The Controversial Molecular Turn in Prenatal Diagnosis

CGH-array Clinical Approaches and Biomedical Platforms

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Abstract: How and why are new gene-array techniques, which have been successfully introduced in medical contexts such as "post-natal" genetics, marked by uncertainty and dispute when they change context and are used in prenatal medicine? The so-called "molecular turn" in prenatal diagnosis has created a controversy that still divides the genetic community worldwide. The availability of an increased variety of high resolution-genetic data, including uncertain findings, divides the genetic community regarding production, treatment, and articulation with the older technologies, cytogenetics. Drawing on the methodological and conceptual framework of the "biomedical platform" (Keating and Cambrosio 2003), this paper intends to analyse these new biomedical molecular entities in the space where biology and medicine, science and technology, innovation and routine are intertwined. Empirical data from an ethnographic thick description of the intense debate that took place between Italian geneticists is used to analyze the different ways in which the material and immaterial elements of these platforms are organized. The different positions that emerge from the debate are traced back to two positions regarding the overlapping of biomedical work, technology transfer and research. This case study does not only reconstruct the fast-paced advancements of genetics in prenatal medicine, but also sheds light on the important questions at stake in structuring the expansive movement of molecular biomedicine.

Keywords: genetics and society; prenatal diagnosis; molecular turn; biomedical platform; biomedicine and innovation.

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I. Introduction: The Establishment of a Biomedical Platform

The development of biomedicine seems to be reflected in an increased interaction of biological research, technological innovation and medical work (Gaudillière 2002; Clarke *et al.* 2010; Keating and Cambrosio 2012). The recent introduction of Comparative Genomic Hybridization array (CGH-array henceforth) technology has intensified these exchanges even in medical areas such as prenatal diagnosis, i.e. the detection of congenital molecular anomalies in the foetus. Prenatal diagnosis used to adopt a different technique, cytogenetics, disconnected from the rapid advancements that molecular genetics has seen the last three decades. Dating back to the beginning of the 20th century, and developed without substantial successive changes in the seventies, cytogenetic procedures are based on the analysis of the most visible cellular elements that carry genetic information, the chromosomes. This technique was the disciplinary standard until recently, and is still used in many settings for prenatal diagnosis. Only recently has cytogenetics been partially or even totally replaced by new molecular procedures, which allow for a much more sensitive investigation of Dna sequences. This shift is part of a larger trend, due to the rapid advancement of molecular genetic techniques and knowledge, usually defined as the "molecular turn". Several research projects have tracked the effects of this shift in clinics, in terms of the expansion of care-subjects (from individuals to families), and the shift from symptomatic disease to a-symptomatic risk, and so forth (see e.g. Conrad and Gabe 1999; Cunningham-Barley and Boulton 1999). Although these observations parallel our case study, they tend to revolve around the "diffusion model", according to which technological transfer is a linear and universal process articulated from a scientific discovery to its industrial application and, eventually, to the impact on society, deemed as an empty space endowed only with a variable capacity to resist or accept technology (Latour 1987; Bijker 1995; Akrich and Callon 1988a; 1988b). Other more recent approaches from Science and Technology Studies have recently criticized the monolithic conception of the evolution of genetics. Some authors have shown that genetic tests are not immutable and self-confined tools, but are moving entities with no "pre-defined" content (Palladino 2002; Parthasarathy 2005). In a similar manner, the socio-historical narrative of the introduction of molecular techniques in the medical domain is presented here not as part of the general evolution of biomedicine, but rather as an overall reconfiguration of biomedicine characterised by multiple and tiny imbrications between laboratories and clinics produced at the intersection of innovation, work and research.

The theoretical and methodological framework of "biomedical platforms" (Keating and Cambrosio 2003) addresses the contemporary cross-fertilization that has occurred between medicine and biology since the

Second World War, by focusing on its epistemological and organizational shifts. Drawing on the French original meaning of *platte-fourme* (literally "flat-form"), a "biomedical platform" is defined as the material support on which the new regime of production and regulation of biomedicine can be arranged and connected. In so doing, these theorists provide a pragmatic perspective on biomedicine as a new space where new biomedical entities bridge the gap between the qualitative, synthetic clinical evaluation of the pathology, and the quantification of biological variables:

> biomedical platforms [are] material and discursive arrangements that act as a bench upon which conventions concerning the biological or normal are connected with conventions concerning the medical or pathological.
>
> (Keating and Cambrosio 2003, 4)

Instead of assuming a paradigm-ordered or theory-driven analysis of biomedicine, this pragmatic stance resorts to the constitution of laboratory-clinic relations as enabled by the mediation of material and discursive objects, such as protocols, reagents, instruments, procedures, representational spaces, clinical indications, etiologic accounts and scientific categories. These elements constitute the material and discursive infrastructures where new biomedical entities are mobilized. The material organisation of their various parts, which "do not need shared understanding in order to operate, but just consistency" (Keating and Cambrosio 2003, 15), are thus intertwined with the epistemological production of knowledge. At this point a second significant aspect of biomedicine emerges: the continuous monitoring of patients' physiological variables in relation to environmental stresses on the human body. This trend towards the increased production of health-data implies new connections with the industrial production of instruments that "move the problem of automation out of the sphere of pathology and human judgment into the sphere of biology and quantification" (Keating and Cambrosio 2003, 60-61). In synthesis, this perspective insists on dissecting the well-accepted oppositions not only between biology and medicine, but also between science and technology, innovation and routine.

