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AN ETHNOGRAPHY OF TRANSLATION IN GENOMIC MEDICINE

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BY
COLIN MICHAEL EGENBERGER HALVERSON

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INTRODUCTION

Death of the Clinic

The Center for Individualized Medicine (CIM) was in its second year of existence when I began my fieldwork. Its purpose was to translate a certain set of cutting-edge scientific practices into diagnostic and therapeutic interventions. In particular, it focused on large-scale genetic tests. The Center was meant to supplement standard practice – but not just to supplement it. It was meant to create standard practice through its introduction. The clinic's purpose was to 'mainstream' these new techniques, eventually canceling its specialist expertise in interpreting genetic test results, at which time general practitioners would take over that responsibility. The clinic's administrative head told me she would judge her success by the clinic's ever-decreasing necessity in the hospital. A medical ethicist summarized the project to me: "The goal is to become obsolete."

All that is to say, the Center's demise had been written into its charter; its conception foretold its dissolution. During my fieldwork, the knowledge of and power to interpret genetic science rested decisively with the experts in this specialist clinic. They were the official gatekeepers to a number of large-scale tests, and they were the traditional authorities to whom general practitioners turned in order to translate emergent science into therapeutic practice. However, clinicians, administrative staff, and scientists at the clinic were all constantly forced to grapple with the ultimate intention to dissolve their place of work and to make its knowledge accessible to non-specialists. The specialists' twilight brought the opening of expertise to general practice. The clinic had a strange temporality – epitomized by the rapid pace at which the science shifted, by the characters

that came and went, by the medical artifacts that emerged and disappeared, and by the way in which the future was predicted, preempted, and incorporated into the present.

Why did the clinic exist, and why did its mission statement provide for its ultimate and certain dissolution? Genomic medicine was a novel space. It was by no means healthcare as usual. Scientific understanding of human genes and their relationship to disease was very limited. A contemporary study demonstrated that large-scale genomic tests provided diagnoses for as few as 25% of the patients who underwent them (Yang 2014). And that was for diagnosis; it did not even address these tests' ability to suggest treatment or – much less still – cures.

The limitations of the science were largely due to the incredible complexity and enormity of the information from which medically relevant evidence had to be culled. An often-cited statistic in the clinic was that genomics posed as much of a challenge for the computation of Big Data as did Google and astrophysics, each of which was at the toe of the 'avalanche of printed numbers' (Hacking 1982). Meanwhile, clinicians and scientists alike said that of the 24,000 genes humans had, only one percent was well enough described to provide potential insights for healthcare. Even then, the information returned by these tests needed extensive parsing.

On a particular patient's case, for instance, a large-scale test (called whole exome sequencing) returned 317,973 distinctive genetic variants. Each of these variants was suggested as a possible cause of what the clinicians on the case assumed was a single, unified disorder. First, several computerized algorithms produced by the bioinformaticians in the laboratory combed through these variants. This process eventually reduced the number of candidate variants to 134, and after the use of another algorithm, to 20.

Although this was still an overly large number, it became necessary at that point for humans to intervene. After reviewing the literature on each of the 20 variants, scientists in the laboratory were able to reduce the number to four potential candidate mutations. Then a committee of the clinic's specialists convened and spent 20 minutes selecting one of those variants to pursue with further testing.[1]

Such labor was characteristic of the patient cases that came through the Center. 'Interpretation,' as the process was called, was costly, time-consuming, and limited in scope. And even among the expert staff of the clinic, it was contentious. During case conferences, specialists nearly always disagreed on the significance of at least one of the variants. Cytogeneticists argued over what counted as a "real amplification;" pathologists complained that spikes in certain genes were merely the result of copy number variation; an oncologist realized that he had misread a mutation as wild type, or signaling, or binding. My point with the preceding jargon is to point out the intense specialization of expertise necessary to make these types of nuanced observations.

The unique specialization of genetics set it apart from other healthcare practices in the hospital. Its limited diagnostic utility meant that testing was often viewed by clinicians and their patients alike as having value beyond therapy (see also Taussig et al 2005; Rose 2007). Much was atypical of the Center relative to other clinics. In fact, medical genetics was not even typical of (molecular) genetics (see Chapter Four; Stotz and Griffiths 2013:33ff). Even the genetic counselors in the Center were distinguished from other genetic counselors in the hospital – sometimes being called *genomic* counselors (though

[1] For a detailed analysis of this process, see Chapter One and Chapter Five.

the counselors themselves scoffed at this) – since their focus was rarely on prenatal issues (contrast Rapp 2000).

Genomic medicine was considered so unique to and distinct from healthcare in general that in order to undergo sequencing, patients were required to give a special consent. They had to meet beforehand with a genetic counselor, who would provide them with a wide swath of information – about the science behind the test, the reliability of the results, and the ethical implications the results could have on their genetic kin. Only with this 'informed' consent could testing proceed (see also Chapter Three). Several clinicians noted to me how strange that was. Radiology faced similar difficulties in interpretation, they said, but no patient had to meet in parallel fashion with a radiology nurse before getting an x-ray. The very existence of the genetic counselors as an expert class was seen as testimony to the radical alterity of genomic medicine.[2]

There was a general concern about the utility of specific forms of genetic testing. Each new service the clinic offered underwent enormous moral and scientific scrutiny. In order to determine whether the Center should offer a certain large-scale test, they held an entire symposium, which was attended by specialists from around the country. A medical ethicist explained to me, "We can set the standards ethically and in terms of practice if we jump into the race." Other hospitals and private companies were already offering these tests; if the specialists wanted a say in how to proceed, what limits to impose, and how to determine the quality of the intervention, they had to engage the future head-on. Moreover, mainstreaming would make the tests cheaper, faster, and accessible to a wider population.

[2] Over the course of my fieldwork, the role of the genetic counselor constricted. In Oncology genetic counselors had almost ceased to be used at all by 2015, their tasks having been taken over by non-specialist physician.

Several oncologists confided in me that they would prefer to have every one of their patients get a genetic test as soon as they came to the clinic, but such testing was not the standard of care. Mainstreaming genetics was recognized as necessary for the hospital, for its patients, and for the state and status of medicine in general (contrast Latimer et al 2006).

Specialists never imagined that general practitioners would gain as nuanced a grasp of the science as they had. The task of the clinic was necessarily to reduce the information, to create an automated process that would transform it into something accessible and actionable for the general practitioner. But such reduction was considered problematic and potentially misinformative. Conflict was inbuilt into the Center's destined dissolution. One geneticist told me that if scientists could reduce the laboratory report to a single page, it would be acceptable for oncologists, "but when it has 25 pages, it confuses them. They only understand *KRAS*," he said, referencing a well-described cancer gene. There were, of course, hundreds of other genes linked at the time to the dysregulations associated with tumor growth that, he contended, were not understood by the average physician.

There was also a concern about the popular understanding of genetics. One laboratorian discussed with me news reporting on genetics, saying, "It's kind of disgusting, overly hyped. A lot of the time, it's just not true." The media's predilection to present discoveries as "a gene for X" was a constant source of scientists' ire. But *clinicians* were also criticized for their lack of understanding of genetics. For instance, the gene *MTHFR* had originally been linked to some blood-clotting disorders, but the science supporting that assertion had since been dismissed as junk.[3] Despite that fact, physicians in Hematology still regularly ordered that gene sequenced, yielding patients who had undergone testing

[3] *MTHFR* testing is discussed in detail in Chapter Two.

for no scientifically acceptable reason. A cardiologist told me that he had seen patients who had inappropriately been given defibrillators by physicians who did not understand the meaning of the genetic test results they had ordered: "This is a storm that is coming."

Furthermore, the pace of science was incredibly fast – yet another strange aspect of the clinic's temporality. Patients were told to come back once a year in order to check whether science had progressed so as to make any of their test results newly interpretable. Laboratories changed which genes they included in their panel tests with such regularity that even specialist physicians did not know by memory all of the genes that would be tested on some of the panels that they ordered multiple times a week. Bioinformaticians told me that the algorithms they were developing for interpreting genetic results needed to use a database of medical literature that updated every few months in order to stay relevant. (One of the largest public databases only updated once a year, and for that reason it was considered more or less worthless.) The hospital's own biobank database loaded 3600 new patient samples in just the first six months I was working there.

The temporality of the clinic was a difficulty for its own staff,[4] but it was also a difficulty for me as an ethnographer. Even over the course of my tenure, the clinic saw significant shifts in personae and practice. The head of the clinic was replaced; the lead genetic counselor left; they hired the hospital's first genetics nurse; a new class of patients was ratified; the category of 'project manager' was created to assume some of the medical ethicists' tasks. Over the course of a year, whole exome sequencing came and went as the primary test for patients with cancer. Whole genome sequencing supplanted exome as the

[4] In fact, Isabelle Stengers says that modern medicine is defined by its awareness of the "changeability" of its practice (Stengers 2003:14)

largest test the clinic offered. Pharmacogenomics panels were added. Mate-pair and RNA sequencing became standard supplements to DNA assays. And so on, and so on.

The imagination of the future was also evolving and contested. A certain subset of oncologists began to push for a new method of classifying cancers. Rather than the traditional taxonomy, which was based on tissues of origin (e.g., lung cancer, breast cancer, colon cancer), they suggested a genetic taxonomy: Which molecular pathway was activated? Many treatments now targeted the protein results of these pathways rather than segments of gross anatomy like the lung or the breast. For instance, the common chemotherapeutic drug critzotinib worked to inhibit a protein called ALK (see Figure I.1). Crizotinib had traditionally been used to target lung cancers, but *ALK* mutations were now found additionally to underlie lymphomas, kidney and thyroid cancers, and soft tissue tumors. Rather than divide these cancers, one oncologist suggested unifying them all as "ALKomas" (cf. Mano 2012). When I brought this up with scientists, several dismissed the purported paradigm shift as naïve. A senior geneticist told me, "Tissue of origin will probably never stop being a part of taxonomy," since the cellular context in which the cancer-causing mutation occurred would always be key in both diagnostics and treatment. The social division between clinic and laboratory manifested in imaginations of the future and the path of progress.

My field site, I argue, adds an interesting and important component to the now classic debate over the so-called ethnographic present (esp. Hastrup 1990; Sanjek 1991). The Center was anything but timeless. Its emergence was historical but recent; its future was nonpresent but immanent. When I wrote above that 'humans had 24,000 genes,' I of course did not mean to suggest that since my fieldwork humanity has developed more or

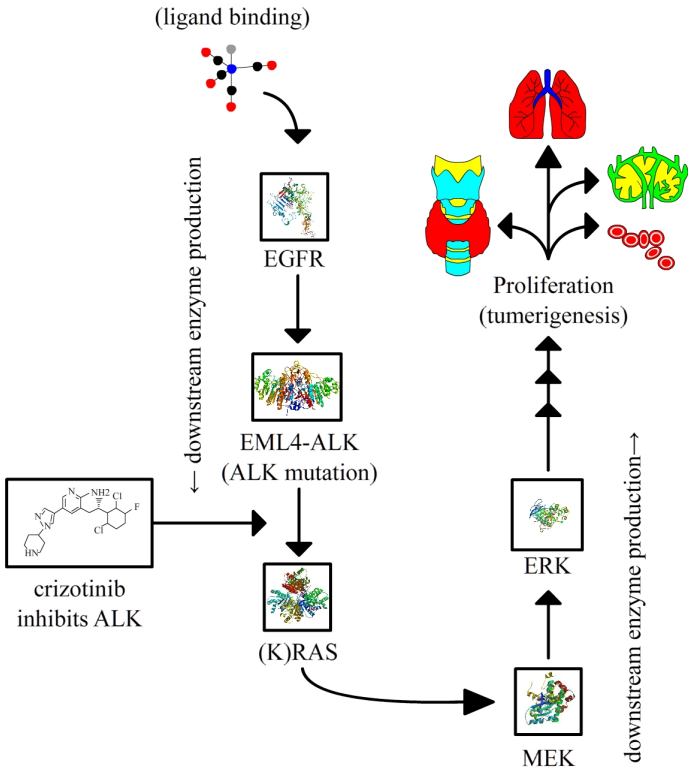

Figure I.1: ALKoma and crizotinib.

fewer genes. In selecting the past tense, I have attempted to draw my reader's attention to the historical nature of my ethnography.[5] My site no longer exists as such; neither do the science and clinical practices I studied. Entailed in site and praxis was imminent and conflicted collapse. I argue that this chronotopic glean of supersession is important to recognize immediately, at first glance. My project in this monograph is not to teach genetic science, but to teach *about* genetic science, about a specific historical, cultural phenomenon and not something perduring or transcendent. Occasionally in medical anthropology and

[5] All of the clinicians at my site readily acknowledged the conjectural nature of statistics related to the number of genes, often saying that it was "somewhere between 21 and 24 thousand." Relatedly, the given number of chromosomes (46) has also shifted relatively recently. It was not until 1956 that Tijo and Levan overturned the previous assumption that humans had 48 chromosomes (Tijo and Levan 1956)!

social studies of science and technology, science is fetishized, and its vernacular authority is seen as adding to the ethnographers' own. The truth of such stories then ends up beholden to the truth-claims of their interlocutors' stories.

While the medical assemblage I discuss herein in some fundamental way no longer exists in the living world – in similar fashion to all ethnographic objects – I argue that it provides us with insight into some enduring truths. In what follows I introduce three further themes of my monograph: the role of abject trust in tenuous translation, the conception of agency with regard to disease, and ideologies of the individual and individualization. In so doing I bring together three often parallel bodies of theory: semiotics and linguistic anthropology, science and technology studies and medical anthropology, and the local theorizations of my interlocutors at the hospital. I intend my citational practices in this chapter to be conspicuous, in Heidegger's sense, the pairing of academic texts with what has traditionally at best been called ethno- or folk theory by my discipline. It is not my interest to conflate epistemologies, but rather to suggest correspondences between domains; not to suggest commensurability, but to draw my audience's attention to the ideological character of all knowledge, to its situatedness and its pragmatic commitments.

God is Not Dead.

About six months after completing my year of fieldwork, I returned for a summer of follow-up research. I was struck by several important changes that had, in the intervening time, become relatively standard in undertaking patient cases. One of the most significant of these changes was the new use of "mate-pair sequencing" in order to supplement more

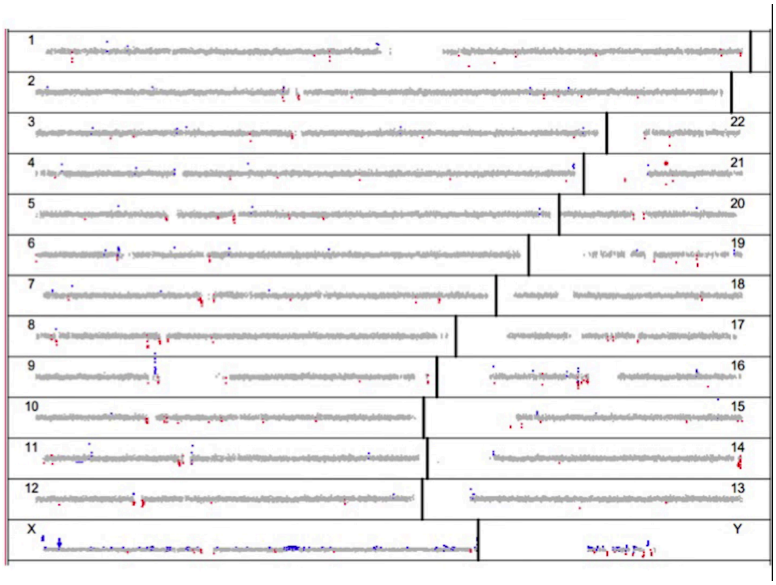

Figure I.2: A mate-pair graph of DNA from a normal tissue.

traditional tests for cancer patients. Mate-pair was used to detect structural variation in cancer DNA – for instance, to determine whether during the cancer's evolution genetic material had been deleted, duplicated, inserted, or rearranged across a patient's chromosomes.

In order to represent the data produced by this test, bioinformaticians produced "graphs" such as the figures below. Figure I.2 portrays a healthy patient's genome, with each chromosome laid out in bars. The grey dots were the "normal" genetic material, i.e. those segments of the patient's DNA that matched the "reference genome" (see Chapter Five). The red and blue dots represented presumed benign variation in the form of deletion and duplication, respectively. Figure I.3 portrays the genome as sequenced from a cancer cell. The colored lines connecting the grey bars represented the translocation of genetic material from one chromosome to another. This insight was the key function of mate-pair and the main purpose of these graphs.

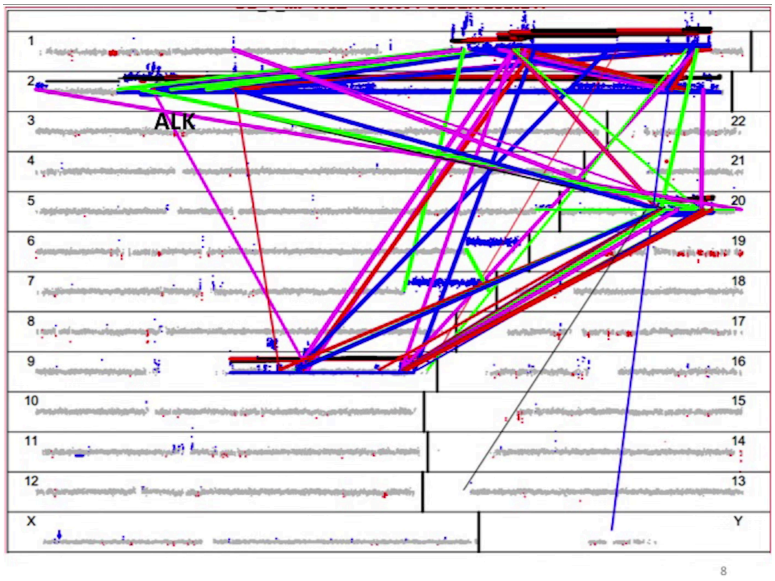

Figure I.3: A mate-pair graph from a cancer biopsy.

The graphs were meant to be presented at the Tumor Board's case conferences. These conferences were weekly interdisciplinary meetings of specialists – oncologists, hematologists, biologists, geneticists, bioinformaticians, ethicists, and many others – for the discussion of a small number of patient cases (usually two to four). The bioinformaticians who worked on mate-pair generally attended the conferences only when one such test had been used in a case, and for the singular purpose of aiding in the data's interpretation.

The graphs were displayed midway through a clinician's PowerPoint presentation of a case, for the ostensible purpose of disambiguating data that had been obtained via standard cancer genetics panels. One of the bioinformaticians would take the floor in order to discuss the structural variation illuminated by mate-pair. He or she would conclude the brief analysis with a recommendation for further testing or treatment based on those data.

The graphs were almost always accompanied by comments about their visualization. The following 'requestion' (Sadock 1974) from a prominent oncologist was characteristic: "I'm just wondering why there are lines on the graph." He could derive not even minimal significance from the occult artifact. Fellow scientists also had difficulty with the graphs. "What am I supposed to get out of that?" asked a cancer biologist of the presenter. These interjections were met with rudimentary explanations, such as I have outlined above.[6]

At the end of the discussion, the clinicians would accept the bioinformaticians' interpretations and incorporate their suggestions (for treatment or testing) into the final decision regarding the patient's healthcare.[7] This was not always a smooth process, though. For instance, on one occasion the presenting physician listened to the bioinformatician's interpretation and then went on to make a clinical recommendation based solely on the research findings from mate-pair. When this came to the attention of the scientist, he returned to the case conference the following week – not to present new data, but to chastise the clinician for his misunderstanding. "Not a lot of people would act on this kind of data alone," he warned: "None, actually."[8] Even after presenting his knowledge, the bioinformatician remained the "access point" (Giddens 1990), the only participant ratified to deploy the data felicitously. All other participants engaged his authority in an "act of faith and submission" (Durkheim 1973[1899]:46).

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[6] That is not to say that no one in the audience could 'read' the graphs. Two senior scientists occasionally got into heated debates over the graphs' interpretation, while the rest of the attendees sat mutely or turned to one another in tangential sidebar conversations.

[7] This is what Michael Gorman (2002) calls an "élite" form of expertise, one in which interdisciplinary interactions are neither characteristically adversarial nor truly contributory.

[8] For a detailed discussion of the role of research data in recommendations for therapy, see Chapter Four.

I want to point to two forms of incomprehension apparent in the case of mate-pair sequencing. First is the semantic inscrutability of the graph. What information were the signs meant to convey? This was the concern that was most often voiced in the conference and was represented by the quotations from the clinicians provided above. The second concern was the formal inscrutability of the graph. For instance, consider the translocations between Chromosomes 1 and 2 in Figure I.3, denoted by the blue lines. Due to the width of the lines and the dense pixilation, it was literally impossible to determine the specifics of such structural variation from the graphic itself. The data were visualized in such a way that certain information was reduced to the point of erasure.

So what was the point in presenting these graphs if they were illegible to their intended audience? One function was that their incomprehensibility served to reaffirm the bioinformaticians' performative necessity within the competitive medical field (cf. Bourdieu 1991; Decoteau and Underman 2015). This interpretation arose most clearly from the second (the formal) type of inscrutability. The graph was simply a black box (Latour 1987): an unassailable, traveling icon of the bioinformaticians' authority. The focus on the graph as unintelligible reinforced the asymmetries among conference participants qua experts (cf. Wirtz 2005). It performatively entailed a participant structure that reinforced a hierarchy of expert authority, iconically substantiated in the ability of the bioinformatician to interpret. In this reading, the inner workings of mate-pair were not meant to be appresented; the social labor entailed in the knowledge production indexed by the graph was made invisible (Lynch et al 2009). Second-order stereotypes of personal and professional expertise were recast as first-order icons of fact (cf. Gal 2005).

However, I argue that the graphs did something broader: Not only did they underscore the privileged authority of particular individuals, they also made apparent the translator and the act of translation. In a sense, the graphs were the visualized opening of the black box – but rather than making the enclosed networks of knowledge and opinion available to democratic interrogation and public reason (Habermas 1962; Kant 1970[1784]), they simply reaffirmed the epistemic boundary between the two expert cosmologies. They made visible the ideological character of knowledge commensuration across paradigms, and manifested the otherwise denegated ritual necessity of *abject trust* in the interactional achievement of getting (clinical and scientific) worlds to 'hang together.' In interviews after meetings of the Tumor Board, both oncologists and bioinformaticians separately agreed that clinicians did not understand the graphs in such a way as to derive all the salient meaning held therein. The information presented was not equally falsifiable by all participants. They needed remediation and re-mediation.

This was a key feature of the so-called interdisciplinarity of the clinic, where multiple forms of expertise came together in the partially unified project of managing health. In situations of marked disjuncture and incomprehension, such as the mate-pair graphs, experts were not expected to justify their knowledge, or their authority to influence clinicians' decision making. This knowledge and this authority were, rather, presupposed. While interpretation (cf. Peirce 1940) and understanding (Steiner 1975) themselves might be seen as forms of translation, each 'semiotic moment' (Richland 2007)[9] isn't attended with the same anxiety. Communication across socially recognized boundaries – departments, laboratories, professions, etc. – is attended to with particular awareness.

[9] Compare William James's notion of the "specious present" (1893).

Highly anxious interactions, such as those undertaken by the participants in the Tumor Board, highlight the transformative quality of communication across epistemic divides. They make apparent the necessity of the abject trust entailed in determining participants' interpretations as (sufficiently) 'the same.'

Mate-pair provided a clear example of the constraints on 'mainstreaming' medical genetics. Its knowledge was not legible to everyone; despite its visualization, it did not "count as a form of direct … seeing" (Jasanoff 1998:728), but rather manifested the need for biotechnocratic mediation. The graphic rhetoric (see also Chapter Two) of the images proved persuasive – not through iconic, immediated facticity, but rather through indexical, deferred authority.[10] The overlapping lines simultaneously represented the propositional content of genetic structural variation as well as the incomprehensibility of those propositions without abject trust.

Jean Pouillon wrote that "it is the unbeliever who believes that the believer believes" (Pouillon 1982:4). The embedding of a proposition in the matrix "believe-in" (*croire à*) is non-factive, conventionally implicating its dubitative or unreal nature, as assessed by the author of the proposition. Categorizing a proposition as a belief in this way would suggest the potential falsity of the proposition. I argue here that what underlay this so-called interdisciplinary knowledge production was not the mere believing-in, but rather the *croyance-en*, the *credo* of a creed – put another way, the enchanted trust (Knorr Cetina 1999:135; Shapin 1994b) in an unchallenged and unchallengeable (and yet, unverifiable) *other* authority. Belief in knowledge produced in these settings required abject trust.

[10] This was a striking instance in which 'mainstreaming' had not taken place. The goal of mainstreaming was, contrarily, to "downshift" (Gal 2005, Parmentier 1998) expertise from an indexical relation of abject trust in an expert persona to an iconic relation to an affectively imminent and morally obvious truth for subjects of biomedical discourse.

Cancer Gets Smart.

Early in my fieldwork at the Center, I was shadowing a genetic counselor as she attended to a patient with end-stage cancer. She was explaining clonal evolution, that is, how a tumor could persist despite otherwise effective treatment. I was struck by a phrase she used with the patient, viz. "Cancer gets smart." (I quickly learned this rhetoric was common in such interactions.) Cancer got smart, she explained, in the sense that it was "reacting" to her chemotherapy regimen and "learning" to evade the drugs. "Cancer is smarter than us," she told the patient; it could outmaneuver even the most advanced interventions. Tumor growth could continue as new genetic mutations arose, overtaking the particular mutations obliquely targeted by the current therapy. That is, a particular drug could work to kill off many of the tumor cells, but mutations would necessarily arise "randomly," through "bad luck" (Tomasetti and Vogelstein 2015), thus providing new and untargeted avenues for continued cancer growth.

Scientists viewed tumerigenesis as an eminently complicated process. They typically assumed that cancer emerged as the result of "two strikes," viz. one inborn (germline) mutation predisposing a tissue to dysregulation; and another (acquired) mutation that appeared locally (somatically), over biographical time. Germline mutations were called "trunk" mutations, with one variant considered the original "driver" of tumor growth. The primary goal of therapy was to target such a mutation (often by way of inhibiting the activities of certain of its gene products), thus stymying the proliferation of the cells housing the mutation. However, cancer cells were notoriously "mutagenic," with the mitotic offspring of progenitor cells developing their own characteristic genotypes. In this

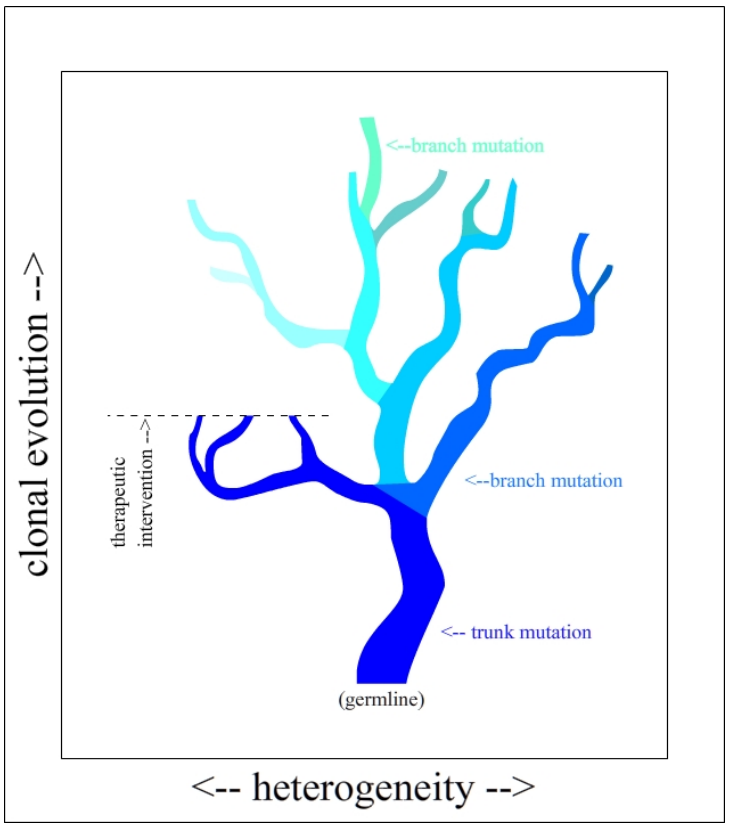

Figure I.4: The trouble with tumors.

way trunk lineages shot off into "branches" with their own, local mutations. These novel mutations were also capable of driving tumor growth. While clinicians considered it ideal to find and attack the trunk mutation, this did not necessarily mean that cancerous growth would cease. From the scientific point of view, tumors were importantly heterogeneous. (See Figure I.4.)

The laboratorians who worked with avatars – mouse models that hosted human tumors for research – were especially concerned with tumor heterogeneity and clonal evolution. Tumors were transplanted into mice, where they grew until ethical dictates

required the host to be "sacrificed."[11] The tumor was then harvested and transplanted into another generation of mice. The first-generation tumor, however, was prized for its "integrity," its relative identity with the primary tumor that was still growing in the original human patient. "Even between mice you might have a significant change," a pharmacologist told me. "Plus, every biopsy sample is different." Grafted tumors in avatars underscored the difficulties of cancer genetics in general: There was diachronic instability of the genotype across generations of cells and organisms as well as synchronic instability across distinct but physically adjacent lineages of cells.

Thus it might seem that scientific discourse about cancer's agency differed markedly from that of the patient-facing genetic counselors and their lay interlocutors. And in some ways it did. Patients often told me they had named their tumors, performatively nominating them into quasi-subject positions. One woman even talked with me on her tumor's "birthday." They discussed the cancer as though it were a coherent, 'other' agency within their bodies (see also Hunt 1998; Panourgia and Neni 1995). Contrarily, in the above description, laboratorians fixated on the *incoherence* of the tumor across time and space.

However, clinicians and scientists participated in such animist talk backstage as well. A cytopathologist discussed how cancers became resistant to particular interventions: "They're doing that somehow. […] They win for a while, until we come up with a new drug that takes them down a peg, and we get a new mutation, and the game goes on." "It changes its signal pathways so it can bypass the drug," a biochemist said of the particular cancer he studied. In these examples, agency was not located in cells, but rather in the cancers

[11] For instance, the tumor was not supposed to exceed "the size of a grape."

themselves. But what kind of coherent agency could a tumor have, given that each was driven in multiple directions by unrelated mutations?[12]

In such discourse the tumors were attributed the will to survive. This is not to say there was no degree of metaphorical intension underlying certain instances of such usage (cf. Ochs, Gonzales, and Jacoby 1996). However, it was certainly clear that tumors were taken as vibrant (Benett 2010), capable of self-direction (Hegel 1998[1830-1831]), and even possessing intentionality and desire (Appadurai 2013:257; contrast Gregory 2014). They were not mere "artefacts" (Godelier 1986) formed by the mapping of semiotic concepts onto material substrates that only partially "tolerated" (Murphy 2013:119) such imposition. They "want[ed] to survive," a genetic counselor said. Patients 'rigidly designated' (Kripke 1980) their cancers, allowing them to persist over time and transformation. Clinicians and scientists portrayed them as reproducing themselves, enacting their ipseity as a self-evident obviousness.[13]

The enactment of tumors as agentive required that internal heterogeneity be erased (Irvine and Gal 2000) and that a particular 'scale' (viz. the tumor rather than the cell or the body) be selected. Despite the local discourse (and its scholastic parallels among the so-called new materialists), cancer did not merely 'throw itself together' (Stewart 2012). It appeared as perduring and active as a function of its conceptualization rather than as a function of some immutable materiality. And it did so in only certain strains of discourse. In

[12] Moreover, tumor "margins" were a constant concern for pathologists, underscoring the incoherence of even the physical territoriality of the growth. See also Chapter One.
[13] See also Stotz and Griffiths (2013) and Maynard Smith (2000) for analyses of the ascription of agency to "genetic information" in scientific discourse, and Levy (2011) for a retort that such rhetoric is "factionalist" and fundamentally framed as something other than literal.

fact, the case of 'smart cancer' speaks to the ontological heterogeneity both between and within classes of person in the clinic (see also Mol 2002).

A Person is a Population.

Near the end of my fieldwork, I met for coffee with an educator and an editor from the Section of Patient Education (SPE). Our coffee breaks were a fairly regular occurrence, but so close to my departure the two women were particularly interested in convincing me to give a talk to their coworkers about my experiences as an intern with the Section. I was the first to arrive at the small coffee shop, having come from my office in Medical Ethics, so I grabbed an Americano and sat down at a table with a few minutes to reflect.

A group of Arab men in white thawbs walked past; some young residents in scrubs ordered pizza next door; a cancer biologist recognized me and waved as he hurried between buildings. Machinery rumbled behind the counter while the barista prepared a macchiato for a man in suit and tie. Meanwhile, I ruminated on doctor–patient communication, informed consent, shared decision-making, and other pop-ethical themes about which I thought the staff of SPE might be interested in hearing me talk.

Soon I was joined by Julie Gustafson and Lisa Campbell, the educator and the editor, respectively. After a brief chat about the brown-bag luncheon at which they wanted me to speak, we began to discuss a project on which they were collaborating with the Center for Individualized Medicine. Knowing the Center's central role in my fieldwork and my interest in linguistics, Julie brought up what she saw as the "strangeness" of the modifier *individualized* in the Center's title. Individualized medicine – in other hospitals, cognate institutions were called personalized medicine, stratified medicine, precision medicine, or

P4 medicine[14] – was typically described as a novel form of healthcare that used new technologies to tailor treatment to the particularities of any given patient's case. For the Center, this meant specifically that patients would undergo genetic testing in order to develop a unique profile for their case.[15]

Julie, who had been working with the Department of Medical Genetics for half a decade and with the Center since its opening two years prior, thought *individualized* was a misnomer. The new focus on genetics had not individualized healthcare practice, in her opinion. We had known each other long enough that Julie and Lisa – usually eminently polite and deferential – felt comfortable airing some complaints. Medicine, they confessed, was not becoming more individualized. In fact, if anything it was becoming less individualized. Patients now spent hours waiting for just minutes of face-time with a physician, Lisa embellished with some humor but more earnestness. "Now *individualized* means 'biological' and 'genomic,'" she lamented.

Real individualized medicine, they contended, was "more human." Rather than consider patients as a string of genes and molecules, this form of medicine should take into

[14] P4 stood for "personalized, predictive, preventive, and participatory." Andrew Lakoff contends that it would be more apt to call it "segmented medicine," since it reimagines types of persons based on "pharmacological specificity" (Lakoff 2007:753). That it, it classifies persons based not on particular conditions of the body itself but rather on the body's relational response to specific drugs.

[15] It was not rare for scientists to say that the Center was too narrowly focused on genetics, and that it should diversify into other avant-garde fields of medical research. The translational space between gene or protein and higher-level biology was said to be complicated by a complex system of mediating dimensions (cf. Bizarri et al 2011). In fact, genetic science had been "radically subverting" its own promise to epistemic primacy for decades (Keller 1995:21-22). Even James Watson, one of the legendary founding fathers of genetics, recently told the *New York Times* that, were he to begin his career again, he would take up biochemistry in order to study metabolism rather than genetics (Apple 2016), changing his previous stance that "our fate is in our genes" (Jaroff 1989).

account patients' emotions and biographical histories. In some ways, they suggested, SPE demonstrated exactly the qualities of truly individualized medicine. In their free education classes, a patient could meet one-on-one with a specialist in order to discuss his or her particular health concerns, diagnoses, and treatments. Educators could take the time to comfort patients, whereas clinicians were overburdened by myriad financial concerns and professional obligations. Educators could treat a patient's condition biographically. Illness was seen as a social phenomenon (*à la* Kleinman 1988) and the product of social relations (*à la* Taussig 1980; Evans-Pritchard 1937). This was why SPE was vital, they said. It allowed a space for the fullness of the patient's context to be addressed, to provide a supplement to the clinician's cosmology of nucleotides and billable hours. Their face-to-face engagement would make patients feel less "isolated" and anonymous (cf. Stevenson 2012). That the Center had given itself the title *individualized* evidenced a shift in focus "from connection to biology," Julie explained.

I told them that I had talked to a number of clinicians working in Oncology and Medical Genetics who were similarly frustrated with the wording of the title. An oncologist once told me, "*All* of [the hospital] has been doing individualized medicine since [the hospital] began. *Medicine* is individualized medicine." These clinicians felt they had always been providing personalized, humanized care to patients.[16] "Populations don't come into my office; I deal with individuals," a medical geneticist had once announced at a symposium on large-scale sequencing.

[16] In fact already in 1823, Jan Purkyně, the founder of histology, noted that some of his contemporaries defined medicine as "the art of individualising" [*die Kunst des Individualisierens*] (Ginzburg and Davin 1980:26).

Likewise, an oncologist collaborating on an ethics project about "patient views" told me she was unsurprised to find no correlation between the vernacular sociological categories she had used (e.g., race, education, income) and "the diversity of opinions" she had collected in patient interviews. "We're all individuals," she explained cleanly. The lack of correlation did not index the inapplicability or invalidity of her categories vis-à-vis her medical research. Instead, she suggested a *reductio ad individuum*: The social world, she posited, was in its particularity ultimately too complex to be modeled. (Such a view was supported by the widespread hierarchical divide within the hospital between "qualitative" and "quantitative" research.)

Another oncologist cautioned that physicians should not rely heavily on guidelines based on abstract types of people and abstract types of disease. He complained that he was supposed to medicate an 82-year-old man with a blood pressure of 142/64, which institutional regulations classified as hypertensive. The man's age, the oncologist contended, was a significant variable. It modulated the analysis of the reading, negating the validity of the standardized interpretation. "I'm supposed to lower that? Are you kidding me?"

For these clinicians, 'the individual' could not be represented accurately or successfully by standard dimensions of identity. Instead, the individual was best understood through the auratic gestalt of physical instantiation. What it meant to be an individual – to practice individualized medicine – was fetishistically portrayed as the rejection of abstraction. "Statistics doesn't apply to individuals," one pharmacist told me quite boldly.

However, my work with scientists in the genetics laboratories gave a very different image of what constituted an individual. "Individualized medicine means 'one size does not fit all,'" a laboratorian told me. "Instead, we use biomarkers [here meaning genetic and protein profiles] to subclassify our patients."[17] In terms of treatment, the individual was thus one of a closed set of biomarkers. Even in less minimalist interpretations, the individual was often suggested to be constituted of a finite number of types of particle (e.g. A, T, C, G), and particularity was simply the result of emergent combinatoric complexity. Bioinformaticians joked about the ethical attempt to 'de-identify' raw data (stored in Variant Call Format (VCF) text files) produced from large-scale genetic tests, which yielded extensive lists of nucleotides for a particular patient. "The VCF file with 100,000 [genetic] variants, how de-identified is that?" The file could not have its link to a particular individual successfully scrubbed because the file – with its exhaustive list of nucleotides – was tautologically identical with that individual. In this ontological reduction (Stotz and Griffiths 2013), the individual was ultimately its component parts.

However, these parts only became meaningful – could only work to pick out an individual as a complex bodily system – epidemiologically. That is, the significance of a certain nucleotide at a certain locus with respect to a certain medical consequence could only be determined by large-cohort studies. A biochemist explained it thus: "You need thousands of samples to work out the [disease] pathway, so then the pathway becomes the average of the whole. And so then when you get down to a single person, their pathway may be unique." The unique person was only comprehensible with reference to those

[17] Ivan Illich (1976) believed that the role of clinician had recently transformed from that of a personal artisan to that of an institutional technician who treated classes of patient rather than individuals.

thousands of other persons whose samples had already been scrutinized. The individual was filled (*chargé*) with other individuals (cf. Rabinow 1996:92).

That is to say, even while considering the gestalt of the individual, it still remained a nexus point at the middle of a number of standard dimensions of identity. It was simultaneously collective and individual (cf. Hull 2003:288), "a unique actualization of a general phenomenon" (Sahlins 1985:108; Geertz 1961:153-154). It was legible only as a macrological type that transcended the accidence of its instantiation (Silverstein 2004). Even as clinicians "individualized" the patient in particular encounters, they either did so along epidemiologically constituted dimensions of abstract identity (say, age), or they 'reduced' the patient to an unthinkable and illegible manifold (cf. Pierce 1868). In the latter case, they were still forced to address the patient's *disorder* in terms of abstractions, disciplining the body and its history into abstractly recognizable parts (Hirschauer 1991; Latour 1986).

At one end of the spectrum of meaning, the professionals of SPE contended that *individualized* best described the biographical patient, embedded within observable social relations. At the other, the laboratorians used *individualized* to denote the 'molecularized' (cf. Rose 2007) and statistically-interpreted body. Of course, the two extremes were discursive models, but they were also discursively schismogenic, each escalating in rhetoric in specific contrast to the other. This schismogenesis also undergirded the different professional identities in the clinic, creating and contrasting different roles and relations to the practice of genomic medicine.

It should be clear, however, that the significance of the term *individualized* was not merely semantic. No matter what one 'picked out' with the word, one made particular

claims with its use. The genetic counselors, who obtained 'informed consent' from patients to undergo testing, ratified their particular authority to understand patients as 'individuals.' Medical ethicists demonstrated their expertise by rooting out patients' "individual value systems." Even SPE's reclamation of the term underscored its pragmatic value. Labeling oneself *individualized* served to justify one's particular professional role and form of expertise. It was taken to denote a sort of epistemic – and associated linguistic – genre. Phrases could be called "individualized" if they "sounded like" the verbiage that would appear on the Center's public-facing advertisements. Certain practices could be characterized as "more individualized medicine" as a comparative modifier. In fact, *individualized* was even locally discussed as "a brand." In choosing the vague but potent designation, one performed his or her authority by citing a particular regime of value with broad circulation (Nakassis 2012) and imposing hype (Sunder Rajan 2006). An educator in SPE could make a claim for her professional value based on the Center's presupposed prestige. An oncologist could promote the importance of a certain test by linking it to the localized regime of what President Obama called the "boundless possibilities" of precision medicine (Pear 2015).

Scenography of the Ethnography

These four themes – figurations of the future of healthcare, the role of trust in the validation of commensuration, power and impotence relative to disease, and conceptualizations of individuality – undergird this monograph on the practice of medical and linguistic translation in the Center for Individualized Medicine. The text begins with a chapter that gives a bird's-eye-view of the circulatory system of the clinic. It is followed by

two paired chapters. The first pair discusses the politics and poetics of simplification as information moves from patient to clinician to laboratorian and back again. The second pair focuses on the encoding of evidence in simplified information and the trust (*croire-en*) that allows for the interpretation of such translation as successful or felicitous. Below, I briefly describe each chapter in turn.

