HHS Public Access

Author manuscript

Pediatrics. Author manuscript; available in PMC 2019 March 25.

Published in final edited form as:

Pediatrics. 2019 January ; 143(Suppl 1): S37–S43. doi:10.1542/peds.2018-1099H.

Returning a Genomic Result for an Adult-Onset Condition to the Parents of a Newborn: Insights From the BabySeq Project

Ingrid A. Holm, MD, MPH[a,b], **Amy McGuire, JD, PhD**[c], **Stacey Pereira, PhD**[c], **Heidi Rehm, PhD**[d,e,f,g], **Robert C. Green, MD, MPH**[f,h,i], **Alan H. Beggs, PhD**[a,b], and **BabySeq Project Team**

[a]Division of Genetics and Genomics, The Manton Center for Orphan Disease Research, Boston Chiidrerí s Hospitai, Boston, Massachusetts;

[b]Department of Pediatrics, Harvard Medical School, Boston, Massachusetts;

[c]Center for Medical Ethics and Health Policy, Baylor College of Medicine, Houston, Texas;

[d]Department of Pathology, Harvard Medical School, Boston, Massachusetts;

[e]Laboratory for Molecular Medicine, Partners Healthcare Personalized Medicine, Cambridge, Massachusetts;

[f]Broad institute of Massachusetts institute of Technology and Harvard, Cambridge, Massachusetts;

[g]Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts

[h]Department of Harvard Medical School, Boston, Massachusetts;

[i]Division of Genetics, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts

Abstract

The return of information from genomic sequencing in children, especially in early life, brings up complex issues around parental autonomy, the child's future autonomy, the best interest standard, and the best interests of the family. These issues are particularly important in considering the return of genomic results for adult-onset-only conditions in children. The BabySeq Project is a randomized trial used to explore the medical, behavioral, and economic impacts of integrating genomic sequencing into the care of newborns who are healthy or sick. We discuss a case in which a variant in a gene for an actionable, adult-onset- only condition was detected, highlighting the ethical issues surrounding the return of such finding in a newborn to the newborn's parents.

Genomic sequencing (next- generation sequencing of the whole genome or exome) is increasingly being used to diagnose rare disorders, individualize cancer treatments, and inform drug selection and dosing (pharmacogenomics).[1–9] In the near future, applications of

Address correspondence to Ingrid A. Holm, MD, MPH, Division of Genetics and Genomics, Boston Children's Hospital, 3 Blackfan Circle, Room 15022, Boston, MA 02115. ingrid.holm@childrens.harvard.edu.

Dr Holm conceptualized, wrote, and revised the manuscript; Drs McGuire, Pereira, Rehm, Green, and Beggs reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

POTENTIAL CONFLICT OF INTEREST: Dr Green is co-founder, advisor, and equity holder in Genome Medical, Inc; the other authors have indicated they have no conflicts of interest to disclose.

genomic sequencing are anticipated to expand in the areas of disease risk assessment, carrier testing, prenatal screening, and potentially more.[10–14] This expansion is facilitated by the increasing feasibility of conducting genomic sequencing on a population level, which has the potential to revolutionize health care and improve patient outcomes. Genomic sequencing may have its greatest lifelong impact on newborns. Not only can genomic sequencing be used to facilitate diagnoses in sick newborns and infants, it has potential utility in newborn screening by identifying risk for future disease that can be mitigated through early intervention. In addition, data provided by genomic sequencing can be a resource for health care providers to query throughout an individual's lifetime.

