The relationship between intervention and representation is currently resurfacing in philosophy of science. Analytical treatments of the specific intersections between *representation* and *intervention* have recently been explored in Hacking (1983), Radder (2003), Heidelberger (2003), van Fraassen (2008), and Keyser (2017). These accounts analyze intervention-based experimental and measurement practice and the *consequences* for representing and model-building. Of particular interest in my discussion is that some of these accounts explicitly differentiate between representational and productive roles in scientific practice. For example, Heidelberger (2003) and van Fraassen (2008) discuss the representational and productive roles of instruments in experiment and measurement. In the former role, relations in a natural phenomenon are represented in an instrument (van Fraassen 2008, 94). In the latter role, instruments create new phenomena or mimetic phenomena, which resemble natural phenomena. Keyser (2017) takes the distinction between representation and production a step further to differentiate two types of experimental/measurement methodologies:

> When scientists measure/experiment they can *take* measurements, in which case the primary aim is to represent natural phenomena. Scientists can also *make* measurements, in which case the aim is to intervene in order to *produce* experimental objects and processes—characterized as 'effects'. (Keyser 2017, 2)

On Keyser's account 'taking a measurement' involves a scientist using a result in the context of theory to represent a given phenomenon (2017, 9-15). In contrast, 'making a measurement' involves setting up experimental conditions to produce a phenomenon—where that phenomenon can be realized in nature but it can also be a brand new

phenomenon (Keyser 2017, 10). The difference between these two methodologies seems to be a matter of passive representation of a phenomenon vs. active intervention to produce a phenomenon. While the distinction between representation and intervention has been useful in classifying methodology in well-documented contexts like thermometry, microscopy, and cellular measurement, I argue that it falls apart in contexts where taking and making are *entangled*—such as in the context of biomarker measurement in the biomedical sciences.

In this discussion, I aim to show that in *complex methodological contexts*, representational and intervention-based roles require re-conceptualization. I analyze the *relations* between representation and intervention by focusing on the role of intervention in *mediating* representations. In Section 2, I show how applied scientific practice challenges the simple distinction between representational and intervention-based roles of experiment/measurement. In Section 3, I discuss the complex interaction between representation and intervention applied to methodology in biomarker measurement.

2. Methodology at the Intersection between Intervention and Representation

In order to understand why the distinction between representation and intervention needs a multifaceted approach, it is important to be explicit about what it means to represent and intervene in scientific practice. In Section 2.1, I draw on van Fraassen (2008) to discuss representation and both van Fraassen (2008) and Keyser (2017) to discuss intervention. Then in Section 2.2, I show how applied scientific practice challenges the simplistic distinction between representational and intervention-based

roles of experiment/measurement. I argue that the distinction between intervention and representation is less about *specific types of methodologies* in measurement/experiment and more about where one philosophically partitions the measurement *process*.

2.1. Representation and intervention

In experimental and measurement practice, representation has at least three important components: First, instruments or experimental contexts yield measurement values; Second, those values can only be interpreted within the context of a well-developed theory; and third, the relation between the measurement values and the phenomenon is determined by a user (e.g., experimenter). Van Fraassen (2008) provides a rich characterization of representation in measurement and experiment, which requires careful analysis. Worth noting is that van Fraassen takes measurements to be a "special elements of the experimental procedure" (2008, 93-94). For my discussion the embeddedness of measurement in experiment is not important. I will focus on the roles or processes within measurement and experimental practice. But to do this, I will sometimes refer to 'measurement' and other times to 'experiment'. Van Fraassen's characterization focuses on interaction and representation in measurement:

> A measurement is a physical interaction, set up by agents, in a way that allows them to gather information. The outcome of a measurement provides a representation of the entity (object, event, process) measured, selectively, by displaying values of some physical parameters that—according to the theory governing this context—characterize that object. (2008, 179-180)