"Signs of Disease," the first chapter, observes the life history of a patient's case in the individualized medicine clinic. When a patient first arrived at the clinic, he or she provided information for the medical case as a sort of speaking subject and embodied proof. While clinicians viewed the talk with some degree of skepticism, these initial visits nonetheless informed clinical interpretations of the case and the plan by which the case proceeded. Blood was subsequently drawn or tissue was taken, and the patient's sample was sent to the Molecular Genetics laboratory, where it underwent numerous physical and chemical transformations in the process of being transformed into digital "information." The major question for this chapter regards the semiotic modality by which such a sample remains tethered to the patient and representative of the case. To this end, I propose a concept I call *reconsecration*, ritual re-nominations of the material at each socially recognized moment of translation, explicitly linking one named instantiation to that which proceeded it. I conclude with a consideration of the consequences that emerge when the self-sameness of the case comes into question with a concern about misattributed paternity.

The second chapter, "You become everyone," provides a close look at the ideology underpinning the 'simplification' of complex medical information to hermeneutically lay patients. Specifically, it considers the work of the Section of Patient Education as writers collaborate with clinicians to produce pamphlets about a variety of medical conditions.

"Plain language," the linguistic register SPE used in writing these texts, had many features that professionals in the clinic viewed as 'simplified' – morphological and syntactic simplicity, second-person address, and what they took to be asymptotically universal legibility. Writers undertook certain *technologies of self*, figuratively 'becoming' their imagined addressees of the text in order to determine how to make clinical knowledge legible to non-specialist audiences. I argue that ultimately the register was typified less by immanent features like lexical coocurrence and more by characterological stereotypes of plain language users.

In the third chapter, "Bad Affect," I continue my discussion of simplification by considering the translation of intended pragmatic effects as writers and clinicians 'reduced' information for patients. Because they believed patients would not understand their propositions well enough to be motivated to take appropriate action, these professionals often focused not on a text's semantic content but on the ability of its poetic structure to provoke particular affective responses. Through *anticipatory affect management*, these professionals worked to influence what decisions a patient could and would make. Moreover, I discuss the ethical commandments against paternalism and coercion, which encumbered the clinicians' and writers' abilities to direct a patient's choices to what they viewed as being in the patient's best interests. However, I argue, the ascription of vague, affective categories to patients and their actions allowed professionals to foreclose particular outcomes while all the while appearing acceptably ethical.

The fourth chapter, "Ethics and Epistemics," begins the second paired chapters. In it I describe the distinction professionals at the Center made between clinical knowledge and research data. The distinction had both ethical and epistemic dimensions: Clinical

knowledge represented scientists' greater certainty as well as an institutional sanction for use in healthcare decision-making. Research data, on the other hand, was understood to be less accurate and officially disallowed from informing decision-making. However, in the extraordinary space of individualized medicine, official standards of care were considered too restrictive. By the time patients reached the clinic, they had already tried all such standards and their presenting concerns were still unmet. I examine the criteria by which clinicians worked to move information from the designated domain of data gradiently closer to the domain of knowledge. In particular, I argue that this scale from scientific uncertainty to confidence is crosscut in significant ways by other dimensions, such as the *survival imperative*, clinical practice guidelines, and risk. The negotiated assessment of knowledge was thus a pragmatic endeavor.

The manuscript closes with the fifth chapter, "Evidence, Confidence, Fact." Having established the practical relevance of the division between clinical and scientific epistemologies, I turn to consider the management of uncertainty and slippage as information was transduced and transformed from laboratorian to physician to patient. Centrally, this chapter dissects the complex naming practices for genes used by these various actors. I argue that the ways in which the gene names embedded descriptive and evidential information worked to represent the pragmatic role the genetic information played in different contexts. For instance, in the clinic where little detail about a gene was needed for it to serve its function in informing healthcare decisions, and thus a relatively simplex name sufficed. By contrast, in the laboratory, the qualities of a gene were under much greater scrutiny and thus the name used to label a gene bore much more semantic

content. The text thus opens and closes with a consideration of the role of names and naming in the practice of ‘translating’ knowledge.

CHAPTER ONE: SIGNS OF DISEASE

Failure in Referring

It was the end of the workday, and the case conference was already running late. However, despite the efforts of Dr. Orlov, who was presenting the case, it was proving too complicated to abbreviate. The patient, a young man in his thirties, was suffering from orthostatic hypotension – sudden dizziness on standing – and, Dr. Orlov stated, "what he calls 'cognitive brain fogs.' The way he describes these episodes, they're severely debilitating." Furthermore, his mother and three maternal relatives had complained about similar symptoms. The patient's mother, in fact, "says they are getting increasingly worse in duration."

However, Dr. Orlov explained, the patient and his family had recently immigrated to the United States, and they could not get any of their previous medical records delivered. "So it's very hard to confirm what they're telling us," he stated.

"Looking at him and his mother," the doctor added, "they just looked completely normal. In fact, the son looked like he was in really good shape." Results from genome-scale genetic testing on the patient had revealed no diagnosis. "This is a very motivated family, so we did already request the expanded report," the doctor noted, but that had not returned anything deemed significant either. "So the big surprise is we didn't find anything," he sarcastically summarized.

"Were you thinking autonomic [neuropathy]?" asked one of the medical geneticists in attendance.

"Autonomic was normal, but then he came back with kidney stones," Dr. Orlov said. "We also tested CK," he continued, referencing an enzyme considered an index of muscle damage, "and that made us curious for a second because of elevated levels, but that's actually common in bulky, muscular men." In fact, Dr. Orlov emphasized, his CK level ended up simply proving how healthy he was.

"I'm thinking psychosocial," concluded Dr. Orlov. "His concern, it's subjective; it's very vague. Actually, I'm thinking he's having side effects to the drugs he was initially given. I think *they* gave him the kidney stones, and now those are listed in his phenotype, and that's misleading our diagnosis." That is, the doctor believed the stones, rather than being symptoms of disorder, were the iatrogenic result of medication.

Several of the physicians in attendance expressed their agreement. They concluded that Dr. Orlov should simply tell the patient that no diagnostic results had been found and that it was unlikely that genetics would prove to be "the answer" to the mystery of his ailment. Perhaps, they worried, there was not even a somatic disorder, merely a diffuse constellation of symptoms provoked by some thing or things "psychosocial." Its grounding in biomedical reality was thus problematized.

This case represented a 'failure in referring' in two senses. The first demonstrates an ontological issue of jurisdiction. In the opinion of my interlocutors, the referring physician had failed to recognize the *type* of disorder or disorders underlying the patient's symptoms. The case was not an object on which they could enact their expertise (cf. Carr 2010); they were incapable of representing it as something subject to medical intervention.

The second sense of the case's 'failure in referring' appeared in Dr. Orlov's assertion that the symptoms did not even constitute a unified entity. The referent of the patient's complaints, posited as a unique object in the world, simply did not exist. The signifier was purported to be 'empty' (e.g. Barthes 1972; Boyer 1986; cf. Lévi-Strauss 1987, 'floating'), finding no hold in the 'real world' of the clinicians.[1]

Despite these shortcomings, however, both kinds of referring had succeeded in a certain pragmatic sense. The patient, now believed to be inappropriate for genetic testing, did indeed have his genes sequenced. And the clinicians did manage to refer to some thing – even while eventually concluding it did not exist – to rally around it, to debate its qualities, and to relate it to purportedly copresent signs. There is no expressed belief that Russellian (e.g. Russell 1905) truth conditions had been satisfied; the clinicians harbored no "misimpression" (Kripke 1977:266) that a disease entity actually existed.[2] Its very lack of existence was the central aspect of the debate at hand, the description predicated of the referent.

These two senses of referring in fact conjoin what Donnellan (1966) calls the twin uses of definite descriptions: Clinicians at the case conference attempted both to ascribe (attributive) and to pick out (referential). They sought to demonstrate the qualities of the object, opening the signs up to interpretation and critique. The clinicians also attempted to delimit the disorder, to fit it into an already established

[1] In contrast to Putnam (1975) and his followers, it is not my contention that the success of a sign in referring is achieved by extending a real existent (cf. also Searle 1969:77, "Whatever is referred to must exist"). However, a belief in an ultimately single reality underlies the semiotic ideology of my interlocutors at the case conference, and as is demonstrated below, at this particular clinic more broadly.
[2] Gal (2017) similarly argues that the appearance of material essence is a function of cultural-historical conditioning.

cosmological and nosological order (and, perhaps, subsequently to dismiss it). In the case conference we see contentions around both the qualities predicated of an object and the picking-out of the object in the first place.

Take, for instance, the hypothetical proposition, "The patient's condition is severe." Based on the conditions of its uptake, Donnellan suggests the definite noun phrase "the patient's condition" has the potential to produce two types of interpretants. If understood as attributive, the proposition would mean something like, "Whatever existent the condition proves to be, it is certainly severe." If understood as referential, it would mean something like, "This specific cluster of symptoms, which are believed to constitute the patient's condition, is severe." Both senses of reference were thus in play in the case conference.

I would encourage my reader to consider the act of reference in a Pragmatist vein (e.g. particularly James 2003).[3] Reference, and even the presuppositional construction of a referent, is an achievement that takes many 'semiotic moments' (Richland 2007). It is not as simple as picking out the apparent object to which a sign is semiologically linked. It is an interactive (if I might allude to Latour's *act*ants) feat. The clinicians in the above vignette spent nearly half an hour trying to determine their referent.

In the following chapter, I interrogate the ways in which signs came to index a specific object, that of the potential disorder in the context of genetic testing at this particular clinic. I describe the radical material and semiotic transductions the

[3] "The percept […] not only *verifies* the concept, proves its function of knowing that percept to be true, but the percept's existence as the terminus of the chain of intermediaries *creates* the function" (2003:32).

referent underwent as it moved across sociotechnical space and time, from a patient's initial visit to the clinic, through the laboratory, to the clinicians' eventual recommendation for an altered course of healthcare. When a patient came into the clinic for genomic testing, she carried with herself an enormous variety of potential signs. As her case moved through the testing process, the types of material-semiotic existents and potentials that served as evidence for the clinicians and scientists working on her case changed dramatically. The object of their analysis might be – inter alia – a speaking subject; a physical body; peripheral blood; a DNA strand; or a printed report of Gs, Cs, Ts, and As. Because of the diversity of qualia thrown up by these divergent avatars of the potential disorder, one must undertake significant semiotic labor in order to maintain the coherence of the referent across its biographical career.

I discuss the transduction (cf. Silverstein 2003) of the potential disorder as its meaningfulness-in-context was calibrated across multiple modalities of expression (or extension). This variability took the form of both signifiers (naming practices) and signifieds (physical and verbal objects). The asymmetrical conversion of one form into the next demanded that broad and anxious semiotic labor be undertaken to commensurate the two instantiations. The material embodiment of signs indexing the potential disorder delimited and determined its ability to refer. What did it mean for an embodied patient, a blood sample, and a test report each to partake in the same identity?

I demonstrate that, due to the very recalcitrant nature of these signs, new baptismal rituals (cf. Kripke 1972) – *reconsecrations* – were needed at specific

moments of transduction in order explicitly to forge new links in the interdiscursive chain of the disorder's emergent reality. That the referent perdured was a specifically *social* fact. It is not that the events of linkage were themselves necessarily invoked chronotopically through reference, though this indeed was occasionally the case. Rather, I establish that the performative re-nominations of objects acted to control for material contingencies but often disappeared from an agent's metapragmatic awareness (Silverstein 2001) in subsequent deployments. These rituals (both as tokens and types) primarily became salient to acts of reference only after the *identity* of two objects linked interdiscursively had become problematic. (I explore this below through a case of suspected misattributed paternity.)

This chapter specifically examines how these objects were sieved (Kockelman 2013) into narratives of disorder (as 'signs of disease') and how the patient's body multiple (Mol 2002) was signified as singular while erasing the multiplicity inherent in these acts of semiosis. Departing from previous work (also Harbers 2002), this chapter theorizes the process of coordination and commensuration, presenting ritual difficulty rather than easy, nominalist presupposition. Specifically, it demonstrates the semiotic act of making an object 'hang together' across radical transformation as a social achievement.

I demonstrate not only that the referent emerged through enactment but even that its barest qualification as an existent was constantly in jeopardy. An array of instantiations were linked interdiscursively and cumulatively reified as a congruent object, functionally made real and existent in a perduring semiotic

identity. I argue that – despite intermodality and the loss of salient qualia through transduction – reference was maintained through multiple ritual reconsecrations linking discrete instantiations explicitly in an interdiscursive chain.

Scene 1: The Clinic

It was a typical Tuesday morning. I was sitting at my computer in the genetic counselors' workroom, casually chatting with Michelle Fisher, the genetic counselor I was shadowing that day. Other counselors were sitting in their open cubicles, typing, reading, and occasionally joining Michelle and me in conversation. Around nine o'clock, Dr. Ivanova,[4] one of the medical geneticists, arrived and ushered the two of us into her office.

"Our first patient is Caroline Osborn," she informed us, sitting at her desk and pulling up the patient's electronic medical record and a web browser. "She was referred to us because she started having symptoms of motor neuron disease at around 45." "That's an early age of onset," Michelle told me. "A full decade earlier than is typical for non-genetic variants of the disorder," Dr. Ivanova added.

Our meeting with Dr. Ivanova was brief and largely consumed with searching online government and hospital databases for specific panels of genetic tests. This second-order abduction was meant to determine what method would be best to determine the patient's underlying pathology. Dr. Ivanova explained that she suspected that an amyotrophic lateral sclerosis (ALS) panel would be most useful,

[4] I follow local naming practices. Most clinician-physician preferred to be called Dr. X, while all others – including medical doctors who worked in the laboratories – were simply called by their first name.

but she needed to find one expansive enough to test for other potential disorders as well. She and Michelle discussed the candidate panels and selected one they determined to be most likely to return results about the greatest number of suspect disorders.

A clinical assistant knocked on the open door and peeked in. “Your patient has been roomed, Dr. Ivanova.”

”You ready?” the doctor asked me. I nodded, and the two of us walked down the hallway to the room in which the patient was waiting. Dr. Ivanova rapped on the door and opened it onto a wood-paneled room. A large window overlooked the curving taupe glass of the clinical laboratory next door. We stepped in and turned to the slight, middle-aged woman sitting on the couch along the wall. Her hair was tied back in a ponytail, and she wore a sweatshirt and jeans. A black walker stood next to her.

“Hi, Mrs. Osborn,” said Dr. Ivanova. “How are you today?” She proceeded to introduce herself, and then me, and then sat down at the desk. I sat on a bench across from the patient. “I’m here to talk to you about your options for genetic testing,” Dr. Ivanova explained, “but first I’d like to do a short check-up.” Dr. Ivanova described the symptoms listed in Caroline’s medical record, and Caroline highlighted her primary concern, namely, her muscle spasms.

“Are you okay showing me how you walk up and down the hallway? Do you think you can do it without your walker?” asked the doctor. The patient affirmed, and we again stood and exited the room. Caroline left her walker against the wall and started slowly down the Medical Genetics hall, toward the front desk. Dr.

Ivanova turned partially toward me and noted aloud her observations about the patient's gait and the swing of her arms. She transduced this continuous process into a series of discrete aspects and phases, rendering them indexical of underlying states, themselves rendered indexical of potential disorder. The patient turned around and headed back toward us. "Look at how stiff her left arm is," the doctor prompted me. "But I think that's probably because she's concerned about falling." Even under these sterilizing circumstances, the doctor was only ever provided with an asymptotically context-free space for the exhibition of qualia. The materiality of their instantiation jeopardized the purity of their form (cf. Keane 2003).

Back in the room, Dr. Ivanova asked Caroline to sit on the examination table, cuff her pant legs to the knees, remove her socks, and pull her sweatshirt's sleeves back to her elbows. As the patient complied, Dr. Ivanova stated, "The right is more affected than the left." Caroline nodded. Dr. Ivanova then delicately grasped the woman's arm, feeling for the muscle spasms she had described. She tapped the patient's knees with a reflex hammer and watched her legs swing. "Does your tongue spasm as well?" "No," the patient replied after reflecting for a moment.

The examination served to provide Dr. Ivanova the opportunity to elicit signs from otherwise opaque matter. In Munn's sense (1986), these were 'qualisigns,' ex-Firsts that were embodied and rendered discrete as signs, parsing the manifold of potential signification.[5] Or, as Manning glosses, drawing on STS theorizations of materiality, they are "the semiotic affordances of a thing" (Manning 2012:14). However, they did not provide transparent access to the existent object, but rather

[5] Cf. Peirce (1991:23) "The function of conceptions is to reduce the manifold of sensuous impressions to unity."

merely mediated it by giving rise to further signs through interpretation, hinting indexically at the potential disorder. Moreover, they did not represent 'obviousnesses' of the world. They were only sensible through the technoscientific connoisseurship of the medical geneticist. In fact, as I demonstrate below, some signs were not even intelligible to those speaking subjects who actively produced them.

"You can hop back down," Dr. Ivanova said, stepping back as Caroline got off the table and returned to the couch, where she subsequently unfurled her pants and sleeves. The doctor sat in her chair and announced that they were now going to discuss the potential genetic tests Caroline could opt to have done. Dr. Ivanova stressed that the tests would be for merely diagnostic purposes. "There is no gene therapy," she cautioned: "The results won't change treatment." After answering some of the patient's questions, the doctor announced that she would send in the genetic counselor to explain more about the tests and review insurance coverage. She handed Caroline her card and exited.

The patient and I chatted a few minutes, until Michelle knocked on the door and entered. She introduced herself, stating that her role as a genetic counselor was to inform her patients about the science and ethics behind their healthcare options. "Before we move on to that, though, I'd like to get your family history."

"Sure," Caroline responded as Michelle flipped open a notepad and clicked her pen. She drew a circle and made two lines going up from it. "Are your parents living?" "Yes." "And how old are they?" Michelle added a circle and a square to the end of the lines and wrote the ages next to them. "How is their health, generally?"

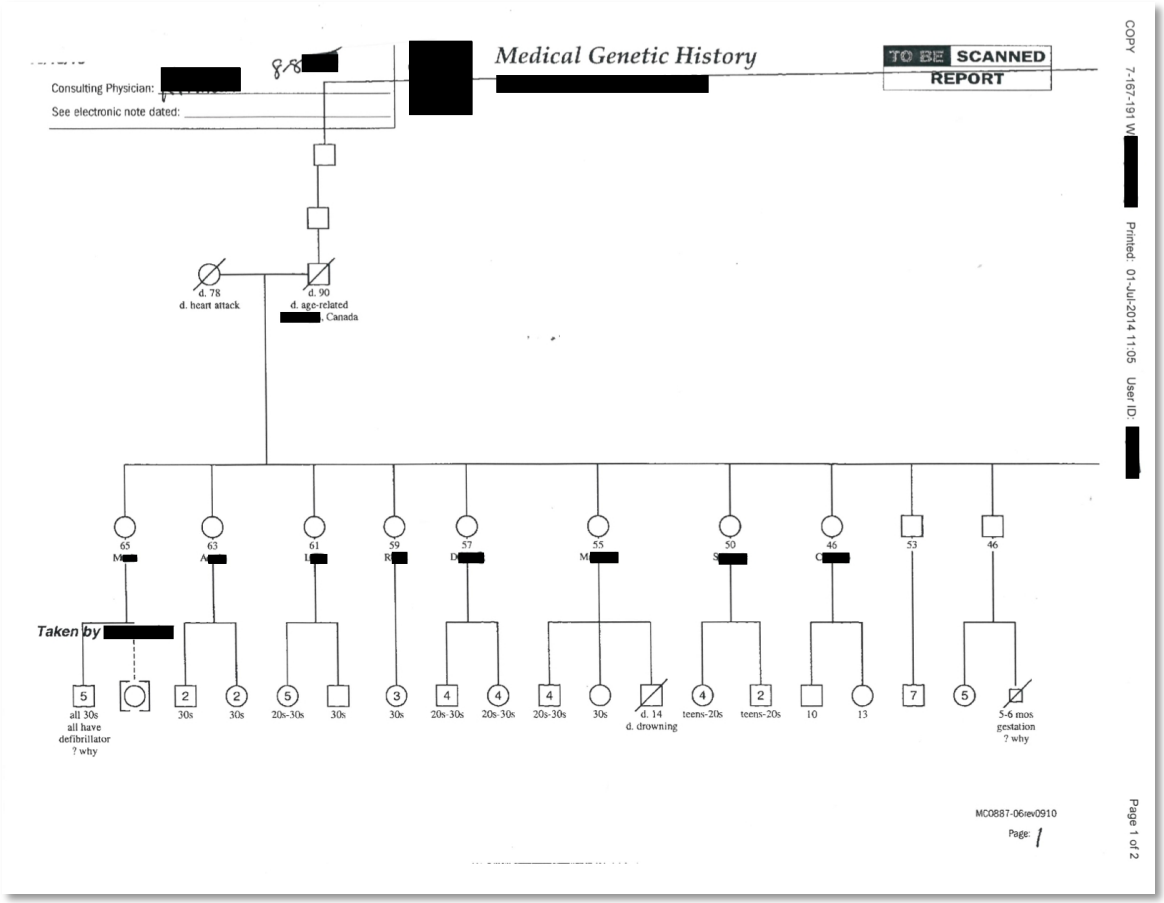

Figure 1.1: The first page of a pedigree.

Next to the circle she wrote, as Caroline narrated, that her mother's arm twitched and that she had difficulty walking.

Michelle continued to ask about other family members – siblings, aunts and uncles, grandparents, cousins – transducing the information Caroline provided into symbols and annotations. The pedigree, as it was called, expanded horizontally and vertically. Individuals became circles (females) and squares (males). Those deceased had a slash drawn through their symbol. The only other data that was recorded were age (current or at time of death) and those health conditions that

Michelle deemed potentially related to Caroline's, with age of onset. (See Figure 1.1 for an example pedigree.)

Not all of the information Caroline provided about her relatives was written on the pedigree. Individuals' career and marital status were ignored as "extraneous qualities" (Abott 1988:41). The patient's narrative data were sieved into symbols of death and disorder. As Kaja Finkler notes, "At present, [consanguineous] family and kinship relations may be defined more by the inheritance of disorders and pain than by the inheritance of status and social attributes" (2001:248). The pedigree, emerging as a diagrammatic index of potential disorder in the patient, conserved and lost certain propositional features of the original verbal object, Caroline's proffered family history. This transduction was only one of many nodes at which the expert gatekeeper mediated the qualities assigned to the referent.

Looking at the genetic counselor's notepad, the patient joked, "It looks like you're drawing stick figures." "I'm *very* artistic," Michelle laughed. "After our session I'll enter this into the computer so other people can read it." A program designed for the purpose of taking family histories was actually available, but several of the genetic counselors preferred not to use it, complaining that it was too slow and ended up encumbering their sessions with patients.

After completing the pedigree, Michelle paused to examine it. "It looks like it's just your mom and niece who have similar symptoms." Caroline agreed. It was typical for the long process of constructing a pedigree to result in such a glib observation. In fact, it was even more common that the genetic counselor found none of the information presented in the diagram at all noteworthy.

Michelle then handed the patient an iPad with a PowerPoint presentation on the screen. "Now we'll go over Genetics 101," she said jocularly. Swiping through the slides, she explained some fundamental aspects of the science of genetics[6] and then proceeded to discuss the two tests available to Caroline through the IM Clinic, viz. an ALS panel and whole exome sequencing. Michelle also suggested a blood test for lactate, the accumulation of which in motor-neuron and muscle cells was associated with the atrophy characteristic of ALS. (Michelle told me afterwards that Dr. Ivanova had suggested this test to her after finishing the examination.)

In the end, the patient opted for the blood test. The Clinic would also send a pre-authorization request to her insurance company in order to determine coverage for the ALS panel. If the test were approved, Michelle and Caroline agreed, they would move forward. Michelle placed orders for blood draws on the computer, and then the three of us left the room. Michelle directed Caroline, who again was using her walker, to Phlebotomy. There a nurse would collect two samples of her peripheral blood, one of which would be stored in a freezer until the insurance company responded to their request.

Scene 2: The Laboratory

The Molecular Genetics laboratory was characterized by silence. In one room, cytotechnologists peered quietly into microscopes. In another, technicians meticulously pipetted tangles of DNA from vials, while others quietly inserted and removed trays from extraction robots. One room was dominated by the subtle hum

[6] The ritual of 'informing the patient' and the decision-making process are central to Chapter Two of this dissertation and are discussed at length there.

of a freezer filled with blood samples from around the world. The transformations enacted upon patients' submitted materials – that is, those existents construed as indexical of (aspects of) the potential disorder – were undertaken predominantly without recourse to verbal exchange. Instead, computers analyzed barcodes and requisition documents, algorithms compared genomes, and sensually available percepts of sample containers (determiners) determined the type of chemical reagents they received. Names and naming, therefore, were materially embodied and relatively stable signs determining the interdiscursive linkage between moments in the sample's evolution. This section documents that evolution and demonstrates the semiotic labor undertaken to maintain the resulting signs' ability to co-refer to the initially baptized object, the patient's potential disorder.

The potential disorder's life in the Molecular Genetics Laboratory began when a courier arrived with a patient's blood samples, stored in vials. The vials bore caps with distinctive colors, denoting the type of anticoagulant used in Phlebotomy in order to keep the blood "fresh." The verbal category was "transmuted" into a visual sign (Jakobson 1959). (This quality would eventually become salient to the process of DNA extraction.) A single sample could consist of more than one vial. The courier also brought a requisition form with them. This form bore printed information about the patient (name, date of birth, ethnic background, and "gender"),[7] about the sample (date of collection and sample type), and about the

[7] I was informed by one of the laboratorians that "gender" actually means "biological sex" here, meaning that the desire was to distinguish samples based on the presence of Y-chromosomes. A genetic counselor admitted, however, that this label was based on self-report, so there was always the possibility of Y-chromosome contamination from bone marrow transplants and cell-free fetal chromosomes. It could also be

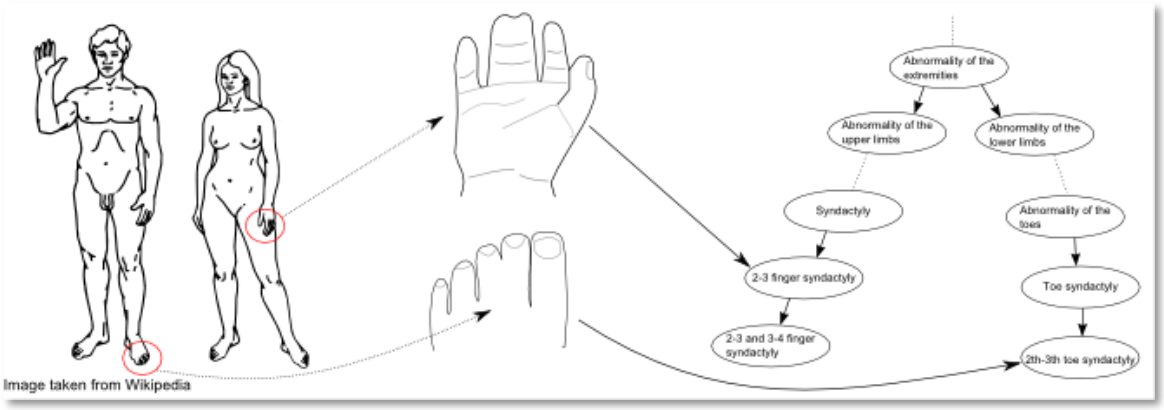

Figure 1.2: The banner from Human Phenotype Ontology's website demonstrating the role of phenotyping.

reporting physician (name, institution, contact information). The form was scanned into the laboratory's electronic database and it was performatively nominated with a new "Lab ID," another series of numbers. The physical paper of the form was then stored in a cabinet and did not reenter any proceedings I witnessed.

The requisition form also provided information about the patient's indication, or presenting concerns, in the form of a check mark next to one or more of a few dozen predetermined phenotypes (e.g., delayed speech, hearing loss, microcephaly, scoliosis, etc.) as well as a brief, free-form description of that phenotype. There were many standardized lists of "phenotype ontologies," each used under different circumstances. Though phenotypes were recognized as ultimately infinitely variable bodily states and conditions, here they were taxonomized, disciplined "according to a grid of perceptions, and not[ed] according to a code" (Foucault 1991:56). In Figure 1.2 one can see an idealized transformation of manifold apparent phenotypes into

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problematized by disorders of the sex chromosomes or nondisclosure of "a trans person."

discrete characteristics using such an ontology. What Clinicians often criticized these taxonomizations as significantly imperfect but they nonetheless continued to rely on them when utilizing electronic genotyping programs.

Take, for instance, the case of one 70-year-old man who came to the Clinic with concerns about the first stages of hearing loss. His clinician duly noted this "phenotype" on his requisition form. After completing the testing, the only mutation the laboratory reported was a variant suggested to cause congenital deafness. His clinician told me he found this report humorous but also saw it as representative of a serious problem with these "ontologies." While congenital deafness and late-onset hearing loss might both fall into the same "ontological" category, they were significantly different to the point that data about the former did not inform an understanding of the latter.[8]

After the sample progressed through Accessioning, where each vial was affixed with a label denoting the sample's order number, it was carried in a tray – along with many other samples – to Extraction. There, a technician scanned the barcode on each vial's label – which had been affixed in Phlebotomy[9] – with a handheld laser, and a new barcode sticker was automatically printed. This sticker was then attached to an empty, larger vial. A cap of the same color as that of the

[8] Similarly, it was a common occurrence that a laboratory would return a result for adult (or "viable child") patients that it had linked to a disorder that clinicians would later characterize as a "lethal congenital syndrome." Such mutations were obviously dismissed, as they were mutually exclusive with the patient's continued survival. These results were viewed more with frustration than humor as they simply added unnecessary labor on the human end of the results' interpretation.

[9] The barcode had seven digits at the time of my fieldwork. The number increased by one each time a sample came through the laboratory. The millionth sample came through Molecular Genetics the month before I began my work there.

previous cap was screwed on, preserving the visibility of the type of anticoagulant mixed with the blood. The technician then scanned both the label on the older, small vial and the label on the newer one in order to make certain they were identical. This scan also recorded the location of each sample within the tray's grid. Another circular sticker was printed and attached to the outer surface of the vial's cap.

These procedures of verification and the multiple forms of redundancy acted to limit the possibility of ritual failure in linking instances in an interdiscursive chain. Were one material sign not performatively made identical to its predecessor, the whole ritual of reference could fail to come off. The conditions for ritual success would not have been met (cf. Austin 1975). (In the next section, I consider the implications of a case in which just such a slippage in an interdiscursive chain was suspected.)

The repetitive circulation of different tokens of the same type through the same, fixed space produced a sort of standardization of the object as process. Commensuration, while the site of anxiety, was not a wholly novel endeavor each time a sample appeared in Extraction. The types of qualia that were sloughed off as 'noise' or 'background' (cf. Knorr Cetina 1999:48ff) were also standardized. Von Uexküll notes that there is an iconic identity between the spider's web and its victim fly (von Uexküll 1934); in a parallel conversation, Kockelman notes the "radical kind of intimacy" between sieves and the substances they filter (Kockelman 2013:36). In just this way, the technologies of the Molecular Genetics laboratory determined the types of 'information' both returned and weeded out. The types of 'noise' that remained nondifferentiable from desirable data become problematic complications

for the purifying process. (Such an issue – and its human intervention – is discussed in detail below.)

After re-nominating the samples, the technician put the tray of vials into an extraction robot. The robot could not read the labels on the sides of the vial, so it used information provided by the cap sticker in order to determine what type of chemical reagent to use with each individual vial. Only certain chemicals could mix with certain anticoagulants, and only certain processes could be performed for certain types of genetic tests. For instance, laboratorians characterized a process that used metallic beads to bind to the DNA as "dirtying" the material. They therefore refused to use it for genome-scale tests like whole exome sequencing, which they considered too sensitive to the iatrogenic 'noise' of such a binding process.

To begin the DNA extraction process, the robot added a chemical to lyse the red blood cells. This ruptured their cell membranes and caused the cells to disintegrate. The robot then added another chemical to lyse the fluffy, white blood cells. Next a precipitate was added to separate the constituents of the blood matter, the protein sinking heavily to the bottom of the vials. The samples were then "washed" with ethanol, removing the contaminating chemicals that the robot had previously added.

Once the robot had finished its task, a technician removed the tray and placed the vials in a centrifuge. The vials spun in the machine, further separating the types of matter they contained. It was at this point that DNA strands became visible

as separate entities to the technician's eyes. They sat as small, whitish knots at the bottom of the vials.

The tray was moved to another table, and the technician delicately but efficiently used a small pipette to transfer the DNA from the large vial to a new one, the smallest of all the sample's containers. The technician scanned the label on the old vial, and a new label was printed. A computer informed the technician which color of cap to screw onto the DNA vial. In this instance, cap color designated what method of extraction had been used to obtain the sample: Had it been derived from peripheral blood, maternal blood, a tissue biopsy, or bone marrow, for example? The remaining material, which was called "blood waste" (conceived in local ethnosemiotics analogously to the cybernetic notion of 'noise,' cf. Kockelman 2010), was poured into a potbellied jug with a hazardous materials label.

Throughout each of these steps, the physical material was reduced dramatically in size – measured in milliliters, micrograms, or semantic content. This loss was seen as a purification of the truly meaningful sample from the waste in which it had been embedded. Qualia that had previously been obfuscated by the brute materiality of the object were always already immanent, but the confusing noise first had to be removed. Nonetheless, some significant qualities of the original sign were lost in the act of transduction. Because the transduced object could no longer throw up this information, which was considered necessary for its felicitous commensuration or interpretation, technicians created an assemblage of auxiliary determinants that followed the sample. Similar to the requisition form, cap color, labels, and stickers served not only to reconsecrate the object as one link in the

interdiscursive chain of reference; they also provided a type of descriptive backing for the transduced material.

Once the DNA had been purified from the 'noise' of the waste blood, the technician brought the tray of small DNA vials into the storage room and placed it in the "Minus Eighty," a freezer kept at -80° Celsius. The location of each vial, denoted both by its laboratory ID and the column and row of the tray into which it was placed, was automatically noted in the laboratory's electronic database. The cold temperature stabilized the DNA in its current state until technicians were ready to begin sequencing it.

A computerized scheduling system notified a technician when certain samples needed to begin the testing process. At this point, the technician consulted the coordinates and names of the vials selected by the algorithm and then removed them from the freezer. The vials were placed into another tray and taken to a machine called a thermocycler.[10] The thermocycler alternately heated and cooled the sample in order to change its molecular structure, making it available to further manipulation. The machine eventually added a primer and an enzyme called *Taq* polymerase. This enzyme amplified a single segment of DNA exponentially, to the point that it was large enough to undergo sequencing. At this stage, the purification

[10] Each thermocycler was individuated by a sheet of printer paper bearing the image and name of various cartoon characters: Pikachu, Popeye, Pac-Man, etc. (Such humor was seen as emblematic of "lab life." Compare, for instance, the official naming of a particular signaling pathway as "Sonic hedgehog." While some have characterized this "descent into whimsy" as impeding communication (e.g. "Obstacles of nomenclature," 1997), they were relished by my laboratorian interlocutors.

of the object in fact required hybridization – in both the Latourian and chemical senses. Its material existence was explicitly partially 'natural' and partially 'artificial.'

Finally, the post-polymerase sample was transferred to a sequencing machine. Most common in Molecular Genetics was the Sanger sequencer.[11] That machine added a fluorescent dye, which caused different wavelengths of light to be emitted by each constituent segment of the DNA. These fluorescent peaks were then translated into the letters A, C, G, and T, denoting the sequence of nucleobases in the constituent genes.

A notification was then sent to a number of clinicians in the PM Clinic that the sequence was complete. A genetic counselor or other clinician assigned to that particular case would then walk to the laboratory to pick up the report. The results were then transported to Bioinformatics for further analysis. (This is described in detail in Chapter Five.) An example of the digital information borne in such a report is presented graphically in Figure 1.3.

Scene 3: The Case Conference

I was the first to arrive for the weekly Individualized Medicine case conference, the final stage in the biographical career of the potential disorder through the IM Clinic. A few minutes before four in the afternoon, I sat down in a chair along the wall and took out my notebook. Soon a few others (project managers, education specialists, bioethicists) were seated next to me, and others (medical geneticists, bioinformaticians, genetic counselors, a pharmacologist, and a

[11] Most next-generation sequencing took place at a different laboratory. Sanger sequencing was also used to validate the results produced by the newer tests.

Figure 1.3: One read-out of a gene's sequencing.

biochemist) took seats at the long table. The afternoon sun cut harshly through the westward windows, leading one of the genetic counselors to click the blinds shut. The laboratorians talked among themselves about a conference many of them had attended the previous week.

This interdisciplinary task force met weekly in order to discuss a few patient cases with results recently returned from the laboratory. The ultimate – though rarely attained – goal was to interpret these results in such a way that a new therapeutic regime could be recommended. Barring this, clinicians hoped they might provide a diagnosis for the patient's rare disease. Even this was an uncommon occurrence, though, and the primary pragmatic role these conferences played was to open up practices and knowledge to collective critique.

Soon Dr. Rosi, the middle-aged head of the IM Clinic, arrived, and the room quieted. Dr. Ivanova asked, "Is my case first?" "Correct," replied Dr. Rosi. A PowerPoint presentation opened on the large screen at the front of the room. On the first slide were listed Dr. Ivanova's patient's IM Clinic identification number, his age, sex, and some bullet-point indications. His personal name was notably absent, the PowerPoint having been "de-identified" in an explicitly ethical move to preserve the patient's anonymity in front of unratified others.[12] Reference, however, was maintained by using the Clinic ID as a surrogate rigid designator. In fact, in some ways the ID was a more appropriate name, referring not to the individual *in toto* but rather to only those aspects of his biography seen to be relevant to medical interpretation and diagnosis.

Dr. Ivanova introduced the case, not reading from the screen but covering much of the same information. "He has intractable epilepsy, global developmental delay. Brain MRI was abnormal. The story is that he had a rough birth with thirty-nine weeks' gestation. He was floppy with a weak cry and lethargic. Within twenty-four hours of discharge, the child had a temperature of one hundred and four degrees and had a seizure."

"How was the brain MRI abnormal?" interjected another medical geneticist.

"The parents describe it as swollen," Dr. Ivanova replied. "It's not in the EMR [electronic medical record]," she clarified, noting that the patient was from out of

[12] The success of de-identification was a central topic of both humor and sincere concern in the IM Clinic. One laboratorian joked about the practice of removing personal names from certain genetic test reports: "The VCF file [raw data] with 100,000 variants, how de-identified is that?" The humor plays off the geneticists' notions of what constitutes individuality, namely, one's unique DNA sequence (see the Introductory Chapter).

state and had the testing done at another hospital. Clinicians viewed with enormous skepticism descriptions produced by parents and others not internally ratified as experts.

"Coincident with the onset of infantile spasms," she continued, "his vision deteriorated. Physically, he was described to have a distinctive look. On exam, I would add: microcephaly, long eyelashes, slightly up-turned ear lobes, and low muscle tone. Next slide, please."

Denise Meyer, the genetic counselor running the PowerPoint, clicked, and a new slide appeared. It was labeled "Previous Genetic Testing." A list of panels and assays spread out below the title. "Previous genetic testing was extensive," Dr. Ivanova said, noting especially that there had been a 53-gene epilepsy panel and a skin biopsy. "I'm not sure why, but they didn't find any abnormalities. Next slide, please."

The image of a digital pedigree appeared, detailing three generations, indicating both maternal and paternal aunts, uncles, and cousins. "The only thing to note here is that there were motor delays that resolved in the sister. Next slide, please."

Denise opened a PDF version of the patient's laboratory report. (An example of such a report is presented in Figure 1.4.) "Michelle, would you like to begin?" Dr. Ivanova asked the genetic counselor. Michelle took the floor in order to discuss the test results. The patient – technically the patient's parents, since he was toddler – had consented to having whole exome sequencing. This was a "trio test," meaning that a patient's DNA was compared to that of both of his or her parents. If, as in the

Table 2: Variants of Unknown Clinical Significance in Disease Genes Related to Clinical Phenotype

Disease	Inheritance Pattern	Gene	Position	Isoform	Location	Nucleotide	Amino Acid	Zygosity	References/Comments	ESP5400 AA/EA	SIFT / PolyPhen-2
Conotruncal anomaly face syndrome [MIM:217095]; DiGeorge syndrome [MIM:188400]; Tetralogy of Fallot [MIM:187500]; Velocardiofacial syndrome [MIM:192430]	AD	TBX1	Chr22: 19754144	NM_080647	exon9	c.1242C>G	p.H414Q	Het	Novel variant; Confirmed by Sanger sequencing. Mother is heterozygous. Father is negative.	N/R N/R	Tolerated/ Probably damaging
Marfan syndrome [MIM:154700]; MASS syndrome [MIM:604308]; Ectopia lentis, familial [MIM:129600]; Aortic aneurysm, ascending, and dissection; Stiff skin syndrome [MIM:184900]	AD	FBN1	Chr15: 48713793	NM_000138	exon62	c.7661G>A	p.R2554Q	Het	PMID 21883168; Confirmed by Sanger sequencing. Mother is heterozygous. Father is negative.	0/3738 1/7019	Tolerated/ Probably damaging
Mental retardation, autosomal dominant 3 [MIM:612580]	AD	CDH15	Chr16: 89256792	NM_004933	exon8	c.1120G>A	p.V374M	Het	Novel variant; Confirmed by Sanger sequencing. Father is heterozygous. Mother is negative.	N/R N/R	Tolerated/ Probably damaging
Rubinstein-Taybi syndrome [MIM:180849]	AD	CREBBP	Chr16: 3820765	NM_004380	exon14	c.2686G>C	p.G896R	Het	Novel variant; Confirmed by Sanger sequencing. Father is heterozygous. Mother is negative.	N/R N/R	Tolerated/ Probably damaging

Figure 1.4: Part of a laboratory report.

current case, a parent were unaffected by the patient's symptoms, this comparison would allow clinicians to dismiss mutations found *both* in the patient and in the parent. If one of the parents were indeed similarly affected, a mutation common to both participants would be placed under greater scrutiny.

