Original Article

Narrating uncertainty: Variants of uncertain significance (VUS) in clinical exome sequencing

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Abstract Exome sequencing is an innovative next-generation sequencing technology that examines the majority of disease-causing genes with a single test. Physicians and patients resort to exome sequencing to probe for a genetic cause of disease. The technology produces about 20,000 variants and many are of uncertain clinical relevance. Drawing from ethnographic field notes and audio recordings of over 1,500 patient cases discussed at genetic data board meetings over a three-year period, this article reports on how a collective of laboratory scientists and clinicians contend practically and conceptually with variants of uncertain significance (VUS). Rather than standardizing the inclusion criteria for a VUS, the collective contextualizes each VUS with its own evidentiary narrative. The VUS then becomes subject to revision based on evolving evidence, further testing, and updated interpretations. We argue that the epistemic uncertainty of VUS becomes productive; it indicates future causality and suggests that genetic causes can explain patients' symptoms even if no known pathogenic variants could be located.
BioSocieties (2016). doi:10.1057/s41292-016-0020-5

Keywords: uncertainty; bioclinical collective; standardization; narrative; exome sequencing; next-generation sequencing; genetic testing; laboratory

In recent years, exome sequencing has transitioned from the research laboratory to the clinic where it has been gradually introduced as a new diagnostic testing option for geneticists aiming to diagnose patients. Rather than sequencing only single genes – or more recently, panels of genes – whole exome sequencing allows geneticists to examine the majority of all presumed disease-causing genes with just one test. The exome, or the genome's exons, constitutes about 1.2 % of the human genome but is involved in an estimated 85 % of disease mutations. By using a targeted approach to sequence the coding regions of the genome, laboratory geneticists can identify about 20,000 variants in every tested person (Biesecker and Green, 2014). For a typical patient, the test yields about 10 genes with homozygous variants, 40–50 genes with compound heterozygous variants, and 250–300 with single heterozygous variants possibly related to a phenotype. If the test sequenced a trio

(typically the affected family member and the two unaffected parents), the test may find an additional 1–2 *de novo* variants (Lee *et al*, 2014).

To capture the broad interpretive range of exome findings, the American College of Medical Genetics and Genomics (ACMG) recommends the use of five genetic test result categories that reflect whether or not the variant causes the patient's symptoms: a variant is either *pathogenic*, *likely pathogenic*, *of uncertain significance* (VUS[1]), *likely benign*, or *benign*. Few labs bother communicating benign or likely benign results since these variants have little clinical value (except to exclude a diagnosis). The interpretive dilemma is drawing boundaries between pathogenic, likely pathogenic, or VUS results. The inclusion of the VUS category is particularly challenging because VUS suggests that there was insufficient evidence to classify the molecular change as either detrimental or neutral. The ACMG has defined VUS as a residual category: if a variant does not fit in the four other categories, it is by default of uncertain significance (Richards *et al*, 2015). While an elegant solution, such a guideline sidesteps differentiating 'likely' from 'uncertain' pathogenicity. In addition, it is unclear whether all residual VUS should be reported out to clinicians and patients or left off the report entirely. This matters because interpreted strictly, the ACMG recommendation could lead to potential several thousands VUS, rendering the classification meaningless for clinical purposes. If laboratories instead focus on the most promising results, they may signal the variants most likely causally implicated.

The stakes of putting VUS on the laboratory report that is returned to the ordering clinician (reporting out) reside in their clinical consequences. If the variant is not reported out, it may as well not have been observed. The variant will disappear among all the other variants of the genome that have been sequenced but not communicated. Not reporting a VUS gives a green light to the variant, stating implicitly that it is not involved in the disease. This means that the clinician and the patient have no opportunity to take action on the variant, which is problematic in a rapidly changing field where genes are constantly reassessed for their pathogenic potential. Yet, reporting the variant may have equally challenging consequences. Singling out a variant as a VUS in a report may signal a red herring by suggesting that it is involved in the patient's condition. Taken overly seriously, a VUS may become the basis for diagnosis, follow-up tests, treatments, prognosis, and may raise concerns for other blood relatives. Alternatively, reporting out a variant as inherently 'uncertain' may suggest that the variant is irrelevant and should be ignored. The interpretive dilemma facing laboratory geneticists sifting through exome data is thus to decide whether to risk misleading either by inclusion or by omission.

In this article, we investigate how a collective of laboratory and clinical geneticists manage the interpretive enigma of defining uncertainty. The staff's answer to the interpretive dilemma was to add narrative context to the VUS category and to report out possible clinically actionable genes. A VUS is uncertain in light of an external referent—something we do know. To paraphrase a master of obfuscation, former U.S. Secretary of Defense Donald Rumsfeld, to qualify as a VUS the variant needed to become a *known unknown* and not remain an unknown unknown. The variant needs to suggest at least the potential for causality and the staff must establish it in reference to things we already know. A VUS category is then

1 Geneticists use VUS both in singular and plural as a noun and a verb and sound it out as the three letters, except for one company, where employees speak about "VOUS" for Variant Of Uncertain Significance, and "VOUSES."

temporally suspended, waiting for more evidence to clarify its status. Consequently, geneticists marshal this epistemic limbo to stake out claims for genetic causality.

Bioclinical Collectives and Epistemic Uncertainty

Bourret (2005) contends that the current era of molecular sifting through the human genome for signs of pathological causality has given rise to "bioclinical collectives" of laboratory and clinical genetic experts. This emphasis on a collectivity reflects the diffusion of expertise among a wider network of people and things, instead of being concentrated among a group of experts (Eyal, 2013). Drawing on genetic deterministic assumptions (Lippman, 1991), bioclinical collectives interpret genomic test results to address diagnostic uncertainty while ascertaining causal links between genotype and phenotype.

Uncertainty, understood as the lack of knowledge about some aspect of reality, is a subjective perception occurring when available information is limited or characterized by probability, ambiguity, or complexity (Han *et al*, 2011). *Diagnostic uncertainty* raises existential questions about what is wrong or what will be wrong with a patient, which can then impact treatment, prognosis, or future recurrence risks. Clinicians and patients faced with diagnostic uncertainty solicit genetic testing to obtain a genetic diagnosis for a set of symptoms or to assess a patient's risk of disease susceptibility. Genetic testing, however, is marred by *epistemic uncertainties*, meaning findings for which the evidence falls short of known pathogenic and benign variants (Lee *et al*, 2014). Epistemic uncertainties relate to genetic susceptibility and risk, the presence of a distinct genetic cause, or the implications of a molecular cause for treatment, prognosis, or recurrence risks (van Zuuren *et al*, 1997). The bioclinical collective then negotiates the meaning of these epistemic uncertainties in order to address diagnostic uncertainty.

