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Review Article

Digging Deeper into Precision/Personalized Medicine: Cracking the Sugar Code, the Third Alphabet of Life, and Sociomateriality of the Cell

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Abstract

Precision/personalized medicine is a hot topic in health care. Often presented with the motto ''the right drug, for the right patient, at the right dose, and the right time,'' precision medicine is a theory for rational therapeutics as well as practice to individualize health interventions (e.g., drugs, food, vaccines, medical devices, and exercise programs) using biomarkers. Yet, an alien visitor to planet Earth reading the contemporary textbooks on diagnostics might think precision medicine requires only two biomolecules omnipresent in the literature: nucleic acids (e.g., DNA) and proteins, known as the first and second alphabet of biology, respectively. However, the precision/personalized medicine community has tended to underappreciate the third alphabet of life, the ''sugar code'' (i.e., the information stored in glycans, glycoproteins, and glycolipids). This article brings together experts in precision/personalized medicine science, pharmacoglycomics, emerging technology governance, cultural studies, contemporary art, and responsible innovation to critically comment on the sociomateriality of the three alphabets of life together. First, the current transformation of targeted therapies with personalized glycomedicine and glycan biomarkers is examined. Next, we discuss the reasons as to why unraveling of the sugar code might have lagged behind the DNA and protein codes. While social scientists have historically noted the importance of constructivism (e.g., how people interpret technology and build their values, hopes, and expectations into emerging technologies), life scientists relied on the material properties of technologies in explaining why some innovations emerge rapidly and are more popular than others. The concept of sociomateriality integrates these two explanations by highlighting the inherent entanglement of the social and the material contributions to knowledge and what is presented to us as reality from everyday laboratory life. Hence, we present a hypothesis based on a sociomaterial conceptual lens: because materiality and synthesis of

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glycans are not directly driven by a template, and thus more complex and open ended than sequencing of a finite length genome, social construction of expectations from unraveling of the sugar code versus the DNA code might have evolved differently, as being future-uncertain versus future-proof, respectively, thus potentially explaining the ''sugar lag'' in precision/personalized medicine diagnostics over the past decades. We conclude by introducing systems scientists, physicians, and biotechnology industry to the concept, practice, and value of responsible innovation, while glycomedicine and other emerging biomarker technologies (e.g., metagenomics and pharmacomicrobiomics) transition to applications in health care, ecology, pharmaceutical/diagnostic industries, agriculture, food, and bioengineering, among others.

Keywords: cellular communication, contemporary art, emerging technology governance, glycans, history of science, personalized medicine, pharmacoglycomics, responsible innovation, sociomateriality, sugar code

''There are no right answers to wrong questions''
Ursula K. Le Guin (1929–2018)

Introduction

PHYSICISTS HAVE KNOWN FOR A LONG TIME the difficulty of obtaining data in science and that nature imparts information and insights only with stubborn reluctance (Naylor and Cavanagh, 2004; Özdemir et al., 2009). However, times have changed over the past decade. We are in an era of data deluge due to improved capacity to generate Big Data with high-throughput multiomics platforms such as genomics, proteomics, and metabolomics, not to forget the recent rise of digital health and the Internet of Things that connect all animate and inanimate objects on the planet. Systems scientists are also developing new approaches for precision/personalized medicine such as pharmacomicrobiomics (the study of microbiome–drug interactions) and artificial intelligence (AI) for multiomics data integration (Aziz et al., 2020; El-Rakaiby et al., 2014; Eraqi et al., 2018; Garvey, 2018; Koromina et al., 2019). The very fast pace with which emerging technologies are evolving requires their critical governance as increasingly demanded by science and engineering funding agencies.

Long considered a type of ''variability science,'' precision/personalized medicine aims to discern the mechanisms of person-to-person and population differences in response to drugs, food, vaccines, and other health interventions (Dandara and Özdemir, 2016a). Historically, personalized medicine has focused on drug–gene interactions to individualize therapeutics. In 2015, the then United States President Barack Obama announced in his State of the Union address the Precision Medicine Initiative, supported by a US$215-million fund. Precision medicine focuses on establishing the roadmaps for the best health interventions for each individual, which are informed by precise diagnostics and promising optimal preventative health. On the other hand, often perceived as a new field, precision medicine ''actually rests on related and much older fields of expertise, including the science of deciphering the causes of variability among persons and populations'' (Dandara et al., 2016b). ''Personalized,'' ''precision,'' ''stratified,'' and ''targeted'' are only some of the various adjectives (Zhang, 2015) used to capture this age-old form of variability science that has gained a new format, speed, and scale with new technologies over the past three decades (Özdemir, 2018). However, the key ideas and focus remain the same: understanding the sources of within and between person, and population variability in host–environment interactions (Kalow, 1962; Kalow et al., 1999).

While genomic sciences have made important contributions over the past decades, a large portion of variability in susceptibility to diseases and responses to medicines remains inadequately understood. There is still a long road to the goal of achieving personalized medicine at a resolution of an individual patient.

While we continue with the term personalized medicine below, we alert the reader to these nuances and the key motivations and aims of the field. The article makes it clearer, later on, that the concept of social constructivism helps explain why some biomarkers might be more popular than others, although biology and the nature do not express such selective preference in biomarkers and the molecular constituents of the cell for use as diagnostics in clinical and public health practice. In fact, it is our sociotechnical understandings of each constituent of the cell that informs how much use we make of each.

Going forward in the next decade to 2030, and as noted by the late Ursula K. Le Guin, an astute writer and analyst of society and everyday life, we first need to ask the right questions in personalized medicine before seeking hasty solutions for diagnostic innovation. There is an unmet need for holistic understanding of the complex interactions of the various cellular constituents, requiring broader sense-making and an integrative approach to personalized medicine. Success will only register once we are truly able to connect the dots across synergistic fields of scholarship and data previously considered unrelated to biomarker development. This makes personalized medicine a form of art as much as a highly interdisciplinary science, inviting the concerned actors to rethink the unchecked assumptions prevalent in biomarker theory and practice.

The reasons for variability in response to medicines are many and include technical, biological, and social dimensions. A previously overlooked source of variability in personalized medicine research is the ''sugar code'' (i.e., the information stored in glycans and their conjugated forms such as glycoproteins and glycolipids) (Kaltner et al., 2019; Liu et al., 2019; Wang, 2019; Li et al., 2019).

This article brings together experts in (1) personalized medicine science from around the world, including colleagues pioneering biomarker research in resource-limited settings, and (2) scholars in emerging technology governance, cultural studies, contemporary art, history of science, political science, philosophy of technology, and responsible

innovation. For robust innovation in diagnostics and therapeutics, we propose that the three alphabets of life, the DNA, protein, and sugar codes (Gabius and Roth, 2017; Gabius, 2018; Kunej, 2019), ought to be considered together, and be seen through both technical and social conceptual lenses to cultivate a culture of critically informed technology governance (Özdemir, 2019a, 2019b).

First, we examine the rationale, history, and the current transformation of targeted therapies with recent introduction of personalized glycomedicine: the use of glycan biomarkers and diagnostics to forecast disease susceptibility and individualize therapeutics (Kunej, 2019; see, for example, Liu et al., 2019; Wang and Özdemir, 2019). Next, we discuss some of the plausible reasons as to why unraveling of the sugar code might have lagged behind the DNA code. We conclude by introducing the readers to the field of responsible innovation. We highlight recent examples of responsible innovation research to inform laboratory scientists and health care workers for broader contextualization of personalized glycomedicine as this new technology transitions to applications in health care, ecology, nutrition, agriculture, bioengineering, food, and pharmaceutical and diagnostic industries, among others.