On the report, there was a single mutation indicated as "deleterious." The report listed mild developmental delay as the symptom associated with this genotype. Michelle reiterated the critical conditions surrounding the patient's birth. "I'm not sure that this can be associated with such a severe phenotype," she concluded.

Jim Bauer, an outspoken pharmacologist, interrupted Michelle's monologue: "I don't understand the nomenclature used in the report." (Practices of naming and describing mutations varied significantly between laboratories. This topic is explored in depth in Chapters Three and Six.) The genetic counselor explained that

that the "F" listed in the table next to the reported variant denoted that it was a frameshift mutation. That is, a single nucleotide (in this instance) had been inserted and was presumed to cause the entire gene to be 'misread' and thus to be disease-causing. "So that's why the lab reported it?" Jim asked, and Michelle affirmed. "To call this pathogenic is bold," Jim said, frustrated. Jim was certainly not the first individual in these case conferences to make such a remark. In fact, I had been witness to instances in which frameshifts were determined to be specifically benign. Jim mentioned two such examples from his own experience. "This could be completely innocuous," he reiterated.

Michelle patiently explained the reason for the mutation's receiving this label: "The lab considers all frameshifts to be pathogenic. They're just following ACMG [the American College of Medical Genetics and Genomics'] guidelines." Nonetheless, she granted that it was not the case that all frameshifts were indeed pathogenic. "The [pathogenicity] calls are only so good – actually, pretty bad – with exome," agreed Joe Farrow, one of the bioinformaticians. "'Calls' is kind of a loose term with Sanger [sequencing], too."

Standardization of interpretation – both machinic and definitional – had been intended to diminish the potential for failure of commensuration. However, in this instance – echoing their complaints regarding "phenotype ontologies," as described above – experts rejected any diminishing of their ultimate authority to act as gatekeepers. Despite official standards, individual clinicians continued to mediate such moments of commensuration.

"And," Michelle added, after discussing and discrediting the reported mutation, "there's a little over three pages of VUSs." VUSs, or 'variants of unknown significance,' were a category of result for which there was no consensus interpretation. The majority of the time that clinicians spent in these case conferences was dedicated to scrutinizing VUSs in order to determine whether further testing might provide enough information about one of them to transmute it eventually into something evidentially sufficient for diagnosis. The average exome sequencing returned only one page of VUSs, so Michelle's announcement of so many pages was met with surprise.

One by one, each variant was considered, if only briefly. As shown in Figure 1.4 above, the laboratory had linked each variant to a disease phenotype. This was achieved by considering the known function of the gene and an algorithm's prediction of how that specific mutation would affect protein synthesis. The report also listed a standardized likelihood of whether the mutation would indeed cause the denoted phenotype. These categories included probably damaging, possibly damaging, and tolerated/benign.[13] Despite the fact that several of the VUSs were listed as damaging, Dr. Ivanova noted, "Overall, I didn't see any condition that I was suspicious for." That is, despite the inauspicious predictions, the listed phenotypes (based on the phenotype ontologies originally submitted by Dr. Ivanova on the patient's requisition form) were unrelated to the patient's presenting concerns. Michelle agreed, and no one else in the room pressed the issue. Again, clinicians held the ultimate authority to determine the significance of genetic signs. Despite the

[13] For more information on VUSs and 'variant calling,' see Chapter Five.

ready-made standard for interpretation – based on epidemiological statistics and authorized by the most dominant institution in American medical genetics – clinicians maintained their ability to render these signs indexical of disorder or not.

"There's something else to discuss here, too, though," Michelle said. "We wanted to discuss the high number of de novo mutations," meaning variants found in the patient that were absent in both parents. As I mentioned above, such mutations in 'trio tests' were viewed as potential keys to diagnosis.

Denise asked Michelle how many such mutations had been found. "I don't have a number," Michelle admitted. Denise wondered aloud how frequent de novo mutations might actually be. If they were as widespread as she expected, she doubted the validity of treating them as indexes of pathogenicity. She explicitly paralleled Joe Farrow's earlier concern that the report was treating common forms of variation as unusual enough to be interpreted as likely pathogenic.

Joe, however, noted that the laboratory did not report *all* variants. "They'll only tell you the ones collocalized on genes known to be linked to the phenotype. It'll start high, but not with all those qualifications." Variation on genes not explicitly linked to those thought to be related to the reported phenotypes would not make it through the algorithmic sieve.

Michelle interrupted at this point, redirecting the conversation. "We're concerned that there might be non-paternity or sample mix-up because of the number of de novo mutations."

"I'm surprised the lab wouldn't have caught that," Denise mused. "Why wouldn't they suggest submitting a new sample if that were true? Don't they have enough data to determine whether it was a sample mix-up?"

"No," Michelle replied. "It's only confirmatory." She explained: Despite being a 'trio test,' whole exome sequencing only interrogated those portions of the parents' DNA that could be used to compare potential disease-causing mutations in the patient's interpreted data. Too few variants in all three DNA samples were considered in tandem to determine something like paternity.

Michelle said she would recommend not re-testing the father, since she would not expect the mutation to have come from him. Furthermore, she thought broaching the topic of misattributed paternity would be "more detrimental than beneficial."

This concern was fairly typical in the hospital. In fact, two months before this case was presented, I had attended with several clinicians from the IM Clinic a symposium dedicated solely to the ethics of disclosing such findings. Many of the presenters – mainly ethicists and geneticists – concluded that it was most often improper to do so. "There are acts of violence associated with these types of findings," said one medical ethicist, describing the hypothetical abuse of a husband who had discovered that his wife had been unfaithful. A geneticist described an actual case in which misattributed paternity was determined to be "the product of incest," and the disclosure left the mother in tears. Finally, Dr. Ivanova, who was also presenting at the symposium, noted that without confirmatory tests, most genetic results would only be *suggestive* of misattributed paternity. Without requesting that

the trio undergo further testing, the specter of doubt over such an interpretation of the results, she said, was simply too great.

As I previously mentioned, this type of ethical reasoning was very common in discourse on misattributed paternity, to the point that Michelle's comment was met with no calls for explanation or counters to the implicit logic. However, another geneticist advocated for getting a new sample, since her suspicion was that there was some issue with inaccurate labeling in the laboratory. Rather than a failure in the ascription of a quality (parentage) to the referent, she proposed a slippage in the interdiscursive chain underpinning the very act of reference. Perhaps it was the result of a human error in the ritual re-nomination, rupturing the linkage. Perhaps this laboratory report, so full of de novo mutations, referred not to the case named by the IM Clinic ID, but to some other case. Both interpretations made salient certain links in the chain of reference that had otherwise remained outside this particular act interpretation.

"So what's the consensus?" asked Dr. Ivanova.

"It seems like it would be best not to re-test," Dr. Rosi quickly responded. A medical geneticist who had remained silent to this point, however, interjected that while she did not think it was necessary to redo the exome sequencing, she would recommend sending the patient to Neurology for other tests. "There are intellectual problems with other system involvement," she explained. Dr. Ivanova agreed with this assessment, and Michelle noted the recommendation in the patient's IM Clinic record.

"Any other thoughts on this case?" Dr. Rosi asked. None were volunteered, and the discussion closed.

The Ritual of Referring

A patient's potential disorder emerged as a ratified referent through an initial baptismal moment. When a patient is referred to the IM Clinic, "I turn it into a case," one of the project managers told me. She did this by entering certain information about the patient into an electronic database specific to the Clinic and then assigned to it a unique number. While I was conducting my fieldwork, these numbers all had three digits, increasing by one integer each time a new patient was referred. This name, the so-called IM Number, represented the first instance in which the potential disorder was ratified as an intersubjectively available semiotic object. The name – which linked in the database to the patient's personal name, among other things – became a rigid designator of the potential disorder itself.

All subsequent deployments of signs describing or referring to the potential disorder relied on the ritual success of that initial baptism. The IM Number and its cognates came to refer to the identical entity in every doxastic world, in a classical instance of rigid designation. The act was made asymptotically context-independent; in fact, even the predicational qualities of the referent itself could change dramatically. However, certain iterational forms were understood by clinicians to be radical departures from the baptismal object in its initial instantiation. In these instances, further acts of performative nomination were required.

All the qualities that emerged through transduction were understood to have always already been imminent in the object but remained mere potentials until unleashed through the specific techno-semiotic interventions. The potentialities of the manifold were predicables of the referent, transforming it through what I call *semiotic modes of attention* (cf. Csordas 1993). The referent remained open – a process more than an object – for most of the course of its intersubjective availability (see also Gal 2017, Lynch et al 2008). It was an underdetermined object, one characterological aspect of which was its potential not to have existed in the first place.

Reconsecration, through procedures of verification and supported by multiple ritual redundancies, linked the object back into the interdiscursive chain of reference. Because of the interest in hidden qualities, invocations of the referent are not simple *renvois* to its originary meaning. Not only did the 'meaning' of the object – its salience within larger cosmological and corpological orders – change over its career at the IM Clinic, it was understood and expected to change. The recognition of certain changes, in fact, became necessary to the felicity of the speech act of reference at particular moments. Nonetheless, not every event of interdiscursive linkage was made salient in reference, nor was it even available to affect the interpretant. In fact, when I discussed aspects of this chapter with my interlocutors, many if not all highlighted at least one transductional moment of which they had not been aware.[14] Upon the recognition of an individual consecration's felicity, many of

[14] Asymmetries in knowledge became important to many forms of evidential boundary work. This is a central concern of Chapter Four, which centers on uncertainty.

the interdiscursive links that had preceded it were blackboxed for these individual actors.

The case was finally closed in the ritual form of a recommendation, but even that did not necessarily 'determine' the object; it simply removed it from discourse. In fact, in some instances – like that described in my final Scene – lapses in the interdiscursive chain were even admitted. While the reference, in a sense, came unanchored, the rigid designator continued to pick out some discrete individual entity. However, certain qualities purported of the object hinged on the success of the reference, and they fell out of intersubjective imagining.

In this way, it becomes apparent that commensuration is no easy feat. Aligning conceptualizations of the case over epistemic divides requires extensive coordination, and congruence is often explicitly standardized in order to remove the accidence of chance from the ritual of referring. Nonetheless these steps may still prove insufficient for the act of unifying the 'body multiple' to succeed.

We have thus seen how reference acts not as a sign's simple extension of a ready-made existent. Reference is a social achievement that takes place over multiple semiotic moments. The object that emerges as the referent is also not simply 'picked out.' It is created through a process that leaves it constantly open and in jeopardy. A single recognized act of baptism might suffice to allow interactants to refer to an object shared in the common ground. However, multiple reconsecrations become necessary when linking otherwise hidden or radically disparate realities within the same interdiscursive chain.

CHAPTER TWO: YOU BECOME EVERYONE.

Project Planning

In the late summer, the Section of Patient Education (SPE) sent its representative, a project manager in early middle age named Julie Gustafson, across campus to the Department of Medical Genetics in order to discuss that department's needs for new educational materials. This was an annual event, with a representative from Patient Education going to each of the clinical divisions and returning with a list of projects for the Section to complete over the course of the year. The vast majority of requests were for pamphlets that would be handed to patients in order to explain new tests or procedures being offered. Other types of projects could include DVDs, information sheets, or education sessions (available free of charge to patients).

I met Julie outside her office and walked down the street to the tall, blue-glass building whose top floor housed Medical Genetics. As we walked, enjoying the summer sun, Julie explained her expectations for the meeting. Each clinical division had a "physician liaison" who acted as a "content expert" and served as Patient Education's primary contact. Julie had been working with Medical Genetics for several years and knew many of the clinicians, but the previous liaison had moved out of country earlier that year. Part of the purpose of this meeting was for Julie to introduce herself and make sure the new liaison understood the distinctive role Patient Education held in the hospital.

The task of the liaison in Medical Genetics, she explained after we walked through a revolving door and entered an air-conditioned lobby, was particularly hard "because genetics is complicated. That's just the nature of the beast. His job'll be to talk

with the Medical Genetics group and say, 'Gosh, what do we need?" In fact, that was the main purpose of the upcoming meeting. As a group, they would need to determine how Patient Education could best spend its time and resources helping the department.

We took the elevator to the top floor and came to the Medical Genetics conference room, taking seats at the long laminate table. We continued chatting while waiting for the rest of the attendees to appear. We had arrived right on time, but it was nearly always the case that clinicians came late to meetings with Patient Education. First to arrive was Dr. Orlov, the new liaison, quickly followed by three genetic counselors. It was a lunch hour meeting – the most common kind – so the counselors brought with them sandwiches from Subway and Jimmy Johns, Nalgenes of water, and cans of soda.

Julie introduced herself, shaking Dr. Orlov's hand. "So how new are you to [the hospital]?" she asked.

"I've been here a couple years now." He leaned back in his chair and crossed his arms over his indigo button-down and black suit jacket. It was common for physician liaisons to be relatively junior, as the position was seen to help them integrate into the hospital system beyond the boundaries of individual divisions – and because hierarchies of seniority often displaced this type of extra labor onto the lower ranks.

"I've been with [the hospital] for *twenty-six* years," Julie admitted in a humorously dramatized stage whisper. "Since birth, then!" Dr. Orlov joked and the attendees chuckled.

After a brief round of introductions – one of the genetic counselors was also new to the collaboration – Julie gave a brief explanation of the role of Patient Education. She

and her colleagues would work to simplify information about medical treatments and procedures for a lay patient readership. She handed Dr. Orlov a series of "white papers" concerning the Section and the types of projects its staff undertook. She also gave him some exemplary pamphlets they had produced with Medical Genetics in the past.

Patient Education

Here I want to step back for a moment in order to provide the reader with some context. Who worked in Patient Education and what were their jobs? How did SPE interface with the clinicians and the hospital more generally?

In terms of finances, Patient Education received its funding from the individual divisions that made use of its services either by recommending patients to its education programs or by requesting the production of educational materials. SPE was a nonprofit, and all of its materials and services were available to patients free of charge. Thousands of people attended education programs put on by SPE each year. Education specialists offered hour-long classes, some of which – such as "Preparing for Surgery" – were offered daily, while others – everything from "Relaxation Techniques" to "Fibromyalgia" to "Breast Cancer Awareness" – were offered individually upon request.

The staff of Patient Education were mainly female. Out of nearly 60 employees,[1] only about five were men – including, notably, the two highest-level administrators. Among the staff were project managers, writers, editors, educators, and administrators. They were mainly White and middle-class, and all had at least a college education, but several also had PhDs. Most writers came to Patient Education from another career:

[1] Most of these employees were not full-time.

Some were teachers and professors, others were nurses, and still others had a background in business and management. Nearly everyone in Patient Education had grown up in the Upper Midwest.

Having a separate, centralized unit devoted to patient education was seen as one of the distinctive features of the hospital. Writers told me time and again that most hospitals "don't even have a Section of Patient Ed." Moreover, the artifacts Patient Education produced were seen to be unique in their high quality. Several writers confided that their work had "won awards." Even some clinicians made mention of this fact. For instance, one physician liaison told me he had worked with SPE on a video for inpatients with bipolar disorder, which had won several awards as well as significant esteem for the collaboration. "It was like a movie," he intoned.

The central problem for the staff of Patient Education was determining how to communicate complex topics in simplex ways, to relatively unknown individuals. Their solution was to develop a partitioned register, which they called "plain language."[2] Plain language was in specific paradigmatic contrast with an unnamed and unnumbered set of expert registers indexically linked to the scientific and clinical communities of the hospital. Plain language consisted of a sort of ideal fashion of writing (and speaking) whereby one could more or less 'say the same thing' as the expert and yet be understood by laypersons, despite perceived ontological incommensurabilities between

[2] Nearly every written instance of the name "plain language" used all lower-case characters, i.e. rather than <Plain Language>. It was also never abbreviated in the mode of the productive form "X ~~language~~," i.e. as simply "plain," with "language" elliptically elided (as is done, e.g., in the phrase "translated from the German ~~language~~"). I follow this native practice despite my understanding of the language form as deserving of the status of proper noun, which I discuss in more detail below. Needless to say, there were clear ideological implications for the use of the lower case.

the worlds the two represented. This seemingly contradictory and complicated task is the focus of the present chapter, but in order to understand the language, one must understand the practice. For this reason, I return first to the Project Planning meeting already under discussion. I then consider the sociohistorical emergence of the register, and finally turn for the rest of the chapter to a theorization of the ideology undergirding plain language's practice of simplification.

In this chapter, I am particularly interested in laying out the language ideology and metapragmatic practices that regiment the translation of expert registers into plain language. In the following chapter, I consider the relatively more covert structural impulses that produced plain language in its particular sociohistorical form. Centrally, Chapter Three concerns the attempted management of patients' affect and reason in healthcare decision-making. While the present chapter concerns itself with the ideology of simplification as such, the following chapter engages the corollary practice of eliding information not because it is seen as irrelevant but because it is seen as excessive.

Pamphlets

Julie turned from introductions to the question of what projects the Department of Medical Genetics would like to see completed. Last year, she said, the department had come up with more projects than time would permit, and she thought perhaps this year they could finish some of those that remained.

First, however, she wanted to suggest a project put forward to her by a physician in Rheumatology, viz. a "patient-friendly karyogram." The idea would be to develop a sheet with a graphic spread of the chromosomes, each labeled with its number and

perhaps annotated with some basic information, or with spaces for clinicians to add information relevant to a patient's specific case. This suggestion was met with a general mumble that no one would use such a sheet. "We wouldn't circle chromosomes for patients," explained Jaime Smith, one of the counselors. In fact, the clinicians did not consider the knowledge of the chromosome on which a mutation was found to be pertinent information for the majority of patients.

"That's great feedback," Julie responded encouragingly, turning then to a printed list of other possibilities. "One of the previous suggestions was for a piece on WES."[3] WES, or whole exome sequencing, was a genome-scale test (meaning it theoretically sequenced each of an individual's genes at once, though only the protein-coding exons were interpreted) that was currently the mainstay of the Individualized Medicine program and was, for most of my tenure at the hospital, the largest test Medical Genetics performed. The clinicians were very enthusiastic about this suggestion. "It's what we do the most," said Dr. Orlov. Moreover, he added, such a pamphlet would be useful for other clinical divisions – such as Neurology and Pediatrics – as well.

"What exactly would you like it to be about?" Julie asked. "What are some questions you get [from patients]?"

"Patients mostly ask about insurance and how much does it *cost*?" Jaime replied. Melissa Dubois, another genetic counselor, cut in, noting that actual cost would depend

[3] Julie always pronounced this as three separate letters, though individuals more intimately engaged with the test (clinicians, scientists) pronounced it as a single syllable or – most commonly – referred to it simply as "exome." This was a clear index of Julie as relatively out-group, though such an alignment was already stereotypically presupposed of professionals from Patient Education – both by clinicians and by those professionals themselves. "You're the experts," was a common refrain from writers to their clinician collaborators. However, I describe below the particular expertise uniquely claimed by Patient Education as well.

on the specific insurer and that the laboratory does a pre-authorization before proceeding with sequencing, so it would not make sense to put that information in writing. This was a key concern for Patient Education: how to produce an artifact with sufficient detail to be useful, but abstract enough that it could apply to whatever patient might come across it.

Melissa stated that it would be important to include information about the types of results that such a test might return. "Finding something [i.e., a mutation] does not mean it's treatable, and we find something in twenty percent of the cases."[4] Amanda Nelson, the third genetic counselor, described the "three kinds of results: positive, negative, and variant." Positive results were the rarest, denoting a mutation in the patient's genes understood to be the cause of his or her symptoms. Negative results – in this formulation – were regions or genes originally suspected to hold a disease-causing mutation but in fact were returned without the anticipated mutation. "Variants" were those mutations whose ultimate relation to phenotype was unknown or unproven based on current scientific consensus.

This tripartite distinction was characteristic of patient-facing, simplified genetic taxonomy. This was also how clinicians explained the "kinds of results" to their patients. However, it was notably not the same classification system that genetics specialists used backstage. This is discussed in depth in Chapter Five, but here it is worth mentioning that it was reduced from a five- or seven-part taxonomy. The three

[4] The number that Melissa gave was significantly lower than both the official statistic (29%) and the percentage I had personally calculated and heard announced in case conference (25%). When the WES pamphlet was completed, it used the latter statistic.

categories were seen as sufficient for the pamphlet's purposes, and if necessary, the clinician would provide further elaboration at results disclosure.

Although the tripartite classification was seen as satisfactorily informative, there was another pragmatic "kind of result" that the clinicians determined needed mention. Jaime brought up the so-called "ACMG genes." The ACMG, or American College of Medical Genetics and Genomics, had come out the previous year with a recommendation to report certain mutations from any genome-scale test even if these mutations were not the reason for the test (Green et al 2013). Dr. Orlov described these as "incidental findings." He explained that they consisted mainly of "well-described" hereditary cancer syndromes and heart conditions. While the College lightened its position to allow an 'opt-out' policy the following year (ACMG Board of Directors, 2014) – in the middle of my field work – the 56 genes affected by the original recommendation were still singled out. Patients could choose to get information on that series of disorders regardless of the issue that initially brought them to Medical Genetics.

Melissa jumped back in: The pamphlet should also note the amount of time the test takes to complete, which regularly surprised some patients. "How long does it take?" Julie asked her. "For now, it's four months, approximately." "It's just a blood test, right?" asked the project manager, and Melissa affirmed.

"When would the patients be receiving these pamphlets?" Julie questioned. Amanda said she thought they would hand them out not just to WES candidates but also to patients whose first choice would be to get a smaller genetic panel done and then fall back on WES if the original test proved unable to find the cause of their disorder.

Whole exome sequencing had a number of shortcomings, including – most prominently, in the patients' minds – the price and the duration. From the geneticists' perspective, another significant drawback was its "depth of coverage." Because of limitations to the chemistry used, about 15% of the potential data held within the genome was consistently left 'unread' by the test. As one biochemist put it, "There's no such thing as complete testing."[5] For these reasons it was preferable to recommend a smaller, less expensive, quicker, and more discerning test or panel when the clinician could put forward a specific hypothetical diagnosis.

"Alright, this is a great start," Julie said. She suggested that this pamphlet could be their first priority in Patient Education. "Does one of you want to be my touch person on this one?" Dr. Orlov interjected that Julie should get in touch with Jen Miller, a genetic counselor who was not present at the current meeting. He noted that she was the counselor who saw most of the candidates for WES.

Next on Julie's agenda was a possible educational video on genetic testing for cancer patients. "Have you been using the Medical Genetics video?" she asked. Melissa affirmed but said that she did not see a need for another video. The original was broad enough in its content and covered everything she thought would be useful for a cancer patient. Jamie admitted that she did not even remember what was on their video, but she did not imagine it would be different enough to warrant a separate video. Julie crossed that off her list as well.

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[5] A joke I heard recurrently from a number of different people – from bioethicists, genetic counselors, and physicians – was that it should be called *hole* exome rather than *whole* exome. (The perfect homophony prevented it from being a particularly punchy joke, but it persisted nonetheless.)

"Okay," said Julie, "so is there something else? Although streamlining is good, too." Melissa immediately jumped in with a suggestion: "*MTHFR*. Do you think it would be helpful?" "Probably," Jaime agreed. "What's that- *MTHFR*?" asked Julie, writing the name down on her sheet. Melissa explained that it was a gene that a lot of non-geneticists had tested but was "worthless." "What does it do?" asked Julie. "It means nothing," Dr. Orlov complained, but Melissa clarified: "It can affect homocysteine levels." Jamie rebutted, "*Sometimes* with a mutation you have to check them [i.e., homocysteine levels], but only sometimes." "Thirty to forty percent of the general population carries [a benign] mutation," Amanda explained.

Primary or specialty physicians ordered the test without understanding that geneticists had, several years earlier, come to the conclusion that testing the gene did not provide clinically relevant information regarding the conditions for which it was originally ordered, namely thrombophilia and recurrent pregnancy loss. In fact, the preceding year the ACMG had published an official recommendation *against* testing for *MTHFR* (Hickey et al 2013). Uninformed physicians had continued to order the test, and their patients then were directed to Medical Genetics in order to have their "meaningless" results interpreted.

While frustrated by this influx of confused patients and by their clinicians,[6] the specialists at the meeting did not fully blame them for their ignorance. Genetics was a rapidly changing science; it took a specialist to keep up, they explained. "It sounds like a [healthcare] provider education issue," said Julie. "It is," Dr. Orlov affirmed, but Melissa defended her pamphlet suggestion: The majority of requests for interpretation came

[6] In fact, a year later when I returned to the clinic for follow-up work, I found that the genetic counselors were still complaining about *MTHFR* results' being sent to them.

from other hospitals, not as internal referrals. Simply educating the providers at the hospital would not be sufficient. Amanda added that patients got a lot of misinformation from the web.

"What do you tell the patients when they come in?" asked Julie, clicking her pen back open. Amanda said she told them that their results were "polymorphism [here meaning 'variant' in the above-presented trichotomy], so, not even a disease-causing mutation." Dr. Orlov explained that it was difficult to get patients to accept the meaninglessness of such official-seeming results. Their perceived meaninglessness was actually a general concern for clinicians, as such results were seen to promote an irrational emotional response in patients. The results would either create too much hope that they could provide an answer, or they would cause harmful fear in something that was at most indeterminate.[7]

"When would you want to work on this?" asked Julie. "The sooner, the better," Dr. Orlov responded. Again, Julie asked who would be her "touch person" on this project. Melissa turned to Jaime: "You're the expert." Jamie and Amanda agreed to write up the key information on the topic and send it to Julie.

The final item on Julie's schedule was the "five-year review." Five years after each pamphlet was published, it was re-vetted for accuracy and utility in order to keep up with changes in practice. (Any changes in practice that had occurred before that period concluded could also be addressed, if the clinician noticed an error.) Julie asked the group to provide her with a specialist reviewer for documents on a series of conditions: Lynch syndrome, Ehlers-Danlos, cleft palate, hearing loss, Fabry disease,

[7] I discuss reason and affect management in detail in the following chapter.

and a number of others. After each item, the group debated who from Medical Genetics and its affiliated practices would be most competent for that particular project. After each condition had been assigned a reviewer, Julie asked, "Anything else?" No one had any other concerns, and the meeting concluded. The genetic counselors and Dr. Orlov walked down the hall to their workroom and office, and Julie and I began our way back to Patient Education.

History of plain language

Plain language arrived in SPE in 2008, when the Section received a new research program director who brought the concept with her from her previous work in the Department of Psychology. In the ethnohistory of the Section, staff regularly referenced the "mandate" to use plain language. This mandate was declared by the hospital's administration in 2010 after recommendations were handed down by the Joint Commission, an independent, not-for-profit organization that accredited and certified healthcare programs across the United States.[8] (This was also the year that Congress passed the Plain Writing Act, requiring all Federal agencies to produce many types of documents in 'plain writing,' something writers in Patient Education associated with plain language.)[9] The mandate institutionalized plain language and transformed it from a descriptive phrase (language that was 'plain') into a referential one (the unique

[8] In fact, the Joint Commission was already recommending the use of "plain language" in 2007 (Joint Commission 2007).
[9] The Act defined "plain writing" as "writing that is clear, concise, well-organized, and follows other best practices appropriate to the subject or field and intended audience" (Plain Writing Act of 2010). It made no further attempt to delimit the scope of or provide falsification criteria for "plain writing."

register used in SPE). The mandate served as formal legitimation of the practice, the practitioners, and the linguistic variety thus denominated.

The mandate marked one milestone in a general trend in Patient Education's development, from "serving the practice to helping the community," as one of the section directors told me. Julie Gustafson, the project manager, explained that SPE had become "more wellness-focused" over the preceding ten years, working as "a liaison between the patient and the [healthcare] practice." The adoption of plain language reinforced this shift, giving Patient Education a unique authority to communicate with patients.

After the mandate, Patient Education began to act as a gatekeeper to certain venues of display and dissemination. For instance, patients received a Patient Appointment Guide (PAG) before their appointments. The PAG explained the reasons for meeting with different professionals, and laid out everything that the patient might need to do in preparation for the visit, such as fasting or gathering information on his or her family history. Patient Education arbitrated what was allowed to be attached to the PAG. "Patient Ed owns the PAG," one genetic counselor told me. Moreover, genetic counselors were technically not allowed to give to patients any documents that were not first approved by Patient Education. Which materials were made available in waiting lobbies was also under Patient Education's control; patient-facing textual communication was now officially mediated by Patient Education. Plain language became linked to SPE (and vice versa). An editor described the situation to me by saying, "Patient Ed has a certain brand."

An institutional distinction became cemented between what were called materials of patient *education* and those of patient *information*. Those deemed education – namely, those that "[told] a patient what to do," as one educator explained – were the purview of Patient Education. Educational materials could recommend to their reader how to put certain information to use. Patient information, on the other hand, could be produced by anyone, but could not be construed as suggesting the reader take any particular action.

One of the directors of Patient Education told me he found "a fuzziness" to the boundary between the two genres of text, and this certainly proved to be the case in many instances. For example, instead of producing a pamphlet describing how one should prepare for a colonoscopy, Oncology might instead have created a handout that merely described the procedure. Nonetheless, were the boundary to have been clearly crossed, one would have needed "a whole other set of rules," a genetic counselor told me. They would have needed the final product to be modified and certified by Patient Education as a legitimate instance of plain language.

But what *was* plain language? In its most straightforward guise, it was construed as a Standard-lexifying register of reduced breadth and variability. Metapragmatically set apart as a register, it was considered an intralingual phenomenon; one translated from (expert) English into (plain) English. "Instead of 'hematocrit,' it'll say 'red blood count,'" explained a genetic counselor.[10] It was "how real people talk." Plain language

[10] One might note that 'hematocrit' and 'red blood count' do not refer to the same objects within nuanced expert 'corpologies' (Sahlins 2008:23). The commensuration here is more concerned with the pragmatics of uptake (therapeutic management) than pure referentiality (scientific accuracy). The question of reducing expert concepts is

was often defined by its perceived (or at least ascribed) qualities. According to one of the white papers Julie gave Dr. Orlov, plain language was "clear, concise, useful, and easy to read." When I asked writers, they described it as accurate, precise, and professional. First and foremost, however, plain language was a practice. In order to explore this further, one needs therefore to examine how Patient Education completed a project.

MTHFR, the Gene that Dare Not Speak its Name

A month after the meeting at which the *MTHFR* pamphlet was requested, Julie Gustafson, a writer named Rachel Adams, and I returned to the conference room in the Department of Medical Genetics in order to discuss beginning the project. We were joined by Jaime and Amanda – the genetic counselors – and Dr. Orlov.[11] Prior to that meeting, we had all read the five-page review detailing the history and problems of *MTHFR* testing that Jaime and Amanda had emailed us. After 45 minutes of discussion, Rachel set down her pen and notepad and said, "Okay, I think I'm good to go." She told them she would send them the first draft of the pamphlet in fifteen business days and they would subsequently have seven business days to make comments and edits before she moved on to the next draft.

"I'll send you a Word document," Rachel said, "but that doesn't mean it has to be that way at all." They were free to make any changes in order to fix its accuracy. She

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addressed in detail below, and tension between the pursuits of clinical utility and scientific discovery is the theme of Chapter Four.

[11] In other meetings about ongoing projects, it was common to see in attendance nurses, social workers, chaplains, and illustrators, as well as clinicians and writers.

reiterated that, noting that their role was specifically to address content. It was a major concern for writers in Patient Education that clinicians would take it upon themselves to change a document's wording or poetic structure. That was the role of Patient Education and the purview of plain language. "We're the only ones at [the hospital] that know how to do this," explained an editor. Simplification was an expert practice.

The *MTHFR* pamphlet eventually went through three drafts. The first draft was extensively rewritten, but the subsequent drafts saw only minor changes. Some of the simplifications included the removal of the full gene name (methylene tetrahydrofolate reductase) and the names of the two major mutations occurring in it (C677T and A1298C). These were considered superfluous and confusing. The sentence "One of your doctors may have had you tested for genetic variants in your *MTHFR* gene" was reworded as "Your doctor may have had your blood tested for genetic variants in your MTHFR [sic] gene." Note also here that "*MTHFR*" was de-italicized. Rachel told me that "Technically it's supposed to be italicized," referring to the orthographic practice for all gene names. However, the consensus among writers in Patient Education was that italics were bad for "readability," and therefore it was preferable to break with prescriptive norms of the expert register and conform to those developed in plain language.

The final section of the pamphlet was originally titled "I have already had testing. What should I do?" This was renamed "Follow Up." Much of the information provided in this section was also removed. "*MTHFR* testing is not recommended for thrombophilia, pregnancy loss, or heart disease" was reduced to the comment that "Most people who

have a change in the MTHFR gene will likely never develop any health problems." A closing statement on the changing state of science was removed entirely.

In the series of emails that accompanied the exchange of edited drafts, the genetic counselors also asked to have additional information added. Jaime noted that clinicians might nonetheless recommend that patients check their homocysteine levels if certain mutations appeared in the test results. Every time Rachel and Julie returned a draft, they included – by way of valediction – "Please review for clinical accuracy," again enacting the boundary of competence in the simplified register that was being mobilized in the production of the pamphlet.

However, for this discussion of plain language, the most salient aspect of producing the pamphlet on *MTHFR* was the gene's very name. Initialisms were disliked for being opaque and therefore confusing, as was "medical jargon" in general. What was most concerning for the Patient Education team, though, was a perceived similarity between the graphic appearance of the acronym and a particularly devalued phrase.

When I sat down with Julie to discuss the progress of the project, she gave me an amused smile and handed me a copy of the original draft, pointing to the title: "Understanding *MTHFR* Testing." Specifically, she pointed to the gene name. "What does it look like?" She would not say it aloud, but I did not have to guess what she saw in the initialism. One of the genetic counselors had previously told me in private that the gene was jokingly called the "mother-fucker gene." Julie told me that once one of her colleagues had mentioned to her that the initialism looked like a curse word, "that was all I could see." She then took it upon herself to allay that connotation without removing the word completely. She changed the title of the pamphlet to "MTHFR gene testing." In

the first sentence, she included the full name of the protein that the gene produced and after which it was named; she even underlined the letters that made up that initialism: "methylene tetrahydrofolate reductase." She admitted this was indeed antithetical to the precepts of plain language, but felt the taboo perlocution trumped the distraction provided by the complex and expert-register phrase.

This case demonstrates some of the regular concerns writers faced in using plain language to 'simplify' expert utterances and expert thoughts. The primary demands of this translation were to remove the markedly expert-register gene name. However, the writers anticipated a negative perlocutionary potential in the otherwise acceptable abbreviation <MTHFR> and opted for a sort of homophone avoidance (Fleming 2011; Haas 1964). The ideologically rich process of simplification was dynamic and contextual.

'Pharmacogenomics' and the Travails of Simplification

'Simplification' was viewed as a type of translation. One physician liaison even repeatedly referred to Julie Gustafson as "a translator." Simplification consisted in the commensuration of expert-register utterances with acceptable plain-language alternants. One patient educator characterized her job as "convert[ing] things to plain language."

Selection of 'the right' plain-language lexical alternant was a complicated task. Plain language did not mean simply choosing a shorter or less morphologically complex word to replace an expert-register form, as the case with *MTHFR* demonstrated. Writers had to consider a number of other factors as well, including what might overwhelm, frustrate, or frighten their readers (see also Chapter Three). In the above case, an

expert-register phrase (methylene tetrahydrofolate reductase) was 'borrowed into' plain language in order to prevent a particular implicature from arising.

The fundamentals of simplification, however, were more straightforward. 'Approximately' is replaced by 'about,' 'hypertension' with 'high blood pressure.' Writers also removed what Orwell called "verbal false limbs" (1948:3), in which thoughts were expressed in complex phrases stuffed with Greco-Latinate lexemes rather than their simplex synonyms. 'Difficult' and verbose language, writers explained, was replaced with "familiar and everyday speak." Polysyllabic words in particular were treated as *negative shibboleths*, overt markers that a segment of text was not an instance of plain language.

While a "sixth- or eighth-grade reading level" was considered ideal, writers used "medical language" if they expected the clinician to use a certain phrase in face-to-face communication. For instance, "arrhythmia" was defined in the first sentence of a pamphlet on the topic; throughout the remainder of the text, that word alternated with the phrase "heart rhythm." Rather than a failure of conforming to the register's metapragmatic model, the readiness to borrow from expert registers was an inbuilt feature of the ideology.[12] In fact, plain language was notably heteroglossic in this way, standing as a contact zone between multiple socially recognized registers (see also Chapter Five). The clinician's voice could never be entirely erased, and the indexical *renvoi* (Silverstein 2005) cued by such appropriations brought with them a technoscientific backing that provided a further source of authority to the text.

[12] Singh (1989) describes another linguistic phenomenon (viz. politeness in Maithili) in which shibboleths are borrowed between metapragmatically partitioned registers for pragmatic effect.

Moreover, the scientific and clinical registers themselves diverged significantly one from the other with marked incommensurabilities and transductive slippages of their own (see the Introduction and Chapter Four).

"Billions of our diseases and our conditions have horrible medical names that nobody can pronounce even," one writer told me. For instance, this particular writer was working on a pamphlet on cholangiocarcinoma. "I've got seventeen pages to fill where I'm talking about this type of cancer you have, and after about the second page I've dropped into either calling it a tumor or the cancer or cancer, and I don't reference 'cholangiocarcinoma' except maybe every fourth or fifth page." This writer felt compelled to use the otherwise inappropriate lexeme 'cholangiocarcinoma,' she told me, because the patient would hear it during his or her appointments. The writer did not use it often, though, because "at the end of the day, my responsibility is to make sure that [the patient] can store that information in their brain," and the multisyllabic, Greco-Latinate neologism would hinder that.

Plain language specialists were concerned that plain language in fact could not represent the same world with the same nuance as the expert register, which had been developed for exactly that purpose. Julie Gustafson told me that she would leave the phrase "the urinary tract system" in expert register because it didn't have an acceptable plain-language alternant. Certain terms for "internal organs and guts" – such as the pancreas and the spleen – could not be distinguished successfully in plain language, and so lexical (and attendant conceptual) borrowing was necessary. Similarly, in the pamphlet on whole exome sequencing, it was determined that some additional details regarding the science (which would otherwise have been avoided as unnecessary and

overwhelming) would be included. This was because Medical Genetics needed to explain why WES was more expensive and took longer than other genetic tests.

Writers understood certain concepts to have vernacular forms that would not maintain the appropriateness to the context for which plain language was specified. "Mucous, urine, and drainage," said one writer, were not ideal in themselves, being "higher level words." However, they were the best options in contrast to other potential lexemes in their paradigm (such as "snot," "pee," and – worse still – "piss").

There were perceived legal constraints as well. The use of the future tense as borne by the auxiliary 'will' was considered unacceptable. One writer explained that "'Will' is taken legally as a guarantee [by readers]. 'Expect' is another promise." Instead, statements about future events needed to be modalized with modifiers such as "typically" and "usually." After another writer explained this constraint in a meeting with clinicians in Pediatrics, the physician liaison lamented: "We're in a society now where every single word-" he held up the pamphlet under review, "'If I do all this, I'll have a perfect child.' If people would just be reasonable." (Despite this common concern, it was officially and practically at the writer's discretion which texts to send out for legal review.)

Early in my fieldwork, a biologist told me that the writers of Patient Education "hate" the word 'pharmacogenomics.'[13] The biologist explained that words in plain

[13] Although the term "pharmacogenomics" was most commonly used in the hospital (and appeared in its official literature), certain specialists considered it inaccurate, preferring instead "pharmacogenetics." A molecular pharmacologist explained that *genomics* entailed an investigation of the interaction between genes, something the tests that were offered at the time did not do. Writers, made aware of this counter-discourse, determined that a patient would hear 'genomics' from their clinicians and

language should not contain more than three syllables, and that pharmacogenomics "doesn't lend itself to plain language." A genetic counselor later told me, "I don't know what you would do with pharmacogenomics" in plain language. Despite these doubts, the writers managed to produce a pamphlet on the topic. They decided to gloss pharmacogenomics as "drug–gene interaction." While scientists working on the project at first critiqued this phrase as "a simplification" (a term members of Patient Education did not traditionally regard as negative), they eventually agreed that it was a "good-enough" gloss. The original concern of denotational equivalence gave way to the doctrine of pragmatic sufficiency. (An educator summarized the two-hour discussion for me afterwards: "This is too vague, and this is too specific. It's kind of like Goldilocks.")[14] Nonetheless, they determined that more work was needed: they needed to make it "very, very clear." They accomplished this by embedding the loan word in a firmly plain-language definition and by including images alongside the text. Like *cholangiocarcinoma*, *pharmacogenomics* was used only sporadically after its initial appearance.

Pharmacogenomic results used a taxonomy different from the generic one presented above. The clinical salience of this set of eleven genes was that they were related to a patient's variably successful uptake of certain medicines. Such tests could determine whether a medication would work for a particular individual, the dosage that should be prescribed, and whether the medication could cause negative reactions. In fact, before physicians could prescribe certain drugs (e.g. Warfarin), they were required

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therefore this term was preferable. Again, accuracy was subordinated to pragmatic utility.

[14] Compare Silverstein 1996:292.

to order a pharmacogenomic test for the patient. For this reason, laboratorians assigned certain results (that is, particular variants found in these genes) to categories such as "poor metabolizer" and "rapid metabolizer." One writer attempted to use the standard nomenclature already developed for other genetic test results – viz. "positive" and "negative" – but the scientists immediately complained. "It completely lost the essence," an educator on the project explained. "It was completely and absurdly wrong." They had to return to the original, expert verbiage in order to "keep the truth in that."

Writers relied heavily on their clinician collaborators in determining (and maintaining) the "accuracy" of their simplified texts. The process was a form of 'transduction' (Silverstein 2003), an asymmetric conversion of meaning between registers, with – significantly – a slippage and loss. Writers made no claim to medical expertise, and clinicians were employed at each node of simplification in order to ensure that the entailed slippage did not invalidate the truth of the produced texts. Accuracy was a question of "adequate precision" (Shapin 1994a), where pragmatic concerns persistently trumped denotational ones.[15]

Standard, Standardization, and Charisma

While conducting interviews on plain language in Patient Education, I was given not only pamphlets but also reference documents that the writers and educators had on hand. These documents contained lists of Internet links to information on plain language; partial word lists correlating "excess words" with their plain alternants (I

[15] Austin represents this is a general feature of communication, noting that the felicity (accuracy) of the statement 'France is hexagonal' is dependent on the context and goals of its use (Austin 1975:143ff).

