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REGIMEN STRIKES BACK
DIAGNOSIS, GENES AND THE PATIENT

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SUMMARY

The paper focuses on the conceptual innovations introduced by recent developments in genetics and genomics in diagnosis, both in its cognitive and clinical aspect. Genetic diagnosis started as the recognition of statistically significant occurrence of symptoms within families, and later became the simple test to diagnose a molecular disease, by highlighting the presence of a single pathological gene (or of a few of them). The advent of cheap genomic technologies allowed for genome-wide data collection, so that even complex traits, physiological as well as pathological, may be diagnosed. However, genome analysis has revealed that most phenotypic traits are the result of the interaction of multiple genes and of the environment. Diagnosis in the genomic age is no longer the act of connecting symptoms and the recognition of a pattern, but it crucially involves statistical concepts such as "risk" and "contribution", leaving a wide space of uncertainty for therapeutic action. The lifestyle of the patient is back again at the center of the stage: in order to stave off disease, an individual regimen may be the best available option.

Diagnosis has been deeply affected by the introduction of genetics. Until mid-XX century, heredity played some role in the classification of diseases and in the medical practices. Some pathologies were known to be hereditary since a long time: polydactyly was identified as such already in 1751 by Maupertuis[1], and medical significance of hered-

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ity was widely discussed[2]. Archibald Garrod's analysis in Mendelian terms of some "inborn errors of metabolism" is usually considered to be the founding act of modern medical genetics. However, diagnosis in patients - that is, in daily medical practice - did not take considerable advantage from this scientific development. A "genetic diagnosis" was usually only *a posteriori*, when the disease was already apparent. Medical practice could only go as far as pre-marriage counselling, when a pathological trait was known to occur in the families of a couple. Without the technologies for identifying traits before birth, there was little that could be done to prevent pathologies. Yet genetics has introduced several novelties in our idea of disease, as well as in medical practice. In time, a larger spectrum of pathologies have been shown to be of genetic origin, with familiar recurrence or with a single genetic or chromosomal aberration as the cause of disease. Genetic counselling was the only instrument - or device - to try to "realign" biology and medicine in practice, though only after deep cultural and technological changes it was possible to enact clinical procedures: prenatal diagnosis, abortion, pre-implantation diagnosis, as well as a better ability to screen potentially affected individuals, finally allowed to effectively fight genetic hereditary diseases.

However, this is true only when the genetic disease is relatively simple, that is, caused by a relatively small number of mutations in a single gene or for other anomalies such as chromosomal aberrations. Examples are Huntington's disease (due to abnormal repetitions of a trinucleotide in the gene coding for protein Huntingtin, located on the short arm of chromosome 4) or Duchenne Muscular Distrophy, in which a mutation in the gene coding for protein Distrophin - on the short arm of X chromosome - causes the disease.

What's in a name?

When discussing this sort of disease - "easy" genetic disorders, whose genetic-molecular origin has been thoroughly described – the

wording immediately reveals a mix of two aspects. On one side, we have the usual naming process: a set of symptoms and signs, identified by a name (in this case, the name of two physicians) and/or by the main symptom (distrophy). On the other side, it is possible to use a genetic-molecular lexicon, so that the disease is identified by such terms as "C-to-T transition at nucleotide 9152" in Xp21.2-p21.1, as reported by the Online Mendelian Inheritance in Man (OMIM) web catalogue[3]. The same clinical object is thus indicated by two different notations, usually the first one preceding the other. The usual path is: description of the symptoms, introduction of the new name within medical nosology, and then fundamental research takes over, defining the causal mechanisms and the whole path leading from the genotype to the phenotype. The pathological phenotype is traced to protein malfunction, due to mutated Rna, caused by mutated Dna. "Beginning with the abstract, we move through the operational to functional and structural levels of genetic definition, ending with positional cloning of specific genes. Thus does the ontogeny of diagnosis recapitulate the phylogeny of definition[4]."

