Published in final edited form as:

Annu Rev Genomics Hum Genet. 2013 ; 14: 535–555. doi:10.1146/annurev-genom-091212-153425.

Growing Up in the Genomic Era: Implications of Whole-Genome Sequencing for Children, Families, and Pediatric Practice

Christopher H. Wade,

Nursing and Health Studies Program, University of Washington Bothell, Bothell, Washington 98011

Beth A. Tarini, and

Child Health Evaluation and Research Unit, Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, Michigan 48109

Benjamin S. Wilfond

Treuman Katz Center for Pediatric Bioethics, Seattle Children's Research Institute, Seattle, Washington 98101

Christopher H. Wade: cwade@uwb.edu; Beth A. Tarini: btarini@umich.edu; Benjamin S. Wilfond: benjamin.wilfond@seattlechildrens.org

Abstract

Whole-genome sequencing (WGS) has advanced to a point where it is beginning to be integrated into pediatric practice. With little consensus on how to maximize the benefits of WGS for children, there is a growing need for focused efforts that connect researchers, clinicians, and families to chart a path forward. To illustrate relevant concerns, two contrasting applications of pediatric WGS are explored: clinical use with children who have undiagnosed conditions, and population-based screening. Specific challenges for health care services, policy development, and the well-being of children are discussed in light of current research. In the interest of ensuring evidence-based pediatric WGS, strategies are identified for advancing our understanding of what it means for children to grow up with WGS results guiding their health care.

Keywords

genetic testing; newborn screening; pediatrics; policy; ethical, legal, and social implications; ELSI

INTRODUCTION

Broad public support for providing children with the highest-quality care available is likely to spark interest in new genomic technologies that could be used in pediatric practice (27, 44). Indeed, some have envisioned a future where children have whole-genome sequencing (WGS) performed at birth and grow up with that information providing insight into clinical

Department of Pediatrics, University of Washington School of Medicine, Seattle, Washington 98101

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

prevention and treatment options (17). Unlike traditional genetic testing approaches, which typically target a single disease-causing gene variant, pediatric whole-genome sequencing (P-WGS) provides detailed sequence information across the full genome, and pediatric whole-exome sequencing (P-WES) generates sequence information for segments of the genome that encode proteins. The idea of using genomics in children's health care has moved from conjecture to reality, as P-WGS and P-WES are being provided for children with undiagnosed conditions and the price of WGS is rapidly becoming affordable for routine clinical use (6, 16, 24, 87).

Optimistic visions for the swift adoption of P-WGS can be at odds with approaches that emphasize ethical and practical concerns about providing genetic services to children. These concerns are hardly new; they became prominent during the premature implementation of state-sponsored newborn screening programs in the 1960s and gained increasing attention as new diagnostic, carrier, and predictive tests propagated in the following decades (28, 61, 112). These cases demonstrate the importance of examining key characteristics of P-WGS, such as the likelihood of medical benefit, the potential impact of genetic testing on children and their families, and the effectiveness of clinical services that could provide care based on test results. Because of these considerations, many clinical associations have adopted precautionary guidelines that discourage testing children in the absence of a demonstrated medical benefit during childhood (10, 14, 18).

Debate among health researchers, clinicians, ethicists, policy makers, and public advocates about when genetic testing of children is appropriate has resulted in many excellent commentaries and reviews (11, 25, 30, 44, 62, 65, 82, 98, 99, 102, 111). A common concern is that there is a limited body of empirical data on how different types of genetic tests impact children and their families (25, 76, 107). Therefore, it is unclear whether we will be prepared to translate P-WGS into pediatric practice using an evidentiary approach (where action is guided by evidence, ethical considerations, and public involvement) or will forge ahead using a less ideal extemporaneous approach (where political pressure from advocacy, commercial, legal, or professional organizations leads to adoption prior to the demonstration of beneficial outcomes) (110, 112).

The purpose of this review is not to restate the work that precedes it with respect to all uses of genetic information in pediatric care. Rather, the focus is on the distinct issues raised by WGS of children (defined here as individuals between birth and the age of legal majority). More specifically, the objectives are to examine the factors determining when P-WGS will be useful in pediatric practice, discuss what can be learned from current research that is relevant to P-WGS, and recommend paths toward research and policies that would help prepare for a future where P-WGS may be part of standard care.

P-WGS IS ALREADY IN USE AND IS LIKELY TO EXPAND

It would be hard to overemphasize the speed at which WGS technologies are developing. Whereas the cost of sequencing a human genome in 2003 was \$2.7 billion, that price had dropped to ~\$4,000 by 2012, and WGS is expected to be affordable for routine clinical applications once it reaches \$1,000 (94). The time that it takes to sequence a genome has

also decreased: It is now possible to complete sample collection, sequencing, and analysis in less than 50 hours (87). At this pace, regular WGS in clinical settings will be both technologically feasible and affordable in the near future.

P-WGS and P-WES are currently available, although in limited contexts. They most frequently occur as part of research studies exploring childhood health conditions, some of which return test results to study participants (22, 35, 87, 92). There are also some early cases where P-WGS has been used clinically for children with serious undiagnosed health conditions in an attempt to gain insight into disease causation (6). Parents have also gone through commercial services to obtain genome sequencing (20, 80), which is controversial because some direct-to-consumer genetic testing companies provide genetic risk information without involving a health care practitioner (12).

There is reason to believe that the current uses of P-WGS are only the beginning of a trend. Aside from interest among researchers and clinicians in the potential health benefits of genomic technologies, there has been considerable enthusiasm expressed by the public (19). In particular, parents often express interest in obtaining genetic health information about their children, who, in turn, appear to be similarly inclined (9, 15, 72, 100). Although hypothetical interest in obtaining genetic testing is often higher than actual test uptake (57, 71), if even a modest percentage of the public sought WGS, it could have significant impact on the provision of genetic services, an effect that is being anticipated by health insurance companies (104). It is plausible that, as has been seen for previous genetic tests, public demand will play a role in speeding the integration of P-WGS (112).

Prior to widespread use, it would be prudent to ask some questions about the overall impact of P-WGS on children, their families, and the provision of pediatric care. For example, does the genomic information provided by P-WGS improve children's health? Also, if P-WGS is used, how can families be effectively informed of testing options and supported when genetic risks are identified? Furthermore, how prepared is the pediatric health care workforce to conduct P-WGS testing, interpret results, and explain the findings to patients? Finally, are there key policy concerns that should be addressed before implementing P-WGS? Answers to these questions will be needed if P-WGS is to be successfully integrated using an evidentiary model.

CHILDREN'S HEALTH AND WGS

Under the evidentiary approach to clinical translation, the strength of data demonstrating that P-WGS provides health benefits will be a major factor in determining the speed with which it is adopted. When viewed comprehensively, simply showing that P-WGS can indicate health risks for children is inadequate to justify use. Rather, P-WGS must be shown to possess advantages over existing approaches to pediatric genetic testing (Table 1) in aspects such as efficiency, accuracy, capacity to produce actionable information, and overall health outcomes (105).

Criteria for assessing whether a genetic test should be integrated into practice have already been developed in the ACCE (analytic validity, clinical validity, clinical utility, and ethical, legal, and social implications) model, which will be applied to P-WGS in the following

discussion (42). Specifically, this approach for evaluating tests recommends first delineating the purpose and context within which P-WGS will be used. The characteristics of the test itself should then be determined, including its analytic validity (whether it can accurately detect the presence of a genetic variant) and its clinical validity (whether a genetic variant has a replicable and significant association with a disease outcome). Beyond these factors, a thorough assessment of P-WGS would require data on clinical utility (whether sequencing has positive outcomes for health care provision overall) and examination of important ethical, legal, and social implications of using P-WGS. Although this model for evaluating tests has considerable support among policy makers, it is important to recognize that many genetic tests that are widely available in pediatric care do not have strong evidence for the criteria described above, and stakeholders have divergent opinions on when it is appropriate to begin clinical use of a genetic test (85, 103, 112).