Excess words	Plain Alternatives
accordingly	so
addressees	you
as a means of	to
as prescribed by	in, under
at a later date	later
at the present time	now, currently

Figure 2.1: List of excess words and their plain alternatives, from one of the Section's white papers.

return to this subject below); and a miniature manifesto of the hospital's policy toward plain language, complete with an "Appendix" of 23 cited works, tracing plain language's history back – interestingly – to George Orwell's (2013 [1946]) polemical "Politics and the English Language."

I was surprised that all of this material was simply on hand; only one of the reference lists needed to be printed, and my interlocutor had the link to it bookmarked on her web browser. Furthermore, it was not that a presence such as mine was commonplace. Other than the 60-person staff, the only people in SPE were patients who came to the library for free, hour-long sessions with professional medical educators in order to discuss their conditions and/or their treatments.

The ideology of simplification had resulted in a variety of attempts at standardization. One of the writers in Patient Education gave me a list that they used to correlate "excess" and "plain" words (see Figure 2.1), and others directed me to a number of resources they had in the library or on their intranet site. For instance, one resource was a "Dictionary of Plain English" with over 400 entries, from "accomplish" to "voluminous."

There had also been attempts to create computer programs that could determine whether a text was simple enough to be read by the plain-language public. For instance, I was shown a number of "readability calculators" that would review a document and return the grade-level at which the text became comprehendible. Writers variously told me that "sixth" or "eighth grade" were ideal thresholds for comprehensibility. Plain-language specialists recommended against overreliance on these prophylactics, though. "They should really just be a check point," an editor told me. Nonetheless, this woman noted that writing was "a soft skill set" and "anything we can do to quantify it is great, since it lends some credibility." The writers in Patient Education believed that representing their work to their clinician colleagues in the form of numbers would make their expertise more legible and would make obvious the power of plain language.

Despite these standardized commensurations, I never witnessed (nor even heard of) a writer deferring to these lists in her own production of plain language, and the readability calculators were treated as safeguards. In fact, a dependence on these materials was seen as an impediment rather than an aid. They were understood to replace the direct experience, spontaneity, and creativity characteristic of the 'best' plain language (cf. Bourdieu 1984:68).

Similar concerns about constricting the art of writing were expressed when Microsoft Word's relatively free format was replaced by a different program that provided standardized modular text fields. What information to include, and where, were predetermined by machinic agency. "It's not just blocks; it's a story," one editor complained of the fundamental mismatch between the new program and plain language.

The use of such standards was seen as replacing the text's iconic relationship to the individual writer, something necessary for it to represent "how real people talk." Rather than being the transparent representation of a "real person," it was mediated and distanced, iconic of something else.

Plain language had a similar relationship to the prescriptions of Standard English. Although many features of 'correct' English were used as models – "In plain language, we don't want to compromise good grammar," an editor told me – the Standard did not hold a non-defeasible authority over the writing practice. For instance, a meeting was held to discuss wording in a piece on preparing for a visit with a genetic counselor.[16] One section was entitled "Who will I meet?" The question arose whether it should in fact say "Whom will I meet?" An educator did an inversion: "I met *him*. Yep, 'whom' is right." But after a pause, she complained that "'whom' is very formal." A second educator agreed: "We want to be casual." At another meeting, an editor rejected a sentence that included the phrase "the means by which," calling it "much more formal than it needs to sound" and "artificial and stilted."

In another meeting, the issue of contractions came up. One writer contended that they should be allowed since "it's standard English." Another writer retorted that "lots of things are standard English," meaning that simply saying they were standard did not constitute a legitimate argument. However, consensus was reached in the end that the phrase "if you do not have one," *sans* contraction, sounded "stiff." It was agreed

[16] I noted afterwards that the pamphlet seemed to be of limited value since the vast majority of patients didn't realize they were going to meet a genetic counselor until they were actually in the room with her.

to use "don't" instead.[17] Nonetheless, what won the debate was not the recourse to the authority of standard usage but to intuitions about symptomatic indices related to tone (cf. Hervey 1992; see also Chapter Three).

The only standards to which writers in Patient Education happily referred were those texts they as a group had written (and only *after* the onset of plain language). Writers would refer back to pamphlets on similar topics in order to see how an expert phrase had previously been resolved. This was certainly not always the case – nor could it have been, given the diversity and novelty of topics the writers were asked to cover. However, it was a common enough occurrence that questions like "Did we worry about that verbiage in any other documents?" provoked no surprise or concern.

All writers were understood to have slight idiosyncrasies with their use and competence of plain language. They each specialized in writing for a particular group of clinical divisions, and this taught them how to meet particular demands. For instance, writers working with Geriatric Medicine and Oncology were understood to navigate discussions of death more skillfully. One major internal division in plain language was the subordinate "teen language." This was described as "very relatable" and "much more engaging." It also entailed a significantly different graphic aesthetic (see below). One writer was considered most expert in writing for teenagers, and she moved between clinical divisions more frequently than others in order to fill the need for such materials. There were no official subsections within Patient Education, though, and specialists switched with some regularity which clinical divisions they supported.

[17] The second writer nonetheless maintained that better still would be to rewrite the whole sentence so as to avoid the issue altogether.

In place of standards, plain language specialists deferred to a sort of charismatic authority (Weber 1922). "Some people have an innate ability," one educator explained. A certain writer with a PhD in English was considered by everyone to be a particular virtuosa. "She has perfectionist tendencies," Rachel Adams said in praise. At meetings, writers regularly turned to her in order to resolve issues of wording and to provide insight.

Writers were socialized into the practice of plain language through meetings such as those described in the above vignettes and through the metapragmatic commentary provided by recognized experts. However, plain language was seen to be immanent in English rather than supplementary to it. "My style throughout my career has been plain language-y, even if not officially," one writer explained. While she noted she had learned much about the practice since the implementation of the mandate, she maintained that her writing had always had tendencies toward the qualities entailed in plain language.[18]

Low Tech, High Sci

Propositional content was not always the most significant aspect of pamphlet construction for the staff of Patient Education. They were also highly aware of the poetics of the graphical space that embodied their text artifacts (Silverstein and Urban 1996).[19] Plain language mobilized not just linguistic channels. "You can have great

[18] Johnstone et al. (2006) note that registers always emerge from sets of linguistic features already immanent in use. See also Halliday 1988:172.
[19] These objects have qualities of Matthew Hull's (2003) notion of a "graphic artifact" in particular.

writing and terrible design," cautioned one writer: "About half of plain language is design."

"Design and Print" was the final step in the production of a pamphlet. Once the team of expert clinicians had approved the final draft, the writers sent it as an MS Word document to Print Media Services. There, professional designers would transform it into something that was "easy to consume and entertaining." One designer, who had a PhD in Design, called it "a form of rhetoric" (referencing Plato's *Phaedros* specifically), with a "grammar" of its own. He understood the use of space itself to be deeply implicated in the same ideological project as the written text: Its appropriate use persuaded its reader to take action, simplified the transmission of information, and convinced its audience of its value and authority. Nonetheless, writers maintained final say over the acceptability of the proofs.

"The layout is an important part of plain language," Julie Gustafson told me. In editing their documents, paragraphs were regularly broken down into smaller paragraphs or transformed into bullet lists. Oftentimes the concern in editing was not to reduce content but rather to space that content out better. "It could just look a lot lighter," Julie said. "You have to think, 'Where do you want your eye to go?'" Writers described design as meant to minimize distraction and direct attention to particular parts of the text whose propositions were considered most important.

Writers also had ultimate control over what images were included in the pamphlets. At one meeting of just writers, a woman told of her experience working on a project for Gastroenterology. An illustrator had produced an image of villi in the small intestine, damaged by celiac disease. One of the clinicians had complained that "villi

aren't quite that high" and asked to have it redrawn. This story was greeted with amusement and laughter from the writers. Patients would not know what a villus looked like, the writers intoned, and furthermore their height was not relevant to the information being disclosed in the pamphlet. The writer on the project had told the clinician as much, and the original illustration had remained in the pamphlet. Another writer noted that illustrations were the main aspect of a pamphlet that could go wrong in meetings with clinicians.

Color was another visual quality that held potential meaning within the ideology of plain language. "Ninety percent of the time, color means nothing," one writer told me. However, the significance of pamphlet covers' colors was fairly elaborately theorized. "Red incites passion," said one writer, to which another added that red would be inappropriate for texts discussing bloody surgeries. They noted a general preference for a gender-based color system as well, with pamphlets on men's issues receiving dark blue covers and those on women's issues receiving purple and lavender.

It was certainly a concern that non-simplified lexicogrammatical forms could prove inscrutable to readers. However, writers also worried that an overly dense graphic space would appear too daunting for patients even to attempt to read. Appropriate use of the material page was understood as similarly implicated in successfully 'informing' a reader.

Pronouns, Agency, Voice

"Plain language is not dumbing down; it's simplifying," was the mantra of Patient Education. A competent writer would not simply choose a shorter or less

complex word. She would choose language based on a deep understanding she had cultivated of her addressees. She first imagined herself *as* the addressee of her writing. In this section I explore the ways in which plain language created its addressees. I also contemplate the dialectic between self and imagined other that emerged from the practice of plain language.

The joint voice of the writer-cum-patient was in paradigmatic contrast with that of the expert. This imagined other was also defined by its (negative) relationship to the personae associated with plain language. Clinicians were said to "really struggl[e] with plain language." Writers not only had a particular ability to know how to *commun*-icate with patients; they had an ability that contrasted explicitly with that of clinicians. Quotations like the preceding were relatively common and served to make manifest and overtly demarcate the boundaries of plain language expertise.

In explaining the process of writing in plain language, the writers in Patient Education described an ethnotheory that in some ways mirrored Althusser's (2008) notion of interpellation. One of the major commandments of plain language practice was the use of second-person pronouns in address. One ought to say 'when you go to your doctor' rather than 'when one [or a patient] goes to the doctor.' The purpose of such "personalization" was explicitly stated in the hospital's 'manifesto' on plain language.[20] Such usage was said to "mak[e] it clear what is to be done and by whom." It rejected passive verbs and abstract nouns and opted for the second-person pronoun in

[20] However, one of the writers in Patient Education told me that in general they avoid using second-person pronouns in describing traumatic hypotheticals. One would say, for instance, 'If a child is born with Down syndrome' rather than 'If your child…' In the hospital's handout on Marfan syndrome, it is stated that "People with Marfan syndrome commonly need heart surgery," rather than the 'personalized' 'If you have Marfan syndrome…'

place of the impersonal third (cf. Benveniste 1966). The second-person pronoun as seen to calibrate the interactional text of reader and pamphlet with the denotational text of patient education. It was not a generic 'you' but the indexing, interpellating finger pointing out of the page. In fact, one of the most important aspects of plain language was that it was constructed in such a way as to motivate patients.[21] The replacement of third- with second-person reference was one of the first things writers changed during five-year reviews, translating into plain language those pamphlets that were made before the mandate.

At the level of the pamphlet, addressees were 'unreal;' they were never concrete or individuable. Pamphlets were not a conversation between "actual people" (Warner 2002:58), but rather an address to an imagined *type* of person. The other – that is, the imagined addressee – became a characterological stereotype, a potential agent, only through the imagination of the writer.[22] Writers curated their language in order that one of these abstract individuals could find him- or herself addressed by it. When a genetic counselor handed patients a pamphlet, or when passersby's eyes were caught as they walked past a rack of pamphlets, it was hoped that they would recognize themselves as the addressees.

The imagined other of plain language was therefore intrinsically multiple and multivocal. The writer needed to be aware of the diversity of her audience. She needed to attempt to produce texts legible for people with a low level of literacy but also to

[21] This topic is covered in more detail in the following chapter.
[22] Most centrally, writers were engaged in a sort of *affective* stereotypy (see Chapter Three). Note here, however, that explicit discourse concerned an addressee emptied of diacritics linked to dimensions of identity under liberal regimes of personhood.

avoid appearing condescending to those with higher levels. The writer needed to write *simply* but also "to be able to speak to patients who are very well educated and engaged," an educator explained. Plain language, the hospital's manifesto declares, is "not anti-literary, anti-intellectual or unsophisticated;" in fact, "people with high literacy prefer and benefit from plain language" as well. As the writer Rachel Adams told me, "Research has shown, people with multiple PhDs love plain language."

There were concerns that choosing the wrong word would prevent a pamphlet from successfully interpellating its reader and implicating him or her in its moral obligations. For instance, there was once a debate about the use of the term 'loved one' in a pamphlet about caregiving after surgery. "What if they don't love them?" queried a writer. "What if it's a hate relationship?" Another person mentioned that the caregiver could be a hired nurse. If so, the reader would not be able to imagine him- or herself to be truly addressed by the pamphlet and thus would not attend to the instructions and information it held (cf. Briggs 2003).

For the plain language specialist, it was of utmost importance that the addressee-other be in some essential way *the same* as the self. There was an intrinsic aspect of sharedness between the addressee and the authoring self. In broad terms, the plain-language other was a sincere – if imperfect – attempt to imagine a universalizing 'human' subjectivity based specifically on a variety of non-expert forms of life.

The most central and most vital feature of the plain-language ideology, from an emic perspective, was its "reader-centered approach." To write in plain language entailed writing as though one were her addressee. As one writer told me, "My first job isn't to act like a writer. My first job is to act like a patient […] I literally act like I've

never heard of the subject before." The practice of plain language was a sort of *technology of self*. That is, it was a set of "operations on [the writers'] own bodies and souls, thoughts, conduct, and way of being, so as to transform them in order to attain a certain state" (Foucault 1988:18), viz. the state of being the other. Practicing plain language did not merely produce a text artifact; it produced a particular form of self.

The plain-language technology of self constituted a self by transmuting itself into the self of the other. A writer's success in producing plain language came from her ability to 'put on' the other's mind, to inhabit that way of being. Such an act was seen to performatively constitute an empathic engagement with that other perspective. It might seem as though this would be a relatively simple process; however, it was a technique that had to be cultivated and refined. "Writing in plain language," one editor told me, "doesn't come naturally."

Writers started to re-center themselves deictically as soon as they began gathering information and preparing to write. They imagined themselves as the patients who would eventually read their work. They even expressed this shift with a parallel shift in pronoun usage. The patient-addressee became the first person. 'What do I need to know before having X procedure?' they would often ask physician liaisons. For instance, when working on the above-mentioned pamphlet about whole exome sequencing, Rachel Adams voiced an imagined patient when she asked Jaime Smith, "If I change my mind, can I choose not to get results back?" The genetic counselor responded that "some [results] are mandatory to learn." "I have to emotionally be ready for something like that," Rachel replied, making note to address this potential dismay in the pamphlet.

A key practice in transforming one's self into the plain-language other was to excise the influence of distancing rarefication from one's thoughts. There was an imagination that *underneath* the ornament of expert culture existed a 'simpler,' more fundamental way of being that was accessible to the writer and constitutive of the other. "The baseline of human experience, that's what we're trying to find," an editor told me.[23] By accessing this *shared* form of being, one could engage the other in Simmelian stranger sociality. Social behavior became legible to the widest possible population by being "based on merely universal human similarities" (Simmel 1972:148). As one writer told me, she was particularly qualified to write for Medical Genetics "because I don't have a medical background," no such rarefaction, which thus endowed her with a patient's perspective.

One educator cautioned that working among specialists on a pamphlet for extended periods of time could be detrimental to a writer's transformation. "Sometimes we get stuck in our own world. You know, you've lived in this world too long and you forget" how a naïve patient would see the material. She described sharing with a non-specialist associate a pamphlet on a particular pharmacogenomic result – namely, the variant *HLA-B*1502* – which was associated with the metabolism of the seizure-drug carbamazepine. When her associate told her he wanted to discuss 'halaba' ([həˈlɑbə]), she said she "didn't even recognize the word." The scientists with whom she had been working always pronounced the variant name "letter by letter." She said this encounter made her consider adding something about pronunciation (though this task was considered particularly difficult in plain language). More importantly, however, it had

[23] See also Chapter Three's discussion of the relationship of 'reason' to ascribed personhood and its attendant rights.

made her realize how obvious (cf. Althusser 2008) or common-sensical (cf. Geertz 1983) she had let that expert register become.

Writers of plain language regularly engaged with their own imagined other-selves in a Socratic dialogue, further complicating the self-other boundaries. All of the material presented in the text artifacts was supposed to come from an active imagination of what would be relevant to the writer's audience as well as what would move that audience to action. This was made most explicit in the headers that opened new sections, which were presented in the form of questions. 'What causes Down syndrome?' a writer might have rhetorically asked herself before listing answers in a bullet-point list. Here the other and the self, the addressee and the speaker blended almost completely. The writer was simultaneously the questioner and the respondent, the layperson and the translator of expertise.

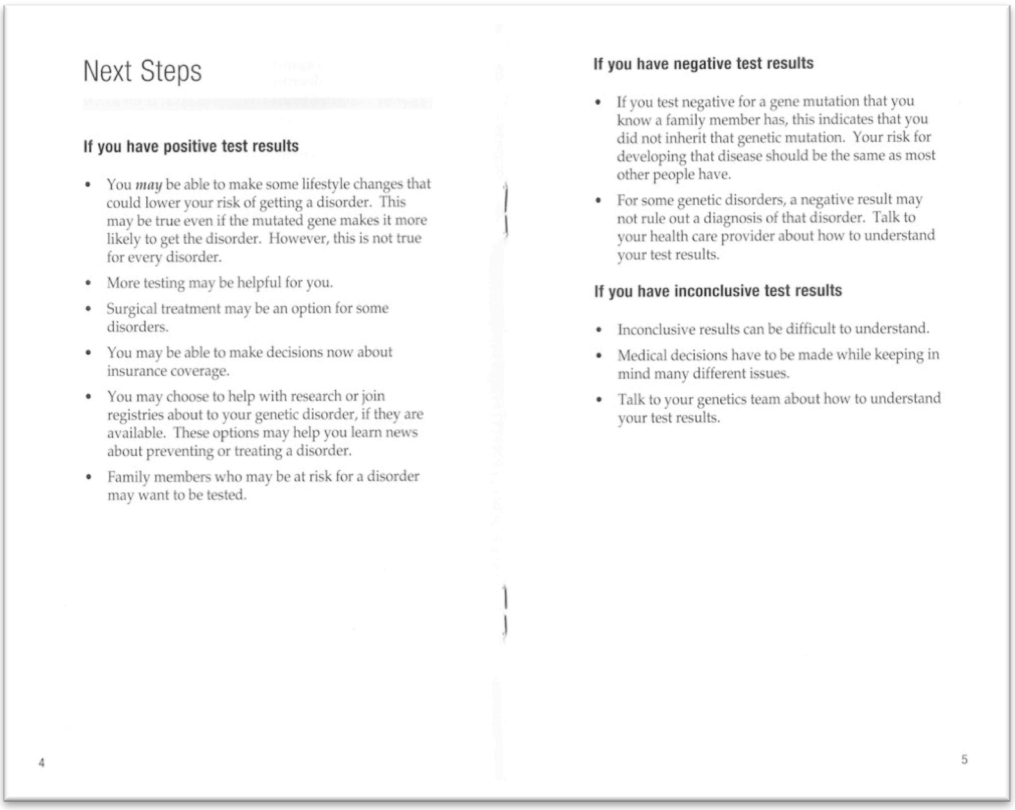
In an hypertrophied fashion, the rare pamphlet contained quotations that appeared specifically to be the voice of a patient. This language was in fact "an amalgamation of a quote that's really contrived from a lot of different patients," an editor explained. The quotations were constructed using information the writers gathered from people with "personal experience" with the text's topic – either patients or their clinicians. The quotations "made up" by the writers thereby became "authentic," abstractions grounded in the truth of particulars. This worked to assuage the persistent anxiety felt in the production of relative immediation (Mazzarella 2006). However, it was equally important to filter these propositions through plain language, removing overt markers of particularity, such as register shibboleths and characterological features like gender and race. "What if it's a woman and I'm a guy?" a writer explained.

Such concrete representation would have interfered with the universalizing aspirations of plain language interpellation.

The universalized addressee was clearly a liberal subject, with limited but equal qualities, a functional least-common denominator. He or she was subject to affective states that could be managed through the poetic use of language (see Chapter Three), but in explicit conception was considered essentially rational. Writers understood the impassionate aesthetic quality of plain language to produce calm and considerate addressees. Through visual and verbal aesthetic practices, they aspired to hold their readers in a composed, rational state.

A fascinating aspect of the plain-language pedagogical materials was the iconic way in which they represented the very ideology they described. Instruction on how to practice plain language was itself given in plain language. One can compare the hospital's pamphlet "Genetic Testing: A Fact Sheet" (Figure 2.2) with a section of its 'manifesto' on plain language (Figure 2.3).[24] The vocabulary was 'simple,' the reader was addressed in the second person, and bullet-point lists were extensively deployed. In order to make the text appear easy to read, writers recommended the use of very little space on the physical page and a large, serif font – and they presented this recommendation in just such a fashion. This was the plain-language technology of the self at a meta-level. Like the map of an island drawn in the sand of that very island (Peirce 1940), specialists iconically re-presented for ease of uptake and deployment the very ideology they described.

[24] The proliferation of footnotes all led to citations of other texts.



Next Steps

If you have positive test results

- You *may* be able to make some lifestyle changes that could lower your risk of getting a disorder. This may be true even if the mutated gene makes it more likely to get the disorder. However, this is not true for every disorder.
- More testing may be helpful for you.
- Surgical treatment may be an option for some disorders.
- You may be able to make decisions now about insurance coverage.
- You may choose to help with research or join registries about to your genetic disorder, if they are available. These options may help you learn news about preventing or treating a disorder.
- Family members who may be at risk for a disorder may want to be tested.

4

If you have negative test results

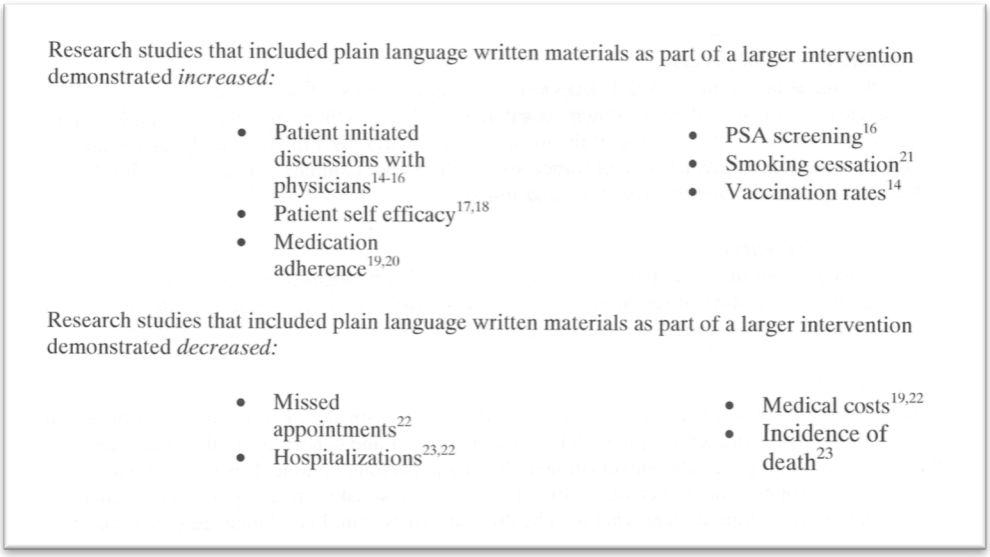
- If you test negative for a gene mutation that you know a family member has, this indicates that you did not inherit that genetic mutation. Your risk for developing that disease should be the same as most other people have.
- For some genetic disorders, a negative result may not rule out a diagnosis of that disorder. Talk to your health care provider about how to understand your test results.

If you have inconclusive test results

- Inconclusive results can be difficult to understand.
- Medical decisions have to be made while keeping in mind many different issues.
- Talk to your genetics team about how to understand your test results.

5

Figure 2.2: Page from a pamphlet on genetic testing.



Research studies that included plain language written materials as part of a larger intervention demonstrated *increased:*

- Patient initiated discussions with physicians[14-16]
- Patient self efficacy[17,18]
- Medication adherence[19,20]
- PSA screening[16]
- Smoking cessation[21]
- Vaccination rates[14]

Research studies that included plain language written materials as part of a larger intervention demonstrated *decreased:*

- Missed appointments[22]
- Hospitalizations[23,22]
- Medical costs[19,22]
- Incidence of death[23]

Figure 2.3: Segment from the manifesto on plain language.

The plain-language other was not the binary opposite of writer's self; rather, the two *shared* in their essential qualities. Furthermore, by imagining oneself as the other, the writer realized a fundamental part of herself that had previously been unaddressed. The writer trained herself to become the other in this "extreme form of subjectivity" (Ochs et al 1996) and thereby both undertook a better way of being (or at least, of behaving) and discovered the fundamental fraction of the other that had always-already existed as a part of the self. The writer, however, did not see herself in any holistic sense as the same as her addressees. She might have shared some fundamental mode of being with the other, but still she remained distinct. She had expert knowledge that needed to be translated in a moment of simultaneity, laminating the two roles.[25] She needed both to *be* the other and to *be* the self. Despite constant slippages between the two, their essences, at least on some level, were imagined to be distinguishable.

There were, however, boundaries to what personae the writers felt comfortable with or capable of voicing. The first person "I" or "we" were seen to suggest "the voice of your healthcare team," an editor told me: "We have a guideline not to use it." One writer explained to me that pamphlets were "the voice of [the hospital]," the gestalt accumulation of clinical expertise. The writers of Patient Education were not the principals of the text, merely its authors (Goffman 1981). They could claim neither responsibility for its content nor authority for the

[25] This act is reminiscent of Kiesling and Ghosh Johnson's (2010) notion of "production indirection," in which speakers strategically and playfully mobilize the indexical presuppositions of certain linguistic forms in order to inhabit multiple personae at once. In Patient Education, however, it was more a conflation of roles than an ambiguity between them.

expertise it represented. They refused to conflate the two voices, maintaining what might be called the *intervocal gap* (cf. Briggs and Bauman 1992) between the roles and between the forms of expertise. Unlike with lay patients, the clinician-self was expert rather than simplified or reduced. It was not immanent or universally shared.

One instance in which the first person plural was allowed was in the introductory phrase, "We encourage you to read this." During a discussion of the pronoun, a writer expressed her concern about beginning a pamphlet in this way. However, the woman leading the meeting said she thought this was "okay," and another writer suggested this was because the hortation concerned the pamphlet as such and not a healthcare decision. The other writers agreed, and the phrase was accepted into the final draft. Beyond metatextual propositions explicitly referring to the text as such, however, writers attempted to avoid revealing their mediation in the translation process so overtly.

The Enregisterment of plain language

Plain language was treated metapragmatically as a register (cf. Agha 2003) with minimal consistent linguistic forms. This is not necessarily unique of register phenomena, though it is distinctive (Agha 2007). More noteworthy, plain language was chiefly characterized by the removal – rather than addition – of lexical items from a relatively Standard base and expert source. Its recognition often took the form of commentary on *negative shibboleths*, words and grammatical structures that were markedly *not* plain language. Greco-Latinate loans, neologisms, the tense marker 'will,' and embedded phrases all worked against a text's being read as plain

language. However, many more linguistic – and non-linguistic – signs were potentially at issue under different contexts. Some forms were indeed pre- rather than pro-scribed, such as the second person in address and the use of large swatches of empty graphic space.

Plain language was an historical formation, distinctly partitioned from Standard English in 2008, when the practice of writing for Patient Education was unified under its banner. It had since become "ritualized," acquiring its distinctive value by its functional claim through its mandate to patient-facing textual communication (cf. Halliday 1988). At the time of my fieldwork, it was a socially recognized form of communication in the hospital among clinicians and writers. They both found instances of plain language differentiable from other modes of communication.

The unique and privileged status of plain language was recognized throughout the hospital. (Note, however, that writers did not assume that patients – their ratified addressees – would recognize their texts to be plain language *as such*.) Clinicians would defer to writers from Patient Education (at least in face-to-face encounters) as experts in the performative success of the register and the 'prestigious' forms associated with it. For instance, at a non-SPE meeting during which genetic counselors were discussing some information on their website, one counselor suggested rewording a phrase from "patients with similar conditions" to "people like you." Another counselor lit up at the turn of phrase: "Patient Ed always says things like that, 'you!'" Both counselors had recently been involved in a project with Patient Education. Clinicians came to recognize plain language through such

collaboration, not through reading the pamphlets thereby produced. While it was certainly in significant part a metapragmatic denomination, the label of plain language also picked out specific co-occurring linguistic properties.

There was a general competence of recognition even if not of (authorized and therefore ritually successful) production. At a five-year review, for example, a writer suggested describing the amount of fluoride to put on a child's tooth as "the size of a rice- a piece of rice." "Perfect!" commended the physician liaison happily. "That's why you do what you do, and we don't!"

The practice of plain language blurred the boundaries between author and addressee, self and other, by thoroughly implicating each in the formation of the other. In fact, the technology of self that plain language provided required the self to become the other. This aspect was taken seriously by the writers, and didactic material produced by specialists treated the writers-cum-readers as though they had already undergone this transmutation. This process entailed an almost unending circle of imaginings.

In this way "plain language" could be understood to represent a register and an ideology. It was distinctive as a register for being extremely open and context-dependent in terms of what linguistic forms it would permit. In many ways, it partook interestingly in aspects of genre (cf. Briggs and Bauman 1992), its recognition being often more a result of the context of its performance than the immanent qualities of its text. Interestingly, however, it was both genred and generic, in Manning's senses (2008). That is, plain language was seen both as a marked, historical formation as well as an underlying, inborn sociocultural form.

What is most important to my argument in this chapter, though, was that it was metapragmatically constituted, its boundaries drawn up not by objective standards of calculating coocurrence but by interactional and institutional presupposition.

Plain language rejected standards and many classical forms of regimentation while preferring appeals to charisma. Plain language's tokens were never isolated but instead were deeply co-textualized. They were more defined by negative shibboleths than positive. Despite this, plain language demonstrated all the traditional metapragmatic trappings of a register. In fact, its conventionalized ability to determine and mediate social relations was its most potent feature. Plain language may serve to highlight the importance of register phenomena (e.g. the stereotypic linkage of semiotic forms to social types) in the metadiscursive delimitation of linguistic forms. Rather than 'objectively' apparent structural and formal regimentation, the register was more saliently partitioned from other varieties by the perceived qualities of its users.

CHAPTER THREE: BAD AFFECT

The Argument

In this chapter I examine *anticipatory affect management* in medical communication. Specifically, I discuss how affect and reason are used as variables in patients' decision-making whether to get genetic testing. Among my interlocutors, language was imagined to embody and generate affect. That is, clinicians worried that the way in which they said things would cause patients to experience certain affective states, which could affect their ability to make rational choices about their healthcare. This runs up against American biomedicine's legal and ethical commandments to be nondirective so as to allow the patient autonomous decision-making. In this chapter I demonstrate how specialists attempted to incorporate supposedly disinterested and unbiased educational texts and information covertly into larger political projects of decision management.

Despite the inherent difficulties of communicating specialist knowledge to lay patients and 'informing' them of their healthcare options, specific beliefs about language allowed interactions to proceed relatively unencumbered. This achievement hinged on the construction of patients as rational subjects, free of *bad affects* that could upset their ability to make informed decisions about their healthcare.[1] As long as decision-making processes could be understood to be

[1] By *bad affects* I do not mean "resonances independent of content or meaning" (Shouse 2005) or "prereflexive … primitive experiential richness" (Massumi 2002:29), which conceptions have been soundly critiqued on their own terms (cf. Leys 2011; Mazzarella 2009). Rather, I aim with this rhetoric to propose that cultural domain of mental life counterposed to that of reason, an equally cultural

rational and free of paternalistic effects, hospital staff could dub interactions successful, and future healthcare could be planned and undertaken. Without at least the ritual event of 'informing' having been undertaken, healthcare decisions could fall under scrutiny in terms of their legitimacy or success.

In this chapter I also consider the role of paternalism within systems of specialist knowledge, such as the Center for Individualized Medicine (CIM) at which I worked. At the time of my fieldwork, American medical ethics condemned all forms of paternalism, that is, any impingement on the 'autonomous will' (e.g., Beauchamp and Childress 2009:208) of the patient.[2] However, I argue that the socially recognized specialist division of intellectual labor between clinician (and scientist) and lay patient entailed what was taken up as unequal comprehension. A patient was seen as necessarily failing to understand medical information with the same accuracy and acuity of his or her clinicians. I argue that a heavy-handed rejection of paternalism *tout court* would therefore also be a misrecognition of the intimate relationship between the social legitimation of knowledge and power in healthcare decision-making.

To begin, I consider a particular writers' meeting in the Section of Patient Education (SPE) to see how this kind of language work takes place. Then I detail the question, linking it to the ethical concern with so-called therapeutic privilege: the

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category. I also hope to capture in the phrase the imagination of these states' unintentionality on the part of their subjects.

[2] Note that while there existed a particularly valued discourse rooted in moral philosophy that was arbitrated by special classes or particularly charismatic individuals (e.g. bioethicists and particularly "ethically-minded" physicians), the usage of "paternalism" in the vernacular of the clinic had a different semantic domain. Paternalism was neither as precise, for instance, nor perfectly cognate with its cognate in expert discourse

privileged control clinicians have over medical knowledge. Finally, I pose a counterpoint by addressing the necessity of this privilege by theorizing the notions of choice and coercion.

"Hopeless"

I now turn to the Patient Education meeting. It was a Friday in the dead of winter, in the midst of the so-called Polar Vortex. When I woke up, the radio said it was -55°F with wind-chill. Arriving at the hospital, I was greeted with almost giddy declarations from my coworkers: "Did you hear that it's colder than Mars today?"

As was regularly the case, I spent my day rushing between clinics and boardrooms in a number of different buildings. Everything was connected by a labyrinth of skyways and pedestrian subways, so I never had to brave the frigid outdoors. I was not unique in my mobility. The people I worked with at the Center necessarily split their time between multiple spaces: one building housed Oncology, one Medical Genetics, another the genetics laboratories, another administration, and yet another Bioethics.

At five to two I was making my way through the warm skyways to the Section of Patient Education, located on the top floor of one of the taller buildings. It was nearly time for the quasi-weekly writers' meeting. In the hall I saw Suzie Kulick, one of the writers, who was also heading to the meeting. She was still bundled in her winter garb: scarf, hat, mittens, down coat. Most of the Patient Education staff were not full-time employees, and in fact most of the writers came onto campus

specifically for the writers' meetings. Suzie waved and held the elevator door for me. "It's colder than Mars out there!" she announced, amusedly.

When we arrived at the boardroom, the seats at the table were already nearly full. Several women had paper cups steaming with tea that they had procured from the kitchen around the corner. The conversation in the boardroom was again about the weather. "We'll have a high of zero tomorrow," one woman noted jocularly, if also with some pride. Another woman had teleconferenced into the meeting from one of the hospital's campuses in the American South. "It's cold here, too," she gibed: "I wore a jacket this morning!" A writer retorted that it was so frigid her car wouldn't start when she tried to drive to campus. "You can get free jump-starts from [the hospital]," advised one of the more seasoned employees.

In addition to me, there was only one other man in the room. He had come to talk about the new provider for stock photos, to which SPE had recently switched. His discussion was just a preliminary addendum, though. The real meeting started only after he had left and Lisa Campbell, the head of SPE, had taken the floor. We were gathered to discuss the new annual theme, "tone." Lisa began with a story that I will paraphrase here, which she used in order to describe what she meant by *tone* and why it was of paramount importance to the writers in Patient Education.

Several years prior, Lisa had been managing a project in which a pamphlet on a certain terminal illness was constructed. After the pamphlet had been completed and was circulating through the clinic, a patient suffering from the disorder came to her, still clutching the text. "This is the most hopeless thing I've ever read," he lamented to her. Lisa said she was completely devastated by the criticism. She read

through the pamphlet again. All the information was factual; it was presented clearly and at a low readability level. It contained no images, gruesome or otherwise. However, she was forced to agree, it had a bluntly stoic tone.

The meeting's attendees chimed in that the patient's loss of hope was a major failure of their writing and, specifically, of their use of plain language.[3] They viewed correct register deployment as entailing the pragmatic effect of maintaining the reader's rational mental state. A loss of hope was a sort of *bad affect* – it might lead a patient to disregard clinical recommendations as futile, that is, to engage in irrational behaviors. Professional medical ethics also discouraged the pessimistic disclosure of information, something called "hanging the crepe" and condemned as an "abandon[ment] of *reason*" (Siegler 1975:856, emphasis mine). Contrarily, too much hope – and "false hope" – could be seen as bad affect as well, to which I return below.

"Tone has to be our goal," Lisa reiterated. "You can't just spew out facts. It has to be more humane than that. How do we offer assurance and calm [patients] down? Even if their life is going to end, how do you still provide them with hope?"

Lisa related another story she felt demonstrated the importance of tone. She had brought a stack of pamphlet drafts with her to review at a coffee shop. When she opened a particular piece on rectal prolapse – a condition in which the rectum slips out of place – she was mortified. In fact, she immediately shut the pamphlet and looked around to see whether anyone else had seen the salacious image she'd

[3] Plain language is discussed in detail in the preceding chapter. It is sufficient here to note that plain language was a metapragmatically demarcated register formation distinguished by its intended universal comprehensibility in contradistinction to the specialist lexica in the employ of the hospital's clinicians and scientists.

just exposed to the world. “If you open a piece and the first thing you see is a piece of anatomy, it’s insensitive,” she declared to a room of chuckling, middle-aged women. “Large, and on the first page there was a reclining woman with her rectum coming out her anus!” Encouraged by the successful uptake of this story, she related a similar anecdote about a piece on penile health, which she concluded by noting, “An enormous penis on the front page is bad tone.”

On a more serious note, Lisa brought up another project, one on hemipelvectomy, i.e. the amputation of half of the pelvis and the associated leg, often as a result of cancer. “This is truly awful,” she concluded after a relatively graphic description that I spare my reader. But instead of calling it *awful*, the writers on this project decided to call it *life-changing*. “This is a much more neutral tone,” said Lisa. “It’s awful and devastating and all those words, but you have to leave hope.” Calling the procedure “awful” might deter the reader from pursuing the medically indicated intervention.

How to Make People Do Things with Words

Over the course of the year, the writers in Patient Education developed *tone* into a highly elaborated ethnometapragmatic term of art. Tone was meant to transform the implicit affective aspects of plain language into explicit ones. It provided writers an analytic with which they could address the pragmatic – rather than merely semantic – aspects of their verbiage and style. My interviewees in SPE said the hospital had a particular tone, which one writer described as “compassionate and healing.” Lisa added that its tone was “patient-centered.”

Patient Education was to develop its own tone as well, one that would encourage patients not to lose faith in their healthcare, that would engage their interest, and that would walk the fine line between being patronizingly simplistic and being illegibly complex (see Chapter Two). However, what proved most central to the concept of tone was the affective potential that writers saw as entailed in the poetic structuring of their propositions.

They understood this power to affect affect as both a blessing and a curse. At a meeting near the end of February, Suzie Kulick explained this double-edged sword to me by making reference to a project she'd worked on that dealt with "street drugs." In particular, she was interested in an utterance's ability to provoke fear. "You want to reinforce the horrible things the drug does to your body." One might choose to list all of the potential negative consequences of drug use. Usually such lists were considered as bad form, as both intellectually and visually overwhelming the reader: "Wow, that's too much information!" Suzie voiced her imagined reader. But in fact, she explained, leaning heavily on such gruesome information might sometimes be the best way to motivate a patient to follow a clinically recommended regimen.

Patient Education was jurisdictionally distinct from other forms of distributed texts ("patient information") because the former was said to "motivate" its readers (see Chapter Two). Motivation as an ethnometapragmatic category was closely aligned with the concept of illocutionary force (Austin 1975), that is, the *conventional* power (e.g. Levinson 1983:236) of an utterance to cause an effect in the world. Illocution was thus part of the premeditation, design, or intent with

which a writer constructed an utterance in relation to her addressee. Motivational statements were *directives* in Searle's (1976) sense, though often their directivity was actively made covert. Directives were often stated as though they were simply denotational facts.

For instance, at a writers' meeting, the writer Stacy Jacobsen described her current project, which was a piece on prediabetes, a condition preceding type 2 diabetes. "Patients often think that genetics and age make diabetes inevitable," Stacy lamented. "But if you go down *that* medical track, you can get all caught up in 'My mother, my father!'" meaning that the patient would blame his or her genetics for the condition. "And," she declared, "that's not helpful," adding that a genetic etiology would leave the patient with no hope for avoiding his or her fate. "We should talk about lifestyle instead," she put forward. "Education is not just about facts; it's about motivating change." The other writers at the meeting concurred that dwelling on the genetics of prediabetes could consign a patient to hopeless resignation. Instead, they chose to elaborate the effects of 'healthy living,' transforming the condition from fateful to volitional, and motivating the patient to take moral responsibility for his or her health (cf. Parsons 1951b; Farquhar and Zhang 2005:307).

Getting asymptomatic patients to change their lifestyle, however, was seen as a challenge. Prediabetes had no outward symptoms; it was a state of risk. If such patients did not modify their lifestyle, they hazarded the complications of "full-blown diabetes," Stacy explained. She then listed several of those complications: peripheral neuropathy, elevated blood sugar levels, fatigue, failing eyesight, etcetera. "You can use that," said another writer, referring to the series of complications. After

some discussion about the role of fear in motivation, Stacy agreed: "We'll describe it not as a scare tactic, just as the reality of it." Lisa agreed: "The goal is not necessarily to scare you, but to let you know what you can do." Another writer added, "If you tell me it might turn harmful, I'm more likely to contact my doctor."

In the foregoing conversation, it becomes apparent how the 'disclosure' of certain information could be used strategically. By either incorporating or leaving out potentially fear-inducing facts, the writers acted to motivate their readers to comply with clinically recommended behaviors. Thus, they were able to erase the backstage poetic labor spent on determining potential uptake. That is, they framed both their removal and their inclusion of specific information in the terms of bad affects, papering over the directive role such tailoring of disclosure would have on the patient's ultimate decision making. All that remained visible and a ratified part of discourse was the denotational text. Their act was glossed seamlessly as the translation of complicated data into plain language. Anything paternalistic or coercive about the poetic structuring of plain-language utterances was erased, staving off potential ethical scrutiny. The writers believed they'd altered the *tone* of the text without substantively affecting its content.