For van Fraassen, measurement interaction between an object of measurement and apparatus generates a physical outcome—the "measurement outcome" or "physical correlate of the measurement outcome"—, which provides information content about the target of measurement (2008, 143). The contents of measurement outcomes convey information about *what is measured* through the mediation of theory. Van Fraassen posits that theoretical characterization of measurement interaction requires 'coherence':

> The theoretical characterization of the measurement situations is required to be coherent with the claims about the existence of measurement outcomes, their relation to what is measured, and their function as sources of information. (2008, 145)

In short, the theory tells a coherence story about "how its outcomes provide information about what is being measured" (145). Furthermore, the information content is representational. Van Fraassen says, "The outcome provides a representation *of* the measured item, but also represents it *as* thus or so" (2008, 180). To understand how the representational relation works, it is important to refer to van Fraassen's 'representation criterion':

> The criterion for what sorts of interactions can be measurements will be, roughly speaking, that the outcome must represent the target in a certain fashion—, selectively resembling it at a certain level of abstraction, according to the theory—*it is a representation criterion*. (van Fraassen 2008, 141).

Two aspects of the representation criterion require explanation: First, the distinction between "target" and "outcome"; and second, the role of theory in the operation of measurement. I begin with the former. Van Fraassen makes a technical

distinction between the target of measurement ('phenomena') and the outcome of measurement ('appearances'):

> Phenomena are observable, but their appearance, that is to say, *what they look like in given measurement or observation set-ups*, is to be distinguished from them as much as any person's appearance is to be distinguished from that person. (2008, 285)

For van Fraassen, phenomena are observable objects, events, and processes (2008, 283). He emphasizes that phenomena include all observable entities—whether observed or not (2008, 307). A given phenomenon can be measured in many different ways. The outcome of each measurement provides a perspective on a given phenomenon—meaning that the content of measurement tells us what things *look like*, not what they *are like* (2008, 176, 182). The *content* of the measurement outcome is an appearance.

An important qualification is that for van Fraassen, a representation does not represent on its own. The scientist selects the aspects/respects and degrees to which a representation represents a target. This relation can be expressed as: Z uses X to represent Y as F, for purposes P.

Now that the target and outcome of measurement have been characterized, we can specify van Fraassen's role of theory in measurement. According to van Fraassen, "Measurement is an operation that locates an item (already classified as in the domain of a given theory) in a logical space, provided by the theory to represent a range of possible states or characteristics of such items (164). Three things are worth noting about van Fraassen's discussion of logical spaces. First, a logical space provides a multidimensional mathematical space that locates potential objects of measurement (2008, 164). By

measuring we assign the item a location in a logical space. However, according to van Fraassen, it does not have to be on a real number continuum. As van Fraassen points out, items may be classified (by theory) on a range that is "an algebra", "lattice", or a "rudimentary poset" (2008, 172). Second, theoretical location depends on a "family of models" and not just an individual model (2008, 164). Third, an item is located in a "region" of logical space rather than at an exact point (2008, 165). Simply put, theory provides a classificatory system for what is measured. Importantly, theory is *necessary* for this type of classification. Van Fraassen says, "A claim of the form "This is an X-measurement of quantity M pertaining to S" makes sense *only* in a context where the object measured is already classified as a system characterized by quantity M" (2008, 144 my emphasis).

We can summarize the above discussion into four conditions for van Fraassen's account of representation in measurement/experiment practice:

i. Physical Interaction Condition: The interaction between apparatus an object produces a physical correlate of the measurement outcome.

ii. Theoretical Characterization Condition: The content of the measurement outcome is given a location in a logical space, which is governed by a family of theoretical models. An item's location within a logical space can change in content and truth conditions as accepted theories change.

iii. Representational Content Condition: The content of a measurement outcome provides a selective representation of a given target of measurement (phenomenon). Because representations do not represent on their own, users and pragmatic considerations set the representational relation such that: Z uses X to represent Y as F, for purposes P.

iv. Perspectival Information Condition: Measurement generates appearances, which are public, intersubjective, contents of measurement outcomes. Appearances provide selective information about phenomena. Thus information from measurement tells us what something *looks* like and not what something *is* like.

