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Dr. Pangloss's Clinic: Prenatal Whole Genome Sequencing and a Return to Reality

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If there is an overarching theme shared by academic medicine and the social sciences it is this: context matters. No medical innovation can be effectively imagined, studied, evaluated, or applied outside of its social, political, and clinical context. Reading Wasserman and Chen's proposal from the perspectives of sociology, health services, and clinical genomics, we are particularly struck by the disconnect between their vision for unrestricted noninvasive prenatal whole genome sequencing (NIPW) and the reality of the healthcare environments in which prenatal care takes place.

The authors' proposal addresses the question of whether there are any constraints we, as a society or a medical profession, might reasonably place on the ability of parents to access genomic information about a fetus. They argue that allowing parents to be the ultimate arbiters of any and all information about the fetus they wish to receive is the most ethical and efficient solution under the following circumstances:

1. A genome-wide sequencing algorithm has been developed, in cooperation with 'professional groups', in which consensus has been reached about the threshold of analytic and clinical validity and penetrance for all possible genomic conditions that might be relevant to reproductive decision-making (Chen and Wasserman 2016, 12);
2. This panel is universally available and covered under all public and private health insurance plans (Chen and Wasserman 2016, 25);
3. This panel can be performed in such a way that the algorithm can generate a unique report that accommodates the unique requests of each set of potential parents for the return of only certain results (although a "generic panel" is also available) (Chen and Wasserman 2016, 19);

4. Prospective parents present for prenatal care early in the pregnancy in order to take advantage of the ‘additional time’ afforded by NIPW (Chen and Wasserman 2016, 2);
5. Parents watch, and absorb the contents of, a ‘mandatory’ presentation about NIPW’s capabilities (Chen and Wasserman 2016, 14) (pg 14) in which they are told that it is not be used to “indulg[e] their curiosity” (Chen and Wasserman 2016, 24);
6. They have access to, and sufficient time with, a prenatal care provider who is educated about NIPW and can discuss all the available conditions for which they might test and their implications (Chen and Wasserman 2016, 18);
7. They have time, access, and inclination to follow up on information about a wide variety of genomic conditions for which they might test (Chen and Wasserman 2016, 17);
8. In collaboration with their health care provider, they make a clear, informed decision about the scope of results they wish to receive.

In short, in order for the authors’ proposal to function, we must exist in a frictionless healthcare setting in which all concerns of scientific limitation and resource allocation have been removed. We agree that, in a setting such as they describe, there would be little, if any, reason to restrict parental access to the panel in question. It is also clear that in such a setting there are many other amazing—and infeasible—feats of prenatal (or, indeed, any kind of medical) care that we could accomplish. Unfortunately, there is significant evidence that such a utopia is unattainable for many reasons. Here, we explore a few.

The Science

There are unavoidable barriers to any discussions that might approach what the authors suggest. First, while the authors espouse faith in the ability of science and medicine to “intuitively” parcel genetic variation into neat and clear boxes, the reality is that neither genetics or genetic science appears to function in such a manner. It is axiomatic in clinical medicine to avoid ordering tests that you are unable to interpret; the reality is that we do not now, and may never, know how to interpret a whole genome sequence. The authors’ attempts to avoid this issue by calibrating by how “serious” each variant is does not represent a workable solution (and, indeed, directly contradicts their stated goals of avoiding a “eugenic agenda”). As a field, we have been attempting to classify genetic variation into basic compartments for years with little success in achieving any kind of consensus on the issue. Even the American College of Medical Genetics and Genomic’s attempt to identify a baseline of ‘serious’ or ‘treatable’ conditions was criticized on epistemological grounds (Burke et al. 2013). Among clinical geneticists, it is well-known that the pathological or benign nature of a genetic variant is frequently a matter of whom you ask. Our current clinical experience with invasive prenatal microarray testing has taught us the complexities of acquiring and applying complex genomic sequencing in a pregnancy (Bernhardt et al. 2013). Our experience with noninvasive screening for microdeletions using cell-free DNA is showing us the consequences of introducing uncertain genomic information into the

psychosocial and clinical experience of pregnancy. Neither provides encouraging examples for the kind of clear, measured, and infinitely customizable experience Wasserman and Chen envision.

