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Abstract

What are the social consequences of the recent expansion of newborn screening in the United States? The adoption of new screening technologies has generated diagnostic uncertainty about the nature of screening targets, making it unclear not only whether a newborn will develop a disease but also what the condition actually is. Based on observations in a genetics clinic and in-depth interviews with parents and geneticists, we examine how parents and clinical staff work out the social significance of uncertain newborn screening results. We find that some newborns will experience a specific trajectory of prolonged liminality between a state of normal health and pathology. Based on a review of related literatures, we suggest "patients-in-waiting" as an umbrella concept for those under medical surveillance between health and disease.

Keywords

diagnosis, genetics, medical technologies, newborn screening

Newborn screening has been in place in the United States since population-wide phenylketonuria (PKU) screening was made possible in the 1960s and 1970s, and for the last decades PKU screening has exemplified the promises and pitfalls of population-based genetic screening. When it was first introduced, PKU seemed a perfect candidate for screening: Advocates argued that early identification of affected infants and prompt dietary changes could prevent mental retardation. The program became controversial, however, when researchers discovered that many assumptions about the incidence of the disease and the length of treatment proved inaccurate, screening produced many false positives, and some children had been unnecessarily deprived of nutrients (Paul 1997). The harbinger function of newborn screening for population screening is likely to continue since recently the number of conditions screened for has rapidly expanded. In 2005, the American College of Medical Genetics issued an influential report that endorsed the use of multiplex technologies in newborn screening (Watson et al. 2006). The report recommended that states screen for 29 core conditions. With support from the March of Dimes and professional organizations, by 2009 all 50 states and the District of Columbia screened for 21 of the 29 recommended conditions, and the full recommendations have been adopted by 44 states. Almost all 4.1 million infants born yearly in the United States are thus currently screened for a broad range of rare genetic conditions.

While expanded newborn screening is technologically feasible and justified by the assumption that families will welcome information about rare genetic conditions (Bailey et al. 2006), little is known about how these technologies actually affect families' lives and patient-doctor visits (Grob 2006; Grob 2008). The objective of newborn screening is to identify newborns with rare genetic conditions before symptoms develop, in

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order to intervene early in life. Thus, for example, population-based PKU screening aims to identify infants with PKU so that dietary measures may be taken to avoid mental retardation. Despite this straightforward logic, the expansion of newborn screening to 29 core conditions introduces a different set of cost-benefit relationships for each condition: For some conditions no treatment is available; for others treatment is not as straightforward as dietary change but involves invasive medical procedures such as bone-marrow transplantation; still others constitute extremely rare and ill-understood conditions; for still others early detection has no discernible health benefits. Moreover, rather than diagnosing asymptomatic patients with clear-cut diseases, expanded newborn screening has identified newborns with screening values outside a pre-set normal range that do not always clearly correlate with defined disease categories.

We will refer to these newborns as *patients-in-waiting* because they hover for extended periods of time under medical attention between sickness and health, or more precisely, between pathology and an undistinguished state of "normalcy." The major issue facing a newborn patient-in-waiting is not only whether he or she will develop a disease but also what the condition actually is. At stake in patient-doctor interactions are the social and biological characteristics of the condition. A major consequence of expanded newborn screening is thus the management of new patient populations marred by fundamental uncertainty about the nature of screening targets. Such management goes beyond identifying a patient group and includes settling upon a diagnosis, monitoring developmental milestones, recognizing potential symptoms, and developing a plan for intervention. The stakes are high in such encounters. Unlike prenatal genetic technologies where interactions are dominated by the quest for the perfect child (Landsman 1998; Rothshild 2005), newborn screening implies imperfection after the child has been born. For genetic conditions, imperfection may mean developmental delays, neurological deficits, and sudden death.

This article has two distinct contributions. First, relying upon recorded observations of clinical interactions and in-depth interviews with parents and geneticists, our main purpose is to lay out the specific trajectory of newborn patients-in-waiting under medical care. We examine how geneticists and families collectively make sense of the information provided by the newborn screen and work out the medical and social implications of the condition and the possibility of a diagnosis. We show how the prolonged use of ambivalent messages makes it difficult for parents to relax preventive measures even if physicians are ready to redefine the results as biochemical quirks. Second, in the discussion section we relate the concept of newborn patients-in-waiting to other patient populations. In particular, we examine similarities with the literature on risk, susceptibility screening, and protodisease states, and the scholarship on developmental delay assessment. We argue that patients-in-waiting can be used as an overarching concept to elucidate common experiences among people trapped between a state of sickness and health characterized by uncertainty about disease.

THEORETICAL FRAMEWORK: DIAGNOSTIC UNCERTAINTY

Drawing from Talcott Parsons' distinction between the social and biological aspects of health, medical sociologists distinguished illness from disease, where illness referred to the experiences of feeling sick and disease indicated an underlying organic and pathological condition that causes adverse effects. Sociologists focused on illness as a thoroughly social experience that interrupts daily life (Bury 1982; Charmaz 1991; Corbin and Strauss 1987). Diseases remained medical categories wielded by physicians to legitimate illness experiences. Illness and disease met in the patient-doctor encounter, where an extensive literature analyzed how patient concerns found or eluded medical validation in the process of diagnosing (Heritage and Maynard 2006).

Historian Charles Rosenberg (2007) noted that when modern medicine shifted from viewing disease as part of a patient's constitution to the perspective that diseases were specific stand-alone entities, the process of diagnosis became more central in clinical encounters. A chronological analysis of internal medicine textbooks maps the ascent of clinical diagnostics over the course of the 20th century (Christakis 1997). A diagnosis may be thought of as a cognitive schema that offers a plan of action for both patient and clinician. Patients typically present physicians with a number of complaints, signs, and symptoms to be organized into a clear-cut diagnosis (Atkinson 1995). Diagnosis constitutes both a process of deliberate judgment and a preexisting set of categories (Jutel 2009) initiating a set of experiences, identities, life strategies, and subsequent medical actions (Charmaz 1991).