These are some of the reasons why investigating the development of new genetics seems so pertinent. Studying the expansion of predictive genetic diagnosis and testing for cancer after the discovery of the two susceptibility genes for breast and ovarian cancer, Brca1 and Brca2, Pascale Bourret (2005) investigated the implications for clinical work. New forms of collaborative, multidisciplinary activities cross professional skills and specialties as well as laboratory and clinical data and tools, and they constitute what she terms "bio-clinical collectives". Recently, this concept was expanded and more specifically applied to investigating how both genetics and clinics work together to give clinical meaning to new syndromes and pathologies. Accordingly, their interactions shape the very

content of work, which consists in "simultaneously producing the clinical relevance and the biological significance of mutations" (Rabeharisoa and Bourret 2009). The endogenous elaboration of these new bio-clinical entities results from the production of evidence derived by their mobilization in a clinical context. In some cases, the nosological explanation of a pathology is derived from a genomic anomaly, and not from clinical symptoms. Daniel Navon (2011) has recently established the concept of "genomic designation" to indicate syndromes and diseases that did not exist before molecular analysis. An even clearer example of this trend is the attempt to isolate genetic entities that are considered "actionable", i.e. that can be articulated through current protocols, procedures, treatments and clinical interventions (Nelson *et al.* 2013).

In this sense, the molecular turn of prenatal diagnosis provides a valuable fieldwork, in that it offers the possibility to scrutinize the establishment of a biomedical platform marked by uncertainty and controversy. Even if the CGH-array technique has already been set as the gold standard of other clinical practices, such as in the post-natal diagnosis of psychiatric impairment or other congenital syndromes, its application to prenatal diagnosis has raised issues that have not yet been settled. This dispute, which divided the medico-scientific community over the world, as well as, remarkably, the two most important medico-scientific societies on the opposite shores of the Atlantic (Eca 2012; Acog 2013), is multifaceted and shifts according to the perspective assumed.

In the scientific literature, the quarrel is presented in a rather abstract fashion. Not accidentally, the main issues that emerge concern the war of numbers instead of the actual increased detection rate in molecular procedures as compared to cytogenetic ones. An exact evaluation is also complicated by two factors. The first regards the uncertain clinical meaning that characterizes the new biomedical entities mobilised by CGH-arrays, i.e. the "sub-microscopic anomalies". The sensitivity of CGH-arrays is so high that not all of the detected genetic data is necessarily clinically encoded. Technically they can be called "variants of uncertain significance" (Vous). The second factor regards CGH-arrays limitations, as compared with traditional cytogenetics. While producing more quantitative genomic data, CGH-arrays are blind to so-called "structural or balanced anomalies", which are however very rare and usually not related to a genetic disease or syndrome. Amazingly, if we turn our attention to the exchanges within the geneticists' community, we find totally different arguments. The different positions refer not so much to scientific justifications, rather to matters that are strictly organizational and professional. The Italian controversy provides a good framework with which to analyse the process of organizing and fine-tuning this new biomedical platform, because it provides a case study that is, both representative of many other settings and specific. On one hand, the final statement of the Italian Society of Human Genetics (Sigu, Società Italiana di Genetica Umana) reflects, as we will see later in detail, the position that was also assumed by

the European Cytogeneticists Association (Eca). On the other, the Italian debate assumed decidedly heated tones and drew widely on arguments of extra-scientific nature, as each side implied that opposite party position lied about economic and professional interests. This situation, thus, gave a symmetrically opposite perspective than that provided by scientific literature.

This paper intends to reject both positions as two different reductionist versions, based respectively either on a purely epistemological evaluation of a technique, or on economic or professional interests. Building on the conceptual framework of biomedical platforms, the epistemological status of the "sub-microscopic anomalies" produced by CGH-arrays is strictly connected to organisational arrangements. In other words, the production, circulation and interpretation of these new biomedical entities requires a multi-layered biomedical platform which involves intimate and dynamic connections between equipment, tools, concepts, medico-scientific guidelines, biotech companies, databases, health services, and so forth.

So far, interdisciplinary collaboration and bio-clinical collectives have not particularly addressed prenatal diagnosis, even if it is one of the first, and still remains one of the most important, applications of genetics in the medical routine. In prenatal medicine, the cytogeneticist works in isolation, without the possibility to triangulating genetic findings with "non-genetic" information of the same level of reliability, and at best handles the diagnosis communication (Turrini 2011). This clear division between the laboratory and the clinic is partially comprehensible due to the nature of the test-subject, the fetus. The subject is in a movement of rapid change, not fully developed or organically autonomous (i.e. healthy in the common sense). In addition the subject is located in the womb, where the clinical observation is clearly difficult. The only obtainable phenotypic information is anatomical measurements obtained by ultrasound visualization technology. Given that the clinical observation provides little and uncertain data on the fetus, cytogenetic analysis has to and actually does provide solid data, on which important clinical decisions are made. Aside from the rare cases of surgery on a fetus (Casper 1998), the only available practice after the diagnosis is the voluntary interruption of the pregnancy. Genetic counseling is offered only in case of a positive result that indicates the presence of a given pathology, and, since the most common anomaly that this technique detects is the well-known Down syndrome, even physicians without a specialty in genetics may communicate the diagnosis. Afterwards, the pregnant woman or couple is then often left to their own resources regarding their decision.

The advent of a molecular technique such as the CGH-array has dramatically changed the practices of prenatal diagnosis under many respects. The doctor-patient relationship explodes into a complex constellation of elements. Genetic counselling becomes mandatory before any examination due to possible uncertain outcomes. Likewise, any referral of

the anomaly requires a consultation with international databases, and, therefore promotes a tighter interface between pre-natal and post-natal diagnosis by collecting and correlating genetic anomalies detected in individuals before and after birth. Further, the relationship with research as well as with biotech companies grows more dynamic, as equipment is constantly advancing to keep pace with the ever-increasing amount of new diseases and the ever-higher sensibility needed to detect them. The last point, indeed, emerges from our analysis as the crucial bone of contention, in that it affects the way in which to locate and organize submicroscopic abnormalities.

After an introductory section on materials and methods, and a brief explication of the aforementioned process, we will expand the description of this emerging biomedical platform through a discussion of the scientific controversy. First, we will indicate the general terms in which the technology is presented in scientific literature, and, second, we will look closer at the Italian debate. In the final section, we will analyse the controversy in terms of two different ways to conceive and organise the biomedical platforms, by focusing in particular on the important relationship with technological transfer and biomedical research.