Why Personalized Medicine? Why Now?

Personalized medicine would not be necessary if safety and therapeutic effects of drugs were predictable and did not vary from person to person, which is not the case. Most drugs come with side effects, some of which can be serious and fatal, while drugs produce the desired therapeutic effects in a proportion of patients. Understanding the mechanisms of individual variations in drug safety and efficacy is the first step toward personalized medicine and rational therapeutics (Şardaş and Kendirci, 2019).

A frequently cited large-scale meta-analysis of adverse drug reactions (ADRs) in the United States reported an overall incidence of serious ADRs as 6.7% (95% confidence interval [CI], 5.2–8.2) and of fatal ADRs as 0.32% (95% CI, 0.23–0.41) in hospitalized patients (Lazarou et al., 1998). A serious ADR was described as those patients who ''required hospitalization, were permanently disabling, or resulted in death'' (Lazarou et al., 1998). Even by a conservative estimate using the lower limit on ADR fatalities, these reactions would constitute the sixth leading cause of death in the United States, ahead of pneumonia and diabetes (Lazarou et al., 1998).

On the other side of the Atlantic Ocean, in Sweden, fatal ADRs were estimated as a comparable public health burden, the seventh most common cause of death (Wester et al., 2008). Studies undertaken on drug safety over the past three decades have collectively shown that ADRs are common in clinical practice, occurring in about 5–10% of patients and resulting in unscheduled hospitalizations, or occurring during hospital stay or after discharge from the hospital (Coleman and Pontefract, 2016). It is important to note that ADRs are often underreported in clinical practice. Hence, ADRs are likely more frequent and their negative public health impacts are much broader in real-life health care settings, than is reported.

Interindividual variability during drug treatment is not limited to side effects. The intended therapeutic effects of drugs also display large variability across patients and populations. An analysis of drugs in major therapeutic areas such as Alzheimer's disease, cancer, and analgesics found that, on average, only about 50% of patients respond to drugs, or conversely, 50% of patients do not respond to pharmacotherapy across therapeutic indications (Spear et al., 2001). While more pharmacoepidemiology research is needed on variability in drug efficacy, inadequate therapeutic response remains a major challenge in routine clinical practice. In the absence of personalized medicine, a trial and error approach is required to find the optimal dose of a drug or the type of prescription medicine. For progressive diseases, the time lost during such trial and error might mean that patients' illnesses advance in the meantime.

In addition to significant morbidity and mortality, ADRs and poor therapeutic response can damage the trust between patients and their physicians and other health care workers. Personalized medicine offers the promise of greater predictability in drug safety and efficacy, and advances rational therapeutics (Fig. 1), while building (potentially) greater trust among patients and health care providers.

Drug discovery and clinical trials stand to benefit from personalized medicine as well if they are conducted in a mechanistically targeted manner with biomarker guidance, and in subgroups of patients who are more likely to respond to a new drug with lesser side effects. In drug discovery, high-throughput screening can be tailored to identify novel lead compounds that specifically target, for example, a subtype of a receptor that is more likely to result in therapeutic response. Hence, personalized medicine is a broad-spectrum science that spans the continuum from drug discovery and clinical trials to optimal use of therapeutics in health care and public health practice.

History of Personalized Medicine

A science of and art on variability questions

Diagnostic medicine is a compass for personalized medicine. These two fields are linked conceptually and in practice. Also, both fields have a storied past dating back to antiquity (Ozdemir et al., 2009).

The morals and values of the ancient times were such that they did not allow invasive tissue sampling and permit only the use of biological specimens that are naturally passed from the body such as urine. As early as 4000 BCE, the Sumerians and Babylonians in central-south Mesopotamia (present-day Iraq) analyzed urine samples to gauge the health of a person. On the Island of Cos in Greece, Hippocrates (460–ca. 370 BCE) suggested that a urine containing bubbles is a sign of chronic renal disease (White, 1991).

The mathematician and philosopher Pythagoras is often noted as one of the forerunners of the idea on host–environment interactions, and by extension, of personalized medicine. A native of the Samos island in the Eastern Aegean Sea, Pythagoras had a rule: ''be far from the consumption of fava beans,'' a practice strictly adhered by his followers, including the refusal to walk through fava bean fields (Meletis, 2012). One alleged reason for this Pythagorean puzzle was that he noticed, in 510 BCE in Croton, Italy, a connection between fava bean ingestion and a type of hemolytic anemia that results in abnormal breakdown of red blood cells in some, but not all, individuals. While the fava bean (*Vicia*

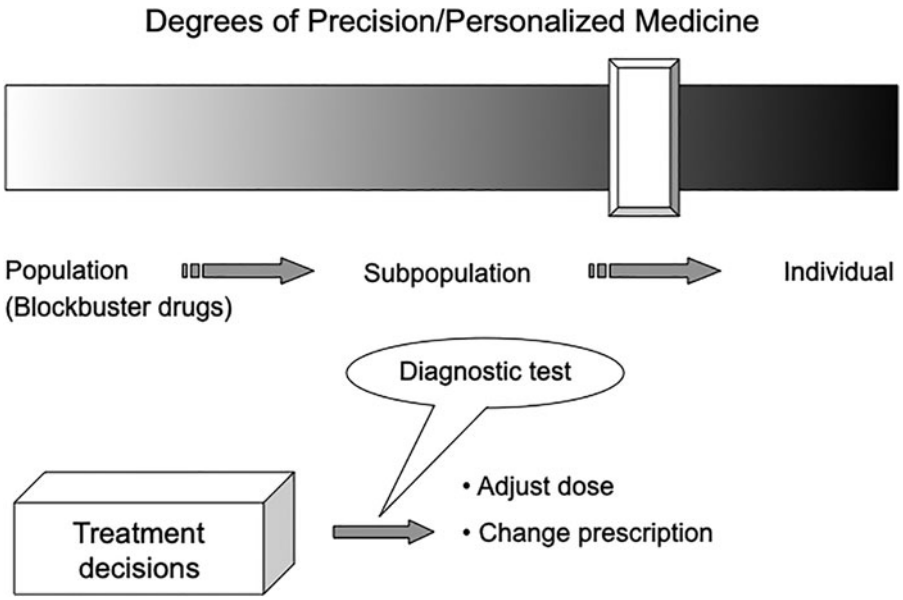

FIG. 1. Degrees of precision/personalized medicine. Personalization of therapeutics ranges from blockbuster drugs targeted for the entire population without individual tailoring to those highly personalized for an individual patient. Personalized medicine, to some degree, is a misnomer in that individualization of therapeutics actually occurs in subgroups of patients who share a certain biomarker signature. Following a biomarker test, two key decisions to customize drug therapy include (1) titrating the medication dose and/or (2) changing the prescription for another medicine.

fava) has been cultivated in the Mediterranean since the Prehistoric era, the molecular basis of this Pythagorean puzzle was discovered nearly 2500 years later in 1956 by Carson et al. as the inherited deficiency of glucose-6-phosphate dehydrogenase enzyme, one of the early documented accounts of metabolic genetic polymorphism.

