Drawing technical contrasts to address prenatal testing

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Destroy another fetus now
We don't like children anyhow
Leonard Cohen, The Future

Dance me to the children who are asking to be born
Leonard Cohen, Dance me to the end of love

Introduction: a technical contrast

Let's start by the beginning, that is with the middle. For a bit more than a year, I have been immersed in the middle of the GIGA biomedical research center, located in the University hospital in Liège. I happened to be around when a particular protocol was introduced step-by-step in medical practice, and this protocol carries forth non-invasive prenatal testing – NIPT, which most notably allows to detect Down syndrome — Trisomy 21. "Non-invasive" simply means that you do not need to take biological sample from the fetus itself but that you can get some information only by taking a sample of the mother's blood. So I thought I'd go along with NIPT and follow its introduction into the clinical setting.

As it turns out, NIPT is widely heralded as a great achievement of medical genomics. Much money went through the sequencing and assemblage of a Reference Genome under the aegis of the Human Genome Project, finally some medical applications come out of it! It is no wonder that a "milieu" where a university hospital is intimately associated with a large biomedical center

developed an early focus on genetics, then genomics, and now attempts to account for all the research carried forth. Not only is medical progress down the road, but also the fulfilling on somehow exorbitant promises that have been made before. As in many similar institutions of the civilized world, NIPT timely arrived to satisfy a thirst for *actual* medical genomics.

So please forgive me for sticking to the ground. I will not raise higher impacts or promises of medical genomics, nor will I impact directly the shifts and problems raised with respect to public health systems and solidarity. It's not that I don't care. Simply I do not wish to anticipate and jump too quickly into well-bounded and clearly defined sociological arguments. Instead, I would like to propose a *technical contrast* between the most routinized practice of amniocentesis, the "invasive" diagnosis as it were, and the "non-invasive" one that is the NIPT, so as to question how these technologies operate and what we can learn from it.

Weighing the stakes

But before I get to it, I would like to address the very sensitive, vital stake of prenatal testing, the famous "elephant in the room" Stefan talked about during his keynote speech: abortion. The deliberate termination of pregnancies. Of course, this has nothing to do, in my view, with a moral problem, but rather with a technical, pragmatic one: how to relate to unborn fetuses? How to confront the absence of these lives which will never come to being? In a beautiful text, William James raised the dramatic question: "is life worth living?". His answer was clear-cut: "life is not worth living the whole army of suicides declare" (*The will to believe*). It follows that no one holds a right to embrace or dismiss a singular life, as a value in itself, except for those who are ready to endorse the consequences of such a dismissal.

When it comes to fetuses, this creates a hole in the realm of the thinkable. It is a difficulty for someone like me who has been nurtured with relational ontology, i.e. an idea that human as well as non-human beings exist and consist through their multiple relationships and interdependencies (Cléo). This perspective somehow faces… an abrupt shortcoming, because abortion precedes the very possibility of the relationship. In a magnificent paper, "Inheriting from the incubator", Gabriel Dorthe reflects on his experience as a highly premature baby put into an incubator. With a lot of care, he unfolds the tenuous, precarious, fragile linkages between the newborn and the

surrounding technological apparatus, the controlled environment which aims at keeping him alive. Nothing like that much care and precaution is rendered possible by "null and void" existences. Yet, I would hate the idea that we are left with no other choice than naturalizing "abortion as usual" or, at least, rendering this harsh decision unproblematic.

Of course, this problem is not specific to NIPT. It is the problem of abortion in general, as the most dramatic consequence of prenatal testing. However, I think it matters to depart from this gap, this hole in the order of possibilities, to properly address what is at stake. Isabelle Stengers helps me out in order to get out of this dead end. She once wrote (my translation): "(…) we can't address ourselves to something so as to question its properties without engaging into a relationship with this thing. The demands associated with the relationship take a critical value as long as the thing which is being questioned is alive — biologists cannot or should not be able to elude the fact that they themselves are living beings" (in Combes 2011, p. 5).