Purpose and Context of P-WGS

Like most clinical tools, P-WGS could be used for a range of purposes (Table 2). Therefore, meaningful assessment of P-WGS can be accomplished only when a clear health care context has been specified, including the population target and purpose of testing (105). To provide focus for this review, the following discussion is narrowed to two distinct applications: problem-based P-WGS and population-based P-WGS. Because their justifications represent different poles in clinical contexts, they are illustrative of the divergent benefits and challenges that P-WGS may present for pediatric practice.

Problem-based P-WGS—The first approach is problem-based P-WGS, where the test is conducted with a specific diagnostic or therapeutic purpose in mind (6) (see Figure 1*a*). This is most likely to occur in cases where (*a*) a child presents with symptoms that do not suggest a specific diagnosis and that may have a genetic origin, or (*b*) a child receives a diagnosis for which additional information may guide therapy. In this context, the target population is limited, the likelihood of finding beneficial information is relatively high, and P-WGS will be provided and analyzed by clinical specialists. Currently, P-WGS for undiagnosed conditions typically occurs after a graded diagnostic workup, where the clinician will have previously ordered tests (e.g., karyotypes, fluorescence in situ hybridization, or chromosomal microarray analysis) that can help determine whether there are significant insertions, deletions, or rearrangements in the child's DNA. When these tests have failed to find a diagnosis, the more refined data of WGS or WES might be used to identify possible disease-causing mutations and potentially suggest treatment strategies. In most cases, analysis of the P-WGS results will focus foremost on genes with known or suspected association with the observed symptoms.

Population-based P-WGS—Another approach would be to use P-WGS for screening purposes (2, 37, 46, 74, 96) (see Figure 1*b*). Here, the WGS would be performed on children from the general population in the absence of a specific clinical question to determine whether any genetic risk variants are present that deserve attention. Because the target population is very large (in theory, any child would be a candidate), the cost to the health care system would be higher, and more children would be exposed to potential harms of testing. The probability of finding critical health information is also lower when preexisting

symptoms are not present. Furthermore, population-wide implementation would likely require the involvement of pediatric clinicians without specialized training in genomics. These challenges illustrate why more-stringent requirements for evidence of benefit are typically applied to screening tests (3).

An important characteristic of population-based P-WGS is that it asks whether any health risks can be found for a child with “normal” risks of disease prior to testing. This is the same rationale that justifies the public health practice of newborn screening, where almost all children are screened to identify rare cases of genetic diseases that require prompt special treatment. Similarly, population-based P-WGS would likely occur during the newborn period because this timing would be easiest to integrate into existing structures and would have the greatest prevention potential (1).

Because problem-based P-WGS and population-based P-WGS have different purposes, populations, and interpretation strategies, they are evaluated separately in the following discussion.

Accuracy of WGS for Detecting Health-Related Genetic Variants

Depending on how WGS is viewed, it may be seen as having a high or low analytic validity. Estimates suggest that high-quality WGS has excellent accuracy (near 100%) when it comes to correctly identifying an individual base pair (79). In this sense, the analytic validity is high. However, even for an extremely accurate measurement tool, when enough individual “tests” are made (and in this case there would be 6 billion, one for each base pair in a human genome), the probability of incorrect results rapidly accumulates. For example, when an accuracy of 99.9% is assumed, WGS will result in as many as 6million inaccurate base-pair calls; although most of these mistakes will be irrelevant, the likelihood that an individual will receive one or more false positive results is high (54). It should also be noted that WGS does not technically cover a “whole” genome: As much as 10% of the genome sequence might be missing (7). Therefore, despite the overall accuracy of WGS, both positive and negative test results need to be interpreted with caution.

The analytic validity of WGS technologies will have different implications for problem-based P-WGS and population-based P-WGS. Because problem-based P-WGS is addressing a specific question for a child, interpretation will focus on specific regions and variants, where the high overall sequence accuracy should make it equivalent to or better than most other genetic testing options. When potential errors occur in problem-based P-WGS, specialists will likely be available to address the issue during follow-up care. The imperfect analytic validity of WGS presents a more serious concern for screening applications. For population-based P-WGS, there will be proportionally fewer findings with health significance and more energy expended to resolve false positives.

Ability of WGS to Predict Disease

The clinical validity of P-WGS will vary depending on the genetic variant and disease in question (42). In the context of explaining undiagnosed signs and symptoms, sequencing strategies can successfully reveal new and rare mutations that clarify the etiology of the child’s condition (6, 35, 66). Because many of these findings are novel, there will often be

little data on clinical validity, and the probable impact of the variant will need to be assessed by a genetic specialist.

The clinical validity of population-based P-WGS varies widely depending on the application. For example, some cases of cystic fibrosis are missed in current newborn screening practices because only the most common mutations are tested for. P-WGS could detect the less frequent deleterious mutations, leading to improved clinical validity over existing methods (24). However, P-WGS will also identify variants that suggest susceptibility to disease (but no substantial prediction) as well as many variants with uncertain significance. In these cases, clinical validity is likely to be low, negligible, or nonexistent.

Overall Impact of P-WGS When Used in Clinical Practice

A genetic test that has promising test characteristics (analytic and clinical validity) becomes a candidate for explorative use in health care settings to assess clinical utility. This process integrates a wide range of information relevant to overall benefit, such as the impact on children's health outcomes, the existence of other effective interventions, the cost effectiveness of testing, the presence of high-quality testing, and the accessibility of patient support services (42).

The diversity of health information within P-WGS data would require a prioritization process. It has been suggested that the results of such a test could be sorted into three categories with different implications: "clinically actionable," "clinically valid but not directly actionable," or of "unknown or no clinical significance" (5). Clinicians would likely restrict attention to results in the first category, unless there were a specific reason for extending the scope of consideration. Although this approach is promising and necessary, the exact methods for accomplishing it are still being developed (4, 40).

Children for whom problem-based P-WGS is ordered typically already have significant health issues. In the case of undiagnosed conditions, P-WGS is currently the last step in a difficult and often expensive chain of tests aimed at explaining the etiology of the disease (although in the future, with decreased cost and increased evidence of utility, it may be used earlier in the process). Several reports have indicated that P-WGS can provide a diagnosis and suggest paths to clinical management (6, 35, 67, 87). Limited information on success rates is available, but informal estimates suggest that P-WGS would assist diagnosis in about 25% of cases, improve disease management for about 3% of tested individuals, and lead to a greatly beneficial treatment for perhaps 1% of tested individuals (55). Because (a) symptoms already exist for these children, (b) families typically have a strong desire for a diagnosis, and (c) test results could inform health and reproductive decisions for family members, problem-based P-WGS will likely come to be seen as having acceptable clinical utility.

Using population-based P-WGS to target children with a low preexisting risk will mean higher cost, decreased probability of obtaining clinically useful information, and magnification of risks given the number of children exposed. Despite these concerns, however, it remains an open question whether the "catch all" approach will have a net

benefit, as population-based P-WGS could uncover health information capable of improving treatment and prevention efforts (Table 2). If P-WGS is conducted after birth, it could replace and improve upon many existing newborn screening tests, which are generally viewed as having clinical utility for preventing morbidity and mortality. It might also assist in the selection and dosing of pharmaceuticals, which already have demonstrated utility for children in some contexts (49). Finally, with knowledge of genetic associations with disease accumulating daily, WGS information will have increasing utility as a predictor of a range of health states. Nonetheless, it is generally recognized that there should be a high burden of proof demonstrating the clinical utility of population-based tests (3, 74), and the nonexistence of evidence supporting population-based P-WGS suggests that extensive research will need to be conducted prior to implementation.

Although WGS holds considerable promise as a tool to identify genetic variations that increase health risk, a careful assessment of the overall risks and benefits of P-WGS must include a larger range of considerations, such as informed decision making, psychosocial impact, service provision, and policy issues. Therefore, these topics are addressed in more detail in the following sections.