2. Materials and Methods

The methodology adopted combines the analysis of scientific literature with the more traditional methods of qualitative research, like in-depth interviews and ethnographic observation of laboratory practices. More precisely, we collected all of the relevant literature on PubMed that had a title and abstract related to "array comparative genomic hybridization" and "prenatal diagnosis". After reading the abstracts of the 143 results, we have selected those that have been considered the most relevant articles from a clinical point of view. They include, for example, two special issues that two important journals, "Human Mutation" and "Prenatal Diagnosis", devoted to this topic in 2012, entitled respectively "Focus on Cnv detection with diagnostic arrays" and "New Cytogenetic Technologies in Prenatal Diagnosis".

Beyond the scientific literature, we also gathered the position statements and guidelines of the most important US, EU and Italian medical-scientific societies: The American College of Obstetricians and Gynaecologists, Acog, and the already mentioned Eca and Sigu. We conducted extended, and in some cases multiple, interviews with 16 geneticists (either biologists or physicians) from nine different clinics (all Italians apart from one, in Austria). In order to reconstruct the development of this technique in Italy, we addressed both the "core group" involved in the Italian debate, and those involved in the research aimed at the establishment and validation of CGH-array technology. Regarding the Italian controversy, I

was able to reconstruct parts of the Cytogenetic Working Group of Sigu meeting in which the dispute broke out, as well as the criticism that followed, through the testimony of individuals present at the event. We also gathered the opinions of those who, after having worked for several decades in cytogenetics, saw their expertise (and therefore jobs) threatened by the molecular turn. In this case, the intergenerational separation between older practitioners, and those who started their career in the mid-2000s with CGH-array research, is clear. We selected three different groups of professionals: first, young researchers who have worked at least for several years of research in Italian health service as Ph.D. students, post-docs or with other forms of research funding; second, directors and managers of genetics departments, or big laboratories who handle the process of clinical genetics; and third, older cytogeneticists. We supplemented this aspect with the direct observation of genetic laboratories in order to unpack how CGH-array works.

3. The Molecularization of Clinical Genetics

The introduction of molecular instruments in clinical genetics represented a radical alternative to traditional methods encompassed by the family of cytogenetic practices. Up until a few years ago, these two kinds of genetic methods were complementary. Whereas the older cytogenetic techniques gave a broad overview of the entire set of chromosomes, the molecular techniques, like Pcr, were used to detect specific targets with a higher sensibility. In the 21st century, this distinction became obsolete with the development of new molecular, high-throughput (hyper-fast) techniques like CGH-arrays and Next generation sequencers, which can produce an overview analysis of the whole genome at a high-resolution.
Cytogenetics was the only technique able to obtain an overview of the whole chromosomal set and therefore the most used technique in clinical genetics. However, it is a rudimentary and artisan discipline, essentially based on manual manipulation and microscopic diagnosis. It is a residual exception on the verge of extinction in an era when most clinical testing has become more and more automated or "high tech". It is not by chance that its craft-like practices have recently captured the attention of several social scientists (Rapp 1999, 193-222; Martin 2004; Turrini 2012). It is a long and articulated procedure that consists in arresting the cell cycle during the metaphase, just before the process of division, when the chromosomes are most visible, and then fixing them on a slide and banding them. In addition to being more time-consuming, this procedure requires the counting and analysis of the chromosomes under the microscope. The width, brightness, and the arrangement of the stripes – *bands* according to the laboratory vernacular – constitute the specific appearance by which each chromosome can be recognized by peering into microscope.

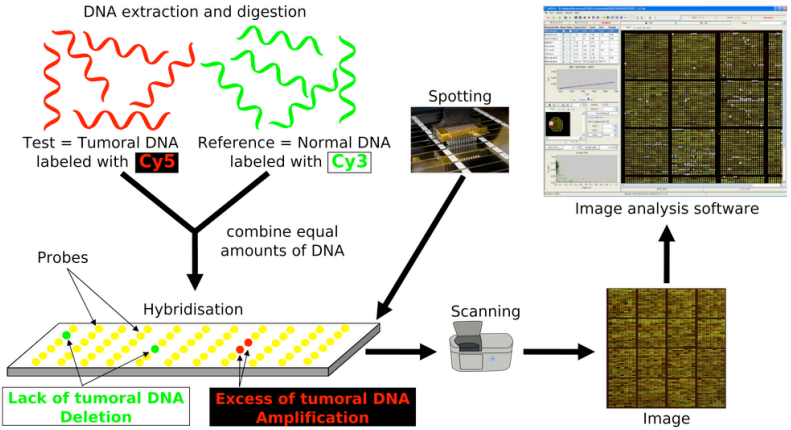

Fig. 1 – CGH-array protocol (source: Emmanuel Barillot, Laurence Calzone, Philippe Hupé, Jean-Philippe Vert, Andrei Zinovyev, *Computational Systems Biology of Cancer,* Chapman & Hall/CRC Mathematical & Computational Biology, 2012).

Comparative genomic hybridization is a technique that was developed at the beginning of the 1990s in the field of clinical research on cancer. Its principle action is to compare small fragments of a genome sample to the same fragments of a "reference sample" deemed "normal" and, thus, see if there are extra or missing pieces of genetic material. At the end of the 1990s this technique was conducted by Dna microarrays. The arrays allowed for a visualization beyond the "metaphase plate", in the "digital space" of a matrix, in which each square corresponds to a specific chromosomal region, according to the library of cloned Dna fragments with known locations throughout the human genome that was produced by the Human Genome Project. In practical terms, in CGH-arrays, Dna is chopped into thousands of shorts sequences (called "probes") that are then labelled, coloured, arranged on a slide with a precise grid (it is called a "biochip" for that reason), and finally compared with probes of a different colour from a reference sample. The resulting gains and losses of chromosomal material are read by a scanner, which provides an analysis as broad as cytogenetics but with a definitely higher resolution that is automated and fast.

While cytogenetics produces chromosomes analysed by the human eye under the microscope (fluorescent or not), the CGH-array produces signals that are automatically read by an electronic scanner. In describing this innovation some geneticists use a telling geographical analogy. If the images of chromosomes produced and analysed by cytogenetics are com-

pared to a traditional map of any given country level, then the maps produced by the biochips are a sort of Google Earth that permit us to zoom-in down to street level. To make things still clearer, the image in figure 2 compares a *conventional chromosome* as it appears through microscope and a *digital chromosome* image from an array.