In most social science literature, uncertainty is viewed negatively: it leads to confusion, anxiety, and indecision (Han *et al*, 2011); it is an issue to be managed (Lock, 2011; Sarangi and Clarke, 2002); it pushes the boundaries of human rationality (Beckert, 1996); and it turns clinicians-in-training dogmatic (Atkinson, 1984). Here, we show how epistemic uncertainty can be used productively as a means to spread a genetic agenda, create new genetic knowledge, and keep patients under genetic purview. Rather than simply freezing or limiting decision-making, uncertainty generates more social action. We argue that reporting out VUS reflects a negotiated compromise between a more conservative commercial laboratory ethic to only issue known variants and a more liberal clinical ethic to let clinicians interpret variants in the ways that they consider optimal for their patients. Epistemic uncertainty acts as the proxy for establishing genetic causality, thereby expanding the turf of causal variants to explain disease when there is only a hint of such causation.

Commercial laboratories draw a clear regulatory demarcation line between the use of exome sequencing as a clinical and a research test, encouraging them to interpret clinical test results conservatively. While research involves an experimental dimension in order to produce generalizable knowledge, clinical genetic testing in the US has to fulfill stringent federal laboratory requirements to ensure accuracy, reliability, and timeliness of test results. The Clinical Laboratory Improvement Amendments (CLIA), passed by Congress in 1988, regulate laboratory testing and require clinical laboratories to be certified by their state and

the Center for Medicare and Medicaid Services before they can accept human samples for diagnostic testing.[2] Exome sequencing is considered a highly complex test and the certification process covers standards for every aspect of sequencing. In terms of reporting requirements, CLIA does not specify what qualifies as a reportable result but states that criteria for reporting out results should be made available upon request. In addition, the ACMG has issued two sets of formal guidelines related to reporting incidental findings (genomic findings unrelated to the phenotype but that may signal other risks) and reporting categories (Green *et al*, 2013; Richards *et al*, 2008). Consequently, laboratory personnel are inclined to interpret genetic test results conservatively and only report out known pathogenic results.

Uncertain genomic findings tip the results more to research than to clinically useful findings. Why, then, would members of the bioclinical collectives even consider reporting out VUS results? The answer relates to the situational pressures of clinicians facing patients searching for a cause of their symptoms. While patients may have had a clinical diagnosis for years, many still embark on long diagnostic odysseys to find a cause for their phenotype in the hope that causal knowledge may translate into prognostic or treatment interventions. Exome sequencing is often not their first genetic test but patients hope that this most advanced test may bring their search to an end. Clinicians reinforce this expectation when they evaluate the patient for exome sequencing and present it as the most comprehensive test. In light of the institutionalized expectation that clinicians can solve diagnostic uncertainty (Jutel, 2009), physicians have the professional authority to interpret exome findings and go beyond the interpretation of the report, similar to their prerogative to prescribe drugs 'off-label' (Radley *et al*, 2006). Such interpretative clinical judgment, however, is impossible if the laboratory decides not to report out the genetic variant (unless the clinician independently analyzes the raw exome data). While a known pathogenic or likely pathogenic variant makes the news delivery relatively straightforward, the category of VUS imbues a variant with lesser causality that leaves its interpretation up to the clinician. Although clinicians may wonder whether the increased availability of genomic data translates into clinically useful information (Cox and Webster, 2013), they may still want the opportunity to assess the data for themselves. The VUS category then functions as a clinical hypothesis put forth by the bioclinical collective as a possible cause of disease that clinicians can use to address the existential exigencies of diagnostic uncertainties.

The tension between the clinical and commercial laboratory worldview also centers on the primacy of the phenotype or the genotype. Genetic variants explain patients' phenotypes in clinics, but the causal relationship can be inversed in the testing laboratory. Navon (2011) outlines the rise of genomic designation, in which molecular coherence trumps phenotypical manifestations. Rather than searching for the genetic marker that creates phenotypic difference, in genomic designation molecular genetic difference is the starting point of identifying pathology. As we show below, bioclinical collectives may jumpstart genomic designations during their deliberations of what findings to report out. Dialectic feedback loops between the clinic and the laboratory drive genomic knowledge expansion.

2 Genetic testing also requires accreditation by the College of American Pathologists or the Joint Commission. The Food and Drug Administration has also begun to consider regulating genetic tests.

Faced with epistemically uncertain results, the bioclinical collective has two primary options for determining which variants to report out. They may either develop specific standardized criteria for including such variants on reports, or they may provide a narrative that specifies the grounds for reporting a specific variant. Standardization can be performed based on technical criteria, allowing for speeding and scaling up the interpretation of exome data (Timmermans, 2015). The advantages of standards include their authoritativeness, their ease of use, their trustworthiness regardless of who deploys the standard, and the comparability of results across geography and time (Porter, 1996). However, even if continuous tinkering is required in the deployment of standards (Lampland and Star, 2009), standardized decision-making tools require a priori specification of how different kinds of uncertainty will be classified.

Narrating uncertainty, in contrast, is much more time-intensive but allows for customization of specific variants. Each variant can be plotted in a context of uncertainty, delineating not only where the variant falls short but also where its promise lies and how causal ambiguity may be resolved in the future (Somers, 1994). Narrating the inclusion of VUS depends upon the scientific authority of the bioclinical collective, but the narrative creates transparency that allows stakeholders of the exome results to reject, accept, or modify this epistemic account. Resolving uncertainty with standardization or narration thus implies a different stance on genetic causality and on how it should be resolved: are causal ambiguities predictable and classifiable a priori or are they still too idiosyncratic, and should we trust standardized shortcuts or experts to render uncertainty visible?

The bioclinical collective's strategy to resolve causal uncertainty specifies both the clinical relevance and biological significance of molecular diagnostics (Cox and Webster, 2013; Bourret, 2005). Depending on the decision-making processes, the results constitute a particular view of genetic causality (its scope, variability, durability, revisability, etc.); they suggest who qualifies as a patient to be followed by geneticists, they reflect the professional jurisdiction of geneticists engaging next-generation sequencing technologies (Shostak, 2013), and they reveal what diagnostic, prognostic, and therapeutic information geneticists offer patients. Exactly because epistemic uncertainty forms the sharp edge of genomic testing (Hughes, 1945), the bioclinical collective has the potential to redefine the role of genetic causality as it affects all implicated stakeholders.

Weighing clinical and regulatory concerns, bioclinical collectives have thus a choice in whether to report out uncertain findings and how many should be reported out. They may employ more standardized or narrative criteria. Whatever their chosen modus operandi, the set of reported VUS advances a particular understanding of genetic causality. And exactly because uncertain results can be omitted or included in various quantities and based on different criteria, the collective interpretation becomes a sensitive indicator of the anticipated role genomic information will play in the future. Hedgecoe (2003) argued that lack of knowledge is no impediment to determining the usefulness of molecular diagnostics. We show how reporting out specific uncertain variants in narrative form allows the bioclinical collective to make a claim for expanding a genomic worldview, even if the genomic promise of diagnosis and treatment remains for now largely unfulfilled.