From the perspective of western medicine, doctors are encouraged to quantify and describe clinical phenotypes and decipher the mechanisms underpinning patients' symptoms. In this sense, western medicine has progressed by constant questioning between the unknown and the known, and imperfect and perfect (Kaptchuk, 1982; Wang et al., 2014; Yun et al., 2012). Traditional medicine, on the other hand, has been practiced in various geographies with a greater emphasis on the complete individual, including a person's biological, social, and environmental context in a holistic manner to establish diagnosis and offer treatments based on patterns of disharmony in these dimensions. In this sense, personalized medicine has a long history, in part, drawing from the worldwide traditional medicine.

Throughout the 20th century, diagnostic medicine continued to expand its scope from biochemical genetics and applications in human diseases to a new generation of tests that blended therapeutics and diagnostics, theranostics, to individualize health interventions broadly (Fig. 2). A historical analysis of diagnostics in therapeutics is available elsewhere (Kalow, 2001; Özdemir, 2015, 2020a). The following salient events in the second half of the past century are, however, noteworthy for the purposes of this article:

> These advances in human biochemical genetics in the first half of the 20th century set the stage for the idea (role of genetic factors in drug effects) proposed by Arno G. Motulsky (Seattle), in his seminal article in October 1957, with the programmatic title ''Drug Reactions, Enzymes and Biochemical Genetics,'' indicating the confluence of biochemistry and genetics within the specific context of pharmacology (Motulsky, 1957). Two years later, the term pharmacogenetics was coined by Friedrich Vogel of Heidelberg, Germany (i.e., long before ''pharmacogenomics'' became a popular term and research topic) (Vogel, 1959). The first book on pharmacogenetics was published by Werner Kalow (Toronto), which definitively established the field of pharmacogenetics (Kalow, 1962; Ozdemir et al., 2009).

Subsequently, several seminal twin studies provided support to the idea that heredity plays an important role in drug metabolism and pharmacokinetics (Endrenyi et al., 1976; Vesell and Page, 1968), which buttressed personalized medicine science and paved the way for the discovery of the sparteine/debrisoquine (*CYP2D6*) monogenic polymorphism

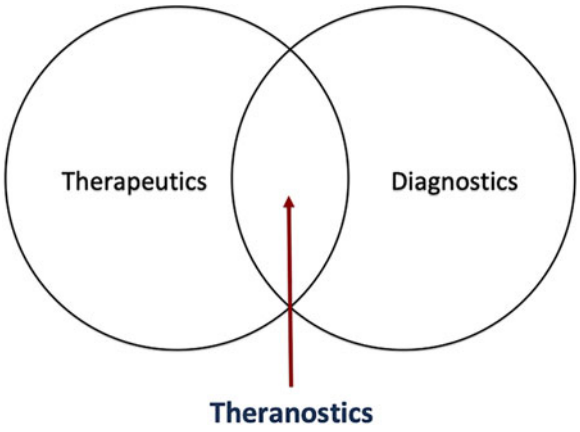

FIG. 2. Theranostics is the intersection and overlap of therapeutics and diagnostics.

in Germany (Eichelbaum et al., 1975a, 1975b, 1979) and England (Mahgoub et al., 1977).

Beginning in the 1990s, the Human Genome Project cultivated the expectations for and investments in personalized medicine further. On the other hand, while the early 1990s witnessed the rise of hypothesis-free omics research, biological plausibility, clinical sense-making, and societal contextualization of omics data remain relevant to robust and responsible personalized medicine science.

Personalized medicine is, however, in need of a renewed vision that extends beyond genomics, and one that triangulates knowledge from multiple omics (multiomics) technologies (Ma et al., 2018) as well as social sciences and humanities (Conley, 2018; Fisher, 2018; Garvey and Maskal, 2020). To these ends, there is evidence, for example, that laboratory research thrives better upon integration with natural and social sciences, enhancing the creative processes in the laboratory and helping generate novel ideas in scientific practice (Conley, 2018; Fisher, 2018; Fisher et al., 2010; York et al., 2019a).

In the next two sections, we discuss the ways in which a social science and humanities conceptual lens on molecular constituents of the cell might help explain the ''sugar lag'' in personalized medicine diagnostics, or put in other words, why carbohydrate-based biomarkers are not yet recognized as much as they ought to be, and on par with genomics and proteomics.

Sociology of the Cell and Biomolecules

Chief among the attributes that make biology intriguing and fascinating is that it is never static. Dynamic feedback systems continuously sense and respond to an ever diverse and broad range of biochemical signals within and between cells, organs, and biosystems. This intense molecular communication across biological networks is not, however, detached from the social, economic, and political environments in which personalized medicine science is embedded. We have recently termed this broader framing of the environment with its physical, social, and political constituents as the ''environtome'' (Hekim and Özdemir, 2017).

The values and interests of the scientists, funders, and innovation actors enact on the cell constituents, attributing greater or lesser importance to some biomolecules, and thus creating sociotechnical hierarchical organizations that do not necessarily exist in nature or within the materiality of the cell itself. Indeed, genes, proteins, and carbohydrates perform delicately coordinated and interdependent functions together in a cell. A notion of hierarchical importance of one molecule over another is neither tenable nor compatible with survival of the cell and the whole organism. Life, as we know it, would cease to exist if nucleic acids, proteins, or carbohydrates, any one of them, were removed from the interdependent molecular machinery in the cell.

Such knowledge artifacts on greater/lesser importance of one biomolecule over another are co-created by human values and the materiality of the technology. We discuss below the sociomaterial construction of scientific knowledge in relationship to why the sugar code might not (yet) have achieved the commensurate attention it deserves from personalized medicine science, policymakers, regulators, or the pharmaceutical and diagnostic industry.

Life Needs More than Nucleic Acids and Proteins

Broadening personalized medicine vision and its molecular targets

There are four, and equally important, major building blocks of life, comprising nucleic acids (e.g., DNA and RNA), proteins, lipids, and carbohydrates (glycans). Yet, an alien visitor to planet Earth attempting to read the contemporary textbooks on molecular biology and diagnostic medicine might think that life and biology are primarily governed by two omnipresent biomolecules: nucleic acids and proteins (Fig. 3). The latter are also known as the first and second alphabet, respectively, of biology. A crucial actor missing in the above account of the cell is, however, the carbohydrates, and glycans in particular. Glycans are polymers of simple sugars (monosaccharides) that conjugate with proteins and lipids forming glycoproteins and glycolipids, respectively.

Carbohydrates are the underappreciated building blocks of life that have broad physiological significance as signaling molecules, in addition to serving as a source of energy, component of the nucleic acid backbone, and biological cement of the cell wall structures. Carbohydrates serve as executive molecules coordinating finely tuned strategic communication within and between cells and biological networks (Gabius, 2017; Wang, 2019). To this end, it is noteworthy that the cell surfaces are often covered with a fuzzy ''sugar coat'' or the glycocalyx.