Quite obviously, genetic analysis may lead to a classification according to a genetic definition of disease. In this respect, genetic mutation becomes ideally the main diagnostic "sign" as well as the cause of the disease[5]. In this ideal path, the clinical act of diagnosing a disease in a patient follows the nosological act of naming and classifying the disease. In the scientific and clinical practice, however, this diagnostic trajectory has been frequently challenged. Only in few cases phenotype has been linearly connected to the genotype by tracking the disease along the pathways gone awry as a consequence of a mutation. In some cases, a pathological mutation in a gene has been identified by creating large familial databases and searching for a "candidate gene". That is, by searching a common genetic mutation in families where a disease is recurrent, it is possible to identify the genetic origin of a disease. However, physiopathology is

somehow out of the picture in these early steps of gathering genetic knowledge: connecting a mutation to a syndrome does not entail any special insight regarding the pathological processes occurring in the diseased body. Only when some sort of "reverse engineering" is enacted, the black box connecting genotype and phenotype can be finally opened. This has been the case for cystic fibrosis: the CF locus has been identified by means of a population genetics investigations and linkage disequilibrium studies, but as the authors of the discovery stated:

> *[…] these studies were based on linked DNA markers whose exact relation to CF was not entirely certain. Further understanding of the pathophysiology, haplotype association, and population distribution of CF would require detailed molecular knowledge about the mutations*[6].

The introduction of genetic models and techniques have actually expanded the diagnostic process as a gathering of knew medical knowledge. Going beyond physiopathology, genetic diagnosis (as a nosological act) involves data collection, new theoretical and practical tools for data analysis, as well as a definition of what is normal and what is pathological. Large numbers are needed in order to reach statistical significance for an association between a mutation and a phenotype, and even larger numbers are needed in order to define the mutation as pathological[7]. The evolution of large-scale genomic projects, from the Human Genome Project, to the Hap-Map and the Thousand Genomes projects, is a testament to the need of greatly enlarging the statistical foundation of medical research. In this respect, IT tools for data mining and analysis are becoming more and more essential for producing new medical knowledge, bypassing the traditional use of the human body and its processes. This new approach, that can be described as data-driven, is also departing from a more typical mode of scientific enterprise, based on the progressive hypothesis refinement by means of experiments in controlled

conditions[8]. Heredity, moving from the individual level of genetics to the population level of genomics, is progressively disembodied, removed from the usual setting of the organism. As a matter of fact, it may be considered the result of a century-old process involving the "coding" of the genetic body with several instruments, such as maps or pedigrees, entailing an increasing abstraction within genetic medicine[9].

However, as the reverse engineering for cystic fibrosis shows, the molecular findings may eventually lead to new clues about pathophysiology. When this is the case, a genetic test, yielding an exact and clear cut result, becomes the strongest evidence for a diagnosis. It's a digital result, a Yes or No response that - technological failures aside - will give a precise diagnosis for a known condition, even when symptoms are somewhat difficult to decipher. Ideally, a mutation (or some sort of genetic abnormality) appear to be the basis for some sort of "arch-nosology", being at the same time the main diagnostic sign and the main cause for the disease. This sign - in the case of heritable diseases – may be even followed through time, by the use familial studies and pedigrees.

However, this holds true only for a limited part of the set of human pathologies. The connection between the genotype and phenotype is extremely complex, and even when a mutated gene is pinpointed as the cause of the disease, a closer scrutiny may reveal a different picture. Again, cystic fibrosis can help us to understand how genetic testing and diagnosis may act at different levels. We know that the disease is caused by one in large group of mutations within the so-called Cystic Fibrosis Transmembrane Receptor (CFTR). The problem is, there is no direct correspondence between having the mutation(s) and showing signs of the disease: genetic diagnosis and traditional clinical diagnosis do not always match. Mutation and symptoms have a peculiar and complex relation, and disease severity is not easily inferred by the sheer use of genetic testing: genetic (and etiological) certainty

