Title
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Journal
Current Anthropology, 54(SUPPL.7)

ISSN
0011-3204

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Publication Date
2013-10-01

DOI
10.1086/670971

Peer reviewed

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Source: *Current Anthropology*, Vol. 54, No. S7, Potentiality and Humanness: Revisiting the Anthropological Object in Contemporary Biomedicine (October 2013), pp. S26-S35
Published by: The University of Chicago Press on behalf of Wenner-Gren Foundation for Anthropological Research
Stable URL: http://www.jstor.org/stable/10.1086/670971
Accessed: 30/12/2013 19:31

Potentializing Newborn Screening

by Stefan Timmermans and Mara Buchbinder

Virtually all 4.25 million babies born annually in the United States are screened for more than 50 rare genetic conditions. In a country plagued with widespread health-service access problems, this remarkable public health achievement depends on policy visions of newborn screening as the linchpin of secondary prevention and saving children's lives. Based on ethnographic research and drawing from a semiotic framework, we illustrate that newborn screening has had a much wider range of effects in the clinic than those anticipated by policy makers. How does the disconnect between policy potential and clinical experience affect the technology? We demonstrate that only some discrepancies are considered in policy circles and that instead, parents, geneticists, and policy makers renew visions of potentiality that preserve the technology's benefits in spite of evidence to the contrary. While rearticulating the potential of technologies may help actors cope with situations that do not measure up to expectations, the inevitable cost of reformulating potentiality once a technology has been implemented is that some accumulated experiences will be rendered invisible.

In the US health care system—in which market structures mediate access to services, and large portions of the population are de facto excluded from care—newborn screening represents an important exception. Ninety-nine percent of all 4.25 million newborns born annually are screened for rare genetic conditions regardless of the family's ability to pay (Lloyd-Puryear and Brower 2010; Weaver et al. 2010).[1] The United States and many other countries have had universal newborn screening programs for a handful of conditions, such as phenylketonuria and hyperthyroidism, since the 1960s. In 2006, however, US newborn screening underwent a dramatic expansion and standardization process when the American College of Medical Genetics (ACMG) issued a report that recommended screening for more than 50 additional conditions (Watson et al. 2006).[2] Soon after, the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children endorsed the recommendations,[3] and individual states adopted the expanded screening panel.

The confluence of factors that enabled this dramatic expansion involves both serendipity and concerted action by parent advocates, medical professionals, government officials, and industry representatives. Critical observers have focused on the role of the ACMG report in breaking precedent with 40 years of screening principles, particularly the stipulation that the individual patient must stand to benefit from screening (Baily and Murray 2008; Botkin et al. 2006; President's Council on Bioethics 2008). Here, we examine the potentialities of newborn screening articulated at the policy level and relate those visions to the experiences of making newborn screening work in the clinic.

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1. Infants born in hospitals, birth centers, or other medical settings are screened before checkout, and infants born in domestic settings are screened when parents register their child's birth. Except for in the District of Columbia, parents are not asked to provide consent for newborn screening. Thirty states allow exemptions on religious grounds, and 13 states allow for any kind of exemption, but parents are rarely informed of the possibility to opt out, and the default action is to screen (Toiv et al. 2003). Screening targets include metabolic, endocrine, and hematological conditions as well as cystic fibrosis. While current screening technologies use a biochemical platform, the screening targets are considered genetic disorders; thus, newborn screening is often described as a genetic screening program. The screening is paid for by either public or private insurance programs. Only the actual screening test is available to all, however. Access to follow-up treatment is stratified based on ability to pay or insurance coverage.

2. Before the expansion of newborn screening programs in the United States, large discrepancies existed between different states in the number and kind of screened disorders. Thus, a baby born in the United States might be screened for eight or 30 conditions depending on the state in which she was born—a situation that was unacceptable for many health advocates. See AAP Newborn Screening Task Force (2000).

3. The US Health Resources and Services Administration commissioned the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children in February 2003 to advise the secretary of Health and Human Services on how to reduce genetic-disease-related morbidity and mortality in newborns and children. Committee members, who are appointed by the secretary, include medical, technical, or scientific professionals with expertise in children's genetic disorders as well as members of the public with a special interest in heritable disorders.

 0011-3204/2013/54S7-0004$10.00. DOI: 10.1086/670971

The process of charging a biomedical technology with potentialities creates a series of real-life semiotic challenges. Charles S. Peirce's semiotic grammar classifies signs according to his broader universal tripartite system of hierarchically ranked logical categories. This system offers a vantage point from which to explore the power of potentiality relative to realities. In Peirce's system, "firstness" involves only "possibilities, and nothing more" (Peirce 1992:269). "Secondness" refers to the level of actualization, the realm of "hard facts" (Peirce 1992:268). "Thirdness" refers to generalizations. The key issue for our purposes here is the fundamental hierarchical relationship between the three levels. Potentiality implies being unrelated to other phenomena: "For as long as things do not act upon one another there is no sense or meaning in saying that they have any being" (Hartshorne, Weiss, and Burks 1931–1958:25). For potentiality, we do not know whether signs will ever be realized. Actuality presumes potentiality yet differs from it through resistance and effort. With actuality, there is a "struggle" involved, an effect or "happening *then* and *there*" that leads to some modification (Hartshorne, Weiss, and Burks 1931–1958:324; emphasis in original). Actuality requires relationships to other phenomena. Peirce thus presumed a hierarchical relationship between potentiality and actuality (and actuality and generalizability), with the latter superseding the former. However, Peirce argued that at any point, multiple semiotic relationships could be dynamically enacted, complicating the overall tension between potentiality and actuality.

