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## Cases in Precision Medicine: Is There an Obligation to Return Reinterpreted Genetic Results to Former Patients?

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### Abstract

Interpretation of many genetic test results can change over time as new data accumulate. Hence, physicians who order genetic tests may subsequently receive revised reports with important implications for patients' medical treatment—even for patients who are no longer in their care. Several of the ethical principles underlying medical practice suggest an obligation to reach out to former patients with this information. Discharging that obligation can be accomplished, at a minimum, by attempting to contact the former patient with their last known contact information.

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Having ordered genetic testing for a patient with a family history of breast cancer, the ordering internist receives a report indicating that no pathogenic or likely pathogenic variants were identified. However, a variant of uncertain significance (VUS) was detected in the *BRCA1* gene. Pathogenic variants in *BRCA1* are associated with a greatly increased risk of breast, ovarian and other cancers. A year later, the patient informs the physician that she is moving to another part of the country and terminates their relationship. Three years after the original testing, the physician receives an updated report from the genetic testing laboratory. Routine reinterpretation of the earlier test results has led to a revised classification of the VUS that indicates the variant in the *BRCA1* gene is now considered likely pathogenic, putting the patient at a lifetime risk of 55%–72% for breast cancer and 39%–44% for ovarian cancer.<sup>1</sup> Those risks can be mitigated by prophylactic surgery and more intensive cancer monitoring. Given that the internist has not been responsible for the patient's care for over two years, she is uncertain whether she has a legal or ethical obligation to reach out to her former patient to inform her of the revised interpretation, and if

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she does, what efforts are required to contact her and what duties might follow if contact is made.

## Why Might Physicians Receive Updated Reports from Genetic Testing Laboratories?

Classification of genetic variants included in genetic test reports is continuously evolving.<sup>2</sup> That evolution is driven by the increased amount of genetic data on individuals with and without disease (in public databases such as ClinVar<sup>3</sup> and gnomAD<sup>4</sup>), more experimental data on the functional impact of genetic variants, and more accurate machine learning methods for variant interpretation<sup>5</sup>, all of which facilitate resolution of variants of uncertain significance and building consensus interpretations across clinical diagnostic laboratories. Even so, genetic test results today show a high frequency of VUS, which are particularly important to reclassify. For genetic testing related to hereditary cancer risk, the overall reported VUS frequencies from several large cohorts have ranged from 34% to 41%.<sup>6,7,8</sup> In a study of women who had undergone *BRCA1/2* testing, 12.4% of variants were reclassified over a 5-year period.<sup>9</sup> Reclassifications may occur disproportionately for patients from non-European ancestries; one study tracked, over a 20-year period, nearly 1500 variants in cancer genes originally classified in a category other than benign, reporting an overall reclassification rate of 18.1%, but rates as high as 42.9% in *BRCA1/2* and 24.4% in 40 other cancer genes for patients of African ancestry.<sup>10</sup>

The frequency with which ordering physicians receive updated results is likely to accelerate in the coming years. In the U.S., at least one large commercial laboratory has announced that “reclassification alerts to clinicians will be sent when a clinically significant variant classification update occurs.”<sup>11</sup> Another laboratory has implemented routine case level reanalysis of exome sequencing data (which analyzes the majority of the protein-coding parts of the genome) “with reporting of new positive findings for 3 years.”<sup>12</sup> A report of interviews of genetic clinicians in Europe, Australia, and Canada suggests that laboratories in other countries are also beginning to adopt such practices.<sup>13</sup> A recent study that our team conducted, involving a series of focus groups and surveys with stakeholder groups involved in the genetic testing process (patients and parents of patients who have undergone genetic testing, clinical genetic providers, laboratory genetic providers, and non-genetic providers in specialties that frequently use genetic tests) found strong support for routine reinterpretation of reported variants.<sup>14</sup>

## Do Physicians Have a Legal Obligation to Contact Former Patients When New Information Becomes Available?

Only a small number of legal cases have considered whether a physician has a legal obligation to contact former patients with updated medical information. Although such a duty sometimes has been recognized in cases involving medications or devices the physician used in the patient’s treatment, the courts have not been unanimous on this question.<sup>15</sup> For example, while one court found that a physician who implanted an intrauterine device (IUD) had a duty to inform the patient when previously unknown risks were discovered three years

later,<sup>16</sup> another court in a similar case involving an IUD found no duty to a former patient.<sup>17</sup> There is, however, strong support among legal commentators for a duty to former patients when the newly discovered risk derives from a medication that the physician prescribed or a device that the physician put in place.<sup>14,18</sup>

