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Genomic medicine: evolving science, evolving ethics

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Abstract

Genomic medicine is rapidly evolving. Next-generation sequencing is changing the diagnostic paradigm by allowing genetic testing to be carried out more quickly, less expensively and with much higher resolution; pushing the envelope on existing moral norms and legal regulations. Early experience with implementation of next-generation sequencing to diagnose rare genetic conditions in symptomatic children suggests ways that genomic medicine might come to be used and some of the ethical issues that arise, impacting test design, patient selection, consent, sequencing analysis and communication of results. The ethical issues that arise from use of new technologies cannot be satisfactorily analyzed until they are understood and they cannot be understood until the technologies are deployed in the real world.

Keywords

autosomal recessive diseases; children; disclosure; ethics; genetics; policy; regulation; research; sequencing

Genomic medicine is rapidly evolving and changing the ways in which we think about the ethical, legal and economic regulation of this powerful biotechnology.

Public perceptions of genetic testing are complex and ambivalent. They have been shaped by some of the more unsavory uses to which genetics has been put in the past. It is difficult to separate our thoughts about current genetic screening for medical care from practices such as the eugenics movement, racial profiling based upon faulty understandings of genetics and compulsory sterilization programs throughout Europe and north America [1].

Past controversies about the appropriate use of genetic testing have led to many of the ethical and regulatory safeguards that surround genetic testing today. Genetic testing created a backlash due to it being used against people, rather than for them. Genetic testing came to be seen as fundamentally different from other forms of testing, one in need of more rigorous and explicit policies regarding informed consent and voluntariness [2].

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This genetic exceptionalism continues today; however, it is taking new forms. We still tend to treat genetic testing as if it is ethically and legally distinct from other sorts of testing. However, technological advances, particularly those that allow testing to be done quicker, less expensively and with much a higher resolution, are pushing the envelope on existing moral norms and legal regulations. Genetic testing is one of the first types of testing that is being offered directly to consumers. Today, one can send a sample of saliva to a direct-to-consumer genetic testing company and receive results about one's risk factors for a variety of medical conditions. Often, the information is difficult to interpret, probabilistic and based on algorithms that are proprietary and thus somewhat mysterious. Still, genetic testing joins a relatively small group of other diagnostic tests, such as home pregnancy tests, blood pressure testing and glucometers in its ready availability to the consumer without a physician intermediary.

The day may be coming, and quite soon, when whole-genome or -exome sequencing will be readily available. It is hard to know whether to think of this as a good or a bad thing, whether people who undergo such testing – whether they are patients, research subjects or consumers – will be helped or harmed by it. In this article, we will speculate about the near future of genetic testing by analyzing the way such testing is used as a new and inexpensive way of diagnosing rare genetic conditions in symptomatic children.

Next-generation sequencing for the diagnosis of rare Mendelian conditions

One of the most difficult challenges facing pediatricians is that of diagnosing rare genetic conditions in children who present with signs and symptoms that suggest an underlying genetic cause, but for whom the etiology remains elusive despite costly and often lengthy etiologic investigations. Such cases arise commonly in clinics that evaluate children for, among other things, cognitive impairment, neuromuscular disorders and congenital anomalies [3]. Such diagnostic odysseys often include serial molecular testing of one or a few genes; a process that can be emotionally taxing to families and frustrating to physicians, who must decide together how long to pursue the quest for diagnosis [4].

The advent of next-generation sequencing (NGS) coupled with advanced bioinformatic processing is changing this diagnostic paradigm. At Children's Mercy Hospital in Kansas City (MO, USA), we have introduced a highly multiplexed molecular diagnostic test that enables simultaneous interrogation of genes associated with more than 500 X-linked, autosomal-recessive and mitochondrial-pediatric diseases, including some genes for which no commercially available molecular test exists [5]. Currently available on a research basis, this test is being offered to complex pediatric patients by subspecialists in our institution. As we move toward clinical implementation, it is projected that the cost will initially be less than that of a single conventional molecular test (<US\$1000), and will continue to fall rapidly [101]. Furthermore, turnaround time will rival conventional molecular tests which commonly have a time-to-result of 2–8 weeks. Thus, NGS-based diagnostic testing will lower the threshold for physicians to pursue gene sequencing, and ultimately advance knowledge of the biologic underpinnings of challenging pediatric diseases.

