Incidental findings and future testing methodologies: potential application of the ACMG 2013 recommendations

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ABSTRACT

Reactions to the first clinical recommendations for the return of incidental findings (IFs) from genomic sequencing published by the American College of Medical Genetics and Genomics (ACMG) were polarized and resolute. Exploring the three main points of controversy: mandatory testing, testing children for adult conditions, and selection of conditions to be reported on, illuminates concerns for and conservation of bioethical principles—specifically, autonomy and non-directiveness. With the historical context of genetic testing in mind, this article studies the potential application of the ACMG recommendations to embryonic testing in the form of preimplantation genetic diagnosis. Theoretical extension of the current recommendations assists in the identification of bioethical dilemmas and possible societal impacts. The recommendations make a statement on the importance of diagnosis and intervention for specific genetic conditions, setting a precedent for disease classification and patient autonomy. In the extreme, the clinical application of such recommendations prenatally may result in discarded embryos, and less societal tolerance of specific conditions. Skilled professionals, such as genetic counselors, researchers, and lawmakers must work together to maintain patient autonomy, providing care in the best interest of each patient.

KEYWORDS: ACMG recommendations, autonomy, incidental findings, preimplantation genetic diagnosis, whole genome sequencing

INTRODUCTION

In March 2013, the American College of Medical Genetics and Genomics (ACMG) published recommendations for reporting incidental findings (IFs) after whole-exome
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Robert C. Green et al., ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing 15 GENET. MED. 565, 574 (2013).

Id.

To date, no formal recommendations have been made regarding the return of IF in genetic research studies. However, a vast body of literature exists on the duty to re-contact research participants with significant findings. See Susan M. Wolf et al., Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations, 36 J. L. MED. ETHICS 219 (2008).

Robert C. Green, James R. Lupski & Leslie G. Biesecker, Reporting Genomic Sequencing Results to Ordering Clinicians—Incidental but not Exceptional, 310 JAMA 365 (2013).

Robert Klitzman, Paul S. Appelbaum & Wendy Chung, Return of Secondary Genomic Findings vs. Patient Autonomy Implications for Medical Care, 310 JAMA 369 (2013).

Amy L. McGuire et al., Point-Counterpoint: Ethics and Genomic Incidental Findings, 340 SCIENCE 1047 (2013).

Lainie F. Ross, Mark A. Rothstein, Ellen W. Clayton, Mandatory Extended Searches in All Genome Sequencing—“Incidental Findings,” Patient Autonomy, and Shared Decision Making, 310 JAMA 367 (2013).

Susan M. Wolf, George J. Annas & Sherman Elias Patient Autonomy and Incidental Findings in Clinical Genomics, 340 SCIENCE 1049 (2013).

James A. Anderson et al., Predictive Genetic Testing for Adult-Onset Disorders in Minors: A Critical Analysis of the Arguments For and Against the 2013 ACMG Guidelines, CLIN. GENET. (2014).

Green et al., supra note 1, at 570–572.

Megan Allyse & Marsha Michie, Not-so-Incidental Findings: The ACMG Recommendations on the Reporting of Findings in Clinical Whole Genome and Whole Exome Sequencing, 31 TRENDS BIOTECH. 439 (2013).

Ross et al., supra note 7, at 367.

Wolf et al., supra note 8, at 1049.

Symplur, #ACMGMtg Healthcare Social Media Hashtag Analytics, http://www.symplur.com/healthcare-hashtags/acmgmtg/ (accessed Jun. 1, 2014).
the article concludes with a call for skilled genetic counseling in order to maintain core bioethical principles in clinical practice.

**BACKGROUND AND ACMG RECOMMENDATIONS**

Incidental, secondary, or unexpected findings describe medically relevant information detected by testing, unrelated to the original indication for ordering such a test.\(^{15,16}\) IFs are not unique to the field of genetics; they have been a possible outcome since the advent of medical screening and testing. Consider a classic example of identifying malignant thyroid nodules by routine computerized tomography screening for lung cancer.\(^{17}\) Technically, only the patient’s lungs are being examined, but as the thyroid is within the field of vision, the radiologist has a duty to report the malignancy, and recommend appropriate follow-up care. Managing the reporting of IFs has been a concern to the genetic community for several decades as older testing methodologies, including array comparative genomic hybridization (aCGH), can also detect IFs. An aCGH ordered to determine the cause of intellectual disability could also detect Y-chromosome deletions that will cause infertility.\(^{18}\) The probability of detecting IFs with WES/WGS is significantly greater than with any previous genetic test, based solely on the quantity of genetic material being examined.