There was also a self-aware evangelizing quality to the writers' use of plain language. Plain language opposed itself to the dense and jargon-filled style of more traditional medical writing in large part because it viewed such a style to be inefficacious in 'moving patients to take action.' If a pamphlet or handout did not awake in its readers a desire to follow the procedures it laid out in pursuit of improved health outcomes, writers viewed it as a failure.

A writer named Kim Simons told me about a pamphlet she had been writing with the help of several clinician experts. The text included a bullet-point list of things a patient needed to do before arriving at the hospital for surgery. As Kim had written it, the list was a series of imperatives of the sort "Do not eat or drink anything after midnight." The clinicians suggested that Kim add the word "please" to the imperatives, "to speak in a softer way." Kim refused, believing that the addition would conditionalize or potentialize the propositions, making the patient think the list was a series of "optional" items. "They gave us a lot of pushback, Colin, on plain language," she told me. "They didn't like the directive language." Kim noted the simultaneous goals of 'directive language' and 'soft tone,' which she found contradictory here. In the end, Kim succeeded in keeping the bald imperatives as they stood, convincing the clinicians with her argument that the insertion of "please" would not provide the sentences with enough force to motivate the patients to comply.

Preparing for short attention spans, the writer was supposed triage her material, so "[a]ction points come first," as one of the internally produced white papers on plain language exhorted. The patient would not necessarily understand his or her desires to be the same as the writer's. Part of the role of plain-language health literature was didactic: to coax (perhaps surreptitiously) the patient into pursuing the writer's telos. While the writer might well expect some (or many) of her addressees to share her desires, she needed to prepare for this not to be the case. She needed to work actively to transmute her desires for the patient into a form the

patient could (mis)recognize as arising from within him- or herself, rather than as imposed from without.

Perlocution and Taboo

Writers in Patient Education expressed significant concern, however, that their words could do more than motivate. They could have unintended affective consequences as well. The production and discussion of patient-facing language was thus always haunted by the potential bivalence (Woolard 1999) of its surface forms.

The states of hope and fear both had potential positive as well as potential negative valuations. This also made them incredibly labile for ideological employment, for denominating choices as rational or irrational. In this chapter, I focus especially on the role of Patient Education and so-called plain language, but my description is more broadly relevant. While SPE cultivated a particular jurisdiction and authority over the semiotic practice of simplification, beliefs about the relationship between language and affect circulated throughout the hospital. In certain instances, clinicians and other professionals were uncomfortable making strong assertions about poetic structuration or word choice without deferring to the external expertise of SPE. However, they still actively engaged in such "verbal hygiene" (Cameron 1995).[4] From here on, therefore, I incorporate the beliefs and

[4] Though Cameron (1995:219) equates "verbal hygiene discourses … which warn (or promise) that language can be used to control people's thoughts" with the mysticisms of religion and magic, I'd note also the powerful effects of more secular semiotic rituals, such as medical placebo (cf. Cannon 1942; Kaptchuk 2002; Raikhel 2010) and the mundanity of illocution as elaborated above.

attitudes of non-SPE professionals into my evidence, demonstrating more generally the institutional ecology of such discourse.

A key example was the case of the word "mutation." In standard parlance – among geneticists, genetic counselors, oncologists, laboratorians, and other professionals at the Center – the word meant any permanent difference in nucleotide sequence between an individual and the so-called 'reference genome' (cf. Chapter Four). This was also more or less the current definition as provided by the American College of Medical Genetics and Genomics (ACMG), the central authority on such issues in the United States (cf. Richards et al 2015, but see below). Despite this standard usage, the word was central to my interlocutors' metapragmatic reflexivity (cf. Silverstein 2001). Because it had been flagged in a number of discourses of proper language usage, people attended explicitly to the ways in which *mutation* was deployed both by themselves and by others.

In the sociolinguistic domain of the clinic, the term was in paradigmatic competition with several other terms with slightly (though saliently) different semantic fields, such as *variant*, *variation*, *polymorphism*, and *change*. Among clinicians, *mutation* was the most common lexeme connected with this concept, although there was debate among professionals on that front. At the conference held by the ACMG during my year in the field, it was recommended that *mutation* be dropped from biomedical discourse. *Mutation* was said to be semantically too vague, with a domain ranging from deleterious variation to simple variation to even specifically benign variation. Geneticists and genetic counselors debated this recommendation for a couple weeks after the conference, and many of these

clinicians made a concerted effort to avoid the term, at least in the immediate aftermath. Nonetheless, *mutation* remained in circulation, in part due to set phrases such as *point mutation*, *nonsense mutation,* and the ilk.[5]

Among the writers of Patient Education, *mutation* was considered inappropriate as well. The reason for their opposition to its usage, however, was in stark contrast to that given by the clinicians and scientists. The main concern these specialists described was for the adverse affective indexicality they believed it would bear for nonspecialist readers. An education specialist told me that *mutation* had "a negative connotation." A genetic counselor, voicing a patient in order to explain a native speaker's intuitions, said, "I have a mutation, so I must be bad." For this reason, *mutation* was generally translated into plain language as *variant*. "*Variant* doesn't have a connotation," explained one genetic counselor.[6] (Clinicians still complained that *variant* would – following in the sociolinguistic trajectory of *mutation* – eventually take on negative indexicalities of its own as it began to circulate among the lay public. They would eventually have to come up with another term for the concept, they said.)

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[5] These modifiers described particular types of nucleotide sequences. *Mutation* in the common sense took a genotypic referent, pointing to transformations at the order of molecules. Modifiers like *deleterious* (mutation) and *benign* (mutation), which would be necessary to specify *variant* to the point of clinical utility, correlated the genotype with phenotype, linking a specific set of genetic material with a specific bodily state of disease or health, either micro – at the level of proteins – or macro – at the level of systems.

[6] *Variant* did not work as a simple substitute for *mutation*, though. For instance, when a writer tried to replace *mutation* with *variant* in the sentence "Some [genes] have a change in the gene called a 'mutation,'" a genetic counselor complained that the sentence now was simply "false." All genes contained variants, and the conventional implicature of *some* foreclosed such an interpretation. *Variant* evacuated the proposition of its non-tautological specificity.

Both the scientific and affective perlocutionary concerns circulated in discourse about plain language. However, I only twice witnessed patients react to the word *mutation* when it slipped into front-stage dialogue. In both instances the word functioned as a site of lighthearted humor. One patient compared herself to the *X-Men*, and one father joked of his daughter, the patient, "I think she's an alien, actually." I never saw a negative reaction to the word in anything but imagined discourse, and genetic counselors similarly described to me their personal experience with the term. The bad-affective perlocution of lexical and phraseological choice were projected based on local understandings of language at least as much as they were based on experience.

However, I did see negative reactions when another solely backstage lexeme entered frontstage. *Retardation* was a word that was used often in Medical Genetics, but only backstage. One genetic counselor explained the problem to me: It was the "medical name," the most accurate one, for a few conditions, including *mental* and *growth retardation*. However, "it has a very negative connotation" in the non-medical public, where it "doesn't necessarily refer to a medical issue." Thus, in the registers that plain language was supposed to represent, *retardation* both failed to refer and wielded a potentially negative perlocution. I don't know that patients do understand that doctors used the phrase in a different way, the genetic counselor told me. Instead of the disfavored phrase, clinicians opted for terms like *developmental disability* and *intellectual delay*, although another genetic counselor told me "developmental delay doesn't really get the point across" and could even be quasi-oxymoronic. For instance, I observed a child with a progressive neurological

condition, who had previously been able to stand and even talk and who now was wheelchair-bound and nonverbal. This child's regressive disorder received the diagnosis of "developmental delay," *delay* being somewhat counterintuitive here. Furthermore, in biomedical parlance, the phrase *global developmental delay*, *intellectual disabilities*, and *mental retardation* each referred to distinct conditions. Nonetheless, nuance was forgone in this case in order to avoid effecting potential affective distress.

At a results disclosure in Medical Genetics, an infant patient's parents were handed the report from their test, which listed the medical conditions associated with the patient's mutations of interest. One was listed as "growth retardation." The father turned to the clinician and asked, "That means mentally, though, right? Not growth?" Of course, it in fact referred to an abnormally limited growth rather than the intellectual disability the father feared. The term *retardation*, however, limited his analysis of the phrase.

Thus, diagnosis – the primary purpose of much genetic testing – could pose a concern for clinicians as they contemplated how to disclose it to patients. "Some of the [cancer] diagnoses themselves can be taboo," one oncology nurse told me. "They're hard saying them, like *Voldemort*: 'the cancer that we will not name – but it's *down there*.'" She was referring to cancers of the primary and secondary sex organs: penile, ovarian, prostate, and similar cancers. Recognizing the dangerous potential of linguistic surface structure was part of "the art of communication," an educator told me. "You learn that finesse and that subtlety over time."

"*Cancer*, the word itself, used to be taboo," added another nurse. "You never said that." *Cancer* used to be "a death sentence," she explained, and thus using the term could cause the patient to despair: "death and dying, the taboos of all taboos." "We kind of pussyfoot around them," a writer said. "They're hard to write, because it's really a conversation the providers need to have. [It's] written versus spoken in those types of things. It's really easy to misinterpret; it's really easy to scare people." These topics as such could provoke the bad affect of fear, disarming a patient's reason, were they not given the appropriate ritual attention.

"The Patient is Overwhelmed."

Reason was considered a prerequisite for ethically and legally legitimate healthcare decision-making. However, in local discourse, many affective states were seen to be mutually exclusive with reason. Alleviating the problem of bad affect, then, was a central concern for writers and clinicians alike.

There was also a concern with negotiating the right amount of information to provide a patient. For an attentive patient, too little information could provoke complaints. Too much information, on the other hand, was seen to be potentially interaction-ending. That is, it could cause the patient to stop taking up new information altogether. Clinicians often cited the statistic that patients only retain around 20% of the information they were told during a consultation. Providing an excess of data was said to "overwhelm" patients, stalling their comprehension and preventing them from engaging rationally in decision-making. The status of 'being overwhelmed' was therefore one of the direst of bad affects.

A debate that lasted my entire tenure at the Center regarded whether patients should be allowed to receive the complete report of their genetic testing data, something called the "expanded report." A single such report took up approximately 125 megabytes of memory and was delivered to the clinic in the form of a USB drive. It listed around three million variants on average[7] and was presented in a document that required a special browser in order to view it. The debate – which reared its head in ethics meetings, writers' meetings, among geneticists, and at case conferences – was always framed as a question of whether the thousands of individual pieces of data on the report would *overwhelm* the patient. Proponents argued that "patients are smarter than they're given credit for," contending that they wouldn't be overwhelmed by full access to their data. Meanwhile, opponents cautioned that it would confuse patients and lead them to make misinformed decisions about their healthcare, perhaps inundating the Center with imprudent concerns.

Anticipated affect figured centrally in such blackboxed events. Fear and hope could be used purposefully to dissuade or persuade the writers' addressees to take certain actions. Even the uniformly negative claim of overwhelming information could be deployed equally in order to prevent or demand the addition of certain information in a text. Lisa Campbell, the head of SPE, once called it "the magical word that we can't argue against." That is, writers took the denomination of a

[7] These were those variants that distinguished the patient from the "reference genome." Scientists believed that humans had approximately three billion base pairs, which meant that the expanded report represented about 0.1% of the total amount of information produced by the genetic test.

certain proposition as 'overwhelming' to be an ethically unimpeachable veto against its disclosure, or – at the very least – of its disclosure in its presented form.

It then became incumbent on the writers either to excise it from their text or to reconfigure the utterance poetically in order to allay the potential bad affect. This choice – though it was rarely formulated explicitly as a choice – allowed the authors control over what content entered their texts while simultaneously obfuscating their subjective influence over the addressee's uptake of that text. These ritual acts of verbal hygienics featured centrally in the felicitous production of their texts.

Within the institutional ecology of the hospital, communication with patients faced a number of constraints. Ethical and legal regulations demanded that patients be "informed" with regard to their healthcare decisions. Through this educational process, patients were seen to come to rational decisions and to recognize – and realize – their best interests. While deliberation was often framed as a process shared between clinicians and patients (e.g., Siegler 1981), the former needed to beware that they not impinge on a patient's autonomy. Claims of paternalism and coercion could threaten to undermine the legitimacy of consent and healthcare more broadly. These concerns were pan-modal: they affected verbal as well as written modes of communication and underlay virtually all interactions.

Privileged Communication

Clinicians removed from conversation certain data that they feared might provoke unreasonable responses. The vague use of affective categories like 'overwhelmed,' 'afraid,' and 'too hopeful' provided a modality for clinicians to exert

what was called in the ethics literature 'therapeutic privilege' – intentionally withholding significant medical information when full disclosure was thought to be detrimental to the future health of the patient. The patient might lose hope and abandon medical recommendations, misinterpret, or misremember recommendations, for instance. The exertion of therapeutic privilege was a controversial practice, but overly vague affective categories provided clinicians with a modality that – on its surface – seemed to offer a liberally acceptable means to this end. In order to prevent an 'irrationally emotional' decision, clinicians and other professionals tailored the information they disclosed, which had the effect of determining the outcome of the patient's choice situation.

In 1847 the American Medical Association (AMA), in its *Code of Medical Ethics*, called it the physician's "sacred duty" not to discuss things that "have a tendency to [discourage] the patient and depress his spirits" (qtd. in Bostick, et al., 2006:303). Over a century later in 1972, legal opinion on the matter was that "patients occasionally become so ill or emotionally distraught on disclosure [of risk], as to foreclose a rational decision" about their healthcare (*Canterbury v. Spence*, 1972).[8] Behavior viewed as irrational when seen from the perspective of the clinician was considered to exclude the possibility of legitimate decision making and thus to permit the paternalistic rationing of information to patients through only-partial disclosure. The American Medical Association described partial disclosure as valid when full disclosure was "medically contraindicated" (Berger 2005; see also

[8] The case focused on a surgeon, who argued that disclosing the risk of an operation would deter a patient from receiving a necessary procedure and would moreover cause "psychological harm," which would in turn affect the outcome of the operation (cf. Berger 2005:94).

Ethcells et al. 1996), meaning that disclosed information would cause distress regardless of whether or not it would "impair decision-making."

However, in recent years, therapeutic privilege has often been viewed as a problematic artifact from the *ancien régime* of medical paternalism. At the time of my fieldwork, the AMA no longer supported withholding information (though it did "leave[] a loophole for the persistent temptation to rationalize nonetheless doing so" (Pirakitikulr and Bursztajn 2006:308)). In place of therapeutic privilege, clinicians were obligated to foster *patient autonomy* and *shared decision making* as a function of the patient's right to self-determination (cf. Fox 1990). It was for this reason, I argue, that the vagueness of affective categories became such a potent resource for clinicians as they attempted to manage their patients' healthcare. Bad affect, as the opposite of well-considered reason, persevered as justification for therapeutic privilege under appropriately liberal pretext.

Of course, it was well documented that not every patient preferred full disclosure or wanted to be 'individually autonomous' in healthcare decision-making. Medical literature often cited that elder sons in Japan and many Pacific-Island nations traditionally made major healthcare decisions, for instance (e.g., Yeo 1995; Orono et al 1994; Kimura 1991). In Italy as late as the turn of this century, patients took it for granted (and for ethical) that clinicians wouldn't fully disclose many morbid and mortal diagnoses (Good et al 1990). Even the American patients with whom I worked regularly told me they would opt not to know certain – often

traumatic – information about their health.[9] "The dementia thing … this is just something that is probably going to happen to you that is really going to be horrible. I would rather not know," the parent of a toddler with severe brain deformities told me.

Nevertheless, American bioethics declared that therapeutic privilege was not appropriate, at least in the American context – and, based on the philosophical profession's universalizing aspirations, ought not be presupposed anywhere. As Renee Fox noted, bioethicists imagined their professional doctrine ("dogma," in Bourdieu's (1977) sense; cf. also Keane's (2015) notion of "morality system") to emerge directly from reason, and thus to be transcultural, fundamentally denying its "intellectually provincial" character (Fox 1990:208). Except under the specific, feminist rubric of relational autonomy (e.g., Mackenzie and Stoljar 2000) – which itself was still often constrained by classic Enlightenment notions of the individual[10] – bioethics literature and institutional policies privileged the model of the self-determining, rational chooser over that of the affective, uninformed, or supplicant patient. Following Kant, these policies were premised on a belief that patients expected clinicians to disclose fully, and the omission of information available to the clinician was understood by patients as its denial (see Brown 2008). For instance, if a clinician did not tell a patient that he or she had a particular

[9] A 2012 study found that nearly a quarter of American women surveyed opted not to learn their breast cancer risk that had been discovered with genetic testing (Melnyk and Shepperd 2012).

[10] Discussions of relational autonomy often fell back on a conception of the individual as fundamentally discrete, having unique desires and reasons and "autonomously chosen" obligations to his or her social relations (e.g., Burnell et al 2015; Zeiler et al 2010).

mutation, such bioethicists contended that it would be reasonable for that patient to assume that no such mutation had been discovered. In fact, the patients I interviewed were surprised when they learned that particular types of results obtained through genetic testing would not be returned to them.[11] (I discuss this in more detail below.) Nondisclosure – and even partial disclosure – therefore represented precarious territory for clinicians as they engaged their patients in situations.

Is Enough Enough?

However, full disclosure also represented precarious territory for clinicians and writers. In order to explain this, I turn to the category of results from genetic testing called "variants of uncertain significance," or VUSs. These were results whose clinical impact was unknown according to the scientific and medical literature. Without further investigation, VUSs could equally be benign or pathogenic. (For more information on VUSs as a category, see Chapter Four.)

Patients in the Center would first receive an "initial report" of their genetic test results. Such a report contained a distillation of the most medically relevant (or, more precisely, the least medically irrelevant) information procured from testing (see also Chapter Five). The report would announce at best one known deleterious mutation linked to the patient's condition, but more typically it would suggest four to six candidate VUSs that could be the cause of the patient's disorder. After

[11] Such nondisclosure contrasted with so-called "mutual pretense" (Bluebond-Langer 1980), in which patients and clinicians were equally aware that a diagnosis was being hidden, which was also discouraged.

discussing this report with his or her clinicians, a patient could subsequently request the "expanded report" from the test. Although this was still not the complete or raw set of data from the test, it was much lengthier and consisted of many times the number of results listed on the initial report. One genetic counselor characterized this report as "a dump of pretty much all the other variants […] really not a very quality report." If a patient chose to receive his or her expanded report, the vast majority of the results to be returned would fall into this category. For rare disease patients, even on their initial genetic test report, only VUSs were returned in 75% of the cases. Moreover, in all but a single case I observed, at least one VUS was listed on the initial report. Interestingly, when it came to VUSs, clinicians struggled not to communicate these variants' meaning for the patient's healthcare, but to communicate their lack of such meaning. Genetic counselors in the clinic, whose job it was to relay test results to patients, almost always spent their time downplaying the significance of VUSs returned on laboratory reports.

It was not merely patients who were at risk of misunderstanding, though. For instance, one laboratorian described the problem with explaining the expanded report to clinicians:

> They are many, many pages [long] and they are in very scientific jargon. The results, currently, are in table format that are just completely not understandable to someone who doesn't have any genetic background. They can even be hard for people with genetic backgrounds sometimes, hard to understand what they are saying. So at this juncture, I don't think it's something that should be given back to a general physician or to a patient

> directly and say, "Here you go. Here's your result." […] I have seen many times where basically if there's a change in a gene of any type on a lab report and in a medical record, I cannot tell you how many times a general physician and/or patient has just decided that because there's something that's different about my gene, that's the cause of what's going on. […] It doesn't mean it's real. It may just be benign; it might not mean anything.

Patients, however, were particularly susceptible to misinterpreting the relevance of VUSs. When I returned to the clinic the first summer after completing my year of fieldwork, I conducted a couple dozen follow-up interviews with patients who had undergone testing during my initial tenure. The slight majority of these patients had pursued some sort of change in their healthcare based on one or more VUSs that their testing had discovered. I interviewed a young couple who had received no definitive results from the large-scale test that had been conducted on their daughter, who suffered from "global developmental delay" ("kind of a lame diagnosis," the mother told me, since it neither explained nor predicted much about her daughter's health). They had, however, received a VUS linked to a disorder causing the deficiency of a particular enzyme. She explained that they felt as though they were "kind of at a stand-still" with the clinicians after the results disclosure. However, "we tried giving [our daughter] supplements [of the enzyme] to see if we saw any kind of change in her, to see if that would be an actual problem." They were glad they had the VUS results, because they saw them as "something that we can take into our own thought process and say, 'Hey, is this something that we want to try anyway, even if they don't think it's the cause?'"

Such re-interpretations on the part of the patient were relatively common. "They decided [the result] wasn't significant. That's fine; I decided it was," another young woman told me. Recall also the father of a patient discussed above, who became distraught when he saw one of his son's VUSs had been linked to "growth retardation." He believed his cognitively normal son had been condemned to develop an intellectual disability. In a separate case, a physician at another hospital had suggested to one of the Center's patients that she undergo a highly invasive gastrectomy based on a VUS in the *CDH1* gene, which was linked to gastric cancer. The genetic counselors at the Individualized Medicine clinic were mortified at when they heard of the recommendation of such an invasive intervention based on such dubious information.

Such distress was clearly not the clinic's intention in returning these results. VUSs were returned for two purposes: First, they were returned in order to recommend further testing, testing that might prove that the variant under consideration was really either pathogenic or benign. Second, they were returned in order to give patients something that could be reinterpreted in the future: Patients were often recommended to return every year for a reanalysis of their VUSs, based on new research, which was constantly changing old interpretations and presenting new ones (cf. Introduction).

When I mentioned some of the interventions my patient-interviewees had undertaken based on VUSs, my colleagues at the clinic expressed exasperation at the failure of their attempts to convince patients of the VUSs' current clinical irrelevance. And all this misunderstanding was caused by patients' receiving merely their initial

reports – rather than their expanded reports – and despite having a half-hour debriefing with a clinician guiding them through the significance of their results.

Clinicians almost never recommended that patients request their expanded reports, which consisted in large part of hundreds of VUSs. In fact, some laboratories refused to release complete reports. The concern was that such information would overwhelm patients. They could misinterpret results and experience "iatrogenic harms" in the form of undue worry and fear (that is, bad affects) about disorders that were understood to be statistically unlikely ever to manifest. Even commercial, direct-to-consumer genome tests such as 23andMe went to lengths to censor particular results – like those related to Alzheimer's – with the understanding that these diseases could not be treated and thus foreknowledge would only lead to bad affects and not to medical interventions. As mentioned above, the whole class of variants linked to adult-onset dementias was singled out as provoking bad affects without being medically actionable.

Patients generally disapproved of such censorship. While many agreed in interviews that they would personally not want to know such information about themselves, they believed it was each patient's right to choose to know everything about him- or herself. In this, it is necessary to recognize both the plea against partial disclosure and the rejection of the inherent goodness of uncontextualized full disclosure. While this also was the general opinion of contemporary American bioethics in the abstract, it is important to consider closely – as I have evinced above –what it means for someone to "know" anything about a VUS (see also Chapter Four). Therapeutic privilege as a category needed also to contend with the problem

posed by VUSs, namely that of communicating *ignorance* – that is, knowledge about the limits of knowledge (Gross 2007) – which was equally necessary in determining what counted as a "rational" healthcare decision.

The Ritual of Informed Consent

In order to proceed with genetic testing, patients met with a genetic counselor[12] to discuss the test, signed a few forms, and then left the clinic to get their blood drawn for the test in another building. This was all part of the ritual process called "informed consent." Consent itself culminated with the patient's signature, but – as I was repeatedly told by clinicians and medical ethicists – the entire educational session was necessary to the successful ordering of a genetic test.

The session with the genetic counselor was in large part mediated by an educational PowerPoint presentation, which had been produced during the first months after the Center opened by patient educators, genetic counselors, laboratorians, and clinicians. The genetic counselor would hand the patient an iPad tablet with the presentation, and swipe through its slides while explaining the images on the screen.[13] The slides included images of pedigrees (family trees annotated for medically relevant information), karyograms of chromosomes, and

[12] Toward the end of my fieldwork, cancer patients typically no longer saw a genetic counselor before signing up for testing. This shift was explained as resulting from oncologists' developing a basic comprehension of the mechanics of testing, of how to select good candidates, and of the process of ordering the tests. The oncologists then took over the process of 'informing' their patients, without resorting to specialist mediation.

[13] Outside the Center, genetic counselors did not have access to iPads and instead used three-ring binders with plastic sleeves full of printed pages of, for instance, cartoon images of the double helix, diagrams of chromosomes, and photographs of hand and foot anomalies.

diagrams of inheritance patterns. They had bullet-point lists of the limitations, risks, and types of potential results of genetic testing.

Most important for my discussion here, however, the presentation began with a slide that some of the genetic counselors jocularly called "our central dogma." It showed a cartoon cell – amorphous, glistening, and olive green – at the center of which was a clear nucleus with visible chromosomes. At a larger magnification, a single chromosome appeared and unraveled into a double-helical strand, eventually scaling large enough to make visible individual base pairs, colored red, green, orange, and yellow. (See Figure 3.1.) The genetic counselor narrated: "In your body you have trillions of cells. Each of your cells has a nucleus. In the nucleus are your 46 chromosomes. You get half of chromosomes from your mom and half from your dad. Your chromosomes are tightly wrapped packets of your DNA, which is made up of different molecules we call As, Cs, Ts, and Gs."

This was "the basics of genetics," one of the counselors told me.[14] It provided patients with "the building blocks" of the science, introducing them to the fundamental concepts and terms needed to understand what the scientists and clinicians would be doing

[14] In fact, the name "central dogma" was cribbed from the formulation of Francis Crick (one of the cultural heroes of genetics, canonized for his legendary co-discovery of the molecular structure of nucleic acids). For Crick, the central dogma (originally, see e.g. Fujimura 1996) was that "information" was transferred unidirectionally from DNA, through RNA, and eventually precisely determining protein gene products. The analogic parallel drawn by the genetic counselors figurated this simplified model in the mode of Crick's "pillar[] of molecular biology" (Kay 2000:174).

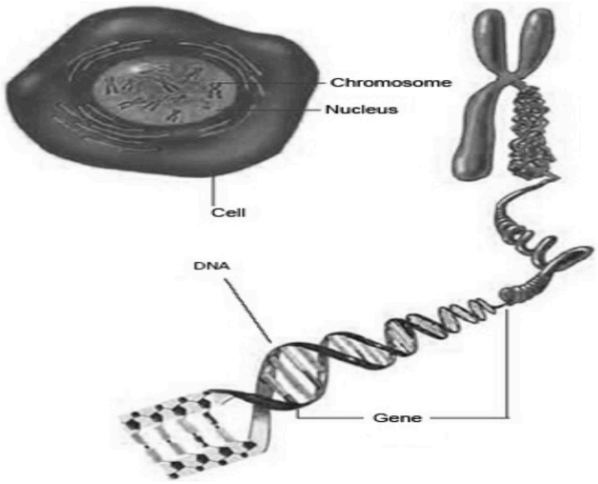

Figure 3.1: The central dogma of ritual informed consent.

during the sequencing. When a writer asked a room of genetic counselors what would be necessary to include in a pamphlet on genetic testing, Lacey Hagen, one of the counselors, responded that the "central dogma" should certainly be on the first or second page. The writer, concerned about readability for her imagined low-literacy audience (see also Chapter Two), asked whether so much information was really pertinent. All of the other counselors in the room immediately voiced their agreement with Lacey.

A few weeks later, I had the opportunity to talk with Lacey about the importance of the central dogma. Beyond the general applicability of such knowledge, Lacey noted that seeing what a chromosome looked like could aid a patient in understanding what a chromosome microarray was and how it differed from genetic sequencing.[15] Hearing the numbers of cells – although lacking much by

[15] The differences were in fact complex, but Lacey's basic concern was to demonstrate that the microarray could detect large-scale abnormalities of

way of specificity – could underscore the complexity of the work being undertaken. However, when I asked about the necessity of such knowledge to a patient's ability to give consent, she suggested that the patient did not need to be able to reproduce the proffered information:

> At the end of the day, are you really going to- if somebody *wants* to consent, are you really going to deny them testing, even though you've explained it and they think they've got it, but we think they don't? I've never actually seen somebody say, "No, I'm not going to let you sign this form to have your blood draw." Now, that being said, if [a patient's] saying those things where it's just *blatantly* obvious they're not understanding what the test is or what's being done, you know, I would probably still let them consent, but I would normally try and circle back. Although you can spend four hours with somebody and they could still not get it.

This was also my experience. Beyond the central dogma, a variable amount of information was provided to patients based on the genetic counselor's judgment of their interest and background knowledge (often gauged based on the patient's profession, age, and use of medical terminology and concepts in presenting their complaints). However, no matter the amount of confusion or the explicit lack of understanding the patients expressed at the end of the session, I never saw a patient disallowed to consent. Genetic counselors certainly did their best to re-explain, to simplify, and to rephrase the offending information, but I never witnessed the breach of some minimum threshold. Counselors always concluded by asking

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chromosomes invisible to sequencing tests, but that it could not detect small-scale mutations.

whether patients had any questions. This was often met with silent bafflement or good-humored expressions of unconcerned ignorance: "It's all Greek to me," one patient admitted, and both she and her counselor chuckled.

In such instances, *informing* appeared largely to be a mutual pretense. It manifested the clinicians' and scientists' elaborate expertise, fundamentally inscrutable to lay patients even in its "basics." It reaffirmed the necessity of faith in the translational practice (see also the Introduction). But most importantly and most prominently, it was in its pro forma performance – rather than in uptake or repetition – that the ritual of consent was deemed successful. The practice's ostensible purpose to provide the necessary data by which a patient could make a rational decision proved auxiliary to the actual structure of the clinical encounter.

Coercion and Choice

Decision-making was clearly a complex social phenomenon in the clinic. To understand it interactionally, it behooves the analyst to consider its central feature, viz. the operative notion of choice, and the local ethics surrounding its mobilization and limitation. Choice can be conceptualized as the selection of an alternative from among an array of simultaneous possibilities (e.g. Kull 2015). That is, actual choice necessitates that at one given moment, an individual has at least two equally real and actionable options. This is the patient's so-called "choice situation," and his or her relative "freedom" is in the ability to choose between these options with little or no constraints (e.g., Wertheimer 1987).

The liberal politics of American bioethics was fundamentally concerned with the role of paternalistic coercion in limiting the freedom of a patient's choice situation. John Stuart Mill famously condemned coercion as comparable to the "degradation of slavery" (Mill 1976:943). But what exactly did it mean for a patient to be coerced into or out of a particular choice? Coercion was said to be the opposite of voluntariness. As it was explicitly set out in the philosophy and policy of bioethics, it was the narrowing of a patient's choice situation, making a certain choice irresistible. In this sense, the manipulation of a patient's options through the privileged use of vague emotional categories could have been taken to be coercive. However, coercion was also said to be a threat rather than an offer. If a particular option were not selected, an undesirable consequence needed to follow that would not otherwise have occurred.

Coercion could supposedly only take place between two agents, not between an agent and his or her environment. It was said that a patient could not be coerced by his or her disease. Cancer limited a patient's choice situation in a huge number of ways, but it did not coerce the patient in his or her decisions. However, I argue that a strong moral distinction between individual and circumstance is philosophically untenable. Freedom and oppression are both subjective and contextual experiences rather than obvious and necessary features of any given relationship. Making such a distinction erases the significant role of the social and technological environment in emic assessments of coercion. For instance, in-vitro fertilization transformed the choice situation surrounding family planning. The technological development made finances and healthcare access appear to be constraints on an individual's choice to

get pregnant, while before it, infertility could not have been experienced as a lack of freedom (without recourse to divinity or a similar, agent-like mechanism). This does not even touch on the coercive power of the institution of biomedicine over the patient, the clinician, and their relationship to each other, in all decision-making within its domain (Pippin 1996).

Therapeutic privilege may not be coercive in the classic sense, as it certainly is not a threat. Nonetheless, it proved ethically significant in its ability to impose limitations on a patient's choice situation. Such limitations could still be considered "paternalistic" if not coercive (e.g., Fox 1990:206). As we saw in the vignette from the writers' meeting, the use of vague emotional terms could radically transform a patient's choice situation. For instance, not disclosing the risks of a particular cancer or enumerating the risks of neglecting one's prediabetes both narrowed the set of possible choices placed before a patient.

Clinicians and educators used vague language in order to construct patients as irrationally emotional. These vague categories could equally be used to justify the disclosure or the withholding of information related to a patient's healthcare. By describing a proposition as potentially resulting in fear, hope, or worry, that proposition could be retained or removed from communication. Since these categories were vague enough so as to prevent them from being verifiable, it became possible for clinicians to delimit the disclosure of a wide range of information without appearing blatantly paternalistic. Claims about bad affects were claims about rational decision-making in the first place. They were claims about whether there was a legitimate choice situation at all.

When clinicians worried that a patient would be overwhelmed by the disclosure of certain information, they avoided a consideration of exactly what that vague emotional category meant. Certainly, overwhelming a patient with information could have iatrogenic effects, causing unnecessary stress or intervention due to misinterpretation. However, the diagnosis of being overwhelmed also smuggled in a potentially paternalistic, quasi-coercive narrowing of the patient's choice situation, which was made all the more suspect by the felt need to disguise it.

At a case conference in the late autumn, a genetic counselor was discussing the case of a man in his early thirties who was having severe cognitive issues. The laboratory had just returned the results from a large-scale genetic test, and the genetic counselor announced that among the several pages of VUSs was a mutation in the *APP* gene, a gene that had been overtly related to Alzheimer's disease on the report. "This is scary. This is very scary," one of the medical geneticists remarked. Her concern, however, was not that Alzheimer's disease was itself scary, but that the laboratory should not have listed such a result on a report that was destined to be seen by the patient. Alzheimer's was a neurodegenerative disorder, one of the dementias that were officially (in terms of both national recommendations and that specific laboratory's own stated policies) obliged not to be disclosed.

There was a general uproar in the audience: condemnations of the laboratory, concerns for the patient's mental state, even aborted plans for removing the result from his record. The genetic counselor interrupted the discord: In fact, she said, the patient had already gotten access to his results and was not disturbed by the

disclosure. He had been overwhelmed by the "slew of VUSs" and had come to the conclusion that the testing had produced no meaningful medical information. Yet again this demonstrates the phantasmic quality of the persistent concerns with bad affect.[16]

Paternalism and Expertise

Clinicians always acted as translators, simplifying complex medical information for lay patients. This was an intrinsic aspect of their expertise. As the Supreme Court of California declared, "The patient, being unlearned in medical sciences, has an abject dependence upon and trust in his physician for the information upon which he relies during the decisional process" (*Cobbs v Grant* 1972). Clinicians existed as a professional class and were patronized by patients due in large part to that expertise, to their perceived asymmetric understanding of the body and its disorders. Simplification necessarily meant reduction; some information was lost, and it was the necessary and significant privilege of the expert to determine which information was necessary to successful decision-making and which was not. Moreover, even under the exceptionally good circumstances of the clinic at which I worked, patients still did not understand the test results in a way close to that of their clinicians. Clinicians did not have the time to explain everything

[16] However, it is important to note *what* prevented these bad affects from arising in lived reality. It is not obvious that they failed to arise because there was no causal relationship between poetics and affect. Rather, one must remember that patients often did not attend to or comprehend everything relayed in the process of their being 'informed.' That specialists, for whom this information was comprehensible, were deeply considerate of such potential (if only ever virtual) concerns is not in itself condemnable – in fact, quite the reverse.

about VUSs to their patients, patients did not possess the background assumptions to make sense of them, and VUSs' intrinsic uncertainty only further complicated the situation.

Due to this privilege, clinicians and their collaborators from SPE determined what counted as health benefits, and what counted as health itself, neither of which was necessarily obvious. These factors played an important role in the selection of relevant, legitimate, and good choices. Clinicians had already determined which choices were in the patient's 'best interest' when they undertook the ritual of informed consent. Valuation of a (hypothetical) patient's (hypothetical) mental state therefore worked backward, from decisional outcome to the acceptability of the (hypothetical) affective cause.

For instance, an oncologist expressed such sentiments to me in an interview. We were discussing patients who rejected expert interpretations of their health, in particular patients who "were in denial" about late-stage cancer diagnoses. "Is it necessarily a bad thing?" the oncologist asked me rhetorically. "If it's not hurting them, I think denial's not necessarily a bad thing." However, he admitted there were limits to how far he would allow this potential bad affect to affect his patient's decision-making:

> When I get concerned is that if people are not processing the information correctly or getting the message, and they're pursuing therapies that are hurting them, or not pursuing therapies that could really help them. So they're harming themselves, or going to cause harm to themselves: That's when you have to do something to try and intervene to get the message

> across. You know, if what they're doing is not particularly harmful and not particularly crazy, and they just don't want to admit that they're going to die from the cancer, that's fine – as long as that's not interfering with our chance to help them. If it is interfering, then you *do* have to do something, and you have to try and – the best you can – crawl inside the patient's head and try and figure out what's going on.

If they relied on their affective impulse, viz. here 'irrational hope,' they could still make what would count as a rational decision. In these instances, the affect could be deemed, proleptically, good – or even "rational," as this particular oncologist often told his patients. "I can read your mind; that's not what you want me to do," one patient told him, suggesting that he did not want her to get a prophylactic mastectomy. "There's only a four to eight percent risk of recurrence," he told her, "but that's a rational choice, even if it just stops you from worrying." If the patient seemed inclined toward an 'irrational' decision, on the other hand, he deemed the affect interfering and resorted to further attempts at 'informing' the patient.

With that in mind, it should be clear that a blanket condemnation as paternalistic of the power dynamics inherent in the doctor–patient relationship would leave no potentially ethical forms of healthcare, or at least none that could sustain the specialist division of knowledge. What is apparent from the analysis I have presented in this chapter, however, is that the opposition between reason and affect posited by hospital staff was a precarious one. It provided them with the power to control the disclosure of a vast array of types of significant healthcare information. Such vague categories of affective distress – like fear, false hope, and

being overwhelmed – acted equally as ethical justification for either disclosure or nondisclosure. They were vague enough that they bore either interpretation equally.[17] Clinicians had privileged access to relatively non-simplified knowledge, generally considered as *expertise* by hospital staff and patients alike. It was the clinician who narrowed the patient's choice situation, and it was his or her power to determine which of the original options were legitimate and would remain for the patient to choose among them.

Interestingly, a strong belief in the expert division of knowledge had the following entailments. Should lay patients be unable to understand information relevant to their healthcare in a rational manner, they were seen to resort to affect in decision-making. In fact, a reasoned mobilization of the information provided to patients was often only of minor importance to the ritual of informed consent. Affective responses were determined to be good or bad based on the choice they supported, proleptically. Thus staff often saw the choice situation as – *ab initio* – at least significantly grounded in affect. Felicity conditions, however, required – both for the patient and the profession – that the ritual of informing first take place and then a rational decision be made.

Through this ritual, hospital staff managed to motivate patients' healthcare decisions without allowing for claims of subjective bias to arise. By privileging the referential function of language, the pragmatic effects of its poetic structure were

[17] Sharon Kaufman noted that other clinical clichés, like *quality of life* and *death with dignity* were vague and ambiguous enough to serve covertly to bias patients without appearing to be overtly directive. She added – and I would echo this sentiment for my own interlocutors – that though clinicians used the terms "deliberately, they may not use [them] thoughtfully" (Kaufman 2006:209).

neutralized. In this way hospital staff succeeded in framing their acts of communication as fundamentally denotational. Results and facts were merely 'disclosed;' propositional content was merely relayed. The surface structure of the denotational text obfuscated specialists' backstage moves to tailor what information was communicated and how.

Significant semiotic labor was needed in order to achieve this state of affairs. The requirement that a patient be rational proved a boon as well as a constraint. Specialists mobilized excessively open affective categories, in particular the status of being overwhelmed, hopeful, and fearful. If they believed certain information had the potential to lead the patient to an inappropriate decision, they were often able to block it from entering communication by describing it as stereotypically harboring potential negative perlocutionary force. The information could prevent patients from incorporating significant data into their healthcare decisions. It could also scare them into desperation or make them irrationally hopeful.

Writers and clinicians actively monitored the poetic structure and propositional content of their utterances in order to determine certain types of uptake. However, the framing of communication as 'informing,' as a simple relay of knowledge from author to audience, obscured the backstage labor undergirding all forms of clinical communication. In this way, hospital staff managed to enact themselves and their practice as ethical and free from paternalistic influence, while still managing to motivate their patients to make decisions they believed were in their best interests.

CHAPTER FOUR: ETHICS AND EPISTEMICS

Clinical Knowledge and Research Data

In the Center for Individualized Medicine (CIM) – as in traditional biomedical institutions – local actors made a strong distinction between propositions they described as clinical *knowledge* and those they described as research *data*. The former was considered legitimate and faithful in its ability to represent the world truthfully. The latter, on the other hand, could not be presupposed to be true. Clinicians and scientists regarded research data with skepticism. The data were epistemically modalized, curtailed in their reliability and interactional effectiveness. Clinical knowledge could be used to aid in ethically and legally acceptable healthcare decision-making. Research data, on the other hand, were considered below the relevant evidential threshold for healthcare providers to rely on them in therapeutic intervention.

At least that was the model as formulated in the abstract realm of medical ethics. In practice, of course, things were much more complicated. While this has been true of all medicine (Katz 1993), it was particularly the case in avant-garde medicine, the so-called 'bleeding edge,' where current developments in science and theory actively upheld clinical work and corpological imaginaries. Individualized medicine was just such a site, situated between therapy-driven disciplines – such as oncology and rheumatology – and academic sciences – such as molecular biology and biochemistry. This had significant implications for funding and payment structures, ethical and scientific oversights, and the therapeutic potentials of the practice. In this chapter I discuss the interaction between clinical and research propositional domains in the Center. I am concerned not only with the epistemic distinction, but with the institutional-political etiology of that distinction as well. I argue

that my interlocutors determined what counted as 'knowledge' pragmatically. Furthermore, this pragmatics was conditioned by oversight bodies, which regimented ostensibly impersonal standards for such evaluation.