Drawing from Peirce's semiotics and pragmatism,[4] we examine the critical relationship between potentiality and actual experience for newborn screening. How do visions of a biomedical technology's potential affect the experiences of parents and clinicians? Alternatively, how does a discrepancy between actual and projected experiences reflect back on the biomedical program? In light of this special issue of *Current Anthropology*, we describe a set of actors approaching potentiality in terms of the first meaning identified by Taussig, Hoeyer, and Helmreich (2013) in their introduction to this issue: as "a hidden force determined to manifest itself—something that with or without intervention has its future built into it." Potentiality, in this sense, is a political project that imbues, evaluates, and channels claims about, in this case, the power of biomedical technologies to achieve certain aims. As Peirce pointed out, potentiality is disconnected from what may actually happen but paves the way for desirable futures. Once technologies are implemented, the technology may or may not reach that projected potential. When a technology does not live up to its potential, it reflects a shift in the meaning of potentiality, which now appears as "a latent possibility imagined as open to choice, a quality perceived as available to human modification and direction through which people can work to propel an object or subject to become something other than it is" (Taussig, Hoeyer, and Helmreich 2013). In the case of innovative technologies, this choice usually comes down to discontinuing technologies because they fell short of promises or using technologies for new ends. But these are not the only options for technologies that do not reach their potential. They may also be imbued with even grander potentialities. In that case, potentiality is not only instrumentally independent of already present experiences but also helps to buffer inconvenient truths.

We will work out our argument in three steps. First, we examine how policy makers formulated a semiotic network for the potential benefits of newborn screening before the implementation of new screening technologies. We demonstrate that in various policy forums, stakeholders settled on a shared meaning of newborn screening as the cornerstone of secondary prevention to avoid severe disability and save newborn lives. We then draw on ethnographic data collected in a California genetics clinic to examine how genetics staff and parents of children who received positive newborn screens related their experiences to the potential of the newborn screening program. We show here that newborn screening had a much wider range of effects than those anticipated by policy makers. Finally, we examine how the discrepancy between policy potential and clinical experiences affected the technology. We note that only some discrepancies were considered in policy circles. Instead, parents, geneticists, and policy makers renewed visions of potentiality that preserved the technology's benefits in spite of evidence to the contrary. While harking back to the potential of technologies may help actors cope with situations that do not measure up to expectations, the inevitable cost of reformulating potentiality once a technology has been implemented is that some salient experiences will be rendered invisible.

Policy Potentialities

Technology designers—everyone involved in bringing a technology into use—charge new technologies with potential in the sense of a not yet realized desirable future attainable with their implementation. They deliberately or implicitly imagine an ideal scenario in which people will use the technology to achieve goals (Akrich 1992; Woolgar 1991). Designers presume shared interests, aspirations, competencies, and ideal users following technological "scripts" for implementation. These presumptions become inscribed to varying degrees in operating protocols and the material software and hardware of the tools (Hedgecoe 2004). Such presumptions also extend to a physical, legal, and economic infrastructure that enables the technology to do its work (Oudshoorn and Pinch 2003). In fact, formulating technological expectations is instrumental to accumulating resources and buy-in from various stakeholders who might otherwise remain at cross-purposes (Borup et al. 2006).

4. Peirce considered pragmatism a principle of inquiry and account of meaning that emphasizes that meaning derives from practical consequences (Houser 1998).

The expansion of newborn screening depended on the adoption of a multiplex technology—tandem mass spectrometry—which allowed simultaneous screening for multiple biochemical analytes using a single specimen.[5] The previously mentioned ACMG report was critical to the adoption of tandem mass spectrometry. The Maternal and Child Health Bureau of the Health Services and Resources Administration commissioned the report by asking the ACMG to review the evidence for expanding newborn screening. Although the report was presented as a scientific evaluation, it had the policy function of justifying the expansion of newborn screening. Critics charged that the report relied on a weak scientific methodology and was strikingly void of compelling evidence in favor of screening during a time in which evidence-based medicine had substantially codified medical decisions (Moyer et al. 2008). If "science," as Latour (1988:228) put it, "is politics by other means," the unequivocal recommendations for expansion strongly suggested not a neutral evaluation of scientific research but advocacy science in which stakeholders selectively marshaled scientific evidence for preordained policy goals. Not surprisingly, then, the report articulated the potential benefits of newborn screening in great detail:

> States and territories mandate newborn screening of all infants born within their jurisdiction for certain treatable conditions that may not otherwise be detected before developmental disability or death occurs. Newborns with these disorders typically appear normal at birth. The testing and follow-up services of newborn screening programs are designed to provide early diagnosis and treatment before significant, irreversible damage occurs. Appropriate compliance with the medical management prescribed can allow most affected newborns to develop normally. . . . As the model for public health–based population genetic screening, newborn screening is nationally recognized as an essential program that aims to ensure the best outcome for the nation's newborn population.[6] (Watson et al. 2006:S15)