When the diagnostic process does not lead to an established disease, the cognitive roadmap suggesting treatment plans is lacking. *Diagnostic uncertainty* typically takes the form of determining whether symptoms warrant a disease classification, but, as we will show, it can also include uncertainty about both the presence and nature of a medical disorder. As we know from other areas in medicine (e.g., disorders of sex development [Feder 2009; Star 1991]), prolonged ambiguity is uncomfortable for both patients and practitioners, who will exert pressure to fold an incomplete characterization back into more conventional categories (but see Whitmarsh et al. 2007). With the stakes of a diagnosis so high, prolonged uncertainty will thus require extensive interpretive work from all parties involved to maintain a state between health and disease and to try to resolve it.

Diagnostic uncertainty has been most closely examined in people living with chronic pain (Baszanger 1995; Garro 1992; Kleinman 1989; Rhodes et al. 1999) or with contested illnesses such as Gulf War Syndrome, fibromyalgia, or multiple chemical sensitivities (Barker 2008; Kroll-Smith and Floyd 1997; Zavetoski et al. 2004). Chronic pain patients struggle with conditions that resist objective perception. People living with contested illnesses present clusters of symptoms, but, from a medical perspective, the symptoms are too vague to qualify as diseases and they are often rebuffed until the condition gains legitimacy. Chronic pain and contested illnesses thus entertain an ambivalent relationship with medicine: They give rise to lengthy therapeutic journeys with sufferers subjecting themselves to multiple medical specialties and diagnostic tests but at the same time also railing against medical diagnostic hegemony (Kroll-Smith and Floyd 1997). Patients with contested illnesses may see their complaints interpreted as psychological problems (Nettleton 2006), have their conditions rejected outright (Cohn 1999), receive unspecified residual diagnoses (Swoboda 2008), be passed off to other practitioners (McCormick 2000), or receive a diagnosis of a contested disease (Dumit 2006). Because of the mixed reception, people with contested illnesses often find validation for their symptoms outside the clinical encounter—in support groups or patient health movements (Barker 2008; Dumit 2006; Zavetoski et al. 2004). While many of the implications of diagnostic uncertainty in these populations have been generalized to patient-physician interactions (e.g., Zavetoski et al. 2004) and there are several retrospective reflections on clinic visits (e.g., Stockl 2007), this literature focuses on patient narratives and provider accounts rather than on observed clinical encounters.

In newborn screening, diagnostic uncertainty perplexes physicians as well as patients. Not only is there ambiguity about linking signs to disease categories—in part because such signs are often absent in population-based diagnostic screening—but questions also remain about the object of diagnostic detection. The only clue that something may be awry is a test result with values out of a preset normal range. Yet the reliability of this normal range for rare diseases is up for debate, as is the fundamental question regarding whether the abnormal values constitute a true disease. The challenge of the diagnostic process for these newborn screening patients is to create a cognitive roadmap for a landscape without typical markers.

People living with chronic pain and with contested illnesses may find outlets outside the clinical encounter to search for sympathy and certainty, but parents of newborns with rare genetic conditions have fewer options. Due to a widespread shortage of pediatric geneticists, the rarity of these diseases, and the variation of individual screening values, the diagnostic uncertainty from newborn screening results must be dealt with within the clinical encounter. If a diagnosis, as the lynchpin organizing and directing the medical visit, remains elusive, how is the patient-doctor encounter affected? Addressing diagnostic uncertainty for parents and genetics staff comes down to two basic issues. First, staff and parents need to determine what the results mean. Because neither symptoms nor clear-cut diseases are present and conclusive answers are lacking, parents and clinicians may downplay the health risks, treat the screening results as indicative of a serious condition, or move back and forth between those positions. Second, as in most clinical encounters, a primary goal of this interaction is to have both parties agree to the same course of action and avoid conflicts (Anspach 1993; Heimer and Staffen 1998). Geneticists need parents to collaborate with preventive measures, and parents depend on geneticists to provide them with guidance.

METHODOLOGY

Metabolic conditions comprise the large majority of most newborn screening programs. In California, the setting of our research, expanded newborn screening was implemented in August 2005. At the time of this writing, 24 primary metabolic disorders

are screened for, with the possibility of detecting an additional 23 variant forms. Metabolic disorders are rare. According to the California Newborn Screening Program, PKU occurs in 1 in 27,000 births in California, and approximately 15–18 newborns are identified annually through the mandated state screening. Galactosemia, another condition detected by newborns screening, occurs in 1 in 73,000 births, with 4–8 newborns identified per year. In contrast, sickle cell disease is more common, occurring in 1 per 4,400 births, or 125 newborns per year (California Department of Public Health 2007).

Newborn screening begins within 48 hours after birth, when a spot of blood is collected through a prick to the newborn's heel. In a specialized laboratory, tandem mass spectrometry technology analyzes the sample to determine the concentration of specific chemical compounds within the blood. The values of various metabolites within the specimen are then compared to normal ranges for healthy children. If the value lies beyond established cut-off values, metabolic disease is a possibility. Positive results—values lying above the normal threshold—are communicated to regional newborn screening staff, who contact families and health care personnel for retesting, and additional blood and urine specimens are collected. If the values are still high on this second set of tests, the family is referred to one of several regional clinical centers for follow-up care. Thus, the initial screening focuses on metabolite levels and does not involve genetic testing, though geneticists may order DNA analysis at a later phase to confirm or rule-out specific diagnoses with a greater level of precision.