Glycans and their conjugated forms contribute to the glycocalyx and its diversity, cell-to-cell communication, and recognition of host versus foreign cells such as infectious agents or tissues from another organism in the case of organ transplantation. In this sense, glycans are central to health and disease, and mediate our appropriately informed

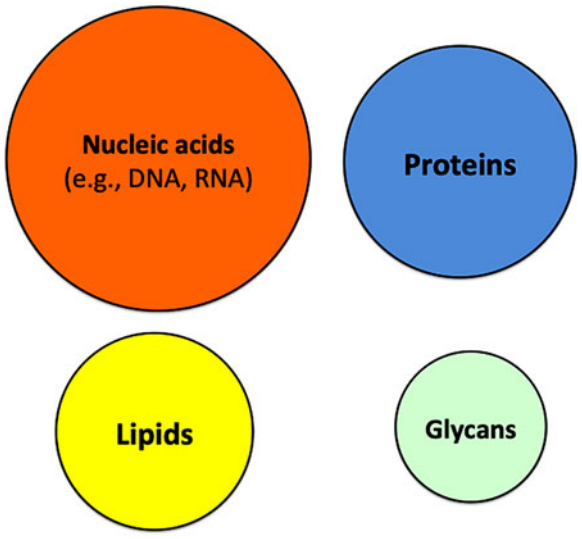

FIG. 3. The four building blocks of life. Nucleic acids and proteins are shown *larger* in the figure to underline the historically greater social constructivism enacted on and attention paid to these two molecules compared to, for example, carbohydrates (glycans) in biomarker development and personalized medicine. In the cell, all biomolecules are essential to sustain life, not to mention for robust diagnostics that can help individualize therapeutics.

responses to hostile or benevolent agents in the intercellular space as well as sensing and interacting with the broader cellular environment.

Packing maximum information in a tight space

For biological significance of glycans, consider the following analogy. Glycans resemble to a communications and press attaché handling high-density information in a small space. Much like downtown New York, Johannesburg, Amsterdam, İstanbul, Beijing, Melbourne, or Tokyo, the physical space is at a premium on the cell surface. Any molecule acting in the capacity of a signaling and communications agent ought to pack maximum information in a minimum space; it does not have the luxury to spread out various functions and utilities across spatial coordinates on the cell membrane—as one might do in a large house with multiple rooms to distribute daily activities such as writing, cooking, laundry, and so on. Cell-to-cell communication on the cell surface takes place in a constrained physical space where many molecular languages ought to be recognized and spoken at the same time.

From an evolutionary and cell physiology standpoint, therefore, any signaling molecule on the cell surface has to be highly versatile and ''multilingual'' in a cramped space to recognize a diverse range of cells and molecular signals. And glycans are perfectly structured to do precisely that (Springer and Gagneux, 2013; Winterburn and Phelps, 1972).

Cell surfaces are interfaces for communication among cells and tissues. Glycans pack high-density information on the cell surface and speak multiple molecular languages for cell-to-cell communication. This is achieved by the unique composition of glycans, and sites of attachment on molecules, which offer such versatile and efficient functions, as described earlier:

> …(glycans) is unsurpassed in nature due to the unique property of independently combining the following parameters with sequence: anomeric status, linkage positions, ring size, addition of branches and site-specific introduction of substitutions. The monosaccharides (letters of the third alphabet of life) thus generate 'words' (signals) of high-density coding capacity. These 'words' are part of the glycans on proteins and lipids, and the glycome represented by these 'words' in their entirety has cell type-dependent features (Gabius and Roth, 2017).

Taken together, glycans and the sugar code are capable to harbor much more information than nucleic acids or proteins of equal size (Gabius, 2017). Glycans occur ubiquitously in nature. Over 50% of all proteins within the cell undergo modification by glycosylation. Glycans and their conjugates with proteins and lipids help steer the molecules and cells to precisely targeted destinations in the tissues and during development of the whole organism. Glycans also shape the structure, function, stability, folding, half-life, trafficking, and solubility of proteins (Wang, 2019). Glycoconjugation is one of the most prominent types of posttranslational modifications in molecular biology.

A Question

If glycans and the sugar code have such significance for life, health, and disease, why have they not taken off in the mainstream personalized medicine discourse in ways proportional to their importance in biology, and on par with the DNA and the protein code or the genomic and proteomic diagnostics?

This question is critically relevant to the futures of personalized glycomedicine (Reily et al., 2019; Wang et al., 2019) and recent discussions on the concept of para-central dogma in cell biology (Ma et al., 2018; Wang, 2019). The question also relates well to efforts for deploying and integrating multiomics biomarker research across genomics, proteomics, and glycomics, and to account for not only genomic and proteomic contributions to drug response but also those from individual differences in glycan structure and function. In support of this much needed multiomics integrative vision of personalized medicine, Liu et al. (2019) have hinted that genomics, alone, will not suffice to solve the puzzle on biological determinants of type 2 diabetes mellitus (T2DM):

> By the end of 2018, >143 genetic variants had been identified as associated with T2DM, blood glucose, or insulin levels, though these only explain <15% of the disease risk (Skyler et al., 2017; Xue et al., 2018), suggesting that epigenetic regulation and post-translational modification play important roles in the etiology of T2DM (Liu et al., 2019).

Still, a multiomics technology frame, alone, does not fully answer what we termed in this article as the ''sugar lag.'' This calls for a broader sociomaterial analysis of the mystery on the sugar lag in personalized medicine diagnostics.

Template-Free Synthesis of Glycans

Why does it matter for sociology of the cell?

A sharp demarcation exists between the materiality of glycans versus the nucleic acids and proteins. Glycans differ from nucleic acids such as DNA as well as proteins in terms of their complexity and biosynthesis. Unlike the template-driven production of proteins by the information stored in nucleic acids (the DNA code), glycan biosynthesis and the sugar code are not template driven, although glycosylation, the key process in glycan formation, is tightly regulated in the endoplasmic reticulum and the Golgi apparatus.

Because the glycan synthesis is not directly driven by a template, it is more open ended, whereas the nucleic acid templates dictate the synthesis of proteins in an orderly manner. The lesson from this material difference, for our purposes, is that glycan structure and its open-ended synthesis create, on the one hand, endless possibilities for glycans to engage with diverse molecules for cellular communication or the ability to ''speak multiple cellular languages.'' On the other hand, the template-free biosynthesis and related material properties of glycans make decoding of the information stored in the sugar code much more complex, labor-intensive, and future-uncertain as a project. By contrast, the DNA code and the sequencing of a finite length of genome come across, in the minds of many innovation actors, especially funders, business community, and investors in personalized medicine, a rather future-proof, foreseeable process, and one that is likely amenable to planning as a project by conventional road maps and milestones.

There are decades of scholarship in social studies of science that the innovation futures are, however, never future-proof and subject to not only technical but also social,

economic, and political risks. That is, risk is more about values, culture, and politics rather than technology, as rightly argued on many occasions by social scientists and humanists (Guston, 2019; Sarewitz, 2015). For every technical risk, there are presumably dozens of political risks on the horizon that can intervene, facilitate, or stall the futures of an emerging technology (Özdemir, 2020a).

Still, the predilection for and the interest in future-proof technologies continue to be a chief consideration for investors and other actors in innovation ecosystems of the early 21st century. If we add to this the pressures placed on scientists, be they in academia, industry, or government, to turn their discoveries to products in short time frames, it is not difficult to appreciate that the discourses on ostensibly future-proof technologies might eclipse or trump the decades of scholarship from social sciences and humanities that argue in favor of a broader lens to understand the nuances and uncertainties of everyday laboratory life.

