GENEWATCH

WHAT THE DOCTOR ORDERS
By CRG staff - interview with Robert Green

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For centuries, human societies have divided population groups into separate races. While there is no scientific basis for this, people unquestioningly accept these classifications as fact.

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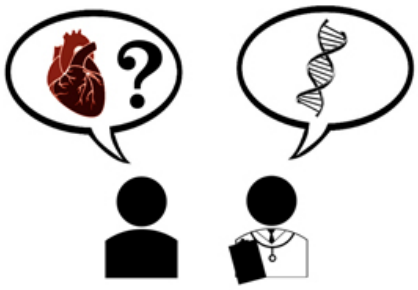
***Robert C. Green**, MD, MPH, is a physician-scientist in the Division of Genetics and Department of Medicine at Brigham and Women's Hospital and Harvard Medical School, Director of the Genomes to People research program, and a member of the Board of Directors of the Council for Responsible Genetics.*



***GeneWatch:* How is it that incidental findings even come to be an issue? For example, if a physician orders a genetic test for a patient with heart problems, why would there be any results besides genetic variants known to be related to cardiac health?**

Robert Green: It's actually not much of an issue in the current way genetic testing is done, where specific genes are explored for suspected mutations as part of the workup for a particular phenotype or disease presentation. But as we move into the genomic era-as it becomes easier and easier, and cheaper and cheaper, to sequence the entire exome or genome rather than just a few specific genes-the issue of incidental findings will become more relevant. It turns out that once you sequence all of the genes, even if you are only looking at one or several for a particular indication, it is relatively easy to also look for known pathogenic mutations that have been associated with other diseases. For example, you could perform whole exome sequencing or whole genome sequencing for a cardiac indication, but it would be relatively easy-especially as informatics get better and better-to also search for mutations in known cancer predisposition genes and therefore be able to tell someone whether they might be at increased risk for a particular kind of cancer.

You have been involved in creating guidelines for the American College of Medical Genetics and Genomics (ACMG) on returning incidental findings from genetic testing. Can you tell me anything about the recommendations that are likely to emerge from this?

There is a working group that has been asked by the ACMG to develop a policy on incidental findings, and I co-lead that working group, along with Leslie Biesecker from NHGRI. We have come up with a number of principles. One is that we think it may be useful for laboratories to look for limited sets of incidental findings, and these should be findings for which there is a well recognized medical intervention. We do feel like the report, both the primary information and the incidental findings, can go back to the physician, and that the physician can contextualize any findings. That's extremely important, because it's a reminder that we're not talking about a direct to consumer scenario here. We're talking about information that has the potential to be interpreted in many different ways, depending on the age, the clinical status, and the medical history of the patient. It is the classic job of a physician to integrate all sorts of laboratory information, using what he or she knows about the patient.

So we're really treating incidental findings in genomics very much like incidental findings in the rest of diagnostic medicine: It goes back to the ordering physician, the ordering physician struggles to put it into context and uses their best judgment to go forward from there.

Does the patient have a point at which they can say: "Here are the things that I don't want to know about?"

They are engaged in a conversation with their physician, and they can make that case about their genomic information the same way they could make that case about an X-ray. It is our position that the things that we would suggest to be on a recommended minimum list of incidental findings would be things that most people-not everyone, but most people-would actually want to know about.

You were lead author on a study published this spring which investigated whether specialists could agree on which variants to return as incidental findings in different situations. Although it was an exploratory study, did you see any important takeaways?

Yes, I thought it was quite interesting for a couple of reasons. First I should clarify that it was a non-representative survey of a number of genetics experts, and it was in no sense a policy document, recommendations, or anything like that. It just asked some expert geneticists and laboratory directors: If you were advising a molecular laboratory on what to return as incidental findings to the ordering physician, which of this following list of things would you suggest for the adult patients, and which would you suggest for children?

What was unique about this study was that no one had really posited this scenario before. Most genetic testing nowadays is ordered by medical geneticists, and it's targeted testing. So here we posited what is really an inevitable scenario in the future, but something no one had asked before. You've got a clinician-they may or may not be an expert in genetics-and you have the capability, through whole exome or whole genome sequencing, to look at all these other disease genes. What would you give back to the physician? And I think the most surprising thing about the study was how many different disease variants the respondents suggested could be given back. That was very surprising.

But there were a few, right, that almost no one said they would return? Like variants for an adult-onset disease with no known medical intervention being returned when the patient is a child?

There were actually a number of people who voted to return things to the clinicians of children that I was frankly surprised about. I think that many people were surprised that so many of these experts would vote to return such information. I think one explanation, anecdotally, is that even if you might not intervene for, let's say, an adult cancer predisposition in a child, you would be indirectly discovering something about that child's parents that could benefit them. I don't know for how many that was an issue, but it may have been behind some of the logic of returning results to children's physicians.

What have you noticed about the range of opinions on how to return incidental findings?

There are clearly clinicians, genetic counselors, and interested laypeople who have widely divergent views on this. There are people who strongly believe that the information should be treated very cautiously and that disclosure should be reserved for unusual circumstances, where there is very clear discussion about the nature of the disclosure before it occurs; and there are other people who feel that genetic information should not be treated differently than other medical information, and people-clinicians, patients, consumers-have a complete right to know information of any type about themselves. So you really have a huge divergence in the degree to which people think that genetic information should be restricted or filtered by professionals.