SUPPORTING INFORMED DECISIONS ABOUT P-WGS

Health care decision making for children is typically deferred to parents or guardians (21, 111). Not only are such choices the purview of parents, but clinicians have an obligation to provide sufficient education that parents can make an informed decision about what is best for their child. Clinicians could explain to parents the general types and meaning of results that WGS could generate. For example, P-WGS results could vary from findings of a minor increase in risk for an adult condition to a prognosis of imminent death. Despite these conversations, there will always be the potential for outcomes that are surprising, confusing, and life changing. As such, the quality of the process that supports informed decision making will play a major role in the acceptability of P-WGS.

To put decision-making processes in context, one must address the attitudes and knowledge with which parents are likely to enter the conversation. Parents will want to make the best decision possible for their child, and it is expected that they will support their child in understanding and responding to risk information (63). Although parents will have differing views on whether P-WGS will benefit their child, research on attitudes suggests that many parents appear to be interested in learning genetic information about their child even when it provides little guidance on intervention strategies (9, 19, 72, 89, 97, 100). The general enthusiasm for genetic information is likely to be combined with misunderstandings common in the public related to gene-environment interaction, conceptualization of probabilities, procedures for genetic testing, and the role genes play in cellular function (19). Therefore, education will be a key component to supporting informed decision making, particularly with testing as complex as P-WGS.

Mechanisms will need to be developed so that parents can make choices about which categories of genomic risk information they want to receive. Studies on attitudes toward genomic tests suggest that the ability to select options in information delivery might be a

high priority for parents (29, 95, 103, 106). For example, a consent process might explain the types of information that fall within the “clinically actionable” tier of risks detected through P-WGS and then could provide an option for additional types of genetic information (5). Also, parents might be given a choice of times during their child’s development that different types of health information would be returned (for example, information on preventable childhood conditions might be returned immediately, whereas risks for nonpreventable adult-onset conditions might be withheld until the child has reached the age of majority).

When possible, testing decisions should also take into account the desires and information needs of the child. Children often have positive views toward genetic testing similar to those observed among parents (15). In situations where children have adequate decision-making capacity and understanding of genetics, it would be appropriate for clinicians to encourage the inclusion of children’s perspectives in the P-WGS decision-making process (23, 34).

Problem-based P-WGS may occur in a clinical context where strong resources will be available to support informed parental decision making. Programs that address undiagnosed diseases are likely to have access to trained genetic specialists, particularly genetic counselors (69), who are available to take the lead in guiding parents through genetic diagnosis efforts. This can be an extensive process. For example, one program reported that genetic counseling sessions totaled six to eight hours, spread over several sessions, prior to WGS (6). Discussions covered topics such as the basics of genetics, inheritance, and gene-environment interactions; the likelihood of developing conditions; the types of information revealed by WGS; the potential for incidental findings and errors; the risks of identifying misattributed paternity; and privacy protections. Such extensive consent processes for WGS can convey key information, but may be taxing for patients (95).

A major challenge for problem-based P-WGS is the high likelihood of incidental findings. Incidental findings are unanticipated test results that provide new health risk information that is unrelated to the original purpose of testing. These findings can be of sufficient medical importance that clinicians would feel obligated to inform parents of the additional unexpected risks. This is a particular issue for WGS because the massive amount of genetic data generated dramatically increases the likelihood of incidental findings. Estimates suggest that people undergoing problem-based WGS have a strong likelihood of at least one incidental finding with substantial health implications and dozens of notable variants that are likely to influence disease states (4, 54, 91). Furthermore, as knowledge of relationships between variants and diseases increases, so will the probability of incidental findings. Although this may ultimately provide health benefits for children, it also presents complications because the families may learn information that was not anticipated or desired prior to testing.

Population-based P-WGS presents even greater challenges for informed parental decision making. In this case, screening would be conducted in a primary care or public health context, where the ability to handle unanticipated genetic risks may be more limited (4, 54, 91). In particular, parents would still need to be educated about the implications, risks, and choices available, but the time pressures in these settings are not conducive to extensive

education, counseling, and consent processes (114). This can be observed in the current newborn screening context, where parents are provided with limited or no information prior to testing and clinicians typically do not support allowing parents to select among different types of conditions on newborn screening panels (64, 83, 96). These issues would likely apply to population-based P-WGS, and would probably justify limiting the scope of such testing to timely and actionable findings with significant health implications.

IMPACT OF P-WGS FINDINGS ON CHILDREN AND FAMILIES

There is limited information available on the psychosocial impact of P-WGS on children and their families. Therefore, the research discussed in this section focuses on studies of single-gene testing for rare genetic conditions. It is worth noting at the outset that parallels between the psychosocial impacts of P-WGS and single-gene testing should be viewed with a critical eye, given the added complexity of genomic data.

Research suggests that the responses of parents who learn that their child has a genetic condition vary considerably depending on the prognosis for the condition; for severe diseases in particular, parents can experience worry, stress, guilt, and other negative impacts on well-being (41, 45). Family support and the services of a genetic counselor can make substantial differences in addressing parental emotional needs (58, 69). Also, parents are often faced with the responsibility of explaining genetic risks to their children, but there is little research on this topic or support resources for parents in this role (63, 73, 86). This route for communication to a child is particularly likely for population-based P-WGS, where such information would likely be obtained at birth and the child would then grow up with those risks guiding his or her care. Deciding when a child is ready to understand a risk can be a challenging task for parents (86, 113). That said, some data suggest that such communication might occur before children reach the age of majority; for example, about half of mothers who test positive for *BRCA* mutations choose to tell their children that they are at risk for breast cancer (101).

A major question for the implementation of P-WGS is what impact genomic risk information has on children's psychosocial well-being. Several reviews have explored this issue for single gene tests (25, 76, 107). A consistent finding is that there is inadequate research on how children respond to genetic risk information, but existing data do not support concerns about a strong negative psychosocial impact. For example, in a systematic review that focused on carrier and predictive testing—which are controversial testing approaches among children—only 17 articles were identified (107). Overall, there were no significant effects for most psychosocial traits explored by the studies, including emotional states (e.g., depression, anxiety, and behavioral problems), self-concept (e.g., self-image, self-esteem, and physical self), and social connections (e.g., parental relationships, sibling relationships, and communication). Although there were some reports of negative effects, such as positive results increasing worry and potential misunderstanding of carrier status implications, these were balanced by indications of strong beneficial effects for those who tested negative and high overall satisfaction. However, the designs of these studies typically had major limitations. Therefore, the current lack of evidence for major psychosocial harms

should not be overinterpreted as meaning that genetic testing (and certainly P-WGS) could not substantially impact children's well-being.

It is also important to consider impacts of genetic risk information on siblings and other family members (31, 78). Each family has a distinct network of relationships that helps determine how support and health information is distributed (51, 52, 113). Families that treat genetic risks as a secret tend to have more negative outcomes, particularly for the children who are at risk (69). Therefore, understanding family communication patterns and systems of support may be essential to designing interventions that maximize the benefits of P-WGS.

P-WGS AND PEDIATRIC PRACTICE

As P-WGS becomes more widely available, the responsibility for testing, interpreting, communicating, and applying these results will increasingly become the purview of pediatric clinicians. In the case of problem-based P-WGS, these tasks will fall on a limited number of pediatric subspecialists. Although this change in technology will result in a substantial increase in genetic information and incidental findings, mechanisms for providing problem-based P-WGS are likely to be similar to those already established for the diagnosis of rare genetic conditions.

The widespread adoption of population-based P-WGS would present major workforce challenges and necessitate significant training of primary care pediatric clinicians. Data suggest a preference among primary care physicians for referring cases to genetic specialists (109). However, there are only approximately 1,200 medical geneticists and 2,500 genetic counselors in the United States (47). Because population-based P-WGS would lead to frequent results indicating increased risk as well as false positives needing to be resolved, coverage of this increased patient load by genetic specialists will likely become untenable without a substantial increase in workforce. This means that responsibilities for providing P-WGS and subsequent patient support could become the domain of primary care clinicians, who may act independently or as part of a care team (50).