Prior to the 2013 ACMG recommendations, national standards for the return of IFs after clinical genetic testing did not exist.\(^{19}\) Laboratories were forced to develop their own IF policies, resulting in variation lab to lab and state to state, with uncertainty on the actual legal or moral obligations to return IFs.\(^{20}\) Aware of the clinical expansion of WES/WGS and the subsequent need to develop a formal policy, the ACMG called a Working Group in 2011. The Working Group spent over a year writing the recommendations, including purposefully seeking feedback from the ACMG community at large. The core recommendation from the Working Group follows:\(^{21}\)

> when a report is issued for clinically indicated exome and genome sequencing, a minimum list of conditions, genes, and variants should be routinely evaluated and reported to the ordering clinician who can place them into the context of that patient’s medical and family history, physical examination, and other laboratory testing. We have recommended that these findings be reported without seeking preferences from the patient and family and without limitation due to the patient’s age.

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\(^{15}\) Mildred K. Cho, Understanding Incidental Findings in the Context of Genetics and Genomics, 36 J. L. MED. ETHICS 280 (2008).

\(^{16}\) Zoe Lohn et al., Incidental Findings from Clinical Genome-Wide Sequencing: A Review, 23 J. GENET. COUNS. 463 (2014).

\(^{17}\) Jong Hoo Lee, Sun Young Jeong & Yee Hyung Kim, Clinical Significance of Incidental Thyroid Nodules Identified on Low-Dose CT for Lung Cancer Screening, 8 MULTI. RESP. MED. 56 (2013).

\(^{18}\) David Dimmock, A Personal Perspective on Returning Secondary Results of Clinical Genome Sequencing, 4 GENOME MED. 54 (2012).

\(^{19}\) Green et al., supra note 1, at 566.

\(^{20}\) Caroline S. Bennette et al., Return of Incidental Findings in Genomic Medicine: Measuring What Patient’s Value—Development of an Instrument to Measure Preferences for Information from Next-Generation Testing (IMPRINT), 11 GENET. MED. 873 (2013).

\(^{21}\) Green et al., supra note 1, at 576.
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The minimum list originally named 57, later revised to 56, genes with causative roles in 30 conditions.\(^{22}\) Eighteen cancer predisposition syndromes, eleven genetic vascular and heart syndromes, and one adverse reaction to anesthesia were selected. Each condition has actionable interventions with early detection, and is not currently looked for by population screening.\(^{23}\) It was originally estimated that as few as one percent of patients undergoing WES/WGS would have an IF identified for a condition on the minimum list. However, small clinical studies indicate that the actual number is higher, perhaps as high as 10–30%, although sufficiently large studies have not been conducted to confirm an exact percentage.\(^{24}\)

Recommendations from professional organizations do not have the power of law themselves. However, they can serve as evidence for the standard of care by which juries and judges evaluate claims of provider malpractice. For example, in Conn v. U.S., 880 F. Supp. 2d 741 (SD Miss 2012), the trial court allowed recommendations from the American College of Cardiology and the American Heart Association as evidence of the standard of care for treating myocardial infarctions (heart attacks). These types of recommendations can also play a major role in guiding insurance reimbursement issues. The 2013 ACMG recommendations were recognized as having the potential to affect both these issues.

DEBATE OVER THE RECOMMENDATIONS

Despite what appeared to be a rigorous evaluation process, the recommendations were met with fierce backlash.\(^{25}\) Numerous genetic professionals blasted the recommendations as premature, lacking sufficient evidence, and missing input from key stakeholders.\(^{26}\) Three controversies dominated the debate: the requirement for testing and return of results on specified conditions, the reporting of adult-onset conditions in children, and the specific group of conditions to be reported on.

The recommendation for laboratories to test all samples being ‘sequenced’ was interpreted as stripping patients of their autonomy for the right not to know specific genetic information.\(^{27,28,29}\) Critics of the recommendations expressed concern with the ‘mandatory return of results’; however, this language was not specifically used in the original publication.