A Hypothesis on the "Sugar Lag"

While social scientists have historically noted the importance of constructivism (e.g., how people interpret technology and build their values, hopes, and expectations into emerging technologies), scientists relied on the material properties of technologies in explaining why some innovations emerge rapidly and are more popular than others. Material aspects of a technology are not limited to physical attributes, but can also include laboratory objects, buildings, physical bodies of scientists, and genome sequencing machinery or digital algorithms and software that are often part of a technology. On the other hand, the theory of sociomateriality (Orlikowski, 2007; Scott and Orlikowski, 2013) integrates these two explanations by highlighting the inherent entanglement of the social and the material contributions to knowledge from everyday laboratory life (Fig. 4).

We present here a new hypothesis on the sugar lag in personalized medicine based on a sociomaterial conceptual lens.

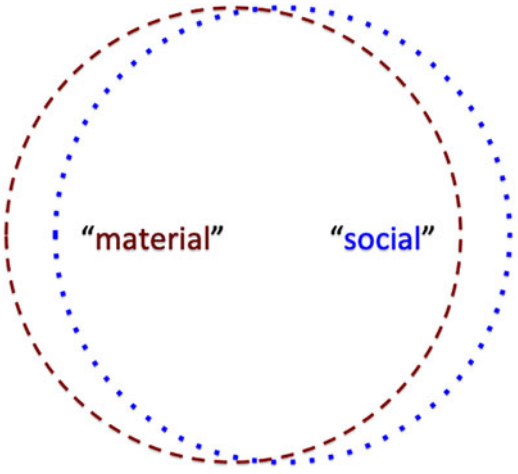

FIG. 4. Schematic representation of the sociomateriality concept: the fusion of the material and social aspects of knowledge in ways that are co-constitutive and inextricably entangled. Note also the porous and fuzzy borders between the social and material dimensions of knowledge that further point at their entanglement.

Hypothesis

Because the materiality and synthesis of glycans are not directly driven by a template, and more complex and open ended than sequencing of a finite-length genome, social construction of expectations from unraveling of the sugar code versus the DNA code might have evolved differently, as being future-uncertain and future-proof, respectively, thus potentially explaining the ''sugar lag'' in personalized medicine over the past decades.

This hypothesis, we suggest, is worth reflecting on by scholars in systems sciences as well as social sciences and humanities.

Sociomateriality

Learning in knowledge interstices

Sociomateriality draws, in part, from the works of Karen Barad and feminist science studies. Barad has, for example, noted the following:

> For all its internal differences, feminist science studies does not hold as its first priority the proper description of what it is that scientists do, but instead asks: How might science be practiced more responsibly, more justly? This issue is my passion, which is what drew me as a scientist into the discussion in the first place. It is no coincidence that so many feminist science studies scholars have been trained as scientists and that we have not shied away from expressing our deep love for science and this astonishingly remarkable, intricate, amazing world of which we are a part (Barad, 2011)

This suggests to the reader that it is possible to engage with both science and science studies or the social dimensions of technology at the same time. For scientists, sociomateriality offers a new dimension and explanation that knowledge and popularity of a technology are a co-product of both technology and social systems that are inseparable and inextricably linked with each other, for example, in ways human values, politics, and power, with capital P, are built into the materiality of the emerging technologies (Fig. 4).

For social scientists and humanists, sociomateriality is an invitation to rethink social constructivism in light of the variable materiality of technologies, and that

- Differences in materiality of technologies can result in different social constructions of knowledge and representations of reality (e.g., in content and intensity of constructivism),
- All technology materialities are not necessarily equivalent vis-à-vis the propensity for social construction of knowledge, as discussed above for the DNA code versus the sugar code.

One might argue that sociomateriality works in a spirit of sociotechnical integration. Importantly, the dimensions of power and politics remain important for social justice and whether we approach to scientific knowledge and emerging technology governance through a sociomaterial lens or other conceptual framings to make sense of emerging innovations.

In sum, sociomateriality invites, on the one hand, the social scientists and humanists to learn more about a given technology's materiality, and on the other hand, the laboratory

scientists to learn about social constructivism and the inextricable entanglement of the social and the material dimensions in science and society.

Such collaborative interdisciplinary learning often happens in hitherto unplanned and occult spatial and temporal interstices. This may demand improvisation, reflexivity, and openness toward new framings of science and technology. The rewards can be enormous, transformative, and enduring in terms of both normative/principled and instrumental contexts of science and innovation. We discuss below the added value of engaging with technical and critically informed social dimensions of knowledge and sense-making in everyday laboratory life in more detail, with examples from the responsible innovation field and governance of emerging technologies.

Seeking the Sociomaterial Roots of Knowledge

The second half of the 20th century has come to see the social context as formative as the materiality of the technology itself in making broader sense from laboratory knowledge and the data that flow from the genome sequencers. At least within the critically informed social sciences and humanities, this was the case (Collins and Evans, 2002). While scientists and engineers trained in the tradition of modernist science have come to view, for the past 400 years since the Enlightenment in the 16th and 17th centuries, knowledge as being value free or unaffected and untouched by scientists' and societal values, social scientists and humanists have gone further so as to view social construction of knowledge and the social context as ''the thing'' or the knowledge in and of itself. At the junction of this two cultures' divide, a little known no man's and no woman's land have long existed, one that advocated for the importance of sociomateriality and that both material differences of technologies and the social and political contexts matter in what we come to accept as reality or knowledge in science and society.

This article aimed to examine how sociomaterial forces might have contributed to the obvious delay in unraveling of the sugar code and glycan-based diagnostics in personalized medicine. However, sociomateriality has been quietly, but surely impacting other fields as well, for example, the contemporary arts, civil engineering, and the architectural design of built environments such as hospital buildings. The latter dimensions are instructive in redesigning personalized medicine with a fresh contemporary and robust vision for its responsible embedding in quotidian science and health care in the 21st century. The examples below help ground the relevance of sociomateriality to rethink knowledge in 21st century.

Contemporary art and sociomateriality

Brian O'Doherty made some of the pioneering observations on the ways in which materiality of the gallery and museum spaces impact how a viewer actually makes sense of contemporary arts, be they presented in paintings, installation art, or other forms and formats. In this regard, there are striking parallels between the modernist science and contemporary art discourses. In fine arts and contemporary art, the maxim ''the art is free to take on its own life'' has remained unquestioned since time immemorial throughout the modern era. This is akin to the science and engineering maxim, ''the data speak for itself'' or the phrase ''raw data,'' as they fail to acknowledge that the values of the data analyst and scientific interpreter co-produce scientific conclusions and judgments. Similarly, no data are actually ''raw'' as they, data, already reflect upstream choices made by scientists in terms of which human disease to study, which funding stream the data are generated by, or which laboratory equipment was chosen and why.

In curious resemblance to the modernist science, contemporary art, art museums, and gallery space architectural traditions have historically attempted to strip out the ''context'' in contemporary art gallery design (O'Doherty, 1999). Ironically, the often clinical settings of the contemporary art museums with their white washed or monochromatic walls, minimalist furniture, polished wood floors, or floors covered with carpets to strip out the context of sound, in fact, point to the very contributions of the social and material contexts that co-produce the meanings and shape sense-making upon viewing an art piece.

The materiality of an art gallery and its social context (have you attended an art exhibition over cocktail, cheese, and appetizers, and did it shape your experience of the art?) are the very sociomaterial elements that shape what we judge as the ''artistic reality'' in much the same way scientific knowledge is shaped by sociomateriality of the everyday laboratory life.