How closely the situation of a reclassified genetic variant resembles those scenarios from a legal perspective has been a subject of contention. Although the reclassification to a likely pathogenic variant in our case example has significant implications for the patient's medical care, when VUS are reclassified they are most often categorized as benign or likely benign,<sup>19</sup> changes that would not alter recommended care. Some commentators have argued that the provision of information to a patient (i.e., test results) is fundamentally different from prescription of a medication or use of a device, and that any obligation to the patient is fulfilled merely by delivering the original test results.<sup>20</sup> Moreover, it is clear, as a recent review found, "that there are no cases, statutes, or regulations at present that support a legal duty to reinterpret clinical genomic tests and return any new analyses..."<sup>21</sup> Although it is always possible that courts in the future might conclude that a legal duty exists to contact a patient with reinterpreted results—and that a physician who failed to do so should be held liable—at present, the law offers no clear guidance for the internist in our case regarding the reinterpreted results that she received.

## What Ethical Considerations Are Applicable to Physicians' Decisions Whether to Contact Former Patients?

Several ethical principles may be relevant for our internist to consider.<sup>2</sup> *Beneficence*, the obligation to benefit one's patient, seems to be in play, since the information that the patient carries a likely pathogenic variant in her *BRCA1* gene could enable preventive interventions that are potentially lifesaving. The principle of *non-maleficence*, the duty not to harm one's patient, represents the other side of the coin of beneficence and could be invoked here as well. Withholding information that is highly relevant to the patient's medical care might well lead to significant—and avoidable—harm. *Respect for the patient* also seems to be at stake, since provision of the new interpretation of her genetic test would allow her to make an informed, autonomous choice about the risks she is willing to run and the steps she wants to take to reduce them. Finally, insofar as physicians have a *fiduciary duty* to act to promote their patients' best interests, that too might support an obligation to disclose the information.<sup>17</sup>

All of these principles and duties are generally recognized to apply to physicians' treatment of their active patients. To what extent are they applicable to former patients? Some scholars would respond that they are applicable to a considerable extent, challenging the assumption that all physicians' ethical duties end with the termination of the formal doctor-patient relationship.<sup>14,17</sup> Indeed, the position that doctors owe at least some continuing obligations to patients may reflect the ethical intuitions of many physicians, who are likely to feel some obligation to act in a case like this one. We suggest, though, that an additional factor comes into play when genetic tests are involved. As noted above, genetic tests frequently yield VUS and other findings that will subsequently be revised. By virtue of ordering a test

where reclassifications are likely to occur, we suggest that physicians incur an obligation to deal with certain predictable downstream consequences, specifically new information that would affect medical care, by contacting both current and former patients with the updated findings.<sup>2</sup>

This position is reflected in the most recent “points to consider” document on the subject from the American College of Medical Genetics and Genomics (ACMG): “If contacted by the laboratory with an updated result, the ordering physician should make reasonable efforts to recontact the patient.”<sup>22</sup> The American Medical Association (AMA) addressed this issue in its Opinions on the Code of Medical Ethics in a way that also seems consistent with the approach we are recommending: “Ethical responsibility includes informing patients of changes in their diagnoses resulting from retrospective review of test results or any other information.”<sup>23</sup> Although this provision is not explicitly applied to former patients, such an application would appear to be in keeping with the AMA’s statement.

Not every change in genetic variant classification will warrant recognition of a duty for the ordering physician to reach out to former patients. In our view, the strength of the argument for recognizing a residual obligation towards former patients increases as: the importance of the information for the person’s medical care increases; the likelihood of the person benefitting from having the information is greater; and the time since last contact with the person decreases. Each of these factors increases either the probability that the person will benefit from receiving the information or the likelihood that the person will expect the former physician to transmit this information. In specific cases, these factors may need to be weighed against each other to determine the reasonableness of recognizing an ongoing obligation. For example, given a high likelihood of benefit from the information, the time since last contact may assume lesser importance. As a rule of thumb, we suggest that, at a minimum, results that would be likely to alter the medical advice or treatment a patient would receive should be communicated to the former patient. Acknowledging an obligation to former patients in these circumstances is consistent with physicians’ ethical obligations of beneficence, non-maleficence, and respect for the people they treat.

## **What Role Do Parties Other than the Ordering Physician Play in Return of Reinterpreted Results?**

Physicians operate within a complex healthcare ecosystem. Other parts of that system should reasonably bear some responsibility for ensuring that when the interpretation of genetic test results changes, patients (including former patients) and their treaters can receive that information.<sup>2</sup> Laboratories that conduct genetic testing need to retain patients’ data to allow reinterpretation; to implement systems that allow identification of patients’ with variants whose classification has changed; to reinterpret test results; and to send revised reports to the ordering physician. However, given that laboratories generally do not have patients’ contact information, lack the ability to counsel patients about the implications of the results and the networks to refer them appropriately, and may face regulatory restrictions on communicating directly with patients, they are not the optimal party to convey reinterpreted results to patients themselves.