To begin, I turn to an exemplary case of a cancer patient caught between the medically known and unknown, between the optimism of intervention and the pessimism of stasis. In this particular example, information based on a clinically-approved DNA panel was pitted against information gleaned from RNA-sequencing, which was at the time still under a research protocol. Following the vignette, I lay out the two epistemic orders in their abstract, purified forms – as they are discussed in official, on-record contexts – before addressing the complexities of trying to maintain such distinctions within the Center's clinical decisions. The epistemic bifurcation was driven in part by what were considered "extrascientific" (Marks 2000) motives – in particular, federal practice guidelines – which are the subject of the subsequent section. I finally turn to the dimension of uncertainty that intersects both the clinical and the research domains and conclude by considering the distinctive ontology of knowledge within the clinic. That is, I am not talking about theories about how we know things, but about what knowledge itself is, its different gradations and socially typifiable varieties. This builds into the following chapter, in which I consider in greater detail the role of uncertainty in the transduction of clinical propositions from laboratory to clinic to patient.

Ethico-Epistemic Jurisdictions

At a weekly session of the Tumor Board, oncologists, hematologists, and geneticists met to discuss potential treatments for a particular patient. The physicians and scientists

sat at the front of the room, at two long tables that intersected, forming a sort of V that opened onto three large LCD displays. The middle screen would eventually display the presentation PowerPoint slides. The flanking screens each streamed live video from two other hospitals, showing clinicians and scientists sitting at similar tables. These individuals also occasionally presented cases, but not today. In the back of the room were two rows of chairs, populated primarily by administrators, ethicists, genetic counselors, and a lone anthropology graduate student.

The treatments under discussion today were based on new data from RNA sequencing, which was meant to supplement a large-scale DNA test that had previously been conducted. The clinicians hoped that they could gauge from the RNA how genetic changes were expressed in the patient's tumor, something impossible to discern from the DNA alone. Since the Food and Drug Administration (FDA) had not yet approved RNA sequencing for clinical use, it was to be considered research rather than a therapeutic endeavor.

The lead oncologist on the present case was Dr Chris Clarke, a man in early middle-age with a Caribbean accent. He began his presentation by opening a PowerPoint, which appeared on the large middle screen at the head of the room. Sitting at the apex of two joined conference tables, he explained that since the case had been discussed a few weeks prior, he would reintroduce the patient briefly. The patient was a middle-aged man with a type of sarcoma, a rare cancer of the connective tissues. The first slide – labeled "Clinical History" – listed his sex, age, identification number, and a brief synopsis of his cancer. Dr Clarke glossed over the patient's history, noting the discovery and subsequent spread of the tumor. The next slide was titled "Pertinent Family History." Slides appeared in a regular

order in case conferences, and this slide was typically empty, as clinicians considered self-reported family history an inferior proxy to the data obtained through genetic testing. Today, as was expected, Dr Clarke breezed past it, calling it "not contributory." A slide on "Previous Genetic Testing" was likewise blank, as the patient had only had the large-scale DNA test that had already been discussed at a previous case conference. The next slide read "Summary of Panel Results." "Celina, will you take over?" Dr Clarke asked Dr Celina Russo, the case's lead pathologist.

Dr Russo, who was sitting at the far end of the table, leaned forward in her chair. Dr Russo was a medical doctor (MD) but nonetheless was – like the other professional pathologists – most closely associated with the laboratory in opposition to the clinic. As a function of their specialist expertise, pathologists were said to "own" the portion of the PowerPoint presentation dealing with laboratory test results. "We ran into some issues with the frozen tissue cores," Dr Russo explained, regarding the DNA panel they had attempted in the laboratory. She continued, "RNA [sequencing] was also subsequently conducted on the material." She clicked forward to a series of histopathology slides, showing cells stained blue and red. "Most are normal-looking hepatic cells, and it was at least predominantly tumor, but," she paused, pointing at the screen, "parts had almost a spindle-like quality; clearly not hepatocytes."

She clicked forward to a slide labeled "Summary of Panel and Research RNA." "Alright, Shelly," Dr Russo said, giving the floor to one of the cancer biologists, Dr. Shelly Baxter. Dr Baxter noted that there were two main candidate mutations for potential drug targets: a likely pathogenic genetic variant in *HDAC1* and a fusion in *ROS1*. She then flipped to the next slide, a graph which she explained "shows the point where the fusion occurs."

The following slide displayed more graphs comparing the expression of *ROS1* in a variety of cell types.

In this way, the PowerPoint proved a sort of teleological gradient of evidence, beginning with the least reliable, self-reported family history, proceeding through visualized pathology data, and ultimately landing on the most meaningful information provided by the genetic tests. The "intrigue" (Saunders 2000) of the case built by crescendo.

"In non-small cell lung cancers, *ROS1* has been shown to respond to crizotinib," Dr Baxter said, adding, "*HDAC1* has shown up in a number of our heme [hematology] cases." Dr Baxter noted that the hospital had a study on the topic that would soon open for the enrollment of research subjects. A hematologist detracted, explaining, "It's gone to the DOG [Disease-Oriented Group, i.e., a specialist research team], but it hasn't gone to IRB [the Institutional Review Board], so 'soon' is not 'soon.'" The audience chuckled knowingly with regard to the bureaucratic hurdle.

Dr Baxter flipped forward to a list of mutations that RNA sequencing had uncovered. She discussed each of the mutations but forewarned the clinicians to "take that with a grain of salt, because we *are* comparing apples to oranges." That is, since RNA sequencing was not an FDA-approved test, comparing it with DNA results was an inappropriate mixing of epistemic orders. She clicked forward to the final slide, a list of potential clinical trials in which the patient could be enrolled. Each trial had federal sanction from the National Institutes of Health (NIH) and was listed on the website clinicaltrials.gov. Each trial also had specific criteria for matriculation, including that the patient be shown to harbor a given genetic mutation. Other considerations included the trial location and the "ancillary money"

required to relocate and participate. Dr Baxter and her colleagues spent hours each week determining which trials were applicable to which patients.

After Dr Baxter concluded her discussion, Dr Clarke summarized his interpretation: "Taking Shelly's data into account, I'm going to disregard the *HDAC1*. I have greater confidence in the *ROS1* data." He said he would recommend to the patient a clinical trial to inhibit the expression of *ROS1* in the tumor.

One of the other cancer biologists asked Dr Clarke whether having done the RNA research had aided in his recommendation. "It gave me additional support and trust," he said. "It could have been the only way to find the fusion." Without the RNA test, they might never have recognized the mutation's specific form. Another oncologist noted that "fusions are the most attractive thing about doing the RNA." Dr Clarke concluded, "We may have one crack, and I suggest the crizotinib [a *ROS1* inhibitor], personally." Since the patient was terminally ill, the clinical team would not have the luxury of multiple attempts to find a therapy that worked.

A bioinformatician interjected his concern with this recommendation: "Are you suggesting a treatment option solely from research?" Dr Baxter agreed: "You're basing this solely on RNA. You're using research findings to direct patient care." A debate broke out among the attendees. Their consensus affirmed the official institutional stance, linking this particular case into the gnomic realm of epistemic orders. The treatment had come about due to a fusion only visible through RNA sequencing, which was not an FDA-approved test and should not be used to inform a clinical recommendation. In the end, Dr Clarke agreed with his colleagues: "We should be very cognizant of whether recommendations are based off of clinical or research findings."

Another oncologist interrupted: "Is there no way to confirm the expression clinically?" Dr Russo thought for a moment and responded, "It's usually something that started us down that path." She paused before continuing: "[The DNA panel] is a clinically validated test." All the data that had emerged from it were therefore considered ethically and epistemically valid. The only reason they would have looked at *ROS1*, she said, was because they had already documented mutations through FDA-approved tests. Since the DNA could be considered actually existent – or "real," in the verbiage of my interlocutors – RNA tests that made reference to those known segments of DNA could likewise be accepted as "real." "Any way," she added, "he'd be eligible for those [*ROS1*] trials anyway," even without the RNA data. Dr Clarke concluded that he would indeed suggest the *ROS1* clinical trial.

Two Socio-Epistemic Orders

This vignette displays one of the more explicit moments of socio-epistemic (Cambrosio et al 2006) conflict that I had the opportunity to witness during my fieldwork. On the one hand, discoveries made through research procedures like RNA sequencing were considered too evidentially impoverished for one to base a clinical intervention on them. Research was an *experiment* meant to create "generalized knowledge" (cf. Levine 1983) about medical genetics, not particular and practical data about a specific patient. Patients even underwent a special consenting process in order to be enrolled in research programs such as clinical trials. During this process, clinicians explained to them that the purpose of research was to enrich science, not to inform their therapy. This was explicitly intended to dissuade patients from "therapeutic misconception" (Appelbaum et al 1982), the wrong

belief that medical research was meant to or even might benefit the research subject as an individual. In fact, it was against institutional policy (with some exceptions, discussed below) even to show a patient the report from research that was conducted with his or her donated samples.[1]

On the other hand, clinical knowledge was allowed to inform ethically and legally legitimate healthcare decisions. It was not an experiment conducted on patients; it was the basis of the so-called standard of care. Clinical knowledge was considered accurate, regular, and morally acceptable. Clinical knowledge in practice often included personal anecdotes from respected experts[2] – as when Dr Baxter noted that mutations in *HDAC1* were relatively common in her personal experience with hematological cancers. However, officially-clinical knowledge in medical genetics emerged only from institutionally sanctioned laboratory tests, passing enough scrutiny to be transformed from research data. For instance, shortly after my arrival at the clinic, its affiliated laboratory received FDA approval to conduct a 50-gene panel clinically. The process of getting that approval took nine months and ended with around a thousand pages of paperwork, which was followed by a compliance period during which the panel remained under review. Moreover, this was just for approval from one governing body. The test also underwent an approval process from the Clinical Laboratory Improvement Amendments (CLIA) Program and from New

[1] In earlier forms of medicine, "full disclosure" was prescribed by ethicists concerned that partial disclosure would impinge on patient autonomy (e.g., Ross 1996). However, because of the tenuousness of all genetic 'knowledge,' full disclosure was considered precarious in case patients misinterpret the significance of their results (see below; see also Chapter Three).

[2] This occurred despite official attempts to standardize such "vagaries of clinical opinion" (Marks 2000:230) out of existence, something I return to in detail below.

York State, each of which had its own special requirements.[3] Therefore, even while each of these agencies had its own validation criteria, the test in its final instantiation would come to embody a form compatible with each (cf. Timmermans and Kolker 2004).

A commonly cited example of the need for such safeguards was the grotesque failure of so-called gene therapy at the turn of the century, which resulted in technical failures and the death of at least one patient. Both the NIH and the FDA rescinded their support of the practice, marking also the potential for currently acceptable knowledge to be rejected as nonsense in the future. Similarly, the American College of Medical Genetics and Genomics (ACMG) – the national advisory board for medical genetics – has taken back previous recommendations for practice as new data become accepted as facts and old data as bunk. Even while these distinctions were tethered to explicitly 'extrascientific' institutions, they were naturalized within the clinic. Clinicians took up the ideological mantle as warranted, as citing authoritative *ethico-epistemic* expertise. Such recourse promised "regulatory objectivity" (Cambrosio et al 2006) in clinical practice, displacing individual, 'subjective' responsibility for decision-making onto collective consensus.

The bifurcatation of these epistemic orders was officialized in 1979 by the famous Belmont Report, the federal, medical ethics response to the Tuskegee syphilis trials and related scandals.[4] However, despite their institutional and canonical recognition, the two orders were invoked under a large number of names, some of which I list here in order to hint at the ideologies of each order's distinctive appropriateness-to-context and domains of

[3] Even when a test's chemistry had been clinically approved, it was not necessarily the case that all of the genes it sequenced would be approved for disclosure. For instance, late-onset neurodegenerative disorders (such as Alzheimers) were considered clinically non-actionable and genes linked to them were therefore not allowed to be returned.
[4] Not coincidentally, this was also the decade during which clinical practice guidelines began to proliferate (Weisz et al 2007). I return to this topic below.

use. Clinical knowledge was called "therapeutic" and "[medically] actionable," pointing both to its role in driving treatment and to its legitimation within the institutional structure. Research data were called "academic" and "scientific," often with the pejorative modifiers "just" or "merely" (as in, "merely of scientific interest"). Intriguingly, although clinical knowledge only reached its elevated epistemic status by going through the laboratory crucible (the ultimate referential index of governmental approvals), research itself constituted a specifically disprivileged domain. While research may have been the most "interesting," clinical knowledge was the most usable, which is to say, trustworthy and ethically exculpatory, in patient care.

This socio-epistemic divide also expressed itself linguistically in terms of the objects of the two orders. *Patients* were specifically those individuals receiving clinical therapy at the hospital. *Research subjects* were those individuals participating in studies that had not been clinically approved. These were not merely 'everyone else,' though. Persons only became research subjects after completing a specific informed consent, constituting their enrollment in IRB-sanctioned experimentation. This lexical divide was also the site of reflexive scrutiny. For instance, at one point the clinic began discussing whether to offer a particular genetic panel that was still under a research protocol. When discussing how to publicize this study, an administrator referred to potential candidates as "patients." She was swiftly met with backlash from others in attendance. "They are not *patients*," her clinician interlocutors scolded.[5] That is to say, they would not be enrolled in the study as

[5] "Research subjects" was nonetheless considered bad verbiage as well, and a long debate unfolded, eventually reaching the conclusion that the term "(research) participants" was preferable. (See also Chapter Two.)

patients, even though they would be recruited from a population of already-ratified patients.

The calculation of effectiveness in the form of risks and benefits was central to the epistemic contrast between clinical knowledge and therapeutic data. This calculation was called clinical utility (cf. Holtzman and Watson 1999). It was also based on concerns about analytic and clinical validity. Analytic validity referred to the reliability of a test in identifying the cause or course of disorder (cf. Burke 2014). Clinical validity referred to a test's accuracy in identifying a particular clinical condition. It entailed concerns that a test be able correctly to pick out individuals who did and did not have a particular health condition. This was a sort of truth-functional analysis, crossing the existence of a patient having a particular condition with a positive test result for such a condition (Figure 4.1).

Oversight agencies such as the FDA and CLIA thus were meant to determine whether a test or intervention was simultaneously safe and therapeutically useful. In fact, such bureaucratic checks on clinical practice came to index the positivist concerns of laboratory science that they ostensibly ostended. Clinicians and scientists alike took the approvals given by these agencies as themselves evidence of a test's analytic and clinical validity. (Lack of approval did not negate a test's utility but did provoke greater skepticism.)

However, there remained a final variable that played a role in such evaluation, viz. what was called "personal utility." Personal utility was the value ascribed to a test by patients themselves, especially as it diverged from classic clinical outcomes such as diagnosis and treatment. For instance, the patients with whom I spoke felt that testing lent an air of legitimacy to their suffering and gave them a sense of closure in their otherwise

p	q	p(q)	p	q	q(p)
T	T	(sensitive)	T	T	(positive predictive value)
F	F	(specific)	F	F	(negative predictive value)

Figure 4.1: A successful test, where *p* is a patient (population) who has a particular condition and *q* is a positive test result for such a condition.

open-ended pursuit of medical care – even when the test provided no "medically actionable" results, even when it proved to have no clinical utility.

While logics of 'personal utility' cannot officially enter into institutional deliberation regarding the status of a test or intervention, they nonetheless have important effects in unofficial discourse and private – but critical – institutional decision-making. For instance, in meetings about administrative matters, pressure was regularly put on making more and newer genetic tests available, as patients made demands for such interventions in their encounters with clinicians. This pressure – based on mass-mediated hype – then translated into important professional considerations: If the tests were already offered elsewhere, would patients leave the hospital and receive care at other hospitals? Could financial incentives counteract concerns with analytic and clinical validity? Taking the moral consequentialist route, could entering the market – albeit before it was ready – help to bend practice in a more positive direction? Reliance on lay public opinion complicated the boundary between the social and scientific authorities that adjudicated the circulation of scientific propositions and medical interventions (cf. Bourdieu 1991).

Take the example of referrals to the Center. Nearly all success cases I witnessed were of patients who had been referred to the clinic by the Department of Medical Genetics.

That is, knowing which patients had a chance to benefit from genetic testing was clearly a function of expertise in genetics itself. Nonetheless, every week genetic counselors at the clinic saw patients who were "self-refers." They saw this population as a burden on the practice, since they rarely – if ever – were allowed to proceed to testing.[6] However, this steady influx of counter-institutional desires affected both discourse and practice. It moved clinical activity even further from its classical jurisdiction over therapy (Foucault 1994) into the Wunderkammer of 'curiouser' half-knowledge, i.e., into the space of research data.

The Middle Ground

Patients who came to the Center had already exhausted all standard therapies and diagnostic technologies. All acceptable chemotherapies had been attempted, and all traditional inroads to diagnosis had failed. The Center's liminality was driven by the status of its patients, who were already outside of otherwise legitimate spheres of action and acknowledgement. The clinic represented a hypertrophic example of so-called translational medicine, medical practice that dealt with the sharp edge of science, moving knowledge 'from bench to bedside.' The Center was squarely at this intersection, and its practice was continuously haunted by its unclear position between the two recognizable epistemic poles. "[The clinic] is all research," one scientist told me during an interview, "but it's gray as gray can be." Comments like this came up among specialists in case conferences as well. "Is this specifically a research project or is it clinical?" one bioethicist asked a room of medical geneticists about a large-scale genetic test offered by the clinic. "It's somewhere in between," explained one of the physicians.

[6] A variety of reasons are discussed elsewhere: e.g. Introduction, Chapter One, Chapter Five.

The genetic tests employed in the clinic had what was seen as minimal medical relevance. Diagnosis of rare disease, for instance, occurred in only about 25% of cases. Even when genetic results did suggest to clinicians a change in medical care, that recommendation had often already been anticipated without the test, as with the Tumor Board case discussed above. One of the cancer biologists asked nearly every week for clinicians to admit that the test they had ordered had not altered their previous plans for recommendation. These clinicians usually stood firm that the test had, at least, strengthened their "confidence" in their decision, though they generally admitted it had done little else. (This question – whether the test altered previously planned recommendations – was eventually incorporated into the standard PowerPoint design.)

Clinical trials – which, despite their name, were research and not a form of clinical therapy – were nonetheless treated in the individualized medicine clinic as a standard part of care for their patients. All PowerPoints at case conference followed a standard outline, the final slide of which unerringly contained a list of potential clinical trials for which a patient was eligible. Recommendations for cancer patients – the final outcome of genetic testing – were always for enrollment in a particular trial. One oncologist called this "the research blurriness," stating that for "everybody who needs a treatment in cancer, the first thing you think is, 'Is this person eligible for a clinical trial?'" Recommendations for rare disease patients, similarly, were also often for further research. In parallel fashion, patients who received clinically approved genetic testing were nonetheless told to return to the clinic in a year's time in order to have their results reinterpreted, as knowledge about

genetics was always in flux due to the constant flood of new data from research.[7] Clinical practice led to research and research led to clinical practice.

Thus case conferences represented a constant mixing of the two epistemic orders, with research data being incorporated into clinical decision-making. In an attempt to maintain the ethical legitimacy of their practice, however, clinicians and scientists engaged in two contrasting acts. First, some preferred to purify the interstitial space. This is what happened in the Tumor Board case discussed above. RNA sequencing was reaffirmed continuously as a research project and its influence over clinical recommendations was denied.

Second, and not mutually exclusively, actors worked to transform the middle ground from an anxious not-yet or *nondum* (cf. Weir 2006) of uncertain value into a regular and regularized space of legitimate, anticipatory knowledge. As a pathologist explained to me, "When things aren't clinically validated, that's where the art comes in." A lack of institutional approval did not mean that the data from genetic tests were unusable, merely that they were not indubitable. In fact, even the 2015 standards and guidelines published by the ACMG – a major authority over such issues – declared that "In determining the propriety of any specific procedure or test, the clinical laboratory geneticist should apply his or her own professional judgment to the specific circumstances presented by the

[7] Official interpretations of a number of genes have changed radically over the years. Recommendations were originally to consider the genes *APOE*, *MTHFR*, and *HFE* to be clearly disease-causing. In 2015, however, the organization making these recommendations (the ACMG) rescinded all three, declaring them as being of uncertain significance for three separate reasons. *APOE*, linked to Alzheimers, was not to be tested for fear of popular overconfidence in its validity. It was pronounced that *MTHFR*, linked to certain clotting disorders, had a dearth of data to support its causative role. Finally, scientists had demonstrated that mutations in the *HFE* gene were insufficient in themselves to cause the iron disorder originally linked to the gene. These are just a few prominent examples of the continuous reinterpretation of clinical knowledge in medical genetics.

individual patient or specimen" (Richards et al 2015:405), thus rejecting the notion that an absolute division between clinic and research could be drawn in practice. Genetic testing represented a frontier zone, which required subjective art to negotiate the untenable evacuation of doubtable data from canonized fact.[8]

Many of my interviewees expressed a parallel concern that rejecting such data meant that the only possible outlets for progressive care for rare disease and so-called 'no-option' cancer patients would be foreclosed. In this discourse, intervention was ethically necessary and inaction was not a legitimate option. Because the technology existed, it was imperative to use it – even while knowing or expecting that it would fail. The patient's survival was a sort of Anselmian good, a good greater than which none could exist. Survival proved noncommensurate with other values, trumping through its mere mention other concerns such as financial investment, the gamble of hope, and – most importantly here – the official *ethico-epistemic* regulations. Once the question of survival was broached, patients often dismissed all other considerations and accepted whatever was with the potential to help in that cause.

I call this the *survival imperative*. It coupled with the "health moralism" (Farquhar and Zhang 2005) endemic to the United States, that ethical obligation on the patient to return him- or herself to 'normal.' Unlike Talcott Parsons's notion of the sick role (e.g., Parsons 1951a), the survival imperative could run perpendicular to or even against the drives of capital. (I return to this below.) In fact, the survival imperative's defining feature was that it came to act as a master logic. It countered bioethics' requirement for "rational"

[8] There were some parallels to the "precautionary principle" (Bryan et al 2007, Wynia 2005), which also deals with clinical recommendations based on incomplete evidence, though in the case of Individualized Medicine, the purpose of such intervention was rarely – if ever – for the purpose of prevention.

calculus in decision-making (see Chapter Three) by privileging survival itself over all other variables. For patients without other recourse, *any* recourse seemed to be the best option.

This imperative was experienced both by professionals and by patients. One cancer biologist told me of discussing research findings with clinicians, "There's nothing, or this." That is, either the patient would fall victim to clinical inaction, or clinicians would make use of data that had not been clinically approved. During a twenty-minute session with a genetic counselor, an older woman had been warned repeatedly that the chance of discovering a new potential treatment for her cancer was very low. "I understand that," she said, holding her husband's hand. "But waiting doesn't do anything." Another older man sat with me for nearly an hour after his genetic counseling session, discussing a variety of things, but most poignantly his decision to undergo multiple genetic tests (the full suite of three offered "à la carte" to cancer patients): "I could leave my grandson those eleven thousand dollars, or he could get to know his grandpa." To reiterate, this happened after a session in which the patient was repeatedly reminded of the low chance for a medically actionable yield from any of the tests. He saw the definite and significant financial cost entailed in his decision to be inconsequential relative to the mere possibility of survival. Some patients I interviewed simply could not afford testing by any stretch of their budgets, and several of these individuals resorted to Internet-mediated crowd funding, with varying success. One woman on Medicaid had a son with an undiagnosed abnormality of the muscles around his eyes. She went on multiple local news programs to fundraise the $20,000 she anticipated to need for diagnostic testing. When I left the Center, she had still not managed to gather enough money.

Cancer patients regularly began their sessions with oncologists by noting their aversion to chemotherapy. It was certainly a traumatic intervention. However, even the suffering induced by such treatment regularly appeared irrelevant to decision-making when the object was survival. For instance, one elderly woman complained at length that she "hated" chemotherapy and was hoping to be taken off it. She was meeting with a genetic counselor to discuss other options. The counselor explained that all she could offer were tests that would lead to other chemotherapies, but that there was a possibility that a different regime could extend her life expectancy. This handily persuaded the patient – which was not the genetic counselor's intent. At the patient's quick change of heart, the counselor asked her to consider carefully her options, but she did not change her mind. I asked her in an interview afterward about the prospect of further chemotherapy. She responded, "Still, it was an obvious choice."[9]

For similar reasons, official policy also included an exception to the ban on returning results from research studies directly to patients. There were two major classes of exceptions. The first was the disclosure of "incidental findings." When analyzing a patient's DNA, scientists generally only attended to those genes known to be associated with a patient's disease state. However, sometimes they discovered known or likely pathogenic variants unrelated to the patient's reason for undergoing the test. Clinicians were allowed to choose whether to return such results to patients, though the IRB was occasionally

[9] Patients often proved non-dissuadable with regard to their attachment to genetic reductionism (Stotz and Griffiths 2013). Non-specialist clinicians occasionally bought into the discipline's hype, something specialists (medical geneticists and scientists) fetishized as proof of such clinicians' relative naïveté and inability to mobilize scientific data appropriately. Laboratorians – at the far end of this spectrum – proclaimed the limitations of genetics for explaining health and pathology.

involved in determining the ethical legitimacy of such reports. In any case, there were provisions for such return of results from research.

The second class of exceptions was the disclosure of the so-called "ACMG 56:" 56 "well-described" genes linked to major, clinically-actionable disorders such as heart diseases and hereditary cancers. The ACMG recommended the disclosure of pathogenic results in these genes to all patients undergoing large-scale genomic tests, regardless of whether these results were requested and even when they were unrelated to the patient's phenotype. (There was a debate whether such results counted as incidental findings, since they were actively sought by the laboratories. Some of my interlocutors insisted they be called "secondary findings" instead.)

These results were to be – or at least *could* be – returned directly to patients, even from research studies without clinical approval. This was another way in which research data were allowed to enter the domain of clinical knowledge through an institutionally legitimated channel. Particular information whose evidential grounds would have otherwise been regarded with skepticism was treated as appropriate due to its potential significance in addressing the survival imperative.

Insuring Doubt

It should be clear that recourse to regulatory apparatuses was another key dimension in the division between clinical knowledge and research data. Such 'elsewhere' authorities had proliferated over the half-century preceding my fieldwork. Two interconnected groups, however, were of particular relevance to the Center. Both of them

have already been mentioned, but in this section I address each systematically. They were federal practice guidelines and health insurance.

At the beginning of the twentieth century, clinicians in the USA "jealously guarded [their] prerogatives against state power," even while in Europe their counterparts' jurisdiction was subordinated to the will of the pharmaceutical industry, insurance companies, and national governments (Weisz et al 2007:700). The American Medical Association (AMA), the largest professional association of physicians, took on the role of generating and regulating standards in the state's stead. However, in the postwar years, the government increased its involvement in healthcare, in particular to support returning veterans. By mid-century the USA had become "the first country to develop practice guidelines on a significant scale" (Weisz et al 2007:702). This shift was due in part to a Taylorist impulse to manage healthcare "scientifically" (Reverby 1981) and in part to the increased collaboration between clinical care and laboratory science (e.g. Introduction; Cambrosio et al 2006).

Practice guidelines have grown rapidly in number and in purview since that time. Some researchers attribute this growth to their promise to rationalize financial expenditure on care (e.g., Zinberg 1998), while others point to their ability to defer responsibility for malpractice in legal settings (e.g., Hyams et al 1996). The validity of both claims can be questioned (e.g., Timmermans and Kolker 2004), but both represented important ideological commitments that were also expressed by my interlocutors at the Center. Moreover, clinicians and scientists regularly relied on government certifications as a sort of shorthand or proxy for judging the epistemic reliability of the results from a

particular test. The impersonality of the guidelines had come to index the 'objectivity' of the propositions they had certified as clinical knowledge.[10]

The most unavoidable way in which these guidelines emerged in the daily life of the clinic was through clinical trials, which served as the source of the "evidence base" for much translational medicine. Such trials were the apotheosis of this historical trajectory, creating 'unbiased' and 'objective' treatments through the mechanics of randomization and double-blinding (Dumit 2012). They also served as a permanent tie between clinical and research practices. They were quintessentially experimental, as there could be no guarantee – or even expectation, as many laboratorians were wont to point out to clinicians – that enrolling a patient would ensure treatment using the drug being tested rather than a placebo. From the perspective of clinicians and scientists, such a feature would land clinical trials squarely in the world of research according to ethico-epistemic hermeneutics. Despite that, their results served as the basis for subsequent healthcare, and more pertinently (though less publically), the trials themselves served as the standard recommendation for 'no-option' cancer patients.

Insurance acted as another major regulatory apparatus in determining the ethico-epistemic value of particular tests and their results. National health insurance in the USA emerged in 1965 in the form of Medicare and Medicaid.[11] Such universal coverage was met with strong opposition by the AMA, who feared it would transform clinicians into "'clock watchers' and 'slaves'" (Wiener 2000:24). Indeed, insurance has become paramount in

[10] Marks bemoans such 'objectivity' as "the usurpation of clinical expertise and physician autonomy in favor of statisticians and bureaucratic dictates" (Marks 2000:225).
[11] The tethering of insurance to the federal government had transformed the indexical field in which it operated. It tied healthcare coverage into biological citizenship (Petryna 2004), whereby claims were made in the idioms of values and rights, representation and responsibility, and contract. Insurance of their health was something patients were owed.

controlling access to – and thus utilization of – particular medical interventions. Genetic counselors, whose job it was to assist patients with payment concerns, told me that most private insurers looked to Medicare, Medicaid, and statements from the Food and Drug Administration for guidance on whether to cover a genetic test and for how much. The Center itself also used Medicare as a referent when determining its own billing process. The "Medicare-allowable charge" was a key variable for the institution in fixing the total amount charged to conduct a particular test.

Most patients with whom I spoke got at least some percentage of their testing covered by their insurers. This was determined through insurance preauthorization, coordinated by the genetic counselors. In some instances, Medicare and Medicaid even paid for more avant-garde, large-scale genetic tests that had lower statistically proven yields. Genetic counselors found it difficult to predict which insurers would cover which tests. Success in this arena, they explained, was in part a function of the clinicians' ability to write a "persuasive letter of medical necessity" to the insurance agency.

Insurance was also a concern in the decision to pursue diagnosis. Some patients expressed a fear that having their rare disease receive an on-record diagnosis could make them uninsurable due to a "pre-existing condition." Genetic counselors tried to alleviate this by noting that the Genetic Information Nondiscrimination Act (GINA) had been established in order to prevent this sort of denial of coverage. Some counselors chose to temper this reassurance by adding that such discrimination would be hard to prove and that the law had not yet been tested in court. The dubious legal standing of GINA was often lamented backstage, as well. One pathologist characterized genetic diagnoses as "the insurance company's way of sort of having an out" from having to insure at-risk individuals.

Contrarily, other patients noted that having an on-record diagnosis could give them access to government-funded support for the disabilities provoked by their medical conditions. For instance, one young mother hoped a diagnosis for her daughter's intellectual disability could provide her with welfare assistance and perhaps a personal care assistant. "I just need a name," she told me. In a plea rooted in a sort of imagined biological citizenship (Petryna 2004, but see especially Ticktin 2006), this mother believed that the state would only intervene in her daughter's welfare if she could make claims based on her institutionally recognized (i.e., diagnosed) poor health.

Both practice guidelines and insurance tied local practice in the hospital to federal debates and regulations. While this adds an important dimension to the ethico-epistemic focus of this chapter, it also underscores the dominant role of the clinic in knowledge assessments. Clinical therapy had the power to drive laboratory science since it was the site of judgments regarding use and billing. In this way, the laboratory was *embedded* in the clinic (contrast Harraway 1985:69; qtd. in Latimer et al 2006), and the clinic was temporally embedded within the larger horizon of approved, actionable knowledge. Research produced validity and accuracy, but it was subordinated to clinical utility. Therapeutic application provided it in large part with its raw materials (samples from patients), the phenotypes necessary to interpret those materials (collected in clinical encounters), and the moneys with which to conduct its experimentation (obtained from insurance due to medical necessity). It was for this reason that laboratorians apologized during case conferences, demeaning their own projects as "just of academic interest." It was also for this reason that laboratorians had to work hard to translate their goals into

ones with clear clinical applications so as to enroll clinicians, the gatekeepers to necessary resources (cf. Callon 1986; Latour 1987).

Managing Uncertainty

While patients were regularly turned away from the clinic without being allowed the genetic test they desired,[12] the threshold for acceptable uncertainty in the translational space of individualized medicine was significantly higher than elsewhere in the hospital. Even the official national standards and guidelines underscored this, noting that "clinicians and patient were willing to tolerate a slightly higher chance of error" from genetic tests than traditional standards of care (Richards 2015:407). Nonetheless, of course, there was a constant concern about how much potential error was too much.

Such tensions were most apparent in genetic test results called 'variants of uncertain significance' or 'VUSs.'[13] VUSs could be returned either by clinically-approved tests or by research, which is to say that despite their constitutive uncertainty, they were not shibboleths of the dubitative epistemic order of research. Nonetheless, VUSs were

[12] Alongside the earnest attempts by clinicians to keep patients from spending large sums of money and hope on doomed endeavors, clinicians were also cognizant of the negative impact unsuccessful tests had on the clinic's professional livelihood. Clinicians occasionally referred to this as "the numbers game." Testing patients with little chance of diagnostic returns meant jeopardizing the clinic's (publically visible) percentage of success cases. They regularly compared the value of their test to those of other hospitals in this way. "Bad referrals" that were not rejected would inevitably harm their standing within the genetics community, their ability to draw new patients, and their receipt of funding to continue their work.

[13] Humorously, what the U in VUS stood for was itself uncertain for many of my interlocutors. While according to the ACMG, it was an abbreviation of "uncertain," "VUS" was commonly pronounced additionally as "variant of unknown significance" and "variant of undetermined significance" by clinicians, and was occasionally even written as such in PowerPoint presentations. Beyond the amusing meta-uncertainty of the VUS, this ambiguity also pointed to the jumbled intersection of alethic (*know*-) and epistemic (*certain*-, *determine*-) modalities (cf. Lyons 1977) it encompassed.

technically considered clinically inactionable, because they did not have enough validated evidence to support their institutional recognition as either benign or deleterious. Clinicians constantly came up against these results. In fact, the average clinical genetic test returned four to six VUSs per patient.[14] Reports returned without a single VUS were viewed with extreme skepticism, as though an error had surely occurred to produce such anomalous certainty.

VUSs were in binary paradigmatic contrast with so-called polymorphisms. The two were divided by a "mystical 1% allelic frequency threshold" (Ackerman 2015:2). That is, any variant that appeared in more than one percent of the (genotyped) population was considered too common to be the cause of disorder, thus making it a polymorphism or "normal variation." The rare disease phenotype would need to be correlated with an equally rare genotype. Anything below that 1% threshold was rare enough to be a candidate cause for disease, thus making it a variant of uncertain – but *potentially* pathogenic – significance. The normal was quantifiable: it was the 99%.[15] VUSs were once described to me as "like Schroedinger's cat:" it was unknown whether the variant was pathogenic or harmless, and once it *became* known, it was no longer a VUS.

When a laboratory returned a report, at the top of that report it listed those one or two variants that had sufficient, clinically-approved evidence to be 'called' as pathogenic – in the uncommon case that such results had been found. Below that followed one to three

[14] This was after several rounds of algorithmic and human reduction of some original hundreds of thousands of VUS results per patient. I discuss this sieving process at length in Chapter Five.

[15] Actual usage in *parole* was muddled, and backstage, clinicians regularly mixed the two (see also Karki 2015). However, this chapter deals with ideological models, and in any case my interlocutors could – and regularly did – correct each other's usage by referring to this standard.

pages of tables describing the uncovered VUSs considered most relevant to the case. Alongside the variant, a slew of other potentially relevant data were listed. (I discuss this in detail in Chapter Five.) Most importantly for the current discussion, the report presented diseases and disordered phenotypes that algorithms had determined – using published research data – were potentially associated with the affected gene (Figure 4.2).

VUSs existed in the tenuous borderland of uncertainty; however, the most common task for clinicians in interpreting genetic test results was to determine one or two VUSs "worth pursuing." That is, the anticipated outcome was to recommend research to limit the uncertainty of the VUS further. Biochemical tests – like the RNA sequencing discussed above – could be used to determine whether a variant was "really" responsible for a given disorder. Functional modeling (for instance, the creation of transgenic mice or zebrafish in order to test gene expression) could be used – like a clinical trial – as a 'standard' form of folding research into clinical practice. Clinicians operated under the assumption that a variant's pathogenicity was gradiently knowable through the evidence present, and that it would in the future be known. (One may again recall the exhortation of patients to return to the clinic annually in order to determine whether new (clinical) knowledge had determined the significance of any of their results.)

Again, a pure division between research data and clinical knowledge could not be maintained under the imperative to act without any otherwise sanctioned alternatives. Clinicians felt compelled to intervene, even though they were working with unsanctioned data and precarious uncertainty. They preempted these threats – folding virtual future (clinical) knowledge into real present action. This double-edged ethical imperative

Table 2: Variants of Unknown Clinical Significance in Disease Genes Related to Clinical Phenotype

Disease	Inheritance Pattern	Gene	Position	Isoform	Location	Nucleotide	Amino Acid	Zygosity	References/Comments	ESP5400 AA/EA	SIFT / PolyPhen-2
Conotruncal anomaly face syndrome [MIM:217095]; DiGeorge syndrome [MIM:188400]; Tetralogy of Fallot [MIM:187500]; Velocardiofacial syndrome [MIM:192430]	AD	TBX1	Chr22: 19754144	NM_080647	exon9	c.1242C>G	p.H414Q	Het	Novel variant; Confirmed by Sanger sequencing. Mother is heterozygous. Father is negative.	N/R N/R	Tolerated/ Probably damaging
Marfan syndrome [MIM:154700]; MASS syndrome [MIM:604308]; Ectopia lentis, familial [MIM:129600]; Aortic aneurysm, ascending, and dissection; Stiff skin syndrome [MIM:184900]	AD	FBN1	Chr15: 48713793	NM_000138	exon62	c.7661G>A	p.R2554Q	Het	PMID 21883168; Confirmed by Sanger sequencing. Mother is heterozygous. Father is negative.	0/3738 1/7019	Tolerated/ Probably damaging
Mental retardation, autosomal dominant 3 [MIM:612580]	AD	CDH15	Chr16: 89256792	NM_004933	exon8	c.1120G>A	p.V374M	Het	Novel variant; Confirmed by Sanger sequencing. Father is heterozygous. Mother is negative.	N/R N/R	Tolerated/ Probably damaging
Rubinstein-Taybi syndrome [MIM:180849]	AD	CREBBP	Chr16: 3820765	NM_004380	exon14	c.2686G>C	p.G896R	Het	Novel variant; Confirmed by Sanger sequencing. Father is heterozygous. Mother is negative.	N/R N/R	Tolerated/ Probably damaging

Figure 4.2: VUSs on a large-scale genomic sequencing report.

simultaneously paid homage to the epistemic dichotomy and demanded the dichotomy's bracketing or circumvention.

"Real Risk"

For professionals in the clinic, risk was a category distinct from uncertainty, because risk was founded on an understanding that discrete quanta were 'known,' at least in the clinic's practical sense (cf. Decoteau and Underman 2015; Gross 2007; Knight 2006). In fact clinicians regularly spoke of "uncertain risk," with the correlate that there was also such a thing as (relatively more) certain risk. Risk had an ontic status. It was definitionally non-existent – indexing a potential futurity – but it was nonetheless real. Clinicians could qualify statements about risk as true or false, medically actionable or inactionable. The ascription of a certain quantum of risk to a particular patient opened or foreclosed veins of action, such as trial enrollment, medical intervention, and diagnosis.

For instance, early in my tenure at the clinic, I was sitting in the genetic counselors' workroom, waiting for a patient to be roomed for a consultation that I would shadow. I spoke with another genetic counselor about a patient she had just seen. She explained that the woman "may have an increased risk for breast cancer," because she had a first-degree relative with the disease. I asked the counselor why it was not already assumed that she was at increased risk, since the concern in medical genetics was, after all, with familial disease. "Real risk," I was told, could not be adduced without a genetic test. This was oddly circular, I thought, since the fact that the patient had been seen in the clinic presupposed her increased risk. Without the risk – or "predisposition" – she would not have been a candidate for genetic testing.

I had a similar experience a few weeks later when I was shadowing in the rare disease clinic. Jen Miller, the genetic counselor with whom I was working that day, had just finished taking a patient's family history. The mother had an undiagnosed vascular disorder, and her son had a similar phenotype. When the mother asked Jen whether her newborn daughter was at risk for the same condition, the counselor told her she did not know for certain. After the session I asked Jen why the patient's family history did not automatically put her at increased risk. Jen told me there was a significant, qualitative difference between saying "a one in four chance" and "less than one percent." That is, the gross nature of risk calculation based on family history – and worse still, the self-report of family history – could not produce *legitimate* calculations of gradiently knowable risk. Genetic testing, she said, made risk "more concrete," and with the increase in confidence, so too an increase in the legitimacy of basing healthcare decisions on it.

It was certainly the case that some sort of risk was being assessed through the long process of family-history taking. (This accounted for the vast majority of a patient's time spent with a genetic counselor.) After all, the key predictor of many heritable disorders was a first-degree relative with said disorder. Nonetheless, this kind of risk did not constitute *robust* risk to my informants at the Center.[16] This was because it did not sufficiently approximate clinical knowledge, knowledge derived from sanctioned genetic tests. Perhaps before the technology and practice guidelines existed, different evidential standards could have applied, but that was no longer the case. Gradiently weaker forms of risk could be determined, but only robust risk could be mobilized in clinical decision-making.[17] While genetics was credited with currently-limited clinical utility, it was still given ultimate priority in this regard. The privileging of a genetic etiology parallels the ascendance of other epidemiological models of knowledge in biomedicine (Hacking 1990; Timmermans and Kolker 2004). Such evaluation regimes "provoke[d] an incipient distrust" of more qualitative measures (Chumley 2013), such as self-reported family histories.

Risk was ontic despite its mere potentiality. Even though it ostensibly pointed to the future or otherwise contingent reality disorder, it came to be treated as a thing in itself rather than a epistemically modalized property or quality of some other thing. It was an index that had become its referent, the Peircean First that had become an embodied and knowable Second. Through a regular form of downshifting or rhematization (Gal 2005, 2013), risk was no longer treated as an index of disease (being *at risk* for a certain disease)

[16] Strikingly, the "25% increased risk" was seen as less robust than the "1% increased risk."
[17] Family histories were still taken for a number of reasons. They were a traditional part of the practice. They could suggest a disorder's heritability pattern, in particular whether it might be de novo (or novel to the patient). Finally, they provided a glimpse at potentially related disorders, bringing to light otherwise invisible syndromic conditions.

but rather as something knowable and manipulable in itself (see also Dumit 2012; Greene 2007). As Pascale Bourret put it, "risk itself has become the focus of intervention" (2005:45).