The Costs and (Lack of) Regulations

While the authors eschew responsibility for detailing how such an elaborate proposal might be funded, the clinical reality is that sequencing will remain a high upfront cost for many, many years. This ignores the cost to develop and maintain the ‘decisional support’ the authors suggest, the cost in clinical time to counsel patients through the model, the cost to maintain clinician education around obscure genetic variants and rare conditions, the questionable rationale for insurance reimbursement for the procedure, and the downstream costs of the inevitable efforts to interpret and follow up on ambiguous results. We can envision no reality in which this enormous process does not exacerbate existing health disparities in prenatal care and maternal/fetal birth outcomes (Bryant et al. 2010). Devoting the massive resources required to support unrestricted NIPW and its follow-up costs would necessarily require deprioritizing other public health goals that are significantly more clinically necessary and ethically justifiable. We might reasonably strive for universal folic acid supplementation, an end to preterm births, universal pregnancy and neonatal care counseling and support, or many other things that would have an arguably more significant material impact on maternal and fetal health than would NIPW.

We are also puzzled by the highly regulated environment into which the authors seem to believe we will be introducing NIPW. The level of clinical conformity required to universally agree on a set of genetic variants, design counseling and decision aids around all of them, *require* patients to engage with those decision aids, and presumably deny them access to prenatal screening if they refuse seems completely out of sync with the reality of medical practice in the US. As just one example, the field has been conducting prenatal biomarker screening for decades and we still have no standardized protocol for timing and content; whether you receive a quad screen or a sequential screen, with or without an NT scan, or some other protocol, depends on some combination of your personal history and the clinic or hospital in which you are seen (American College of Obstetricians and Gynecologists 2007). Nor is this heterogeneity restricted to prenatal care; refusing to regulate the practice of medicine is a hallmark of the medical profession in the United States. It is unclear why and how we might achieve the authors’ vision of perfect compliance with a fixed prenatal care pathway.

The Sociology

The authors also elide any discussion of the logistical parameters of their hypothetical decision aid, beyond proposing that the ability to peruse it at home at one’s own pace will “alleviate anxiety and stress” (Chen and Wasserman 2016, 19). Again, as with any clinical intervention, context matters. Using an online decision aid at home at one’s own pace is only possible for highly literate parents with up-to-date computer and internet resources, and ample time. Doing it at a clinical office requires an extra trip and associated needs for childcare, time off work, and so on. In addition, the self-guided decision aid cannot remove

the time pressure of pregnancy and testing decisions. The “mandatory presentation,” plus the sample NIPW reports, the normative decision aid, and a database of genetic conditions, could easily take a highly-educated couple many hours to peruse, and would likely overwhelm a family with limited health literacy or other barriers (e.g., slow internet access or access only through a mobile phone) (Shieh et al. 2009). Such a decision aid will likely play into the longstanding “collective fiction” that prenatal testing can assure or improve the health of future children (Press and Browner 1993). We have very few prenatal interventions for genetic conditions, and virtually no empirical evidence that “preparation” or “planning” makes any difference for most conditions. Moreover, what this preparation or planning might consist of necessarily varies with the particular condition that is found, so it is nearly impossible to pre-emptively describe such preparation without painting it in such broad terms that prospective parents are likely to overestimate its utility.

Further, decision-making about rare genetic conditions has been poorly done since the beginnings of prenatal testing. Due to the difficulty of conducting research on private termination decisions, there is as yet little published evidence that parents are terminating for less severe conditions (e.g., sex chromosome aneuploidies), but stories from clinical providers and informal sources such as online discussion groups are mounting, especially since the introduction of cfDNA screening. And there are published reports of parents terminating after cfDNA results without diagnostic confirmation, despite clear clinical recommendations—indicating that many parents react poorly to the anxiety and time stress of decision-making about prenatal testing (Buchanan et al. 2014). The authors’ scenario also assumes perfect knowledge of the phenotype of a condition, knowledge which we know is deeply flawed not only among parents, but also among providers. Many parents have reported that providers have given them outdated and overly negative portrayals of how their child’s life would be affected by a genetic condition (Nelson Goff et al. 2013), and these reports likely stem from known limitations on the genetic education of typical prenatal providers and on their ability (due to billing and patient load) to research and properly counsel patients about a huge array of rare genetic conditions.

Conclusion

In short, from a philosophical standpoint, the manuscript’s argument leans far too heavily on the existence of certain real-world circumstances. From a clinical standpoint, it leans too heavily on the existence of philosophically idealized circumstances. As it stands, while the authors make token reference to the impediments to their proposal, they have given us neither a serious attempt to grapple with the ethical problems we are currently facing in prenatal genomic screening and testing nor a pure thought experiment that acknowledges the impossibility of implementation.

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