Patients clearly carry some responsibility as well. Patients who are leaving care with a physician can reasonably be expected to carry the burden of keeping their contact information up-to-date,<sup>24</sup> and physicians cannot be faulted for being unable to contact patients who fail to do so. Creation of a centralized database for patient contact information that patients could be encouraged to update would simplify that process for patients, who would not have to contact each of their providers. At times it has been suggested that patients should have the obligation to inquire periodically of the physicians with whom they have consulted<sup>25,26</sup> whether their genetic results have been updated, presumably relieving ordering physicians of any obligation to notify them. For many patients, however, a genetic test will be just one part of their medical care and, especially if there were no pathologic findings, may not even be very salient in their memory. Given the likelihood that a growing number of laboratories will be issuing revised test reports and sending them to physicians, it seems more reasonable to ask physicians to forward that information than for them to wait until patients inquire about it. That is especially true for situations as in our case where the information could have profound implications for the patient's health.

Most physicians today practice in organized environments, i.e., medical centers, clinics, and practice groups. Such entities will clearly need to shoulder some responsibilities as well. Outreach to patients could be facilitated by staff who identify contact information and set up times for a conversation with the physician to take place. Healthcare organizations will also need to anticipate the situations in which physicians are no longer with the practice. Procedures will be needed to flag incoming revised genetic test reports and to assign responsibility for following up with patients or former patients to appropriate personnel.<sup>27</sup> In some cases, an ordering physician will have referred a patient to a geneticist or genetic counselor to assist in interpretation of the original results. Although it is still the responsibility of the ordering physician to follow-up with the patient when a revised test result arrives, referral to the consulting geneticist or genetic counselor may again be helpful to clarify the implications of the new interpretation.

## **What Practical Guidance Can Be Provided Regarding How to Fulfill the Ethical Obligations to Former Patients?**

With regard to what constitutes discharge of the obligation, we suggest—consistent with the ACMG statement—that it be limited to making reasonable efforts to contact the former patient. This may vary depending on the circumstances, but in general an effort to reach out to the person using the last known mailing address, email address, or phone number would appear to be sufficient, perhaps supplemented by communication through the patient portal of the electronic health record if one exists. Indeed, the ease of discharging the obligation of notification reinforces the argument for recognizing an obligation that continues beyond the end of the treatment relationship. We recognize that many physicians may feel compelled to do more if these efforts are unsuccessful, especially when revised results hold significant implications for patients' health, and we believe that such efforts are in keeping with the ethical principles discussed above. However, we are reluctant to suggest that a physician who ordered a genetic test has a further obligation to search the internet or social media to try to find a patient who is no longer reachable with their last known contact information.

The value of conveying potentially actionable medical findings to a patient must be balanced against the imposition of limitless duties on physicians and the medical care system.

Does a physician who contacts a former patient have additional obligations to counsel the person about the implications of the revised test results? Continuity of care for the person would probably be facilitated by referring them to their current treating physician for discussion of the implications or, if they are not being followed by a physician, by suggesting that they find a new clinician who can assume responsibility for their care. That physician could consult with or refer the patient to a geneticist or genetic counselor if lacking the expertise to advise the patient. Of course, the original physician could always decide to accept the former patient back into treatment—but would not be obligated to do so—for the purpose of follow up.

Should residual obligations of notification be limited in any other way? For example, should they end after a certain period, say five years following the termination of the physician-patient relationship? Although former patients are likely to become harder to recontact as more time elapses, we would argue against arbitrary time limits on residual obligations of notification. Indeed, key stakeholders involved in the genetic testing process, have expressed a strong preference for avoiding an arbitrary time limit for an obligation to reinterpret genetic variants and communicate genetic test results in light of updated information.<sup>13</sup>

## Conclusion

Several important duties and principles converge to suggest that the internist in our case has an ethical obligation to make reasonable efforts to contact her former patient to convey the results of the revised genetic test report and what could potentially be life-saving information.

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### Key Summary Points

- Classification of genetic test results may change over time as new data become available, which may have important implications for patient care.
- Physicians may receive revised genetic test reports for former patients, years after they have left the physician's care.
- There is no clear legal guidance on a physician's obligations to contact former patients with updated classifications of genetic test results.
- Several ethical principles, however, including beneficence, non-maleficence, and respect for the patient, along with physicians' fiduciary responsibilities, suggest an obligation to act, especially when the results may have a significant impact on patients' medical treatment.
- Physicians should be able to discharge their obligations by attempting to contact patients using their last known contact information. There is no obligation to reassume responsibility for the patient's treatment.