Van Fraassen notes that measurement and experiment are not only limited to a representational role, they can take on at least two productive roles. First, instruments can produce phenomena that "imitate" natural phenomena. That is, carefully controlled conditions give rise to mimetic effects that are used by scientists in the context of theory to resemble natural phenomena (2008, 94-95). It is important to note that van Fraassen emphasizes that natural phenomena are phenomena that exist *independent of human intervention* (2008, 95). The second productive role of instruments is that they are used as "engines of creation" to produce or manufacture new phenomena. Van Fraassen is not explicit about whether or not the representational roles can smear with the productive roles. There is no reason to assume that these roles cannot be combined; but that requires explicit philosophical work to see *how*, which I develop in Section 3.

Keyser (2017) is explicit about the relationship between the representational and intervention-based roles in science. He discusses the *use* of intervention for developing causal representations. Scientists intervene, thereby manipulating causal conditions within a given measurement or experimental system, which he calls 'intervention systems', to produce some sort of "effect" (Keyser 2017, 9-10). According to Keyser, "Intervention systems consist of organized experimental conditions and as such the effects that emerge are often sensitive to changes in conditions*"* (Keyser 2017, 10). Once a given effect is produced it can be used in order to be informative about causal relations for theoretical model building.

Keyser (2017) also differentiates between the methodologies of taking measurements vs. making measurements. I interpret that taking measurements involves three components: First, some instrument or experimental arrangement yields a qualitative or quantitative value; second, a 'theoretical representational framework'—which is just a body of models—is necessary in order to characterize that value according to parameters and relations between parameters; and third, a scientist sets up the resemblance relation between the measurement/experiment value and some aspect(s) of a phenomenon (Keyser 2017, 14-15). In contrast, when scientists make measurements they manipulate causal conditions—such as, preparatory, instrument, and background conditions—within an intervention system. This manipulation gives rise to some effect (Keyser 2017, 3-12).

There is something puzzling about Keyser's distinction between making vs. taking, if we apply the aforementioned conditions (i-iv): i. *Physical Interaction Condition*; ii. *Theoretical Characterization Condition*; iii. *Representational Content*

Condition; and iv. *Perspectival Information Condition*. Namely, it seems that 'making measurements' is compatible with conditions i-iv, so it is not clear why there is a need for a distinction in methodological type, but rather just a difference in details for each condition. For example, when a measurement is made, there is a (i) *physical interaction* that occurs, but it is broader than just the instrument and object. The interaction can include "experimental conditions" (Keyser 2017, 3-5). The product of a made measurement is also amenable to (ii) *theoretical characterization*. Keyser emphasizes that theoretical characterization is necessary for experiment/measurement (Keyser 2017, 14); but he does not make the additional move to say that theoretical characterization is *part of the process* of making a measurement. That is, in order to make a measurement about an effect, one needs to also *characterize* that effect. Without the final characterization, one is only dealing with the material conditions, which is an incomplete part of the measurement process. Keyser can accept that theoretical characterization is a necessary component of making a measurement. Otherwise, he risks offering a limited concept of 'making a measurement' that only applies to arranging the material components of the measurement process and nothing further.

The same challenge goes for (iii) *representational content* and (iv) *perspectival information*. An important component of the measurement process is to represent the relation between the produced effect and some aspect(s) of a phenomenon. For example, is this given effect a limited mimetic representation of a natural phenomenon or is it a brand new phenomenon? Without claims about what the effect is and its relation to objects, events, and processes in the world, 'making a measurement' is uninformative about part of the measurement process: the final value of the measurement outcome.

The aforementioned considerations question the need for a distinction between 'making' vs. 'taking'. One conclusion is that making uses the same components (i-iv), just with slightly different detail. But the other conclusion is a bit unsatisfying: making is really only about organizing the material components, which is an *initial* step in the measurement process, and it does not apply to later steps in measurement.