With every phrase in this passage, newborn screening is semiotically enriched with benefit potential. The main rationale behind newborn screening is secondary prevention: the detection of disease in an asymptomatic population to implement therapeutic interventions and offset symptom development. The goal is the prevention of "developmental disability or death" and "significant, irreversible damage." The mechanism of "early diagnosis and treatment" followed by "appropriate compliance with the medical management" leads to the promise of "most" infants "to develop normally." The text situates secondary prevention within a specific vision of human vulnerability and medical salvation. Metabolic and other diseases constitute a hidden danger, meaning that without newborn screening no one would suspect that the infants were at risk: "newborns with these disorders typically appear normal at birth." Because no one would suspect that a "normal"-appearing infant is actually sick, the implication is that when symptoms do appear, it may already be too late.

Potentiality is further encapsulated by the culturally charged image of newborns at risk, which plays on the idea of babies as icons of vitality and future potential (Meckel 1998). Underlying newborn screening is a view of human plasticity: intervening in biology at the beginning of life promises lifelong health benefits. The technology's potential reinforces the perception of infants as adaptable during a critical period of development. However, "testing and follow-up" suggests that screening by itself is insufficient: a lifelong integrative systemic approach is required to achieve health benefits. Prevention is urgent: "early" intervention matters greatly. The program also rests on universality: as a "public health–based population genetic screening" program, all infants will be screened. The potential of newborn screening to prevent disease thus rested on a view of vulnerable but malleable biological humanness. The semiotic translations articulated in the ACMG report specified a focused set of highly valued outcomes: universal newborn screening was the means to prevent developmental disability and death throughout the life course.

Although the ACMG report suggested an ideal scenario to prevent hidden dangers in newborns that would require quick action as part of comprehensive health care, it also inserted qualifiers and conditional clauses that alerted the reader to possible constraints thwarting the promise of screening programs. Such hedges are apparent in the notion that "most" infants will be helped from screening, and any success rests on "appropriate compliance with the medical management." Later in the ACMG report, it became clear that not all of the conditions recommended to the universal screening panel required urgent diagnosis or had effective treatments available. The report distinguished between a primary and secondary set of conditions. While primary conditions were established conditions for which newborn screening should have preventive potential, secondary conditions were derived from the primary set and would be identified by screening for the core panel. The preventive payoff for secondary conditions was likely minimal, but the authors argued that results should be reported because withholding this information would be paternalistic.

When the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children endorsed the ACMG report, the March of Dimes, along with other advocacy organizations, launched a campaign to urge states to adopt screening for the recommended panel. As is often the case, patient advocacy groups aimed to legitimize innovation by performing the technology's promise (Rabeharisoa and Callon 2002). One of the fathers in our study testified to the California legislature to advocate on behalf of expanded newborn screening. His daughter had been diagnosed with a metabolic disorder during a pilot screening program and had remained

5. Note that newborn screening rests on a biochemical analysis of metabolites in the blood even though it provides information about genetic conditions. Some follow-up tests involve mutation analyses.

6. The analysis of this quote is based on Timmermans and Buchbinder (2013).

healthy with treatment. In an interview, the father described how he would recount his experience with a positive outcome from newborn screening and then hand the microphone to a parent whose child had been severely disabled because of a metabolic disorder that might have been detected with newborn screening. The child diagnosed by newborn screening embodied the realization of the technology's potential to save lives and prevent disability once screening is implemented. As an example, the father's testimony implied the avoidance of danger, which could be multiplied for many others. The other parent's testimony implied a past of suffering that could be left behind. The contrast foreshadowed a future in which prevention at the beginning of life is indeed feasible with screening technologies. The juxtaposition between a child saved through newborn screening and one severely disabled without newborn screening further positioned the screening program as the required causal agent of lifesaving efforts. Underlying the policy push for expanded screening again resides the notion of a flexible human biology amenable to biomedical interventions to prevent disability and death.

Articulating the potential of newborn screening to save babies by preventing the onset of disease did much political work to implement new screening technologies. Newborn screening advocates created a semiotic network in which the ability of multiplex technologies to screen for multiple conditions was proposed as an "obligatory point of passage" (Latour 1987:182) to prevent disability and death among newborns. Connected with written and verbal signs that varied from qualities such as avoiding pain and suffering—embedded in common indexes such as flow charts, bibliographies, credentials, and diagrams throughout the report—and enhanced with the symbol of the endangered newborn, the screening technologies scaled up to people, activities, systems, values, other tools, and a common purpose of secondary prevention. Although the network was wide and diverse, the anticipated potential was singularly focused on highly valued outcomes. The general message to policy makers, parents, public health officials, and geneticists was clear: if you want to save babies, you need to invest in newborn screening. However, although the translation of newborn screening as beneficial rested on an argument of biological plasticity, the appendixes of the ACMG report made clear that some conditions added to the screen were not necessarily amenable to early intervention. For some conditions, preventive measures did not exist, and about other conditions, little was understood about their biological parameters even to diagnose them conclusively.