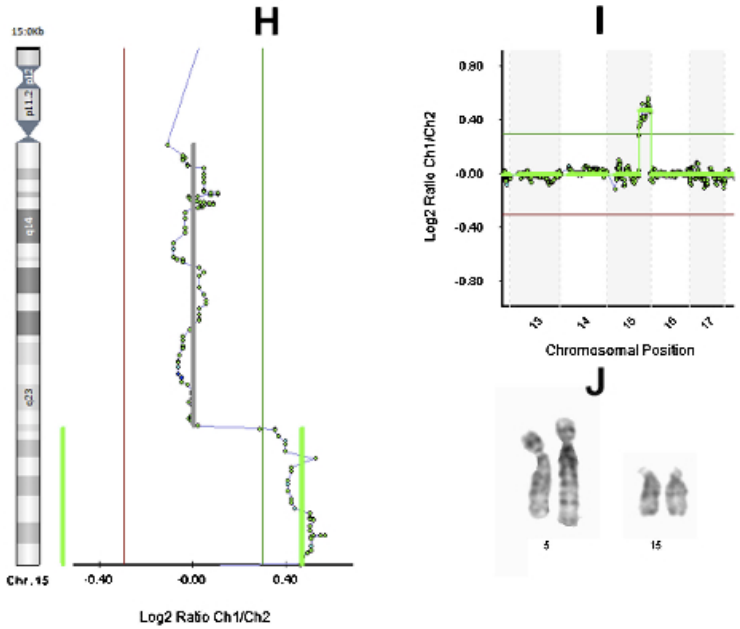

Fig 2 – Digital and conventional chromosomes (Fiorentino *et al.* 2011)

The molecularization and digitization of genetic analysis has several advantages over traditional karyotyping, in that it allows for the detection of thousands of genetic variations, up to one hundred times smaller than those that can be detected by peering into the microscope, in an automatized procedure. Thanks to the detection of these *sub*-microscopic alterations (technically called micro-deletions, micro-duplications, and so forth), new syndromes have been coded, or genetically re-coded.

This is one of the primary reasons why genome-wide arrays have quickly become the primary tool of chromosomal evaluation in certain medical areas, such as oncology. They have also significantly improved "post-natal" diagnostics with respect to conventional karyotyping for children with developmental delays, intellectual disabilities, multiple congenital anomalies, and autism. This led to an international consensus statement according to which gene arrays technologies *should* be used in

the diagnostic workup of such patients (Miller *et al.* 2010), and, as a result, more laboratories are now introducing biochips as the first-tier testing technique. Although this has had a deep impact in the classification of syndromes (Navon 2011), it has raised no controversy within the genetic community.

Due to the reasons we briefly summarised in the introductory paragraph, things are more slippery in prenatal settings, where questions regarding certain aspects of clinical implementation still remain unanswered.

4. A Special Challenge. The Scientific Debate On CGH-array

Biochips were first applied to a clinical practice in the US in 2006 (Shuster 2007). In the same period, genetic laboratories all over the world were experimenting with this technique in clinical practice. Yet, after almost ten years of practice and experiments, the usage of biochips in prenatal diagnosis still raises many issues. In 2011, when array technologies had already replaced conventional karyotypes as the standard for genetic diagnosis after birth, the International Congress of Prenatal Medicine of Amsterdam at "a very well-attended debate" discussed whether CGH-array could be considered as a replacement for this routine testing in the near future (Bui *et al.* 2011, 235). This article intends to look at the reasons for which the use of arrays in prenatal diagnosis is still considered "a special challenge" (Vetro *et al.* 2012), to paraphrase the title of an article written for the Genetic Services Quality Committee of the European Society of Human Genetics by a large group of geneticists working in six different clinics.

In the scientific literature this controversy revolves around *the war of numbers* over the effective rise of detection rates brought about by the passage from cytogenetics to the CGH-array. Findings vary, but in general there is agreement regarding the advantages of biochips over traditional cytogenetic techniques (see. e.g., Wapner *et al.* 2012). What make the assessment of the actual gain provided by the CGH-array so difficult to assess, is, first and foremost, the issues that the increased quantity of results produced by CGH-arrays pose in terms of clinical interpretation. Even if cytogenetic procedures also produce some uncertain results, molecular instruments drive this uncertainty to an extreme, in that some of these results are beyond the current comprehension of genomes. The different methods for organizing the introduction of CGH-arrays for prenatal diagnosis depend on the different approaches to the so-called "variants of uncertain significance" (Vous). The assessment of the actual limitation of CGH-arrays, as compared with traditional cytogenetics clinical definition of the anomaly, also contributes to rendering the assessment of

effective gain provided by the CGH-array even more difficult. While producing more quantitative genomic data, CGH-arrays are blind to some kinds of anomalies. These anomalies may be defined as out of place Dna fragments, derived from the movement of a filament piece from a chromosomal region to another. Since arrays read genomes resulting from a cut and copy process, they cannot detect those anomalies, but only those due to either a gain or a loss of Dna. Similar problems can be found regarding another kind of genetic abnormalities, mosaicism, i.e. the presence of two or more populations of cells with different genotypes in one individual.

Some papers on the debate tend to polarise these different positions into two practical options regarding the introduction of CGH-array in prenatal diagnosis. For some, the use of molecular instruments should be restricted to pregnancies that are considered "high risk" based on observed ultrasound abnormalities, or as a second-tier test to confirm and characterise those chromosomal anomalies that resulted from conventional cytogenetic analysis. For others, this type of test should be provided indiscriminately to all pregnant women who seek invasive prenatal testing, as the universal, primary tool of genomic evaluation of the foetus. Besides the war of numbers, ethical and regulatory issues are mentioned in these debates. They refer first and foremost to the elaboration of new strategies to inform pregnant women or couples about such a test that produces a vast and sometimes incomprehensible amount of information. In any case, beyond this debate, what is really at stake in practical terms is two different ways of arranging the biomedical platform of one of the most important clinical genetic practices in quantitative terms.