Recognizing that genomic sequencing as a component of newborn screening was becoming a possibility, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the National Human Genome Research Institute at the National Institutes of Health funded the Newborn Sequencing in Genomic Medicine and Public Health consortium, 4 projects used to explore "opportunities to use genomic information for broadening our understanding of diseases identified in the newborn period"[15] (https://www.genome.gov/27558493/newborn-sequencing-in-genomic-medicine-and-public-health-nsight/). The BabySeq Project is 1 of these projects and has a primary goal to explore the medical, behavioral, and economic impacts of integrating genomic sequencing into the care of newborns who are healthy or sick. BabySeq is a randomized clinical trial of newborns in 2 cohorts, that of newborns who are healthy at the Brigham and Women's Hospital and newborns who are sick in the ICUs at Brigham and Women's Hospital, Boston Children's Hospital (BCH), and Massachusetts General Hospital. Within each cohort, families are randomly assigned to a modified standard of care (standard newborn screening plus collection of a family history) or to modified standard of care plus whole exome sequencing. For those in the genomic sequencing arm, a newborn genomic sequencing report is generated, which is used to evaluate variants in >5000 genes to identify pathogenic or likely pathogenic variants in genes that have been strongly linked to childhood-onset diseases or diseases for which intervention is possible during childhood.[16] Carrier status for autosomal recessive conditions that fit these criteria is also reported. For newborns with a specific clinical presentation that potentially has a genetic etiology, a more in-depth analysis of the newborn's sequence targeted to that presentation is available (indication-based analysis). Parental DNA is collected but is not sequenced. Parental DNA is tested to inform the interpretation of potential risk variants found in the infant. Parent of origin of carrier status findings in the infant is generally not determined. Parents complete surveys over the infant's first year of life, and the infant's health care provider/s complete surveys over the course of the study.

The initial BabySeq protocol (2014) only allowed for the return of childhood-onset or childhood- actionable conditions (childhood defined as <18 years of age). This included diseases of known childhood onset (regardless of whether onset may also occur in adulthood) or diseases for which there is an indication for a treatment decision in the pediatric age range. The protocol did not allow for the return of results related to adult-onset-only conditions, which include conditions for which there is treatment, screening, prevention, or other actions recommended in adulthood but not in childhood.

There were several reasons why we excluded results related to adult-onset-only conditions in the original protocol. For many years, the standard of care in clinical genetics had been to not test an asymptomatic child for adult-onset- only conditions; it was felt that the best interest of the child was to protect their future autonomy to decide for themselves when they reach adulthood if they would like to know about their affected status for adult-onset-only conditions.[17–20] This standard of care was directly challenged in 2013 when the American College of Medical Genetics and Genomics (ACMG) came out with the recommendation that a list of 56 genes for "highly actionable" conditions be interrogated in all individuals undergoing clinical genomic sequencing for a primary indication and that the return of these "incidental" or "secondary" findings to patients be obligatory, without regard to age or preference; 3 of these conditions were adult- onset-only conditions.[21] This recommendation was hotly debated,[22–24] and, subsequently, the ACMG modified the recommendation to allow for patients to designate their preference for receiving these results; however, they did not change the recommendation that all of the findings, including those for adult- onset-only conditions, be returned regardless of age.[25] Given the lack of consensus about returning results for adult-onset-only conditions to parents of children, we decided to not return these findings in our study.

There were additional reasons behind our decision to exclude the return of results related to adult-onset-only conditions. We were concerned that including adult-onset-only conditions, with the immediate benefit going to other family members as opposed to the child, might cloud a family's decisionmaking process about whether to participate. By only reporting back pediatric-onset conditions, we hoped to better focus the family on the participation and potential benefits to the child. We also wanted to limit the amount of information a family might receive in an attempt to not overwhelm them.

Interestingly, the BCH Institutional Review Board (IRB) questioned our decision to exclude the return of adult-onset only conditions, and they cited pros and cons to not disclosing results for adult-onset- only conditions. The IRB's concerns centered around results for highly actionable (treatable or preventable) adult-onset-only conditions, because they recognized that returning these results to the child could potentially lead to presymptomatic or early detection and treatment of the condition in 1 of the child's parents. That said, they were comfortable excluding these conditions to protect the child's future autonomy and to protect against the unknown risks to the child and the family of disclosing this information. The US Food and Drug Administration (FDA), which exercised oversight over our protocol, was also concerned about the potential risk of returning results for adult-onset-only conditions in children. They eventually determined that our study was a nonsignificant risk device study (ie, it did not meet the definition of a significant risk device under §812.3[m] of the investigational device exemptions regulation [21 Code of Federal Regulations 812]) if we agreed to 3 stipulations, 1 of which was that we report only genetic variants that are associated with pediatric-onset conditions and not on adult-onset- only conditions.

