The Continuing Evolution of Ethical Standards for Genomic Sequencing in Clinical Care: Restoring Patient Choice

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Introduction

Large-scale genome and exome sequencing is rapidly moving from research investigation into clinical care. When cancer patients fail to respond to conventional treatment, sequencing can suggest new molecular targets for chemotherapy and other treatment. When children present with puzzling neurodevelopmental anomalies, sequencing can shorten the diagnostic odyssey by revealing potentially causative genetic variants. Sequencing can even be used to help diagnose critically ill individuals in order to save lives.

With sequencing transitioning into clinical care, controversy has erupted over how to manage incidental or secondary findings. Whenever a physician orders genomic analysis for a particular indication, certain genes are of focal concern and their analysis yields primary findings. However, sequencing, especially on a large scale — potentially up to whole exome or whole genome sequencing — may yield additional findings on genes that are not germane to the original indication but nonetheless may hold clinical significance because they indicate another risk, disease process, or condition. An enormous literature now addresses the question of how to handle these additional findings, both in research and in clinical care.[1]

The American College of Medical Genetics and Genomics (ACMG)[2] — the leading professional society for medical geneticists in the United States — has issued a series of policy statements to guide management of incidental or secondary findings that arise in clinical sequencing. However, the complexity of this issue has thwarted easy resolution. ACMG exercises a leadership role in multiple domains of genomic medicine, from clinical prescribing to laboratory practice, electronic health records (EHR), and insurance coverage. But the question of incidental findings has prompted College statements every year since 2012.

This article traces the evolution of ACMG policy on incidental or secondary findings and argues that further change is needed. Current ACMG policy urges a regime involving a routine search for an expanding set of extra genes, offering patients only an opt-out from the entire set. The routinization of this search continues to constitute opportunistic screening without the empirical foundation for this public health measure. Moreover, routine screening with an opt-out is far different from informed consent offering patients the opportunity to opt-in to extra testing. And forc-

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ing patients to make a decision as to the entire set of extra genes — a heterogeneous and growing collection including cancer risk, cardiovascular risk, and soon pharmacogenomics genes — robs patients of the opportunity to exercise autonomous choice based on their health circumstances and values. These problems with current ACMG policy are even more acute because the policy still includes children on the same footing as adults, but the "all or nothing" opt-out deprives parents, guardians, and adolescents of the option to delay testing for genes associated with adult-onset conditions.

ACMG 2012

The evolution of ACMG policy on incidental or secondary findings begins with the College's 2012 policy statement on, "Points to Consider in the Clinical Application of Genomic Sequencing."[3] Recognizing that large-scale sequencing was moving into clinical use, the policy recognized that sequencing would produce not only "diagnostic results," but also "secondary findings (also called incidental or unanticipated findings)." The policy acknowledged that, "Such secondary findings are highly likely, if not inevitable, whenever WGS/WES is performed."

The policy statement called for laboratories and clinics to establish "clear policies…related to disclosure of secondary findings." The policy called for informing patients of the policies and "the types of secondary findings that will be reported back to them and under what circumstances." However, the policy provided a patient opt-out: "Patients should be given the option of not receiving certain or secondary findings." Nothing in this policy explicitly called for restricting patient choice on secondary findings to "all or nothing."

ACMG 2013

In March of 2013, ACMG issued a new paper focusing on the problem of incidental or secondary findings, the fruit of a year's worth of effort by a working group examining this issue.[4] This lengthier paper used the term "incidental findings," defining these as "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." This paper articulated a list of 56 extra genes that should be analyzed and reported by the laboratory whenever sequencing was undertaken. This roster of cancer risk, cardiovascular risk, and pharmacogenomics genes was chosen based on pathogenicity and clinical actionability, though the paper noted that "[a]dditional genes may be analyzed for incidental variants, as deemed appropriate by the laboratory."

