The Ethical Complexity of Using Whole-Exome Sequencing to Detect Adult-Onset Conditions in the Prenatal and Pediatric Settings

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Background: Clinical Utility of WES

Since whole-exome sequencing (WES) became available in the clinical setting, the utility of this type of testing has been well documented (Iglesias et al. 2014; Nguyen and Charlebois 2015; Yang et al. 2013). By sequencing the entirety of an individual's coding DNA, the diagnostic yield is much higher than traditional techniques such as karyotype, microarray, or sequencing a smaller selection of genes. WES yields a diagnosis in approximately 25–28% of individuals versus 3.5–10% with karyotype and 15–20% with microarray alone (Miller et al. 2010; Shaffer 2005; Shevell et al. 2003; Xue et al. 2015; Yang et al. 2013). The current standard of care is to use a stepwise approach to first rule out the most common cause of a particular disease or symptom and then reflex to the next most common cause until a diagnosis can be made. This method can be both time-consuming and expensive, and, in a large number of cases, a diagnosis may never be reached.

Having a known disease allows healthcare providers to appropriately and preventatively manage their patients based on the expected phenotype. Without a known etiology, healthcare providers are left reacting to symptoms instead of anticipating them. Knowing the natural history of a condition leads to better preparation for potential health complications. Diagnosis can also provide a measure of psychological

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relief to patients and their families because they are finally able to set their expectations and better understand the course of their disease. Otherwise, they may continue to face uncertainty and anxiety about their future.

In the prenatal setting, using a stepwise approach to diagnosis is no longer ideal for a variety of reasons. First and foremost, timeliness of results is imperative when it comes to decision-making regarding the pregnancy. The family's decision to either continue or terminate the pregnancy may be based on their test results, and their decision is time-sensitive depending on local pregnancy termination laws. The time-consuming nature of traditional reflex testing sometimes prevents the family from having a decision at all. More practically, after obtaining a chorionic villus sample or an amniocentesis sample, the fetal cells will only be viable for a few weeks, making the amount of testing available for any one sample finite.

Another important limitation of prenatal testing is the restricted clinical picture. Screening for common aneuploidies such as Down syndrome, trisomy 13, and trisomy 18 can be performed using a combination of ultrasound and blood work, with much greater accuracy than previously available. However, ultrasound alone is the primary screening tool used to detect less common genetic conditions. Generalized ultrasound findings often have a long list of potential etiologies including teratogens, infections, chromosome abnormalities, genetic conditions, multifactorial causes, or sporadic findings. Any single ultrasound finding could be associated with hundreds of genetic conditions. Ultrasound detects major birth defects, but has limited or no capability to predict developmental delays, intellectual disabilities, behavioral differences, or subtle dysmorphic features that would give healthcare providers important clues about the differential diagnosis. Without the entire clinical picture, healthcare providers are left with generalized findings, a broad differential diagnosis, and limited resources for testing.

The advent of next-generation sequencing (NGS) has mitigated some of these issues by giving healthcare providers access to larger gene panels and WES (Xue et al. 2015). NGS uses massively parallel sequencing to conduct high-throughput testing of large amounts of genomic information in a much more time- and cost-efficient manner than Sanger sequencing, which sequences one nucleotide at a time. So, while reflex testing made economic sense in the past due to the costly nature of Sanger sequencing, clinicians are now relying more and more on larger gene panels and WES. With this reliance, a number of ethical concerns have arisen. Here we focus in particular on issues related to secondary and incidental findings associated with testing.

The ACMG's Position on the Return of WES Results

While WES gives information about gene targets known to be associated with the patient's presenting phenotype, it also gives information about gene targets that are well-defined but not associated with the patient's phenotype. There is also a substantial amount of raw data, the significance of which is currently unknown, but

which may become interpretable in the future. Results that are unrelated to the initial testing indication, whether they can be anticipated or not, are known as incidental findings. Secondary findings, more specifically, are incidental findings that have been intentionally sought out (PCSBI 2013).

In anticipation of a variety of logistical issues regarding counseling and returning results for WES, the American College of Medical Genetics and Genomics (ACMG) published a policy statement with points to consider, advocating clear guidelines for the disclosure of results in the clinical setting, including both those that relate to the patient's indication for testing and for secondary findings (ACMG 2012). In July 2013, ACMG made more specific recommendations regarding secondary findings by curating a list of 57 genes, representing 24 distinct conditions, for which reporting should be obligatory. Regardless of age and excluding fetal samples, all patients should receive the results of pathogenic or likely pathogenic mutations in this minimum list of genes. Emphasis was placed on choosing conditions for which treatment is available and/or preventative measures could be taken, as well as ensuring that variants of uncertain significance not be returned. The results from the minimum list should be clinically actionable (Green et al. 2013).