CASE

A newborn male with medical problems was enrolled from the cardiac ICU at BCH and randomly assigned to the sequencing arm. The indication-based analysis did not identify any

genetic findings that explained the medical problems in the infant. Although results for adult- onset-only conditions were not being returned, the diagnostic laboratory's variant annotation and filtration pipeline for the general newborn genomic sequencing report does not specifically exclude genes for adult-onset-only conditions. Rather, it includes all variants reported as clinically significant in either the Human Gene Mutation Database or ClinVar in any gene with a claimed disease association. Although 1514 of these genes had been precurated,[16] genomic knowledge changes rapidly. Thus, the process in BabySeq is that the identification of a pathogenic gene variant in a newborn triggers the study team to conduct a thoughtful analysis and discussion on gene-disease validity, penetrance, age of onset, and actionability for the gene before the final BabySeq team return of results decision. In the case presented, this process led to the identification of a heterozygous known pathogenic *BRCA2* variant in the infant, which is associated with a 45% lifetime risk of breast cancer and 11% lifetime risk of ovarian cancer in women, as well as an elevated risk of other cancers in both sexes.[26,27] Sanger confirmation in the newborn and the previously collected parental saliva samples confirmed the variant and revealed maternal inheritance. The 3-generation family history taken at enrollment revealed negative results for breast, ovarian, or other potentially familial cancers. The infant subsequently died because of his underlying medical problems.

The finding of a *BRCA2* pathogenic variant led us to thoughtfully revisit the question of the return of adult- onset-only genes. The immediate issue was the return of this result to the family. Although we had not set out to identify adult-onset cancer risk variants, once the laboratory's pipeline identified this variant and relayed it to the research team, we felt it was inappropriate to withhold this result, because we believed it would be important for the family because of the potential impact on the health of the mother and other family members. However, the protocol precluded the return of such results, and the FDA nonsignificant risk determination was predicated, in part, on the research team not returning results for adult-onset- only conditions.

We discussed this situation with the IRB, and they agreed that this information should not be withheld from the family. We suggested, and the IRB concurred, that the family be given the option to receive this class of results (adult-onset only) at the same time they are given the results of the general report. If the parents declined, the IRB wanted to be sure that the family was given the option to obtain such results at a later date. The study geneticists and the family's pediatric cardiologist met with the parents and gave them the opportunity to learn about any actionable adult-onset-only findings, and both parents agreed that they would wish to receive such results. The return of the *BRCA2* finding immediately caused the mother to recall additional pertinent family history of more distant female relatives on her father's side with a history of breast and/or ovarian cancer. At the conclusion of the return of results and counseling session, the mother was given a referral and information to schedule clinical follow-up at a cancer genetics clinic.

The second issue was to prevent situations like this in the future. We amended the human subjects protocol to (1) offer optional return of actionable adult-onset-only results, limited to those that meet ACMG criteria (although not limited to the ACMG list) and (2) require that both parents must opt in to receive the results. However, the IRB had 2 primary concerns

about the proposed changes to the protocol. First, they felt that the amendment created an ethical dilemma for the laboratory personnel if they had important information that they could not return to the family: “if the parents do not both consent to receive results for adult-onset actionable conditions, lab personnel may see such a result in the infant, but they will not tell the clinical team and they will not test the parents.” Second, the IRB was concerned that if 1 parent opted in but the other opted out, which would exclude the return of this information, the parent who would have opted in might be prevented from learning important personal information. The IRB stated that in a “situation in which one parent says yes, one parent says no, so parent samples will not be tested, but because infant has [actionable adult-onset finding] it is possible that the parent who said yes would benefit by knowing, even without having [their] own results (could get tested on [their] own) and lab personnel will know that.”

These concerns led us to modify the amendment such that receiving results for adult-onset-only actionable conditions would become a condition of participation in the study, and thus both parents would have to agree to receive such results to enroll their infant in the study. This avoids the ethical dilemma of laboratory personnel knowing something that is widely considered to be actionable but cannot be returned to the family and the dilemma of parents disagreeing about whether to receive these results, potentially depriving 1 parent from receiving information that would be important to that parent. The amendment included contacting all families enrolled under the original protocol and offering them the option to consent to receive the result for this new class of genetic information. For those who opted in, the genomic data sets would be analyzed for the presence of risk variants meeting criteria for return. The modifications to the protocol were also communicated to the FDA shortly after the return of genetic results to the family.