Leaders in translational genomics express concern that many clinicians do not yet have the necessary training to use WGS information effectively (33). In the case of newborn screening, pediatricians frequently misinterpret genetic test results, report mixed familiarity with key genetic concepts, and fail to provide parents with relevant information (83, 96). Pediatricians also express limited confidence in their ability to provide genetic information to patients, particularly across educational and cultural barriers (81). Although concerted efforts are under way to provide resources and educational opportunities to clinicians (including physicians, nurses, and physician assistants), this is an ongoing process that may need to be hastened to meet new demands (47, 50, 88). Without adequate preparation, P-WGS could lead to an unproductive diagnostic cascade, where taxing follow-up visits, overuse of specialists, and unnecessary ordering of tests create unacceptable burdens on the health care system, children, and their families. Although signs of a diagnostic cascade have not been observed in research on the impact of genetic susceptibility scans (8, 75), the added complexity of P-WGS suggests that this possibility should be explored prior to implementation.

POLICY CONSIDERATIONS FOR P-WGS

Policy guidelines will play a key role in future use of P-WGS by providing recommendations for clinicians, framing public debates, and influencing when the technology will be made available. Although existing policies have not extensively addressed P-WGS per se, the issue of single-gene testing of children has been explored by a number of panels and clinical organizations (10, 14, 18, 43, 84). The resulting guidelines support many applications of prenatal, newborn, and diagnostic testing, but discourage carrier and predictive testing unless there is an established and direct health benefit during childhood.

The positions taken in current guidelines are subject to extensive ethical debate (25, 30, 60, 77, 98, 108, 111). Central arguments that arise in this discussion relate to medical, psychosocial, and autonomy concerns (28). The medical and psychosocial categories of ethical concern have been addressed above, where it was shown that implementing P-WGS will present substantial challenges that are highly dependent on the clinical context for implementation. Nonetheless, these issues do not appear to be so insurmountable that net benefits are inconceivable. Therefore, the focus here is on autonomy, which is the only ethical objection that could render P-WGS unacceptable without considering empirical evidence on the impact of integrating P-WGS technology.

Concerns about preserving the autonomy of children have been framed as a right to an “open future,” where children have the maximum range of choice available once they develop an adult decision-making capacity (111). So, for example, it could be argued that a child who tests positive for *BRCA* breast cancer mutations has been harmed, because the child cannot “unlearn” his or her risk and now has the limited future of growing up with this information. For these reasons, many conclude that it is inappropriate to test children unless there is a clear medical benefit during childhood (10, 14, 28, 30). However, this position has faced a number of challenges. Most important, the “open future” perspective prioritizes the future right of children to make their own decisions over the broadly accepted prerogative of parents to make choices that influence the health of their child (111). Typically, parents can make decisions that substantially increase a child’s health risks (e.g., enrolling in contact sports) or even forgo treatments with known benefits (e.g., vaccines) without interference. Although there is room to argue that parents’ authority can be restricted, this would be justified only in situations with serious and demonstrable risk to a child (21). For these reasons, automatic rejection of P-WGS does not appear to be consistent with widely held support for parental discretion. A recent policy statement jointly issued by the American Academy of Pediatrics and the American College of Medical Genetics and Genomics appears to be integrating these perspectives (18, 84). Although they still recommend deferring predictive genetic testing when no childhood prevention intervention is available, the guidelines specifically state that parents can authorize predictive genetic testing and that, in particular, it may be an appropriate decision when diagnostic uncertainty creates a significant burden.

As the debate over the ethics of testing children has shifted, it is worth noting that pediatricians have expressed positive attitudes toward pediatric carrier and predictive testing

(13, 70) and that evidence suggests that a significant minority of clinicians offer carrier or predictive testing to children counter to the recommendations of clinical organizations (26). As P-WGS becomes increasingly accessible, it remains to be seen how guidelines will accommodate the inevitable new challenges and to what extent clinicians adhere to these recommendations.

STRATEGIC PLANNING FOR P-WGS IMPLEMENTATION

Among the top priorities expressed by leaders in health care fields is an increased focus on translational research that can inform evidence-based practice (32). The overarching logic of this push is that carefully planned research agendas have the capacity to provide data that can both improve health outcomes and ensure that promising new health care practices are adopted without unnecessary delays (36, 39).

There is little doubt that WGS, as a technology, will soon be sufficiently affordable for use as a clinical test. This has a range of implications for the overall provision of health care, but presents distinct concerns in the context of pediatric patients. Problem-based P-WGS, which is beginning to be used in practice, has been demonstrated to be beneficial in a number of cases (6, 35). Although limited research has been conducted on methods for optimizing the outcomes of such tests for parents and children, this application of P-WGS may be increasingly useful for pediatricians as a diagnostic tool. More widespread use, such as through population-based P-WGS, is unlikely to be warranted in the near future given the need for research to resolve a host of ethical and practical considerations. It is worth emphasizing here that there are many ways in which P-WGS could be offered, and that these two illustrative strategies will not encompass all relevant concerns. But regardless of the precise approach, we are currently unprepared to offer evidence-based recommendations to guide P-WGS applications. If a planned approach is a valued goal, researchers have limited time to stay ahead of the curve.

This review suggests that there are a number of gaps that need to be addressed to understand the implications of P-WGS. These factors are broken out into three overlapping areas of need: research, clinical training, and policy. The overall structure of the proposed path forward is summarized in Figure 2.

Research Needs

A consistent conclusion of reviews on the genetic testing of children is that there is a substantial need for further research, a finding that this article extends to P-WGS. It is notable that there may be more reviews and commentaries on the impact of genetic testing on children than there are empirical research studies. A number of steps can be taken to address this imbalance in the evidence base.

Parental choice and the return of P-WGS results—Experiences from the implementation of newborn screening suggest that we need improved methods for involving parents (59, 83). Similarly, the implementation of P-WGS would benefit from finding ways to effectively integrate parents into the testing process. Research could reveal what combination of communication and support channels achieves optimal results. Such efforts

would likely involve primary care pediatricians, nurses, genomic specialists, and print and online resources (50, 68, 73). This research should pay particular attention to the education and counseling parents need to make informed choices, as well as parental preferences about the timing and types of risk results that will be returned.

An inherently challenging characteristic of P-WGS is the potential for discovering information that could not be easily anticipated by parents and clinicians prior to testing. This includes genetic associations with disease that are discovered after testing, results that have unclear implications for health, and incidental findings. Research on the impact of communicating this information to families, and the necessary follow-up care, will be essential. Furthermore, in the interest of decreasing the potential for a diagnostic cascade, methods for prioritizing certain categories of risk information (5, 6) and perhaps even preemptively deleting sequence believed to be irrelevant (87) should be explored.

Understanding the impact on children and their families—The social context in which P-WGS occurs will significantly influence the positive and negative impacts of test results. Therefore, it would be ideal for future studies to explore multifaceted interactions rather than focus exclusively on one individual within a family (51, 53, 69, 78, 113). Because genetic risks are shared within families, there are opportunities to help members of family networks refine skills in supporting one another.

There is also a significant need for research that explores the perspectives of a diverse range of populations on P-WGS and that addresses the accessibility of genomic technologies in different communities. Most research on genetic technologies has overwhelmingly enrolled Caucasian participants, and evidence suggests that views on genetics, health, parental roles, and expectations of children vary considerably across cultures, as do usage and access to genetic services (38, 90, 93). Therefore, broadened research efforts will be necessary to ensure that P-WGS does not contribute to existing health disparities.

Exploring children's responses to the complex risk information provided by P-WGS will provide valuable insight (107). These studies should attempt to adopt measurement strategies that are sensitive enough to detect moderate changes in children's emotions and attitudes (because dramatic shifts, such as the development of depression, do not appear likely) and should explore potential positive aspects, in addition to harms, of receiving genetic risk information. Because children are in the process of developing their identities, exploring how growing up with knowledge of risk influences their self-perception will be essential. Ultimately, it will be necessary to gather data that illuminate whether P-WGS influences health behaviors and actual health outcomes.

Understanding the impact of P-WGS risk information on parental emotional well-being and investigating the role of parents in communicating test results to children are key to effective implementation. In this context, effective support and training interventions will need to be developed that assist parents with the difficulty of learning about a child's genetic risks, communicating that information in a productive way, and adopting health recommendations in ways that maximize benefits for the child (63).