Sociomateriality in architectural design and civil engineering

Privacy is one of the most central dimensions for personalized health care. When patients know their private life is secure in a hospital inpatient room, they can speak comfortably and freely with their loved ones about their medical experiences, and risks and benefits of various treatment options. On the other hand, a hospital room that lacks privacy in material construction and design would not be conducive to delivering personalized medicine. Curiously, hospital architecture design and civil engineering, as crucial as they are to patient privacy, and by extension, to personalized health care, have been eclipsed by discourses on diagnostic tests or the privacy framed narrowly in a context of electronic health records.

We cannot think of personalized medicine and health care without considering the architecture of the built environments. This is especially pertinent in mega metropolis such as Istanbul, Toronto, and others. With the hasty construction epidemic in many countries, condominium and apartment buildings are often being built with their kitchens and living rooms facing an internal empty space, a narrow slim corridor space that extends from the basement to the roof of a tall apartment building, which might save space for the builders and constructers, and thus adding to their profitability. However, the same architectural design also transmits sound bites from the kitchen and other lived spaces, threatening privacy of the residents or in the case of hospital buildings, the privacy of patients staying in a hospital. Such interaction of the building material designs and social contexts in everyday life seems so central to how we experience knowledge, be it in the laboratory or while we are surfing the internet for medical knowledge and discussing it with friends and co-residents in an apartment space.

Governance of Personalized Glycomedicine

Personalized glycomedicine is still in its early phases of development, particularly as a multiomics diagnostic, and integration with demographic, clinical, and nontechnical (social) determinants of drug response. Technologies in their early developmental phase offer ample opportunities for anticipatory governance and social shaping of the normative values embedded on innovation trajectories. Such focus on values is important. It is often falsely assumed that technologies bring about social change, but it is the value-loaded decisions made by innovation actors and institutions that cause social change. It follows, therefore, that emerging technology governance calls for the study of human values embedded in quotidian scientific practices that can, in turn, help illuminate and anticipate the futures in the making for a new technology.

Conversely, a narrow approach to innovation governance based on purely technological and market risks that bracket out human values and power asymmetries results in the accumulation of opaque political fault lines that can stall innovations or create seemingly successful innovations that lack, however, a social justice and ethics pillar (Özdemir, 2019b).

Anticipatory governance is an invitation to scientists and entrepreneurs—to think about alternative and multiple plausible futures for a given technology and broaden our collective cognitive sociotechnical imaginations—so as to enable greater resilience in an innovation ecosystem. Resilience is the ''capacity of any entity—an individual, a community, an organization, or a natural system—to prepare for disruptions, to recover from shocks and stresses, and to adapt and grow from a disruptive experience'' [see discussion in Özdemir, 2019a and Whitmee et al. (2015)].

For emerging technology governance, it is instructive to recall the Collingridge Dilemma that remains relevant to date after four decades of its original publication by Collingridge (1980). The ''Dilemma'' suggests that the timing matters if technology trajectories are to be steered, for example, toward societally desirable outcomes, before technologies become entrenched in a complex web of opaque interests, commitments, and interdependencies:

> The social consequences of a technology cannot be predicted early in the life of the technology. By the time undesirable consequences are discovered, however, the technology is often so much part of the whole economics and social fabric that its control is extremely difficult. This is the *dilemma of control*. When change is easy, the need for it cannot be foreseen; when the need for change is apparent, change has become expensive, difficult and time consuming (Collingridge, 1980, p. 11).

Collingridge's observation hints at the ability of persons and societies, through their individual and collective agencies, to actively steer a technology, while its future(s) are still in the making in the present time, and in ways critically informed by human values and unmet societal needs. Yet, this comes with a trade-off, according to Collingridge, to act when relatively less is known about technology futures, for example, during design, translation, or midstream innovation phases in the laboratory. Conversely, one might choose a ''wait and see'' approach to act after more information is available, for example, during implementation in clinical practice, but this comes with relatively limited ability to change the course of a technology at later stages of development.

Timing is not the only consideration, however, for responsible governance of innovations. The types of methodologies we deploy to map the human values, politics, and power asymmetries related to emerging technologies also matter (Balmer et al., 2015; Lopez and Lunau, 2012; Özdemir and Hekim, 2018; Williams, 2006). For example, in the second half of the 20th century and after 1980s in particular, attempts for innovation governance have tended to employ conceptual frames based on technological determinism and market efficiency, focusing narrowly on specific technologies to uncritically enable their transition to products, rather than targeting grand societal challenges or wicked social problems, and with little consideration for the opportunity costs of investing in a given technology or alternative futures (Editorial, 2015; Özdemir and Springer, 2018). Hence, in addition to the sociomaterial hypothesis presented above, such compressed foresight (Williams, 2006) and narrow theoretical framings of innovation governance have also likely contributed to the lack of adequate consideration for the sugar code and glycan biomarkers in personalized medicine.

Broadening the approaches to governance of innovations would help cultivate greater resilience and technological democracy. And these matter both on principled/normative and instrumental grounds.

Democratizing emerging innovations matter because science and technology impact virtually all facets of life in the 21st century. Knowledge-based economies and technology innovations are being sought after by many developed and developing countries as means for prosperity and security of their nations. The words democracy and innovation, therefore, ought to be considered in tandem because without democracy, a purely product and market efficiency-oriented technocratic vision does not necessarily guarantee social justice, how innovation outcomes, benefits are distributed in societies, and whether and to what extent innovations address unmet societal needs, and are designed in a value-sensitive manner. These are also important in shaping how we relate to each other as human kinds and other sentient beings in nature, and what kind of society and environment we leave for the next generations (Özdemir, 2019a; Thunberg, 2019; Unigwe, 2019; van Beinum, 2019).

Democratizing knowledge and emerging technologies is also relevant instrumentally to enable science and innovation. Empirically grounded comparative studies of the historical and current nation states have shown, for example, that prosperity depends on inclusiveness of economic and political institutions —when many people have a say in political decision making (Acemoglu and Robinson, 2012). While the latter work by Acemoglu and Robinson (2012) preceded the rise of the post-truth era (Geiselberger, 2017) and may not explain all current cases of democratic governance and their linkages with prosperity, it is nonetheless a worthwhile resource to consider why democratic institutions matter instrumentally to enable innovations. Moreover, and as noted earlier, considering a broader range of social values might also enhance creativity in laboratory science, as shown in the case of nanotechnology, for example (Fisher et al., 2010).

Responsible Innovation

An opportunity to broaden science and society relationship

Scientific expertise currently faces a problem of legitimacy (Fisher, 2017; van Oudheusden, 2014). This is reflected, for example, in difficulties to reproduce research findings in both established and emerging fields of scientific inquiry, controversies in applications of new technologies such as CRISPR, or the long-standing gulfs between what scientific designs tend to target and what society and public health might actually need or value in terms of preferences or local community priorities. Responses to these questions have generally resulted in calls for standardization of science and technology, which in and of itself can be useful, but still fall far short of the broader types of risks and threats such as the opaque values and politics embedded in emerging technologies and innovations. As noted earlier, for every narrowly understood technical risk, there are often dozens, if not more, of political risks on innovation horizons that pose larger threats to sustainability, ethics, and social justice dimensions of science and technology outputs (Özdemir, 2020a).