DISCUSSION

The “best interest” standard has been a guiding principle for medical decision-making in pediatrics.[28] Both health care providers and parents are held to this standard when making medical decisions for a child. However, defining what is in the child’s best interest is often not clear-cut, especially when it comes to imparting genetic information about future risk, which could be clinically relevant for parents and other family members. If the future risk includes childhood risk, then providing that information to parents is justified because the parents are responsible for the child’s health care and wellbeing, and thus it is in the best interests of the child for the parents to have that information to make informed decisions. On the other hand, if the risk is not manifest until adulthood, medical genetics practice has held that it is in the child’s best interest to protect the child’s future autonomy to make decisions about genetic testing for risk of adult- onset-only diseases. Huntington disease, a nontreatable, autosomal dominant, adult-onset condition, is a prototype example for this policy.[29] It should be noted that this policy was developed in the setting of families with a known and highly penetrant genetic disease risk, and thus the children could be prompted when they reached adulthood to decide if they wanted to know their risk.

However, with the advent of genomic sequencing, the landscape has changed, and defining what is in the child’s best interest becomes more complex. Unlike Huntington disease for

which the condition is known in the family, in the current setting in which genomic sequencing is being performed as a screening tool in those not known to be at genetic risk, the lack of reporting from genomic sequencing may prevent families from ever knowing they have a genetic risk and ever enabling children to act in their own best interest, even when reaching adulthood. In addition, with genomic sequencing, an increasing number of treatable conditions can be identified presymptomatically, and many of the actionable adult-onset-only genetic conditions are autosomal dominant. Thus, frequently, 1 of the parents, as well as other family members, also have the variant and are at risk. In our *BRCA2* case, the mother carried the variant but was unaware of her risk because she inherited it from her father who was cancer free (men who carry *BRCA2* are much less likely to get BRCA2-related cancers compared with women), and her female relatives with breast and ovarian cancer were more distant. In such a case in which the highly actionable adult-onset-only condition is autosomal dominant, the best interest of the child includes not only the child's future autonomy to make a decision about what the child wants to know about him- or herself, but also having his or her parents alive and well.[30]

Broadening of the definition of a child's best interests has led to several ethical models that balance the interests of the child, parents, and other family members.[30,31] The "wide interest model" recognizes that there is often no sharp distinction between the interests of the child and the interests of other family members.[31] The "family interests model"[31] goes further and recognizes that the family unit itself has interests that are neither the sum nor a simple function of the interests of individual family members and argues that these interests need to be considered when making decisions on behalf of children. We would argue that the family-interests model more accurately reflects the ethical concerns in the return of genetic information in childhood than the best-interests model. In genetics, the return of risk information in the child, whether for a childhood-onset condition or an adult-onset-only condition, to the parents provides for holistic medical management for the entire family, which is often in the best interest for the child. These principles may apply in many medical situations, including infectious or environmental risk exposures but are particularly relevant with regard to genetic diseases for which information about 1 family member may have significant implications for genetically related relatives. In our case, once the infant died (which occurred after the *BRCA2* finding was discovered in the child and in the mother), it became clearer that the ethical decision was no longer what was in the infant's best interest but instead what was in the best interest of the family. Highlighted in this situation is the central role that the family-interests model plays in genetics for which results found in 1 family member may be relevant to the health and well-being of other family members, the basis of "cascade testing" (ie, testing other family members who may be at risk).

Highlighted in this case is also the ethical dilemma that occurs when laboratory personnel are privy to information that would be relevant to an individual but are unable to act on it. Some feel that if laboratory personnel have knowledge of clinically important information about a patient or participant or even a family member whose biological specimen was submitted for validation testing, they ought to disclose it or at least discuss it with the ordering physician or researcher. This is, in fact, the genesis of why the original ACMG recommendation on return of secondary findings in clinical practice included the obligatory return of results for these highly actionable conditions.[21] However, in an effort to respect

patient autonomy while fulfilling the physician's fiduciary obligation to act primarily for the benefit of the patient, the ACMG subsequently revised their recommendations to allow patients to decide if they do or do not want to receive actionable secondary findings.[25] As a result, clinical laboratories have developed policies over time regarding what information should and should not be returned, allowing them to avoid the ethical dilemmas and instead follow professional guidelines and specific patient directives obtained during consent. In research, however, unanticipated situations may arise because of the nature of the study. In this study, the BabySeq return of results protocol was not explicit about specific genes but instead was focused on general criteria for return, allowing genomic knowledge and criteria for return to be evaluated on a case-by- case basis when variants are identified in subjects. When the *BRCA2* variant was identified and discussed, it was felt not to meet existing criteria. But because the team felt that existing criteria was not in the best interest of families, the protocol was adjusted.