Supporting research on a structural level—Funding agencies that wish to promote translational genomics could play a major role in promoting research on P-WGS. In fact, there are some indications that priorities may be shifting to emphasize the implications of genomics for the pediatric population (66). Such efforts should emphasize the need for collaborative interdisciplinary teams, because the complexity of using WGS in health care necessitates contributions from a range of perspectives (48).

Another potential approach for advancing P-WGS research would be to address the difficulty of obtaining institutional review board (IRB) approval faced by pediatric researchers studying the impact of genetic testing (98). Clearly, careful IRB oversight is essential for improving studies and preventing harm to participants. However, it has been noted that children are often underrepresented in research, and this has the potential to result in age-based health disparities (34). A factor in this gap may be that IRBs assume major psychosocial risks to children from genetic testing, a perspective that is not supported by current evidence (98, 107). Therefore, IRBs should consider the need for translational pediatric research and the importance of viewing risks of genetic information in the context of existing knowledge.

Clinical Training Needs

Widespread clinical use of P-WGS, and population-based approaches in particular, would require substantial efforts to support the current pediatric care workforce (37, 50). As noted above, the current reliance on genetic specialists, such as medical geneticists and genetic counselors, is unlikely to be sustainable for WGS at a population level. Successful implementation would require training programs to increase comfort among pediatric clinicians in interpreting and communicating genomic information. In particular, there is a need to develop methods for effective collaborative decision making and problem solving between clinicians and families as the prospect of conducting P-WGS is confronted.

Policy Needs

Policy makers are in a position to help prepare for P-WGS by providing clear and regularly updated recommendations that can account for the many anticipated challenges of integrating genomic technologies. It is also necessary to begin preparing policies that support children who have had or are in need of P-WGS. For example, although the Genetic Information Nondiscrimination Act provides some protection from health insurance and employment discrimination, there remains the concern that life, disability, and long-term care insurance have not been addressed (56). Also, if P-WGS information is made available for future use, systems will need to be put in place that protect the privacy of children's genomic information while still making it rapidly accessible when needed by clinicians. Furthermore, clear guidelines would help regulate the boundaries between clinicians, parents, and children when there are disagreements over the use of P-WGS. Additionally, direct-to-consumer genetic testing companies may play a role in the interpretation and use of P-WGS data, and it will be necessary to clearly delineate these boundaries of commercial enterprises with respect to the clinical provision model. Answering such questions will require significant effort and political will.

CONCLUSION

There are reasons to believe that P-WGS will dramatically change the delivery of pediatric care. This could occur in an extemporaneous fashion, where P-WGS is rapidly integrated and problems are addressed as they arise. However, as we enter the genomic era, it would be prudent to adopt strategies where evidence guides P-WGS applications to help ensure the greatest health benefits for children and their families.

Acknowledgments

We would like to thank the Center for Biological Futures in a Globalized World at the Fred Hutchinson Cancer Research Center (Prime Contract HHM402-11-D-0017) and the University of Washington Simpson Center for the Humanities for their support of C.H.W. through the Faculty Fellows Consortium. Support for B.A.T. was provided by the K23 Mentored Patient-Oriented Career Development Award from the National Institute of Child Health and Human Development (K23HD057994). Additionally, B.S.W. received support from the Institute for Translational Health Sciences (ULTR000423).

LITERATURE CITED

- Alexander D, van Dyck PC. A vision of the future of newborn screening. *Pediatrics*. 2006; 117:S350–S354. [PubMed: 16735262]
- Almond B. Genetic profiling of newborns: ethical and social issues. *Nat. Rev. Genet.* 2006; 7:67–71. [PubMed: 16369573]
- Andermann A, Blancquaert I, Beauchamp S, D'ery V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. *Bull. World Health Organ.* 2008; 86:317–319. [PubMed: 18438522]
- Ball MP, Thakuria JV, Zaranek AW, Clegg T, Rosenbaum AM, et al. A public resource facilitating clinical use of genomes. *Proc. Natl. Acad. Sci. USA.* 2012; 109:11920–11927. [PubMed: 22797899]
- Berg JS, Khoury MJ, Evans JP. Deploying whole genome sequencing in clinical practice and public health: meeting the challenge one bin at a time. *Genet. Med.* 2011; 13:499–504. [PubMed: 21558861]
- Bick D, Dimmock D. Whole exome and whole genome sequencing. *Curr. Opin. Pediatr.* 2011; 23:594–600. [PubMed: 21881504]
- Biesecker LG. Opportunities and challenges for the integration of massively parallel genomic sequencing into clinical practice: lessons from the ClinSeq project. *Genet. Med.* 2012; 14:393–398. [PubMed: 22344227]
- Bloss CS, Schork NJ, Topol EJ. Effect of direct-to-consumer genomewide profiling to assess disease risk. *N. Engl. J. Med.* 2011; 364:524–534. [PubMed: 21226570]
- Borry P, Fryns JP, Schotsmans P, Dierickx K. Attitudes towards carrier testing in minors: a systematic review. *Genet. Couns.* 2005; 16:341–352. [PubMed: 16440876]
- Borry P, Fryns JP, Schotsmans P, Dierickx K. Carrier testing in minors: a systematic review of guidelines and position papers. *Eur. J. Hum. Genet.* 2006; 14:133–138. [PubMed: 16267502]
- Borry P, Goffin T, Nys H, Dierickx K. Predictive genetic testing in minors for adult-onset genetic diseases. *Mt. Sinai J. Med.* 2008; 75:287–296. [PubMed: 18704981]
- Borry P, Howard HC, Senecal K, Avard D. Health-related direct-to-consumer genetic testing: a review of companies' policies with regard to genetic testing in minors. *Fam. Cancer.* 2009; 9:51–59. [PubMed: 19488835]
- Borry P, Stultiëns L, Goffin T, Nys H, Dierickx K. Minors and informed consent in carrier testing: a survey of European clinical geneticists. *J. Med. Ethics.* 2008; 34:370–374. [PubMed: 18448719]
- Borry P, Stultiëns L, Nys H, Cassiman JJ, Dierickx K. Presymptomatic and predictive genetic testing in minors: a systematic review of guidelines and position papers. *Clin. Genet.* 2006; 70:374–381. [PubMed: 17026616]