So, how do we get in relation with living entities before they come into being? How do we address ourselves to fetuses? With Stengers, I would like to underline the importance of the modalities of the relation, as they technically play out in both amniocentesis and NIPT (no matter how these two technologies combine or exclude each other, it is not my point).

Drawing a technical contrast

Amniocentesis is a means of diagnosis which is qualified as "invasive". It is performed following an early testing tool called combined test. This test takes into consideration different risk factors through an echography and an analysis of some the mother's markers. If the combined test signals a risk, then amniotic fluid (about 20 ml) can be sampled, at the earliest by the 14-16th week of pregnancy. This sampling is performed directly in the amniotic sac which induces the risk of premature birth defect. Then the sample goes through a rather long process: it undergoes a cell culture process in the hospital laboratory. This cell culture lasts for about 4 weeks, by the end of which it becomes possible to stabilize the cells and stain them. This allows for looking at the actual chromosomes by optical means. That way, it becomes possible to optically detect whether the fetus bears a supernumerary copy of the 21st chromosome – which indicates that the fetus suffers from the Down syndrome condition or not.

By contrast, the NIPT diagnoses reaches this target by "non-invasive" means. But it gets slightly more complicated! As I said, with NIPT, the presence or absence of the Down syndrome will be detected from a sample of the mother's blood through so-called "Next-Generation Sequencing" — NGS. "Sequencing" is the name of the technique itself, I will get to it in a short while. In the mother's blood circulate fragments of the fetus' DNA which is known as "cell-free fetal DNA". But how to distinguish the mothers' DNA from the fetus' DNA?

The first thing you need to do is to enter that room of DNA extraction (pictures). The DNA must be obtained and purified through PCR techniques (polymerase chain reaction), which amplifies the DNA "signal" through a cycle of thermic operations (the biological sample is heated and cooled repeatedly). The substance resulting from this process is then positioned on a chip alongside a copy of the "reference human genome". How this "reference genome" was built and is regularly updated in new "builds" is in itself a story in which I will not dig deeper here. Enough is to say that current version of the Reference Genome, as released by the Genome Reference Consortium, is build 37 patch 13. You don't tell about humanism 2.0… This reference stands for the human genome in general; hence it is deemed to aptly represent the human as a unified species. This "reference genome" serves as a unified backdrop upon which you may contrast the singularities of the particular organism you are looking at.

What you want to detect is the presence or absence of a chromosomal "disorder", or "anomaly" that point out to the Down syndrome. It is not like it is possible to separate physically the mother's DNA, on one side, and the fetus' DNA on the other. The point here consists in detecting a *significant amount* of third copies of the 21st chromosome. If the mother is not affected by the Down syndrome, then it must be the fetus… (although it is not that simple since there can be cases of "mosaicism" where the mother bears some therapeutically insignificant chromosome anomalies). So what you will look at, here, is at a *frequency of repetitions, a number of occurrences, a threshold of supernumerary copies* of the 21st chromosome, which indicate with a fair reliability that the fetus probably bears the Down Syndrome.

[DIA] Carrying forth this contrast between the fetus' cell-free DNA and the Reference genome is the job of Next-Generation Sequencing techniques. To do that, you put your chip into the sequencer *per se* (show image: ho no, sorry, that one is six months old) and the sequencer will

literally “read” the chip, it will recognize a number of base pairs made of A, G, C, T [DIA]. At a first glance, “sequencing” looks like a “sequence” in an animated movie; you have picked up all your disparate drawings that lie on the floor, you have sort them out and then you try to order them so as to make something coherent out of this mess. But unlike an animated movie or a puzzle, with NGS you don’t really know the scenario in advance, nor can you embrace the result at a glance, because it is way too wide. How to proceed then?