In research, it is perfectly acceptable to make a condition of participation in a study the willingness to receive all clinically relevant findings, even those related to actionable adult-onset-only conditions. As a result, our study team pursued a protocol change, now approved by the IRB, to require the return of all actionable findings, including those related to adult-onset-only conditions, back to study participants.

CONCLUSIONS

The "brave new world" of genomic sequencing has brought to the forefront a number of complex ethical issues, especially in pediatrics around autonomy, best-interest standards, and family interests, that challenge previous standards set when genetic testing was focused on known conditions in the family. Genetic findings are often inherited, and the findings in a child are often directly relevant to the health care of the family. Thus, rather than focus only on the best interests of the child, it is important in genomics to also consider the family-interests model. Finally, it is important to have a plan for every scenario and to design a research protocol and consent form that minimizes the discovery of findings that the investigators are not prepared to return.

ACKNOWLEDGMENTS

We thank the families and clinicians for their participation in the BabySeq Project.

The BabySeq Project Team members are as follows: Pankaj B. Agrawal, Alan H. Beggs, Wendi N. Betting, Ozge Ceyhan-Birsoy, Kurt D. Christensen, Dmitry Dukhovny, Shawn Fayer, Leslie A. Frankel, Casie A. Genetti, Chet Graham, Robert C. Green, Amanda M. Gutierrez, Maegan Harden, Ingrid A. Holm, Joel B. Krier, Matthew S. Lebo, Harvey L. Levy, Xingquan Lu, Kalotina Machini, Amy L. McGuire, Jaclyn B. Murry, Medha Naik, Tiffany Nguyen, Richard B. Parad, Hayley A. Peoples, Stacey Pereira, Devan Petersen, Uma Ramamurthy, Vivek Ramanathan, Heidi L. Rehm, Amy Roberts, Jill O. Robinson, Serguei Roumiantsev, Talia S. Schwartz, Tina K. Truong, Grace E. VanNoy, Susan E. Waisbren, and Timothy W. Yu.

FINANCIAL DISCLOSURE: Dr Green receives compensation for speaking or consultation from AIA, GenePeeks, Helix, Ohana, Prudential, and Veritas; the other authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: This work was supported by grant U19 HD077671 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and National Human Genome Research Institute of The National Institutes of Health. Funded by the National Institutes of Health (NIH).

ABBREVIATIONS

ACMG	American College of Medical Genetics and Genomics
BCH	Boston Children's Hospital
FDA	Food and Drug Administration

REFERENCES

1. Green RC, Rehm HL, Kohane IS. Clinical genome sequencing In: Ginsburg GS, Willard HF, eds. Genomic and Personalized Medicine. Vol 1 2nd ed. San Diego, CA: Elsevier Inc; 2013:102–122
2. Biesecker LG, Green RC. Diagnostic clinical genome and exome sequencing. N Engl J Med. 2014;370(25):2418–2425 [PubMed: 24941179]
3. Baylor College of Medicine. Medical genetics laboratories: whole genome laboratory (WGL). 2012 Available at: www.bcm.edu/geneticlabs/index.cfm?PMID=21319. Accessed June 13, 2012
4. Dewey FE, Grove ME, Pan C, et al. Clinical interpretation and implications of whole-genome sequencing. JAMA. 2014;311 (10):1035–1045 [PubMed: 24618965]
5. Krier J, Barfield R, Green RC, Kraft P. Reclassification of genetic-based risk predictions as GWAS data accumulate. Genome Med. 2016;8(1):20 [PubMed: 26884246]
6. Gilissen C, Hoischen A, Brunner HG, Veltman JA. Unlocking Mendelian disease using exome sequencing. Genome Biol. 2011;12(9):228 [PubMed: 21920049]
7. Gonzaga-Jauregui C, Lupski JR, Gibbs RA. Human genome sequencing in health and disease. Annu Rev Med. 2012;63:35–61 [PubMed: 22248320]
8. Macconaill LE, Garraway LA. Clinical implications of the cancer genome. J Clin Oncol. 2010;28(35): 5219–5228 [PubMed: 20975063]
9. McDermott U, Downing JR, Stratton MR. Genomics and the continuum of cancer care. N Engl J Med. 2011; 364(4):340–350 [PubMed: 21268726]
10. Vergano D Baby gene map could cut diagnosis to days. USA Today. 2012 Available at: www.usatoday.com/story/news/nation/2012/10/03/neonatal-genome-sequencing-speed-advances/1610163/. Accessed November 15, 2012
11. McElroy M. Researchers and policymakers point to successes and challenges in personalized medicine. American Association for the Advancement of Science (AAAS). 2009 Available at: www.aaas.org/news/releases/2009/1214personalized_medicine.shtml. Accessed November 15, 2012
12. Butte AJ, Chen D. Translational bioinformatics for genomic medicine. In: Ginsburg G, Willard HF, eds. Genomic and Personalized Medicine Oxford, United Kingdom: Academic Press; 2013:272–286
13. Kennedy S Newborn screening. Saving lives the molecular way. Bitesize Bio. 2007 Available at: http://bitesizebio.com/articles/newborn-screening-saving-lives-the-molecular-way/.Accessed November 15, 2012
14. Whirl-Carrillo M, McDonagh EM, Hebert JM, et al. Pharmacogenomics knowledge for personalized medicine. Clin Pharmacol Ther. 2012;92(4):414–417 [PubMed: 22992668]
15. Berg JS, Agrawal PB, Bailey DB, Jr, et al. Newborn sequencing in genomic medicine and public health. Pediatrics. 2017;139(2):20162252
16. Ceyhan-Birsoy O, Machini K, Lebo MS, et al. A curated gene list for reporting results of newborn genomic sequencing. Genet Med. 2017;19(7):809–818 [PubMed: 28079900]
17. Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. American Society of Human Genetics Board of Directors, American College of Medical Genetics Board of Directors. Am J Hum Genet. 1995;57(5):1233–1241 [PubMed: 7485175]