Two additional issues the 2013 recommendation addressed were patient preferences and reporting incidental findings in children. Initially, the Working Group suggested that patients should not have the opportunity to opt out of receiving results from genes on the minimum list. In other words, all patients undergoing the test would be required to learn specific information about their exome regardless of their preferences. This proposal was based on the selected conditions being adequately prevalent and treatable such that the laboratory's and healthcare provider's fiduciary responsibility to prevent harm would outweigh the patient's autonomy and "right not to know." The Working Group argues that as long as the ordering healthcare provider has had a thorough discussion of the risks, benefits, and limitations of WES, patients could decline testing altogether if they were sufficiently concerned about receiving a secondary finding (Green et al. 2013).

ACMG later updated their recommendation to include an opt-out option, following a report by the Presidential Commission for the Study of Bioethical Issues and results from a survey of ACMG members (ACMG 2015; PCSBI 2013; Scheuner 2015). However, the Working Group recommends that the list be treated as a whole; patients may not choose a subset of conditions for which to receive results. They argue that counseling for each condition separately to decide whether or not to include the results would be cumbersome for both the lab and the healthcare provider. Obtaining proper informed consent would become very difficult if each condition on the minimum list were treated separately (ACMG 2015).

The ACMG Working Group ultimately recommended that test results for children be treated the same as for adults, arguing that they did not wish to prohibit a group of individuals from receiving clinically valuable results. In other words, children and their parents do not have the option of opting out of receiving information about certain conditions unless they are willing to opt out of receiving secondary findings all together.

Return of Incidental and Secondary Findings in Children

A deeper look into the list of conditions raises some concern over the recommendation to return incidental findings in children. While the list includes 6 childhood-onset conditions, it also includes 15 conditions with variable onset from childhood into adulthood and 3 adult-onset conditions. The adult-onset conditions are associated with a hereditary predisposition to cancer: hereditary breast and ovarian cancer (HBOC), Lynch syndrome, and MYH-associated colorectal polyposis (Green et al. 2013). Some of the major concerns associated with returning the results of incidental and secondary findings for children include the creation of a "patient in waiting," overtreatment, negative impact on the parent-child relationship, stress of knowing genetic status (for child and parents), possible social stigma, insurance discrimination, and employer discrimination (Friedman Ross et al. 2013; Davis 1997). The major ethical concern can be framed in terms of a tension between beneficence, or the physician's obligation to benefit the patient, and the child's autonomy (or the autonomy of the future adult).

The adult-onset conditions have some characteristics that contribute to the problematic nature of testing children for them. First, the penetrance is not 100% for HBOC and Lynch syndrome. That is, individuals with pathogenic mutations in the genes responsible for these conditions do not necessarily develop cancer within their lifetime (Kohlmann and Gruber 2004; Petrucelli et al. 1998). Second, the medical management for any of the three diseases does not change until adulthood (age 20–25) unless the family history suggests otherwise (NCCN: Breast 2016a; NCCN: Colorectal 2016b).

Furthermore, even adults may choose to decline testing for cancer predisposition genes, regardless of whether healthcare providers believe the testing would benefit them. Genetic counseling is offered precisely so that adults may weigh the pros and cons of testing and make a decision based on their own values. Indeed, following genetic counseling, many adults who were originally interested in testing did not ultimately decide to test (Friedman Ross 2013). Revealing their genetic status to children denies them the opportunity to make this decision for themselves in the future. For these reasons, testing children for these conditions has generally been discouraged until they reach the age of consent (Botkin et al. 2015; Committee on Bioethics 2013; NSGC 2017). Requiring receipt of these results deprives future adults the right to make influential healthcare decisions. In other words, it violates their future autonomy, or what Joel Feinberg has called the child's "right to an open future" (Feinberg 1980).

Generally, the right to an open future is framed in terms of the limits of parental decision-making; however, in this case, healthcare providers are deciding what the parents should do for their children and denying parents the ability to make discriminating decisions about their children's medical care. The most child-centered approach is arguably to accept information about childhood-onset conditions, but forgo information about adult-onset conditions and/or disorders with incomplete

penetrance. But parents must choose all or nothing, and thus lose the ability to respect their child's rights and health.