Our analysis is based on our close observations of the parents–genetics team interactions at one regional clinical center followed by interviews with parents and staff. Our project follows parents during clinic visits over a two-year period. In the genetics clinic, we audiotaped consultations between parents and staff with a research team member present to observe the interaction and take ethnographic field notes. In between follow-up visits with the genetics team, we conducted open-ended, in-depth interviews with parents to find out how they make sense of the information they receive and to follow the different adaptations they make to their daily life. The interview guide includes questions about the most recent visit to the genetics clinic, pregnancy and reproductive history, additional sources of information consulted about the child's condition, daily management of the condition, possible interruption of family functioning, social and support network, contact with other health providers, labor at home, work, neighborhood, and reproductive decisions. In addition, we attended weekly staff meetings and consulted patient records. This project received IRB approval (#G07-04-020-03).

All English- and Spanish-speaking families of clinic patients who had received a positive newborn screen between 2005 and 2009 were approached for participation in the study during routine clinic visits. Besides infants, our study contained three older children, one of whom was diagnosed during an earlier pilot newborn screening project. Two families refused participation because they declined audio taping, and one family was ineligible because they spoke neither Spanish nor English. We collected data from 55 families from October 2007 to July 2009. Of those, 23 have been first time visits to the clinic. In 32 cases, we met the families first during a follow-up visit. We recorded more than 100 patient visits; while most families were seen for less than three visits, we followed some families for up to six visits. Twelve of the families were Spanish-speaking. The clinic we studied specialized in metabolic genetic disorders. Newborn screening also detects hematological and endocrinal diseases, but these fall beyond the scope of our study.

We analyzed our data in a modified grounded theory and analytical-induction tradition (Timmermans and Tavory 2007), meaning that we systematically coded the empirical material in dialogue with a close reading of salient themes in the medical sociology and genetics literatures. In addition to the literature on diagnosis, we also drew from the work on illness trajectories and careers and the historical literature on newborn screening. We began analysis early in the project and verified the emerging analytical coding scheme with later data to make sure that our analysis captured the full spectrum of empirical manifestations.

Patients-in-Waiting

The main technology that drove the expansion of newborn screening, tandem mass spectrometry, has the ability to screen for large numbers of biochemical components with a single specimen. Whereas previously screening tests had been specifically developed for particular disorders, with tandem mass spectrometry there is no longer a one-to-one correspondence between disorder and test. The knowledge that a biochemical level falls outside a pre-established normal range may indicate several

different disorders, or may be of ambiguous clinical value. Thus, the novelty of tandem mass spectrometry technology is that it reveals an abundance of information that remains profoundly ambiguous but may have serious consequences for both families and geneticists. Diagnostic uncertainty is hardwired in the screening technologies and creates an interactional dilemma. Geneticists have to convey whether to take the information seriously and have to secure the collaboration of parents in interpreting the test results, even though the results remain equivocal. Both parties need to determine whether the test results should be ignored or whether they indicate that the child may develop symptoms.

Our study contained 24 newborns for whom the condition identified through newborn screening was deeply ambiguous. The making of these patients rests upon a prolonged mixture of contradictory messages about the nature of the disease. The newborn screening results oscillate between indicating a biochemical artifact and a potentially life-threatening disease. The pathways that link biochemical measures, genetic markers, test results, symptoms, and treatment remain unsettled. These conditions are both biologically and socially ambiguous—biologically because the clinical significance of elevated levels is not established, and socially because it remains unclear whether the screening result requires adaptations to the child's and the family's life. Once this ambiguity is aroused, it does not easily dissipate. The sociologically fascinating—although expected from a robust anthropological literature on rituals (Turner 1974)—observation is that this betwixt-and-between state still requires social action. The possibility of developmental delays, neurological deficits, and sudden death is so threatening that the condition becomes functional. Still, uncertainty about these measures lingers. From a sociological perspective, the newborn becomes a patient-in-waiting.

One of the unique characteristics of newborn screening is that parents and infant share the patient "role." While the parents act upon the test results, the infant provides blood samples and may exhibit symptoms. As in many pediatric settings, the geneticist questions, admonishes, and reassures parents, but examines the infant for muscle tone, reflexes, and developmental milestones. Yet what is particular to the genetics context is that parents will often be asked to submit to their own genetic testing for confirmatory analysis, which renders them patients in quite another sense. In interviews, parents also used the "we" pronoun when referring to those affected by positive screening results. This sharing of the roles renders the social implications of newborn screening visible: Parents, under medical scrutiny (Heimer and Staffen 1998), are often quite explicit about the kind of measures they are willing to take on behalf of their child, how screening results alter their expectations for their infant, and how these results affect their newly grown family.

Some sharing of the patient roles is presupposed by the expansion of newborn screening. Akrich (1992) noted that the implementation of technologies presumes "scripts" of users with ascribed abilities, desires, and goals. Newborn screening presumes that an adult caretaker will act in the child's best interest. This caretaker can be any adult who has primary responsibility for the infant. As others have noted (Landsman 2003; Leiter 2004; Timmermans and Freidin 2007), in reality the caretaker role remains deeply gendered: The work of caretaking tends to fall on a woman, most often the mother. The shared patient role in newborn screening thus underscores the inescapable social consequences of newborn screening. While unique in the specifics of the newborn situation, such social spillover effects are regularly found in the context of other screening programs, especially those with a presumed heritable component (Van den Nieuwenhoff et al. 2007).

Next, we examine how parents and geneticists make sense of diagnostic uncertainty due to newborn screening. We discuss the shock of the unexpected news, the continued ambiguity of repeated testing, and the diverging perspectives of parents and geneticists on the fading away of diagnostic uncertainty.