15. Borry P, Stultiens L, Nys H, Dierickx K. Attitudes towards predictive genetic testing in minors for familial breast cancer: a systematic review. *Crit. Rev. Oncol. Hematol.* 2007; 64:173–181. [PubMed: 17553690]
16. Brunham LR, Hayden MR. Whole-genome sequencing: the new standard of care? *Science.* 2012; 336:1112–1113. [PubMed: 22654044]
17. Collins, FS. *The Language of Life: DNA and the Revolution in Personalized Medicine.* New York: HarperCollins; 2010.
18. Comm. Bioeth., Comm. Genet., Am. Coll. Med. Genet. Genomics Soc. Ethical Leg. Issues Comm. Ethical and policy issues in genetic testing and screening of children. *Pediatrics.* 2013; 131:620–622.
19. Condit CM. Public attitudes and beliefs about genetics. *Annu. Rev. Genomics Hum. Genet.* 2010; 11:339–359. [PubMed: 20690816]
20. Davies, K. *The \$1,000 Genome: The Revolution in DNA Sequencing and the New Era of Personalized Medicine.* New York: Free Press; 2010.
21. Diekema DS. Parental refusals of medical treatment: the harm principle as threshold for state intervention. *Theor. Med. Bioeth.* 2004; 25:243–264. [PubMed: 15637945]
22. Downing JR, Wilson RK, Zhang J, Mardis ER, Pui C-H, et al. The Pediatric Cancer Genome Project. *Nat. Genet.* 2012; 44:619–622. [PubMed: 22641210]
23. Driessnack M, Gallo AM. Stop, look, and listen: revisiting the involvement of children and adolescents in genomic research. *Annu. Rev. Nurs. Res.* 2011; 29:133–149. [PubMed: 22891502]
24. Drmanac R. The ultimate genetic test. *Science.* 2012; 336:1110–1112. [PubMed: 22654043]
25. Duncan RE, Delatycki MB. Predictive genetic testing in young people for adult-onset conditions: Where is the empirical evidence? *Clin. Genet.* 2006; 69:8–16. [PubMed: 16451127]
26. Duncan RE, Savulescu J, Gillam L, Williamson R, Delatycki MB. An international survey of predictive genetic testing in children for adult onset conditions. *Genet. Med.* 2005; 7:390–396. [PubMed: 16024970]
27. Eisenberg D, Freed GL. Reassessing how society prioritizes the health of young people. *Health Aff.* 2007; 26:345–354.
28. Elger BS. Ethical, legal, and social issues in the genetic testing of minors. 2010:485–522. See Ref. 99.
29. Facio FM, Eidem H, Fisher T, Brooks S, Linn A, et al. Intentions to receive individual results from whole-genome sequencing among participants in the ClinSeq study. *Eur. J. Hum. Genet.* 2013; 21:261–265. [PubMed: 22892536]
30. Fanos JH. Developmental tasks of childhood and adolescence: implications for genetic testing. *Am. J. Med. Genet.* 1997; 71:22–28. [PubMed: 9215763]
31. Fanos JH, Wiener L, Brennan T. Potential impact of genomic information on childhood sibling relationships. 2010:141–161. See Ref. 99.
32. Fed. Am. Sci. Exp. Biol.. *Engaging Basic Scientists in Translational Research: Identifying Opportunities, Overcoming Obstacles.* Bethesda, MD: Fed. Am. Sci. Exp. Biol.; 2012.
33. Feero WG, Green ED. Genomics education for health care professionals in the 21st century. *JAMA.* 2011; 306:989–990. [PubMed: 21900139]
34. Fields, MJ.; Behrman, RE. *The Ethical Conduct of Clinical Research Involving Children.* Washington, DC: Inst. Med. Natl. Acad.; 2004.
35. Gahl WA, Markello TC, Toro C, Fajardo KF, Sincan M, et al. The National Institutes of Health Undiagnosed Diseases Program: insights into rare diseases. *Genet. Med.* 2012; 14:51–59. [PubMed: 22237431]
36. Glasgow RE, Green LW, Taylor MV, Stange KC. An evidence integration triangle for aligning science with policy and practice. *Am. J. Prev. Med.* 2012; 42:646–654. [PubMed: 22608384]
37. Goldenberg AJ, Sharp RR. The ethical hazards and programmatic challenges of genomic newborn screening. *JAMA.* 2012; 307:461–462. [PubMed: 22298675]
38. Greb, A. Multiculturalism and the practice of genetic counseling. In: Baker, DL.; Schuette, JL.; Uhlmann, WR., editors. *A Guide to Genetic Counseling.* New York: Wiley-Liss; 1998. p. 171-198.

39. Green ED, Guyer MS. Charting a course for genomic medicine from base pairs to bedside. *Nature*. 2011; 470:204–213. [PubMed: 21307933]
40. Green RC, Berg JS, Berry GT, Biesecker LG, Dimmock DP, et al. Exploring concordance and discordance for return of incidental findings from clinical sequencing. *Genet. Med*. 2012; 14:405–410. [PubMed: 22422049]
41. Griffith GM, Hastings RP, Oliver C, Howlin P, Moss J, et al. Psychological well-being in parents of children with Angelman, Cornelia de Lange and Cri du Chat syndromes. *J. Intellect. Disabil. Res.* 2011; 55:397–410. [PubMed: 21323782]
42. Haddow, JE.; Palomaki, GE. ACCE: a model process for evaluating data on emerging genetic tests. In: Khoury, MJ.; Little, J.; Burke, W., editors. *Human Genome Epidemiology: A Scientific Foundation for Using Genetic Information to Improve Health and Prevent Disease*. Oxford, UK: Oxford Univ. Press; 2003. p. 217-233.
43. Hadley DW, Ersig ADL, Quattrocchi MKH. Guidelines and policies on genetic testing in children and families. 2010:523–557. See Ref. 99.
44. Haga SB, Terry SF. Ensuring the safe use of genomic medicine in children. *Clin. Pediatr.* 2009; 48:703–708.
45. Hall HR, Neely-Barnes SL, Graff JC, Krcek TE, Roberts RJ, et al. Parental stress in families of children with a genetic disorder/disability and the resiliency model of family stress, adjustment, and adaptation. *Issues Compr. Pediatr. Nurs.* 2012; 35:24–44. [PubMed: 22250965]
46. Hum.Genet. Comm.,UKNat. Screen.Comm.. Profiling the Newborn:A Prospective Gene Technology. London: Hum. Genet. Comm. and UK Natl. Screen. Comm.; 2005.
47. Inst. Med. Natl. Acad.. *Innovations in Service Delivery in the Age of Genomics*. Washington, DC: Inst. Med. Natl. Acad.; 2008.
48. Inst. Med. Natl. Acad.. *Evolution of Translational Omics: Lessons Learned and the Path Forward*. Washington, DC: Inst. Med. Board Health Care Serv.; 2012.
49. Izraeli S. Application of genomics for risk stratification of childhood acute lymphoblastic leukaemia: from bench to bedside? *Br. J. Haematol.* 2010; 151:119–131. [PubMed: 20678159]
50. Kaye CI. Genetic service delivery: infrastructure, assessment and information. *Public Health Genomics*. 2012; 15:164–171. [PubMed: 22488459]
51. Koehly LM, McBride CM. Genomic risk information for common health conditions: maximizing kinship-based health promotion. 2010:407–436. See Ref. 99.
52. Koehly LM, Peters JA, Kuhn N, Hoskins L, Letocha A, et al. Sisters in hereditary breast and ovarian cancer families: communal coping, social integration, and psychological well-being. *Psychooncology*. 2008; 17:812–821. [PubMed: 18688790]
53. Koehly LM, Peterson SK, Watts BG, Kempf KK, Vernon SW, et al. A social network analysis of communication about hereditary nonpolyposis colorectal cancer genetic testing and family functioning. *Cancer Epidemiol. Biomark. Prev.* 2003; 12:304–313.
54. Kohane IS, Hsing M, Kong SW. Taxonomizing, sizing, and overcoming the incidentalome. *Genet. Med*. 2012; 14:399–404. [PubMed: 22323072]
55. Kolata G. DNA test for rare disorders becomes more routine. *N. Y. Times*. 2013 Feb. <http://www.nytimes.com/2013/02/19/health/dna-analysis-more-accessible-than-ever-opens-new-doors.html>.
56. Laedtke AL, O'Neill SM, Rubinstein WS, Vogel KJ. Family physicians' awareness and knowledge of the Genetic Information Non-Discrimination Act (GINA). *J. Genet. Couns.* 2012; 21:345–352. [PubMed: 21927977]
57. Lerman C, Croyle RT, Tercyak KP, Hamann H. Genetic testing: psychological aspects and implications. *J. Consult. Clin. Psychol.* 2002; 70:784–797. [PubMed: 12090383]
58. Lipinski SE, Lipinski MJ, Biesecker LG, Biesecker BB. Uncertainty and perceived personal control among parents of children with rare chromosome conditions: the role of genetic counseling. *Am. J. Med. Genet. C*. 2006; 142C:232–240.
59. Lloyd-Puryear MA, Tonniges T, van Dyck PC, Mann MY, Brin A, et al. American Academy of Pediatrics Newborn Screening Task Force recommendations: How far have we come? *Pediatrics*. 2006; 117:S194–S211. [PubMed: 16735249]

