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Making the most of uncertainty: Treasuring exceptions in prenatal diagnosis

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ABSTRACT

Throughout the 20th century, human genetics research was driven by the identification of new variants. As pioneering geneticist William Bateson put it, novel variants were "exceptions" to "treasure". With the rise of human chromosomal analysis in the postwar period, the identification of genetic variants became increasingly significant to clinical and prenatal diagnosis. Human geneticists had long sought a broader sampling of human genetic variation, from a largely "normal" population. The expansion of prenatal diagnosis in the late 20th century offered a new resource for identifying novel genetic variants. In the prenatal diagnostic setting however, many of the exceptions to be treasured were of uncertain clinical significance, which raised anxiety among parents. In the early 1990s, providers reported that specific uncertain results from chorionic villus sampling (CVS) facilitated prenatal diagnoses that were not previously possible. Based on this, some prenatal diagnostic providers began to embrace uncertainty, when properly managed to reduce anxiety, rather than prevent it. The potential to produce uncertainty in prenatal diagnosis grew with whole genome microarray in the 2000s. Rather than outcomes to avoid, or accept as inevitable, providers presented uncertain results as starting points for research to improve the scope prenatal diagnosis, and bring future certainty.

In 1908, pioneering geneticist William Bateson offered this advice to his colleagues, "Treasure your exceptions! When there are none, the work gets so dull that no one cares to carry it further" (Bateson, 1908, 19). Bateson's career was enhanced by multiple genetic "exceptions", including a particularly notable anomaly that was called to his attention by physician Archibald Garrod around 1900. Garrod had seen an infant patient with alkaptonuria, a rare and largely benign condition that turned urine black. Together, Bateson and Garrod demonstrated that the condition represented a Mendelian recessive trait, an early example of this in humans. In this case, the exception to be treasured was of great interest to geneticists, while of little implication medically: the best of both worlds. In many other instances of genetic variation described over the next century, the exceptions that geneticists treasured were more consequential in the clinic.

After 1950, the study of human genetic variation increasingly involved the microscopic examination of chromosomes (cytogenetics). By the late-1960s, chromosomal analysis had become standard practice for examining putatively genetic conditions. This offered a significant influx of new samples for study: a windfall for human cytogeneticists, but one heavily skewed towards those with clinical disorders. Cytogeneticists believed that they needed a wider source of samples from healthy individuals to improve their understanding of "normal" and "pathological" variation (Brown et al., 1966; de Chadarevian, 2010; Lindee, 2005; Lubs & Ruddle, 1970; Santesmases, 2010). As I describe in this paper, bringing genetic screening to a broader population promised geneticists many new opportunities to identify exceptions to treasure.

Scholars have demonstrated that the clinic became an increasingly important site of knowledge production during the late 20th century for geneticists and molecular biologists, who were drawn by intriguing disorders, and the promise of uncovering new phenomena (Hogan, 2015, 2016; Keating & Cambrosio, 2001, 2003; Löwy, 1996; Morange, 2007). Throughout this period, clinical chromosomal analysis was a valuable experimental system for geneticists, which generated significant new questions for biomedical research (Rheinberger, 1997). While this situation was advantageous for many researchers, it also posed problems for the medical care of patients. The exceptions that geneticists treasured were often synonymous with the potentially anxiety inducing ambiguous results that many clinicians and their patients preferred to avoid.

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Efforts to detect and interpret new genetic mutations were central to late-20th century clinical practice. As sociologist Daniel Navon (2011) has described, genome wide analysis in children was frequently set in motion by a "phenotypic incubator" (11–12), such as intellectual disability. The identification of a potentially causative mutation from this analysis was frequently not the end of the diagnosis, but one part of and ongoing interpretative process. Physicians and geneticists were constantly developing novel disease models, which gave new meaning to genetic findings. They frequently acknowledged the initially uncertain clinical significance of many genetic variants, and were open to an ongoing reassessment of the implications and categorization of these potential mutations (Featherstone and Atkinson, 2012; Rabeharisoa & Bourret, 2009).

In contrast to child and adult clinical cases, the management of uncertainty in prenatal genetic diagnosis posed particularly stark challenges for clinicians. While the prenatal diagnostic process and its results often involved many shades of gray, the decision that women had to make was black-and-white: continue or terminate the pregnancy. Managing uncertainty in the prenatal context sometimes involved weeks, or even months, of delay and further testing in the hope of gaining more certainty. However, in the end, the choice remained the same, and had to be made under significant time constraints. In prenatal diagnosis, there was no opportunity for reinterpreting the implications of mutations over the years (Rapp, 1999; Rothman, 1986).