In this regard it is important to recall the socio-economic dimension of this phenomenon. The first medical practice to bring genetics to the public, prenatal diagnosis is still nowadays one of the genetic practices with the most experience in the clinics[1], used on over one hundred thousand pregnant women a year in Italy alone. These different approaches, which can be summarized as either indiscriminate use or the use as a second-tier test, have a deep economic implication and are dividing the genetic communities all over the globe. The strong discrepancy between the last guidelines of the American College of Obstetricians Committee on Genetics (Acog 2013), which changed its position from the previous ones (Acog 2009), and the Europeans Cytogenetic Association (2012) lies just in that choice. The former is in favour of a total replacement of cytogenetics with gene array technologies, which would then be used as a first-tier test, while the latter is in favour of partial use only, just for at-risk cases. The Italian controversy tellingly counters this perspective on the debate by providing a diametrically different one.

[1] Nowadays, genetics techniques as applied to the study and treatment of cancer are rapidly expanding, and are undoubtedly the most promising sector of genomics both from a clinical and economic point of view.

5. The Italian Controversy: Socio-economic Interests and Technology Transfer

While scientific literature has focused on the technicalities of gene array technologies in terms of diagnostic sensitivity, in the Italian scientific community this dispute has taken a decidedly animated tone, which is more focused on socio-economic aspects. There are undoubtedly structural reasons behind this controversy. It suffices to mention here that genetic laboratories are fragmented, often of small or even tiny dimensions. A recent survey counted over 160 laboratories (Dallapiccola *et al.* 2006). This number includes private laboratories, many of which operate on a larger scale (including Toma in Busto Arsizio (Va), Genome in Rome), and also respond to the demand of public structures, mostly of small dimensions.

In any case, the controversy arose almost by accident, after a meeting of the Sigu (the Italian Society of Human Genetics) Working Group on Cytogenetics, in which they attempted to re-elaborate the guidelines for the use of the CGH-array. During the meeting that took place on April 7 2011, a clear majority position emerged which desired to limit these techniques to subsequent diagnostic investigation, and consequently, to discourage the hasty replacement of traditional procedures. Dissenting voices were raised. In particular a private laboratory that was betting on CGH-arrays, involved in research aimed at evaluating its benefits among other things, railed against this measure. The aim was to produce empirical results regarding the usefulness and reliability of the CGH-array-technique in prenatal diagnosis. In practical terms, this would mean switching to an analysis procedure that examined biological samples "in parallel", making use of both the traditional cytogenetic techniques and those of molecular genetics, so as to be able to compare the results of the two. The research had by then reached a conclusive stage and the results, which would be submitted one month later to an international scientific journal (Fiorentino *et al.* 2011), seemed encouraging. The representatives of this facility rejected this prudent attitude, and proposed a chromosomal array approach as first-tier approach for all pregnancies. During an animated correspondence that took place immediately after this meeting in the mailing list of Sigu Working Group between these two positions, an advocate of the immediate and indiscriminate application proposed to initiate a large-scale multi-centred study involving the most important Italian centres, and thus creating prestige for Sigu.

The position that was agreed upon, however, was decidedly more cautious. The introduction of gene array technologies for prenatal diagnosis thus became the central issue of a bitter dispute that seemed to divide critics and advocates of this innovation. On one hand, Sigu reiterated its

cautious attitude first in a public document in Italian, distributed amongst its members, and then in a position statement, that is the public stance of a scientific society, published in an international scientific journal. As from this last document: "we recommend the use of Cma [*chromosomal microarray analysis*] in prenatal testing: 1) never as a substitute for conventional karyotyping; 2) for specific diagnostic purposes in selected pregnancies and not for general screening in all pregnancies" (Novelli *et al.* 2012, 386). This approach echoes the European Association of Cytogenetics guidelines, which were published in those same months (Eca 2012).

On the other hand, the private Italian laboratory's adverse position did not subside, if anything, it intensified. In addition, in virtue of the positive results obtained by the previously mentioned research, the company definitively abandoned cytogenetics in favour of chromosomal array analysis, which was then used as the only first-tier test for all women undergoing invasive prenatal tests. Their dissent was then expressed in an official manner through a "correspondence" (e.g. letters sent to a scientific journal to distance oneself from one of its articles) in which the Sigu position statement is described as anachronistic and ignorant of the most recent results that have emerged from research. A group of geneticists from the National Taiwan University Hospital intervened in support of this critical position, signing a second "correspondence" in the columns of the same magazine. In these letters, we find a discussion that rests on arguments that are quite similar to those mentioned in the previous section on scientific literature. The subject of discussion is the manner through which to objectively evaluate the actual detection-rate increase of the array techniques in light of the loss of certain types of data and, above all, the uncertainty of some of the results. However, as we have mentioned, what is at stake in practical terms is the way in which to arrange the biomedical platform of one of the most important arenas in quantitative terms.

If we turn our attention to the exchanges between the more prominent members of this controversy, we find not only decidedly heated tones, but also reasoning of entirely different nature. The different positions refer not so much a scientific justification, as to matters that are strictly organizational and professional. It created a situation in which a constructivist agenda, committed to exposing those contingencies that are usually deleted or forgotten in scientific literature, was adopted outside of social science research. The Italian debate on the molecular turn in prenatal diagnosis activated "a sociology of knowledge machine" (Lynch, 1996) which promoted a passage from scientific arguments to others grounded on social interests that lay behind the adversaries' position[2]. The following

[2]Deconstructivist efforts conducted within scientific controversies to discard adversaries' arguments have been widely analysed within STS. See, for example, Collins and Pinch (1979) and Lynch (1996).

opinion stated by a protagonist of the controversy has been reiterated by others interviewed, especially by experienced geneticists:

> The reasons why the scientific community takes a certain path can be understood through many different factors. Science was not what was mainly used in this circumstance.

