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HUMBIO 158G

The Ethics of Whole-Genome Sequencing in Newborns

Introduction

Medical technology continues to advance, constantly providing new and innovative ways to save and extend human life. Leaps in genomic research have provided access to vast amounts of information about the human genome, allowing users to detect variants in the genome associated with disease. Such information, given the potential applications, presents a significant ethical dilemma. We are not far from a world where a newborn's entire genome could be screened, and utilized to make health related conditions about specific conditions. Despite this, there is a strong likelihood of encountering incidental findings, defined by the NCBI as, "a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study" (Wolf 1). In addition, there are several considerations pertaining to accuracy, interpretation and communicating result. This paper will begin with an overview of incidental finding protocol in research, direct to consumer, and clinical settings, before exploring the ethics of mandatory whole genomic sequencing in United States' newborns.

Bioethics Commission & AMCG on Incidental Findings

The U.S. Presidential Commission for the Study of Bioethical Issues has issued some recommendations in regards to incidental findings. The first recommendation is "that all practitioners—clinicians, researchers, and DTC companies—should anticipate

findings and describe (wherever feasible) what incidental findings are likely to arise from the tests and procedures before they are conducted." Transparency in terms of expectations is crucial. It is important to inform any participant, patient or buyer about any information that might arise. In addition, practitioners are encouraged to specify "what findings will and will not be returned." In sharing this information, the commission emphasized that there should be no disparities in terms of access or informed guidance (Guttman 1).

While open communication is undeniably critical moving forward, the American College of Medical Genetics and Genomics (ACMG) has issued recommendations pertaining to the disclosure of cryptic test results. The AMCG notes that "genetic variants of unknown significance, or associated diseases that are not amenable to treatment, should not be reported to patients." The logic behind such a recommendation is that the disclosure of medical information we cannot currently interpret will only cause undue stress on the patient. In addition, sharing such information comes "without any corresponding benefit." The U.S. Presidential Commission for the Study of Bioethical Issues recommends that in order to minimize difficulties, that clinicians should engage in "shared-decision making" with patients. Within this process, "clinicians and patients engage in a dialogue to arrive at pathways forward that reflect the best interests of the patient," respecting a patient's right to remain ignorant of secondary findings (Guttman 1).

Incidental Findings in Research

In considering the ethics of genetic screening for newborns, it is imperative to understand the current discussion surrounding incidental findings. One of the primary benefits of whole-genome sequencing (WGS) for newborns would be the availability of research data. Despite this tempting opportunity, the presence of incidental findings does complicate future actions. Incidental findings may be treatable, untreatable or have an unknown clinical meaning. There is a notable lack of federal guidance pertaining to addressing IFs, which is particularly difficult since 47% of "supposedly normal adult control research participants" end up with IFs in neuroimaging studies. CT scans of the colon show extracolonic findings in about half of supposedly asymptomatic participants and genetic family studies find misattributed paternity about 10% of the time. In the context of research, many argue that research scientists are not obligated to share IFs since they are not providing clinical care. Others argue that participants should have access to all information discovered about them. The courts remain unresolved on the issue. Currently, the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule does grant access to "protected health information," which could include research data under certain contexts. However, this is only if the participant requests such information. The ethics become far more complicated when the participants does not request this critical information, leaving the research community to grapple with the delivery or withholding of this knowledge. The topic gains entirely different nuances when viewed through the lens of private companies (Wolf 1).

Incidental Findings in Direct-To-Consumer Models

Direct-to-consumer genetic testing is defined as " either the marketing and/or the offer of genetic tests directly to the public, often without any involvement from health care professionals," and has been around since 2000. Research has shown that the majority of the companies providing this service test on minors, presenting a clash with the standards of the scientific community. Within the scientific community, "availability of therapeutic or preventive measures is necessary for testing to be performed in asymptomatic minors." If a clinician is going to test for a particular disease, there must be treatment available. Private companies are not bound by such guidelines, with most not even basing their guidelines on professional protocol (Howard 1).