Clinical Experiences

Peirce's pragmatist maxim suggests that the meaning of phenomena become apparent in the practical consequences they produce.[7] It is through the effects that we know what newborn screening is. Newborn screening is thus what it does. Screening advocates have imbued newborn screening with potential, but it is in the lived experiences of families and geneticists that newborn screening emerges as consequential.

In the clinics across the United States where families meet geneticists to discuss positive screening results, newborn screening experiences were much more diverse than anticipated. Secondary prevention may occur at a population level, but the pressing concerns in the clinic relate to the clinical relevance and broader meaning of a positive screening result for a specific baby. Here, we will draw on our ethnographic observations of 75 newborn screening patients we followed in a metabolic-genetic clinic over a 3-year period. We observed and audio-recorded 193 clinical consultations between families and the genetics staff, attended the weekly genetics team meetings at the end of each clinic day, consulted patients' medical records, and interviewed parents and clinicians about their experiences with newborn screening.

We limit our analysis to explicit statements about newborn screening made by geneticists and parents to explain the child's current situation. In those moments, newborn screening as object was charged with signs aimed to advance a new set of meanings regarding what the screening program was about. Such metacommentaries were uncommon because most of the clinical interactions focused on the immediate tasks of follow-up testing and the implementation of treatment. Occasionally, however, geneticists and parents reflected on whether the current situation conformed to the intended potential of newborn screening. At such junctures, newborn screening became embedded in more expansive semiotic networks.

Alignment of Potential with Clinical Experience

In some cases, the patient's diagnostic journey aligned with the potential of newborn screening as envisioned by policy makers. Thus, a geneticist reviewed the events for one patient diagnosed with short-chain acyl-CoA dehydrogenase deficiency (SCADD):[8] "So, the last time we saw him back in January, we went over his newborn screening results. And then we did the blood test to look for the genetic changes with the SCADD. So, what they did show is, they do show that he has the change—changes that would explain the SCADD. So, it was real; the newborn screening was real. But we've been treating him as if he's had that the whole time." The last sentence refers to the fact that the clinicians and family had already implemented precautionary measures—in this case, feeding the boy frequently to avoid periods of prolonged fasting, which can result in metabolic crisis—even

7. On the relationship between pragmatism and semiotics, see Meyer (2008).

8. SCADD is a fatty acid oxidation disorder that can lead to difficulties metabolizing certain fats.

though the geneticists were not yet certain whether the screening results indicated the "real" presence of the disease or even whether SCADD was a true disease.[9] Here, we have the elements of early diagnosis and early treatment arranged as intended by the policy logic of newborn screening. The mother of another patient observed, "The great thing I guess you can say is that his condition was detected in a newborn screening. So we knew what his condition was as opposed to finding out when it was too late. Or what have you." This mother reiterated the key intended benefit of newborn screening: detecting patients before symptoms occur.

Unfulfilled Potential

False positives. The experiences of most families in our study visiting the clinic for follow-up of positive newborn screening results, however, differed from the intended potential of secondary prevention. Many children did not walk away with a clinical diagnosis. For each clear diagnosis there were many more false positives. Between July 2005 and May 2009, the ratio in California was about 4.5 false positives for every true positive (Feuchtbaum, Dowray, and Lorey 2010). This is because a screening test depends on a balance between sensitivity (the ability to identify actual cases) and specificity (the ability to rule out negative cases). Inevitably, screening programs identify some false positives and let some false negatives slip by. "Newborn screening is a screen," a geneticist explained to one couple, "which means it just gives us a general idea of who to look at more closely than others. But it is not a diagnostic test. It does not tell us for sure that this is what he has." The geneticist did not present newborn screening as a powerful preventive measure but rather downgraded it to an initial triage mechanism.

Faced with ambiguous results, geneticists' modus operandi was to conduct increasingly specific follow-up tests. This typically involved a series of repeat biochemical tests followed, if necessary, by DNA sequencing. The determination of a false positive was the outcome of a lengthy process that could take days, weeks, and in some cases months to figure out. Meanwhile, geneticists were still faced with the original positive result, and the possibility of a disorder could not be fully excluded even if other evidence suggested a false positive. In this interim period, geneticists clung to the possibility of a false positive while also leaving open the possibility of true disease. A geneticist explained, "So one thing about these disorders is that the newborn screening is a very sensitive test so it could pick up levels that are abnormal, okay. And then after that we find out that, for example, if we test DNA mutation that it might not be a true—that's something that we call a false positive and in that case, it may not really mean too much."

In such explanations, newborn screening emerged as a more ambivalent technology than policy visions suggested: it produced, as one geneticist put it, "many more" false positives that could unnecessarily alarm parents. As social scientists predicted about standardizing technologies more generally (Star 1991), parents facing a false positive lost something they did not know they had (Grob 2011). During pregnancy, they had braced themselves for interrupted sleep, feeding schedules, and juggling a newborn with all other aspects of life. Instead, they were forced to ponder the possibility of a metabolic disorder based on a seemingly authoritative blood test. Yet the determination of a screening result as a false positive is at least a final determination that serves as a clinical exoneration of the child.