Responsible innovation is a new conceptual framework and practice in thinking about the politics of and the relationships among science, technology, and society, as well as a social movement to redress the deficits in the global research and innovation ecosystem. It is also an effort to introduce the crucial political science scholarship and critically informed approaches that tended to be absent in previous social analysis of emerging technologies. For example, responsible innovation in the new field of planetary health emphasizes the need to question ''Who is framing the social issues emergent from a new technology, and why?'' as much as ''What social issues emerge from a new technology?'' (Kilic, 2019; Özdemir, 2019a). This expansion from content to framing of social issues is necessary to avoid the reductionist, single variable driven or simplistic analysis of the ethical issues attendant to new technologies.

As with systems sciences that question the frames of knowledge and the big picture in science, we also need ''systems ethics'' that bodes well with the concept and movement of responsible innovation. Calls for responsible innovation have varied reasons, some of which are highlighted in Table 1.

Responsible innovation is not just a call to broaden our thinking on science, innovation, and critically informed governance. Many funding agencies around the world require responsible innovation research as part of the application dossiers for health, engineering, or other science and technology funding.

Along these lines, the United States National Science Foundation (NSF) instituted the ''broader impacts review criterion'' for peer review and project funding (Holbrook, 2005) and the United States Congress mandated the integration of societal concerns into nanotechnology research, development, and commercialization in 2003 (Fisher, 2019a). The Netherlands Council for Research (NWO) has a dedicated internationally oriented program on responsible innovation. The Research Council of Norway has created the responsible innovation and corporate social responsibility (SAMANSVAR) program, while the NSF has funded the Virtual Institute of Responsible Innovation (VIRI), and the United Kingdom Engineering and Physical Sciences Research Council had a long-standing interest on the subject for at least a decade (see, for a discussion, Owen, 2014; Von Schomberg and Hankins, 2019a; Von Schomberg, 2019a, 2019b).

Table 1. Rationales for Responsible Innovation

- Outcomes of innovations need critically informed governance and steering of science and technology in ways attuned to broader societal values.
- There is an acute need to broaden the market efficiency criterion so as to deliver on societally desirable innovations.
- Governance of science and technology is a society-wide endeavor and cannot be limited to governmental control, scientific autonomy, or privatization.
- Reliance on the market efficiency criteria, alone, does not necessarily guarantee societally desirable or ethical innovations.
- Principals of responsible innovation—anticipation, inclusiveness, reflexivity, and responsiveness to broader societal values—can be explicitly incorporated into research, education, and entrepreneurial efforts. There is ample and long-standing expertise across social sciences and humanities from which scientists in personalized medicine can productively draw from.
- There is a need to shift from technological potentials to societally desirable outcomes and Value-Sensitive Design (VSD) in governance of innovations.
- We need to shift to open scholarship and surface the human values and power asymmetries embedded in emerging technologies for critically informed, ethics-driven, democratic, and sustainable science, technology, and innovation practices in the 21st century.

Synthesized from Von Schomberg (2019a), Fisher (2018), and Özdemir (2019a).

The readers in systems sciences, health research, and medical practice can find the diverse conceptual and practical approaches to responsible innovation in the Journal of Responsible Innovation, launched in 2013 (Fisher, 2019b; Guston, 2015), and the International Handbook on Responsible Innovation. A Global Resource, published in 2019 (Von Schomberg and Hankins, 2019b).

Before we discuss recent examples of responsible innovation research and what scientists, health researchers, and engineers might need to know on new funding streams that involve and require responsible innovation, for example, in the European Union, we present below two definitions of responsible innovation by von Schomberg (2011) and Fisher (2018):

> Responsible Research and Innovation is a transparent, interactive process by which societal actors and innovators become mutually responsive to each other with a view to the (ethical) acceptability, sustainability and societal desirability of the innovation process and its marketable products (in order to allow a proper embedding of scientific and technological advances in our society) (von Schomberg, 2011).
>
> RI is an ideal aspiration for the process of governing emerging technologies in society. Like several of its predecessors, this aspiration points to the challenging yet urgent need to combine distinct, sometimes conflicting values and categories that are normally treated separately in modern

> societies and their institutions. RI is an expression of the need to integrate the promotion and regulation of scientific and technological novelty and its development and dissemination. Importantly, RI recognizes that the governance of science and technology is a society-wide endeavor that cannot be limited to governmental control, scientific autonomy, or privatization. In short, it requires scientific and innovation processes to be continually responsive to a wide variety of societal inputs, signals, and values (Fisher, 2018).

At what developmental stage of an emerging technology and innovation shall we then consider responsible innovation? What are the ways in which the emerging fields of personalized glycomedicine and carbohydrate (glycan)-based diagnostics might engage with responsible innovation research? Moreover, glycomedicine relates to allied fields of expertise within the umbrella term and field of personalized medicine, such as pharmacomicrobiomics and metagenomics, which collectively stand to benefit from responsible innovation scholarship (Aziz et al., 2020; Eraqi et al., 2018).

Other personalized medicine fields to benefit from responsible innovation

It has been a decade since the term pharmacomicrobiomics was coined (Rizkallah et al., 2010) to describe the mutual interactions between drugs, human systems, and the microbial cloud associated with human organs—the microbiome (Elrakaiby et al., 2014). The extended metabolic potential of the human microbiome surpasses and expands the human metabolic potential, and thus has much more potential to modulate drug therapy at the pharmacokinetic and pharmacodynamic level. Accordingly, pharmacomicrobiomics was defined as follows:

> … the (systematic) study of drug-microbiome interactions. More specifically, it is the study of how intra- and inter-individual microbiome variations affect drug action, disposition, efficacy, and toxicity. The emphasis here is on the effect of microbiome (i.e., microbial community) variations on pharmacokinetics and pharmacodynamics of drug therapy, rather than interactions between drugs and individual microbes (Aziz, 2018).

Although dozens of drug–microbe interactions have been described in the past century, two major dramatic changes have been initiated by the Human Microbiome Project: (1) previously reported interactions were scattered and came from sporadic studies, not following any particularly systematic approach (Aziz et al., 2020). (2) Previously reported interactions focused on the action of particular microbes or microbial enzymes on drugs, or the interaction of microbial metabolites with drugs; however, pharmacomicrobiomics is centered on the effect of microbiome variations on precision therapeutics (Aziz, 2018). Both of these old and new perspectives have overlooked the involvement of glycoproteins and glycolipids in drug metabolism. While glycosylation of drug molecules has been considered, the role of glycosylation in post-translational modification and how it may affect drug–microbiome interactions have not been systematically considered—to the best of our knowledge.

Metagenomics is an important driver of the field of pharmacomicrobiomics and stands to benefit from responsible innovation theory on its developmental trajectory. Metagenomics is now an essential tool to carefully identify and investigate the variable key players in any ecosystem. Metagenomic analysis includes microbial community structural analysis, functional potential and pathway analysis, full genome analysis through assembly of shotgun sequences, or functional screening for a particular gene activity, and identification of metabolic pathways leading to degradation or production of certain compounds. In addition, metatranscriptomic analysis allows whole gene expression profiling of complex microbial communities.

Spatial and temporal microbial community structural differences of aquatic environments contribute to the ecosystem on both a local and a global level. The marine phytoplankton contributes to almost half of the photosynthetic reactions occurring on a global scale (Behrenfeld, 2014). Freshwater systems (rivers, lakes, streams, and even glaciers) need microbial community analysis to monitor the influence of xenobiotic and anthropogenic inputs, particularly in urban and industrial settings (Abraham, 2011). Wastewater treatment plants are an integral component of any society and the microbial community compositions in their effluents, as besides the distribution of antibiotic resistance genes, need careful investigation.