The primary goal when considering testing asymptomatic children for adult-onset conditions should be the child's medical benefit, followed by psychological benefit. Factors in support of testing include changing medical management to reduce morbidity and mortality, reducing unnecessary surveillance, and reducing anxiety and uncertainty (often in the case of adolescents). There are cases where the medical and/or psychological benefits are clear. In these cases, the parents and healthcare provider would decide that testing is in the child's best interest and that the testing should therefore be performed. Whenever possible, the children should also participate in the conversation and their assent should be elicited (ASHG and ACMG 1995; Botkin et al. 2015).

On the other hand, factors supporting the discouragement of testing include harms associated with overuse of surveillance measures and the psychological harm of creating a "patient-in-waiting" (ASHG and ACMG 1995; Botkin et al. 2015). The term "patient-in-waiting" refers to the state of prolonged ambiguity between disease and wellness for asymptomatic patients diagnosed with a medical condition (Kwon and Steiner 2011; Timmermans and Buchbinder 2010). Diagnosis of a disease before symptoms arise is becoming more common as technology improves, leading to potentially harmful consequences of unnecessary preventive interventions and the psychological burden of these additional measures (Westbrook et al. 1998).

There are a variety of ways in which an asymptomatic child may be harmed by the psychological burden of being diagnosed with a genetic condition. The diagnosis may foster a loss in self-esteem or otherwise have a negative impact on their self-image. The specter of disease may cause parents to be overly cautious or create an atmosphere of anxiety in the face of impending disease. As children mature and develop, they may make significantly different choices regarding continuing education, career, domestic partnering, and family planning (ASHG and ACMG 1995). In the case of predictive genetic testing, when it is clear that the child will develop the condition in the future, making different life choices may be in order; however, for conditions with incomplete penetrance, such as the cancer predisposition syndromes, the benefit of making different life choices is less clear.

Considering testing for adult-onset conditions in the prenatal setting adds an additional layer of ethical complexity. Generally, the same principles and concerns apply as when thinking about genetic testing in children. Unless there is a compelling reason to perform the testing immediately, prenatal genetic testing for adult-onset conditions has also historically been discouraged. Autonomy of the fetus or future child should be considered because testing takes away their right not to know the results. However, when pregnancy management would change or the parents would choose not to continue a pregnancy based on test results, parental autonomy supersedes fetal autonomy (NSGC 2014). Gaining information about genetic conditions prenatally allows parents to prepare to have a child with a genetic condition or to use the information for family planning such as making an adoption plan or pursuing in vitro fertilization with preimplantation genetic diagnosis (ASHG and ACMG 1995).

The ACMG's Reasoning

The ACMG Working Group acknowledges that there is a precedent for treating genetic testing differently in children versus adults based on issues surrounding informed consent. However, the group recommends that the minimum list be treated the same among all patients, regardless of age. Early professional statements, as well as subsequent national and international guidelines, recommend against testing minors for adult-onset conditions (Friedman Ross 2013). This ensures that children retain the ability to make certain decisions for themselves upon reaching an age of maturity. Put otherwise, this practice respects the right of children to an open future and the right of these future adults not to know certain information about their genetics (Feinberg 1980). It also respects the privacy of future adults, who may not wish their family members to know certain personal health information or who may have concerns about genetic discrimination by employers, insurance companies, or society more broadly.

Testing for genetic diseases complicates this picture in that the impact of test results extends beyond the individual to other family members. But this complexity does not negate the weight our society places on individual rights. To shift from the traditional position to one that permits the release of information about future adults to their parents and prevents parents from making discriminating judgments about their children's care would seem to require either new empirical information about the benefits and harms of this practice or powerful argumentation and novel insight about the value of altering the practice. However, the ACMG's arguments lack either quality.

For instance, the ACMG argues that stratifying results by age may place an undue burden on a laboratory's logistical infrastructure (Green et al. 2013). While straining the lab's logistical infrastructure may be of practical concern to the lab, it is not a justification for an ethical position. Many requirements for ethical and safe practices are not convenient and do not represent the path of least resistance. Furthermore, there are ways to parse the disorders such that providers would not have to explain each and every disorder on this list. For instance, the disorders could be divided into childhood-onset, adult-onset, and variable-onset disorders. These categories could be further broken down to specify incompletely penetrant disorders. Explaining these three to four concepts in order to obtain informed consent seems feasible; perhaps these concepts ought to be discussed in an informed consent regardless of options for opting out of information.