Ethical considerations affect all aspects of the implementation of this program, including test design, patient selection, consent, sequencing analysis of patient DNA and delivery of results to patient and family. Potential unintended consequences of multiplexed genetic testing in children include: detection of carrier status for recessive diseases; and discovery of predisposition to adult onset disease. Conservative estimates are that humans carry at least ten recessive Mendelian diseases [6]. With the possible exceptions of cystic fibrosis and sickle cell disease, it is rare for individuals to have knowledge of the single recessive alleles residing in their genome. The American Society of Human Genetics (ASHG; MD, USA)/

American College of Medical Genetics (ACMG; MD, USA) guidelines for genetic testing of minors prohibits predictive genetic testing for adult onset diseases and discourages reporting of carrier status to minors [7]. In all such testing, physicians and scientists should be concerned about violating the child's right to what has been called 'an open future', that is, a future not involuntarily shaped by information of uncertain accuracy that the child did not ask for or necessarily want to know.

Informed consent

Informed consent for NGS testing is complex. The 2012 ACMG policy statement on clinical application of genomic sequencing recommends pretest counseling with a medical geneticist or genetic counselor, and that formal consent should be a part of the process [102]. Specifically, patients must be informed of the expected results from testing, including the likelihood of incidental findings. A significant challenge to this process is the lack of a clear consensus in the genetics community on how incidental findings should be handled, especially in the pediatric population. Currently, each individual laboratory is responsible for determining how incidental findings will be handled and reported. Further complicating the process is the recommendation that patients be offered the option of not receiving results from secondary or incidental findings.

We have also encountered an additional layer of complexity in the consenting process at our institution. In our experience, some families with children suffering potentially fatal conditions and/or progressive disease ask very few questions when we explain gene sequencing and seek their consent. For parents, the urgency to help an ill child is paramount and overshadows potentially thorny issues such as discovery of their child's (and potentially their own) carrier status or future disease risk. Our challenge then, is to build protections into the testing process. In our institution one such protection has been to develop a team of core users: 20 medical geneticists, pediatric subspecialists and genetic counselors who participated in test design and implementation policies. This process necessitated an uncommon understanding of genomic medicine including, but not limited to, knowledge of: ACMG/ASHG pediatric guidelines, the Genetic Information Nondiscrimination Act [8], and the potential benefits and limitations of NGS. The goal is for these clinicians to become uniquely suited to offer this test to the appropriate patients and, in collaboration with knowledgeable genetic counselors, engage in a meaningful informed consent process with families.

Test design & interpretation

A unique patient protection strategy developed in our institution is Sign and Symptom Assisted Gene Analysis; a component of our bioinformatic pipeline that reduces the risk of violating ASHG guidelines by not identifying genetic findings unrelated to the patient's presenting condition [Saunders CJ *et al.*, Rapid whole genome sequencing for genetic disease diagnosis in neonatal intensive care units (2012), Manuscript in preparation]. Physician who order our NGS diagnostic panel are required to select up to ten clinical signs and symptoms from a controlled medical ontology of 225 terms. Sign and Symptom Assisted Gene Analysis generates a unique candidate gene list specific to that patient. Genes not on the candidate list are not analyzed computationally, thereby greatly reducing the likelihood of unintended findings such as carrier status or future disease risk unrelated to the child's clinical condition.

Even with such protections, expert interpretation is necessary. For example, two very different conclusions may be made when a single heterozygous pathogenic variant in an autosomal recessive locus is detected. Such a finding may be inadvertent detection of carrier status in a child. However, it may also be diagnostic in the case of a compound

heterozygote; such individuals may have a second undetectable variant derived from the other parent in the same gene but outside the sequenced region. A careful review of the literature, knowledge of the gene in question, phenotypic plausibility and genotyping of the parents must factor in the interpretation. The size of the candidate gene list also impacts interpretation of such a case. A single pathogenic variant is more likely to be thought of as disease-causing when interrogating 20–30 genes for a child with ambiguous genitalia, while the probability is lower for a patient with intellectual disability, which is associated with more than 300 genes on our multiplexed test.

Interpretation of nucleotide variants is further complicated by the ubiquity of variants of unknown significance and the lack of a comprehensive clinical grade reference databases. In a verification study, Bell *et al.* reported that 122 out of 460 literature-annotated disease mutations are either erroneous or benign polymorphisms, as evidenced by a frequency of >5% in samples tested and/or homozygosity in unaffected individuals [9]. This highlights the need for cautious and informed interpretation, which in some cases will require functional studies, confirmatory testing and sequencing of family members.