60. Malpas PJ. Predictive genetic testing of children for adult-onset diseases and psychological harm. *J. Med. Ethics*. 2008; 34:275–278. [PubMed: 18375680]
61. Markel H. The stigma of disease: implications of genetic screening. *Am. J. Med.* 1992; 93:209–215. [PubMed: 1497018]
62. Marteau TM. The genetic testing of children. *J. Med. Genet.* 1994; 31:743. [PubMed: 7837247]
63. Metcalfe A, Coad J, Plumridge GM, Gill P, Farndon P. Family communication between children and their parents about inherited genetic conditions: a meta-synthesis of the research. *Eur. J. Hum. Genet.* 2008; 16:1193–1200. [PubMed: 18431405]
64. Miller FA, Hayeems RZ, Carroll JC, Wilson B, Little J, et al. Consent for newborn screening: the attitudes of health care providers. *Public Health Genomics*. 2010; 13:181–190. [PubMed: 19776551]
65. Moore CA, Khoury MJ, Bradley LA. From genetics to genomics: using gene-based medicine to prevent disease and promote health in children. *Semin. Perinatol.* 2005; 29:135–143. [PubMed: 16114576]
66. Natl. Inst. Child Health Hum. Dev.. Newborn Screening in the Genomic Era: Setting a Research Agenda. Rockville, MD: Natl. Inst. Child Health Hum. Dev.; 2010.
67. Need AC, Shashi V, Hitomi Y, Schoch K, Shianna KV, et al. Clinical application of exome sequencing in undiagnosed genetic conditions. *J. Med. Genet.* 2012; 49:353–361. [PubMed: 22581936]
68. O'Daniel JM. The prospect of genome-guided preventive medicine: a need and opportunity for genetic counselors. *J. Genet. Couns.* 2010; 19:315–327. [PubMed: 20440545]
69. O'Daniel JM, McConkie-Rosell A. Process in genetic counseling: considerations for children and their families. 2010:87–107. See Ref. 99.
70. O'Neill SC, Peshkin BN, Luta G, Abraham A, Walker LR, et al. Primary care providers' willingness to recommend *BRCA1/2* testing to adolescents. *Fam. Cancer*. 2010; 9:43–50. [PubMed: 19390990]
71. Persky S, Kaphingst KA, Condit CM, McBride CM. Assessing hypothetical scenario methodology in genetic susceptibility testing analog studies: a quantitative review. *Genet. Med.* 2007; 9:727–738. [PubMed: 18007141]
72. Peshkin BN, DeMarco TA, Garber JE, Valdimarsdottir HB, Patenaude AF, et al. Brief assessment of parents' attitudes toward testing minor children for hereditary breast/ovarian cancer genes: development and validation of the Pediatric *BRCA1/2* Testing Attitudes Scale (P-TAS). *J. Pediatr. Psychol.* 2009; 34:627–638. [PubMed: 18385162]
73. Peshkin BN, DeMarco TA, Tercyak KP. On the development of a decision support intervention for mothers undergoing *BRCA1/2* cancer genetic testing regarding communicating test results to their children. *Fam. Cancer*. 2009; 9:89–97. [PubMed: 19609726]
74. Pres. Coun. Bioeth.. The Changing Moral Focus of Newborn Screening: An Ethical Analysis by the President's Council on Bioethics. Washington, DC: Pres. Coun. Bioeth.; 2008.
75. Reid RJ, McBride CM, Alford SH, Price C, Baxevanis AD, et al. Association between health-service use and multiplex genetic testing. *Genet. Med.* 2012; 14:852–859. [PubMed: 22595941]
76. Rew L, Mackert M, Bonevac D. A systematic review of literature about the genetic testing of adolescents. *J. Spec. Pediatr. Nurs.* 2009; 14:284–294. [PubMed: 19796327]
77. Rhodes R. Why test children for adult-onset genetic diseases? *Mt. Sinai J. Med.* 2006; 73:609–616. [PubMed: 16758099]
78. Riper MV. Genomics and the family: integrative frameworks. 2010:109–139. See Ref. 99.
79. Roach JC, Glusman G, Hubley R, Montsaroff SZ, Holloway AK, et al. Chromosomal haplotypes by genetic phasing of human families. *Am. J. Hum. Genet.* 2011; 89:382–397. [PubMed: 21855840]
80. Rochman B. Test your DNA for diseases—no doctor required. *Time*. 2012 Oct. <http://healthland.time.com/2012/10/23/drugstore-genomes-whos-pushing-the-sequencing-industry>.
81. Rosas-Blum E, Shirsat P, Leiner M. Communicating genetic information: a difficult challenge for future pediatricians. *BMC Med. Educ.* 2007; 7:17. [PubMed: 17577408]

82. Ross LF. Predictive genetic testing for conditions that present in childhood. *Kennedy Inst. Ethics J.* 2002; 12:225–244. [PubMed: 12472077]
83. Ross LF. Mandatory versus voluntary consent for newborn screening? *Kennedy Inst. Ethics J.* 2010; 20:299–328. [PubMed: 21338027]
84. Ross LF, Saal HM, David KL, Anderson RR. Technical report: ethical and policy issues in genetic testing and screening of children. *Genet. Med.* 2013; 15:234–245. [PubMed: 23429433]
85. Roth JA, Garrison LP Jr, Burke W, Ramsey SD, Carlson R, et al. Stakeholder perspectives on a risk-benefit framework for genetic testing. *Public Health Genomics.* 2011; 14:59–67. [PubMed: 20407215]
86. Rowland E, Metcalfe A. Communicating inherited genetic risk between parent and child: a metathematic synthesis. *Int. J. Nurs. Stud.* 2013; 50:870–880. [PubMed: 23026156]
87. Saunders CJ, Miller NA, Soden SE, Dinwiddie DL, Noll A, et al. Rapid whole-genome sequencing for genetic disease diagnosis in neonatal intensive care units. *Sci. Transl. Med.* 2012; 4:154ra35.
88. Scheuner MT, Sieverding P, Shekelle PG. Delivery of genomic medicine for common chronic adult diseases: a systematic review. *JAMA.* 2008; 299:1320–1334. [PubMed: 18349093]
89. Segal ME, Polansky M, Sankar P. Adults' values and attitudes about genetic testing for obesity risk in children. *Int. J. Pediatr. Obes.* 2007; 2:11–21. [PubMed: 17763006]
90. Shields AE, Burke W, Levy DE. Differential use of available genetic tests among primary care physicians in the United States: results of a national survey. *Genet. Med.* 2008; 10:404–414. [PubMed: 18496223]
91. Solomon BD, Hadley DW, Pineda-Alvarez DE, Kamat A, Teer JK, et al. Incidental medical information in whole-exome sequencing. *Pediatrics.* 2012; 129:e1605–e1611. [PubMed: 22585771]
92. Solomon BD, Pineda-Alvarez DE, Hadley DW, NISC Comp. Seq. Program. Teer JK, et al. Personalized genomic medicine: lessons from the exome. *Mol. Genet. Metab.* 2011; 104:189–191. [PubMed: 21767969]
93. Sterling R, Henderson GE, Corbie-Smith G. Public willingness to participate in and public opinions about genetic variation research: a review of the literature. *Am. J. Public Health.* 2006; 96:1971–1978. [PubMed: 17018829]
94. Stone K. Genomic testing update: Whole genome sequencing may be worth the money. *Ann. Neurol.* 2012; 71:A7–A9.
95. Tabor HK, Stock J, Brazg T, McMillin MJ, Dent KM, et al. Informed consent for whole genome sequencing: a qualitative analysis of participant expectations and perceptions of risks, benefits, and harms. *Am. J. Med. Genet. A.* 2012; 158A:1310–1319. [PubMed: 22532433]
96. Tarini BA, Goldenberg AJ. Ethical issues with newborn screening in the genomics era. *Annu. Rev. Genomics Hum. Genet.* 2012; 13:381–393. [PubMed: 22559326]
97. Tarini BA, Singer D, Clark SJ, Davis MM. Parents' interest in predictive genetic testing for their children when a disease has no treatment. *Pediatrics.* 2009; 124:e432–e438. [PubMed: 19706561]
98. Tarini BA, Tercyak KP, Wilfond BS. Commentary: children and predictive genomic testing: disease prevention, research protection, and our future. *J. Pediatr. Psychol.* 2011; 36:1113–1121. [PubMed: 21816897]
99. Tercyak, KP., editor. *Handbook of Genomics and the Family: Psychosocial Context for Children and Adolescents.* New York: Springer; 2010. p. 615
100. Tercyak KP, Hensley Alford S, Emmons KM, Lipkus IM, Wilfond BS, et al. Parents' attitudes toward pediatric genetic testing for common disease risk. *Pediatrics.* 2011; 127:e1288–e1295. [PubMed: 21502235]
101. Tercyak KP, Peshkin BN, DeMarco TA, Brogan BM, Lerman C. Parent-child factors and their effect on communicating *BRCA1/2* results to children. *Patient Educ. Couns.* 2002; 47:145–153. [PubMed: 12191538]
102. Tercyak KP, Streisand R, Peshkin BN, Lerman C. Psychosocial impact of predictive testing for illness on children and families: challenges for a new millennium. *J. Clin. Psychol. Med. Settings.* 2000; 7:55–68.