Incidental Findings in Clinical Genome Sequencing

Whole-genome sequencing (is becoming more common, and has borne a variety of promising results. Laboratories that provide genome sequencing (GS) find a causative mutation in an estimated 27% of cases. In addition, a "preliminary report of GS for developmental delay claimed a 15% to 35% diagnostic rate in identifying the genetic cause." In addition to providing crucial information for neonates, GS allows clinicians to screen for individualized tumors and pharmacogenic variants (Krier 1). If used correctly, clinical genome sequencing possesses the potential to revolutionize medical care for the greater good. Unfortunately, much of the genomic sequencing we have access to is often difficult to interpret. While the Bioethics Commission offers recommendations for addressing these interpretations, they become especially complicated for healthcare providers.

It is no secret that even the most well trained clinicians may have differing opinions on interpreting tests and symptoms. This is no different in the world of genomics. Unfortunately, there is "no data available on the downstream risks and benefits of disclosing incidental genomic findings at all," making it particularly difficult to identify when the patient should be notified. Currently, radiologists are obligated to report all abnormalities seen in a given test, giving some precedent for sharing incidental findings as a physician. However, it is worth remembering that the information accessible through genome sequencing is far more expansive. Most molecular laboratories are close to examining "all disease-associated genes in the exome or genome," with relative ease (Krier 1). With such technology available to us, ethics pertaining to genome sequencing for newborns in clinical settings is an increasingly common source of debate and discussion.

Ethics of Mandatory Genomic Screening for Newborns

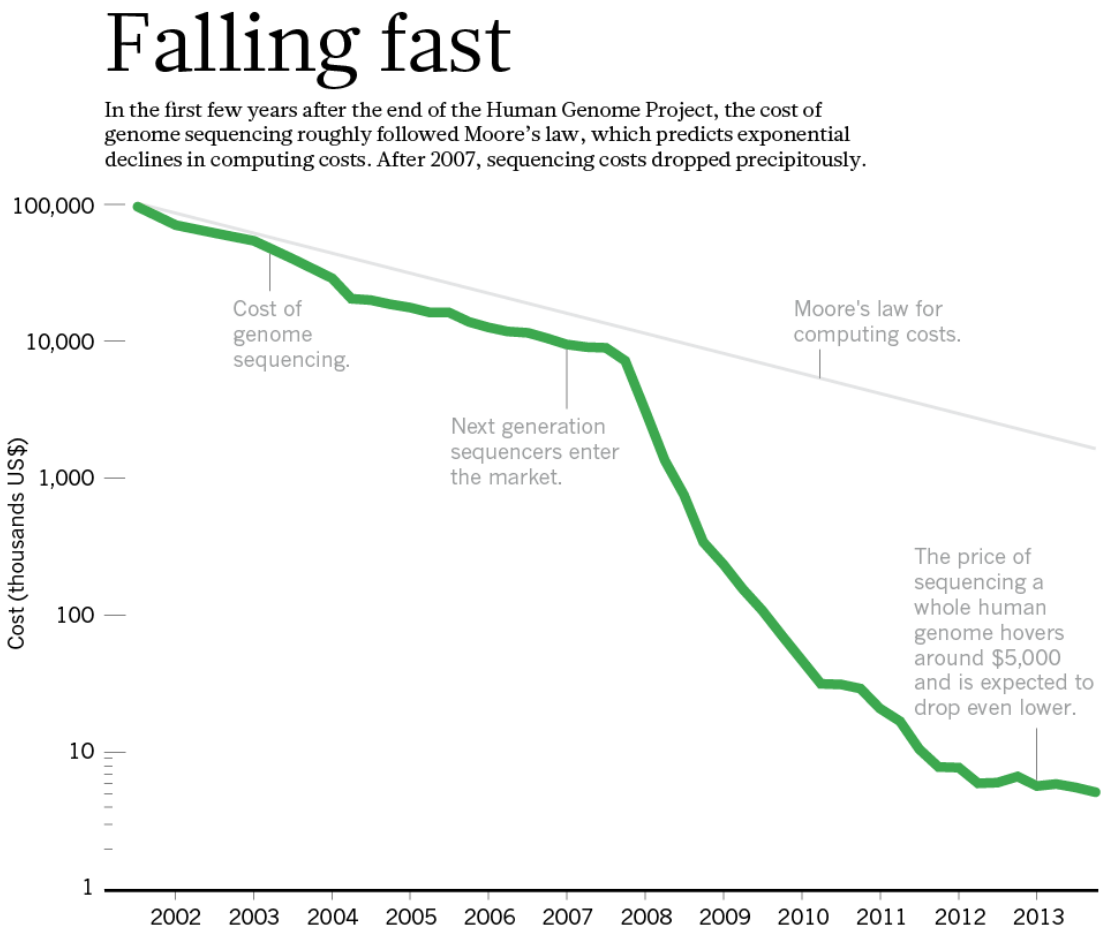
Newborn screening tests seek out disorders in the infant, allowing for early treatment. Blood tests require that a few drops of blood be taken from the child's heel before analysis. A hearing test is either given through the use of a tiny earpiece, microphone, or electrodes placed on the baby's head (NIH 1). Among the parents of the 4.3 millions newborns born each year, 98% participate in newborn screening (Waisbren 1). Newborn screening tests differ across states, with the majority requiring 3 to 8 tests. Currently, "The most thorough screening panel checks for about 40 disorders," with all 50 states screening for congenital hypothyroidism, phenylketoneuria (PKU) and galactosemia (NIH 1). The United States' most rapid advance in the average number of

