that is, someone to be held medically and legally responsible if something goes wrong or is missed).

Sometimes the sample tubes have barcodes; sometimes they have only hand-written labels. Often, the researchers themselves extract the DNA, using standard reagents or a 'kit' available from many different companies, but there is rarely any tracking of the reagents used. DNA is sometimes extracted at a core facility using one of any number of methods, and the transferral of the samples to the core facility requires that the tubes are passed from researcher to researcher, increasing the chances of human error.

There is also extreme variability in how DNA samples are used, managed and stored. Some researchers might handle the same samples again and again, thus increasing chances for mix-ups or cross-contamination. Indeed, authors of human-genetics papers commonly eliminate samples that they suspect were mixed up. Some researchers store samples in a centralized biobank, but others use any freezer in the lab, creating many opportunities for error. There are no mandated guidelines for handling human-DNA samples in a research setting, precisely because such research is not regulated.

I never expected that a research subject would tell me that he probably had a genetic condition besides the one I was studying at the time. Some people might argue that I shouldn't have looked for the cause of the anaemia, but to me, it seems ethically and morally wrong not to try.

In the case of the Ogden family and the family with ADHD, I labelled samples by hand and gave them to a core facility at the University of Utah in Salt Lake City for DNA extraction. Although I was confident that I had performed each step as rigorously as possible, none of the reagents were tracked in any way similar to a clinical lab test. As such, the results did not meet the very high standards required of clinical tests.

"Most researchers never expect that their results might have a direct effect on the life of another human being."

I have since asked the physician of the man with ADHD to follow up my results with a CLIA-certified genetic test to confirm that the man carries the anaemia mutations, so that this clinician can release the information to him. Even now, many months later, the testing has not been performed, because most clinicians face roadblocks such as finding an available gene diagnostic test, dealing with insurance and arranging for appropriate genetic counselling.

In the case of the woman who I suspected was carrying a male fetus with Ogden Syndrome, I faced a major dilemma owing to time constraints. Given that my results could have been incorrect, and might have caused undue stress and possibly even an unnecessary termination of the pregnancy, I chose to "first, do no harm" — I did not return my research result to her, and I instead attempted to validate it in a CLIA-certified lab at a major diagnostic facility. It was a long and bureaucratic process, but after several months, in July 2011, we had a formal, CLIA-certified genetic test for the specific mutation in *NAA10*, the gene associated with Ogden Syndrome.

Unfortunately, by that time, the woman had given birth to her son. As I had feared, he had the disease. Sadly, he died in June 2011, four days before the paper describing the mutation that killed him was published.

EXPECT THE UNEXPECTED

There are increasingly limited resources for biomedical research, and it can take 20 years or more to translate genetic discoveries into new drugs or other treatments. So why not help the families and research participants now, by deriving the highest possible value from every DNA sample we sequence?

Participants want to be involved in the research process and be told about any medically important findings. I am therefore suggesting that the entire process of DNA collection and genome sequencing for humans could and should be performed in a proper clinical environment, so that physicians can immediately return all relevant genomic information much more easily, and perhaps even link such information to medical records so that it is available for re-analysis as our knowledge expands.

This means establishing suitable guidelines for the collection, tracking and sequencing of DNA samples from human participants, along with training health-care professionals in genetics counselling.

To make these changes possible, grant agencies should consider setting aside funding to establish clinically certified protocols for handling human genomic data, including findings perhaps unrelated to the original research goals[2]. After all, these agencies are supported by taxpayers, and the data ought to be given back to those donating their time and DNA to the research. We cannot forget the wise words of the late geneticist Charles Epstein, from his 2001 William Allan award lecture: "the operative word in 'human genetics' is 'human.' Human genetics is about human beings — about humanity and humaneness."[3] ■

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