Methodology and Setting

This paper is based on 3 years of observations (2011–2014) and audio recordings of weekly data board meetings at one of the first U.S. academic centers to offer whole exome sequencing as a commercial service to clinicians. Exemplifying Bourret's bioclinical collectives, the data board meetings are modeled after tumor board meetings in which a multidisciplinary team of clinicians and laboratory specialists meets regularly to prospectively review patient cases and management decisions. Observations began during the initial meetings in which the team discussed how to set up the exome sequencing laboratory. Afterwards, observations continued for more than 1,500 exome cases (in which trios counted as three cases). This research received IRB approval.

Once the data board meeting recordings were transcribed by a professional transcription service, we analyzed the transcripts following the guidelines of abductive analysis (Tavory and Timmermans, 2014). Abductive analysis is a qualitative data analytic approach aimed at theorizing. This approach depends on iterative processes of empirical data analysis in conjunction with a broad and diverse social science literature. The three authors met weekly for 4 months to analyze all the transcripts related to VUS discussions. We coded the transcripts independently and then shared our data impressions in light of the social science, bioethical and medical literature on genetic testing, diagnosis, and uncertainty. Once recurrent themes became clear, we wrote memos that captured the different strategies team members used to get a handle on what constitutes a VUS. These memos formed the basis of this article.

Clinicians interested in prescribing a clinical exome test first conducted pretest genetic counseling with the patient and family members if the test involved a child. They then requested the test with a requisition form indicating the reason for testing and added a clinical note describing the patient's clinical symptoms. Patients being tested signed a clinical consent form and gave a blood sample, which laboratory personnel then used to extract DNA and sequence the exomes. After checking quality measures and filtering out technically unconvincing variants using algorithms, the laboratory analyst prepared the data for the data board meeting. The goal of the meeting was to decide which genetic variants played a role in the patient's symptoms.

The meetings took place in a small conference room with nine seats around a table, surrounded by a second row of about twenty seats. Usually about fifteen people were in attendance, including bio-informaticians, laboratory analysts, laboratory directors, clinical geneticists, genetic counselors, clinicians, and support personnel. This mixture of clinicians and laboratory personnel constituted the bioclinical collective interpreting the exome results. Sometimes the clinicians were specialists who referred a patient for clinical exome sequencing and could provide in-depth knowledge about the patient. In other cases, however, the team dealt with referrals and had more limited knowledge. At each two-hour meeting, the team discussed the sequencing data of between eight and sixteen patients by projecting the data in the form of an excel document on a screen at the front of the room. The data analyst – or if present, the ordering clinician – then went over a short description of the patient's clinical symptoms, followed by a detailed review of the genetic results that highlighted promising alleles. The genes under discussion appeared as rows in the document. The discussion of VUS could take anywhere from a couple of minutes to ten–fifteen minutes,

which was extensive in light of the time pressures. At most meetings, delineating VUS results was the main point of contention, bringing out differences between clinicians and laboratory staff. Although differences of opinion were common, the discussions were collegial and focused on determining the causal role of variants with appeals to scientific evidence.

The data board meeting is one of two models used in interpreting exome sequencing results. While the data board meeting follows a 'jury' model, the alternative is a 'judge' model where a single laboratory expert interprets and reports out the exome data. This model is more common in commercial laboratories but we have no information on how decisions about causality are made in these settings (articles reporting exome VUS data gloss over the interpretative process). We cannot be sure about the representativeness of our observations but the laboratory we studied advertised its data board made up of experts as a unique competitive advantage. However, social science access to the actual decision-making of genetic testing provides rare insight in the range of interpretive dilemmas surrounding VUS results and how they could be resolved collectively.

The VUS Interpretive Enigma

We begin with the discussion at the data board of a potential VUS result. The patient is a 53-year-old man with a history of Crohn's disease and bilateral calf pain. He also has difficulty walking on his toes, and has leg atrophy. Several tests for various suspected conditions have been negative. Two male relatives have similar symptoms. At this point in the discussion, the data analyst has gone over homozygous and compound heterozygous but does not find anything promising until she comes to two heterozygous variants: one the team considers likely pathogenic and a second variant that is a candidate VUS. The dialogue starts with the discussion of the second variant.

Data analyst: The other variant is in the *SCN4A* gene. This is a missense variant towards the end of the protein. We can check. It's not highly conserved. It's predicted benign, so this is autosomal dominant myotonia gene. So you don't think this fits?
Clinician: I don't think.
Data analyst: Okay, so not report or VUS?
Clinician: For the first one?
Data analyst: The first one I think is likely pathogenic. The second one; it's rare, it's in a dominant disease gene, but if you're fairly convinced it's not relevant to the case, then I don't need to report it.
Data analyst: I would sort of lean towards 1836. Sorry. I would sort of lean towards VUS. It's sort of towards the end of protein, but…
Clinician: It's no extra work. [chuckle]
Laboratory director: Only need to add it in.
Data analyst: No extra work for us, but the genetic counselors and the clinicians have work, but I don't know… There's no reason genetically why this couldn't be disease-causing. It's not present in the population. It's not…. So I think it's a VUS. And that's it.

The data analyst has found a rare missense variant towards the end of the protein that is in a myotonia gene usually inherited as autosomal dominant, which makes it a potential candidate for reporting out. At the same time, the prediction algorithm suggested the variant may be benign and the variant is not highly conserved in different species (suggestive of the variant not being that critical). Weighing this evidence after having stated initially that the phenotype associated with this gene does not fit the patient's symptoms, the clinician decides that 'There's no reason genetically why this couldn't be disease-causing' and agrees to the inclusion. The dialogue signals that if the team had viewed the evidence differently, they may as well have decided not to include the variant on the report. The question for each potential VUS result is: should we report it out or not?

The VUS category enters exome sequencing as a holdover from commercial laboratory geneticists' experience with cytogenetics, single gene tests, and panels testing a handful of genes, but its implications are far murkier in the exome context. Genes (or chromosomes, in the case of cytogenetics) included in these earlier tests had been extensively studied and clinically validated with variants strongly associated with disease. With increased test volume, testing patients for these limited genes will inevitably reveal potentially pathogenic but unfamiliar variants. The laboratory staff would report these findings as variants of uncertain significance and monitor new evidence for the variant. If the variant were subsequently reclassified as benign or pathogenic, the laboratory would issue a corrected report. Thus, even tests for *BRCA1* and *BRCA2*, the two best characterized clinical genes tested in over one million women for hereditary breast and ovarian cancer, still yield 2.1 % VUS results. Myriad, the testing company that held the patents for these two genes until the 2013 Supreme Court decision, continuously reclassifies these variants as more data become available because company scientists can keep track of the few genes involved (Eggington *et al*, 2014). In contrast, exome sequencing tests cover thousands of genes, many of which have not been associated with disease or have only been found once or twice in a patient. Rather than reporting out all VUS findings, data board members need to decide whether and how many of the VUS to report out.