Patients-in-waiting. Besides false positives, a second way in which clinicians' and families' experiences with newborn screening differed from policy aims was the situation of lingering uncertainty. For 42 patients in our study, follow-up testing did not unequivocally clarify the status of the disorder because a second mutation could not be found or a genetic test was not available clinically. In other words, the sign eluded interpretation. Clinicians and parents continued to wonder whether the child had a disease or simply a nonpathological form of biogenetic variation. We have referred to these patients as "patients-in-waiting" because they were kept under medical supervision in a liminal state between pathology and an unmarked state of normality for a prolonged period of time (Timmermans and Buchbinder 2010). These patients faced an iatrogenic (because it was screening generated) diagnostic odyssey.

Geneticists directly attributed the situation of patients-in-waiting to the unintended consequences of newborn screening. A geneticist relayed to one couple the following: "Right. Yeah, so, that's the pluses and minuses of doing this newborn screening—it's good when you can find something and you're sure, but then, when you're kind of in this gray area, you're kind of just not sure." "Kind of just not sure" refers to the lingering uncertainty due to a positive screening result that resisted dismissal from the clinic.

Such positive newborn screening results nevertheless developed a social and clinical life of their own. One geneticist explained to a mother that he had little choice but to keep seeing her son as a patient even though the condition—hyperprolinemia[10]—was likely benign:

> One of the amino acids in the blood is very much elevated, but it's a disorder in which 90 plus percent of the kids with it are completely normal. And it's a disorder for which there's no treatment anyway. Maybe even more than 90%

9. One of the consequences of screening large, asymptomatic populations via newborn screening was that clinicians' understanding of diseases shifted radically, including whether some conditions previously considered diseases were clinically relevant disorders or benign forms of biogenetic variation. See Timmermans and Buchbinder (2012).

10. Hyperprolinemia is a metabolic disorder characterized by a buildup of the amino acid proline in the blood.

> are normal because until newborn screening, we would never detect it automatically. We only found it in people who were having tests for other reasons. So I don't think this amounts to a hill of beans. I don't think this is meaningful. What I don't want to do is throw you out on the street because that's not fair either. But I would anticipate no illnesses.

Even though the results did not add up to "a hill of beans," the geneticist felt compelled to keep monitoring the patient. The initial positive result created a momentum of clinical supervision that was difficult to scale back even once signs pointed away from disease. Similarly, families prioritized newborn screening as a pressing concern during the period of retesting. It structured visits to the clinic, affected how parents perceived their newborn, fostered increased vigilance, and depending on the condition, changed the infant's diet and sleeping patterns. Newborn screening thus came with a social opportunity cost for parents.

The standard modus operandi of ordering increasingly refined tests might not offer resolution in newborn screening because, as a geneticist explained, "Now, of course, when you don't find a second mutation, it's always possible that it's there and you just didn't detect it." Newborn screening thus exposed the limits of the metabolic-genetic knowledge base that had been hinted at in the appendixes of the ACMG report: the program was screening for at least some poorly understood and ambiguous conditions. The result was that newborn screening had mixed effects. As one geneticist said,

> There have been a lot of benefits to the newborn screening and some frustrations with the newborn screening. The benefits are that it's caught a lot of things. Otherwise babies wouldn't have been treated till they had gotten sick later in life. But one of the things that's a little tricky about the screening—and it's true in this case here—is that sometimes it's designed to be more sensitive so that it catches everybody. But sometimes it will catch people who ultimately won't go on to develop symptoms or who might in fact even be normal or have a normal variant of their enzymes.

Rather than offering clarity on disease status, newborn screening may cloud the clinical picture. In some cases, some metabolic and genetic markers of disease are present but not in a form that mounts sufficient evidence to count as true disease. Because the screening signs fall outside the expected normal range, they cannot be dismissed out of hand. Rather than the potential to save lives, the technology produces an experience of extended ambiguity in which parents and clinicians grapple with the fundamental question of whether a child is a patient or not.

Harm due to screening. A third way in which experience in the clinic deviated from policy potentials occurred when the positive screen harmed families. The ability of newborn screening to do damage was clearest in the situation of a couple that had lost a child because of very-long-chain acyl-CoA dehydrogenase deficiency (VLCADD).[11] The child had screened positive at birth and remained asymptomatic but nevertheless died suddenly at 11 months after developing influenza. In a subsequent pregnancy, the parents opted for chorionic villus sampling (CVS) to test for VLCADD prenatally. The fetus was identified as a heterozygote carrying the father's mutation. This prenatal genetic test should have provided more conclusive information than the newborn screen, but when the newborn screen indicated a slight elevation for a secondary biomarker of VLCADD, the family was summoned to the clinic.