Onset

The *contradictory messages often begin with the very first communication* between the screening program and the parents. Representatives of the state's newborn screening program usually try not to scare the parents unduly. Thus, they told parents of a baby with elevated levels suggestive of MCADD (Medium Chain Acyl-CoA Dehydrogenase Deficiency) that the initial levels probably indicated a false positive result. In the same conversation, however, the parents were urgently advised to retest the same day. Depending on the suspected condition, the request to retest may be accompanied with some preventive measures such as not letting the newborn sleep for more than 6 hours without feeding, avoiding breastfeeding, or using a soy-based formula. Parents also receive instructions about possible symptoms and warning signs.

The initial positive results of newborn screening come as a *shock* to almost all parents. They had been focused on pregnancy and delivery and gave understandably little thought to rare genetic conditions. Parents usually are unaware that their newborn had been screened: Informed consent is not mandated in California (and all but two U.S. states—Maryland and Wyoming), and families do not always receive information about the screening. A mother recalled the shock after the first communication about screening results with her pediatrician:

> He was five days old and we got a phone call from our pediatrician. We just talked to her about him sleeping through the night, if that was even possible, and she was, like, yeah, go ahead, try to do it. So she frantically called me when he was five days old and said, don't let him sleep through the night. You have to feed him every three hours or basically he can die. That was pretty surprising and shocking. We had to take him when he was five days old to get his blood drawn, and they did a blood test to reconfirm that he had a metabolic disorder. (Observation March 2008, Family 15)

The shock is enhanced by the fact that many couples opted for ultrasounds and other prenatal tests during pregnancy: "we really didn't have any concerns. And all of our ultrasounds were really, really good. And so we were unconcerned about any of the genetic stuff, was our general feeling" (Interview September 2008, Family 28).

The newborn screening program's aim for a careful balance between not panicking but still taking the condition very seriously is destabilized when parents conduct an *online search* or *consult any kind of information* provided by health care providers because these sources will turn up the worst-case outcome (see also Schaffer, Kuczynski, and Skinner 2008). A mother described her reaction to reading the material about genetic testing that she had "sloughed off" when it was initially presented to her by clinic staff:

> And actually the first time that they had suggested that he might have PKU, you go back to read the material, and it's, like, a blur. . . . Basically, it says, we test for this. PKU is this, and basically in a nutshell, because of a deficiency in an enzyme, your child can become mentally retarded. So, I'm, like, what? And then you go on the Internet and it's, like, if the levels are like this, you know he'll become retarded. He's losing IQ points by the second. And I'm, like, oh, my gosh! I'm looking at him, and, like, he seems fine. Is his brain, you know, getting destroyed by the protein that's in my breast milk? (Interview September 2008, Family 28)

Parents find out that in the worst-case scenario hyperprolinemia may be associated with schizophrenia; MCADD patients may die a sudden death; untreated PKU may lead to mental retardation; carnitine deficiency may cause muscle weakness, including weakness of the heart muscle; and glutaric acidemia type II may be life-threatening. Even if the parents do not yet have a diagnosis but simply know that a particular biochemical is elevated, the information search will produce worst-case results. This information expands the spectrum of possible outcomes, and the result is not reassuring: Either the screening leads to nothing, or it implies something very serious.

In spite of the information available on the Internet, the encounter with the genetics team remains the primary source of knowledge about the genetic condition. The physicians and nurses in our study warned parents not to look on the Internet or at least not to believe everything they read. Unlike for other conditions, the Internet offers limited and outdated information on rare genetic conditions. To back up their recommendations, the geneticists often referred to information that was still in press or recently published, or to personal conversations with leading researchers. Parents may quickly learn more than their pediatrician about the genetic conditions, but they did not surpass the knowledge of the geneticists. Often, however, even the geneticists did not have the answers, shaping the liminal state of a patient-in-waiting.

The parents' experience of diagnostic uncertainty thus originates in wildly disparate mixed messages from a variety of sources following a positive newborn screen: The state newborn screening program tries to reassure families that the results likely indicate nothing serious, but a quick search for information produces a long list of horror stories. Before families even see a geneticist, the momentum across a wide diversity of families is to take the condition seriously. Newborn screening is set up to convince parents that the results demand immediate retesting and require preventive measures. Although shocked by the unexpected news, most parents comply with retesting and visiting the geneticists in hope that a resolution can be found.

Repeat Testing

The initial anxiety-provoking communications and bewilderment are typical for all parents contacted for a positive newborn screen. The screen only flags the possibility of positive results and requires more specific follow-up tests to rule out a false positive. At this point there are three possible scenarios. First, in more than 90 percent of the cases, the retesting will reveal that the initial screen was a false positive and the parents may not even meet with the genetics team because the pediatrician conducts the repeat test. Second, in a small number of families (less than 1%), the retesting or sequencing shows the unambiguous presence of a serious, well-established disease.

The third scenario entails patients-in-waiting because there is no immediate resolution and *the ambiguous messages continue*. The weeks or occasionally months of suspense can be an intensely anxious period for these parents, and during that period the newborn remains, in the eyes of the parents and the genetics team, a patient-in-waiting. The follow-up tests do not exclude the possibility that something is wrong, but the results are typically not serious enough to indicate a clear-cut disease. Thus, in meetings, geneticists will repeatedly express their hunch that this will probably be a clinically insignificant biochemical finding. At the same time, parents fail to receive clear answers about the implications of the elevated measures. An example from our field notes of a first visit between a foster mother and a geneticist about a child with elevated proline levels:

> When the geneticist talks to the foster mother, he states, "from my perspective, it is quite reassuring. First of all, proline levels are high, but they are not super high." He explains that hyperprolinemia comes in two variations: "The first one is simply a biochemical finding. It is a random finding. No symptoms, nothing." He adds that if it were not for newborn screening, he would never have detected it. He qualifies that the difference between type 1 and 2 does not depend on levels alone but on different genes. "The ultimate way of figuring this out would be to test the genes. Those tests are not available clinically. They are available on a research basis." The foster mother asks when these symptoms would appear, and the physician answers that they should show in the first year of life. When the foster mother presses the question whether the symptoms could appear later, the geneticist admits, "They could. We don't know. I can't guarantee anything but the fact that she is developmentally perfectly on target is a good sign." The foster mother asks about warning signs besides seizures. The physician explains that they should be attuned to regular developmental landmarks such as sitting, walking, and babbling in time. (Observation notes December 2007, Family 2)

As the geneticist explained to the foster mother, little is known about this condition because few children with this condition came to medical attention prior to newborn screening. Most of the symptoms that may indicate the beginning of a problem remain rather vague and nonspecific. The geneticist pointed to general developmental milestones. In other conditions, the warning signs include symptoms that many babies experience, such as muscle weakness, deep sleep, vomiting, diarrhea, or developmental delay. To make matters even more ambiguous, deterioration can occur without advance warning. Thus, any bout of vomiting or any childhood cold may signify irreversible damage. The geneticists at the staff meeting later that day also disagreed about the fundamental question of whether hyperprolinemia is a true disease that required any kind of action. Diagnostic uncertainty thus encompasses the ontological status of the condition as a disease (Mol 2002).

While for most patients diagnostic tests escalate in precision until a disease is confirmed, for patients-in-waiting the *supposedly definitive test remains inconclusive* and the trajectory is open-ended. In newborn screening, the expected sequence of events is to do confirmatory blood or urine tests, followed by DNA sequencing for the genes associated with the condition if this may affect the treatment course. In the hyperprolinemia case, DNA sequencing was unavailable for clinical purposes and the blood and urine levels were retested. The other means to see whether hyperprolinemia has biological effects is to check whether infants meet developmental milestones or experience any of the symptoms associated with the condition, although even then it is difficult to causally link generic developmental symptoms to the condition. Developmental milestones are associated with certain time points, but failure to meet such milestones does not necessarily indicate that the genetic condition was the source of the delay, since there are many possible reasons for a delay. Thus, in a child diagnosed with citrullenemia whose onset of speech was delayed, the parents and staff referred to the fact that boys generally talk later than girls.

In spite of diagnostic ambiguity, the positive screening results *receive traction as the focal point of a set of medical and social practices* in the lives of the parents and their interactions with the health care team. Interestingly, even if repeat testing is inconclusive, it does not dispel the possibility that something might be wrong with the child. These diagnostic procedures generate a trace of paperwork that turns ambiguity into a bureaucratic disease entity (Rosenberg 2007) and create a set of routines and repeat consultations for the parents and geneticists. The geneticist will also prepare an emergency letter to present to health care providers in case the baby goes into a crisis. Parents will be again instructed to watch and treat the baby as if he or she has the condition, even though the geneticist sometimes suspects that such safety measures are unnecessary. Such precautions further help settle the condition as real disease in the lives of many parents of patients-in-waiting. In the case of the hyperprolenimia patient described above, for example, the disorder gained currency as a means to access educational services, as part of disability assessment, and in the adoption-family reconciliation process.

> At the second visit six months later, the foster mother reviews developmental steps with the possibility of hyperprolinemia. Thus, when telling about her daughter's difficulty transitioning to solid food, the mother adds, "We were not sure whether it was simply a delay where it would soon happen or there was something that is going on inside." She had the girl tested at a service center focusing on developmental disabilities and she was diagnosed as being 4–5 months behind in her motor development and qualified for physical and occupational therapy. The "diagnosis" of hyperprolinemia has had consequences in the adoption process. Social services intervened because the children were generally neglected. From a variety of issues, the court focused on malnutrition and the lack of follow-up for positive newborn screening. Consequently, to show that she is qualified to parent, the foster mother has to document that she takes hyperprolinemia seriously. (Observation Notes, October 2008, Family 2)

Such actions that prove the social relevancy of hyperprolinemia create resistance to a biological redefinition of the condition as benign based on additional test results.

While DNA sequencing was not available for hyperprolinemia, it is for MCADD. In order to qualify as a "classic" MCADD case, the patient should have a mutation in each of the two copies of the MCADD gene, and each mutation should be known or suspected to cause substantially reduced activity of the product protein. Elevated levels of the metabolites may occur, however, with two mutations of suspected lesser severity or of the classic and a different mutation. In such cases, the geneticist will recommend that the parents consider the child mildly affected because no one with two nonclassic mutations has been known to develop symptoms. At the same time, however, the geneticist will keep the emergency provisions in place. A mother of an MCADD baby with two different mutations expressed the mixed message she received: "[The physician] said, 'She still has MCADD and we'll need to treat her as if she does—if she *did* go in metabolic crisis or if she was vomiting or had diarrhea you still need to do the same as if she had a severe case of MCADD.' So he didn't ever say, 'She doesn't have it anymore'" (Interview August 2008, Family 10).

In sum, because retesting does not provide the hoped for closure, geneticists and parents err on the side of caution and act as if there is indeed a disease that is serious and requires preventive measures. Diagnostic uncertainty is thus marshaled to emphasize the potential seriousness of the condition. For most families, these precautionary measures gradually become part of family routines and, depending on the condition, they check with the genetics team's dietician before they put the child on solid food. Our study contained three families who were not as vigilant as the staff would have preferred, but diagnostic uncertainty worked in their favor. The issue of noncompliance did not escalate because the genetics team lacked clear evidence that not following their recommendations was harming the infant.

Fading Away

Precautionary practices, repeat testing, and regular consultations have fostered a partnership between parents and genetic staff exemplified in close surveillance of the infant (Armstrong 1995). Clinicians often reminded parents that the condition could be benign, but that aspect of the mixed message has not been incorporated into practices because normalcy does not require any action and receives little social traction. When, after time has passed, the infant remains fine, clinicians may have trouble getting the parents to tone down the level of vigilance. At this point, parents and physician may be at odds about the course of action.