Current ACMG policy urges a regime involving a routine search for an expanding set of extra genes, offering patients only an opt-out from the entire set. The routinization of this search continues to constitute opportunistic screening without the empirical foundation for this public health measure. Moreover, routine screening with an opt-out is far different from informed consent offering patients the opportunity to opt-in to extra testing. And forcing patients to make a decision as to the entire set of extra genes — a heterogeneous and growing collection including cancer risk, cardiovascular risk, and soon pharmacogenomics genes — robs patients of the opportunity to exercise autonomous choice based on their health circumstances and values.

The working group urged that the clinician ordering sequencing "discuss with the patient the possibility of incidental findings," with patients having "the right to decline clinical sequencing if they judge the risks of possible discovery of incidental findings to outweigh the benefits of testing." However, the paper contemplated that patients would either accept sequencing with a laboratory search for the full set of incidental findings or decline sequencing altogether. There was no option to accept sequencing for the primary indication but to opt-out of the search for incidental findings. And there was no option to choose some incidental findings (say, perhaps, cancer risk findings in a patient already facing cancer) but not others (for example, cardiovascular findings). Thus, if a patient needed clinical sequencing (as presumably most relevant patients would, given the fact that sequencing

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was ordered), then the search for incidental findings was a required part of that process.

This represented a retreat from the 2012 position that patients could accept clinical sequencing but opt out of a report of secondary or incidental findings. While the 2013 paper technically left communication of these findings to the clinician, the possibility that the clinician might refrain from communicating pathogenic and actionable findings in the laboratory report seemed remote, given that patients have direct access to their health records under HIPAA.[5] (Indeed, as of 2014, patients have direct access to their laboratory reports.[6])

ACMG's 2013 paper anticipated the outcry that ensued due to the call for mandatory inclusion of secondary or incidental findings analysis whenever clinical sequencing was performed. The paper itself said,

> the Working Group did not favor offering the patient a preference as to whether or not their clinician should receive a positive finding from the minimum list of incidental findings described in these recommendations. We recognize that this may be seen to violate existing ethical norms regarding the patient's autonomy and "right not to know" genetic risk information.

Vigorous objections to the 2013 policy focused on several issues.[7]

First, as ACMG anticipated, mandatory analysis of secondary or incidental findings and the reality that clinicians would feel impelled to communicate those results deprived patients of choice and vitiated the "right not to know" that has long obtained in clinical genetics. Second, ACMG acknowledged that instituting routine analysis of secondary or incidental findings whenever patients undergo sequencing constitutes "opportunistic screening."[8] Yet opportunistic screening is a public health measure that requires empirical demonstration that the criteria for instituting such screening have been met, including positive predictive value and net population benefit. As Burke and colleagues pointed out, those criteria had not been met.[9] Third, some challenged the working group's roster of 56 genes; given that the list was meant to capture highly pathogenic and clinically actionable genes, critics questioned the list on grounds of both over-inclusion and under-inclusion.

Finally, a robust debate erupted over ACMG's inclusion of children in its recommendations: "Incidental variants should be reported regardless of the age of the patient."[10] Policy had long favored confining genetic testing of minors to those results needed for medical management in childhood, delaying other genetic testing until the child achieved the age of majority and could choose for him- or herself whether to undertake that testing. Indeed, a 2012 technical report published in early 2013 from ACMG together with the American Academy of Pediatrics (AAP) had reiterated this view:

> Early professional statements recommended that predictive genetic testing of minors be considered only if effective medical interventions were available to treat, prevent, or retard the course of the disease. Since then, more than two dozen additional national and international guidelines have concurred.... The AAP and the ACMG continue to support the traditional professional recommendation to defer genetic testing for late-onset conditions until adulthood.[11]

The technical report recognized that there might be exceptional cases warranting testing for genes associated with risk of adult-onset conditions "to resolve disabling parental anxiety or to support life-planning decisions that parents sincerely believe to be in the child's best interest."[12] However, this case-by-case approach was in effect rejected by ACMG's 2013 policy that secondary or incidental findings should be routinely ascertained and reported, even in children and even when the genes in question were associated with adult-onset disorders.