The extra-scientific interests referenced here are of a purely socio-economic nature. On one hand, the National Health Service (Servizio Sanitario Nazionale – Ssn) is essentially accused of adopting a conservative position. The reasons for this reside in an inability to keep up with innovations due to the slowness of bureaucracy and, above all, the desire to defend a particularly important national scientific tradition as advanced as cytogenetics. By scientific tradition we intend to refer here to a series of "scientific styles" developed over the years (Turrini 2012). These "styles" involve both skills and job positions that are framed in the context of clinical laboratories and universities. In the event of a radical technological substitution, these components would be put at serious risk. Using once again the words of a protagonist in this controversy:

> There is a shift from cytogenetics to molecular genetics. What does that entail? Where will this situation bring us? When we no longer perform cytogenetic karyotyping, the cytogeneticists will no longer have power or a role, meaning they will no longer have work. (Francesco Fiorentino, Director of Laboratory Genoma of Rome)

In this regard, it is important to clarify the importance of prenatal diagnosis in terms of employment. Just to give an idea, in 2004, out of 283601 cytogenetic tests done in Italy, 51.7% were prenatal (Dallapiccola *et al.* 2006). The prevalence of prenatal diagnosis touches not only the number of workers employed in various capacities (technical, biologists or doctors) in this area, but also an economic volume that is extremely relevant in the context of genetics.

On the other hand, CGH-array enthusiasm is mainly attributed to the purely commercial private laboratories:

> Everything that is introduced into clinical practice, and therefore in its routines, has to be assessed and developed by disease control centres, a system that provides a record of safety and effectiveness. [...] What I pose as a problem is that it shouldn't be the market to decide, it should be a relaxed scientific community that does not have other interests in the decision regarding what you can and can't do. (Antonio Novelli, Chair of Cytogenetics Laboratory of Istituto Mendel of Rome and Chair of the Working Group "cytogenetics" of Sigu)

The interests at stake are many. Antonio Novelli balances the reduction of personnel costs related to procedures with a level of automation with a prudent attitude towards innovations that are quickly commercialized by biotech and pharmaceutical companies. According to this perspective, the presentation of any given procedure as the most effective and rapid, which reduces waiting times from an average of two weeks to a handful of days, seems to respond more to economic interests than a substantial improvement in the service of care. Not surprisingly, the private Roman genetic laboratory's report, along with the previously mentioned Taiwanese's study, appear in a brochure in which a British biotech company introduces biochips for clinical diagnosis to the market – CytoChip Focus produced by BlueGnome[3].

The controversy "heats up" when these two divergent attitudes lock horns, caution versus enthusiasm, towards the innovative proposals that biomedical companies put on the market. However, describing the two factions as simply private and public would be inaccurate. The cautious attitude seems to depend on the desire to both better protect the patient from illusions generated by the medical industrial complex, and ensure greater sustainability of medical services. This position is criticized as medical paternalism. Supporters of the introduction of CGH-array techniques also add that a conservative and "directive" strategy is a rhetorical means used to justify an economic and technological inability to keep up with the pace of current technological transfer.

While this article adopts the analytical-perspective of biomedical platforms, it also attempts to examine the political aspects that the analysed dispute presents in the first place. As it has already been pointed out, the opposition between advocates and critics is deliberately simplistic. The controversy does not divide those in favour of the use of this technique from those who oppose it. Instead, the variety of stances and positions developed inside the different choices reflects the relationships of the invested parties to the issue. In this regard, this debate provides insight onto complexity involved in gene array technologies, new procedures, other existing procedures, medical and scientific associations, biotech companies, work groups, publications, and so forth. It also points out the relationship between the "biomedical collectives" (Rabeharisoa and Bourret 2009) and the biomedical industry. However, we do not intend to explain the differences of these position with a causal model based on economic and professional interests. Even if they undoubtedly play a crucial role, we would like to grasp the epistemological and organisational difference of the "biomedical platform", articulated around the molecular genetic diagnosis of the foetus, in greater detail.

[3] BlueGnome, *Delivering decisions from DNA*, "CytoChip", (http://www. cambridgebluegnome.com/products/cytochip-isca/product-information/cytochip - oligo-spike-in-controls/, last visited on the 3rd of May 2014).

6. A "Lab-on-a-Chip"

"It's the platform that makes the difference."
A geneticist interviewed

The notion of biomedical platform is used in this article with a semantic ambiguity much like the synecdoche rhetorical figure. Biomedical platform does not refer only to a specific conceptual framework. In the fieldwork the term "platform", without the adjective "biomedical", was used quite frequently to mean the slide, the matrix on which the analysis is physically carried out. This meaning is more limited and specific, basically indicating the glass slide on whose grid the thousands of short sequences of Dna are arranged.

The two meanings, despite their apparent differences, are actually contiguous under different aspects. The first meaning comes from a reflection on a tendency towards biologization and automation in contemporary medicine, and the second comes straight from the biomedical field in which this transformation has already reached a very advanced stage. These objects share not only a historical and technological proximity, but also some functional/operational elements. The biochip incorporates a wide range of tasks that were previously conducted by hand. Thanks to the chip, even the reading of the results themselves is performed by a computer scanner. In other words, biochips are the result of scaling several laboratory procedures down to a chip-format. This is the reason for which they are generally referred to as "lab-on-a-chip" (Loc), which, curiously, is another synecdoche widely used for this kind of miniaturization processes. All of these considerations indicate the extraordinary closeness of the two semantic levels of platforms. Through sociological reflection "biomedical platforms" are defined as criteria for the arrangement of the various discursive elements and materials. In molecular genetics, "platforms" are defined as extremely flexible and encompassing variables in much the same way, on which however, the entire material and epistemological data production cycle depends on. This correspondence is not an accident, but is rather understood through ethnomethodological reflection on "perspicuous phenomena", i.e. overlapping areas where concerns of particular groups resonate with social science categories or issues (Lynch 1993). Indeed, the arrangement of the slide where the analysis is carried out reflects on the broader regime of production and regulation of the new biomedical entities analysed by CGH-arrays. If one were to play with the multiple meanings of this category, one could argue that the physical type of platform chosen for the lab predominantly influences the articulation of the overall biomedical platform. Returning to the debate in the light of this perspective, the type of array that will be used emerges as one of the primary obstacles upon which the controversy was built. As the researcher seen at the beginning of this section states, "it's the platform that makes the difference!"