The collective was aware from first-hand experience of the risks of leaving a variant off a report entirely. In one discussion, they spent a half hour revisiting the case of a young boy in which the team had originally decided not to report anything. The ordering geneticist, who was a member of the team, requested the raw data and he noticed a heterozygous variant in the *ATM* gene that was inherited from the mother. The child's phenotype could also be explained through the combined action of the *ATM* and another heterozygous variant. Importantly, the *ATM* gene could put the mother at higher risk for breast cancer. The dilemma for the clinician was that he could not alert the mother to her increased cancer risk without some information on the report. He would have no basis for talking to her and her insurance company would not approve any follow-up testing. If the report could be amended for the child with a VUS for the *ATM* gene, he could then also discuss the changed risk profile with the mother. There were many concerns with this case[3] but one of the take-home points was that a VUS was sufficient to make a variant actionable in the clinic. "If you don't report it," a clinician noted in a similar situation, "nobody knows."

3 The exome team's informed consent form did not allow for informing relatives at that time. Also, not all *ATM* mutations are necessarily actionable.

The data board team also experienced the drawbacks of putting VUS on reports. Even though a laboratory director observed "it costs zero dollars and zero cents" to report out a VUS, the inherent uncertainty of the category can create confusion. The data board members were asked several times to conduct exome sequencing for a patient who had previously received a VUS result on a single gene test. The team could not do anything but confirm that the variant was indeed a VUS. They presumed that the ordering clinicians did not know how to interpret a VUS, as a laboratory director surmised here: "I think it was one of the times where [the clinicians] read the report and saw VUS and thought it wasn't meaningful." Or the team presumed that clinicians would misinterpret VUS categorizations, "if you throw it in the VUS category, a lot of people that aren't in this room would just say that that has absolutely no significance." They repeatedly conjured a proverbial physician in Bakersfield, a city not known for medical advances. A geneticist said: "There is one thing I'm little bothered about by this reporting of [VUS]. We're having this discussion with the requesting physician in the room who's a sophisticated geneticist. If we send the same report to Dr. Doe somewhere in Bakersfield…. Would you explain a little bit?" A laboratory director responded: "You made a good point. In fact, the Coalition for American Pathologists, CAP, which is what regulates all the genetic testing and laboratory testing, mandates that when we write the reports, they have to be written in a way that a non-geneticist can understand." Finally, the clinicians and the genetic counselors on the team were acutely aware of how tremendously time consuming it could be to convey the causal subtleties of a VUS to patients and their families. Not knowing what to make of the variant had left some families stressed out by even the possibility of a genetic cause. "The most harm," a clinician noted sarcastically when considering reporting out a variant as a VUS, "is that [patients] would spend the rest of their lives freaking out. But that's okay."

The interpretive dilemma of reporting a VUS out is that the bioclinical collective could not be sure that clinicians would understand what an uncertain result meant for their patients. A known or likely pathogenic or a benign variant was relatively easy to understand but what would a clinician do with a variant that is inherently uncertain? Not surprisingly, a laboratory director suggested avoiding the difficulties of deciding which uncertain variants should be reported out by getting rid of VUS:

> *Laboratory director:* I mean if we wanna decide as a group that we're gonna sort of reduce or eliminate VUS from our reports, that's a different thing. And then we're only reporting variants that we're saying are pathogenic, known, or likely pathogenic because this group thinks they're worthy of reporting. That may assist a clinician in heightening their sense of, "I should pay attention to this." Which is what we want anyway.

This proposal, however, was unacceptable because it would void the opportunity to alert clinicians to variants that could prove clinically relevant in the future. To strike a balance between keeping track of promising VUS findings and not creating an unsustainable amount of work, the data board members opted for only reporting out a few – one or three per case – of the most meaningful VUS. Note that this was not the only possible policy decision: the team could have decided to report out 30, 100, or even more VUS. With the decision to limit the number of VUS, the collective crafted results that corresponded to Mendelian dogma in which single or a couple of variants explain phenotypes. A laboratory director

explained to a visitor: "The idea is not to spam people with data so that the meaningful things can rise."

Singling out a few variants was complicated by how a VUS differed from the other categories used to report out variants. The VUS category is circumscribed by how much it is *not* a known pathogenic variant, *not* a completely unknown variant, and also *not* likely pathogenic. Both the categories of 'likely pathogenic' and 'VUS' contain already, as a data analyst noted, "a degree of waffling." They fall short of strong evidence of pathogenicity required for a molecular diagnosis, usually an already known loss of function associated with a disease. The keyword for pathogenic situations is *known*: genetic databases such as Human Gene Mutation Database (HGMD) or Online Mendelian Inheritance in Man (OMIM) classify the variant as pathological and offer references to the clinical literature that the staff and clinicians can verify. A laboratory director explained: "Here's my litmus test. If somebody handed me a paper to review and said, 'This is the cause of this person's disease,' would I believe it based on the evidence that we're showing here?" Pathogenicity grounded in the medical literature is the least ambiguous category: it is the gold standard of which the other categories fall short.

At the other side of the certainty continuum, *unknown* variants, where the team has absolutely no idea about the gene's functionality or how it was involved in the phenotype, could still technically be reported as VUS by default ACMG standards. Their inclusion, however, caused frustration because the same term of VUS then covered a broad spectrum spanning complete uncertainty and as yet unprovable but likely implicated variants. An important difference between *unknown* and *uncertain* variants is that they are not clinically meaningful; knowing they exist does not inform any particular course of action. As a team member noted, for a new VUS that just presented new information rather than "useful new information," "we wouldn't have reported it…it's not related." For these cases, the data board may consider no information to be better than new but unhelpful information. By excluding completely unknown variants from the VUS category, the included VUS were rendered more meaningful.

Of course, it is more useful to know what something *is* than to be suspended in uncertainty, and accordingly, the data board members commented that labeling a variant as likely pathogenic is far more informative than a VUS. But variants that teeter on the edge of being 'known' or being uncertain must be categorized carefully because they can have lasting clinical implications. When discussing a patient's results, for instance, a team member noted that "the concern is if we put [a VUS variant] as likely pathogenic, that someone might think this is the sole cause of disease." If so, reporting a variant as likely pathogenic versus as a VUS could mean that the data board members may unintentionally associate the patient with a diagnosis and all of the tests and treatments that come with it. Although 'likely pathogenic' is technically not diagnostic and also assumes uncertainty, this is not the clinical reality. The team members then saw clear categorical differences between VUS and, on the one hand, likely pathogenic, and on the other, unknown variants.