2.2. Dynamic relations between intervention and representation

I argue that the distinction between intervention vs. representation is less about *specific types of methodologies* in measurement/experiment and more about where to philosophically partition the *measurement process*. To make this point clear, I make two sub-points: 1) Measurement in the biological sciences offers complex and sometimes blurred relations between instrument and object of measurement such that representation and production take on dynamic roles; 2) There is a difference between the act of measurement and the total process of measurement. I briefly describe (1) and (2).

On van Fraassen's (2008) and Keyser's (2017) characterizations of *representation* in measurement, the role of the instrument/apparatus seems to have an important mediating function. It may be the case that philosophical focus on case studies (e.g., thermometry, microscopy, cellular bio, and bacteria) that are instrument-intensive provide a certain support for an instrument-centric account of representation in measurement. Whether or not the necessary mediating role of instruments is an explicit part of both accounts, there is room to develop a richer philosophical view of the role of representation in the total measurement *process*. Without such philosophical development, we risk missing complex cases of measurement where intervention occurs

side-by-side with representation. For example, in some cases of biological measurement, scientists use the organism to measure processes in that same organism but also to represent larger phenomena (Prasolova et al. 2006). For example, mouse diets are manipulated in order to measure chromatin pattern changes. I characterize this as the mouse *constituting experimental conditions* that are being manipulated in order to measure some sort of process. The manipulation of conditions indicates an interventionist approach (or 'making' a measurement). Moreover, without manipulating the mouse's diet scientists would not be able to make a reliable measurement on chromatin structure at all. So the organism is not only being manipulated as part of the experimental/measurement set-up, it is a crucial part of that set-up. That is, without intervention, there is no reliable result. In addition to the organism being used as part of the measurement set-up, it also serves as a physical *representation* of the dynamics of chromatin pattern change. That is, a given model organism can serve as a data model for a specific phenomenon of study—e.g., chromatin pattern in organism X. So, in this case the organism serves a dual function: it constitutes a set of experimental conditions to be manipulated and it serves as a physical representation of a phenomenon. Because of the dual function, this seems to be a case of both 'making' and 'taking' a measurement.

This brings me to sub-point (2). The total process of measurement is often complex in the biological sciences and requires multiple stages of intervening and representing. As mentioned in the model organism example representation and intervention are often *entangled*. Measurement is not merely putting an instrument up to something and waiting for a reading, which can be classified as an *act* of measurement. Measurement is also not merely creating effects out of material conditions. Measurement

requires manipulation of conditions that is *used* in order to generate a representation. For example, identifying a mysterious fungus that is entangled with other fungus in a sample is an active process that requires both intervention and representation. One method is to take a sample and scrape it over a petri dish. What grows are spores that are passively deposited. But if common fungi were commingled with the mysterious fungi in the sample, and the common fungi grew faster, it would be impossible to identify the mysterious fungus. That is, coming back in a couple of weeks and seeing the petri dish covered with familiar species would lead to a false conclusion. Another way to perform the measurement (i.e. culture samples) is as follows. Take the samples and grind them up. Then sprinkle them into a petri dish. Put the dish under the microscope and, using a fine needle, pick out fragments of the mysterious fungus and transplant them to their own dishes (Scott 2010). Once the fragments have been transplanted through this fine-grained intervention, each dish can be left to grow the colonies. The final dishes will offer visual representations that serve as data on the nature of the mysterious fungus. Notice here that intervention is a precursor to reliable representation.

Representation is not only reserved for the final instrument reading. It can also occur at other stages in the measurement process. Likewise, manipulation does not have to occur only at the earlier stages. For instance, organic matter can function as an instrument, like in the case of FourU thermometers, which are RNA molecules that act as thermometers in Salmonella (see Waldminghaus et al. 2007). Suppose that a scientist sets up an experiment to iteratively measure to what extent modifying RNA factors in FourU thermometers changes thermometer readings in Salmonella. In such a case the scientist could modify molecular factors and use the organic thermometers as temperature

measures over many iterations, which would culminate in some sort of data model that organizes the relationship between molecular factors and FourU function. In such a case, there are multiple layers of intervention and representation.