This paper is not about efforts to reduce the incidence of uncertainty in prenatal testing. Rather, it is about the embrace of uncertainty by some prenatal diagnostic providers, primarily teams of obstetricians and clinical geneticists working in academic research institutions. Instead of a problem to be avoided, I examine how these physicians and geneticists valued uncertain results as an important means for improving scientific understandings of human development and disease, which they believed could enhance the range and accuracy of prenatal diagnosis. I argue that, in the 1990s, a growing group of research-oriented prenatal diagnostic providers shifted their focus from improving the targeted prevention of a small number of high-risk disorders, such as Down syndrome and inherited diseases in carrier families, to facilitating the detection of many rare and unanticipated genetic disorders. Throughout this paper, I focus on efforts by these clinical teams to manage the clinical challenges posed by the identification of new and uncertain prenatal results, with the goal of greatly expanding the scope of diagnosis.

Scholars have highlighted many driving forces behind the growing uptake and diagnostic reach of prenatal testing since the 1970s, including the desire to prevent Down syndrome and inherited disorders, the introduction of non-invasive screening options, increased social focus on individual genetic risk and responsibility, and the corresponding potential for financial gain (Cowan, 2008; Lindee, 2005; Lippman, 1992; Löwy, 2014a,b; Markens, 2013; Remennick, 2006; Resta, 2002; Stern, 2012; Williams, Alderson, & Farsides, 2002). One factor that has remained largely unexplored is the interest of biomedical researchers in identifying new targets for genetic testing. Expanding the population of women that underwent prenatal diagnosis meant that more genetic data would be collected from a largely "normal" and healthy population, likely leading to the identification of new genetic variants. Some providers presented expanded prenatal genetic testing as a win–win for everyone involved. Parents received more information about the developing fetus, while biomedical researchers gained a wider exposure to human genetic variation. Providers recognized that results of unknown clinical significance would produce patient anxiety, and had to be carefully managed. Many were confident however, that embracing ambiguity in the present would generate more scientific knowledge, and greatly reduce prenatal uncertainty in the future.

1. Training for certainty

Ambiguous or unanticipated findings are common in all areas of medical diagnosis. Results often straddle the border between two or more categories, making it difficult for physicians to provide or agree upon a diagnosis (Bowker & Star, 1999). Testing may also result in "incidentalomas", unexpected findings that have different or broader health implications for a patient than initially anticipated (Wolf et al., 2008). Scholars have long been interested in how uncertainty is interpreted and managed in the clinical setting. Beginning in the 1950s, pioneering medical sociologist Renée Fox studied how medical students learned to cope with uncertainty. She explained that for physicians-in-training, what began as a bewildering problem of frequently encountering the unknown was eventually accepted as an inevitable part of medical practice. As she put it, "Students gradually evolved what they referred to as a more 'affirmative attitude' toward medical uncertainty. They became more able to accept uncertainty as inherent to medicine, to sort out their own limitations from those of the field, meet uncertainty with candor, and to take a 'positive, philosophy-of-doubting' approach." There were always going to be unknowns in medicine, and students learned to identify which instances of uncertainty resulted from the incomplete knowledge of their discipline, rather than their own. A significant component of medical education, Fox explained, was "training for uncertainty" (Fox, 1980, 7).

While young physicians inevitably encountered uncertain results during their training, sociologist Paul Atkinson suggested that they were still taught to believe in the potential for a certain answer. In a corrective to Fox's work, Atkinson (1984, 952) argued that medical students were instead "training for certainty", and learned to see medical problems as "puzzles" that had definite solutions. Their field may not have solved a particular puzzle yet, but medical students were trained to have great reassurance that an answer was out there. As Atkinson put it, "any 'uncertainty' can only temper an underlying faith and commitment to medical science, to the research enterprise, to the potential success of experimental techniques and so forth" (953). Medical training did not encourage physicians to be open to "existential doubt", but rather to maintain a "pragmatic empiricism" about uncertainty (954). In their "training for certainty" physicians inculcated the belief that, faced with ambiguous results, scientific study would always eventually find an answer. This approach to managing uncertainty, I suggest, later influenced these physicians when they collaborated with geneticists in basic research on clinical samples.

In this paper, I specifically consider the impacts of medical "training for certainty" on research-oriented obstetricians. I examine a shift in aims, after 1990, away from improving the detection and prevention of a few high-risk disorders, and toward treating all pregnancies as being at risk for disease causing genetic variants. Like other forms of medical risk assessment, prenatal diagnosis grew significantly in scope and uptake during this period, independent of advances in effective treatment options, aside from abortion. As historian Robert Aronowitz has described, risk interventions often spread in medicine based on a, "seemingly self-evident logic of identifying risk factors," and are broadly accepted because they appear to, "reduce fear and restore control," even when the results have no therapeutic value (Aronowitz, 2015, 10).

This paper focuses on the uptake of two new approaches for prenatal risk analysis: chorionic villus sampling (CVS) and DNA microarray. Based on their experience with the potential benefits of uncertain results in CVS, some obstetricians and geneticists developed a new narrative about the purpose and scope of prenatal