Objections to all four dimensions of the 2013 paper produced vigorous debate whose importance went well beyond the question of how to handle secondary or incidental findings. At issue was the scope of patient autonomy in the new era of genomic medicine, the relationship between patient autonomy and physician paternalism, protections for children and adolescents, the ethical use of pediatric testing to warn family members of their own possible genetic risks, and the criteria for public health screening using genomic technologies. The importance of the issues and the outcry provoked by the 2013 paper prompted ACMG to issue a clarification statement later in 2013 defending the paper by emphasizing its "focus only on unequivocally pathogenic mutations in genes in which pathogenic variants lead to disease with very high probability and cases in which evidence strongly supports the benefits of early intervention."[13] On children, the clarification attempted to reconcile the longstanding policy disfavoring testing for adult-onset conditions in children (as reiterated in the ACMG/AAP technical report) with the 2013 paper by saying, "The ACMG affirms its recommendation not to perform diagnostic testing for an adult-onset condition in children but believes that reporting an incidental finding of a severe, actionable,

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pathogenic mutation falls outside this recommendation."[14] The furor, however, would not abate.

ACMG 2014

To ACMG's great credit, the organization took seriously the continuing concerns. In April 2014, ACMG's Board issued a news release modifying the policy articulated in the 2013 paper and subsequent clarification. The release reinstated the opt-out created by the 2012 policy, but clarified that the patient should be able to opt out of analysis of secondary or incidental findings, not just opt out of receiving a report of those findings:

> There appears to be a consensus among ACMG members that patients should have an opportunity to opt out of the *analysis* of medically actionable genes when undergoing whole exome or genome sequencing. While the ACMG Board still considers the IFs 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.[15]

Meanwhile, ACMG undertook a survey of their membership on a range of questions raised by the 2013 paper. In early 2014, they emailed a survey link to the membership, with the results published in November. The survey found high agreement (80.7% combining "agree" and "strongly agree") that patients "should be able to opt out of laboratory analysis of the 56 genes on the ACMG list."[16] There was less agreement that patients "should be able to decide which genes will be analyzed for pathogenic variants among the 56 genes on the ACMG list" (46.2% combining "agree" and strongly agree"), though only 34.8% rejected this idea (combining "disagree" and "strongly disagree").[17] There was no consensus on how to manage secondary or incidental findings in children.

ACMG 2015

Informed by this survey, the ACMG issued updated policy in 2015.[18] This policy maintained that genetics professionals should seek written informed consent from patients for large-scale clinical sequencing. That consent process should address "the inevitable generation" of secondary or incidental findings. However, rather than stating that these professionals should seek patient consent for what the 2013 paper made clear was a "deliberate search" for these extra findings, the 2015 policy stated that patients "should be made aware that, regardless of the specific indication for testing, laboratories will *routinely* analyze the sequence of a set of genes deemed to be highly medically actionable so as to detect pathogenic variants that may predispose to a severe but preventable outcome."

Once the patient was informed of this routine search and analysis, the patient would be offered the choice of opting out, but with a warning as to the potential consequences: "Patients should be informed during the consent process that, if desired, they may opt out of such analysis. However, they should also be made aware at that time of the ramifications of doing so." There was no parallel recommendation that patients be warned of the potential consequences of *failing* to opt out (e.g., discovery of secondary or incidental findings that proved to be false positives, creating an unwanted record of susceptibility to disease unrelated to the reason for sequencing, potential vulnerability to discrimination, or other consequences). In addition, the 2015 update made clear that patients could not choose analysis and report of some secondary or incidental findings but not others: "it is not feasible for patients to be offered the option of choosing a subset of medically actionable genes for analysis. Thus, the decision regarding routine analysis should apply to the entire set of genes deemed actionable by the ACMG."

Thus, the bottom line remained a routine search for the full set of secondary or incidental findings every time clinical sequencing was ordered for any indication. Rather than seeking opt-in consent from patients for this extra search with information on the potential benefits and risks, patients could only opt out and with a warning of the potential consequences of exercising that option.

There was no discussion of whether this routinized opportunistic screening was now supported by greater evidence than when the policy was first put forth in 2013. Similarly, the 2015 update made no change to the inclusion of children in the 2013 paper, despite the lack of consensus on this point in the 2014 survey of the membership. "[T]he board recommends that the same policy should be adhered to in children as in adults; i.e., analysis of a set of selected genes to identify pathogenic variants associated with severe but preventable disease should be routinely performed."