meets clinical fuzziness. However, the fact that the clinical entity is connected to several mutations makes the picture more complex, and diagnosis with different tests (classic clinical diagnosis, sweat test, genetic test) may not agree in the results. Smith has argued that a genetic version of Koch postulates would not be met when trying to causally correlate mutations in CFTR and the clinical diagnosis[10].
Cystic fibrosis and other "simple" genetic diseases define a trajectory of expansion of diagnosis from a clinical starting point. In recent years, however, the availability of large-scale genetic screening has significantly changed the relationship between genotype and phenotype. Navon coined for example the concept of "genomic designation" to identify "the discovery, delineation, and diagnosis of medical conditions on the basis of observations made at the level of the genome, be it whole chromosome aberrations observed through karyotype analysis or tiny mutations detected by contemporary genomics technologies[11]." Genomic designation arises when the discovery of a specific genetic mutation is not readily framed within existing nosologic categories. The new diagnostic entity is thus defined by genomic tools, with the clinical signs following the detection of the genetic trait. Especially in the earliest stages of this process, the creation of the diagnostic/nosologic entity is essentially aimed at grouping together symptoms reported by individuals under the aegis of the genetic cause. Ultimately, according to Navon, genetics and genomics are tools aimed at grouping individuals in discrete units ("human kinds", following Ian Hacking's definition[12]) with a gene-related tag[13]. An example is the so-called Phelan-McDermid Syndrome, initially termed as "22q13 Deletion Syndrome". In this case, research started as an investigation in order to find a genetic correlate to autism. In time, it became clear that autism spectrum behaviors were only a part of a larger set of symptoms. In Navon's terminology, autism acted here as "phenotypic incubator", that is, what Michel Foucault had identified as the "surfaces of emergence":

> *where "individual differences, which […] will be accorded the status of disease, alienation, anomaly, dementia, neurosis or psychosis, degeneration, etc., may emerge, and then be designated and analysed*[14].

Within the broad surface of autistic symptoms, a circle of ripples started to form when a candidate gene was investigated: research eventually showed that deletion in a particular genomic region was correlated with a set of symptoms. However, this set is different from patient to patient, with new exceptions constantly added to the clinical definition. For this reason, "in many cases it is unlikely that diagnosis could, even in principle, take place on a clinical basis[15]."

Genomic designation is recent, though some characteristics of this nosological act may be found at the dawn of medical cytogenetics. Jerome LeJeune's work on Trisomy 21, mapping the multifarious and complex phenotype of the so-called Down Syndrome to the karyotype anomaly, provided a new diagnostic instrument and a new perspective for the syndrome to be framed in. However, Down Syndrome and Trisomy 21 are completely overlapping, and the nosological category was clearly established long before the advent of cytogenetical techniques. Genomic designation - in Navon's reconstruction - follows a different pattern, where genomic gaze replaces the Foucaultian clinical gaze, leading to the identification of a set of signs and symptoms, and then to the creation of a whole process of nosological and clinical diagnosis, ultimately creating a social category.

While focusing on the 22q13 Deletion Syndrome, Navon states that there are "at least 16 syndromes, ranging in size from a handful to thousands of subjects"[16] that match exactly the ideal type of genomic designation. However, there are "countless other syndromes" that almost match the description, and are useful in order to show the shift towards a molecular gaze complementing and eventually replacing the clinical gaze. Even if Trisomy 21/Down Syndrome does not perfectly fit the picture of a genomic designation, LeJeune's work really did marked a milestone: after he published his research