In support of treating all samples the same, regardless of age, the Working Group argues that more emphasis should be placed on a parent's ability to make decisions in their child's best interest (Green et al. 2013; Wilfond and Friedman Ross 2009). Given that the medical management for some of the conditions tested, such as the cancer predisposition syndromes, does not change until age 20–25, and given that the child may never develop cancer even in the context of a positive test result, there is little evidence of a direct clinical benefit from having these test results prior to adulthood.

The Working Group argues that, in some cases, WES may be the only opportunity for a family to obtain the results contained therein. For hereditary breast and ovarian cancer syndrome (HBOC) and Lynch syndrome, which are autosomal dominant conditions, a positive test in the child usually means that one of the parents is also positive for the familial mutation. The test results would likely have an immediate impact on the parent's medical management and could also benefit other family members. The parent may then undergo risk-reducing surgery to prevent cancer or engage in increased surveillance to detect cancer at an earlier stage. This would indirectly benefit the children by reducing morbidity and mortality in their parent (ACMG 2013; Green et al. 2013).

It is not clear that learning about parental risk for a predisposition to cancer is an appropriate reason to perform testing in a child. Curiosity about their own genetic status may cloud the parents' ability to make a decision in the best interest of their child. The ACMG argues that their position prioritizes the parents' ability to make decisions in their child's best interest at the same time that they emphasize the utility of the child's test results to the parents. The best interest standard, according to Beauchamp and Childress, concerns "the value of the life for the person who must live it, not the value the person's life has for others" (Beauchamp and Childress 2009: 140). To broaden the child's best interest to include benefiting family members, or even indirectly benefiting the child, may stretch the already imprecise concept of *best interest* too far.

Furthermore, using a child to find out the parents' genetic information is problematic from a Kantian perspective as a clear instance of using someone as means to an end. One could argue that children are not used "merely as a means" because the results could benefit the children by saving their parent. However, the combination of disrespecting the future adult's autonomy and using the child to find out information about the parent appears not to respect the dignity of the child as an end in and of itself.

Besides, there are clear clinical criteria for performing testing, so if parents are interested in learning their own genetic status, cancer genetic counseling to discuss the appropriateness of testing may be warranted. It is also important to keep in mind that not all parents and family members wish to know these results. That is, the ACMG should not assume that knowledge of these results will be viewed as exclusively beneficial to all family members. If the family history does not meet clinical criteria for testing, it is less clear what significance a positive result has. Because of the incomplete penetrance of cancer predisposition syndromes, even people with concerning family histories and a genetic mutation may never develop cancer; however, there may be even further reduced penetrance in people without a family history. This is an empirical question to be answered with research, not clinical experimentation without appropriate consent. Testing individuals who do not meet the clinical criteria for testing may result in an ambiguous situation with respect to determining appropriate medical management for families with an uncertain risk of cancer.

The Working Group offers that it is important to obtain results on these conditions, especially in the absence of a family history, because children may not then

find out about their genetic status until they have developed the disease (ACMG 2013). If this is a significant concern, then the idea of population-based screening for these conditions should be taken into consideration. That is, if it is important enough to uniformly receive these results, even in the absence of a clinical indication, perhaps testing should be offered to everyone in the general population.

The Working Group asserts that return of these findings in the context of testing for another indication constitutes "opportunistic screening" and does not cause the same burden on the healthcare system as population-based screening (Green et al. 2013). However, if it is truly in the best interest of children whose families have no indication for cancer genetic testing to proceed with testing, then opportunistic screening unfairly benefits some children and not others. Since WES is expensive, the likely benefits will go to families who have good insurance and/or can afford this testing.

And if this testing is not primarily about the best interest of children, but rather about the best interests of family members, then the Kantian argument against this testing gains more force: children's need for WES is used opportunistically as an occasion for their parents to gain information without taking into consideration the wishes of the children as future adults. The ACMG concedes as much when they say that they consider this "a transitional moment in the adoption of genomic medicine where the parents of children undergoing sequencing do not have easy access to inexpensive, readily interpretable exome or genome sequencing" but that "[i]n the future, when parents might all have such access, the identification of adult-onset disease variants in their children could be restricted" (Green et al. 2013: 568). In other words, it's acceptable to use children's testing for their parents' information now, but in the future we can go back to respecting children's autonomy.