103. Townsend A, Adam S, Birch PH, Lohn Z, Rousseau F, et al. "I want to know what's in Pandora's Box": comparing stakeholder perspectives on incidental findings in clinical whole genomic sequencing. *Am. J. Med. Genet. A.* 2012; 158A:2519–2525. [PubMed: 22903777]
104. UnitedHealth Cent. Health Reform Mod.. Personalized Medicine: Trends and Prospects for the New Science of Genetic Testing and Molecular Diagnostics. Minnetonka, MN: UnitedHealth Cent. Health Reform Mod.; 2012.
105. Veenstra DL, Piper M, Haddow JE, Pauker SG, Klein R, et al. Improving the efficiency and relevance of evidence-based recommendations in the era of whole-genome sequencing: an EGAPP methods update. *Genet. Med.* 2013; 15:14–24. [PubMed: 22955111]
106. Wade CH, Shiloh S, Roberts JS, Hensley Alford S, Marteau TM, et al. Preferences among diseases on a genetic susceptibility test for common health conditions: an ancillary study of the Multiplex Initiative. *Public Health Genomics.* 2012; 15:322–326. [PubMed: 22688356]
107. Wade CH, Wilfond BS, McBride CM. Effects of genetic risk information on children's psychosocial wellbeing: a systematic review of the literature. *Genet. Med.* 2010; 12:317–326. [PubMed: 20445458]
108. Wertz DC, Fanos JH, Reilly PR. Genetic testing for children and adolescents: Who decides? *J. Am. Med. Assoc.* 1994; 272:875–881.
109. White DB, Bonham VL, Jenkins J, Stevens N, McBride CM. Too many referrals of low-risk women for *BRCA1/2* genetic services by family physicians. *Cancer Epidemiol. Biomark. Prev.* 2008; 17:2980–2986.
110. Wilfond BS, Nolan K. National policy development for the clinical application of genetic diagnostic technologies: lessons from cystic fibrosis. *JAMA.* 1993; 270:2948–2954. [PubMed: 8254856]
111. Wilfond BS, Ross LF. From genetics to genomics: ethics, policy, and parental decision-making. *J. Pediatr. Psychol.* 2008; 34:639–647. [PubMed: 18647793]
112. Wilfond, BS.; Thomson, EJ. Models of public health genetic policy development. In: Khoury, MJ.; Burke, W.; Thomson, EJ., editors. *Genetics and Public Health in the 21st Century: Using Genetic Information to Improve Health and Prevent Disease.* Oxford, UK: Oxford Univ. Press; 2003. p. 61-81.
113. Wilson BJ, Etchegary H. Family communication of genomic information. 2010:163–189. See Ref. 99.
114. Yarnall KS, Pollak KI, Ostbye T, Krause KM, Michener JL. Primary care: Is there enough time for prevention? *Am. J. Public Health.* 2003; 93:635–641. [PubMed: 12660210]

SUMMARY POINTS

1. Researchers and clinicians have started to use P-WGS as a diagnostic tool, and access to such testing is expected to expand rapidly and provide new options in pediatric care.
2. The ability of P-WGS to provide health information is inadequate on its own to justify widespread use; careful assessment of the analytic validity, clinical validity, clinical utility, and ethical, legal, and social implications of P-WGS is essential prior to implementation.
3. The broad scope of information provided by P-WGS will present substantial challenges for informed consent and communication of genetic risks to parents and children.

FUTURE ISSUES

1. Extensive research is needed to determine under what conditions children and parents benefit from receiving risk information from P-WGS, and methods need to be developed for providing appropriate education, options, and support to families.
2. Systems need to be put in place to ensure that the pediatric care workforce is prepared to work in collaboration with parents and children to deliver P-WGS.
3. To maximize potential benefits for children, practice policies should be developed that can accommodate the complexity of information generated by P-WGS.

Figure 1. Outline of possible delivery methods for (a) problem-based and (b) population-based pediatric whole genome sequencing (P-WGS)

Shaded boxes indicate stages that differ between the two approaches. Dashed arrows indicate paths that may be contingent on results, changes in genomic risk information, or child age.

Figure 2. Related areas in need of development to create a strategic approach for implementing pediatric whole-genome sequencing (P-WGS)

Table 1**Genetic Testing Approaches, Information Types, and Technologies**

Category	Definition
Testing approaches	
Prenatal testing	Testing conducted on an embryo or fetus prior to birth to assist parental reproductive decision making
Newborn screening	Screening conducted as part of a public health program that tests most newborns for rare genetic conditions that have treatment options
Pediatric testing	Testing conducted on children before they have reached the age of legal majority
Family health history assessment	Use of information about the health status of relatives to estimate risks for an individual based on shared genes and environment
Types of test information	
Diagnostic testing	Testing to determine whether symptoms are caused by a genetic disorder and potentially to guide treatment
Predictive testing	Testing to predict the future onset of a health condition with reasonable certainty
Susceptibility testing	Testing for variants that somewhat increase risk for a disease but where many people who test positive will not actually develop the condition
Carrier testing	Testing for variants that will not influence the health for the person tested but may cause a genetic disease in his or her children
Pharmacogenomic testing	Testing for variants known to influence how pharmaceuticals are processed, leading to personalized use or dosage recommendations
Testing technologies	
Single-gene testing	Testing for variants in a single gene that are typically predictive of a disease
Chromosomal microarray testing	Testing that detects significant chromosomal rearrangements
Whole-exome sequencing	Sequencing of all DNA elements that encode proteins, representing about 1% of the genome
Whole-genome sequencing	Sequencing that aims to obtain an organism's complete genetic code

Table 2**Health Information that Can be Detected by Pediatric Whole-Genome Sequencing (P-WGS)**

Type	Example of pediatric health use	Example(s) of challenges when detected by P-WGS
Single-gene and preventable childhood-onset condition	Testing for sickle cell disease, a part of standard newborn screening, helps prevent a range of negative childhood symptoms	A large number of false positives need to be resolved
Single-gene and nonpreventable childhood-onset condition	Early identification of Tay-Sachs disease, a fatal condition, could decrease time seeking a diagnosis	Unanticipated findings of a severe nonpreventable condition could have a particularly negative impact on parental well-being
Multi-gene and preventable childhood susceptibility	Findings of increased asthma risk could lead to earlier detection and prevention efforts	Evidence of clinical validity and recommendations for prevention are not established; a large number of people need to be treated per case prevented
Single-gene and preventable adult-onset condition	Beta blockers can be prescribed to children with Marfan syndrome to prevent cardiovascular events	Prevention recommendations need to be developed and adherence effectively supported
Single-gene and nonpreventable adult-onset condition	Huntington's disease testing could relieve uncertainty for children with a high-risk family history and could benefit those who test negative	Concerns about harms to children and unclear benefit mean that high-quality information and opportunities to decline would need to be provided
Multi-gene and preventable adult susceptibility	Knowledge of increased cardiovascular disease risk could lead to public health interventions, encouraging preventive health behaviors	There is only limited evidence of clinical validity and utility; a large number of people need to be treated per case prevented
Pharmacogenomic information	<i>TPMT</i> gene function can inform acute lymphoblastic leukemia treatment for children	Clear, evidence-based treatment recommendations need to be developed; WGS results need to be made rapidly available to prescribing clinicians
Carrier status	Knowledge of cystic fibrosis carrier status could help prepare teens for future reproductive choices	Health benefits are unclear; reproductive risk may be confused with personal health risk