

Paternalistic personalized medicine: Testing biosamples without consent in clinical genome sequencing

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Introduction

Personalized medicine has been hailed as the most important revolution in the history of medicine. [1] By tailoring medical care to individuals, it promises a much more person-specific approach to healthcare rather than the traditional “one size fits all” approach. Genome and exome sequencing is perhaps the ultimate expression of PM: the ability to detect genetic defects and diseases and tendencies towards developing particular conditions offers a wealth of information that can be used to prevent and treat a plethora of diseases. However, personalized medicine also tends to put a greater emphasis on personal responsibility. In order to obtain the advantages offered by personalized prevention and treatment, patients (or consumers, as they are increasingly referred to) must undergo more monitoring and tests than in conventional medicine. These tests often yield “incidental findings”, which may be medically relevant but were not originally sought. Patients who do not want these tests (because they do not like being tested or they are worried about incidental findings, or for some other reasons) can of course opt out, but then they will not receive the benefits of PM. Until recently, the great importance accorded to individual autonomy has meant that choice has played a very important role in personalized medicine, and the phrase itself suggests that PM is all about choice. However, a recent example from the United States indicates the dangers of attempting to provide paternalistic personalized medicine.

The ACMG guidelines

Reporting of incidental findings in genetic testing is recognized as a highly sensitive issue in bioethics, in both the clinical and research contexts. While the clinical benefit of informing patients about highly relevant results is sometimes clear, proponents of a “right not to know” argue that patients should only be given results to tests that they have requested. Given the comprehensive literature and debate on this topic, there was great surprise and much controversy over the American College of Medical Genetics and Genomics’ (ACMG) recommendation [2] that genetic testing services should report incidental findings to patients without their consent. [3] The ACMG guidelines are a troubling example

of how poorly designed processes in personalized medicine can actually violate patients’ autonomy.

The guidelines entitled “ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing” were first published on the 22nd of March 2013. Its 14 authors were all members of the ACMG’s Working Group on “Incidental Findings in Clinical Exome and Genome Sequencing”, which was appointed “to make recommendations about responsible management of incidental findings when patients undergo exome or genome sequencing”. The core of the guidelines is composed of a recommendation and a list of conditions. The recommendation states that “Constitutional mutations found in the genes on the minimum list should be reported by the laboratory to the ordering clinician, regardless of the indication for which the clinical sequencing was ordered. It is the responsibility of the ordering clinician/team to provide comprehensive pre- and post-test counseling to the patient.” [1] The ‘minimum’ list is actually extremely extensive, covering 57 genes and 24 disorders. [2]

There are three major problems with the ACMG’s main recommendation. First, it widens the scope of “incidental” to include additional extra testing for genes and conditions that have nothing to do with the patient’s original request. Second, it essentially changes the paradigm to assuming that patients should be told about incidental findings rather than making decisions on a case-by-case basis by weighing the potential harm of not disclosing against the need to respect patients’ autonomy. Third, the “minimum” list goes even further in specifying 24 conditions that should be tested for, even if the patient did not want to be tested for any of them. Taken together, this means that any patient requesting any exome or genome sequencing in the United States while these guidelines were in force would have tests conducted on their biosamples, even without consent, and the results for all these genes and disorders reported to their doctor, with the presumption being that the doctor should pass on the results to patients.

“Incidental” findings

At the root of the ACMG’s recommendations lies their redefinition of the term “incidental findings”. As they themselves admit, the term is normally used in a very different way:

This term has been used in a variety of clinical and research contexts to indicate unexpected positive findings. Other terms have been used to describe these findings, particularly when they are actively sought (rather than being unexpectedly discovered). These terms include “serendipitous and iatrogenic” findings, “non-incidental secondary findings”, “unanticipated findings”, and “off-target results”. We use “incidental findings” in this article to indicate the results of a deliberate search for pathogenic or likely pathogenic alterations in genes that are not apparently relevant to a diagnostic indication for which the sequencing test was ordered. Although some definitions of incidental findings allude to findings that are discovered without actually searching for results, this was not the basis for our recommendations. The Working Group recommended that the laboratory actively search for the specified types of mutations in the genes listed in these recommendations. [1]

The key point here is in the second sentence: “incidental” is not used to describe findings that are actively sought. Three of the other terms offered here do not concern actively sought results: only “non-incidental” does. In fact, the ACMG uses “incidental findings” in an entirely new way that completely inverts the usual meaning of the phrase and completely contradicts all previous definitions. Their advice is to carry out a whole array of additional tests without the patient’s consent, and then report them as “incidental.” It is dishonest to use a widely-recognized phrase and use it to convey the opposite meaning to its usual one. (The ACMG does something very similar when it argues that its guidelines are respectful of autonomy: no one would recognize this as true autonomy.) This attempt to call sought findings as incidental is indicative of a paternalistic move towards disclosing all results to patients, regardless of whether they have consented to have their biosamples tested for these conditions. Furthermore, this particular attempt to help patients without consent is quite likely to do more harm than good – not only to the patients, but also to their doctors and families.