The interpretive problem of VUS exome results is then to communicate the meaning of uncertainty to a physician looking for a patient's genetic diagnosis. The question is where to err: communicating any VUS may suggest that exome sequencing located a definitive cause but leaving a potential VUS off the laboratory report may forego the opportunity to provide

the clinician with information that could be relevant in the future. Both options could be justified from a clinical perspective. The collective decided to give greater weight to the anticipated clinical utility of VUS and report out a selection of the most promising variants. In a rapidly moving field where databases were updated daily with new genotype–phenotype associations, a VUS could give the clinician the opportunity to at least follow this literature. Flagging a potential causal variant also gave the appearance of a laboratory on top of the literature, which was important if the variant later proved to be pathogenic. The collective therefore adopted the solution of reporting only the most promising variants that were clearly not unknown, benign, or pathogenic.

Standardization?

Deciding which variants were promising was further exacerbated by the need to remain both flexible in deciding what epistemic uncertainty to report out and to remain consistent across cases. The data board team needed to be flexible with their criteria because a VUS is by definition uncertain; as new information comes to light, they need to be able to adjust their reports in order to account for the changes that emerge over time. Given the huge amounts of new data that become available with every test and in the medical literature, this flexibility is part and parcel of reporting uncertain results.

At the same time, the goal of the discussions about the boundaries of VUS is to develop a 'consistent,' and 'logical' set of inclusion decision points that serve as precedents for future decisions. The data board members anticipated how each decision about reporting the VUS at hand might affect their group's internal logic about similar cases at future meetings. If they chose to report a liminal variant as a VUS, likely pathogenic, or not at all, they made themselves accountable to the same choice later on in order to maintain some level of internal consistency.

In commercial laboratories, a common way to obtain consistency and still remain flexible to the task at hand is to *standardize* decision-making via operating procedures. In fact, much of the reduction of 20,000 variants produced by exome sequencing to about 300 candidates possibly involved in the patient's phenotype rested on the reliance on various standardized forms, filters, algorithms, and databases (Timmermans, 2015). The data board entertained various standards to determine how many and what kind of VUS to report out. They considered making all VUS of good technical quality available. They contemplated finding a bioinformatic solution in which variants that met certain technical criteria would automatically be reported out as VUS. They even started crafting a list of technical criteria for VUS but quickly abandoned the attempt when it became clear that standardization would lead to many missed potential VUS. Both of these suggestions would also lead to hundreds of VUS, which would only reintroduce the initial problem of saturating reports with VUS to the point of meaninglessness. They also deliberated the opposite approach of not reporting out any VUS and instead revisit cases on a regular basis to examine whether newly published information rendered promising genes pathogenic. They did not, however, institute such a follow-up system because they considered it too cumbersome to follow the literature on all these genes. Standardization was thus not feasible because uncertainty remained itself an unknown category.

Narrating Causal Uncertainty

Absence and presence of evidence

The data board members became genomic causality brokers, adjudicating whether uncertain findings are to be transformed into factual causes on a report or lost among thousands of other omitted unknown or benign variants. In addressing the interpretive enigma of uncertain findings, the team settled upon two broad criteria that led to the inclusion of different kinds of VUS results. First, a VUS implied *a presence and absence of evidence*: there needed to be a modicum of evidence that may suggest plausible pathological involvement but the evidence cannot be strong enough to establish even likely causality. Without the clinical literature as the final arbiter, the assessment of a VUS involved an entire *gestalt* of the phenotype. Each variant had some strikes against it but also some indications that suggested a potential causal role. The uncertainty needed to be specific: the team needed to know where the variant falls short. A laboratory director summarized the thinking: "I think we crystallize around reporting VUS when there is some evidence that something is going on even though it's not clinical…" The variant could still end up being benign, but the available evidence supported some plausible causality even if the causality had not yet been confirmed as pathological in humans. The team's judgement in evaluating candidate VUS was an assessment of the possible role of the variant in the patient's symptoms. Rather than a straightforward reference in the literature of the same variant associated with a phenotype similar to the patient (as in the case for pathogenic variants), the team considered more indirect evidence such as population frequency (variants common in the population were unlikely to cause a rare Mendelian disorder), evolutionary conservation score (variants preserved across species were presumed to be critical), prediction algorithms of pathogenicity, the kind of genetic change, the role of the gene in the genetic pathway, animal research, the inheritance pattern, the location of the variant in the gene, an incomplete fit with the phenotype, a partially convincing clinical journal article, etc.

Cutting down the VUS category to include only variants with some indication of pathogenicity created a new problem: *how much evidence* is sufficient for a finding to be considered a VUS versus likely pathogenic? According to the team, the statistical difference between likely pathogenic and VUS is that likely pathogenic variants are 90 % certain that the variant is causally implicated, while VUS are somewhere between 51 and 90 %, i.e., the variant is more likely than not implicated. The exact line between uncertain and likely pathogenicity depended on whether the team members wanted to populate the likely pathogenic category. In their meetings, for example, the data board members discussed whether or not to base their decision between likely pathogenic and VUS on just one previous paper. In one case, for example, a variant had been associated with one other child in the literature with only partially overlapping phenotype, and this child was a much younger girl, while the patient being tested was a boy of very different ethnicity. Was the boy the second case in the literature or were the two children too different to assign causality to the same variant? To be pathogenic, the team would look for multiple independent reports of the variant associated with the same phenotype in several families. The evidence under discussion fell short, but how short? Inevitably, even the criterion of requiring some evidence that could support a VUS classification would lead to including completely different variants

in the same category, some of which almost qualified as 'likely' pathogenic and others of which very little was known.

Without clear criteria defining sufficient evidence to qualify a finding as a VUS, the data board members opted for *narrating the epistemic uncertainty*; they provided the clinician with their rationale for why they included the variant as a VUS on the report and their interpretation of it. A laboratory director concluded a long discussion about the pros and cons of including a variant with "So interpretation should explain all the literature." Team members agreed to retain the original label of the VUS category yet redefine the form: the confusion around applying the same term to a broad range of variants was resolved by providing the clinician with a more extensive scientific narrative communicating the individual character of each VUS. The narrative could then be tailored to the case as needed, detailing why they thought the variant should be reported as a VUS and which references informed their decision. A clinician attending the meetings summarized the consensus: "Whenever we're talking about something, whatever you do, never use the term 'VUS' without explaining the context." In a case where the team only found one variant in a typically recessive gene that had, in one paper, also been reported as a dominant gene, they justified their classification as a VUS with a larger narrative that would explain the reason for the classification.

> *Laboratory director:* So, how about as a compromise, you report it as a VUS and you actually have a narrative that says, "This particular VUS was reported in this one paper… And was shown to be associated with this disease… "
> *Clinician:* That's exactly what I said.
> *Laboratory director:* And then it becomes purely semantics of whether we call it…
> *Clinician:* Exactly. It's typically recessive but has been reported dominant in one case.