The complex layering of intervention and representation is apparent in biomarker measurement in the biomedical sciences, where biological components serve as representations of disease conditions, but are also intervened on in order to make more reliable representations. I turn to this case study in the subsequent section.

3. Intervening in Representations and Representing Interventions

Biomarkers are used in biomedical measurement to reliably predict causal information about patient outcomes while minimizing the complexity of measurement, resources, and invasiveness. A biomarker is an assayable metric—or simply, an indicator—that is used by scientists to draw conclusions about a biological process (De Gruttola et al. 2001). The greatest utility from biomarker measurement comes from their ability to help clinicians and researchers make conclusions with limited invasiveness. The reliance on biomarkers to make causal conclusions has prompted the use of 'surrogate markers'. These biomarkers are used to substitute for a clinically meaningful endpoint such as a disease condition. A major scientific methodological issue is that the use of multiple biomarkers will produce disagreeing results—and this is true even in the context of biomarkers that use similar biological pathways. To make methodological matters worse, theoretical representation is often not equipped to fill in the causal detail for each biomarker measurement. This amounts to an unfolding methodological puzzle about how to use intervention and representation in biomarkers to produce reliable measurements.

My interest in this case study is not in solving the methodological puzzle, but rather in showing the *relations between intervention and representation* in such a complex case study. In this section, I discuss the complexity of intervention and representation in biomarker measurement to illustrate how intervention mediates the measurement process.

To understand the complex methodology in biomarker measurement it is important to detail the use and limitations of biomarkers. Some biomarkers are used as a substitute for some clinical endpoint. For instance, LDL cholesterol (LDL-C) is a biomarker that clinicians and physicians use to correspond to a clinical endpoint—e.g., heart attack. Moreover, the biomarker is associated with risk factors such as coronary artery stenosis, atherosclerosis, and angina pectoris. Katz (2004) argues that all biomarkers are candidates for 'surrogate markers', which can serve as substitutes for clinical endpoints. That is, surrogate markers are reliable biomarkers that have a one-to-one correspondence with the disease condition such that they can be used to provide reliable predictive and causal information about a given clinical endpoint. There are a couple of points worth noting. First, notice that biomarkers and surrogate markers are being used as representations of a clinical endpoint. That is, to figure out the likelihood of developing a disease condition and to understand the risk factors associated with that disease condition, scientists use biomarkers that indicate information about the endpoint. This means that these physiological components can be used by clinicians and physicians to *represent disease conditions to respects and degrees*. The second point worth noting is that there are many biomarkers but limited surrogate markers and even more limited validated surrogate markers ('surrogate endpoints')—which are surrogate markers that are reliable in multiple contexts of interventions. The importance of this will be relevant

shortly when I discuss the complexity of biomarker measurement. For our purposes, this means that most biomarkers in biomedical practice provide very limited representational information.

Surrogate markers are not passively used as physical representations of disease conditions. Their use is often more effective for representational purposes if there is a *mediating intervention*. For instance, surrogate markers can constitute "response variables". This is where a surrogate marker is manipulated in order to produce an effect that is relevantly similar to the effect with the same manipulation on the clinical endpoint. This means that an adequate surrogate must be "tightly correlated" with the true clinical endpoint; but it also means that any intervention on a surrogate marker must be tightly correlated with the intervention on the true clinical endpoint (Buyse et al. 2000). I interpret this as a dual role for a reliable surrogate marker. It is to act as an epidemiological marker that *represents* some clinical endpoint but also to act as a responding variable that can be used in an *intervention* to causally influence the clinical endpoint. An example of the dual role of the surrogate marker is that high concentrations of LDL cholesterol (LDL-C) correspond to cardiovascular risk (Gofman and Lindgren 1950). But if a therapeutic interventions is used—such as, 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins)—that intervention can lower LDL levels, which in turn reduces cardiovascular disease (LaRosa et al. 2005).