From the genetics team's perspective, diagnostic uncertainty fades in relevancy when further genetic testing is unlikely to clarify the diagnosis and the evidence suggests that the condition is unlikely to be serious. In addition, by the time this point is reached, the child is at least one year old and has remained asymptomatic for that year. The persuasiveness of this message, however, is undercut by lingering uncertainties and measures taken to keep the patient-in-waiting under medical supervision. The geneticist does not unequivocally state that the child is "disease free." In a case of elevated phenylalanine levels, the physician summarized the patient as, "not sick, but he's not normal." Even if the child is discharged from the practice, the geneticist will state that their team is always available for consultation if needed, leaving open the small possibility that a complication may occur.

Seeing the opposite image in a gestalt picture, the majority of parents tend to obsess about the lingering dangers and downplay the qualified reassurances. Parents continue to watch their child carefully and incorporate the worst possible outcome as a contingency in their lives. For them, the child is the same as before and without a critical time period defined in advance, it is difficult to accept that the child is now out of danger. For example, a family had been in the habit of waking up their eighteen-month-old son with a mild case of MCADD in the middle of the night to feed him. When the physician found out that they were still waking him up, he tried to discourage them, stating that it is "optional" to wake the baby up, except when he is sick. In this case, the DNA test only showed one mutation, yet the doctor presumed that there was a second, unidentified mutation that would explain the elevated levels. Not only does this patient have, in the eyes of the geneticist, a benign condition but he also may have a mild form of it. In this family waking up the baby might also function as a strategy to keep the peace between husband and wife. At an earlier visit without the father, the mother confided that since her husband had learned of the child's MCADD, he did not trust anyone—including his own mother—to watch the baby. Letting the baby sleep thus would not only affect the parents' perception of their child's health but also the emotional tenor of their relationship.

The final test results often take months to obtain and by that time parents have incorporated a broad array of preventive practices in their lives. They have taken measures to offset the "real" disease, measures such as waking up the child during the night for extra feedings, distributing copies of the emergency letter, providing nutritional supplements or limited proteins and other foods, closely monitoring the child for developmental delays, accessing therapeutic services, routinely disinfecting eating surfaces, limiting play dates, and adjusting child-care arrangements. Taking the possibility of disease seriously can have far-reaching consequences for the parents' own lives: postponing a return to work or a move to a less well-medically serviced area, sticking with a job because of health insurance, changing social activities, and reprioritizing life. Often such changes are driven by fear: A survey of parents of children with urea cycle disorders showed that 50 percent of them thought daily about the possibility of their child's death, and three-quarters thought of it at least weekly (Cederbaum et al. 2001).

Consequently, parents may resist changes and, cashing in their acquired "cultural health capital" or the ability to engage health care providers on their terms (Shim 2010), plead their case based on lingering diagnostic uncertainty. At an observed visit for a family with a five-year-old daughter with 3MCC (3-Methylcrotonyl-CoA Carboxylase Deficiency), the geneticist would have liked to discontinue the supplements and the diet, but the parents were resistant. The geneticist explained his rationale for "liberalizing" the diet:

> All levels of scrutiny and vigilance can just be scaled back. We talked about this [in the past], but we were in a different place and different amount of knowledge. Most of the kids with this are going through life without any episode. Germany is not testing for this because they think that it is not in most instances a serious disorder. And certain U.S. states are going to stop. Our level of concern is reduced. (Observation notes April 2009, Family 46)

The father, however, turned the tables on the doctor by citing an article provided by the physician at a previous visit that stated that one should never relax the diet. The geneticist dismissed it as an opinion and noted that a more recent expert consensus recommended against a special diet for 3MCC. The father also insisted on taking further blood tests but the geneticist argued that the results would be difficult to interpret.

Diagnostic uncertainty about rare conditions is difficult to resolve because part of this kind of fundamental disease-based ambiguity is that there is no conclusive endpoint. Consequently, in most situations families ended up taking the condition more seriously than geneticists. There were a

number of families in our study that were exceptions to this general rule. In two Latino families, the physician took the condition more seriously than the parents. We suspect that in those families the doctor was unable to communicate the seriousness because of language barriers in spite of interpreters, but other structural and cultural factors may play a role (Grineski 2009). In one non-Latino white family, the father questioned continued follow-up after the physician had lowered the level of concern because he "felt part of an experiment" that risked turning him into a "hypochondriac." This father felt that the cascade of tests benefitted medical science but was no longer of use to his daughter. He noted that even if the DNA test turned up an anomaly, he would be very skeptical about the results. In fact, the test showed that his daughter had several mutations for SCAD deficiency. The parents were dismissed from the clinic after they failed to appear for three appointments.

DISCUSSION: LIVING BETWEEN HEALTH AND DISEASE

Newborn screening for biological entities with tenuous links to rare, poorly understood genetic conditions has created a population of newborns with suspicious biological measures. Physicians and parents have to determine whether these abnormal levels indicate a biological quirk or an actual disease, and, if a disease, what kind of disease. The trajectory of patients-in-waiting is characterized by mixed and ambivalent messages that signal either a biochemical anomaly or a very serious condition. The ambiguity ends when the staff determines that the results indicated a false positive after all, when sufficient time has passed without the emergence of symptoms, or when genetic markers or symptoms appear. Parents may end up at odds with clinicians because in their experience no clear benchmark of reassurance has been reached.