Communication of results to physicians

The communication of NGS results to clinicians poses many challenges. Great care must also be taken to educate physicians, particularly about variants of unknown significance (VUS) in the face of enthusiasm for diagnosis and gene discovery. Previous guidelines, developed in the context of serial single-gene testing, called for reporting of all VUS, a practice that would overwhelm physicians and patients with data that may be anxiety provoking and susceptible to misinterpretation. In our institution, whole-exome sequencing from a single individual reveals 130,000–140,000 variants. Approximately 98% of these are category 4 variants (unlikely to be disease causing) for reasons such as high allele frequency [10]. When faced with a variant in a gene of interest, physicians unfamiliar with NGS and the ubiquity of nucleotide variation may be dubious that a variant is not likely to be disease causing. A challenge when drafting NGS result reports is to accurately characterize pertinent findings in a format that is meaningful to a variety of subspecialists [11]. An electronic report is in development, which will contain the key findings and interpretation. We envision ‘point-of-care’ educational resources such as hyperlinks to disease information and resources or brief education modules that physicians would have the opportunity to view when pertinent to the case at hand. As McGuire and Burke noted: “If genomic research is to achieve its promise, investments in health outcomes research, health technology assessment, clinical practice guidelines and information tools will need to increase” [12].

Communication of results to patients & families

For patients, post-test counseling with a geneticist or genetic counselor is important. In addition to diagnostic findings, an institution may determine that secondary findings will be conveyed to patients who have chosen to receive them following meaningful pretest counseling. As defined by ACMG, secondary findings are “gene variants known to be associated with a phenotype, but not believed to be related to the condition that led to the testing” [102]. In order to facilitate the discussion of results, some institutions have adopted a staged release of results where diagnostic results are included in a primary report, including incidental findings that have clear medical interventions. An optional full report including all variants may also be requested. Our current approach to pediatric patients is to report only variants predicted to be causative of the child’s symptoms. Confirmatory Sanger sequencing of research results is performed such that all results are clinically actionable.

In cutting-edge genomic medicine, novel variants and genes are routinely identified that may be associated with unknowns such as: pleiotropy (the effect of a single gene on multiple

phenotypic traits), epistasis (gene–gene interactions), phenotypic heterogeneity, incomplete penetrance and epigenetic processes. An additional complication is that variant interpretation may change. Some of today's VUS will become interpretable as genomic reference databases improve. There is a lack of consensus about whether there is a duty to recontact patients and families whose interpretation has changed, and if so, who is responsible for contacting families [13]. Furthermore, the practicalities of such reanalysis have scarcely been considered.

A vital member of our research team is a genetic counselor who is well versed in the complexities of molecular medicine and NGS, and will guide and support families. The need for highly specialized patient and family support is exemplified by the case of a family whose first-born child suffered a rapidly painful and life-threatening neonatal disease [Saunders CJ *et al.*, Rapid whole genome sequencing for genetic disease diagnosis in neonatal intensive care units (2012), Manuscript in preparation]. Clinical testing was nondiagnostic and the parents consented to NGS for themselves and their child. Shortly after consent the patient passed away, and the family was faced with the decision of whether to seek a postmortem molecular diagnosis. Their decision-making process necessitated contemplation of complex scientific concepts, including that of *de novo* dominant mutations versus rare recessive disorders, and the implication of such findings for family planning. In a case as this one, a misinterpreted variant could have serious unintended consequences for future pregnancies.

A recognized psychosocial benefit of genetic testing in symptomatic children is reduction of uncertainty. For both treatable and untreatable conditions, patients and family members may derive benefit from identification of a definitive etiology or elimination of specific genetic diseases from the differential diagnosis. The power of NGS to change pediatric healthcare, and most importantly to affect the lives of children today was seen among the first patients enrolled at the Children's Mercy Hospital Center for Pediatric Genomic Medicine [Soden SE *et al.*, A systematic approach to implementing monogenic genomic medicine (2012), Manuscript in preparation]. We enrolled siblings with progressive neurologic symptoms who, despite a 5-year etiologic investigation costing more than US\$20,000 had not been identified with a causal etiology. Using NGS, a diagnosis was made and confirmed in our clinical laboratory within 6 weeks. These findings brought a diagnostic odyssey to an end for the family and their healthcare team. At the time of diagnosis the younger sister was 5 years of age, the same age at which her older sister's symptoms, particularly cerebellar atrophy and ataxia, accelerated. At the time of diagnosis the younger child had only very mild ataxia. However, her sister's condition had progressed such that a wheelchair was needed for ambulation, speech was dysarthric and upper extremity dysmetria and chorea were prominent. Faced with uncertainty about both daughters' prognoses, and a differential that included fatal neurodegenerative diseases, the quest for diagnosis had intensified. Following molecular diagnosis with NGS, the literature could be drawn upon and the family reassured that individuals with this genetic diagnosis commonly live into adulthood with intact cognitive abilities. Furthermore, reports of coenzyme Q10 deficiency in individuals with this diagnosis, who responded to coenzyme Q10 administration, prompted cautious optimism that a treatment to potentially slow disease progression had been identified.