it became clear that cytogenetic techniques could be used in order to look for new conditions and as a diagnostic tools for existing ones. Over time, the progress in medical genetics have yield two main, albeit opposed, results. While on one side genetic knowledge united what was once divided - symptoms that were considered unrelated, or not included in the same diagnostic category - conversely it also divided what was thought to be one. Cancer typifies this nosologic process: genetic analysis of the mutations involved in cancer lead to the development of new medical entities, with different diagnosis, prognosis and therapies. Breast cancer is - for example - now divided in several diseases, according to the various markers identified in the pathological tissue, each of them to be treated accordingly. Although this new categorization is not strictly genetic, nor inherited, the most striking example is indeed genetic and inherited. In the 1990s, the identification of the BRCA1 and BRCA2 variations in women with a familial history of breast cancer opened the path for a new classification of the several "breast cancer" kinds. For each category, prognosis and therapy vary accordingly to the genetic makeup of the cancerous cells. As said, some of the mutations involved in the cell transformation from normal to pathogenic are not inherited, while others are, including the BRCA1 and BRCA2 mutations. For these two clinical signs, advanced screenings are possible and widely applied in affluent countries when a case is detected in a family. Positive result will obviously affect the tested woman's life, in terms of continuous control on body's health as well as of psychological distress aroused by the sword of Damocles over her head. In the specific case of BRCA1/2, positive tests may even lead to preventive surgery in order to minimize the risk of breast and ovarian cancer. Inheritance plays a key role in several respects. For example, the assessment the penetrance[17] of BRCA cancerogenic mutations is extremely dependent on whether the analyzed patients group comes from families "at risk" (i.e., with women of two or more generations being diag-

nosed with breast cancer) or are participating in a population screening. According to a recent study, risk estimate for breast cancer for BRCA1 and 2 carriers is of 60% and 55% respectively[18]; or "55 to 65 percent of women who inherit a harmful *BRCA1* mutation and around 45 percent of women who inherit a harmful *BRCA2* mutation", as stated by the US National Cancer Institute website[19]. But when the population is limited to hereditary germline mutations in BRCA1/2, risk is estimated up to 80%[20]. This is what is considered to be one of the best-defined cancerogenic mutation in medical practice, one where the nosological and the clinical acts of diagnosis are largely overlapping. However, uncertainty still looms over medical practice as well as over the lives of patients.

Before the advent of the large scale sequencing techniques, the nosological diagnosis was strictly connected to patho-physiology. As shown by the cystic fibrosis example, some sort of ingenious insight was needed in order to connect phenotype to genotype, involving a painstaking work made difficult by the complicate handling of genetic material. However, at the turn of the new millennium new technologies became available that made easy to read the whole genome sequence. This led to the dramatic increase in the size of databases, and the search for the pathogenic mutations became largely silicon-based, as opposed to wet biomedicine. In turn, the so-called association studies became the main approach used to map the phenotype onto the genotype. Roughly, scientists searched within the sequence databases some genomic traits (from a single nucleotide alteration to haplotype) frequently associated with a given phenotype[21]. However, the results of this big-data search are heavily dependent on how big are the data really are, and on how they have been obtained. Just like LeJeune described a sort of "karyotipic" frenzy getting hold of his community after Trisomy 21 was identified[22], even before the completion of the first draft of the human genome in 2001, triumphant statements on the future of genome-based medicine were not infrequent:

> *By the year 2000, [all] drug companies in the world will use genomic data as their Rosetta stone for the development of new drugs and diagnostic procedures. No science will be more important to the future of medicine than genomic research*[23].

However, recent reassessments of genomic association studies started to point at potential pitfalls. According to a *Nature* paper, "a radical revision of human genetics" is now in progress[24], due to new databases[25] collecting data not only from patients but also from healthy individuals with a wider diversity in ethnic background. This has led to a broad-spectrum reconsideration of "gene pathogenicity"[26], since in the case for rare variants, "there is an unacceptably high likelihood of false-positive interpretation"[27]. But in other cases, "diagnostic laboratories may be overly conservative when assessing variant pathogenicity"[28]. Scientists became fully aware of the need for a careful reappraisal of the meaning and the significance of the diversity in human genome:

> *whole-genome sequence data sets are in some ways more prone to misinterpretation than earlier analyses because of the sheer wealth of candidate causal mutations in any human genome, many of which may provide a compelling story about how the variant may influence the trait*[29].