Finally, the board made clear that the list of extra genes to search would evolve. They referred to "an ever-changing list" and ended the policy statement by saying, "A multidisciplinary working group has been formed to develop a process for updating and maintaining the list of genes to be routinely analyzed for secondary findings."

ACMG 2016

In late 2016, the ACMG Secondary Findings Working Group published an update to ACMG's policy state-

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ment on secondary findings.[19] The committee had requested that ACMG members nominate genes for inclusion or deletion from the list: "The Secondary Findings Working Group will review nominations periodically with a plan to publish updates to the Secondary Findings Gene List twice per year."[20] The first update, published in November, added five genes to the ACMG list of 56 and removed one — the "ACMG 56" became the "ACMG 59."[21]

In addition, the committee indicated they would now consider adding pharmacogenomics (PGx) genes to the list in future updates. As the committee co-chair explained, this was a notable shift:

> Pharmacogenomics genes 'don't fit into the same model of disease which we're used to for the other genes'.... PGx genes are fundamentally different from the genes that are currently on the list because they do not predispose to disease or an adverse event on their own, but only in combination with exposure to a drug.... Secondly, the information gleaned from PGx genes may not be immediately actionable but might only be relevant in the future, when a drug is prescribed.[22]

Thus, ACMG is contemplating significantly expanding the scope of routine extra analysis when clinical sequencing is undertaken.

Continuing Problems with ACMG Policy

ACMG's 2014 clarification and 2015 update to policy on secondary or incidental findings represented an important improvement, but failed to resolve the underlying issues. While ACMG removed mandatory analysis of secondary or incidental findings by creating an "opt-out," the updated policy failed to embrace informed consent. Instead, the presumption that such analysis would be undertaken remained in place. Thus, ACMG policy continues to treat such analysis as "routine."

The opt-out is also circumscribed. Patients may only opt-out of the full (and expanding) set of secondary findings; they have no option to omit the genes irrelevant to their condition and concerns, while allowing those they deem more germane. Thus, there is no opportunity for patients to make the customary risk/benefit analysis they make in other clinical decision contexts, to reject analysis of those genes that fail to offer sufficient benefit from the patient's perspective. And patient capacity to perform this normal risk/benefit analysis is further hampered by the fact that ACMG policy calls for warning patients only of the implications of opting out, not providing information on the risks and benefits of accepting or rejecting secondary findings analysis across the roster of extra genes to be analyzed. While ACMG has argued that counseling patients on all of these genes would be too time-consuming,[23] commentators have pointed out that the genes cluster into types (e.g., cancer risk, cardiovascular risk, pharmacogenomics) that are quite amenable to explanation and counseling.[24]

A substantial ethics and empirical literature contrasts customary informed consent allowing patient to opt in to diagnostic or treatment interventions with the more unusual practice of categorizing an intervention as "routine" and allowing an opt-out.[25] The former robustly protects patient autonomy and decisional authority. The latter does not. Its weaker protection must be justified by demonstration that compromising patient autonomy is required to meet a public health goal or other imperative that cannot be entrusted to patient choice. A classic example of this is found in states that perform newborn screening as a routine practice, subject to parent opt-out. The ethics of this decisional approach have been extensively debated. The primary justification for limiting parental decisional authority is the best interests of a separate human being — the newborn.

In the case of secondary or incidental findings, no demonstration has yet been made that the search for these extra findings confers adequate population benefit to justify treating it as a routine practice subject only to opt-out, rather than an option that patients can affirmatively choose through opt-in. Indeed, the ACMG secondary findings committee acknowledged in its 2016 publication that the net utility of their entire approach to ascertaining secondary findings through opportunistic screening whenever clinical sequencing is ordered has yet to be established. First, as the committee noted, the list is based on an assumption of high penetrance that could prove incorrect for various genes included:

> [W]e recognize the presumption of high penetrance for these genes and diseases based on potentially biased case ascertainment. Specifically, literature reports for many of these conditions represent assessment of disease probands and their families. Over time, we may discover that penetrance for some of these conditions is lower than current estimates suggest.[26]