Conclusion

This early report from the frontlines of genomic medicine suggests some of the ways that genomic medicine might come to be used and some of the ethical issues that might arise. The technologies are changing rapidly. The uses to which those technologies can be put are also rapidly changing. The ethical issues that arise from new uses of new technologies cannot be satisfactorily analyzed until they are understood and they cannot be understood

until the technologies are deployed in the real world. Uncertainty is inherent in these projects. One response to uncertainty is to assume the worst, become risk-averse, and put roadblocks in the way of innovation until innovation has been proven safe. But innovation cannot be proven safe in a risk averse environment. The only way to assess the risks of a new technology is to use it – cautiously, carefully, with an open mind and a willingness to collect data that will allow an assessment of the risks and benefits. We should strive, as hard as we can, to minimize risks to the early adopters, even if doing so means we slow progress, prohibit certain seemingly desirable and potentially beneficial activities, and restrict the range of human choice. But we should not become so risk-averse as to abjure progress because of fear of unlikely, unproven, and even unnamed risks.

Such an approach would allow experimentation even as we remain exquisitely attentive to the ethical issues that arise as we innovate, and respond to those issues in a tentative but cautious way. Many of the fears that swirled around the early use of genomic technology have not been realized. Instead, adults have shown themselves to be more capable of dealing with troubling information, potentially bad news and uncertainty than they were once thought to be [103]. They have also shown themselves capable of deciding for themselves what they do and do not want to know [14].

Testing children, of course, raises different concerns – but not so different. As with adults, genetic testing can either provide a precise diagnosis or it can provide probabilistic information about the risks of developing particular diseases. Both sorts of information may be useful, even crucial, to parents. Current guidelines dictate that testing should not be done for conditions that do not have any health implications during childhood. Such rules are probably wise in most circumstances. In some situations, as we learn more about the natural history of genetic conditions, or as we develop interventions that might prevent the onset of such conditions, the conventional wisdom about testing children for such conditions might change.

It may be, then, that the proper question to ask is not whether genetic information should be treated like other medical information – but instead, why other medical information should not be treated like genetic information. That is, why is all medical information not the property of the patient, rather than the property of the doctor? Why do patients not have the right to see all of their test results, rather than having those results reported to their doctors?

Genetic information may transform other medical information in part because it is becoming available at a time and in a form that makes it similar to other information that is widely and publically available. Steven Pinker, who was one of the first people in the world to have his whole genome sequenced, wrote: “People who have grown up with the democratization of information will not tolerate paternalistic regulations that keep them from their own genomes” [15].

We should continue to innovate, analyze the implications of innovation and allow the technology to shape the questions to which ethics offers responses.

Future perspective

Inexpensive and accurate whole-genome sequencing will soon be available to all doctors and to all citizens. The availability of this technology will challenge prevailing ethical and regulatory paradigms not just in genetics but in all of medicine. Massive amounts of complex data will require doctors to learn more about genetics, information scientists to develop ways of making sense of the data and patients (including parents of patients) to make decisions about what they want to know, when they want to know it, and how they want to access the information. Today’s projects are the pilot projects in which we must

carefully explore the risks and benefits of new approaches to testing and to talking about test results.

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Executive summary

- Current regulation of genomics reflects past eugenic abuses.
- New technologies, which allow rapid and inexpensive whole-exome or -genome sequencing, raise questions about whether restrictive regulation is either feasible or appropriate.
- We describe a program that we are developing at Children's Mercy Hospital in Kansas City (MO, USA) to use next-generation sequencing techniques to test symptomatic children for hundreds of known autosomal recessive conditions.
- We have developed an approach to informed consent and to disclosure of results that tries to balance clinicians' desires to make the correct diagnosis, parents' rights to make medical decisions for their children, and the child's right to an open future.