With this solution, the data board members were able to achieve the balance between standardized logic and flexible decision-making; narration allowed them to maintain internal consistency with reported VUS while still having the freedom to distinguish the nuances of their findings. The VUS classification constituted a state-of-knowledge snapshot of the variant, acknowledging that evidence fell short and was still uncertain but that there was also reason to postulate that this particular variant may have pathological potential. Enumerating the reasons for and against causality provides the geneticists with flexibility to include a diverse group of variants in the VUS category. Even if the reasons for including a variant shift over time, they become traceable in the weekly group discussions as evidence-based inferences rather than wild guesses. The consistency resides in a reflexive awareness of the kind of reasons that justify inclusion as a VUS for this particular variant rather than in applying the same reasons for inclusion across variants. The team needed to wait for the literature to catch up, but as there is no guarantee that the necessary knowledge about the VUS will come to light, some ambiguity remains about whether the causal status of these variants will ever be resolved.

Clinical actionability

The second criterion used to report a VUS involved its *clinical actionability*. Actionability is a recent term in genomics that covers a wide range of possible uses of genomic information

(Nelson *et al*, 2013). Variants reported out as VUS under this criterion often had trouble meeting the 51 % threshold the team set for a reportable finding that might have a role in pathology. However, clinicians could order relatively straightforward non-genetic follow-up tests of physiological changes that might nudge the finding from unknown to uncertain. Some VUS were then reported because the clinician could check biomarkers that would be expected to be affected if the variant had a role in the patient.

The narrative contextualization of this kind of VUS resides in the recommendation to conduct a follow-up test to clarify the variant. The data board geneticists specify in their recommendation that if the variant is causal, phenotypical changes should be expected. A stronger sense of the phenotype, as revealed through follow-up testing, would dialectically reflect back on the variant and imbue it with a stronger causality. This reasoning reverts the typical genetic testing logic in which a phenotype is queried for genetic causality. The recommendation starts from a genotype and looks for the expected phenotype through follow-up testing. The VUS status may still depend on new insights in the clinical literature, but the confirmation of a hypothesis implies that the variant is doing something in this particular patient. In the following discussion involving a non-verbal 16-year-old patient with seizures and a clinical diagnosis of severe autism, team members articulated both these criteria. The data analyst found a *de novo* variant in the *SH1L* gene. The reason the variant came up was that it had been associated with intellectual disability in one patient but the phenotype did not match.

> *Laboratory director 1:* We can report the *SH1L*.
> *Data analyst:* We can report this as a VUS; there is a paper to reference. It's high quality, it's a missense, so we can VUS that.
> *Laboratory director 2:* Absolutely, I would report that one for sure. And then, they can also have the brother assessed. And that will be a tiny little bit of additional either confirmation or refutation.

Testing the unaffected sibling for the *SH1L* gene has the potential to clarify the causal role of the gene because there was in this case a 50 % chance that the unaffected sibling inherited the same variant. In that case, the variant would likely be benign. Actionable then does not require a diagnostic or therapeutic payoff but has the low threshold of additional non-genomic testing that may clarify the variant's causal status.

Classifying a variant as a VUS based on clinical actionability sets the clinician on a particular investigative path so that the variant's causal status remained suspended in anticipation of further clinical testing. The clinician becomes part of the process of figuring out the exact causal role of the variant, conducting 'research' on the patient. There is no formal 'experimental' dimension to the board meetings in the sense that exome sequencing does not translate into, for example, creating a laboratory mouse to examine gene functionality or other standard genetic research practice. The VUS aims at a different kind of 'research': the trial-and-error of clinical practice (Armstrong, 2002) where clinicians generate patient-specific knowledge by working through a series of hypotheses (for example, by sequentially prescribing drugs and seeing what most benefits the patient). For example, during one meeting in which various team members argued both in favor and against reporting out a variant, a laboratory director swayed the decision by pointing out that

checking the patient for the presence of elevated biochemical values also associated with the variant might adjudicate between benign and pathogenic status of a VUS: "The variant's not been described before, so it's possible that it's benign. So I think it's a VUS for now, then your follow-up testing will let us know whether it's pathogenic or not." The logic is that if the variant would have a measurable (but as yet unchecked) effect in the patient, it may also suggest that it affects the patient's phenotype. These clinical tests thus would provide corroboratory evidence about the variant's role in the patient's condition and would involve the clinicians in genomic causality brokering along with the data board members.

The Productivity of Epistemic Uncertainty

Embedding the VUS category in an evidentiary narrative allows the bioclinical collective to hedge their epistemic bets with ambiguous genetic causality. A VUS has a liminal and temporal dimension; at the time of the data board meeting, it is suspended within epistemic uncertainty but the expectation is that over time more evidence will become available and the VUS will be reclassified as benign or pathogenic. While the laboratory team relied extensively on standards as shortcuts for reducing the abundance of exome data to the most promising variants and to meet federal laboratory requirements (Timmermans, 2015), the bioclinical collective explicitly abandoned further standardization when interpreting phenotype–genotype connections. From the literature on standardization (Porter, 1996), we could expect that a return to face-to-face interactions among experts and an evidentiary narrative may come with a loss of trust in the objectivity of the results. Yet, because these genetic findings are fundamentally – by name – uncertain, an expert interpretation that spells out the reasons for inclusion may actually imbue trust in the process. Compared to an authoritative classification of variants without explanation, the evidentiary account produces transparency. But the evidentiary narrative goes beyond providing insight into a causal logic. The narrative renders uncertainty productive in three ways: it expands the realm of genomic causality, it enrolls clinicians and patients in the process of resolving causal ambiguity, and it blurs the boundary between research and clinical use of exome sequencing in a distinctly clinical context.

First, including VUS on exome reports gave the collective of clinicians and laboratory staff a means to expand genomic causality. The VUS category transforms something that is inherently categorized as uncertain into a sign of potential genetic causality. With every VUS designation, the collective renders one element of the vast genomic terra incognita potentially clinically relevant by associating it with evidence and anticipating a causal role for a variant. Taken together, VUS designations then anticipate the expansion of clinical genomics with increased roles for variants as causal factors. Similarly, the ACMG took the controversial position that patients are not allowed to opt out of incidental findings in exome sequencing. These policies and official statements point to a long-established belief that even though current technologies may still be suboptimal, we are at the vanguard of a genomic knowledge explosion that will gradually be revealed (Keller, 2000).

The result is that instead of limiting decision-making, epistemic genetic uncertainty generates social action centered on a genomic way of thinking. Andrew Abbott (1988) put professionals' jurisdictional battles with competitors at the heart of professionalism, but here

we see a professional 'land grab' in less antagonistic and more subtle, epistemic ways (Eyal, 2013). By singling out only the most promising uncertain variants and staying away from completely unknown variants, the collective envisions a future in which more genetic variants will explain more and more disease, while refraining from limitless territorial expansion. If the bioclinical collective had embraced a more conservative commercial laboratory ethos, variants now reported as VUS would have been systematically excluded. If, in contrast, they adopted a research perspective, every patient could have been a depository of promising research leads and many more variants could have been included on the report. Instead, by flagging the most promising yet epistemically uncertain variants, the bioclinical collective rendered uncertainty compatible with Mendelian genetics.