The parents' agony on contemplating the possibility that their son could have VLCADD after all was palpable in the examination room. The mother was teary-eyed throughout the consultation, holding her son tightly. The geneticist opened the conversation with strong reassurance: "I don't doubt for a minute that the baby is unaffected, that the [CVS] is correct." The mother explained the grounds for her anxiety: "Well, we were told to be optimistic with our first child and we retested her and everything. So, we were, you know, we were trying to be optimistic and then got the bad news, you know, so now it's like, it's hard to be optimistic right now." Pointing to the mother and infant, the geneticist replied, "You and he are collateral damage of the newborn screening. And since he's too young to care, it's you who are the collateral damage." The term "collateral damage" refers to unintended outcomes and is commonly used as a euphemism for civil casualties in war situations. By using this term, the geneticist left no ambiguity that newborn screening could be harmful and that this harm was inevitable in screening programs.

In the end, the follow-up test confirmed the CVS results, but by then the damage had been done. The harm of newborn screening resided in alarming parents who had already lost a child to a disease that their next child could be affected by the same disease, even though a prenatal test should have ruled out the presence of VLCADD. Here, the potential of newborn screening to issue a warning signal trumps the situated reality of parents and clinicians for whom the news was not only unnecessary but also experienced as a devastating blow because it rekindled the possibility that the newborn was affected after all.

Symptomatic patients. The final way that the experiences of parents and clinicians did not align with the promise of screening is with symptomatic children. In the case described above, although the couple's older child was diagnosed through newborn screening, the advance knowledge of a disorder was insufficient to avoid sudden death. Eleven children in our study exhibited developmental delays and other symptoms of metabolic disorders despite early detection through newborn screening. Several developed symptoms before the

11. VLCADD is a fatty acid oxidation disorder that can lead to the inability to metabolize certain kinds of fats.

return of screening results, and three children died. These children were true positive cases, but treatment did not prevent the manifestations of serious illness. For these children, the promise of secondary prevention dissolved into the harsh reality of unrelenting disease momentum. In fact, newborn screening's potential became a burden in such cases because it confronted families with the failed promise of salvation.

In the clinic, then, a diverse and nuanced set of newborn screening consequences developed during interactions between geneticists and parents (Mol 2002), only some of which fit the potential of the screening program to prevent the onset of disease trajectories. The growing experience of expanded newborn screening revealed the boundaries of infants' biological malleability and limits to intervention. Biological recalcitrance emerged as a lack of understanding of diseases in the sense that the screened conditions did not behave as they had been understood. Clinicians wondered whether newborn screening identified true diseases or clinically insignificant abnormalities. As such, disease ontology in its "natural history" and biological parameters became an object of intense knowledge production. What are these conditions we are screening for? What treatments are indicated? How long should we treat these newborns? Answering questions such as these also led to revisions of how much intervention is possible at the beginning of life.

This biological reassertion of the boundaries of human plasticity is also apparent in the observation that even if clinicians knew about the possibility of disease and took recommended preventive measures, the disease could still lead to disability and death. The key question was whether the screening information provided was actionable in the sense of providing advance knowledge that lends itself to intervention. Throughout most of the interactions in the clinic, geneticists were preoccupied with figuring out what the newborn screening results implied for a child's health: did they herald a true disorder or a clinically insignificant genetic variant? The problem motivating clinicians was not that the human beneficiary envisioned by policy makers did not exist but that it was crowded out by the unintended consequences of population screening. By seizing biochemical measures, newborn screening revealed a spectrum of abnormalities only some of which were biologically relevant but all of which were socially significant. In other words, even if the screening result was clinically ambivalent, families and geneticists still needed to respond.

In sum, the implementation of the expanded screening program unmasked the program's presumed potential to prevent as overly simplistic and optimistic. Conditions were more complex, recalcitrant, and varied than anticipated. If, as Peirce suggests, a technology's meaning emerges from its consequences, frontline workers in newborn screening increasingly saw the technology as occasionally preventative but also as harmful for some families and more often needlessly worrying parents. The dominant experience of screening results was figuring out what the results meant, not how they could save a baby.

Discrepancies between Potentiality and Experiences in the Clinic?

Peirce presumed continuity between potentiality and reality, but in newborn screening, dissonance reigned. The initial policy expectations for expanded newborn screening set the broad parameters for the experience of screening in the clinic. Yet policy visions of newborn screening making a difference in newborn lives fell short of the anticipated "benefits." The reality of newborn screening was more ambivalent, including both "pluses and minuses," "benefits and frustrations," and even "collateral damage." The meanings of newborn screening thus emerged from how a positive screen became networked into the operating procedures of the clinic and the lifeworld of parents. In light of the discussion of potentiality in the introduction to this special issue of *Current Anthropology* (Taussig, Hoeyer, and Helmreich 2013), the gap between presumed benefits and actual experience mobilizes a second meaning of potentiality as a choice through which actors drive an object (in this case, newborn screening technologies) to transform. Policy makers could either redefine newborn screenings' potential to save babies, or they could change the technology to achieve the purported goal. This, however, is not what happened. Instead, the technology's original potential was reinvigorated in spite of growing evidence that the consequences of screening were not exclusively beneficial.