disorders screened occurred from 1995 to 2005, when the value went from 5 to 24. States are not bound to follow federal recommendations for screening, but there is intense political pressure to do so (Tarini 1). Patient advocacy groups have been a critical part of the newborn screening regulations since the 1960s, beginning with mandated testing for PKU (Paul 1).

The word "mandatory," takes on an interesting meaning when applied to newborn screening. Currently, "[s]tates support mandatory screening on the basis of *parens patriae* power, which gives them inherent authority to act to promote the welfare of children," to the point where they can override parental authority if forgoing screening could bring harm to the child. Though the state can test newborns without parental consent, parents who do not want their children tested "religious or other reasons," do not usually face any sort of criminal penalty (Tarini 1). The nature of mandatory screening will likely become more complicated as genome sequencing becomes more commonplace.

As our knowledge base grows, more advanced screening processes are rapidly becoming available to us. With modern technology, whole genome sequencing could soon be part of the newborn screening process. Whole genome sequencing is now cheaper and more widely accessible, "with the prospect of personal genome sequencing for under $1,000 now widely said to be in sight" (Greer 1). A recent article from *Nature* shows that the cost of genomic testing is falling at unprecedented rates, with the most striking drop beginning with "next generation sequencers" entering the market around 2007 (see graphic below). While the process is not currently cheap, there is strong evidence that the price will continue to drop, lessening the need for serious ethical

considerations pertaining to finance. There is already a strong precedent for mandatorily screening newborns, and it would be ethically acceptable to obtain potentially beneficial health information for what will likely be an affordable price.



(Graphic from http://www.nature.com/news/technology-the-1-000-genome-1.14901)

As we consider the ethics of mandatory whole genome sequencing for newborns, it is important to consider whether parents/caregivers desire the information we have access to. Are parents even interested in obtaining such knowledge? It could certainly be unethical to force unsettling knowledge on unwilling parents. Conversely, depriving eager parents of their child's medical knowledge is equally unethical. A 2014 study

surveyed 514 new parents within 48 hours of the birth. The study found that: "Parents reported being not at all (6.4%), a little (10.9%), somewhat (36.6%), very (28.0%), or extremely (18.1%) interested in genomic testing for their newborns. None refused state-mandated newborn screening" (Waisbren 1). This constitutes a majority of parents having at least some interest in genomic testing, with 46.1% at least being "very" interested. With such data in mind, it does seem ethical to provide this information to parents who seek it. However, it is worth nothing that nearly all parents undergo mandatory testing, with many not realizing that refusal is even an option (Waisbren 1). It seems that, if newborn genomic screening were to be implemented, that parents would end up receiving the information regardless of their desire to read it. With this in mind, it is important to consider the effects this information would have on parents.