Second, the VUS narrative specifying the strengths and weaknesses inevitably shifts the interpretative burden to the clinician, situating the category within a trajectory of future interactions that keeps patients under genetic purview. As Rabeharisoa and Bourret noted, "The clinic has to constantly produce the meaning and relevance of mutations and biomedical entities that tend to proliferate and regularly invade the clinical settings" (p. 691). "Clinicians," as Cox and Webster observed (p. 403), consequently "exercise their expertise and judgement at the interface between the genotype of the laboratory and the phenotype of the clinic." The data board team articulated their reasons for including the VUS on the report but they can "leave it up to the clinician" to decide what to tell the patient about the meaning of the VUS. The collective enrolls ordering clinicians and patients in the epistemic process of figuring out causality by inviting them to keep an eye on the evolving genetic literature. As Eyal showed in his analysis of autism expertise (Eyal, 2013), such invitations for participation expand the network of stakeholders implicated in resolving causal ambiguity. The data board recognizes that 'leaving it up to the clinician' could mean that the VUS leads the patient down any number of paths, including some dead-ends. Narrating the VUS, however, puts some limitations on the potential interpretations that can be made and helps to steer the genomic expansion aspired in the report.

Third, even though exome sequencing is explicitly used here as a clinical test to diagnose a patient and not as a depository of promising research projects, epistemic uncertainty blurs the line between research and clinical testing. We have already shown that the clinical process of deductively testing patients generates knowledge but the feedback between research and clinical care is more extensive. With each VUS designation, the collective offers a hypothesis about genomic causality by flagging otherwise ambiguous variants for internal follow-up. This creates a database of potentially causal variants, and if the same variant recurs, they may decide based on their own internally accumulated knowledge that a variant is more accurately classified as 'likely pathogenic' than as a 'VUS.' Similarly, reporting VUS results can also lead the collective to 'expand the phenotype' beyond manifestations that have already been established in the literature; because uncertain variants invite querying about alternative phenotypical manifestations in patients and their relatives, this gives the collective a means to fine-tune the symptoms associated with each variant. On a smaller scale, the collective may ask permission to publish unique cases where patients present with symptoms that differ from what is known in the literature. On a larger scale, when repeated exome sequencing of similar patients does not produce any genomic causes, they may launch a research program to determine whether something else – epigenetic or environmental – is

causing these symptoms. In all these instances, commercial genomic testing spills over into research because research forms the foundation for known pathogenicity; generating epistemic feedback loops between commercial laboratory, research laboratory, and the clinic (Navon, 2011).

Conclusion

Patients and geneticists order exome sequencing as a comprehensive test to examine a broad range of genes to resolve diagnostic uncertainty for a patient with unexplained symptoms. When reviewing thousands of variants, a hybrid bioclinical collective of clinicians and laboratory personnel needs to decide which variants to report out. Communicating known or likely pathogenic variants is easy because the medical literature already demonstrates a similar genotype–phenotype match (Richards *et al*, 2015). Omitting or including uncertain variants, however, is complicated and potentially misleading. After rejecting more standardized approaches, this bioclinical collective decided to report out only the most promising variants with a narrative justification to contextualize epistemic uncertainties. The qualified narrative presentation of the VUS represents a fluid hypothetical diagnosis subject to both revision and interpretation. Yet, the narrative does not herald a new form of genomic causality; the anticipation is that over time the variant may become a real pathogenic or benign variant rather than watered down causality. The singular narratives accompanying each VUS are instead constitutive of a larger story envisioning a future in which genomic testing will be able to conclusively diagnose patients, a future in which the unknown unknowns will gradually diminish (Rabeharisoa *et al*, 2014). In the meantime, the bioclinical collective relates uncertainty to known phenotypical or genotypical aspects suggestive of causality, even if the whole evidence falls short of pathogenicity.

In spite of the promise of exome sequencing as a *genomic* test, the collective's management of VUS reinforces the Mendelian belief that a limited number of single genes explain disorders. Exome sequencing is thus implemented as a more limited *genetic* technology. There is little room to acknowledge gene–gene or gene–environment interaction, verify variable penetrance, or designate epigenetic processes. The clearest genomic aspect of exome sequencing is comprehensive access to genetic variants across the exome in one test but even then, as the management of the VUS shows, the collective works to make the data conform to single gene causality. Partly, this is due to the lag in the published biomedical literature – there are very few articles that have established multigene or gene–environment causality that would back up a genomic interpretation for clinical patient care and partly this is due to limits of the technology to capture interactions of any kind. These limitations, however, did not hamper strong belief in the genomic potential of sequencing in the future.

Consequently, the bioclinical collective uses epistemic genetic uncertainty to advance genetic causality in three ways. First, by parsing evidence and focusing on actionable results, the collective leaves open the possibility that genetic causes can explain patients' symptoms even if no known pathogenic variants could be located. They therefore single out variants that otherwise would have disappeared as unknowns among the countless variants every person carries. An important implication is that variants reported out as VUS are diverse: of

some little is known but a clinical test may clarify causality, while others are already close to meeting the standards of likely causal variants. Second, the collective spreads the possibility of genetic causality among a highly relevant group of stakeholders by designating clinicians and patients as collaborators in the process of figuring out genetic causality. Clinicians are tasked with follow-up testing or with keeping an eye on the genetics literature, situating the VUS within an interactional sequence that keeps patients who may otherwise not have a genetic diagnosis under the supervision of geneticists. Third, the reported VUS blur the line between research and clinical testing, directly and indirectly generating the evidence that will reveal a variant's causal potential. The bioclinical collective thus turns epistemic uncertainty into a force for genomic causality.

Does this make genomic expansion based on epistemic uncertainties a rather benign form of knowledge production with implications for patient subjectivity, professionalism, and causality (Novas and Rose, 2000) or a novel instantiation of genetic imperialism (Duster, 1990)? We can find some clues to adjudicate this question with a deeper look at what is at stake with upgrading VUS causality for patients and clinicians. Even though deeper questions about treatment and prognosis motivate patients and clinicians to engage exome sequencing, at the data board meeting the causal role of the variant remains the issue of contention. Clinicians also have the professional prerogative to ignore the VUS results. If a VUS turns out pathogenic, or even if the team reports out a pathogenic variant, the implications of genomic knowledge for patient care, treatment, or prognosis could thus remain quite limited. The added value of a genetic cause may be different when considering susceptibility genes or when considering reproductive decisions, but for diagnostic purposes the main benefit of locating a pathogenic variant is the knowledge that a gene caused the symptoms. In that sense, VUS results represent a promise of knowledge yet to come, but some existential diagnostic uncertainty will remain unresolvable.

