POINT-COUNTERPOINT

Patient Autonomy and Incidental Findings in Clinical Genomics

Returning genetic incidental findings without patient consent is misguided.

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Exome and whole-genome sequencing are rapidly moving into clinical application to aid diagnosis and treatment. However, a startling statement by the American College of Medical Genetics and Genomics (ACMG) may prove to be a stumbling block (*1*). Rather than reconfirming well-established principles of patient autonomy and informed consent that have long applied in medical genetics and in medical practice more broadly, ACMG recommends an abrupt change.

When clinical sequencing is undertaken to look for a "primary finding" (i.e., "a pathogenic alteration in a gene or genes that are relevant to the diagnostic indication for which the sequencing was ordered"), the ACMG calls for laboratories to search for "pathogenic and likely pathogenic variants" in an additional 57 specified genes and report results without seeking patient consent. These "incidental findings" are "results that are not related to the indication for ordering the sequencing but that may nonetheless be of medical value or utility to the ordering physician and the patient." However, the ACMG addresses only "the results of a deliberate search" for specific variants, not other genetic findings discovered unexpectedly, the more common use of the term "incidental findings" (*2*–*4*).

The ACMG calls for clinicians to report the results of the deliberate search for incidental findings to the patient, with no opportunity for the patient to decline unwanted information. The patient's only choice is to decline sequencing altogether, even if medically indicated. The ACMG imposes these requirements even when the patient is a child who has no medical need for these results during his or her childhood. The ethical and legal problems raised are profound. A recent ACMG clarification of this practice statement, in response to concerns, makes the problems worse (*5*). The clarification reiterates that patients cannot opt-out of testing on the 57 genes and now says that failing to report these test results would be "unethical."

Patient Decisions and the Right Not to Know

The ACMG rejects the need for the patient's informed consent to a deliberate search for these incidental findings, claiming that the amount of genetic counseling required would be too great. Yet the report marshals no data to support this conclusion and never considers proposals in the literature for streamlining the consent process when large numbers of genes are evaluated, such as "generic consent," which would allow the patient to consider categories of genetic tests together (*6*). The report also rejects the idea that laboratories should mask analysis of certain genes when there was no consent to search for them or could tailor reports, based on unsubstantiated fears of "unrealistic burden upon laboratories."

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. Circumstances in which clinicians can test without consent are rare exceptions. In a medical emergency that prevents seeking consent—for example, when the life or health of an incompetent or unconscious patient is in imminent danger, and no one is available to consent—society allows physicians to treat without consent (*7*). However, this does not apply when laboratories and clinicians perform clinical sequencing, because they are not responding to a medical emergency threatening imminent harm and preventing them from seeking consent.

ACMG suggests that their recommended search for incidental findings is analogous to a radiologist spotting and reporting an unexpected tumor or other finding of concern on an x-ray. The analogy is misplaced. A deliberate hunt on a predetermined list of genes unrelated to the diagnostic reason for which sequencing was ordered is very different from the unexpected finding of a tumor in or near the area of primary concern in the field imaged by an x-ray. Patients would have no reason to expect a hunt for incidental findings in the 57 disparate genes on the ACMG list, especially when the list includes genes whose analysis and reporting have long required patient consent.

The ACMG is mistaken in basing their search and disclosure recommendations on a "fiduciary duty" to prevent the harms these findings may suggest. In both ethics and law, the clinician has a core fiduciary duty to respect the patient's right to decide what testing to undergo and what information to receive. Patients have an established right to refuse unwanted medical tests and the information they might disclose, even if that information would offer potential medical benefit (*8*, *9*). Indeed, the ACMG has recently affirmed the right to refuse unwanted incidental findings in clinical genomic sequencing (*10*). If the ACMG is now worried about potential liability for failing to return results from their list, they should urge clinicians to document the patient's refusal, not strip patients of the right to decide. Inflicting unwanted information on patients carries its own risk, as unwanted information may lead to anxiety, further clinical workup, and potentially burdensome interventions.

"Autonomy protects the patient's right to make a decision different from what the clinician might choose."

The ACMG's "minimum list" includes mutations in genes that patients have long been able to refuse testing for, including cancer risk mutations (such as *BRCA1*) and cardiovascular risk mutations. There are many circumstances in which a patient may decline such testing and information, even if the results could open avenues for intervention. The patient may already be battling another disease, such as advanced cancer, or be late in life and see more burden than benefit in

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added genetic information. The patient may also fear that "extra" results in their medical record will invite risk of discrimination (*11*).