How, then, did the growing dissonance affect policy discourse? Most of the myriad effects of newborn screening did not travel easily into the policy world. The semiotic networks were only loosely connected. The suffering of the family who lost a child to VLCADD was private, and the frustrations of newborn screening's ambiguity were buffered in clinical interactions; neither is included in evaluation statistics. Policy makers' responses took three forms: dismissal, repair, and reenvisioning newborn screening. When journalists or social scientists publicized some of these unintended consequences, parent advocates argued categorically that "newborn screening saves lives every day" while their allies at the ACMG equally emphatically asserted that newborn screening was "the most significant public health program of the past 50+ years" (Watson, Howell, and Rinaldo 2011:278).[12] The bottom-line reaction was dismissal. At best, policy makers interpreted these reports as indicative of the need for better education and clinician-family communication rather than epistemic uncertainties deeply embedded in screening programs.

Newborn screening stakeholders have engaged in an impressive research endeavor to repair one inevitable conse-

12. See the comments section following the MSNBC article on false positives: http://today.msnbc.msn.com/id/42829175/ns/today-today_health/t/babies-blood-tests-can-end-false-positive-screening-scares/ (accessed May 30, 2011). See also our reply to this defense of the program (Timmerman and Buchbinder 2011).

quence of any screening program. Policy makers were most concerned with the high rate of false positives as recorded in outcome statistics. To address this problem, one of the Regional Genetics and Newborn Screening Collaboratives funded by the Health Resources and Service Administration of the Maternal and Child Health Bureau created a web-based data reporting and collection system to pool newborn screening data. By March 2011, the project had gathered data from 47 US states and Puerto Rico and an additional 80 newborn screening programs in 45 countries. This enabled researchers to compare data from approximately 25–30 million newborns whose newborn screening results were negative with 10,742 true positive cases. With these data, the researchers were able to refine screening cutoff points for various biomarkers (McHugh et al. 2011). This international collaboration thus attempted to avoid needlessly alarming parents by reducing false positives and avoiding what might be preventable morbidity and mortality by reducing false negatives. In the context of our analysis, this project aims to fine-tune disease biology to determine the conditions under which newborn screening is most effective.

It was the third reaction of policy makers—invigorating newborn screening's potential for prevention—that was most striking. In December 2010, the National Institute of Child Health and Human Development, the National Human Genome Research Institute, and the National Institutes of Health (NIH) Office of Rare Diseases Research sponsored a summit in Rockville, Maryland, to set a research agenda for the future of newborn screening.[13] This imaginary future—as articulated by academic and industry experts, lay advocates, and federal agency officials—envisioned a further expansion of screening to include exome or genome sequencing. The implementation of comprehensive genetic sequencing technologies at birth would aim to identify a wide spectrum of adult-onset diseases and additional clinically relevant information, such as behavioral traits, drug response, and carrier status. In this paradigm, parents might be informed not only that their infant had a metabolic condition but also that he had increased odds for male pattern baldness or ulcerative colitis, an abacavir sensitivity, or that he was a carrier for hemochromatosis. Such screening could be integrated into electronic health records to provide a set of personalized health guidelines. Although the workshop participants agreed that the technology for such screening was still too slow, imprecise, and costly, they discussed preliminary pilot studies that could test the feasibility of their visions. In this summit, newborn screening was presented as a gateway for universal personalized medicine.[14]

This molecularization of newborn screening reaffirms human biology as both a limitless source of knowledge and as a site of intervention that can pave the way for a better future. Such visions of technological potential reinscribe genetics as a divination of humanness (Nelkin and Lindee 2004). That such an image would emerge at birth suggests endless opportunities for manipulation across the life course. As with the initial expansion of newborn screening, this ascribed potential aims to gather resources for technology adoption.

It is not only policy makers who reinvigorated potentiality in spite of recalcitrant realities. Clinicians and parents in our study also fell back on reiterating the promises of the screening program. A geneticist reflected to the parents of a child diagnosed with propionic acidemia, a condition that can lead to complications in spite of early treatment: "We had that discussion today about newborn screening for another family of disorders, which is becoming possible, but the interventions are even more dicey than these, and you know, I point out childhood leukemia. When we first started treating it we made the kids miserable and they died anyway. Now, 80% or 85% are cured. [If] we didn't do [the experimental treatment], then you wouldn't be where you are now. So you only want to do better each time." Comparing newborn screening to childhood leukemia suggested that more visibility translated into more knowledge about disease and would, it is hoped, transform into better treatments because of incremental learning. And nearly all families, regardless of their actual experience with newborn screening, agreed with the mother who reiterated the promise of newborn screening in her own words: "Better to be safe than sorry, we really believe."

Surrounded by accumulated clinical experience, potentiality did not always yield but lingered persuasively. Potentiality—as parents, geneticists, and policy makers intuitively knew—was powerful precisely because it was independent of other phenomena but could become dependent on anything. And in turn, other phenomena could become dependent on it. Pragmatically speaking, potentiality mattered not because of the consequences it manifested but because indeterminacy left all consequences open. Newborn screening demonstrated the power of potentiality—dreams, visions, action plans, promises, aims—to trump facts and generalizable laws. One of the powers of potentiality is to raise hope, a "what if" question (Altelius 2007; Shim, Russ, and Kaufman 2006). That "what if" essence is lost when potentiality does not match experiences; yet, for the time being, potentiality helps buffer inconvenient truths about the limitations of newborn screening to fulfill the promise of secondary prevention in every positive screen. As Latour's (1987) reanalysis of Evans-Pritchard's work on the Azande shows, an apparent irrationality may disappear if we follow how semiotic networks strengthen some links and weaken others.