Regimen strikes back

What became clear in the last few years is that mutations in single genes cannot usually be considered as digital switches, so that the connection from the genes and the genome, and the pathological phenotype is - at best - complicate. Reliable and binary predictions can be made only for a handful of diseases whose mechanistic relation with a mutation has been demonstrated beyond any doubt. Diagnosis by genetics is usually a blurred affair, and as a clinical and nosological act it involves wide margins of uncertainty. Other issues concur to make the picture even more complex. An association between a

gene and a function - especially when related to pathologies - may be not only a scientific matter, but also a commercial enterprise[30]. Personal genetic testing outside usual research/hospital setting has been gaining momentum in recent years[31], though analysis of the results may greatly vary according to the lab performing the test. In 2008, a journalist sent his samples to be tested to several companies:

> *According to deCODEme, I had a 2% higher than average risk of developing Crohn's disease, a chronic bowel condition, while 23andMe put it at 47% lower than average. GeneticHealth said my genes put me at "significantly increased risk" of hypertension, or high blood pressure, yet 23andMe defined me as at "moderately higher risk". With so many contradictions and inconsistencies I was left not knowing what to believe*[32].

Uncertainty is a structural component in correlating genome and the phenotype[33]. Several scientists point at the fact that phenotypic traits are influenced by several genomic features. Asbury and Plomin, for example, focus on the so called QTL hypothesis:

> *apart from a group of mainly rare and severe single-gene disorders, all common human traits are influenced by many genes and each gene has only a tiny effect*[34].

Each genomic character bears a partial responsibility for any phenotypic trait: the latter is a mosaic made of several tesserae, each one with a limited contribution to the overall picture. According to a study in primary school pupils, a connection between a large set of SNPs (Single Nucleotide Polymorphism) and mathematical ability is spotted, though the connection is comprised of a series of thin wires:

> *As expected, each individual SNP had a small effect, with the largest accounting for just over 0.5% of the differences in mathematical achievement between these 2,500 children, and the smallest only 0.13%. But when these ten DNA markers are combined to form a set they can explain 3.4% of the differences between people*[35].

Whole-genome sequencing would be needed in order to create a full profile for the single individual, and identify her/his predisposition towards specific diseases or talents. However, as seen before, after such an enterprise, we would be left with the uncertainty of environmental influences, epigenetic mechanisms, etc.

The complexity of the relation between genome and phenotype has radically changed what scientists are searching when trying to connect the "two natures" of the individual. Genes act in a tangled web, largely unknown for most of the phenotypic traits - including diseases. We see a shift in both the nosological and clinical meaning of diagnosis. The process of identification of a pathological identity is enriched by the "genomic designation", while the clinical act when dealing with a patient and his/her present or future, become blurred in probability. The recent epistemological history of genomic medicine points at an unforeseeable future: for the patient and the discipline itself. In fact, sociologists and ethnographers have recently introduced terms such as "divination" and "horoscopes" when tracing the patient narrative of the expansion of genetic testing, pointing at the fact that the person undergoing such practices faces uncertainty as well as arbitrariness in the process. Furthermore, it has been argued that for specific diagnostic tests such "divination of the future has no clinical or personal utility but nevertheless inevitably has the allure of 'future promise'[36]."

However, if divination and horoscopes recall a long - and deservedly - forgotten age of medicine, there's another word that should be used: regimen. In the new age of genomic medicine, it is probably true that we will have specially tailored drugs for each and every individual, and that any diagnosis will be complemented by a genetic test, taking into account inheritance. Yet, most of these diagnosis will be probabilistic: the single individual will be left with few hard facts and a handful of forecasts. And a series of simple suggestions - mostly common-sense - to stave off disease and preserve health. Are we back to ancient "constitution" and "regimen"? It may be. Without humors and miasma, the

new diagnosis is not only targeting disease (as in creating a genetically based nosology and in identifying a disease in the patient), but it aims at creating an individual made up of gene-based predispositions. This brings us in a realm where genetics works as a kaleidoscope: single causes, multiple causes, risks, predispositions[37]. Accordingly, in the next future everyday medical practice will be made of the same fabric of its long past: life-style advices, apparently tailored on what the physician (or the testing geneticist) saw in the genetic future. Within the doctor-patient relationship, just little bits of history repeating.

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