The question that remains is how unique this kind of prolonged diagnostic uncertainty is in contemporary health care. To answer this question, we propose a conceptual generalization (Glaser and Strauss 1967): an evaluation of the extent to which the characteristics we distinguished in newborn patients-in-waiting can be found in other populations. We noted that most of the literature on diagnostic uncertainty draws from people who experience symptoms that evade medical classification. The newborns we studied experience a different form of diagnostic uncertainty characterized by markers of disease in the absence of symptoms. Yet there are other recently distinguished groups that share this liminal experience.

The closest group of people similar to newborn patients-in-waiting are people who undergo genetic susceptibility testing for conditions such as breast cancer, thrombophilia, Huntington's disease, or Alzheimer's disease (Aronowitz 2007; Klawiter 2009; Konrad 2003; Lock et al. 2007; Saukko et al. 2006). They are typically presymptomatic or asymptomatic but may be at an increased risk for a condition. Presymptomatic patients are often detected through genetic technologies checking for susceptibility (Yoxen 1982). A second group of people who are neither sick nor healthy are those who suffer from "protodisease states" (Rosenberg 2007), conditions such as elevated blood pressure, high cholesterol levels, or obesity that once indicated contributing factors or symptoms but now are treated as incipient diseases. These conditions are also often expressed as a probability of being at risk rather than a true disease (Novas and Rose 2000). Another group consists of children with suspected developmental disabilities undergoing broad assessments to determine their eligibility for social services or medical care. The assessment findings remain contested and span a wide range of outcomes varying from normalcy to developmental delay to mental retardation (Leiter 2007). Comparing these groups with the newborns we studied allows us to refine the conceptual dimensions of patients-in-waiting and explain the persistence of this form of liminality in contemporary health care.

These different groups share at least four characteristics, and we suggest patients-in-waiting as a general concept for their common experiences. First, *patients-in-waiting inhabit a liminal state between sickness and health, or more specifically, between pathology and a state of normalcy*. Observational assessments, screening, and test results may hint at something awry but leave ambivalent whether patients-in-waiting are already sick, are going to become sick and, if so, what their sickness will entail. Like the newborns, all patient groups remain largely asymptomatic and they are preoccupied with the uncertainty of disease: "to be 'at risk' is to feel well, to be asymptomatic, yet always to be aware of the potential for becoming otherwise" (Scott et al. 2005:1870). In this kind of liminality, illness experience and medical diagnosis have been severed and people experience illness in spite of symptoms or a diagnosis. While in traditional medical encounters symptoms needed to be

reconciled with diagnostic categories, for patients-in-waiting health professionals suggest diagnostic categories in the absence of complaints. Yet the ontological status of the diagnostic categories is also unclear: Is hypercholesterolemia truly a disease or an underlying marker for a pathological process? As we showed for newborns, the sociomedical phenomenology of patients-in-waiting is thus defined by uncertainty, a rollercoaster ride between alarm and hope. Liminality is actively produced by the discrepancy between the typical diagnostic tools of medicine and the results that they are designed to produce. Rather than specificity, we find profound disease ambivalence.

While it may be true that all of us inhabit a hinterland between normalcy and disease (Armstrong 1995; Aronowitz 2009; Goffman 1963), for patients-in-waiting anticipation is no longer a hypothetical scenario. Our second point is that *patients-in-waiting face externally imposed uncertainty about the nature of disease*. Patients-in-waiting are a byproduct of health policies centered on secondary prevention to avert the progression of disease, avoid complications, and limit disability. Early disease detection is here instituted through the adoption of broad rather than disease-specific screening technologies that produce a wide range of results. Liminality follows from the trade-off between sensitivity and selectivity inherent to population screening; for every true positive case there are many more cases with uncertain results. The production of patient-in-waiting relates to the way screening and testing is implemented with shifting alliances between vocal patient groups, testing companies, and public health programs, combined with varying heuristic practices for interpreting results. The conditions faced by patients-in-waiting are iatrogenic in the sense that they result from health care policies aimed at identifying people in presymptomatic and asymptomatic stages. A geneticist in our study wryly referred to patients-in-waiting as the "collateral damage" of newborn screening.

Third, *the experience of becoming a patient-in-waiting is marked by a lengthy trajectory of medical gate keeping to establish or relinquish a diagnosis*. Protodisease states, newborn screening, disability status, and disease susceptibility originate in abnormal test results, which, as we showed in detail, trigger a regimen of repeated testing at regular intervals and meetings with health specialists. Medical surveillance with knowledge gaps reverses the established momentum in health care to dispose of patients by treating them efficiently (Berg 1992). Instead, Latimer et al. (2006) noted that when definitive tests are unavailable and diagnosis remains provisional, clinicians keep patients under medical observation for long periods. The clinic thus serves as a site of knowledge production, although fears of liability for prematurely discharging patients may also play a role in sustained contact.

The predicament of living in an in-between state reflects, paradoxically, the tremendous professional success in measuring and validating symptoms as indicative of bona fide diseases in order to give them therapeutic, bureaucratic, and social traction (Jutel 2009; Timmermans and Haas 2008). A specific diagnosis has become normative (Rosenberg 2007), although diagnosis is not as simple as applying preset categories. Diseases evolve (Aronowitz 1998): They depend on micro negotiations between professionals and patients, and the activities of macro actors such as pharmaceutical knowledge production and marketing (Greene 2007). Using established measures and incorporating categories in clinical practice guidelines or reimbursement procedures may temporarily reify diseases, but diagnostic uncertainty highlights the moving periphery of knowledge production. Diagnostic uncertainty is a form of categorical work (Bowker and Star 1999) that helps construct, refine, contest, and establish diagnostic categories. Some of this uncertainty is built into the disease frameworks under consideration; geneticists designing susceptibility testing emphasize that genotype does not predict phenotype (incomplete penetrance), and it is thus unclear whether people with higher susceptibility will actually develop diseases (Welch and Lurie 2000). Similar knowledge gaps plague mental health assessments (Horwitz 2003).