Sensitive information must be communicated clearly. It is unreasonable to assume that all parents will be able to accurately interpret the entire genome of their children. In the event that such sequencing becomes mandatory, meetings with the physicians involved should be as well. Before the sequencing is initiated, parents should utilize shared-decision making with the health providers. This is supported by the President's Commission on Bioethics, and allows for all parties to minimize anxiety and miscommunications. Parents and physicians could ideally come to an agreement on what genomic variants to focus on interpreting. Unfortunately, primary care physicians are often uncomfortable relaying the results of GS to parents, with many parents rating the explanations unfavorably (Tarini 1). It is unethical to present medical information unclearly, as it endangers the welfare of the child, and could severely affect the

psychological health of the family. Mandatory WGS for newborns can only be ethically implemented if information can be shared clearly.

Even if communication is flawless, there are still valid concerns about false positives. Unfortunately, most screening methods come with a margin of error. There will be some who are diagnosed inaccurately. For parents of newborns, this can be especially debilitating. Such difficulties led to "PKU Anxiety Syndrome" in the 1960s, seen in parents who are convinced their children have the disorder in spite of multiple negative tests generated after the false positive. This syndrome was characterized by symptoms ranging from "mild, periodic bouts to acute anxiety hysteria" (Rothenberg, 691). Such issues with false positive induced anxiety have carried into the present time, and present a serious ethical problem. One can only imagine the level of anxiety forced upon parents, and the subsequent distrust is the medical establishment that may follow upon learning their child received a false positive. Careful consideration must be given to how accurate the entire genome can be screened, especially concerning variants associated with disease risk. Failure to do so could lead to an unnecessary emotional tax on the family involved.

Indeterminate results and overdiagnosis also present serious ethical dillemas. The scientific community has found that children often yield genomic results that are "neither normal nor classically abnormal" (Tarini 1). This can be a dangerous gray area, as the nature of some treatment is too dangerous for asymptomatic patients. Krabbe disease, which leads to neurological decline and death in a child, and cystic fibrosis, often yield indeterminate results. Overdiagnosis occurs when a newborn screening for a particular disease is positive, but the child does not develop clinically significant symptoms. This problem is common in cancer screening, and can often lead to aggressive treatments for a

disease that will never truly manifest. When deciding whether WGS should be mandatory, it is crucial to consider the accuracy of the test. If use of the test leads to an abundance of unnecessary procedures, then it will be difficult to justify the mandate on ethical grounds.

Members of the AMCG are also hesitant about any sort of newborn GS mandate. A recent survey of the AMCG found that 85% felt WGS should not be used at all in newborn screenings, and 86.5% felt that if used it should not be mandatory. Respondents also felt that accurate interpretation of results, a more extensive consent process, counseling before and after the test, cost and turn-around-time should be a critical part of usage. Despite this hesitation to make WGS a mandatory screening process, 75.7% foresee that it will be utilized in the future on newborns (Ulm 1).

Given the current state of WGS, it would be unethical to mandate its use. There are still rampant disagreements on how to handle unexpected findings across fields, and the lack of uniform protocol across disciplines with make interpretation and relaying of results exceedingly complicated. The price is decreasing at a startling rate, and parents do have a demonstrated interest in the results, but it is important to realize that even clinicians are not entirely comfortable explaining this information to parents. It is irresponsible to access and share information we cannot ensure an appropriate response. Enhanced accuracy must also be pursued, as inaccuracies in diagnosis and the consequential treatment may cause intense anxiety for the family and potential damage to the child. Experts in the field are hesitant about this technology, and with good reason. While WGS in newborns is undeniably promising, it should not be mandated nationwide before we can adequately interpret, communicate, and address the results.

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