Consent and harm to patients and families

It would be an understatement to say that the ACMG’s guidelines are challenging in terms of consent and could have harmful consequences. Conventionally, patients can consent to tests that they want and can refuse tests that they do not want. Even if they consent to being tested, they can later decide that they do not want to be told the results. The ACMG’s main recommendation is extremely unusual in that it completely overturns this convention, as several commentators pointed out:

Rejecting the need for the patient’s informed consent to look for mutations in a predetermined list of 57 genes is a profound departure from prevailing law and norms. Informed consent is a well-established legal requirement designed to protect patient autonomy – not a matter susceptible to modification by experts in human genetics, no matter how learned. [2]

As noted here, it is not only an ethical requirement but also a legal one that patients should have the right to choose which treatments and tests are conducted upon them. Astonishingly, the ACMG attempts not only to claim that the violation of autonomy was justified by the prevention of harm, but also that their guidelines did not necessitate violation of autonomy: “Autonomy is preserved since patients have the right to decline clinical sequencing if they judge the risks of possible discovery of incidental findings to outweigh the benefits of testing.” [1] It is hardly representative of the spirit of personalized medicine to claim that it respects patients’ autonomy to tell them that they can simply choose not to be tested for potentially fatal conditions if they do not want to learn about 24 other conditions that they could theoretically have, but have probably never heard of. The consent failures of the ACMG’s policy are threefold: the patient did not consent to tests; the patient did not consent to receiving results; and the patient’s family did not consent to learning about genetic information potentially relevant to themselves. If a patient was told genetic facts regarding conditions that he or she was not interested in and did not request regarding tests, he or she is presumably more likely to share this with family members, some of whom might also have the condition(s) in question.

These consent failures in turn risk harm to both the patient and his/her family. First, there are clearly psychological consequences for the patient, who may feel angry that tests were conducted without his/her consent even if no results were positive. More importantly, a patient who gets a positive result on a test would rightly be very angry to be given results to a test for a condition that he/she had never even heard of. Third, finding out that one has a potentially fatal condition is likely to be very distressing, and this distress will only be increased by the feeling that one’s autonomy was violated. And that is just the psychological harm to the patient. There will probably be financial consequences too, as the patient may have to declare any conditions detected as a result of the tests when applying for insurance, mortgages and jobs (unless specific legislation prohibits the use of genetic data in this way). Getting any of these could be more difficult as a direct result of the ACMG’s policy. Even if the patient’s doctor decides not to tell him the results (see below), these will still form part of the patient’s medical record, which companies can request access to. Furthermore, the increased volume of genetic testing required to meet the

ACMG's recommendation will increase costs, which will be passed on to patients through increased insurance premiums (and increase the profits of sequencing companies, in which most of the authors of the ACMG policy have shares; see below.) There are also likely to be consequences to the patient's family, as mentioned above; the distressed patient is likely to share this distress with the family, in turn sharing with them genetic information that might be relevant to them and which they might not want to know. If family members learn that they have or are likely to have a fatal or seriously debilitating condition, they too may have to disclose this fact and also face financial consequences.

It should be noted that the ACMG recommendations are somewhat atypical. No other guidelines on clinical sequencing anywhere else in the world adopt either the ACMG's stance on consent or their definition of "incidental findings". In the United Kingdom, the advice is that "Where there is a significant potential for incidental findings to arise, that possibility should be included in the initial consent process." [4] The European Society for Human Genetics (ESHG) took the trouble to issue an official response to the ACMG report:

The ESHG position is that whenever possible, such testing should be targeted to genome regions linked to the indication. Wider testing requires a justification in terms of necessity and proportionality. Adding screening targets to a diagnostic test violates the necessity criterion. Imposing this extra testing upon patients who need an answer to their clinical problem is at odds with respect for autonomy. [5]

These examples indicate the unique and unconventional status of the ACMG guidance. That there are numerous problems with their recommendations is obvious from reading the document itself, but this contrast with expert advice from other international authorities further undermines any authority that the ACMG recommendations may have had.