From the perspective of patients, diagnostic uncertainty does not lead to a repudiation of medical power. As Aronowitz (2009) noted in the case of false positive results from breast cancer screening that may have led to unneeded prophylactic treatment, "being given a cancer diagnosis and then having it taken away is experienced as a victory over cancer, leading to a greater sense of control over cancer and fears of cancer" (p. 428). Disappointment and resistance may follow, as we showed, when physicians declare that ambiguity points to health. Once suspicion of disease has been raised, the routine of medical checkups and the certainty of disease may be preferable over the lingering uncertainty of ambiguous pathology. These routines and checkups provide security that

the patient-in-waiting is under best available care. The state of sustained liminality manifested by profound disease uncertainty thus reinforces rather than undermines a medical interpretive framework. The exception is when diagnostic uncertainty may signal a deeply marked category such as mental retardation (Landsman 2005).

Fourth, and less clear-cut for the newborns, is that the position of a *patient-in-waiting may shape illness identity profoundly, leading to a shared if not always collectively expressed political consciousness*. Social scientists have been interested in how new technologies generate new patient populations (Casper 1998; Foucault 1978; Novas and Rose 2000; Thompson 2005). Screening technologies, in particular, have this potential to "make up people" (Hacking 1986), since they identify people who are at risk for diseases that may have crucial implications for their identities. Elevated cholesterol levels often serve as a wake-up call that health cannot be taken for granted: "with our increased diagnostic capacities, we have provided altered narratives for millions of people who might otherwise have lived out their lives in ignorance of nemeses lurking in their bodies" (Rosenberg 2007:70). Diagnostic uncertainty renders the organizing narrative of lives difficult to plot in light of broader cultural discourses (Landsman 2003). The extent of biographical disruption will depend on the stage of the life course—either as chronological age or life expectancy (Richardson, Ong, and Sim 2006)—and on the broader sociohistorical accommodation to disruptions (Pavalko, Harding, and Pescosolido 2007; Williams 2000). Still, even in an era characterized by "somatic individuality" (Novas and Rose 2000), test results are often only one signal to the self (Whitmarsh et al. 2007). As we noted, in newborn screening and in the assessment of developmental delays in children, these existential challenges to identity and selfhood are transferred to the family's projection of the normality of their child and their existence as a family unit.

Patients-in-waiting thus inhabit a liminal state between normalcy and pathology, imposed by medical screening and testing technologies aimed at secondary prevention, characterized by a lengthy process of medical surveillance to resolve diagnostic uncertainty, which may spill over into personal identity and other areas of life. Patients-in-waiting experience a declassification without reclassification (Gillespie 2009): No longer healthy but not really sick, they hover in an in-between state due to abnormal test results. Without illness experiences but with novel harbingers of disease, they experience the anticipation of a disease that they may never acquire. The sociomedical literature contains several concepts that capture some aspects of living between illness and disease. Konrad (2003), for example, writes about the "presymptomatic person," and Greaves (2000) about "partial patients," while Finkler (2000) refers to "perpetual patients." We propose patients-in-waiting as an umbrella concept to highlight the iatrogenic liminality between an unremarkable state of "normalness" and disease and to emphasize the patience required of those in waiting. The recent proliferation of patients-in-waiting follows from the incommensurability between the promise and capability of medical technologies and the still-salient motivation of the patient-doctor script centered around obtaining a diagnosis as a turning point in a medical visit. The gap between technological promise and expectation of a medical resolution creates a set of interactional dilemmas in which health care providers and patients-in-waiting feel an obligation to act yet the usual diagnostic roadmaps that order medical work are no longer relevant.

CONCLUSION

As newborn screening has been throughout the past 50 years, it is again a bellwether of the tremendous increase in information made available by genetic technologies. The pressing issue brought up by the expansion of newborn screening is how to manage this flow of information, some of it with little or indeterminate clinical value. While the technical acumen is available, some fundamental residual issues such as what actually qualifies as a genetic condition have been hardwired into the infrastructure and need to be resolved in meetings between geneticists and parents. The actions by genetic staff and parents as exemplified by a cascade of more and more definitive test results (if only by repetition), insurance reimbursements, changes in daily life, discussions at staff meetings, and tools such as emergency letters tentatively settles the social and biological properties in individual cases. While larger questions about the significance of the condition remain unaddressed, the staff's immediate strategy is to move cautiously without scaring the family, a very precarious balancing act. Once such precautionary measures are taken, parents find it difficult to scale back because the child remains asymptomatic and no clear marker of danger has passed.

We are thus witnessing how geneticists and families collectively and interactionally work out the social and biological properties of genetic anomalies under conditions of diagnostic uncertainty. This is an ongoing experiment imposed upon everyone involved. While we expect that with the collective learning curve fewer ambiguities will be confronted, at the same time, more conditions will be added to the screen, and each presents a new set of issues to be worked out. Other vanguards in this development are the many companies providing direct-to-consumer genomics to people for a fee, as well as the drive toward personalized pharmacogenetics. And as our conceptual generalization shows, genetic screening is not the only hotspot for patients-in-waiting. Patients-in-waiting will likely multiply with the normalization of biomarkers, new technologies such as full body scans, and patient activism around specific categories. The social significance of diagnosis has always been its functionality: the ability to structure medical encounters, institute health policies, shape life strategies, even control deviance. In the case of patients-in-waiting, this social significance has now been extended to those living between health and disease.

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Bios

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Mara Buchbinder is an assistant professor of Social Medicine at the University of North Carolina, Chapel Hill. Her research examines how families and health care practitioners collaborate to manage children's chronic health conditions. Her dissertation, an ethnographic study of a multidisciplinary pediatric pain program, considers how care for adolescents with chronic pain is articulated and organized in various clinical and family settings.