In actuality, the Working Group outlined an option for patients to decline learning about IFs identified by the testing laboratory, through pretest informed consent conversations with a genetic professional. This would shift discussion and decision-making about IFs to the more suitable context of patient and medical provider, rather than

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\(^{22}\) ACMG, *Incidental Findings in Clinical Genomics: A Clarification*, http://www.genomicslawreport.com/index.php/2013/07/30/the-amg-gene-screening-recommendations/ (accessed Jun. 1, 2014).

\(^{23}\) Green et al., supra note 1, at 570.

\(^{24}\) Frederick E. Dewey et al., *Clinical Interpretation and Implications of Whole-Genome Sequencing*, 311 JAMA 1035 (2014).

\(^{25}\) John Conley, *The ACMG Gene Screening Recommendations*, http://www.genomicslawreport.com/index.php/2013/07/30/the-amg-gene-screening-recommendations/ (accessed Jun. 1, 2014).

\(^{26}\) Klitzman et al., supra note 5, at 369–370.

\(^{27}\) Sequencing is commonly interpreted as WES/WGS, but is actually not clearly defined in the ACMG publication.

\(^{28}\) Ross et al., supra note 7, at 368.

\(^{29}\) Wolf et al., supra note 8, at 1049.
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between patient and lab, or provider and lab. With proper documentation of their preferences, patients can choose not to learn about certain IFs and still obtain test results. However, some argue that with the recommendation to test for specific IFs, labs may report IFs regardless of patient preference, and this information will become part of the patient’s electronic medical record. Therefore, other providers and even the patient may have access to the unwanted IFs, potentially resulting in accidental disclosure. Physicians may also feel compelled to inform patients of IFs due to fear of malpractice suits for incomplete disclosure.

The second controversial recommendation was the suggestion to test and report on IFs for adult-onset conditions in children. The ACMG has never before recommended testing children for adult-onset conditions. In fact, there is a long-standing tradition to only testing adults for adult-onset genetic conditions, like Huntington disease and HBOC. Of the 30 conditions on the recommended list, only three are solely adult onset: HBOC, Lynch syndrome, and MYH-associated polyposis. The inability of children to give informed consent to testing, and the subsequent lack of future autonomy to decide on testing as an adult, was a common concern. The Working Group qualified the value of testing children for adult conditions with the potential to detect familial conditions. In such circumstances, pre-symptomatic parents could have early medical intervention, which would ultimately be in the best interest for the entire family.

Finally, commentators criticized the selection of conditions and genes on the minimum IF list. Despite the Working Group having a robust knowledge in genetics and bioethics, and openly stating the difficulty faced in deciding which conditions to include on the list, critics lamented that no members of the Working Group were specialists in cardiology or cancer. Green et al. provided justifications for the conditions selected in the original publication, and stated that the list of conditions would be curated and expanded over time. Unfortunately, no information was provided on the process, timeline, or stakeholder selection to review the expansion. Additionally, laboratories were instructed by the recommendations on which genes needed analysis, but were not provided with specific guidelines for variant interpretation. Basic standardizations on variant calling, timeline for variant re-interpretation, and assigning who holds

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30 Green et al., supra note 4, at 366.
31 Id.
32 Christopher H. Wade, Beth A. Tarini & Benjamin S. Wilfond, Growing Up in the Genomic Era: Implications of Whole-Genome Sequencing for Children, Families, and Pediatric Practice, 14 ANN. REV. GENOM. HUM. GENET. 535 (2013).
33 Conley, supra note 25.
34 Jennifer K. Wagner, Playing with Heart and Soul…and Genomes: Sports Implications and Applications of Personal Genomics, 1 PEAR J e120 (2013).
35 HBOC stands for hereditary breast and ovarian cancer syndrome.
36 Only patients with appropriate decisional capacity and legal empowerment can give informed consent to proceed with specific medical care. Minors are therefore typically unable to provide informed consent.
37 Anderson et al., supra note 9, at 5–6.
38 Green et al., supra note 1, at 572.
39 ACMG, supra note 22.
40 Ross et al., supra note 7, at 368.
41 Green et al., supra note 1, at 574.
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responsibility for informing patients of new variant interpretations remain in question for clinical WES/WGS.42

