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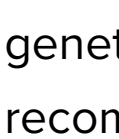
ACMG Recommendations Are a Controversial but Necessary Step Towards Genomic Medicine



By Robert C. Green, MD, MPH

A little over one month ago, on March 21, the American College of Medical Genetics and Genomics (ACMG) announced a set of recommendations on incidental findings in clinical sequencing.

I co-led the group that developed these recommendations... the first specific guidelines provided by any professional organization to try to harness the power of DNA sequencing to anticipate unsuspected illness.

The recommendations state that laboratories performing a sequencing analysis of the protein-coding regions of DNA (the exome) or of the entire genetic code (the genome) for any medical indication should also examine 57 genes for well-recognized mutations that might signal a risk for one of 24 life-threatening but treatable conditions. While there are literally thousands of genes that could potentially influence a person's future health, the ACMG felt that discovering mutations for these 24 conditions (such as hereditary cancers or heart conditions that could cause sudden death) was so important that a laboratory sequencing the genome should deliberately search for these mutations, and that these were genetic "panic values" that should always be returned to the ordering physician. The recommendations called for analyzing and returning this information without seeking the

patient's explicit permission for each and every gene to be tested, and regardless of the age of the patient being sequenced.

No sooner had the recommendations been released than well-intentioned critics expressed dismay about violations of patient autonomy as well as the rights of children not to be exposed to genetic information about adult onset conditions. I will address the issue of children in a future blog post. Here I respond to critics who believe that patient autonomy is compromised by these recommendations. In a nutshell, their argument is that patients should always have the right to refuse a test that might produce an incidental genetic finding. Their argument is misguided because it creates exceptions for genetics that violate common medical practice and because it defines autonomy far too narrowly.

The Search for Rare Incidental Findings Is Routine in Medical Practice

If your doctor orders an x-ray of your heart, and the radiologist sees something unrelated but suspicious in your lungs, this is called an "incidental finding." There is no controversy around the expectation that the radiologist who reads your x-ray has a professional duty to visually examine the entire x-ray (not just look at your heart) and must report any suspicious incidental findings.

This has long been true in every branch of medicine. The dermatologist who examines your rash cannot ignore the suspicious mole nearby that might be melanoma. The laboratorian who prepares a blood test report for suspected anemia cannot ignore an elevated white count that suggests leukemia.

Doctors don't ask for your consent to look over the entire x-ray or make a note of the suspicious lesion on your skin or disclose to you the surprising blood test. And they certainly don't sit you down before every examination, x-ray or laboratory test and have a long discussion with you about all the thousands of possible incidental findings that might show up. Rather, it is understood that when doctors perform a medical examination or send away a test for one reason, clues to an entirely different disease may emerge. Sometimes (thankfully) those clues are going to be wrong, and sometimes they will provide an early warning that will save your life. Exceptionalizing the incidental information discovered through genetics has no rational basis except to maintain traditions that are becoming increasingly impractical as genomics medicine arrives.

Autonomy Does Not Vanish When Incidental Findings are Routinely Reported

Autonomy and consent are not ethical principles in isolation. They are balanced against competing ethical principles and in this instance, the competing principle is non-maleficence. The short list of conditions and genes selected by the ACMG cannot be discovered by any other means than by examining the sequence and reporting on them, and such an action could save the life of an unsuspecting patient or his/her family member.

Also, we should think carefully about how informed consent actually works in clinical medicine. Even for the short list of 24 conditions, we estimated that fewer than 1 in 200 patients who undergo sequencing would have an incidental finding from the ACMG list. Leading geneticists at Medical College of Wisconsin have reported that preparing a patient's family for all possible incidental findings in conjunction with sequencing can take at least 2-3 hours of genetic counseling before testing and several more hours after! As genomic sequencing scales up from a few thousand tests annually to millions of tests a year ordered by physicians from all sorts of backgrounds...does anyone imagine that a physician could adequately counsel 200 patients in advance about 2 dozen rare disorders in order to preserve the right of refusal for the 1 who might receive a frightening result? And even if we could, would a laboratory interpreting thousands of sequences a year somehow customize the incidental findings to match the preferences of each and every individual patient?

In our recommendations, the expression of autonomy is not removed, but shifted to a more appropriate place. The ACMG recommendations suggest that ordering physicians should receive a report that includes the potentially dangerous incidental mutation, and thus informed, the physician and patient together can choose to learn more about the illness that it implicates. Together, they can evaluate the level of evidence for the mutation, incorporate the personal and family history of the patient and make an informed decision about whether to pursue surveillance or preventative treatments. Absent the knowledge that such a mutation exists, patients will not have any authentic opportunity to inform themselves or exert any choice over this danger.

Medicine Enters the Genomic Age

The field of genetics has, for too long, held itself apart from the rest of medicine by assuming that incidental genetic risk information is dangerous *sui generis*. This is unsupported by accumulating evidence, and, as sequencing and interpretation will soon be

inexpensively available, ignores the potential for recognizing known mutations that increase the risk of serious yet treatable disorders.

The ACMG recommendations on incidental findings in clinical sequencing are the first by any professional organization to acknowledge that genomic analysis should be aligned with the standard practice of medicine and point the way to an exciting future in which genomic information will begin to fulfill its lifesaving potential.

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