COMMENTARY | Genetics inMedicine

When is a medical finding "incidental"?

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Not surprisingly, the recent guidelines from the American College of Medical Genetics and Genomics (ACMG) regarding the return of incidental findings[1] continue to generate controversy. At the heart of much of the controversy lies a single question: what makes a medical finding truly "incidental"?

Implicit in the new recommendations is a mandate to laboratories that when genome-scale sequencing is performed, the resultant data be actively and systematically queried for specific types of mutations in a selected set of genes. How can such a call for an active search be reconciled with the designation of those results as "incidental"? And why is this not tantamount to a call for overt screening for mutations in those genes? The details of how genome-scale sequencing is carried out, as well as long-established norms of clinical medical practice, are critical to resolving these questions.

Genome-scale sequencing involves two phases, both of which are vital to the overall process. The first phase consists of the actual generation of sequence data; the second consists of complex informatic analysis of those data. Let us examine how the ACMG's new recommendations would play out in the context of a typical patient who might undergo whole-exome sequencing or whole-genome sequencing for unexplained, progressive neurological deterioration and examine the ACMG's call to look for mutations in, among other selected genes, *MSH2* (which, when mutated, is responsible for Lynch syndrome).

In the first phase of this patient's whole-exome sequencing testing, physical capture of all exons in the patient's genome is carried out, libraries are prepared, and the captured and processed DNA is subjected to sequencing. If whole-genome sequencing is pursued, essentially all of the patient's genomic DNA is processed and directly sequenced. At this point, testing is incomplete. No matter the indication for testing, no matter the use to which the results will be put, an extensive series of complex informatics filters must now be applied to the data in order to render it suitable for interpretation by the laboratorian and clinician. Informatic algorithms will determine quality scores of each nucleotide, and predetermined decisions will be made regarding mapping fidelity and the threshold required for calling of nucleotides. Sequence data will be compared with external databases to weed out innocuous variants, and methodical parsing of the data by informatic filters will pluck out those few variants most likely to be relevant to the patient at hand. In other words, an exhaustive series of preordained analyses will necessarily be carried out by whatever informatic system is employed by the laboratory to ultimately determine which of the many thousands of genomic variants present in the raw data deserve human inspection and interpretation.

The point of my summarizing the testing process is to highlight the fact that in any genome-scale sequencing test, if a deleterious, life-threatening mutation in *MSH2* exists, it has already been sequenced and now resides in the data that will soon be subjected to a whole series of obligatory and methodical informatics analyses. We must therefore make a conscious decision as we formulate the analytic algorithms by which the data will be analyzed—do we ignore the possible presence of this *MSH2* mutation or, while we are already implementing extensive informatics algorithms, do we also ask those algorithms to pluck it out of the patient's already generated sequence data and reveal it to the clinician along with the diagnostic information that is being primarily sought in the context of the patient's neurological disorder?

This decision must be driven, in part, by how burdensome it is to query the patient's data for the presence of the possible *MSH2* mutation and whether detecting it necessitates departing in a qualitative manner from the normal analytic process. If such a query were to rely on the application of different technology or a new test, or necessitate a "work flow" unrelated to how such data are normally analyzed, then it would indeed seem a stretch to classify the elucidation of the patient's *MSH2* mutation as "incidental." But this is not the case. Any genome-scale sequencing process necessarily involves the application of myriad informatics filters. Complying with the ACMG's recommendations asks laboratories only to apply one more straightforward filter to check whether a recognizable *MSH2* mutation is present in the patient's data files that have already been generated. The burden to the laboratory is minor and does not introduce qualitatively new demands.

As genomics enters medicine's mainstream and as our community struggles with the meaning of "incidental," it is instructive, especially for those not familiar with long-established routines of medical practice, to understand how incidental findings are generated in the rest of clinical medicine. It is incorrect to think that incidental findings in other medical settings are "stumbled upon" or jump out at us. Indeed, they are systematically and methodically ascertained by whoever is responsible for analyzing the primary data, whether in the context of the radiology suite or the clinical chemistry laboratory. Take the well-established setting of the radiologist who reads a computed tomography scan of the chest, obtained because a patient has