18. Botkin JR, Belmont JW, Berg JS, et al. Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. Am J Hum Genet. 2015;97(1):6–21 [PubMed: 26140447]
19. Committee on Bioethics; Committee on Genetics; American College of Medical Genetics; Genomics Social, Ethical, Legal Issues Committee. Ethical and policy issues in genetic testing and screening of children. Pediatrics. 2013;131 (3):620–622 [PubMed: 23428972]
20. Ross LF, Saal HM, David KL, Anderson RR; American Academy of Pediatrics; American College of Medical Genetics and Genomics. Technical report: ethical and policy issues in genetic testing and screening of children [published correction appears in Genet Med. 2013;15(4):321]. Genet Med. 2013;15(3):234–245 [PubMed: 23429433]
21. Green RC, Berg JS, Grody WW, et al.; American College of Medical Genetics and Genomics. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med. 2013;15(7):565–574 [PubMed: 23788249]
22. Burke W, Antommaria AH, Bennett R, et al. Recommendations for returning genomic incidental findings? We need to talk! Genet Med. 2013;15(1 1):854–859 [PubMed: 23907645]
23. McGuire AL, Joffe S, Koenig BA, et al. Point-counterpoint. Ethics and genomic incidental findings. Science. 2013;340(6136):1047–1048 [PubMed: 23686340]
24. Wolf SM, Annas GJ, Elias S. Point- counterpoint. Patient autonomy and incidental findings in clinical genomics. Science. 2013;340(6136):1049–1050 [PubMed: 23686341]
25. Kalia SS, Adelman K, Bale SJ, 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 [published correction appears in Genet Med. 2017;19(4):484]. Genet Med. 2017;19(2):249–255 [PubMed: 27854360]
26. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies [published correction appears in Am J Hum Genet. 2003;73(3): 709]. Am J Hum Genet. 2003;72(5):1117–1130 [PubMed: 12677558]
27. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. 2007;25(11):1329–1333 [PubMed: 17416853]
28. Ross LF. Predictive genetic testing of children and the role of the best interest standard. J Law Med Ethics. 2013;41(4):899–906 [PubMed: 24446947]
29. Bloch M, Hayden MR. Opinion: predictive testing for Huntington disease in childhood: challenges and implications. Am J Hum Genet. 1990;46(1):1–4 [PubMed: 2136787]
30. Wilfond BS, Fernandez CV, Green RC. Disclosing secondary findings from pediatric sequencing to families: considering the “benefit to families”. J Law Med Ethics. 2015;43(3):552–558 [PubMed: 26479565]
31. Groll D Four models of family interests. Pediatrics. 2014;134(suppl 2):S81–S86 [PubMed: 25274879]