Second and more globally, the net utility of this opportunistic screening has not yet been established: "The reporting of [secondary findings] presents significant opportunities to prevent disease, but this process may introduce fiscal and other costs, including those associated with further confirmatory testing.... [I]t will be

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important for the genomics community to study the impact."[27]

These committee acknowledgments reinforce the point made by Burke and colleagues in arguing that the ACMG policy has instituted opportunistic screening without the empirical demonstration of positive predictive value and net benefit to support it.[28] The fact that ACMG's secondary findings committee is now considering expanding the list of genes based on member nomination does not provide reassurance that rigorous demonstration will be required that the criteria for instituting opportunistic screening have been met for each gene.

Indeed, research is demonstrating that few people test positive for the genes on the list of 56, at least in the populations studied so far.[29] This makes it all the more puzzling to routinize the practice of searching for and reporting these extra genes, rather than offering it as an option that patients can elect with information and guidance from their clinicians. The importance of individual patient decision making based on the individual's circumstances and values is reinforced by the ACMG committee's acknowledgment in 2016 that judging the actionability of a given gene in deciding whether to test for it involves a subjective determination of the "acceptability of the proposed intervention [to address the gene or condition] based on its risks and benefits."[30] This subjective judgment of the acceptability of a clinical intervention is exactly the sort of values-based judgment that patients are asked to make all the time in other clinical contexts. To instead routinize the practice of searching for an expanding set of secondary findings removes an important step of individualized clinician counseling on secondary findings analysis options and individual patient decision making. This diminishes the crucial role of both the clinician and the patient.

The Association of Molecular Pathology (AMP) itself convened a working group on incidental findings that departed from ACMG's endorsement of routine analysis with opt-out only. Instead, the AMP group endorsed "opt-in or opt-out…in the precounseling session."[31] The group elaborated,

> [P]ersons undergoing WES or WGS should have the opportunity to *opt-in or opt-out* of receiving a report that documents variants that are not relevant to the initial reason for testing.… Most patients will likely opt-in, given the opportunity to receive additional information that could be used to improve their health. However, health care professionals must be sensitive to the possibility that patients dealing with a difficult medical issue that led to the need for WES or WGS may not wish to have an additional burden of concerns placed on them about future health issues. In addition, the needs of specific cultural and ethnic groups must be accommodated.[32]

The last point is particularly telling. The Havasupai case against Arizona State University stands as a reminder that members of some groups may object to generating certain genetic findings but not others.[33] In addition, routinizing genetic analysis of a set of genes based on pathogenicity and clinical actionability in populations analyzed to date may not be appropriate for other populations underrepresented in current databases.[34] The AMP working group further pointed out that "the expressivity of genetic variants known to be highly penetrant in high-risk communities is unknown for low-risk communities."[35]

Finally, on analyzing and reporting secondary or incidental findings in children, the ACMG policy continues to draw fire. Not only did the survey of membership fail to show consensus support for ACMG's policy on minors, but a 2015 report from the American Society of Human Genetics (ASHG) failed to support the ACMG position as well. Instead of a routine report of secondary or incidental findings "regardless of the age of the patient" (as ACMG recommended),[36] ASHG urged limiting the report of secondary findings to those cases in which "the information has clear clinical utility for the child and/or his or her family members."[37] And instead of relying on an opt-out, ASHG called for "a robust informed-consent process" and recommended that children "be included in the informed-assent or -consent process to the extent that they are capable."[38]

Conclusion

The future of genomic medicine rests on public trust that respect for patient preferences and values will obtain in this domain of clinical care, as it does in others. The quantity of results in large-scale sequencing and potential complexity of interpretation do not justify a genomic exceptionalism that exempts genomic analysis of secondary findings from informed consent. While ACMG clearly called for informed consent to clinical sequencing, the failure to maintain respect for patient choice on the distinct question of whether to undertake an extra search for secondary findings warrants reconsideration. As ACMG noted in 2013, the search for secondary or incidental findings requires "a deliberate search."[39] And as others have pointed out, embarking on a search for findings unrelated to the indication for sequencing is a separate effort,[40] which can be accepted or declined. Indeed, the AMP group maintains that secondary or incidental findings "are