Data on patient reactions to disclosure of IFs in a clinical context remain sparse, but return of WGS results in a research setting can provide insight. Williams et al. found that research participants wanted to learn as much information as possible about their WGS results.43 In another study, over 80% of parents said that they would want to know all IF information found on their children, even for non-treatable conditions.44 While some laboratories embraced the ACMG recommendations, others allowed complete opt-out of analysis for conditions on the recommended list.45,46,47 Following member feedback, the ACMG issued a 2014 update to the original recommendations, clarifying that patients should be offered the option to opt-out of learning about IFs. This perspective aligns with the bioethical principle of a fundamental right not to know information.48,49

PREDICTING THE IMPACT ON FUTURE GENETIC TESTING
The Working Group makes a very clear point that the current ACMG recommendations are not intended for population screening or prenatal use.50 Considering the not unlikely extension of the recommendations to such testing, let us explore complex ethical issues and potential future implications.

Easy PGD
A futuristic advance in reproduction, ‘easy PGD’ would involve WGS of gametes from induced pluripotent stem cells. This process would allow prenatal implantation genetic diagnosis (PGD) after in vitro fertilization (IVF) without the current required complications of egg retrieval.51 Egg retrieval is currently the most medically dangerous and rate-limiting aspect of IVF. Easy PGD could revolutionize how children are conceived within the next 20 to 40 years, opening IVF to the general public.52 Easy PGD provides a plausible futuristic scenario to examine potential implications of the ACMG recommendations, using current WGS technology to analyze embryos.

42 Catherine A. Brownstein et al., An International Effort Towards Developing Standards for Best Practices in Analysis, Interpretation and Reporting of Clinical Genome Sequencing Results in the CLARITY challenge, 15 GENOME BIOL. R53 (2013).
43 Janet K. Williams et al., Disclosure of Incidental Findings in Children, Are We Making Progress?, 10 PERSONALIZED MED. 519 (2013).
44 Conrad V. Fernandez et al., Attitudes of Parents toward the Return of Targeted and Incidental Genomic Research Findings in Children, 16 GENET. MED. 633 (2014).
45 Ambry Genetics, Exome Q & A, http://ambrygen.com/exome-qa (accessed Jun. 1, 2014).
46 Baylor College of Medicine Whole Genome Laboratory, Whole Exome Sequencing Requisition, https://www.bcm.edu/geneticlabs/index.cfm?PMID=21320 (accessed Jun. 1, 2014).
47 GeneDx, XomeDx—Frequently Asked Questions, http://www.genedx.com/wp-content/uploads/2013/03/XomeDxFAQs.pdf (accessed Jun. 1, 2014).
48 ACMG, ACMG Updates Recommendation on “Opt-Out” for Genome Sequencing Return of Results, https://www.acmg.net/docs/Release-ACMGUdatesRecommendations_final.pdf (accessed Jun. 3, 2014).
49 Bartha M. Knoppers, From the Right to Know to the Right not to Know, 42 J. L. MED. ETHICS 6 (2014).
50 Green et al., supra note 1, at 572.
51 HANK GREELY, THE END OF SEX (forthcoming 2015).
52 Id.
Historical Context of Genetic Testing

To appreciate future implications of the ACMG recommendations, a basic understanding of the evolution of genetic testing and screening is necessary. Genetic testing in the United States started in the late 1950s, with the use of cytogenetics to identify frank chromosome abnormalities, such as Down syndrome. Linkage analysis studies in the 1980s allowed tracking of single-gene disorders in affected families, followed by discovery of specific mutations causative of conditions like Huntington’s disease in the 1990s. Today, WGS can analyze almost every base pair of DNA in the human genome. Although genetic tests are imperfect, many people feel that the information provided is useful, even when no treatments are available.