Types of risk fell along a continuum. Uncertain risk based on data from research studies could still be considered evidentially strong enough to enter into clinical decision-making. Soft risk, derived from non-genetics algorithms, still produced recognizable evidence, but its interactional effectiveness was curtailed. While it was necessary for the legitimation of candidates for genetic testing, soft risk such as that ascertained through family histories was not sufficient to determine legitimate targets for healthcare intervention. Such was the domain of "real," robust risk, the domain of risk based on genetic variables. While officially 'uncertain,' such risk was strong enough to constitute acceptable evidence in the extraordinary space of individualized medicine.

Robust risk bifurcated along official epistemic orders as well. Information from RNA-sequencing was clearly robust, representing the most clinically and popularly privileged, viz. genetic, form of evidence. Nonetheless, as a type of research data it was limited in its acceptability in healthcare decision-making. The robust and the uncertain were not isomorphic with the clinical and the research.

Hierarchies of the Knowable

Determining the accuracy (clinical or otherwise) of evidence was difficult in the 'translational' realm of the Center, where the truth-functional knowledge required for such determination was still in the domain of hypothesis, hope, and hype. The discovery of novel and rare genetic variants was common – especially in so-called 'diagnostic odyssey' cases,

in which patients had often spent their entire life seeking a diagnosis for a troubling condition. Furthermore, the information required for clinical decisions categorically did not have a non-research – that is, an otherwise acceptable – alternative. If a clinical alternative existed for an individual, he or she could not be ratified as a candidate patient in the clinic. Nonetheless, ethical pressures demanded that quasi-therapeutic decisions be made.

There was an epistemological hierarchy whose zenith was clinical knowledge, which stood in paradigmatic contrast to research data at the hierarchy's nadir. While such a hierarchy had parallels to the more general folk epistemological bifurcation between knowledge and belief (e.g. Good 1994), such binarism did not prove analytically sufficient for three important reasons. First, there was a gradient scale of evidential acceptability between the two (partially hermeneutic) poles, the pragmatic negotiation of which was often more important than their purification. Second, there were dimensions of evidence external to the hierarchy, which were nonetheless incorporated (both on and off the record) into clinical decision-making. Third, the logics of accuracy and validity underlying the two poles were importantly and to a significant extent *different,* if not *incommensurate* (Mair and Evans 2015; see also Kuhn 1962). Below, I review each of these arguments in turn.

First, the middle ground, the 'gray zone' of the Center could have been paralyzed by its reliance on data culled from the disprivileged epistemic order of research. Instead clinicians and scientists worked to manage the uncertainty entailed in the weak evidence they mustered, often linking that evidence citationally to relatively stronger data provided by clinically certified tests. One could frame an assertion – all things otherwise equal – as indebted to or embedded in institutionally authorized knowledge. Without changing the

propositional content, one could, say, link a recommendation based on research data to information derived from a clinically validated test. This is what happened in the case Dr Clarke brought to the Tumor Board: RNA data was raised to the level of clinical knowledge by connecting it to an approved DNA test. While simultaneously recognizing the official hierarchy, such pragmatic negotiation allowed therapeutic decisions to be made, and to be made ethical.

Second, underlying much clinical decision-making and research hypotheses was patient self-report, largely understood to be the most dubious source of evidence in the clinic. Family history, culled from a patient's narrated memory, was often demeaned as insignificant. In case conference, information gleaned from a patient's expressed complaints was regularly cordoned off with cautionary evidentials: "Mother *says* she had bronchiectasis, and that's all we know." "Parents claim the older brother died at 18 months of Menkes." Nonetheless, it was necessary for clinicians and scientists alike to rely on patients to provide evidence for things that were interior, subjective, or historical. As was demonstrated in the section on risk above, non-genetic forms of evidence were considered weak but were still necessary to legitimate a patient as a candidate for a genetic test in the first place.

Third and finally, clinical knowledge was more dubitative than it often appeared to lay patients. It was not valid or accurate in the same way the science of research strove to be. It did not portray timeless truth, even though it was warranted by the highest evidential standard available within the clinic. The significance of genetic variants was constantly in flux and under revision. In this way clinical knowledge was deictic, shifting (Silverstein 1976) as the horizon of the present shifted, and tied to the present moment rather than to

some exterior, unmoved realm where words and worlds met in immediacy. It was not the case that researchers and clinicians formulated knowledge in the same way (see, e.g., Pouillon 1982) nor that they put that knowledge to the same use. "Scientific" and "academic" endeavors had different goals from clinical engagements, tethered as they were to therapy. Clinical knowledge was presumptive; it was an hypothesis (Peirce 1991[1868]).

A view of 'knowledge' as simply representational – even modally or gradiently – would prove insufficient. An illocutionary logic (e.g., Searle and Vanderveken 1985) would leave us with defeasibility and factivity[18] to explain whether a proposition could count as an agent's knowledge. That is, we would be left with questions like: Does the assertion of knowledge hinge on the 'objective' and ultimate truth of its proposition?[19] Such logic requires of knowledge the possibility for an evaluation of truth vis-à-vis some absolute and intersubjectively accessible world. This sort of evaluation disturbs the now-traditional aspirations of a relativist anthropology, an approach that distances itself from claims of empty signifiers (contra Boyer 1986) and true-though-hidden essences (contra Putnam 1975). 'Justified true belief' is anti-relativist in both ontological (truth) and epistemological (justification) senses. More importantly, though, such evaluation disturbs clinicians' and scientists' practical notions of knowledge as well, viz. that what counted as knowledge today would of no necessity count as knowledge tomorrow (cf. Introduction).

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[18] Hazlett, for instance, rejects knowledge as factive, claiming that falsehoods can be 'known,' but denies that a plurality of contradictory *truths* is acceptable (calling this "unlovely relativism" (Hazlett 2010:502). I would argue that such relativism is exactly the Latourian approach to epistemology and the approach that makes the most sense in explaining the ethico-epistemic world of CIM.

[19] Take, for instance, the proposition "This gene is pathogenic" (which bears the presupposition that genes can be pathogenic) and compare: "I know that this gene is pathogenic" and "I believe that this gene is pathogenic." (Note also that the hearsay evidentials used to cordon off patient self-reports worked specifically to make the presupposition of their truth defeasible.)

I am not arguing against philosophical debates about knowledge as a universal, human attribute or possession. Instead, I am interrogating a cultural category local to the individualized medicine clinic at which I worked. Knowledge as a representation of un-situated truth is so limited in its descriptive value as to be empirically inadequate to the task of explaining knowledge assessment in the Center. What counted as knowledge was determined pragmatically. It was not necessarily a function of representational truth versus falsity, but of intervention versus inaction, driven in part by the survival imperative. The particularities of regulatory apparatuses were naturalized into medical epistemologies and conceptions of truth and best practice. While the institution was committed to avoiding the conflation of the research and clinical epistemic orders – through discourses such as that on therapeutic misconception – it simultaneously put research forward at the end of therapeutic engagements. This underscores the ever-shifting social role of the clinic as it moved from the classical space of Foucauldian history, viz. therapy, into one increasingly invested in predicting and preempting the future. Standard of care and standard of proof became mutable ideals, and the evidence of research hypotheses became the evidence of clinical knowledge, with only the necessary poetic alterations.

CHAPTER FIVE: EVIDENCE, CONFIDENCE, FACT

"Sec. 10. The spleen. Of the spleen, gentlemen, we know nothing. So much for the spleen." – Emil du Bois-Reymond[1]

Power/Non-Knowledge

I once observed a patient meet with a genetic counselor to discuss the results of a large-scale genetic test. After the session the patient said she was "overwhelmed" and explained that she did not fully understand what she had been told. "The main thing," the genetic counselor said, pointing to a list of four candidate mutations on the laboratory report, "is that none of these are clear matches for you." Nothing on the annotated report rose past the threshold of what clinicians considered reliable information. The patient stared blankly. "Do you have any questions?" the counselor asked kindly. "I don't know." There was a pause. "No," the patient then concluded. I left the interaction rather deflated by what I took to be a failure in communication. When I said as much to the counselor, however, she had the opposite interpretation. "She [the patient] got it." I pressed her for an explanation. The patient's nonplussed attitude, the counselor reasoned, proved a more fundamental understanding: She had recognized the limits of her knowledge and the limits of scientific knowledge itself. Rather than an easy and unreflective conviction in the power of medical genetics, the patient was actively grappling with non-knowledge, knowledge of what remains unknown (Gross 2007).

This attitude proved relatively routine among the clinicians at the Center for Individualized Medicine (CIM). They told me that it was harder and more important

[1] Quoted in Weber (1922:15), see also Coon (1991:407).

to convince a patient of the uncertainty of genetic test results than of their meaning (cf. Katz 1984:37). Sir William Osler, one of the founders of Johns Hopkins Hospital, once famously characterized medicine as "a science of uncertainty and an art of probability" (Bean and Bean 1950; qtd. in Meldolesi et al 2015:132). A recognition of the uncertainty entailed in clinical therapy was a recognition of that therapy's very essence. This also seems to be at least a partial explanation for the pro-forma nature of informed consent (see Chapter Three) for which the expression of non-knowledge ("It's all Greek to me") did not forfeit the ritual success of the process. The patient could still count as informed even after having pronounced an explicit lack of understanding.

In this chapter I consider the ways in which uncertainty and evidence get embedded in linguistic practice. The sociolinguistic ecology of the Center was characterized by its diversity of spoken and written registers. I have already explored the 'plain language' of the Section of Patient Education (SPE) and the elaborate methods by which expert verbiage was 'simplified' for lay readership (Chapter Two). In this chapter I turn to one particular feature of expert language: the names and descriptions of genetic mutations. Under this scrutiny, even greater heterglossia emerges. The expert register of scientists and clinicians – taken as a gradiently accessible yet relatively discrete pole by SPE – in fact consisted of many mutually unintelligible codes.

I argue that each code filled a specific ecological niche, formulating its lexical items to carry information that was pragmatically salient to its stereotypical contexts of use, tailoring its acknowledgement of uncertainty and evidence to the

needs of its particular audience. That is, code choice was conditioned by its use in, e.g., a pathology report, a case conference, or a "drive-by consultation" in the halls of the Oncology unit. In the preceding chapter (Chapter Four), I demonstrate the socioethical anxiety clinicians experienced with regard to the epistemic status of their propositions: Was certain information sufficiently 'clinical' to serve as a warrant for a certain action? Or did it hold the dubious epistemic status of research data? In what follows, I describe the ways in which evidential claims and warrants were embedded in various classificatory schemata for gene names and gene descriptions.

Rather than encumber the performance of expertise and the social interactions it structured, the assertion of uncertainty underpinned claims to authoritative knowledge and discretion. It was not seen as a hindrance to the fiduciary relationship between clinician and patient (contra Good et al 1990) or between specialists, but rather stood as a socioethical virtue. Claims of non-knowledge were almost as potent as claims of positive knowledge. The insistence on doubt both furthered the "intrigue" that electrified diagnostic case conferences (cf. Saunders 2009; see also McGoey 2009) as well as reinforced professional boundaries of expertise necessary to the interdisciplinarity of the project of individualized medicine.[2] Such non-knowledge was not a castrating ignorance that discredited its subject (*à la* Matthews 2005) but a form of hypertrophied expertise that called attention to interlocutors' non-commensurate access to courses of

[2] Individualized medicine necessarily transcended disciplinary boundaries. It became *individualized* (as I describe in the Introduction) by being the nexus point of multiple, discrete dimensions of knowledge.

legitimated social action. The management of uncertainty was a modality whereby specialists simultaneously created a domain for the exertion of power and limited access to it. *Non-knowledge/power* (cf. Foucault 1995) was the central feature of medical genetics expertise.

Transduction of Evidence

This chapter considers in particular the relationship between evidential and epistemic information. I borrow both concepts from linguistics with some qualifications. Following Basso (2008), and Dendale and Tasmowski (2001), I highlight the distinction between evidential information about sources and epistemic information about confidence and certainty. By evidential information, I mean that information which describes "the nature of the evidence on which a statement is based" (Aikhenvald 2003:1). In French the term is *médiatif*, drawing explicit attention to the fact that evidential markers make salient the act of mediation in the transmission of propositional content. Evidential markers describe the source of that information. By epistemic information I mean that information which evaluates the reliability of the proposition. This evaluation can range from certainty to possibility, all the way to an absence of knowledge altogether (cf. Lyons 1977).[3] The key differences between these forms of information are twofold: First,

[3] The evidential markers I discuss in this chapter were not truly evidential by many accounts, in that they were not deictic. They did not denote a relative relationship to the author of the proposition but rather an absolute source. Their meaning did not 'shift' when produced by a machine, written by a scientist, or repeated by a clinician. Each class of actor certainly used the information borne by the morpheme to make different inferences about the reliability of the proposition, but that was not determined by the evidential in itself.

an evidential marker provides specific information about a proposition's source while an epistemic marker is agnostic to it. Second, an epistemic marker provides an explicit evaluation of a proposition's reliability while an evidential marker is agnostic to it.

This distinction between evidential and epistemic information highlights the variable role of expertise in the interpretation of a proposition. Simply providing the source of some information requires that the receiver of that information be able to come to a determination regarding the reliability of said source. Contrarily, providing an overt evaluation of some information requires that the receiver believe in (*croire en*, see the Introduction) the reliability of the evaluator itself.

For instance, a typical laboratory report from Molecular Genetics described a mutation discovered by one of its tests in a complex table, representing everything from the location of the mutation, to the inheritance pattern, to the disease predicted to be associated with it (see Figure 5.1). These reports also provided information about the method whereby the variants were confirmed, which was called Sanger sequencing. Checking a result using this kind of sequencing was considered necessary for affirming its clinical validity. Seeing this kind of evidential marker reassured specialists that a baseline had been met. However, laboratorians occasionally noted the technical limitations of this methodology. "'Calls' is kind of a loose term with Sanger," one bioinformatician declared during a case conference (see also Chapter One), deriding its reliability to a room of clinicians who had previously been treating the candidate mutation as well evidenced. Everyone could see the source of the confirmation information, but only those with particular

Disease	Inheritance Pattern	Gene	Position	Isoform	Location	Nucleotide	Amino Acid	Zygosity	References/Comments	ESP5400 AA/EA	SIFT / PolyPhen-2
Conotruncal anomaly face syndrome [MIM:217095]; DiGeorge syndrome [MIM:188400]; Tetralogy of Fallot [MIM:187500]; Velocardiofacial syndrome [MIM:192430]	AD	TBX1	Chr22: 19754144	NM_080647	exon9	c.1242C>G	p.H414Q	Het	Novel variant; Confirmed by Sanger sequencing. Mother is heterozygous. Father is negative.	N/R N/R	Probably damaging

Figure 5.1: A laboratory report's description of a mutation.

expertise could successfully interpret the uncertainty immanent in it. Contrarily, the epistemic marker on the laboratory report – viz. that the candidate mutation was predicted to be *probably* damaging – was only disputable with reference to *its* source, viz. the algorithms SIFT and PolyPhen-2 (which were indeed occasionally disputed).

Authority thus interacted differently with the two modalities. Epistemic information provided a modification that was "external to the content" (Halliday 1970:349). Attitudes of evaluation had already been completed and the process blackboxed. It did not open itself up to expert scrutiny. On the other hand, the only way evidential information became salient in the interpretation of a proposition was through expert presuppositions about the reliability of the source. As I demonstrate below, various data requiring scientific expertise for their interpretation were expunged from genetic information as it moved toward the clinic, being replaced by the signature traces of expert evaluation in the forms of epistemic markers. Meanwhile, clinical descriptions that were inscrutable or extraneous for laboratorians were simultaneously added to that information.

There was also a socioethical motivation (see Chapter Four) for the inclusion of evidential and epistemic markers in propositions about genetic test results. These markers had the ability to ascribe and deny responsibility for the information they

modified (cf. Babel 2009). Determining the locus of responsibility for healthcare decisions secured both the moral and the legal standing of the clinicians involved. Moreover, the explicit tracking of this information acted to support the perlocution or sequelae of a proposition. By noting a particular level of confidence or a particular source of evidence, the sender of the information could control the ends to which it was put (see also Chapter Three). By deriding the reliability of Sanger sequencing, the bioinformatician quoted above worked to have the candidate mutation removed from further discussion, even though all the other mutations under consideration had also been confirmed by Sanger sequencing.

Information provided by genetic testing originated in the laboratories. It then moved through multiple iterations of reports, eventually reaching the clinic. Each subsequent report was aimed at a different audience and therefore took on a different form so as to be legible and useful within that new setting. It was not perfectly translated but rather was 'transduced' (Silverstein 2003), changing in content and structure in some salient ways while maintaining the appearance of identity. Certain information was sloughed off or transformed to accommodate the target code and its users. For instance, inefficacious evidential markers were 'reduced' to expert epistemic evaluations, fully meaningful in the new interactional context.

As the iterations moved closer to the clinic, the specificity of the information they carried became more phenotype-centric than genotype-centric. The process was not merely a reduction of information. The reports supplemented clinical for

scientific insight. As the goals of the users changed, the ways in which accuracy and utility were evaluated changed in step.

In order to explore this process, I begin by explaining the 'reduction' of genetic information as it moved from laboratory to clinic and the different roles it played in providing evidence for diagnosis. I then give a typological overview of the different systems used to name and delimit genetic test results. Next I consider the specific qualities of the systems as they related to the roles the codes played in scientific and clinical interactions. This section is followed by a sociohistorical look at the emergence of standards among these systems. I conclude with an examination of 'language contact' (cf. Galison 1997) between the codes, the processes of reduction in transduction, and the auxiliary systems that emerge in order to counteract excessive loss.

Transductional Medicine: From Laboratory to Clinic

As described in the previous chapter, the clinic and the laboratory stood as emblems of two separate (or at least separated) epistemic domains: clinical knowledge and research data. The domains differed in the presupposed scientific accuracy and specificity of their propositions: Clinical knowledge had reached the threshold (both evidential and bureaucratic) of knowledge and become actionable, that is, it could serve as a warrant for medical intervention. Research data, on the other hand, tarried in the realm of explicit uncertainty.

For the purposes of the current chapter, an additional salient contrast between these two domains was the role of "discovery." The laboratory dealt with

potential entities, working to stabilize and legitimize hypothetical objects within a biomedical framework. Was a reported genetic variant actually "there" in the patient's DNA? The clinic was meant to deal only with "discovered" entities, objects with sufficient socioethical warrant, whose arguments were ideally not ones of referential but of attributive description (Donnellan 1966; see Chapter One). That is, by the time genotype information reached the clinic, clinicians assumed it was valid except where contraindicated by information external to report itself. Most typically, such contraindication took the form of a mismatch between the presented genotype and clinical interpretations of the patient's phenotype. For instance, a laboratory report might suggest that the patient should have a different blood type than he or she actually did, or that the patient could not be the offspring of his or her parents.[4] Instead, the evidential question in the clinic was one of attribution: Was the mutation (now presupposed in terms of its existence) accurately described as, say, disease-causing?

For this reason, greater scrutiny was given to propositions made within the context of laboratory work. In order for genetic information to be appropriately interpreted, it needed to be backed by explicit evidence, which came in a number of forms. This produced an interesting circumstance: In the laboratory, genetic information was formulated with greater specificity while nonetheless being viewed as less reliable. In the clinic genetic, on the other hand, results were relatively vague

[4] This was different from concerns about the actual pathogenicity of a particular genetic variant. This latter concern was one of 'attribution,' of correct interpretation of actually present variants, rather than of 'reference,' or the existence of those variants. I return to this distinction below, through the native lens of "description" and "nomenclature," respectively.

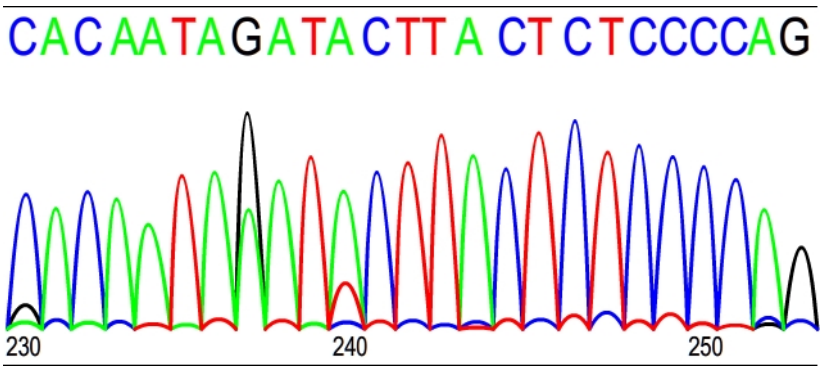

Figure 5.2: A chromatogram, demonstrating the first determination of a genetic sequence.

and yet clinicians presupposed their validity. Discovery in the laboratory was exploratory, gathering data so as to come to 'knowledge' about a potential entity. This knowledge then became objectualized and extracted from the webs of evidential warrant that constituted its reality within the laboratory.

Before elaborating these epistemological issues' expression in linguistic form, it is necessary to understand in more detail the transduction and reduction (cf. Hanks 2010) of 'raw' genetic data into 'cooked' (Lévi-Strauss 1983) clinically relevant evidence. The ritual goal of sequencing was to discover true genetic information about a patient and then to "interpret" those findings so as to ascribe them significance within a paradigm of biomedical causation.

During the testing of a patient's sample, specifically genetic data first emerged in the laboratory as a result of sequencing. Those data first took the form of peaks on a chromatogram (see Figure 5.2). Each color-coded line represented the presence of a particular nucleobase – cytosine, guanine, adenine, and thymine (or C, G, A, and T, respectively) – at a particular location. The relative height of the lines was determined by the number of "reads" that returned a particular nucleotide at a

particular locus. In order to be sequenced, DNA was "amplified" – producing thousands or millions of copies. Amplification required that the DNA be fragmented into sections (called "reads") of approximately 100 base pairs and then reassembled according to the similarity of each particular read's sequence to the "reference genome," a digital collection of DNA from multiple individuals.[5] For a number of reasons – including misalignment with the reference genome and faulty chemistry – different nucleobases could appear at the same locus in different reads. The nucleobase with the greatest number of reads at a particular locus was determined by machine, and a letter (corresponding to the best-represented nucleobase) was annotated at the top of the chromatogram. Lower peaks represented nucleobases that were sequenced less frequently at the same locus.

The next step in the data's transformation was the determination of abnormal segments that could potentially be the cause of the patient's disorder. Bioinformaticians produced a variety of different algorithms in order to seek out known pathological mutations (that is, nucleobases or series of nucleobases at particular loci described in patients with similar phenotypes) or mutations determined "*in silico*" (that is, using computer modeling) to cause potentially pathological changes to protein production. For instance, even when no previous

[5] The reference genome was skewed in terms of the populations it represented with its averages. It was common for specialists to dismiss clinical descriptions of mutations based on the reference genome when the patient was of, e.g., African descent. Statistics supported these interpretations. One study (Lebo and Grody 2007), for instance, showed that the recommended genetic panel for cystic fibrosis was sensitive for patients with northern European ancestry (90%) but much less sensitive for those with African ancestry (69%). Some mutations considered to be disease-causing in one population had even been found to be entirely harmless in others (Myles et al 2008).

data were available on a particular mutation's phenotypic consequences, it could cut off (nonsense or truncating mutation), change (missense or nonsynonymous mutation), or affect the transcription (frameshift mutation) of the amino acid it encoded in a way predicted to damage the subsequent protein's biological function in the cell. Different tests used different algorithms to limit the number of genetic variants under consideration. The first algorithmic sweep would yield hundreds of thousands of candidate mutations as possible causes of pathology. In the case of one patient, the first sweep returned 317,973 candidates. Subsequent algorithms would filter using different parameters to reduce candidate mutations further. In the case mentioned above, the second sweep returned 757 candidates, the third returned 134, and the fourth reduced that number to just 20. These variants were "called" by the algorithms, meaning they were annotated with a description, qualifying the likelihood or certitude that they were indeed the cause of a particular disordered phenotype.

An assemblage of human actors then gathered to "interpret" these data. Pathologists, biologists, and bioinformaticians – among others – consulted published medical and scientific literature on various mutations. Predicted phenotypic outcomes of reported variants were compared to the patient's actual phenotype as presented in his or her medical record. This was a particularly productive modality for reducing candidates, because the machinic algorithms could only filter mutations using a predetermined and limited set of discrete phenotypic categories (called "phenotype ontologies," see Chapter One). A patient's actual presentation of disorder was recorded with much greater detail and nuance in a clinician's free-

form description. Variants that appeared relevant due to gross similarity in their predicted phenotypic outcomes but failed to be applicable under more fine-grained comparison were removed from the list of candidates. In the aforementioned case, this step reduced the number of mutations from 20 to four.

The final step in the transduction was the case conference. Here an even larger and more diverse group of experts assembled in order to determine recommendations for the future of the patient's healthcare. In the vast majority of instances, the official recommendation was for further testing to determine the relationship between mutations, the proteins they produced, and the actual expressed and experienced symptoms of the disorder under investigation. Attendees brought to bear personal anecdotes, journal articles, and scientific judgments in order to further qualify, reject, or elect the remaining candidate mutations before making their recommendations to the patient in a session called a results disclosure.

In the case conference, claims of uncertainty not only manifested boundaries between professional domains but also between human and machinic interpretations. Clinicians regularly contested *in silico* diagnoses as mere possibilities, criticizing the evidence on which the algorithms had calculated them. "I'm not sure that this [mutation] can be associated with such a severe phenotype [as the patient has]," one geneticist said in very typical fashion, rejecting the certitude of a laboratory report. Pathologists would often temper claims of pathogenicity when they were based on functional features of a mutation, such as protein truncation, which were often treated as definitive by variant-calling

algorithms. “We have seen a lot of truncating mutations that still express the wild type,” one cancer biologist complained during a case conference. “It doesn’t necessarily mean it’s pathogenic.” At another case conference, a laboratorian noted that three different algorithms had been run, and each returned incommensurate results, stating that a genetic variant was, variously, “tolerated, probably damaging, and disease-causing.” This comment drew ireful laughter from the audience of human experts. If the algorithms were to be believed, they should not have returned such radically opposed calls. The anxieties addressed by these types of comments were particularly potent because of the intention to ‘mainstream’ genetic testing, eventually removing human interpretation almost entirely (see Introduction).

Sociolinguistic Overview

There was significant change in the evidential roles played by the genetic test results as they were transduced from laboratory to clinic. What was required for their felicitous deployment in conversation as entities with sufficient truth-conditional warrant shifted. What warrants they in turn could provide for social and medical action also shifted. These shifts were paralleled by shifts in linguistic practices used to refer to the results, which took the form of two discrete sets of codes. The first, locally called “nomenclatures,” were naming systems used to pick out a genetic variant while providing information regarding its genotype with varying specificity. The second, locally called “descriptions” or “variant calls,”[6] were

[6] The latter phrase was most common in speech but has the potential to be confused with Variant Call Format (VCF), a digital bioinformatics text file used to convey raw

systems used to correlate genotype and medical phenotype. Descriptions qualified mutations as pathogenic or benign, marked with varying degrees of certainty.

Although cleanly differentiated, the two systems were not isolated from each other in semiotic practice. Nomenclature interacted with descriptive systems in the composition of a proposition's pragmatic effects. Specific qualities relayed by nomenclature could reduce or enhance the potency of a descriptive label. I return to this topic at the end of the chapter.

Both descriptions and nomenclatures existed in a state of significant synchronic variation. Description systems varied in localized fashion, in a dialect-like distribution across different institutions and different laboratories. Typologically, they all constituted their modifiers along two axes, viz. pathogenicity and certainty (see Figure 5.3). They differed in terms of the number of points along this parabola and the lexemes used to denote those points. The code most commonly used in the Center consisted of a five-point scale: pathogenic variant, likely pathogenic variant, variant of uncertain significance (VUS), likely benign variant, and benign variant. Some laboratories recognized six distinct points along the parabola, and a genetic counselor told me others recognized as many as seven, each with finer gradations of pathogenicity and certainty. The standards by which a variant was called pathogenic or of uncertain significance also varied by laboratory. This was a site of regular distress in case conferences, where multiple laboratories were regularly employed for testing, and – more significantly – clinicians were often unaware of the criteria for such calls in the first place. Clinicians queried

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genetic data, which I discuss below. For that reason I prefer to use the vernacularly less common but also less ambiguous "descriptions" as the label for this set of codes.

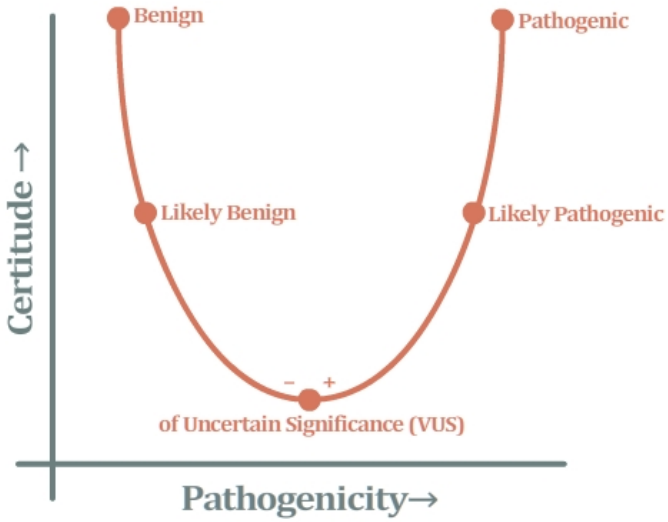

Figure 5.3: A five-point scale used to provide descriptions for genetic test results.

laboratorians as to the rationale behind the assignment of particular descriptions and disputed them aggressively.

There was also enormous synchronic variation among nomenclature systems. In what follows below, I describe the five major systems – FASTQ, Variant Call Format (VCF), cytogenetic nomenclature, molecular genetic nomenclature, and "symbols" (examples of each are given in Figure 5.4 for comparison) – used in the Center in some detail so as to demonstrate the disparity in their abilities to convey any specificity and quantity of information about the test results that they named. In terms of variation, however, it is sufficient to note here that each of the five systems was tethered to particular contexts of uses. FASTQ names were produced machinically and were used only for determining the likelihood that a particular nucleobase was not an artifact or noise, i.e., that it was "real." VCF files listed only the mutations returned by the test. Cytogenetic nomenclature was relatively rare but could be used within the laboratory and in specialist publications. Molecular

Comparison of Nomenclature Systems	
FASTQ	@EAS139:136:FC706VJ:2:5:1000:12850 1:Y:18:ATCACG GATTTGGGGTTCAAAGCAGTATCGATCAAATAG + BBBBCCCC?<A?BC?7@@???????DBBA@@@@A@@
VCF	chr17 43094464 rs1799950 A G 29 PASS DP=100
Cytogenetic	46,XX.ish[hg19] ins(15;17)(q22;q21q21)(PML+,RARA+)
Molecular	c.1521_1523delCTT
Symbol	*BRCA*

Figure 5.4: Comparison of nomenclature systems

genetic nomenclature was given in PowerPoint presentations at case conferences and also appeared in publications. Symbols were the most prevalent nomenclature forms in casual and clinical speech. That is to say that there was significant and regular variation within the institution of the use and utility of these codes.

Code choice varied by context. Other than symbols, nomenclature systems were primarily written rather than spoken. Appropriateness was determined by the circumstances of use – PowerPoint, published articles, laboratory reports – with particular regard to the intended audience of the text. That is, the presupposition of background knowledge conditioned how much specificity was required of the proposition. Ease of use also conditioned code choice, though, with longer and more detailed systems utilized less often or more deliberatively. Once an elaborate nomenclature, such as a cytogenetic name, had been given, the previously provided

information about the result's specificity could be presupposed in the common ground and more simplex nomenclatures could begin to be used.

As test results moved from chronologically most proximate to the act of sequencing to chronological most distal from it, nomenclatures systematically became less morphologically complex while the use or accompaniment of descriptive labels became more prominent. This referential simplification or reduction paralleled the transformation of research data – losing its specificity relevant only to "academic" pursuits – into clinical knowledge (see Chapter Four). This transduction consisted of the removal from the form's explicit structure of those elements seen as sufficiently justified by specialists so as to be presupposed (e.g., whether a variant in fact existed) or erased (e.g., at which specific locus a mutation had occurred). These data were adjudged either useless for or meaningless to the intended audience. A general practitioner, for example, would be expected neither to understand nor to need to understand the reliability of a particular sequencing technique when it had already been certified by the scientist reviewing the results. Much of this transduction was initially done machinically, by computer algorithms making statistical use of "big data." These algorithms were viewed by specialists with degrees of skepticism that varied both by the professional caste of specialist and the specific type of algorithm. The latter skepticism in particular becomes important to my analysis of the codes' morphological structure below.

Contemporary Varieties of Code

In this section I describe the five prominent forms of nomenclature mentioned above. They differed radically from each other in terms of what information they obligatorily or optionally encoded or foregrounded. They also differed in the specificity of information they conveyed and what information they could bear at all. I consider first one of the most morphologically complex of the systems, viz. FASTQ, and proceed in steps to the least, viz. the "symbols."

I. FASTQ Nomenclature

FASTQ was the first way in which a DNA sequence was encoded digitally. An example of FASTQ is presented in (1a–d) below.

(1a) @EAS139:136:FC706VJ:2:5:1000:12850 1:Y:18:ATCACG
(1b) GATTTGGGGTTCAAAGCAGTATCGATCAAATAG
(1c) +
(1d) BBBBCCCC?<A?BC?7@@@@@@@DBBA@@@@A@@

Each "read" was given a particular sequence identifier, presented in the first line of the item (1a) following the at sign <@>. The second line (1b) consisted of the actual sequence of nucleobases in the read, represented by their abbreviations A, C, T, G. This was called the "short read" as it merely represented a segment of DNA or "read." The third line (1c) contained solely a plus sign <+>, connecting the read with the "quality score" in the fourth (1d). The quality score was made of an equal number of characters to that of the read, with each nucleotide paired with one of 93 ASCII characters. The score character represented the statistical probability that the nucleobase "called" in the read actually existed as such in the physical DNA

sequence. The probability was determined based on the peaks represented above in the chromatogram (Figure 5.2). The lowest quality calls were represented by non-alphanumeric characters, while the highest quality calls were represented by minuscule alphabetic characters.

FASTQ names therefore inflected two points of information: specific nucleobase and epistemic status. Locus information emerged as well, though only syntactically. The reads were structured iconically, with each character in graphic space paralleling each nucleotide in genomic space. (Quality scores then followed diagrammatically.) The referent of the code, therefore, could only be determined through the combination of the paradigmatic contrast set of nucleotides and the syntagmatic relation between characters (Saussure 1972). Put another way, the full significance of the read only emerged in the intersection of the axes of selection and combination (Jakobson 1960).

II. VCF Nomenclature

After its FASTQ instantiation as the bare code, genetic information was transduced into the Variant Call Format (VCF). VCF files could occasionally be returned from the laboratory to the clinic as "raw data" concerning variation from the reference genome. Data conserved in the FASTQ format that were the same as those in the reference genome were removed in the VCF file, reducing its semantic content for the sake of clinical utility. However, as a laboratorian told me, this format was still "generally unintelligible to the general population," meaning clinicians – who were not its intended audience.

An interlinear gloss of a VCF name is given in (2).

(2)

chr17	*43094464*	*rs1799950*	*A*	*G*	*29*	*PASS*	*DP=100*
CHROM	POS	ID	REF	ALT	QUAL	FILT	INFO

'Mutation from G to A on chromosome 20 at position 14370, identified in dbSNP [a National Institutes of Health-run database of genetic variation] as "rs6054257," called with high (29) certainty after having passed all filters, and with 100 reads covering this locus.'

A full morphological analysis is presented in the Appendix (I) below. For the purposes of this chapter, however, it is important to note three features. First, VCF names only contained information regarding variation from the reference genome. Based on contemporary statistics, human beings' DNA was said to differ only by 0.1% from the reference genome. Thus a VCF file of an individual's whole genome would cover only a fraction of the full sequence. Second, VCF names continued to exhibit the call's epistemic status – giving an explicit 'quality score.' However, they additionally provided an evidential marker – viz. the number of reads at a particular locus ("DP" or "combined depth across samples"), which allowed scientists to adjudge the reliability of the call. In general, a score between 30 and 50 reads per locus was considered average, and a score of 100 reads, as described in (2), was considered high. An expert interpretation of the evidential DP coupled with the overt epistemic content borne by the QUAL morpheme determined the confidence with which the call could be mobilized in clinical care. Finally, the ID morpheme provided the first link between genotypic and phenotypic data. While not explicit in the VCF name, the unique identifier allowed the user to discover in the database more information about the variant, including its "clinical significance." (In the

above example, the database showed that the variant was a VUS but was located in a gene associated with breast cancer.)

III. Cytogenetic Nomenclature

Next, a name could be transduced into one of two systems, depending on the type of test that had returned the result in the first place. If the test sought abnormalities in chromosomal structure, it would be given a cytogenetic name. If the test sought specific single nucleotide polymorphisms, it would be given a molecular genetics name.

Cytogenetic nomenclature to delimit specific mutations began to be standardized in 1960 at a conference of genetics researchers (Denver Conference 1960). It underwent a number of subsequent changes over the next several years before coming under the jurisdiction of the newly formed International Standing Committee on Human Cytogenetic Nomenclature in 1976 (see Shaffer et al 2013:1-5). The following year the Committee produced the first complete system of nomenclature, called the "International System for Human Cytogenetic Nomenclature" (ISCN), a system that (while since modified multiple times) was still used in contemporary naming practices during my fieldwork. Because of this origin, the code was particularly tailored to laboratory work and circulated primarily among cytogeneticists. Published articles also often used the cytogenetic name, at least initially. Thereafter, authors typically switched to an abbreviated form, which pointed back anaphorically to the specificity of referent provided by the cytogenetic form.

An interlinear gloss of an ISCN name is given in (3).

(3)

46,	*XX*	*.ish*	*[hg19]*	*ins(15;17)*	*(q22;q21q21)*	*(PML+,RARA+)*
CHROM	SEX	METH	BUILD	TYPE	LOCI	PROBE

'An insertion of the segment 17q21 from the long arm (q) of chromosome 17 into the 15q22 band of the long arm of chromosome 15, identified with probes for *PML* and *RARA* genes and using in-situ hybridization.'

A full morphological analysis is presented in the Appendix (II) below. Of particular interest is that this nomenclature gave both a global and a local view of the mutation. In (3) the mutation existed in an individual with 46 chromosomes ("normal") and two X chromosomes ("normal female"). The name also provided the specific location of the mutation, jumping scales from whole chromosome to chromosomal region.

Cytogenetic names were not complete without the addition of morphemes indicating evidential support for the mutation's presupposed existence. Scientists considered certain methodologies to be unreliable or below the standard of practice. For instance, certain chemistries are known to be unable to read particular types of genetic segments. Knowing that could lead scientists to dismiss such results outright as "not real" (see also Chapter Four). The morphemes relating information on the probes and the methodology used in the sequencing would provide the astute scientist with data by which to judge whether the mutation under consideration should be suggested to clinicians as potentially causing a disorder.

The cytogenetic name in (3) included the bracketed morpheme "hg19." This morpheme was optional and bore unique but noteworthy information. It meant that the locus information provided in the name was based on the numbering of genes as

described in the 19th version (or "build") of the human genome. This was important, as more genes and more gene segments had historically been discovered with each new version of the human genome. For instance, the segment on which the gene associated with cystic fibrosis was located was originally named "exon 10" but was at the time of my fieldwork considered the eleventh exon of the gene.[7] Not knowing the build could create ambiguity with regard to the mutation's actual location within a chromosome. Providing the build tethered the reference to a stable map amidst a constant flux of numbering schemata.

As with the VCF names, the morphological complexity of cytogenetic names meant that they were not necessarily transparent in their meaning even for specialists. For instance, while discussing nomenclature systems with me, one pathologist admitted that she did not know what the methodology morpheme "enh" meant. She then retrieved a copy of the 2013 edition of the *ISCN* handbook to look it up. "Here, *enhanced*, oh!" she said when arriving at the appropriate page. "Enhanced fluorescence. Okay, I haven't seen that one [before]. So it's talking about enhanced fluorescence and that methodology." She admitted that unless pressed, she would have passed over the morpheme. Not all morphemes were important for sufficient comprehension; they became salient due to context. Knowing what part of the name on which to concentrate, she said, "would depend on what you're looking at. […] It would depend on what abnormality you're looking for."

[7] An exon was a "coding segment" of a chromosome, a length of DNA that a cell actively transcribed into RNA, eventually leading to the production of gene products.

IV. Molecular Genetic Nomenclature

Cytogeneticists looked for relatively larger mutations visible at the scale of the chromosome. Much of the testing done at the Center, however, was conducted at a significantly smaller scale, that of individual nucleobases. Molecular genetics had its own system of nomenclature to deal with such mutations. An example of this type of name is provided in (4) below.

(4) *c.* *1521_1523* *del* *CTT*
LEVEL LOCUS TYPE BASE
'A deletion of the nucleobases CTT between locus 1521 and locus 1523 at the level of coding DNA.'

A full morphological analysis is presented in the Appendix (III) below. Versions of HGVS-compliant nomenclature appeared in PowerPoint presentations at case conferences.

Molecular genetic nomenclature was regulated by the Human Genome Variation Society (HGVS), the "de facto international standard" (Berwouts et al 2011:3).[8] HGVS was standard in the sense that it provided a series of regularized criteria for describing mutations, not in the sense that it dictated a monoglot 'one-lexeme–one-denotation' attitude (Silverstein 1996). The official rules for notation did not declare mandates but rather expressed 'preferences' and methods for 'compliance.' They thereby allowed for variation in form in order to accommodate the different ends to which notation could be put. For example, including the nucleobases CTT in (4) above was not obligatory. However, HGVS asserted that in

[8] Though hegemonically standard, HGVS (and ISCN) names faced competition from a number of other systems, which I discuss in more detail below.

certain instances, "clarity can be improved by specifying the nucleotides" (Berwouts et al 2011:3).