Limitations and conflicts

As should now be clear, the ACMG recommendations have many shortcomings. However, one good aspect of the report is that it at least acknowledges several limitations. Specifically, the authors identify two key areas that they did not address. The first is "data ownership or the legal ramifications of returning or withholding raw sequencing results from families that request these". This is indeed a limitation, but a rather trifling one in comparison with the problems identified earlier in this chapter. The second acknowledged limitation is that the authors did not consider "the implications of including incidental findings in laboratory reports that will become part of the patient's health record and the potential for discrimination that could arise from this

circumstance". It is incredibly irresponsible of the ACMG to recommend running extra tests and entering the results into patients' medical records without giving them any choice, while at the same time admitting that this might result in discrimination against them. If followed, the ACMG's guidance could result in patients being denied health or life insurance because of test results of which they are not aware – hardly the personalized control over medical decision-making that we expect from PM. In addition, the ACMG seems to have entirely overlooked the limitations of their recommendations in terms of the distress caused to both patients and doctors by their implementation.

Astonishingly, the authors also admit that their recommendations are not based on evidence:

The Working Group acknowledged that there was insufficient evidence about benefits, risks, and costs of disclosing incidental findings to make evidence-based recommendations. Nonetheless, based on available evidence and clinical consensus among its members, the Working Group determined that reporting some incidental findings would likely have medical benefit for the patients and families of patients undergoing clinical sequencing.

Not only did the ACMG invert the conventions concerning consent and the definition of incidental findings, they admit that they did so without having any evidence to support their recommendations, other than "clinical consensus". Furthermore, another admission later in the report makes it seem extremely implausible that there was even any consensus: "the Working Group acknowledged that its membership (and the ad hoc reviewers listed in the Acknowledgments) were not always in complete agreement, could not fully represent the opinions of others in the field, and did not have detailed knowledge of all the conditions that were considered." This makes the ACMG's failure fairly comprehensive: they made recommendations without evidence, without consensus and without their "experts" even having the relevant knowledge. Given these multiple failings, it is perhaps unsurprising that their recommendations should be so extremely flawed.

In addition to mentioning a few of the many limitations that affect their report, the authors also declare many financial conflicts of interest at the end of the publication. Among the 14 authors of the report, only 3 do not have a financial interest in supporting increased sequencing. This may explain repeated references to impracticality of tailored testing, such as "we recognize that laboratories that adopt these recommendations may add significant costs to at least some of their sequencing reports. We do not know the implications that this may have on reimbursement for clinical sequencing". The companies with which many of the authors have links would clearly benefit from the implementation of these guidelines at the expense of patients. These

conflicts indicate how patient protection can be eroded when personalized medicine is aiming at delivering profit rather than care that respects autonomy. In a related development in PM, some insurers are already offering discounts to people who transmit personal fitness data that proves that they exercise regularly. [6] While this might seem a perfectly benign development, the flipside is that pressure is being put on patients both to undergo tests and to share data in order to gain financial advantage. Professionals and members of the public must ensure that autonomy is truly respected as personalized medicine continues to proliferate.

Conclusion

Following considerable controversy, in April 2014 the ACMG issued a press release stating that it was backtracking on one of the key aspects of the original recommendations and decided to change its stance on consent:

While the ACMG Board still considers the IFs [incidental findings] to be important medical information that can be a great value to families, it has voted to recommend that such an “opt out” option be offered to patients who are considered candidates for clinical genome-scale sequencing. [7]

Although the ACMG has belatedly admitted its errors, this example serves as a warning against trying to impose paternalism on personalized medicine. The ACMG’s attempted justification for their misguided recommendations was (of course) that they were intended to benefit patients. But benefiting patients has never been sufficient justification for paternalism, and in this case the real reasons appear to have been that it wanted to give the results to patients in order to justify running the tests, and it wanted to run the tests because of a financial conflict of interest. However, even if no finan-

cial conflicts of interest existed, it would be contrary to basic principles of biomedical ethics and to the spirit of personalized medicine to paternalistically inform patients about results to tests that they did not want. As testing becomes faster and easier, any reporting of incidental findings to patients should remain confined to those that arise from the initial tests requested. To call any other results “incidental” is a massive understatement of a gross ethical violation, even if we do not support a “right not to know”. Like its traditional counterpart, personalized medicine should avoid becoming too paternalistic.

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