Clinical genetic testing has traditionally only been offered for disease-causing conditions. Therefore, tests to predict cosmetic traits like earwax type or eye color have not been offered clinically. Historically, genetic testing first focused on detecting the most devastating genetic conditions. Tay–Sachs disease, a terminal disorder resulting in progressive destruction of nerve cells eventually causing death, is a classic example of such a condition. To have a child with Tay–Sachs disease, both parents must be carriers of the disease and are themselves asymptomatic. The Ashkenazi Jewish population has the highest carrier frequency of Tay–Sachs, and at one time, was the most affected by this disease. Genetic carrier testing, and subsequent impact on sexual partner choice, has facilitated a dramatic reduction of Tay–Sachs in the Jewish population. Through the evolution of modern medicine and genetic testing, it is now possible to test for genetic conditions that are not necessarily life limiting, such as predisposition syndromes. For example, some individuals with hypertrophic cardiomyopathy (HCM) will have the genetic predisposition, but will never develop structural heart changes or symptoms. Having a genetic change but no physiological symptoms begs the question, Are predisposition syndromes, such as HCM or HBOC, actually diseases? This is not an entirely new issue-healthcare providers have grappled with deciding if asymptomatic HIV infection is a disease itself, or a predictor of the disease AIDS. In another example, Are the physiological changes leading to Alzheimer disease the earliest stages of the disease, or merely predictors?

Unlike some medical specialties, genetics as a field has a preoccupation with obtaining incredibly informed consent prior to testing. Informed consent includes learning about the risks and benefits of testing, the risks and benefits of other treatment options, the opportunity to have questions answered, and decision making in the best interest of the patient. It is standard for genetic professionals to discuss all possible test results, including IFs, with patients as part of the consent process. This could be a remnant of single-gene testing, or residual wariness of the eugenics movement. With the availability of clinical WES/WGS, it is no longer plausible to review every possible outcome with patients prior to testing.

53 S. M. Miller, S. H. McDaniel & W. W. Norton, Individuals, Families, and the New Era of Genetics: Biopsychosocial Perspectives (2006).
54 Id.
55 N. Husseine al., Preconception Risk Assessment for Thalassemia, Sickle Cell Anemia, Cystic Fibrosis and Tay-Sachs Disease, (2013).
56 Barry J. Maron & Martin S. Maron, Hypertrophic Cardiomyopathy, 381 Lancet 242 (2013).
57 Lohn et al., supra note 16, at 470.
Implications of Recommendations

By publishing a minimum list of conditions that ought to be tested no matter one’s age or personal preference, the ACMG has made a statement on the importance of those genetic conditions. Inclusion could be interpreted as meaning a condition is not only important to be aware of, but also requires medical intervention. If it is necessary to identify adults and children with these conditions, is it not also important to test for these conditions prenatally? And once the option of prenatal testing is permissible, does it not make sense to extend testing to embryos? Realizing identification of genetic cardiac and cancer predisposition conditions ultimately leads to intervention—partially due to the directive and aggressive history of those specialties—it is possible to imagine scenarios where couples are told not to implant embryos identified as having adult-onset or predisposition conditions. Although the minimum list is specific to IFs and not prenatal testing, if an embryo had WES, variants in genes on the recommended list would likely be reported. The recommendations set a precedent for both disease classification and patient autonomy. In practical application, the ACMG recommendations effectively deny the opportunity for both children and adults to not learn about specific genetic results. This contradicts the basic right not to know genetic information described in the UNESCO ’Universal Declaration on Human Genome and Human Rights’. 58

Genetic testing itself does not place judgement on the value of life for an individual with a genetic syndrome. Instead, the decisions made with genetic test results are interpreted as a personal or social judgement. Ultimately, the most poignant and difficult question to ask is, When is a disease so severe or devastating, it is better to not be born at all? Some pro-life fundamentalists would argue that life is always the best option. Personally, in part as a result of my clinical experiences, I feel it may be more beneficent to an unborn child and family to not continue pregnancies where extremely devastating conditions like anencephaly or trisomy 13 have been detected. In contrast, I think the value of life far outweighs the less than 10% risk of thrombosis from having Factor V Leiden. For many adult-onset conditions like Huntington’s, Alzheimer’s, or HBOC, the end of life disease can be devastating. But does this trauma negate a full life of emotion and experience? Somewhere in the middle of this disease severity spectrum, many parents decide not to give birth to a child with Down syndrome. As pro-life advocates in Down syndrome community attest, deeply personal decisions on pregnancy termination (influenced by factors like culture, religion, and family experience) can be interpreted as a commentary on the perceived value of life with disability.