Symbols

Finally I turn to the most common nomenclature system, and the only one that was regularly pronounced verbally. This system was made up of so-called "gene symbols." Symbols included lexical items such as *APOE4*, *EGFR*, and *BRCA1*.[9] They were spoken in case conferences and in drive-by consultations, and they were written in articles and some patient-facing laboratory reports. They were relatively analytic or motivated, in that the letters that composed the items were often derived from the names of their gene products or the disease states that they affected or effected. For instance, *APOE4* produced apolipoprotein E and *EGFR* produced the EGFR protein, or epidermal growth factor receptor. (Symbols were traditionally italicized in print to distinguish them from their products.) *BRCA1* was understood to be a major cause of breast cancer, hence its name related to an even more derived or distal product of the gene. Many other genes – such as *PARK2* (Parkinson's disease), *CFTR* (cystic fibrosis), and *PGL2* (paraganglioma) – followed this schema as

[9] All gene symbols were orthographically standardized (maintained by the HUGO (Human Genome Organization) Gene Nomenclature Committee), and most had entirely regular pronunciations. However, *BRCA* – which was one of the most commonly discussed mutations in Oncology – had a variety of acceptable phonological realizations. It was pronounced variously as [ˈbɹækə], [ˈbɝkə], or spelled out as [bi.aɹsiˈeɪ], though the first pronunciation was the most common. Others bore more limited variability. *RPTOR*, for instance, was most often pronounced [ˈɹæptɚ], but the unapparent vowel in the first syllable was sometimes realized as [ɪ] instead. It was not obvious whether a gene symbol would be spelled out or pronounced as a word. *HLBA*, e.g., was always spelled out as [eɪtʃ.ɛl.biˈeɪ], but *FLT3* was pronounced [flɪtˈθɹi].

well. In fact, as early as 1979 the Human Genome Organization asserted officially that "the name of the gene should describe the function of the enzyme" which it encoded (Wain et al 1999:162).[10]

Gene symbols were by far the most morphologically simplex of the nomenclature systems, and semantically they appeared relatively indeterminate. They were short, easily memorized, and quickly spoken – characteristics that promoted their use. Most important for clinicians was the explicit link they provided to their gene products. For clinicians, the utility of genetic testing was to determine potential healthcare interventions. Knowing a patient had a *BRCA* mutation, a clinician could immediately suspect breast cancer, or hearing that a *RET* mutation had been found, an oncologist could recommend a RET-inhibitor as treatment.

However, symbols conveyed very little information. They did not demonstrate anything other than the gene in which the mutation existed, making their referents vague relative to the specificity provided by (and in fact required of!) the genetic test. To compensate for the lack of specificity provided by such names, clinicians could also name the general mutation separately, after the host gene had entered the presupposed common ground: "He has a 17p deletion," or "test confirms t(11;14)."[11] These mutation names were still abbreviated, in the sense that they did

[10] However, many genes were multifunctional – or pleiotropic – and the first recognized role of the gene, for which it was named, was not necessarily its most clinically important.

[11] These meant, respectively, that the patient had a deletion from the short arm (p) of chromosome 17 (associated with multiple myeloma), and that the patient had a translocation of genetic material from the chromosome 11 to chromosome 14 (associated with lymphoma). Both of these particular mutations were common enough that their descriptions could be anticipated to cause no confusion among specialists at CIM. Both were also reduced forms of cytogenetic nomenclature.

not convey all potentially salient information that a test had provided. For instance, they failed to tell what specific nucleobases were affected by the mutation they named. (Genes were said to be thousands – sometimes even millions – of nucleobases long.)

Gene symbols were also often supplemented by non-obligatory, auxiliary systems as a strategy to communicate data that was – within this system – considered to be "meta-information." In PowerPoint presentations at case conferences, slides often supplemented the minimalist genetic nomenclature with separate comments (sometimes paragraph-length) including specific information about the mutation under consideration or the patient's genotype as a whole. Other characteristics that were elsewhere seen as part of the genetic information were re-designated as clinical. For instance, sex – which the cytogenetic nomenclature in (3) was denoted as "XX" – was not included on the slide labeled "Summary of Test Results" (considered genetic information) but rather on the slide labeled "Clinical History" (considered biographical information). The essential characteristics of the object had transformed as the focus of nomenclature moved from the genotype-centric goals of the laboratory to the phenotype-centric goals of the clinic.

While symbols like *BRCA* could refer to classes or types of gene – that is, the gene as it existed abstractly as a feature of all human genomes – in actual interaction, clinicians used symbols to pick out a particular mutation within a particular patient's genome. Thus, when a clinician said, "The patient tested positive for *BRCA*," he or she was clearly not saying (merely) that the patient had a *BRCA* gene, but that the patient had one of a number of known deleterious mutations within that gene.

That form was clearly underspecified in that it did not in itself provide enough information to describe a unique individual mutation; however, it nonetheless acted nominally to refer to such an individual, rather than to a class. Specificity was provided through the auxiliary systems described above or through the prior mention of a morphologically more complex name for the mutation. In this way symbols acted as anaphora, being at least partially dependent on preceding text for the resolution of their reference.

Certain gene symbols, like *BRCA1* and *BRCA2* could be reduced to just their alphabetic portions. *BRCA* could refer equally to either specific gene, despite the former being located on chromosome 13 and the latter on chromosome 17 – and despite their producing different proteins. They were merely united in their eponymous link to breast cancer. This set of symbols therefore took on a classificatory quality, not denoting uniform segments of genetic material or their proximate gene products but rather denoting the disease states associated with the genes, that is, the genes' clinical relevance.

Sociohistorical Legacies

The contemporary nomenclatures discussed above were regulated by typically international bodies, which attempted to standardize naming practices within their particular domains. This was not always the case, though. In the early days of medical genetics, each laboratory created its own nomenclature system. When the Human Genome Project (HGP) was underway in the 1990s, the remaining heteroglossia became a consternation for separate teams seeking to conduct

collaborative research. A prominent article in *Nature* called the state of nomenclature "profligate and undisciplined" ("Obstacles of Nomenclature" 1997). Even after the completion of the HGP, synonymy and homonymy continued to trouble the ever more complex and interconnected work in genetics.[12]

Some systems have continued to resist otherwise global standards. For instance, in 1964 two separate laboratories discovered the human leukocyte antigen (*HLA*) gene complex, which was important for the functioning of the immune system. It took four years for the two rival names – *LA* and *HU-1* – to be merged into one standard *HL-A* (Wain 1999:162).[13] An example of HLA notation is provided below.

(5) *HLA-A*24:02:01:02L*

Notation for the *HLA* complex obligatorily encoded information about protein production as well as information about the gene itself. The name in (5) noted that the variant was found in the *A* gene of the *HLA* complex and that the protein it produced had low (L) cell surface expression. This unique nomenclature was still used during my fieldwork because of the clinical significance of these specific data.

Similarly, the role of a group of variants called "star alleles" by my interlocutors was discovered separately by three different laboratories (Robarge et al 2007). Variants in these genes affected an individual's ability to metabolize certain drugs, and for this reason the group was also called "pharmacogenetic"

[12] In a review on the matter, Schijvenaars et al. (2005) noted that "up to one third of human genes" had more than one accepted name in the published scientific literature (2005:149).

[13] It took another seven years before the hyphen was omitted and for the modern *HLA* form to come into use (Wain ibid.).

genes. In 1999 the complexity of the genes' relationship to clinical therapy had already been recognized, and the Cytochrome P450 (*CYP*) Allele Nomenclature Committee was convened to create a standard that would reflect the medical relevance of variation in these genes. An example of star allele nomenclature is provided in (6).

(6) *CYP2D6*3*

CYP2D6 was the particular gene in a larger group of genes that encoded cytochrome P450 (CYP) proteins. The asterisk – or eponymous "star" of the star allele – separated the gene name from the particular allelic variation that had been found within the gene. The variant represented in (6) was the third reported variant in the gene to cause a difference in the function of the protein produced by the *CYP2D6* gene.

These particular genetic variants were locally standardized but escaped global standardization for pragmatic reasons. Otherwise expected names based in standard nomenclatures did not exist; they solely used these unrelated, suppletive systems. Other archaic forms – called "legacy nomenclatures" – that did not meet current standards were also occasionally heard in case conferences or seen in print. Because nomenclature systems strove to convey scientifically accurate information, they evolved alongside current beliefs about the structure and function of human genetic material. For clinicians who had been removed from the lockstep of research, modifying one's own linguistic practice appropriately could be challenging.

For example, one day during case conference, a laboratorian asked the presenting physician whether she had sequenced her patient's *NLRP3* gene. The physician said she had not, taking note that she should pursue such a test. The genetic counselor on the case, however, interrupted and said that in fact such a test had been conducted. A discussion ensued during which the physician was made to realize that the gene she had been calling *CIAS1* – which she had indeed had sequenced – was now called *NLRP3* under current standards. *CIAS1* was simply its legacy name.

Some legacy forms were so common that they appeared in parentheses behind the contemporary, standard-compliant form on PowerPoint slides. This was due to the assumption that for some audience members, the former would be familiar while the latter would be unrecognizable. Some official regulations on nomenclature even recommended the use of legacy forms to supplement current standards. For instance, Sarah Berwouts and colleagues suggested in HGVS's official journal that "Reports should include a description of identified sequence variants in both HGVS and traditional nomenclature [… which] ensures legibility and compatibility with the existing literature" (2011:3).

Codes in Exchange

The case conference was a trading zone (Galison 1997). It was the site of exchange between denizens of the laboratory and those of the clinic, whose individual purposes differed significantly within their own homes: Laboratorians sought to discover: new mutations, new chemistries, new forms of disease.

Clinicians sought to intervene: to put into practice the entities and mechanisms constituted by the scientists. "I'm not sure all [clinicians] have a deep enough understanding of genetics […] and how to use that information appropriately. And probably from the laboratory side, we always need a better understanding of the clinical side of things," one research scientist told me. "I'm not so sure that *any* of us understand the nuances of the other people's practice," said a pathologist.

When they encountered each other in the case conference, each party worked actively to come to an understanding of the purposes of the other. In order to trade, they needed to know how to market their goods, to what ends they would be put, in what form they would be legible. As a molecular geneticist explained, the most important thing for laboratorians attending the conferences was to learn "how the oncologists and hematologists are managing their patients on a day-to-day basis." That knowledge influenced what information they would choose to contribute.

The nomenclature systems represented the differing concerns of their primary users but also acted as mechanisms of exchange between the two domains. Scientific expertise and clinical expertise were relatively separated (see Chapter Four), and intelligibility across that divide was not guaranteed. As reports of mutations moved closer to the clinic, their iterations began to incorporate phenotype-centric information – such as predicted pathogenicity and correlated disorders – into their presentation. They also began to 'reduce' the scientific evidence they presented. By the time a report faced non-specialists clinicians and patients, it had already been vetted and approved by a number of science-literate experts. Moreover, data such as sequencing methodology and the specific location of

a mutation *within* a gene were understood to be meaningless to the average clinician. This information was therefore removed.

However, for the expert scientist, these data could act as critical evidence for or against the candidacy of a mutation. Because they were not legible except through specialist scrutiny, the evidential markers of source were transduced into epistemic markers of reliability. While a clinician might not know that the methodology used in whole genome sequencing would fail to pick up pharmacogenetic variants, he or she could certainly understand epistemic qualifiers such as "of uncertain significance" or "possibly benign."

Each code provided a different array of 'semiotic affordances' to the act of naming. The systems described above obligatorily encoded certain data while making others merely optional or impossible to encode. Auxiliary systems could be implemented to convey information otherwise lost in the transduction of information across codes. For instance, the FASTQ and VCF nomenclatures encoded the quality score of nucleotides – that is, they provided an epistemic marker for them. In the case conference, these forms of "raw data" were considered inappropriate and excessive. Instead, such insight about the reliability of the data was meant to be derived from PowerPoint slides that provided auxiliary information legible to the type of expertise presupposed of clinicians: paragraph-length descriptions of the mutation from authoritative journal articles, specifics of the phenotype with which the mutation was believed to be associated, disease

course, and age of onset.[14] Evidential information about methodology in ISCN nomenclature became an epistemic marker of reliability in the laboratory report.

The recognition of uncertainty was central to the knowledge practices of the Center for Individualized Medicine. Recognizing the limits of genetic medicine was a key modality by which clinicians and scientists alike asserted their expertise and controlled the outcomes of social interactions. The heteroglossic and non-commensurate codes that substantiated reports of genetic mutations in all their iterations bent to the needs of expressing that uncertainty, and were tailored such that each audience might determine its limitations based on its particular needs.

[14] Epistemic information could equally be transduced into evidential information when crossing the clinic–laboratory divide, as clinicians also had specific claims to exclusionary expertise. This did not reconstitute the source of information to which the laboratorian attended. Rather, it constituted an entirely new source of information, one specifically under the jurisdiction of clinical expertise.

CONCLUSION: TRANSLATIONAL IDEOLOGIES OF MEDICINE

Each of the chapters in my dissertation has dealt with an aspect of what has been called 'translation' in a wide variety of ways. I have discussed translational medicine, that is, the transformation of scientific practice into therapeutic interventions (Chapters Four and Five). I have analyzed linguistic 'simplification' as a form of translation (Chapters Two and Three). And I have given a sociological account of material transduction (Chapter One).

While the social practices that undergird these processes are significantly different – in particular, with regard to the metasemiotic resources available to the various actors to describe and think about their work – I have problematized in each chapter the stability of the objects ostensibly being acted upon. In retrospect, the chapters each reveal that a narrow focus on denotation cannot explain the social achievement of these 'translations.' Calibration of indexicality and illocutionary force can prove more 'essential' to their success. The patient, the blood sample, and the genetic test report were radically different in their material composition, their informational freight (their ability to signify), and their pragmatic value for an array of social interactions (Chapter One). The 'simplified' text of a Patient Education pamphlet had propositional content dissimilar to that of its clinician-produced antecedent (Chapter Two). The gene names used in the laboratory did not bear the same information or use-value as did their cognates in the clinic (Chapter Five). And yet, each of these various arrays of objects was collapsed in on itself. The patient, the blood sample, and the test report telescoped into a single referent, designated with the label 'case.' The authors of the pamphlet on the *MTHFR* gene understood it to contain "the same" information provided by medical geneticists in some significant way. The gene symbol

BRCA and the cytogenetic name 46,XY inv(9) (p11q21) succeeded in equally picking out a particular genetic mutation within an individual patient.

Despite the supposed self-sameness of the object before and after its diverse transformations, social actors involved in the process highlight the necessity of the semantic and indexical differences in its variously enacted instantiations. Even though the patient and the digital code are seen to point to the same referent, the types of information the two provide are importantly different. The digital code is not necessarily better than the patient in determining the identity of the disease, nor is the reverse true. They do, however, determine it in significantly different ways. The morphologically simplex name for a gene is not merely a reduction of its morphologically complex cognate. It provides information tailored to a different (therapeutic) context, while the latter constitutes an object with greater scientific specificity but with limited clinical description.

My analysis is indebted to a wide range of scholarship on the process of translation: Most prominently and fundamentally I engage with linguistic anthropology's theorization of translation (Gal 2015; Hanks and Severi 2014; Irvine and Gal 2000; Silverstein 2003), with a focus on the ideological and semiotic aspects of commensuration. This parallels in significant ways the work on (in)commensurability that has so interested the philosophy of science since the publication of Thomas Kuhn's famous *The Structure of Scientific Revolutions* (1962; Hoyningen-Huene; Kitcher 1982, 1995). Both literatures insist on the co-constitution of sign and context, and analyze the difficulties – even impossibilities (cf. Mair and Evans 2015; Kuhn 1990) – that that central dialogicality has for translating across paradigms or codes. I have also been informed by the institutional literature of biomedicine, which has lain claim to the phrase 'translational medicine' since the 1990s, denoting its

own heavily theorized and described process of *translating* scientific innovation into clinical practice (Fischer 2012). The Actor-Network Theory (ANT) tradition (e.g. Callon 1986; Latour 1991; Lynch et al 2005; Mol 2002) takes translation as a process whereby inherently dissimilar objects come to have legible agency within some network or social field. Key in such analysis is its focus on the coordination or choreographing (Cussins 1996; Thompson 2007; Myers 2015) goals of a given project such that action can be jointly directed and jointly productive. Here I conduct my own translational meta-coordination, bringing together these disparate texts due to their sufficiently common goals and despite their terminological and methodological differences.

However, my analysis also departs from some of the analyses presented in the aforementioned literature. Specifically, I have worked to dismantle the notion of a perduring essence preserved across translation, or at least of that essence's necessity to the act of referring and the process of identification. In order to explain, let me examine two symptomatic interpretations of translation, broadly construed in this vein. The first is the "semiological–ideological" notion of the sign as presented in Roland Barthes (1972); the second is the description of the boundary object given by Susan Leigh Star and James Griesemer (1989). Neither of these analyses has the benefit of a linguistic anthropological perspective, and I demonstrate below how a semiotic lens addresses the limitations of translation scholarship that these pieces emblematize.

Signs are bivalent in Barthes's interpretation. They can be read on two levels: semiological and ideological. In his Latin grammar book, "*Quia ego nominor leo*" means both 'because my name is lion' and 'example of predicate agreement' (1972:115-116). By semiological, Barthes intends those compositional senses that emerge relatively more text-

internally. By ideological he intends those meanings under a more expansive rubric of co(n)textuality, figuratively drawing meaning into rather than from the entextualized object. Derrida makes a similar point when he declares that *le vert est ou* means (*signifie*) 'ungrammatical' (1988:11). Because a sign (in this case, a syntagm of lexical items, or sign-partials) has material form, it can in itself be taken as an object in the first instance. It may seem odd to say that the French sentence *means* anything, even while we recognize that it can stand as an *example* of ungrammaticality. In fact, this is the point. It has an identity separate from what its constituent parts would otherwise mean individually. It has an ideological as well as a semiological interpretation, in Barthes's terms.

Barthes presents his theory in the form of a diagram, presented below (Figure II.1). The level of "language" is his semiological order. The level of "myth" is his ideological order. Barthes leaves unexamined the relationship between what he has labeled "2. Signified" and "I. SIGNIFIER." In fact, the suggestion is that the concept collapses with the sign vehicle into a sign that then is equivalent with the next-order signifier. It is "formed by a sum of signs" (1972:101). Derrida's intervention is helpful in this regard, highlighting the fact that the qualities of the meanings of the preceding sign do not necessarily rise to be meanings of the subsequent sign. For instance, the meaning of *vert* ('green') in Derrida's example has nothing to do with the meaning "ungrammatical" on its own.

I have argued that in fact the qualities of subordinate objects and the meanings of preceding terms need not carry over into later instantiations. Rather, I contend that the central organizing site of the transforming signs that I discuss is not the concept those signs are meant to represent but the sign vehicles themselves. The *labels* that stand as emblems

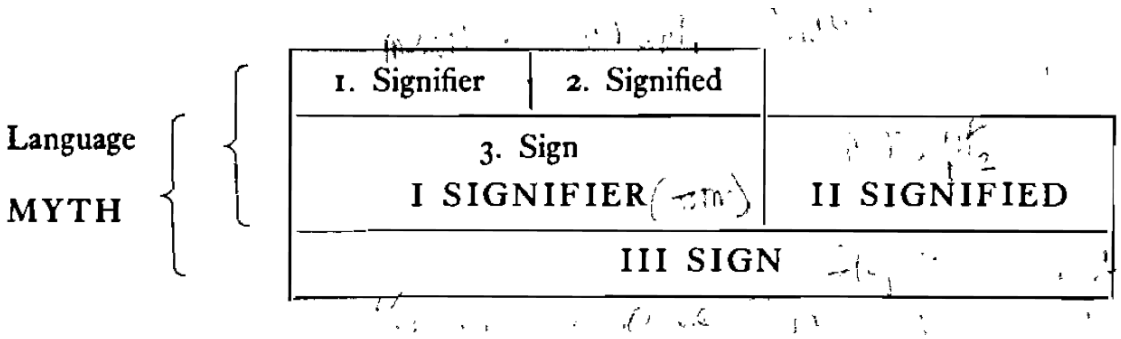

Figure II.1: The collapse of signifier–signified (reproduced from Barthes 1972:115).

do the coordinating work. It is not that there is a recognized qualitative similarity between patient and test report or some minimum threshold of essence that constitutes their identity. Rather, they are equated in the act of naming; their identity is performatively constituted through their mutual nomination. Although socially understood as an act of translation – that is, as a transformative process enacted on some perduring object – we might instead analyze it as an act of commensuration – that is, the making-equal of two separate (albeit dialogically engaged and emerging) objects. This semiotic argument has significant analytic consequences for the canon of sociocultural studies of biomedicine.

To understand those consequences more intimately, let us consider the boundary object. This is an object that inhabits "several intersecting social worlds *and* satisf[ies] informational requirements of each of them" (Star and Griesemer 1989). It is not entirely dissimilar from Kathryn Woolard's notion of the bivalent word, in which a single socially recognized sign vehicle "'belong[s] equally, descriptively, and even prescriptively" to multiple "codes" (Woolard 1999:7). That is, it has a mutually recognized discreteness in form but a multiplicity of distinct intensions and values based on the framework within which it is interpreted. The boundary object sits between social worlds and is ascribed

disparate meanings embedded in disparate systems of indexically presupposed background knowledge. Because the object appears on its face to be 'the same' to all parties despite their different intensions and intentions for it, the object can equally be a site for heated dispute or unrecognized confusion.

Of fundamental importance, though, is that the object stands as a thing-in-itself. It hangs together regardless of the different presuppositions that constitute it as socially meaningful. This is a central necessity for the ontology of much sociology stemming from Michel Callon's (1986) and Bruno Latour's (1987) path-defining work in the social studies of science. In the mode of Actor Network Theory, stability is presupposed of nonhuman 'actants.' Although they may be taken up in different ways, their essence somehow survives across transformations as it continues to act on the world (social and otherwise).

Annemarie Mol does much work toward this end, demonstrating the multiplicity of ontological understandings of the human body in disunited medical science. "Coordination into singularity doesn't depend on the possibility to refer to a preexisting object. It is a task" (Mol 2002:70). However, Mol's notion of enacting disease still represents an (albeit emergent) object in the shared common ground around which multiple actors can congregate. The different enactments "need not be the same" (ibid. 115), but they still represent "a single multiple object" (ibid. 142). "Incompatibilities between objects enacted […] disappear into the background" (ibid. 115), characterizing such an achievement as ultimately and transcendently possible.

I push this mode of analysis further. There need not be conceptual compatibility between the commensurated object's *multiple* avatars. As I discussed above, what is key in the social success of the forms of translation in the preceding chapters is the equation of

materially and semantically dissimilar objects under a nominalist (Hacking 2004) sign vehicle. This marked dissimilarity is erased in two ways. First, the disparate constellations of presuppositions that give an object value are black-boxed (Latour 1999). They are decontextualized and entextualized (Urban 1996), and the object comes to stand as a thing-in-itself. Second, the objects are collapsed into each other; the qualities of one instance become latent qualities of all other instances. These qualities can in fact be recognized to be mutually exclusive or incompatible, because they can be segregated into different material realizations.

The semiotic analytics of intertextuality and interdiscursivity are productive in understanding this process of translation. Interdiscursivity entails the trope of movement across time and social space. It is both temporal in its realization and directional in the relation between its instantiations. In an interdiscursive chain, "semiotic tokens […] appear to 'move' from point A to point B in some culturally conceptualized deictic plane" (Harkness 2010:142). This is generally contrasted with intertextuality, which entails a sort of co-presence and synchronicity. Intertextuality foregrounds the social-contextual aspects of the event being indexically presupposed, while interdiscursivity focuses on the 'forward' or 'backward' directionalities of the event.

If we take an object under translation as a sort of event or text (Smith 1978), we can use these analytics as a way to understand how the object comes to stand as an instantiation of a simultaneously more capacious and more limited concept or form. The object in such an instance can be taken as a token-sourced (Silverstein 2005; see also Dunn 2006) chain. Through indexical *renvoi,* interactants can ascribe qualities that are not apparent in the object's current instantiation. Through its specific enactment as

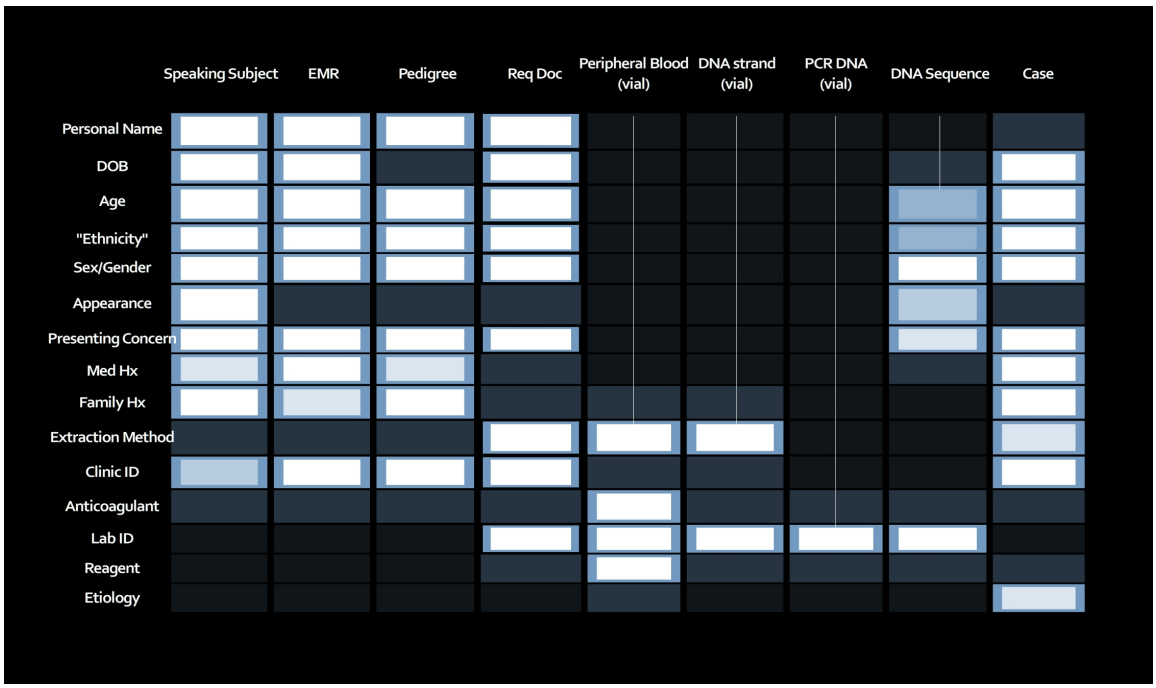

Figure II.2: Transduction of qualities in a patient's case.[1]

interdiscursive, its qualities can be linked chronologically, maintaining its instantiated essence but accounting for non-commensurable and particular accidence within the same chain as well.

In what follows, I turn to specific examples from the monograph. With these examples I demonstrate the ways in which this semiotic analysis provides distinctive insight into the diverse processes of translation I have described. I begin with the first chapter, "Signs of Disease," in which I discuss the recruitment of numerous radically different materials into the project of diagnosis and their translation into a singular object, viz. the named disease. Some other scholars of science and technology have attended to similar processes (Latour 1999; Lynch et al 2005; Mol 2002); however, they are limited by

[1] EMR = electronic medical record; Req Doc = requisition document; PCR = polymerase chain reaction

their theoretical inattention to language (cf. Wolfgram 2016). In particular, I focus on the way in which language itself gets objectified, allowing for the ever-changing universe of material 'things' to be stabilized with a direct reference to the realm of perduring identity.[2]

I demonstrate that the various instantiations the patient's case takes on fluctuate widely in their potential to represent certain qualities. In Figure II.2 I have visualized these transformations to highlight the flexibility with which the case is transformed all while successfully maintaining its socially recognized self-sameness. The case is instantiated and subsists in material forms that along these dimensions of manifest qualities might seem inherently dissimilar. However, I argue that the translation of the case – the commensuration of each of its instantiations with each other – hinges not on an isomorphism of qualities but on the ritual success of consecutive performative nominations. The object is made identical by baptismal *reconsecrations*, multiple ritual redundancies, concretizing the object as the scope of an interdiscursive chain of materially distinct instantiations.

In my second chapter, "You Become Everyone," I analyze the production of pamphlets on medical conditions and interventions for a lay public. An initial text – in an abstract sense – is produced by clinical specialists. This is then translated, or "simplified," by the writers of Patient Education, who transform it poetically while maintaining that it has not been significantly altered in terms of its propositional content. While claims for the success of translation in the preceding chapter came from those authorized to speak in the name of scientific validity and accuracy, successful simplification was certified by writers, who made claims to a text's successful instantiation of genre.

[2] See also Nakassis (2013) and Silverstein (1993) for discussions of the calibration of material instantiations with socially recognizable types.

Various quantitative measures tested the text's adherence to target code norms, such as reduced morphological complexity, simple syntax, and an uncluttered graphic space. Most fundamentally, however, I have argued that translational success was primarily judged by the presupposed qualities and charismatic authority of the text's author rather than by its internal characteristics. That is, commensuration and appropriate genre-instantiation were determined based on the text's indexical qualities, its interdiscursive links to particular personhoods and an abject trust in such personhoods' ability to "simplify."

My third chapter, "Bad Affect," continues to consider the process of simplification but turns its focus to the future lives of the texts, to their imagined social efficacy, to their ability to bring about behavioral change and medical compliance. Here meaningful context is expanded from denotation to uptake. Here the process of translation – even as emically construed – turned not on what was being represented but on how it was being represented. Success was determined not (merely) by the accuracy of the propositional content but (also) on the appropriateness of the behaviors and affects its authors imagined it to motivate.

Translation as analyzed in this chapter is about the transformation of a text into an action. That is, it is a tailoring of the form of a proposition (its translation) such that its uptake can be determined beforehand. Key in this process is the deictic realignment of the writer's subjectivity with that of the imagined reader (also discussed in Chapter Two). Translation is regimented not merely by semantic equivalences between codes, but by a pragmatic alignment of – to paraphrase Michael Silverstein (2003:86) – shadow apparatuses of cultural encyclopedias, of different goals and cosmologies. This is what the

sociologists of science in their formulation of translation call "enrollment" (e.g., Callon 1986). Writers and clinicians worked to construct texts not so much with the purpose of getting their audiences to understand the details of what was being recommended. Instead, they constructed texts so that their audiences would feel compelled to act (especially, compelled by themselves or by their circumstances rather than by the author of the text).

The ritual of *informed* consent as fundamentally metaphorical. Clinicians and writers alike determined the successful translation of an educational text (say, a pamphlet or a meeting with a genetic counselor) by the subsequent actions and affects of the patient, not by a surveillance of denotational transference. A translation was deemed successful if it inspired appropriate hope and compliance with medical recommendations, not if, say, it allowed the patient to reiterate the relationship between chromosomes and genes, the "central dogma" of medical genetics.

The fourth chapter of this dissertation, "Ethics and Epistemics," examines what my interlocutors at the hospital called "translational medicine." The form of medical genetics with which I worked, called individualized medicine at this particular hospital, was located in the liminal space between laboratory science and clinical therapy. This chapter deals with the transformation of scientific knowledge and practice into forms that were useful and explicable to healthcare practitioners. Not only were the conceptions (Ezcurdia 1998) of the technical objects transformed in this process; the fundamental category of knowledge with which they were apprehended was re-evaluated as well. That is, not only did scientists modify their practice to fit the parameters of the clinic (the *medical* in "medical genetics"), they also tailored their thresholds for what kinds of results would count as accurate and valid.

As described in the previous chapter, much of translation's success hinges on the alignment of goals between translator and audience. For laboratorians working on genetic tests, it was simultaneously difficult and necessary to determine what aspects and qualities of their work would prove fruitful in clinical practice. For healthcare practitioners, the same was true regarding how they formulated clinical descriptions of patients sent to the laboratory and how they put into practice scientific recommendations.

But this was not merely an issue of coordinating interests (interessement); it was a negotiation of concepts and essences. How severely could a concept be distorted before it no longer could maintain its identity? When could the authorizing scientific discourse no longer recognize the object it had originally baptized? This was also the core translational issue of 'mainstreaming' individualized medicine (discussed in the Introduction). Translation of genetic tests – their uses and their results – for the general practitioner required something like the simplification described in Chapters Two and Three. However, greater care was given to semantic equation in this instance. Unlike lay patients, general practitioners needed not only to act a particular way (follow a recommendation) but also to understand at some level why they were acting in that way so that they could repeat that appropriate action in future, analogous instances. For instance, a patient did not need to understand what a variant of uncertain significance (VUS) was in order to receive a clinically indicated genetic test. Contrarily, it was necessary for a clinician to understand VUSs and their implications in order correctly to refer a patient (see also Chapter One) or to interpret his or her results. For example, it was a constant frustration for specialists that general practitioners continued to order *MTHFR* testing years after scientific consensus rejected its recommendation (see also Chapter Two). The general practitioners did not

understand enough about *MTHFR* testing for its 'mainstreaming' (translation) to be considered a success.

In Chapter Five, "Evidence, Confidence, Fact," I elaborate on the variable conceptions of knowledge circulating within the clinic and laboratory and analyze the translation of genetic nomenclature as it circulated between professional worlds. I argue that claims about non-knowledge – about the limits of scientific knowledge and its practical applications – came to be key modalities by which specialists enacted their expertise. Assertions about and representations of genetic material thus varied in according to different forms of expertise due to how much of their significance was to be drawn from those different forms. The two poles of expertise were – as evinced in the preceding chapter – that of the laboratorians, with their goal of scientific discovery, and that of the clinicians, with their goal of therapeutic intervention.

This ethical and epistemic distinction was embedded in the pragmatics and morphology of the various nomenclatures used to name specific genetic mutations. I describe five such codes, though there were of course more codes as well as gradations between them, paralleling the multiple subspecialties which utilized the names in their work. Name morphology varied significantly between codes. Even while referring to the same entity, the specific definitional entailments of a mutation's conception varied based on what semantic information was borne by these often-unique nominalizations. For instance, a particular mutation could be denoted (as mentioned above) either as *BRCA* or as 46,XY inv(9) (p11q21). Both terms could be used to refer to the "same" mutation within a specific individual's genes; however, the former demonstrated that the mutation was linked (presumably pathologically, that is, causatively) to breast cancer, while the latter

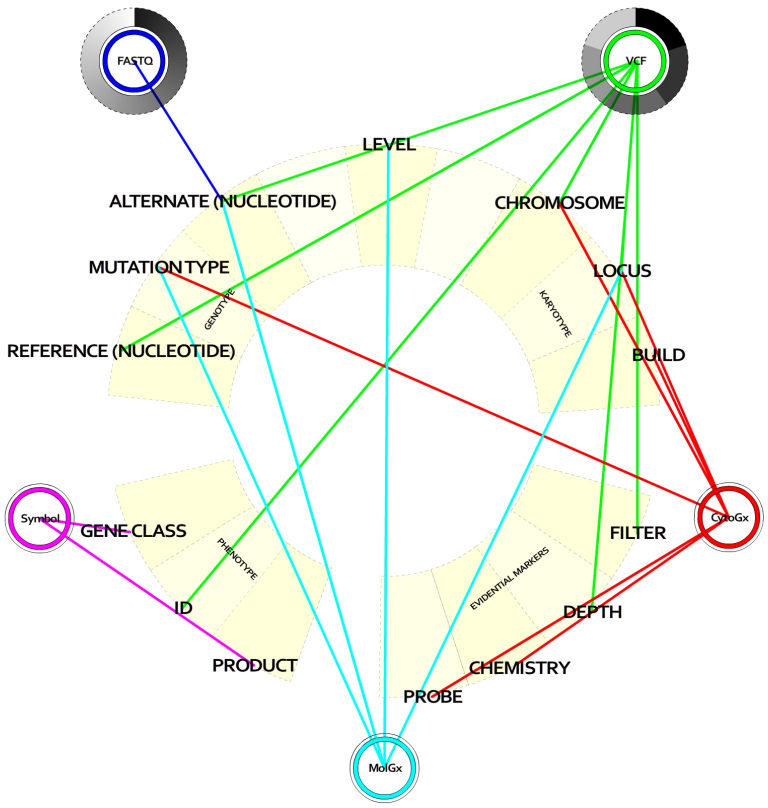

Figure II.3: Polymorphisms of evidence.

made no claims to phenotype but did provide specific locus and mutation information about genotype. Each nomenclature differed in which qualities it obligatorily or optionally encoded (see Figure II.3). *BRCA* (the gene symbol) was the name used in the clinic, while 46,XY inv(9) (p11q21) (the cytogenetic name) was what was used in the Molecular Genetics laboratory. I have argued that the distribution of nomenclatures directly mirrored the utility of the semantic information that each name explicitly bore.

My analysis of translation in this chapter combines arguments I have begun in the previous chapters. I demonstrate first that the gene names represented different conceptions of the mutation to which they pointed. They were linked not by an underlying

object whose particularity was mutually recognizable and appreciable to those using the different codes; rather, they were linked through linguistic practice itself, through the performative identification of these different conceptions with each other. Second, I argue that the nomenclatures were directly correlated with things external to their denotational content. The choice of code was determined by the clinical or scientific utility that the knowledge of a mutation might hold.

Thus there were 'extra-linguistic' (read: extra-referential) conditioning agents in the acts of translation I describe. Moreover, there were 'extra-scientific' strictures as well. In Chapters Four and Five I establish that clinical utility was significantly non-identical with the goals of "merely academic" science. In Chapter Three I show that the success of "simplification" did not depend on patients' understanding of medical science or its goals, but rather on its ability to motivate their behavior through *anticipatory affect management*. Translation in such instances thus rested on neither a referential nor a scientific platform. Finally, in Chapter Four I discuss the ways federal practice guidelines constrain the transformation of scientific practice into medical interventions, and the ways insurance plays into the translation of test results into clinical recommendations. Such externalities demonstrate that any analysis of the process of translation requires a broad understanding of how context conditions the text itself.

While the forms, personnel, and goals of social action differ across the chapters of this dissertation, they are unified in their focus on the semiotic process of 'translation.' They demonstrate that a subsequent sign is not "a sum of [the] signs" preceding it (contra Barthes 1972:101); rather, the sign can be opaque and stand (*qua* sign vehicle) as an organizing site for social action of its own. Semiotic attention to such coordinating behavior

is thus significant for all forms of translation scholarship, from science and technology studies to the medical sciences themselves.

APPENDIX

(I) *chr17* *43094464* *rs1799950* *A* *G* *29* *PASS* *DP=100*

CHROM POS ID REF ALT QUAL FILT INFO

> 'Mutation from G to A on chromosome 20 at position 14370, identified in dbSNP [a National Institutes of Health-run database of genetic variation] as "rs6054257," called with high (29) certainty after having passed all filters, and with 100 reads covering this locus'

The first morpheme (CHROM) in VCF notion represented the number of the chromosome on which the mutation under discussion was found. Humans were said to have 23 paired chromosomes, each of which had a standard numeric label. The next element (POS) further specified the mutation's location, relative to the chromosome. The identifier morpheme (ID) provided a unique identifier to find the specific mutation on dbSNP. The syntactic order of the next two positions was important: The first (REF) represented the nucleobase as described in the reference genome, while the second (ALT) represented the "alternate" nucleobase as it was called by the algorithm. The next two morphemes provide epistemic and evidential information, respectively. The first (QUAL) as the quality score, which was given using the Phred scale. That scale emerged from a logarithmic calculus whose values ranged approximately from 4 to 60, with the higher scores indicating higher predicted accuracy of the call. The following morpheme (FILT), viz. the filter status, noted whether has passed all or merely some (or none) of the algorithmic filters described in the chapter above. Again, the greater number of filters passed, the greater the implied accuracy of the call. However, unlike the quality score, this morpheme provided specific information about types of evidence rather than an

explicit judgment of probability. The final element (INFO) could provide a wide variety of additional information about the call, but most demonstrated further evidential material: the number of reads at the particular locus, the acknowledgement of the mutation in various databases, its presence in cancer (somatic) or normal (germline) tissue, etc.

(II) *46, XX .ish ins(15;17) (q22;q21q21) (PML+,RARA+;RARA+)*

CHROM SEX METH TYPE LOCI PROBE

> 'An insertion of the segment 17q21 from the long arm (q) of chromosome 17 into the 15q22 band of the long arm of chromosome 15, identified with probes for *PML* and *RARA* genes and using in-situ hybridization'

The first two elements in cytogenetic nomenclature (or ISCN) provided a global look at a patient's genotype. The first morpheme (CHROM) represented the number of chromosomes found in a particular cell. This was normally 46, but numbers could vary due to cancer or congenital disorders such as Down syndrome. The second morpheme (SEX) denoted the sex chromosomes. "Normal females" had XX, while "normal males" had XY. Variations took the form, e.g., XXY (Klinefelter syndrome), in which an "extra" X chromosome was present in the cell. When variation in number occurred in an autosome (that is, not a sex chromosome), this was indicated following the sex chromosomes, with a plus or minus sign denoting either an gain or loss of a particular chromosome. For instance, in a female, trisomy 21 – which causes Down syndrome – would be notated as 47,XX,+21.

The second and final morphemes provided evidential information. How was the mutation discovered? The first of these (TYPE) denoted the specific methodology

used in the test. The second of these (METH) provided information about the probe or molecular marker used to find the desired segment of DNA.

Finally, the fourth and fifth elements described the specific mutation. The type of mutation (here, an insertion) took an immediate argument conveying information about location (here, two place: an insertion of material from the first place into the second) within parentheses. The second element (LOCI) further qualified the information provided in the first, delimiting the material actually affected by the mutation presented in the first element.

(III) *c.* *1521_1523* *del* *CTT*

LEVEL LOCUS TYPE BASE

'A deletion of the nucleobases CTT between locus 1521 and locus 1523 within coding DNA.'

Molecular genetic (or HGVS) nomenclature was typically quite short. All lexemes begin with a morpheme denoting the "level" at which the sequencing was performed. Coding DNA was represented by <c>, while RNA was represented by <r> and the protein product of the DNA was represented by <p>. The second element (LOCUS) denoted the location at which the mutation was found. The two numbers separated by the underscore in the above example meant that mutation occurred between these two loci. The syntactic order of the next to elements varied based on the type of mutation being labeled, but in all cases a mutation type was given obligatorily and the exact nucleobases were given optionally. Deletions, duplications, and insertions ordered the syntax of the name as presented in the above example. Substitutions, however, required a syntax of the following type: a reference

nucleobase (using the same terminology as with the VCF notion described above) appeared before the function-marking angle bracket, which was followed by the mutated or alternate nucleobase. For instance, *r.67g>u* represented a substitution of a uracil for a guanine in the RNA at some locus 67. In all but substitutions, the element representing nucleobases was merely optional.

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