The whole idea behind informed consent is that patients are individuals who are entitled to make medical decisions in keeping with their own values. Autonomy protects the patient's right to make a decision different from what the clinician might choose and even to reject information and treatment that might maximize life expectancy. Although ACMG's new clarification refers to "shared decision-making" by provider and patient, there is no recognition of the patient's right to refuse testing and results. Indeed, ACMG's claim that failure to report the findings on their list would be unethical will likely compel laboratories and physicians to report. Yet this claim is incorrect. Patients have the right to refuse testing and findings, even if potentially lifesaving. Just because many patients might want this information does not mean that it can or should be imposed on all.

The Child's Right to Limits on Testing

The report also departs from long-standing consensus recommendations on testing children. The ACMG acknowledges that "standards for predictive testing in clinical genetics recognize a distinction between providing results to adults and providing results to children and adolescents, with consistent recommendations that predictive testing for adult-onset diseases not be offered to children." This consensus has stood since at least 1995, when the ACMG and American Society of Human Genetics published recommendations (*12*). Just this year, the ACMG and American Academy of Pediatrics reiterated that "Decisions about whether to offer genetic testing and screening should be driven by the best interest of the child" (*13*, *14*).

The report emphasizes that searching for incidental findings in the child's 57 genes is an opportunity for other family members to learn of variants that may be important for their own health. Yet this is exactly what past recommendations have rightly rejected, in limiting genetic testing and disclosure of genetic information to what is medically necessary during childhood. Delaying testing and return of genetic information not medically useful in childhood allows the child to reach adulthood and then make a choice based on his or her own values. The child's right to genetic privacy and future choice is preserved. ACMG argues that potential health benefit to a parent may benefit the child, but past guidance has found the clear risk of harms to the child more compelling.

ACMG's clarification now claims that limits on testing children for adult-onset conditions do not apply to the incidental findings on their list. Yet consensus limits on pediatric testing have long applied to variants conferring risk of serious adult-onset disease. When children have undergone clinical sequencing, they can choose at adulthood whether to request their findings. Even for child-onset conditions, past guidelines have required consent to testing (*13*).

Problems with the List

In addition to the problems of unconsented testing and disclosure, even in children, there are problems raised by ACMG's list of 57 genes. These genes and the types of variants that laboratories must search for and report can be broken down into three basic categories covering a wide range of medical conditions: risks for developing cancer and noncancerous tumors (24 genes), cardiovascular risks (31 genes), and adverse reactions to commonly used anesthetics (2 genes). The report indicates that the criteria they used include: "clinical validity and utility," recognized or expected pathogenicity of the sequence variant, "variants with a higher likelihood of causing disease" (although ACMG notes "that there are limited data available in many cases to make that assessment"), availability of "preventive measures and/or treatment," inclusion of mutations that "might be asymptomatic for long periods of time," and availability of "confirmatory approaches for medical diagnosis" (although ACMG recognized "that this standard could not be met for all of the conditions listed").

If the ACMG was trying to justify required search and disclosure of incidental findings without patient consent, the criteria should have been considerably more stringent (such as significant likelihood of substantial harm in the near future if not communicated). The broad criteria used would actually justify a much longer list of genes, including a number associated with risk of other cancers. Singling out this selection of 57 genes appears arbitrary. This problem is exacerbated by the fact that ACMG says a laboratory may look for incidental variants in additional genes "as deemed appropriate by the laboratory." The criteria that laboratories will use remain unclear. The ACMG itself also plans to revisit its list annually. As the list expands, so will the scope of testing without consent and the number of incidental findings potentially reported to the patient.

The report tries to confine the impact of these recommendations by saying the authors chose not to consider preconception, prenatal, or newborn sequencing. However, if testing for incidental findings in the list of 57 genes is so important that they must be looked for whenever sequencing is performed, why shouldn't they be looked for in preconception, prenatal, and newborn sequencing? Starting down the path of unconsented testing and reporting in clinical genomics leads to grave difficulties, and should not be done without more careful analysis.

Next Steps–Restoring Respect for Patients

The ACMG should reconsider this practice statement. Clinical sequencing is a medically important tool, already deployed for certain indications. Access should not be conditioned on patients' surrender of established rights. Especially in the case of children, who will generally not even be able to exercise the option of walking away from sequencing, long-standing protections remain essential. The era of medical genomics requires a trusting partnership with patients, based on respect for their rights.

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