One of the most meaningful differences among the number of array platforms that have been commercially offered by a wide range of companies in recent years regards the optimal resolution of these arrays. Increasing the resolution has the advantage of detecting a larger number of anomalies; however, the number of benign or uncertain significance increases exponentially. Although there are publications that indicate a specific level of sensitivity, each laboratory practically chooses its own in-house detection-rate resolution (Vermeesch *et al.* 2012). At the same time, the two most common families of technologies used for biochips, namely "targeted array" and "whole-genome array", represent the general difference between low and high resolution. Targeted arrays, also known by the technical name of Bac arrays or Bobs, have a lower sensitivity, while whole-genome arrays, or oligonucleotide arrays, have higher sensitivity.

Those who are in favour of immediately replacing the conventional cytogenetics with gene array technologies adopt targeted array biochips. As the name says, these chips target "hot spots", the gene-dense regions where the most common genetic anomalies are located, yet have low resolution for the rest of genome. This mixed resolution responds to the need to facilitate data interpretation by keeping uncertain and unsolicited results to a minimum. The rationale underlying this technology is a strategy that seeks to balance technological innovation with the needs of pregnant women who want the maximum amount of information currently obtainable by prenatal diagnosis. For this reason, the supporters of this platform consider it the only option that is genuinely respectful of the patient, as it allows for "a more accurate test", and the right to have the most accurate analysis of the foetus. Depriving patients of the most advanced medical techniques is therefore considered the effect of a paternalistic medical culture, and a resistance to change, typical of some clinical facilities:

> And what does it involve [the decision of using conventional karyotype, even when the molecular one is available]? It really means medical malpractice, going against everything that should be a goal of a doctor, a biologist, to give the patient at least an option other than the test that has been used for more than forty years, the cytogenetic karyotype. (Francesco Fiorentino, Director of Laboratory Genoma of Rome)

Others, however, do not take kindly to these products. In their eyes the immediate availability of these techniques, especially in an area as sensitive as prenatal diagnosis, would primarily respond to economic interests instead of clinical ones. Of course, the targeted platforms are specifically designed for an indiscriminate and exclusive use at prenatal diagnosis, while whole-genome arrays, although used as a second-tier analysis in prenatal medicine, are also used for the diagnosis of rare diseases and intellectual impairment. Instead of being considered the gold standard, tar-

geted platforms are seen as backward compared to oligonucleotide or genome-wide platforms, which detect even smaller anomalies throughout the whole genome. Here, for example, is the opinion of a researcher specialized in CGH-arrays:

> Making a new technology available is also right, making it available to the patient, and therefore the pregnant woman [...]. Using low-resolution platforms, however it shouldn't mean closing your eyes and saying, "yes, I used a low-resolution platform, I'm at ease because I have no doubts about the interpretation." I don't think that's how it is, because even a low-resolution platform leaves you with interpretative doubts, plus it also leaves you with something you haven't seen. I am very puzzled about this platform, although I realize that from the commercial point of view it makes a lot of sense.

Another researcher, states more concisely: "I'm not crazy about targeted platforms because they limit the *openness* of the array". As emerges from these testimonies, the type of platform one uses is a choice, that is not only related to the commercial volume of extremely sophisticated platforms, but also to epistemological choices that once again involve a reorganization of the medical work. In this regard, the whole-genome platform option provokes closer interaction between prenatal diagnosis and post-natal diagnosis, which is confirmed by the role played by biobanks.

7. Biobanks, the Molecular Body and the Prenatal Medicine to Come

In order to understand how the molecular breakthrough is transforming and complicating clinical genetics, it is worth mentioning the epistemological change produced by it. This advance is not only due to the increased number of coded diseases created by increasingly precise information. It is also a logical step. Up until a few years ago, clinical genetics mainly utilized Mendelian "one gene-one trait" or the "gene for x-disease" logic. This model tied each genetic abnormality to a given condition. The molecular turn promotes the establishment of multiple and flexible relationships. In the diagnosis of intellectual disability, autism, and multiple congenital diseases in the prenatal and postnatal field, the new approach is seen primarily in the evaluation of "penetrance", and interactions between genes (see e.g. Lock, 2005).

The categories and practice of clinical genetics are subverted and rewritten by submicroscopic reality, beginning with assumptions regarding heredity. The first assumption that is subverted is the idea that a genetic variance not present in the parents (technically a *de novo* anomaly) should

always be considered pathological. This principle is still considered valid for anomalies detected with cytogenetics techniques. However, not all microanomalies necessarily have negative health consequences. Therefore, one cannot consider them pathological based on the mere fact that they were not present in either parent.

In a manner symmetrical to the first example, the second principle of clinical genetics to be challenged by molecular techniques is considering an abnormality inherited from the parents benign in the case they do not manifest a genetic condition. This reality does not necessarily protect from the development of a disease, because some microanomalies are activated under particular conditions. It is easy to understand, therefore, that the quantitative difference brings with it a basic qualitative difference regarding interpretation, so much so that the clinical use of these technologies necessitates many years of data interpretation experience.

If, therefore, gene array technologies have automated the long cytogenetics laboratory procedures, they have instead made the clinical interpretation of the data extremely complex and indeterminate. In the words of one researcher:

> Technically, it has become much easier than it was to prepare a chromosome. Technically it has really become much easier to produce the data. What has become difficult is to interpret the data.