If an embryo created through easy PGD were found to have an adult-onset condition, it seems likely that the embryo would be destroyed. Although patients can decide to terminate a pregnancy for any reason, or discard any embryo, the reasoning behind such future choices is troubling. Despite admirable intentions, one legacy of the ACMG recommendations could be increased intolerance for adult-onset diseases. It is easy to imagine a scenario where commercial laboratories conducting PGD WGS report all variant results, regardless of patient preferences, fearful of lawsuits for non-disclosure. Already in this situation, patients have lost the autonomy to not know specific information.

58 Knoppers, supra note 49, at 1–2.
If easy PGD became massively popular, the small size of the genetic profession might necessitate these results to be reported by OBs or family physicians. Unfamiliar with the ethos of non-directive care—a fundamental genetic counseling principle guiding providers to refrain from evaluating or directing patients and instead encouraging patient expression and reflection to make decisions—prospective parents could be told or interpret they cannot implant embryos with adult-onset predispositions.\textsuperscript{59} Patient autonomy is further lost if no embryos are disease-free, and a couple must pay for another round of easy PGD, or remain childless. Other possible outcomes include a decrease in services and research for treating adult-onset conditions, as the number of people with such conditions shrinks. Parents may also experience increased mental anguish from giving birth to a child with a ‘preventable’ condition, as these conditions could now be eliminated prior to birth. Ultimately, the most devastating outcome would probably be the lost life of an individual, who would have never developed the genetic condition they were discarded for.

Although the ACMG publication presented recommendations and not mandates, the document constitutes the current best clinical practice. Therefore, it could be used in legal discourse and cited as evidence in a lawsuit. It seems plausible that the ACMG recommendations could eventually be turned into state laws, mandating testing for IFs. If this seems impossible, consider that today every pregnant woman in the state of California presenting for prenatal care before the 20th week of pregnancy must legally be offered participation in the state prenatal screening program. Similarly, although not law, the American College of Gynecology has issued strong recommendations that every pregnant woman have ethnicity-based carrier testing.

Currently, how an individual acts on such genetic information is still a personal choice. But, it is possible to imagine societies where it is only a short step from legally mandated testing, to legislation how one must act on specific results. Although an unlikely future scenario in the United States, the ACMG recommendations represent a starting point for defining conditions that require medical intervention.

### CONCLUSION

Skilled genetic professionals, such as genetic counselors, are needed to assist patients with interpreting test results, and ensuring the ability to act on results however a patient desires is protected. These professionals provide an important service to individuals and couples. Genetic counselors can operate as a societal checkpoint between the ability to test for conditions, interpreting results, and acting on such findings. Patients have a right not to know unwanted information.\textsuperscript{60} There are situations where information is an essential component of sound decision-making, and individuals can be held culpable for a poor outcome, if they act in voluntary ignorance.\textsuperscript{61} Scenarios do exist where individuals have an obligation to be tested, and have essentially lost the right not to know certain results. Even so, genetic professionals and legislatures must be cautious

\textsuperscript{59} Carl Rogers, psychologist, established the person-centered approach of non-directive counseling. In the most pure form, non-directive counseling encourages free expression from the patient with minimum input from the therapist.

\textsuperscript{60} Knoppers, supra note 49, at 9.

\textsuperscript{61} Rosamond Rhodes et al., Genetic Testing—is there a right not to know?: Con, 31 Am. J. MATERN. CHILD NURS. 145 (2006).
about dictating patient actions to protect the remaining components of patient autonomy and individual freedom.

Moving forward, determining how to handle IFs is important for routine clinical WGS and application to future testing technology. The ACMG recommendations are a first step to working with IFs in clinical practice, removing the previous medical exceptionalism of genetic testing to be more congruent with other medical specialties. If intervention follows identification, it is possible that embryos with genetic conditions will be discarded. Although not illegal, this potential outcome could foster the development of a society intolerant of genetic conditions and disabilities. Perhaps this prediction of disease-ism in a future society is not the worst possible outcome of current genetic testing practice, or perhaps it is overly dystopian. Clinicians, researchers, and lawmakers must work together to continually explore the complex ethical dilemmas of genetic testing, reassessing precedent setting endeavors, while continuing to provide care that is in the best interest of all patients.