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persistent left lower lobe pneumonia. Reading such a film is a complex process; the radiologist does not just "look" at the films. Rather, she is explicitly trained to methodically analyze the data before her. She may focus initially on the pneumonia for which the study was ordered, but the radiologist doesn't stop the analysis there. Rather, she unfailingly and systematically scrutinizes the films for irregularities in the pleural surface, the continuity of the vertebra, the size of the heart, and myriad other aspects of the data generated by the computed tomography to be sure that she has not overlooked something that resides in those data that was unexpected but could be potentially important—indeed life saving—to the patient. The radiologist will not hesitate to report that her systematic analysis revealed the presence of a tumor in the right upper lobe that the clinician and patient did not expect but should know about. Indeed, the radiologist would be legally (and most would argue ethically) liable were she not to engage in such a systematic and methodical analysis of the data to search for readily identifiable "incidental" findings that could be of great consequence to the welfare of the patient. The process she implements is directly analogous to the application of a carefully considered, defined, and minimally burdensome set of informatic filters applied by the laboratorian to genomic data in order to detect readily apparent, unexpected, and life-threatening mutations.

There are profound consequences to patients if they undergo tests, and a minimally burdensome protocol to identify serious, unexpected findings in the generated data is not methodically pursued. The practice of medicine has long held that patients have a right to expect that their providers will exercise a reasonable level of due diligence to warn them of unexpected findings that could prove life saving. The patient who undergoes whole-exome sequencing and is diagnosed 5 years later with metastatic colon cancer would seem to have a legitimate grievance as he poses the following question to his provider (or the laboratory): "Why, when you sequenced my genome, did you not discover my *MSH2* mutation and warn me so that I could have avoided the terminal illness I now face?" The answer that "well … we did sequence it, but we didn't look for it" will likely ring rather hollow.

Given the low prior probability that any given patient will have a deleterious mutation in one of the genes on the recommended ACMG panel, it is critical that a very high bar be set by the informatics filters for "calling" a deleterious *MSH2* mutation. Only known mutations (and in appropriate genes, nonsense and frame-shifting mutations) should be sought. Otherwise, the number of false-positives generated would be overwhelming. Likewise, we must not run ahead of the evidence regarding the list of genes to be queried. It must be appropriately small at this time and be confined to those genes for which reasonable evidence suggests that discovering a mutation in genes on the list leads to well-validated preventive modalities. Moreover, the potential for false-positive results is yet another compelling reason to use whole-genome sequencing and whole-exome sequencing judiciously in the clinical setting in the first place; like any complex medical test, it should be applied in those contexts where it is most likely to yield useful information. Finally, although the current list arrived at by the ACMG seems (to me) a good start, it could be argued that it should be even smaller. For example, the data showing that meaningful preventive measures are possible in Li–Fraumeni syndrome (resulting from p53 mutations) are scant.

If one wishes to avoid problems related to incidental findings in genomic medicine, the logical answer is simply to not do as broad a test in the first place. The use of well-defined panels that physically capture only a subset of genes specifically relevant to the patient's condition avoids the problems inherent in this controversy entirely. No one would argue that a test that relied on physical capture of a few dozen genes involved in cardiac disease be queried for *MSH2*. In that case, the *MSH2* gene would never have been captured or sequenced in the first place, and there thus could be no reasonable expectation of querying it for mutations. The analogous radiology example would be that the radiologist is certainly responsible for methodically and carefully examining the entire chest when a chest computed tomography is ordered. But he cannot be held responsible for failing to detect the patient's abdominal mass because those data were not generated for analysis in the first place.

Finally, it is important to point out the difference between the incidental (albeit methodically sought) discovery of a deleterious mutation and overt population screening. In the latter context, one has made a conscious decision to seek out apparently healthy individuals and test them for a high-risk or a latent condition. This is markedly different from making the decision, in the context of data already generated in a patient, that one has some obligation to carefully examine those data for possibly life-threatening findings that could lead to effective prevention. In an analogous manner, medical science has well established that screening long-time smokers with periodic chest x-rays is ill advised. However, this is an entirely different context than that of the patient whose chest x-ray happens, on methodical analysis by the radiologist, to demonstrate a clinically unexpected mass. The radiologist would be entirely remiss were he to fail to methodically analyze the films in the first place or fail to report the presence of the mass to the clinician.

Medical practice has long recognized a duty of the physician to expend reasonable effort to analyze data generated in the course of a patient's clinical care that could alert him to unexpected but potentially life-saving incidental findings. There seems to be little reason to engage in genetic exceptionalism and treat genomics differently. The most recent ACMG recommendations are consistent with long-established norms of medical practice and bring genomics in line with the rest of medicine. As genomics becomes a part of mainstream medicine, we must not abdicate well-established clinical responsibilities.

DISCLOSURE

The author declares no conflict of interest.

REFERENCE

1. Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med* 2013; e-pub ahead of print 22 March 2013.