Acknowledgements

The authors thank Ruth Baxter, Tanya Stivers, the reviewers, editors, and members of the UCLA Medical Sociology working group for helpful comments. The manuscript consists of original material not under review elsewhere. The research received IRB approval. The research was funded by an NSF Grant (SES-1256874). The authors do not have a financial interest in the research presented.

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References

Abbott, A. (1988) *The System of Professions*. Chicago: The University of Chicago Press.

Armstrong, D. (2002) Clinical autonomy, individual and collective: The problem of changing doctors' behaviour. *Social Science and Medicine* 55: 1771–1777.

Atkinson, P. (1984) Training for certainty. *Social Science and Medicine* 19: 949–956.

Beckert, J. (1996) What is sociological about economic sociology? Uncertainty and the embeddedness of economic action. *Theory and Society* 25: 803–840.

Biesecker, L.G. and Green, R.C. (2014) Diagnostic clinical genome and exome sequencing. *New England Journal of Medicine* 370: 2418–2425.

Bourret, P. (2005) BRCA patients and clinical collectives: New configurations of action in cancer genetics practices. *Social Studies of Sciecne* 35: 41–68.

Cox, H. and Webster, A. (2013) Translating biomedical science into clinical practice: Molecular diagnostics and the determination of malignancy. *Health* (*London*) 17: 391–406.

Duster, T. (1990) *Backdoor to Eugenics*. New York: Routledge.

Eggington, J.M., Bowles, K.R., Moyes, K., Manley, S., Esterling, L., Sizemore, S., Rosenthal, E., Theisen, A., Saam, J., Arnell, C., Pruss, D., Bennett, J., Burbidge, L.A., Roa, B. and Wenstrup, R.J. (2014) A comprehensive laboratory-based program for classification of variants of uncertain significance in hereditary cancer genes. *Clinical Genetics* 86: 229–237.

Eyal, G. (2013) For a sociology of expertise: The social origins of the autism epidemic. *American Journal of Sociology* 118: 863–907.

Green, R.C., Berg, J.S., Grody, W.W., Kalia, S.S., Korf, B.R., Martin, C.L., Mcguire, A.L., Nussbaum, R.L., O'daniel, J.M., Ormond, K.E., Rehm, H.L., Watson, M.S., Williams, M.S. and Biesecker, L.G. (2013) ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genetics in Medicine* 15: 565–574.

Han, P.K., Klein, W.M.P. and Arora, N.K. (2011) Varieties of uncertainty in health care: A conceptual taxonomy. *Medical Decision Making* 31: 828–838.

Hedgecoe, A.M. (2003) Expansion and uncertainty: Cystic fibrosis, classification and genetics. *Sociology of Health and Illness* 25: 50–70.

Hughes, E. (1945) 1971 *The Sociological Eye: Selected Papers*. Chicago: Aldine-Atherton.

Jutel, A. (2009) Sociology of diagnosis: A preliminary review. *Sociology of Health and Illness* 31: 278–299.

Keller, E.F. (2000) *The Century of the Gene*. Cambridge, MA: Harvard University Press.

Lampland, M. and Star, S.L. (eds.) (2009) *Standards and Their Stories: How Quantifying, Classifying, and Formalizing Practices Shape Everyday Life*. Ithaca, NY: Cornell University Press.

Lee, H., Deignan, J.L., Dorrani, N., Strom, S.P., Kantarci, S., Quintero-Rivera, F., Das, K., Toy, T., Harry, B., Yourshaw, M., Fox, M., Fogel, B.L., Martinez-Agosto, J.A., Wong, D.A., Chang, V.Y., Shieh, P.B., Palmer, C.G., Dipple, K.M., Grody, W.W., Vilain, E. and Nelson, S.F. (2014) Clinical exome sequencing for genetic identification of rare mendelian disorders. *JAMA* 312(18): 1880–1887

Lippman, A. (1991) Prenatal genetic testing and screening: Construcing needs and reinforcing inequalities. *American Journal of Law and Medicine* 17: 15–50.

Lock, M. (2011) Learning to live again with uncertainty: Social repercussions of molecular genomics. In Maheu, L. and Macdonald, R.A. (eds.) *Challenging Genetic Determinism: New Perspectives on the Gene and its Multiple Environments*. Montreal: McGill-Queen's University Press.

Navon, D. (2011) Genomic designation: How genetics can delineate new, phenotypically diffuse medical categories. *Social Studies of Science* 41: 203–226.

Nelson, N.C., Keating, P. and Cambrosio, A. (2013) On being 'actionable': Clinical sequncing and hte emerging contours of a regime of genomic medicine in oncology. *New Genetics and Society* 32: 405–428.

Novas, C. and Rose, N. (2000) Genetic risk and the birth of the somatic individual. *Economy and Society* 29: 485–513.

Porter, T. (1996) *Trust in Numbers: The Pursuit of Objectivity in Science and Public Life*, Princeton: Princeton University Press.

Rabeharisoa, V., Callon, M., Filipe, A.M., Nunes, J.A., Paterson, F. and Vergnaud, F. (2014) From 'politics of numbers' to 'politics of singularisation': Patients' activism and engagement in research on rare diseases in France and Portugal. *Biosocieties*, 9: 194–217.

Radley, D.C., Finkelstein, S.N. and Stafford, R.S. (2006). Off-label prescribing among office-based physicians. *Archives of Internal Medicine* 166: 1021–1026.

Richards, C.S., Bale, S., Bellissimo, D.B., Das, S., Grody, W.W., Hegde, M.R., Lyon, E. and Ward, B.E. (2008) ACMG recommendations for standards for interpretation and reporting of sequence variations: Revisions 2007. *Genetics* in *Medicine* 10: 294–300.

Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Grody, W.W., Hegde, M., Lyon, E., Spector, E., Voelkerding, K. and Rehm, H.L. (2015) Committee ALQA (2015) standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics* in *Medicine* 17: 405–424.

Sarangi, S. and Clarke, A. (2002) Zones of expertise and the management of uncertainty in genetics risk communication. *Research on Language and Social Interaction* 35: 139–171.

Shostak, S. (2013) *Exposed Science: Genes, the Environment and the Politics of Population Health*. Berkeley, CA: University of California Press.

Somers, M.R. (1994) The narrative constitution of identity – A relational and network approach. *Theory and Society* 23: 605–649.

Tavory, I. and Timmermans, S. (2014) *Abductive Analysis: Theorizing Qualitative Research*. Chicago: University of Chicago Press.

Timmermans, S. (2015) Trust in standards: Transitioning clinical exome sequencing from bench to bedside. *Social Studies of Science* 45: 77–99.

Van Zuuren, F.J., Van Schie, E.C. and Van Baaren, N.K. (1997) Uncertainty in the information provided during genetic counseling. *Patient Education* and *Counseling* 32: 129–139.