In the policy world and the clinic, pledging to the promise of a biomedical technology offered a distraction from the reality at hand. At the NIH policy summit mentioned above, the vision of whole genome sequencing had the typical function of energizing diverse stakeholders behind a common goal and summoning resources. At the same time, the new vision distracted from the growing pains of implementing the cur-

13. http://www.genome.gov/Pages/PolicyEthics/StaffArticles/Newborn_Screening_Meeting_Summary.pdf (accessed June 2, 2011).

14. This paragraph and the previous one draw from the concluding chapter of Timmermans and Buchbinder (2013).

rent newborn screening program. In the clinic, the reactive character of restating the promise of newborn screening was even more apparent. When parents struggled with the uncertainty of not knowing that their newborn was diseased, the attitude of "better safe than sorry" suggested that the current harm was irrelevant if the future would be safe. The geneticist's comparison with leukemia tapped into powerful moral altruism used to frame medical procedures such as organ transplantation (Fox and Swazey 1974), autopsies (Timmermans 2006), and randomized clinical trials (Marks 1997): you may not benefit directly, but future generations could take advantage of your sacrifice. In all instances, reiterating potentiality helped to downplay the murkiness of current reality in favor of a brighter future. Potentiality had this consoling effect by creating a temporal and spatial separation between the here and now and the far-off there and then. Rather than unmasking potentiality as hype, renewing potentiality thus served to draw attention away from a discrepant present.

Because potentiality is independent of present realities, it inevitably comes at a cost for families whose experiences no longer fit a salvation narrative. As we saw, hope individualized suffering as unique and rendered the variety of consequences in the clinic invisible to policy intervention. Moreover, the line between potentiality and experienced realities could start to blur. Thus, when screening advocates asserted that newborn screening saves lives every day and is the most significant public health program of the last 50 years, they rendered contradictory signs silent for the larger aim of actualizing a promise. Here, we see a displacement of goals in which the potential of newborn screening was upheld as a reality even though there was no epidemiological or public health evidence for either assertion. Such reification of potentialities carries great risk because it depends on the continued suppression of evidence and rhetorical assertion of benefit.

Conclusion

There is a well-known academic joke in which a physicist, a chemist, and an economist are stranded on an island with nothing to eat. A can of soup washes ashore. The physicist says, "Let's smash the can open with a rock." The chemist says, "Let's build a fire and heat the can first." The economist says, "Let's assume that we have a can opener." The punch line of this joke is not only that economists are unrealistic but also the opposite: that potentiality creates a world on which realities travel in spite of unknown feasibility.

A pressing theoretical issue is the relationship of potentiality to actual experiences. From a semiotic perspective, imbuing a medical technology with potential requires broadening and deepening the technology's ability to act in the world, often in a way that is both underspecified and grand. Much is anticipated with few details provided about how goals will actually be achieved. Such translations are relatively open ended: potentiality implies an aspiration, not an actual result. Yet potentiality also sets up an expectation for what a technology should be able to achieve. Within Peirce's categorical scheme, potentiality yields to actuality. The recent history of hyped-up potential in genetics, genomics, nanotechnologies, epigenetics, and stem cell research shows that technologies weather the dissonance between hope and disappointment. Indeed, Brown argued that unfulfilled potential tends not to undermine technologies because "it would be impossible to fully disentangle present hype from future reality" (Brown 2003:16). We noted that within a rapidly innovating field, rearticulating hope and aspiration intrinsic to potentiality can supersede inconvenient realities. The price of downplaying reality for a brighter future, however, is that some realities no longer count. In the clinic and the policy world, potentiality, actuality, and generalizability—even of the same phenomenon—may thus remain distinct, coexisting simultaneously in uneasy tension, each generating different and occasionally contradictory consequences depending on the specificity of the situation at hand.

Visions of the capacity of diagnostic technologies to change the present for a beneficial future enable the collection of resources, the projection of state populations (Zhu 2013), and the construction of futures through past analogies (Gammeltoft 2013). But is this only a story about what it means to be human (Chinese, Vietnamese, or American)? Along with Zhu, Gammeltoft, and other scholars of reproductive technologies (Press et al. 1998; Rapp 2000), we find that rather than reassure and predict, in practice these predictive technologies amplify worry and uncertainty about abnormality or disability. These anxieties follow from deeply rooted sociopolitical and historical national and global developments. At the same time, however, there are other histories at play, histories of machines and of people looking for ways to render these machines functional and, occasionally, fun. Also, there are histories of how biomedicine finds a foothold in certain niches and of how prospective parents across the globe consult white-coated experts. Because it remains unencumbered by practicalities but may connect disparate elements, potentiality goes beyond what it means to be human to tie these heterogeneous elements together into a better future. By following consequences as they develop in multiple areas, a pragmatist approach allows us to see the gains and losses of making health care policy on technology's potential.

Acknowledgments

We thank the reviewers, the editors, and the participants at the Wenner-Gren conference for helpful suggestions.

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