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not evident without significant extra effort directed toward that end."[41]

Undertaking that extra effort to search for secondary or incidental findings warrants informed consent with counseling on the risks and benefits. Patients should have the opportunity to opt in to desired secondary findings analysis based on counsel from their clinicians. Patients and clinicians should be able to discuss what subset of secondary findings to elect, based on a patient-specific consideration of risks and benefits. And secondary or incidental findings analysis in minors should be limited as ASHG suggests, with the robust informed consent and assent process they urge.

ACMG has demonstrated admirable determination to address the important issue of secondary or incidental findings, to collect data on member attitudes, and to evolve policy over time. With sequencing rapidly moving into clinical care and the arrival of precision medicine relying on genomics, ACMG should go the next step to restore informed consent and respect for patients to the practice of clinical genomics.

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Note

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References

1. See, e.g., S. M. Wolf et al., "Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations," *Journal of Law, Medicine & Ethics* 36, no. 2 (2008): 219-248; R. R. Fabsitz et al., "Ethical and Practical Guidelines for Reporting Genetic Research Results to Study Participants: Updated Guidelines from a National Heart, Lung and Blood Institute Working Group," *Circulation: Cardiovascular Genetics* 3, no. 6 (2010): 574-580; J. S. Berg, M. J. Khoury, and J. P. Evans, "Deploying Whole Genome Sequencing in Clinical Practice and Public Health: Meeting the Challenge One Bin at a Time," *Genetics in Medicine* 13, no. 6 (2011); 499-504; E. W. Clayton and A. L. McGuire, "The Legal Risks of Returning Results of Genomic Research," *Genetics in Medicine* 14, no. 4 (2012): 473-477; S. M. Wolf et al., "Managing Incidental Findings and Research Results in Genomic Research Involving Biobanks & Archived Datasets," *Genetics in Medicine* 14, no. 4 (2012): 361-384; Presidential Commission for the Study of Bioethical Issues, *Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts* (Washington, D.C.: Presidential Commission for the Study of Bioethical Issues, 2013), *available at* <http://bioethics.gov/sites/default/files/FINALAnticipateCommunicate_PCSBI_0.pdf> (last visited August 13, 2017); S. M. Wolf, "Return of Individual Research Results and Incidental Findings: Facing the Challenges of Translational Science," *Annual Review of Genomics and Human Genetics* 14 (2013): 557-577; G. P. Jarvik et al., "Return of Results to Research Participants: The Floor, the Ceiling, and the Choices in Between," *American Journal of Human Genetics* 94, no. 6 (2014): 818-826; S. M. Wolf et al., "Returning a Research Participant's Genomic Results to Relatives: Analysis & Recommendations," *Journal of Law, Medicine & Ethics* 43, no. 3 (2015): 440-463; S. M. Wolf, W. Burke, and B. A. Koenig, "Mapping the Ethics of Translational Genomics: Situating Return of Results and Navigating the Research-Clinical Divide," *Journal of Law, Medicine & Ethics* 43, no. 3 (2015): 486-501.
2. For the ACMG website, see <http://www.acmg.net/> (last visited July 26, 2017).
3. American College of Medical Genetics and Genomics (ACMG), *Policy Statement: Points to Consider in the Clinical Application of Genomic Sequencing* (May 15, 2012), *available at* <http://www.acmg.net/StaticContent/PPG/Clinical_Application_of_Genomic_Sequencing.pdf> (last visited July 26, 2017).
4. R. C. Green et al., "ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing," *Genetics in Medicine* 15, no. 7 (2013): 565-574.
5. See Wolf et al., "Returning a Research Participant's Genomic Results to Relatives," *supra* note 1.
6. See B. J. Evans et al., "Regulatory Changes Raise Troubling Questions for Genomic Testing," *Genetics in Medicine* 16, no. 11 (2015): 799-803.
7. For the literature debating the ACMG's 2013 paper, see, e.g., S. M. Wolf, G. J. Annas, and S. Elias, "Patient Autonomy and Incidental Findings in Clinical Genomics," *Science* 340, no. 6136 (2013): 1049-1050; A. McGuire et al., "Ethics and Genomic Incidental Findings," *Science* 340, no. 6136 (2013): 1047-1048; W. Burke et al., "Recommendations for Returning Genomic Incidental Findings? We Need to Talk!" *Genetics in Medicine* 15, no. 11 (2013): 854-589; L. F. Ross, M. A. Rothstein, and E. W. Clayton, "Mandatory Extended Searches in All Genome Sequencing: 'Incidental Findings,' Patient Autonomy, and Shared Decision Making," *JAMA* 310, no. 4 (2013): 367-368; M. Allyse and M. Michie, "Not-So-Incidental Findings: The ACMG Recommendations on the Reporting of Incidental Findings in Clinical Whole Genome and Whole Exome