So far I have presented the representational and intervention-based role of biomarkers. It is not straightforward to say that surrogate markers are *'made'* like an effect. But it is also not straightforward to say that surrogate markers constitute a *measurement outcome that is the final reading on an instrument*. These markers provide

useful representational information *in the context* of an intervention. To add to the complexity of the relation between representation and intervention, biomarkers in the context of Alzheimer's measurement have added methodological steps. In Alzheimer's measurement there are different biomarkers, which are not correlated with each other and change with independent dynamics in the progression of Alzheimer's disease. So *each* of these biomarkers do not provide the same type of representation about the progression of Alzheimer's disease. Furthermore, scientists *only* understand the disagreement between each of these biomarkers in the presence of different interventions.[1] The different interventions are in the form of drugs (e.g., bapineuzumab and solanezumab) and these interventions produce disagreeing representational results for the biomarkers. That is, the biomarkers respond differently to different interventions, which is methodologically problematic because it indicates that all of these biomarkers cannot be reliably tracking Alzheimer's progression in the same way. Interestingly, scientists systematically compare these disagreeing results to make reliable claims about Alzheimer's progression and treatment (Toyn 2015).[2] To simplify the method used, scientists track how interventions

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[1] There has been much work recently on clinical biomarkers like: cerebrospinal fluid (CSF) tau, which is the primary component of neurofibrillary tangles; CSF 42-amino acid amyloid-β (CSF Aβ), which is the protein cleavage product believed to precipitate disease by forming neuron-damaging plaques; and amyloid plaques from PET scans. While the methodological story is beyond the scope of this discussion, there is a complex methodological point that is noteworthy for this discussion (Toyn 2015).

[2] To give a brief picture: The intervention of Bapineuzumab reduces levels of plaque assayed by Aβ PET and CSF tau, but not CSF Aβ; but Solanezumab *does not alter* levels

change properties of biomarkers and then they compare these amalgamated results with how interventions change behavioral/cognitive properties. This type of cross comparison allows scientists to eliminate biomarkers that do not track behavioral/cognitive improvement.

The structure of the methodological complexity in biomarker measurement can be partitioned as follows: 1) For a particular clinical endpoint, there are *limited physical representations* in the form biomarkers (or surrogate markers) which can be *used* to make representational and perspectival conclusions about the endpoint or risk factors associated with it; 2) *Scientists intervene in a process* from each of the biomarkers in order to track the relations between biomarkers and clinical endpoints; and 3) Such interventions prompt *disagreeing results between the biomarkers*, which can 4) be amalgamated by researchers into further representations of the *relations between biomarkers and their clinical endpoints*. The above structural breakdown is merely *a* type of complex methodological process that can occur in biomedical measurement. It shows how interventions on physical representations (biomarkers) can produce other reliable representations. What is important to note about this analysis is the role of intervention in *mediating* further representations. In the case of biomarkers, intervention is necessary to test how close biomarkers are in their representations of clinical endpoints and also to other biomarkers. These representations not only represent the relation between the original biomarker and the clinical endpoint, but they also represent how a given

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of plaque assayed by Aβ PET and CSF tau but leads to a *reduction in* CSF Aβ. Cross comparison of the *intervention* mechanisms allows scientists to begin to make causal claims about which biomarkers are more reliable than others (Toyn 2015).

intervention affects a given biomarker. As such, intervention paves the way for iterations of representations.

4. Concluding Remarks

In this discussion, I have analyzed the role of intervention in mediating representations by using examples from the biological and biomedical sciences. Characterizing intervention as a mediating factor in a larger methodological operation provides an important point about scientific practice. Representation and intervention are not neatly partitioned into contrasting methodologies. In fact, applied science often dictates the complex, and often smeared, philosophical concepts and methodologies. For this reason, I am proposing a *process* view of intervention and representation. This view opens up the diversity of relations between representation and intervention in a given experimental/measurement practice. While I have emphasized how intervention mediates representation, there is more territory to explore about the mediating role of representation for intervention.

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