We could describe this complexity in terms of the loss of the phenotype-genotype correlation that was established in the first period of clinical genetics. Restoring such a connection is a far from easy undertaking, and requires the development of genetic data databases from both healthy subjects and those with intellectual disabilities, developmental disorders, autism and multiple congenital diseases at both global and local levels. The reconfiguration of what is normal and what is pathological occurs through the mediation of these institutions, biobanks, which collect, collate, and compare the vast amount of data produced by clinical laboratories around the world. Biobanks have become a fundamental element of molecular genetic biomedical platforms, establishing a link between anomalies detected in prenatal and post-natal diagnosis, which did not yet exist with cytogenetics. What is most significant is that the relationships between biobanks and laboratories are regulated by the type of platform that is used. Oligonucleotides platforms (those with higher resolution) require a continuous relationship with biobanks. Each result has to be confronted with those stored in several genetic databases, and these references are a mandatory section of the bio-clinical report. In case the result has not been perfectly codified, research for the scientific state of art regarding that anomaly should be conducted and interpreted, and then explained to the pregnant woman or the couple accompanied by other members of the medical team specialized in genetic counselling. In practice, to quote a junior researcher who works with gene array technol-

ogies, it means that:

> we must study the genes that are involved in the relevant region, and see, for example, if there are animal models, or cases partly described in scientific literature on the subject.

At the same time, each new case enriches the database, and helps establish a link between genetic information and disease. Since knowledge in this field is rapidly expanding, new syndromes associated with micro-anomalies are continuously being reported. As a result, a good example of "translational medicine" emerges, where clinical results are used to build a dynamic and ever-changing model of the "genetic molecular body".

The same genetic molecular body is instead incorporated in fixed form by Bac platforms, where the analysis is roughly limited (never fully) to known areas of the genome. In this case, the work of interpretation is largely (but not completely) embedded in the technology itself. There is still a relationship with genetic databases, but that is limited to the few uncertain cases that emerge in the analysis, and to updates that such platforms with targeted designs requires now and again. In essence, the continuous mutation of the molecular body is frozen by these technologies into a series of still images, which serve to lighten the task of interpretation and, therefore, to implement a higher level of automation. Clearly, once again, increased automation, while minimizing the number of uncertain cases and lowering unit costs, potentially extends these tests to a greater number of people and therefore plays into the hands of the companies that manufacture these devices. At the same time, to a lesser extent, increased automation contributes to the codification of the "molecular body".

The platforms build a relationship with the future of prenatal medicine in a second and equally important sector, in relation to other tests that seem to redefine the practice of prenatal diagnosis. A particular comparison can be made with non-invasive prenatal diagnosis (Nipd), which is based on cell-free foetal Dna in maternal serum. Although this is not yet widely available in Europe, it is already widely practiced in North-America. It is possible that in the near future this technique will replace all other current techniques of prenatal screening and diagnosis. Even if, at the moment, it addresses only a handful of anomalies, such like trisomies 21 (Down's Syndrome), 18 and 13, it may be extended to wide set of genetic anomalies, including genes of susceptibility like Brca1 or Brca2. As part of the molecular turn, they will pose again similar issues about how to organise materially and clinically new biomedical entities, which in this latter case are not only molecular/submicroscopic, but also non-invasive.

8. Conclusions

Defined as the biomedical platform, the introduction of molecular genetic techniques in the field of prenatal diagnosis is a far from concluded process based on a stronger interaction between techno-scientific innovation and research and clinical routines. In a recent public speech, Eric D. Green (2013), the Director of the National Human Genome Research Institute at the National Institute of Health, stated that prenatal diagnosis is one of the "hot areas" of genomic research. With the advent of Nipd, genetic analysis seems to have lost one of the main obstacles to its diffusion, that is the inherent risk of miscarriage that the process of foetal biological material extraction carries. The possibility to analyse foetal Dna present in maternal blood opens even new possibilities. Dna sequencing may provide a genetic analysis still more accurate than CGH-arrays, and its clinical application seems not so far. The *Mit Technology Review* mentioned it as among the ten breakthrough technologies of 2013, namely, the possibility for a pregnant woman to obtain the complete Dna sequence of her foetus through a simple, non-invasive blood draw (Regalado 2013). Bioethics approaches the phenomenon with a prescriptive approach regarding the ethical norms that should be applied to the new techniques of prenatal diagnosis and screening. This paper tries to deal with these transformations from a different approach, focusing instead on the pragmatic changes that such innovations bring, and the various methods with which geneticists articulate these new technologies. In this sense, the concept of biomedical platform proves useful as a perspicuous conceptual framework that allows us to grasp the crucial role played by the ever increasing intersection of activities between not only the laboratory and clinics, but also among biomedical routines, innovation and research. The *platform* is not only the complex network of heterogeneous actors involved in the production and reproduction of new submicroscopic anomalies detectable by gene array technologies, but also indicates the central element on which the other elements revolve, namely the biochip.

Consequently, we have analysed the controversy over this embryonic biomedical platform as a multi-layered debate. The selection of submicroscopic anomalies that will be detected depends on the kind of arrays chosen for prenatal diagnosis. At the same time, the differences in the way these biomedical entities are produced affects the arrangement of the platform in which they are mobilised. In other words, this dispute shows the multiple possibilities in which it is possible to mediate relations among procedures, instruments, the representational space of Dna, clinical indications, etiological classification and scientific categories. Through the investigation of the correlations between routines, innovation and research, the organisational and epistemological way in which these material and immaterial entities are collectively arranged appears to impact connections between biotechnology companies, genetic database,

healthcare institutions and practice, the human body, and the normal/pathological divide. The controversy, therefore, drew attention to the important stakes involved in the material and discursive arrangement of the biomedical platform. Geneticists manage the prenatal diagnosis of the present, and prepare the future by playing with the organizational flexibility of the platform. We can identify the political sense of the biomedical platform as the manner in which the material and discursive intertwinement of biology and medicine, the normal and the pathological, is arranged. In synthesis, the framing and structuring of the extension movement of the medicine to come.

Acknowledgements

I would like to thank, first and foremost, the geneticists and researchers who granted me access to the field and spent patiently their time to speak about their work practices. I also am grateful to Alberto Cambrosio as well as to three anonymous reviewers for invaluable comments on drafts of this paper. I would also like to especially thank Federico Neresini and Assunta Viteritti for their encouragement and moral support. Finally, a special thank to Daniela Crocetti, for her help with the English translation.

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