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Sequencing," *Trends in Biotechnology* 31, no. 8 (2013): 439-441; N. A. Holtzman, "ACMG Recommendations on Incidental Findings Are Flawed Scientifically and Ethically," *Genetics in Medicine* 15, no. 9 (2013): 750-751 (Letter); A. Townsend et al., "Paternalism and the ACMG Recommendations on Genomic Incidental Findings: Patients Seen But Not Heard," *Genetics in Medicine* 15, no. 9 (2013): 751-752 (Letter); Presidential Commission, *supra* note 1; E. W. Clayton et al., "Addressing the Ethical Challenges in Genetic Testing and Sequencing of Children: Recent Statements by the American Academy of Pediatrics and the American College of Medical Genetics and Genomics," *AJOB: American Journal of Bioethics* 14, no. 3 (2014): 3-9; G. Lázaro-Muñoz et al., "Looking for Trouble: Preventive Genomic Sequencing in the General Population and the Role of Patient Choice," *AJOB: American Journal of Bioethics* 15, no. 7 (2015): 3-14.

8. Green et al., *supra* note 4, at 572.
9. Burke et al., *supra* note 7.
10. Green et al., *supra* note 4, at 569.
11. L. F. Ross et al., "Technical Report: Ethical and Policy Issues in Genetic Testing and Screening of Children," *Genetics in Medicine* 15, no. 3 (2013): 234-245, at 237-238 (references omitted).
12. *Id*., at 238 (references omitted).
13. American College of Medical Genetics and Genomics (ACMG), "Incidental Findings in Clinical Genomics: A Clarification," *Genetics in Medicine* 15, no. 8 (2013): 664-666, at 664 [hereinafter "ACMG Clarification"].
14. *Id*., at 665.
15. American College of Medical Genetics and Genomics (ACMG), ACMG News, "ACMG Updates Recommendation on 'Opt Out' for Genome Sequencing Return of Results," April 1, 2014, *available at* <http://www.acmg.net/docs/Release_ACMGUpdatesRecommendations_final.pdf> (last visited July 26, 2017) (emphasis added).
16. M. T. Scheuner et al., "Reporting Genomic Secondary Findings: ACMG Members Weigh In," *Genetics in Medicine* 17, no. 1 (2015): 27-35, at 32.
17. *Id.*
18. ACMG Board of Directors, "ACMG Policy Statement: Updated Recommendations Regarding Analysis and Reporting of Secondary Findings in Clinical Genome-Scale Sequencing," *Genetics in Medicine* 17, no. 1 (2015): 68-69 [hereinafter "ACMG Updated Recommendations"].
19. S. S. Kalia et al., "Recommendations for Reporting of Secondary Findings in Clinical Exome and Genome Sequencing, 2016 Update (ACMG SF v2.0): A Policy Statement of the American College of Medical Genetics and Genomics," *Genetics in Medicine* 19, no. 2 (2017): 249-255.
20. ACMG, "The ACMG Secondary Findings Working Group Needs Your Input!" *available at* <http://www.acmg.net/ACMG/ACMG/Publications/Secondary_Condition_Nominations/Secondary_Findings_Working_Group.aspx> (last visited July 26, 2017).
21. Kalia et al., *supra* note 19.
22. J. Karow, "ACMG Plans Update of Secondary Findings Gene List by Year End, Considers PGx Genes for Next Round," GenomeWeb, September 20, 2016, *available at* <https://www.genomeweb.com/molecular-diagnostics/acmg-plans-update-secondary-findings-gene-list-year-end-considers-pgx-genes> (last visited July 26, 2017).
23. See Green et al., *supra* note 4.