[DIA] Among other processes, there are two tools in particular which intervene as operators to perform this relationship between the “reads” from the singular organism, and the “reads” of the reference genome. The first one is an software known as the Burrows-Wheeler Aligner (BWA) made of algorithms (http://bio-bwa.sourceforge.net/). BWA includes a “trimming algorithm”, i.e. a machine learning technique which roughly simplifies too complex results from a training set, by eliminating as much as possible insignificant data. This occurs through successive running decision trees which eliminate the options that have a low power of classification. That way, the “noise” is eliminated and the level of information deemed relevant raised accordingly. What comes out of it is referred to as “low-divergent” data. Passed this operation of conformation, reads after reads, it will inventory; what do we have here? It maps all the base pairs, grouping them into regions, constituting a territory. Then it compares with the reads from the reference genome so as to align them in the “appropriate” order. For each read, it seeks to correspond to the Reference genome.

Those successive operations are known as “data cleaning”, “mapping” and “aligning”. These are *geographical* in a sense; one needs to decide which elements will be deemed important to represent this territory that is the body, to draw a map to orient oneself and then adjust it to the reality, and to making sure that it fits. Except that here, it is impossible to come back to the body itself to check the proper adequacy of the map to the territory, because there is no way you can relocate physically all those reads from the sequencer in the mothers’ body or in the amniotic fluid. Instead, you will relate it to a previously known assemblage, more or less valid and robust, that is the reference genome — another map, in fact, but which has been obtained through so many consolidations that it can now be relied upon to provide the kind of contrasts NIPT seeks.

[DIA] The second operation consists in applying an analytical framework which enables sense-making out of this data. The GATK framework performs a sort of browsing tools. It has been developed by the Broad Institute, based in Cambridge (MA) and jointly hosted by MIT and Harvard. Depending on what you look for, it will allow you to seek and target specific elements in some predetermined "regions" of the genome. It provides a compass for the location of medically significant information. "*At the heart of the GATK is an industrial-strength infrastructure and engine that handle data access, conversion and traversal, as well as high-performance computing features. On top of that lives a rich ecosystem of specialized tools, called walkers*"[1]. One could not say more eloquently the need to explore that vast territory just rendered visible under the form of a map. It illustrates well that they wander around the genome territory, trying to find significant events, even though each of these tools has a specific way of questioning the genomic landscape into which they are immersed. In that sense, GATK takes bunches of single reads and attempts to relate them to the well-known population of reads that is the Reference genome.

After all this journey, of course, you need to make sure that all of this is included in a medical protocol which delivers valid results which you can assess, control, and so on, and this is a whole other story. But simply I wish to emphasize that, really, NGS techniques can be qualified as "*populational operations*" because of the countless moves they make back and forth between a singular organism and the reference genome of the human species. They select relevant reads, conforms them to a preexisting Reference, distribute and align them accordingly, drawing similar regions and allocating similarities and differences.

Conclusion: nothing changes but everything changes

So now, how to characterize these two modes of knowledge production, aka how to compare those two different ways of relating to the unborn?

[1] https://www.broadinstitute.org/gatk/about/.

Amniocentesis is addressed to a fetus: do you bear the Down syndrome condition? The stake is: to determine whether a fetus itself bears this condition or not.

NIPT is also addressed to a fetus but the question is at all different: how do you relate to a population? So this question constitutes "population" as a mandatory passage point, both as a reference standard and as its local declination. The stake is: to detect an anomaly, i.e. a threshold of chromosome depletions which differs from the standard in the population.

This locates the trial at a whole different level; amniocentesis put each singular organism itself to trial (in terms of optical detection), while NIPT integrates singular organisms into a broader frame to which it needs to adjust statistically speaking (in terms of threshold);

In so doing, NIPT establishes a background upon which a contrast can easily be drawn in the case of Down syndrome (bioinformatician: could find it with gloves). But the infrastructure makes a detour by the Reference genome to draw its contrasts, and therefore opens up a space through which many more potential information on the fetus could be gathered. Potentially.

The consequence is that we move from a situation of scarcity with the information provided by the organism, to a situation characterized by the *wealth of potential information*. I'm tempted to say that, currently, it doesn't matter if indeed this potential information is rendered actual by further prenatal testing protocols or next next-generation tools. In the here and now, it simply matters that such a potential space lies wide open.

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