If it is possible that some parents (and/or some children) do not want information about, for instance, cancer risk, then the question of best interest is further complicated. The ACMG's goal is to benefit patients, but if the intended beneficiaries do not want what the ACMG believes they should want, then we can consider the ACMG's overriding of autonomy an instance of hard paternalism. To be fair, since parents are not given or aware of an option to opt out of receiving certain subsets of information, we cannot say what they want or don't want, or whether their wishes are being overridden in favor of what healthcare providers consider to be in their best interest. However, it is worth noting that the ACMG's values, not the parents' or children's, are dictating the meaning of *best interest* here. Particularly with respect to genetic information, and particularly because of abuses of the past, the relevant values for dictating receipt or nonreceipt of genetic information are generally the patient's values, not the values of the medical profession. While it may appear self-evident that preventing cancer is better than not preventing it, there are many instances of treatments that seem self-evidently better than nontreatment, but which patients are nonetheless permitted to refuse. Regardless of whether healthcare providers consider such decisions rational, they are generally obligated to respect the right of refusal (in patients with medical decision-making capacity).

In a position statement on a different topic (noninvasive prenatal screening), the ACMG acknowledges that "[p]atient preferences for information should play a

pivotal role" in screening and that this "is in keeping with generally accepted genetic counseling tenets and respects that clinical utility may vary between patients" (Gregg et al. 2016: 1058). In the case of prenatal testing, the ACMG respects "a patient's unique value system" and "recognize[s] that this construct [value system] is not homogeneous across the United States" (Gregg et al. 2016: 1058). It would be interesting to hear the reasons why patient preferences matter in one context but not in the other, or to learn when clinical utility varies between patients and when it remains stable.

In a clarification of their recommendations, the Working Group reiterated that they only supported reporting known pathogenic variants (ACMG 2013). They did not address concerns about decreased penetrance of those pathogenic mutations. They also did not address the fact that some variants formerly classified as pathogenic or likely pathogenic have been reclassified as VUS's or as benign variants (P. Connors, BUMC 2017, Personal Communication).

Ultimately, the Working Group holds that the parent's right to know about a potentially life-threatening condition supersedes the child's right not to know about a secondary finding (Green et al. 2013). Much has been speculated about potential harm while weighing the risks and benefits of genetic testing and return of secondary findings in children and fetuses. There is some suggestion that the community has been overly cautious about the potential psychological harms of returning genetic testing results to children given lack of evidence. Perhaps the potential for harm has been overestimated, and more discretion should be given to the parents to make decisions about testing for adult-onset conditions (Botkin et al. 2015; Friedman Ross et al. 2013; Wilfond and Friedman Ross 2009). It will be many more years before we can ask adults who underwent prenatal WES what their preferences for return of secondary findings would have been. However, even with this information, the ethical complexity of the issue persists: respect for autonomy, of either present or future adults, is not about benefits and harms. Thus, if children grow up and report in surveys that they feel they have not been harmed, we will not have proved that it is appropriate to test children for adult-onset conditions.

When the ACMG justifies their reasoning by appealing to the parent's right to know about potentially life-threatening conditions, they assume that a parent either wants to know this information or that the benefit of learning it is great enough to trump a parent's (autonomy) right not to know. When the ACMG decides for parents that they ought to and will learn this information when they pursue WES for their children, they are making a paternalistic judgment that the benefit to the parents outweighs the parents' autonomy rights. Since parents do not lack capacity to make their own decisions, this constitutes *hard paternalism*, which can only be justified if a number of conditions are met.

One of the conditions is that "the patient is at risk of a significant, preventable harm" and another one is that "there is no reasonable alternative to the limitation of autonomy" (Beauchamp and Childress 2009: 216). Parents of children undergoing WES are only "at risk" of a significant, preventable harm insofar as they are members of the human species and, like all humans, could have a germline mutation that increases the risk of cancer. However, if risk to have a rare genetic mutation is

sufficient to justify hard paternalism, an absurd number of interventions would seem to be justified as well. And, regarding the other condition, a reasonable alternative to deciding for parents would be to enable them to opt out of certain categories of information.

Conclusion

To conclude, the ACMG's position seems to be a departure from the recent past of allowing patient preferences to dictate whether, when, and which personal genetic information should be learned. When they state that this is a transitional moment on the way toward a time when more people have access to affordable whole-exome or whole-genome sequencing, they make a curious excuse for their position. This may suggest that their position is less an argument for a particular ethical position and more a statement of resignation to a future when genetic information is no longer treated as a highly personal matter. But the routinization of WES is by no means determined, and the assumption that because we can, we should or will, neglects much ethical thought that calls for thoughtful and public deliberation about the challenges raised by new and powerful technologies.

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