24. See, e.g., Wolf et al., "Patient Autonomy and Incidental Findings in Clinical Genomics," *supra* note 7.
25. On the extensive literature contrasting the opt-in regimen of informed consent with opt-out or presumed consent across a range of clinical and research contexts, see, e.g., D. A. E. White et al., "HIV Screening in an Urban Emergency Department: Comparison of Screening Using an Opt-In Versus an Opt-Out Approach," *Annals of Emergency Medicine* 58, no. 1 (2011): S89-S95; J. S. Blumenthal-Barby and H. Burroughs, "Seeking Better Health Care Outcomes: The Ethics of Using the Nudge," *American Journal of Bioethics* 12, no. 2 (2012): 1-10; D. Kaufman et al., "Preferences for Opt-In and Opt-Out Enrollment and Consent Models in Biobank Research: A National Survey of Veterans Administration Patients," *Genetics in Medicine* 14, no. 9 (2012): 787-794; G. Joseph et al., "Parental Views on Expanded Newborn Screening Using Whole-Genome Sequencing," *Pediatrics* 137, no. S1 (2016): S36-S46.
26. Kalia et al., *supra* note 19, at 5.
27. *Id*., at 6.
28. Burke et al., *supra* note 7.
29. See, e.g., M. O. Dorschner et al., "Actionable, Pathogenic Incidental Findings in 1,000 Participants' Exomes," *American Journal of Human Genetics* 93, no. 4 (2013): 631-640; E. Olfsun et al., "Identification of Medically Actionable Secondary Findings in the 1000 Genomes," *PLoS One* 10, no. 9 (2015): e0135193. On the experience across the Clinical Sequencing Exploratory Research (CSER) Consortium projects, see, e.g., R. C. Green et al., "Clinical Sequencing Exploratory Research Consortium: Accelerating Evidence-Based Practice of Genomic Medicine," *American Journal of Human Genetics* 98, no. 6 (2016): 1051-1066.
30. Kalia et al., *supra* note 19, at 2.
31. M. Hegde et al., "Reporting Incidental Findings in Genomic Scale Clinical Sequencing -- A Clinical Laboratory Perspective: A Report of the Association for Molecular Pathology," *Journal of Molecular Diagnostics* 17, no. 2 (2015): 107-117, at 114.
32. *Id*., at 115 (emphasis added).
33. See M. M. Mello and L. E. Wolf, "The Havasupai Indian Tribal Case — Lessons for Research Involving Stored Biologic Samples," *New England Journal of Medicine* 363, no. 3 (2010): 204-207.
34. See, e.g., A. K. Manrai et al., Genetic Misdiagnoses and the Potential for Health Disparities," *New England Journal of Medicine* 375, no. 7 (2016): 655-665; S. Petrovski and D. B. Goldstein, "Unequal Representation of Genetic Variation Across Ancestry Groups Creates Healthcare Inequality in the Application of Precision Medicine," *Genome Biology* 17, no. 1 (2016): 157-159.
35. Hegde et al., *supra* note 31, at 115.
36. Green et al., *supra* note 4, at 569.
37. J. R. Botkin et al., "Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents," *American Journal of Human Genetics* 97, no. 1 (2015): 6-21, at 9.
38. *Id.*
39. Green et al., *supra* note 4, at 566.
40. See, e.g., R. Klitzman, P. S. Appelbaum, and W. Chung, "Return of Secondary Genomic Findings vs. Patient Autonomy: Implications for Medical Care," *JAMA* 310, no. 4 (2013): 369-370; Wolf et al., "Patient Autonomy and Incidental Findings in Clinical Genomics," *supra* note 7.
41. Hegde et al., *supra* note 31, at 111.

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