Metagenomic analysis has essential applications looking into soil composition. Sediments along riverbeds and banks, in addition to seashores and coastal regions, are all potential candidates to be affected by pollution, anthropogenic inputs, and climate change, which can influence their microbial composition. Soil microbial communities are key players in balancing carbon and nitrogen cycles. Consequently, it is essential to carefully investigate microbial community structures and their functional potential and activities in forests and deserts (each representing one third of the planet's biome), mountains, and even mines.

Plants (including crops) are strongly associated with microbial communities existing in their roots (endospheres) and surrounding environments (rhizospheres) (Berg et al., 2014). The influence of drought on the composition and function of such communities is still far from being deciphered (Naylor and Coleman-Derr, 2018). Another critical aspect is the relationship between these microbial communities and various crops diseases that can influence the agricultural productivity in many areas in desperate need to guarantee their food supplies.

Domestic and farm animals' microbiomes as well as their metagenome analysis contribute to the recent rise of planetary health scholarship, linking ecology, sociology, and political science with human and nonhuman animal health. As metagenomics technology and the emerging field of pharmacomicrobiomics are further embedded in society, their social dimensions and corollaries are important to examine in real time as well.

Concepts and Tools to Practice Responsible Innovation

Sociotechnical integration research

In thinking about the ways to embed responsible innovation in various fields of personalized medicine described above, sociotechnical integration research (STIR) is one of the prominent approaches and conceptual frames.

Erik Fisher has provided a definition for sociotechnical integration that allows future collaborators to agree in

principle and on an integrative ideal, while allowing room for a variety of approaches in putting it into practice. Accordingly, ''sociotechnical integration occurs whenever technical experts take into account the broader societal dimensions of their work as an integral part of that work'' (Fisher, 2019c).

Responsible innovation can materialize in upstream, midstream, and downstream stages of innovation, and at multiple levels, time frames, and decision-making sites, nor is it confined to one realm of the science and innovation process.

In the case of STIR, integrating high-impact reflection into routine scientific, medical, and engineering practices serves as a potent means by which to more closely align technology with societal values. While traditional disciplinary perspectives and increasingly outdated policy models seek to keep scientific practice separate from reflection on societal values, STIR collaborations in over 60 organizations across nearly two dozen countries have demonstrated that the two can be synergistically combined. To elucidate choice and prime creative solutions, STIR uses a decision protocol to guide regular collaborative exercises that map sociomaterial uncertainties, options, and values in real time, during routine laboratory and innovation activities.

Typical outcomes include reflexive learning, value deliberation, and practical adjustments over a 12-week period (Fisher et al., 2019a). These ''modulations'' can support scientific discovery, technological advancement, and sociotechnical value alignment.

For instance, in a pilot study, Fisher (2007) documented the sequence of events that led an engineering laboratory to adopt a new, more environmentally benign chemical catalyst for synthesizing carbon nanotubes, thereby reviving an abandoned project and ultimately providing the main doctoral engineering student collaborator with a novel dissertation topic.

Subsequent applications of the STIR process have produced comparable results. Fisher et al. (2010) reported that ''reflections on responsible innovation generated novel ideas for antenna structures and nanoparticle synthesis'' in a case of nanobiotechnology energy research, and Schuubiers (2011) found that two studies that he conducted in synthetic biology laboratories ''confirm the utility'' of STIR in supporting multiple forms of learning. Flipse et al. (2013, 2014) demonstrated in separate STIR studies that innovation managers at one biotechnology firm came to view societal value integration as ''part of the job'' (2013) after initially rejecting the idea, and that innovation managers at a second biotechnology firm report integration were ''functional and useful'' since it ''measurably improved'' research and development performance (2014).

In addition to producing effective modulations in research and innovation, social scientists and humanities scholars also become versed in the theory and methods of their scientific counterparts. Conley and Fisher (2019) recount how a political scientist learned to perform ''exemplary'' polymerase chain reaction experiments in one medical genetics laboratory and subsequently transferred her knowledge, contributing to improved laboratory experiments in a second medical genetic laboratory.

STIR's effectiveness at the organizational level and in engineering-only teams has also been documented. Fisher et al. (2019a) detailed one ''center-level impact'' of the approach, in which STIR collaborations were found to overcome more barriers to interdisciplinarity than other types of interdisciplinary teams. McTiernan et al. (2016) report on productive outcomes of an engineering-led application of STIR. Similarly, the 2016 international Genetically Engineered Machines competition winning team explains their adaptation of the STIR protocol (http://2016.igem.org/Team:Imperial_College/Integrated_Practices).

More recent applications of STIR have explored its effectiveness in diverse organizational and institutional settings, including energy innovation in contrasting United States urban environments (Fisher et al., 2019b; Richter et al., 2017); the Dutch construction industry (Flipse and van de Loo, 2018); nuclear radiation research in Belgium, Spain, and Estonia (van Oudheusden et al., 2018, 2019); and various post-Soviet Hungarian laboratory and science educational settings (Lukovics and Fisher, 2017; Lukovics et al., 2017, 2019). Currently, ongoing STIR studies are being conducted in medical laboratories in Mexico and France. In addition, STIR is being explored as a pedagogical approach in the classroom and in undergraduate capstone projects, piloted by Conley and others as described in the next section.

Scientists working in personalized medicine have several opportunities to engage with STIR practitioners through the VIRI (http://cns.asu.edu/viri) and the related Center for Responsible Innovation (CRI) at Arizona State University. Both VIRI and the CRI host meetings and workshops, and the latter conducts training sessions and organizes STIR studies and collaborations in various locations across the globe.

"Futures Lab" for personalized medicine

As ''makerspaces'' and entrepreneurial design become more in vogue across the world, it became clear to Integrated Science and Technology (ISAT) Professors Shannon Conley and Emily York at James Madison University (JMU) in Virginia, United States, that a new kind of undergraduate laboratory experience, embracing and critically examining sociotechnical complexities, was needed—beyond just ''making'' and innovating for the sake of innovation.

York and Conley approached the laboratory experience with the goal of explicitly connecting and infusing technological work with STIR and other science and technology studies (STS) sensibilities, and establishing an interplay between the two worlds of science and society. With backgrounds in political science, science and technology studies, and communication, Conley and York teach undergraduate classes in the ''social context'' of science and technology in an interdisciplinary science and engineering program (ISAT), and students expressed an eagerness for a ''hands-on'' laboratory experience oriented around social context of new and emerging technologies, much in the same way that they have hands on laboratory experiences for their technically oriented coursework.

Thus, two-and-a-half years ago, the JMU STS Futures Lab was born (York et al., 2019b). The social context laboratory experience has enabled students to become ''engagement agents'' (Conley, 2011) and so as to overcome the ''two cultures'' divide articulated by Snow (1993), in which there is a disconnect and lack of interaction between the humanities/social sciences and technical/natural sciences. Hence, the JMU STS Futures Lab set out to bridge and inform the

students' technical capstone and course work with their work in the Futures Lab, and conversely, enable their technical work to inform how they engage with STS, thus breaking down the knowledge silos and creating a symbiosis between the technical and social science laboratory.

We describe one example below, in which Conley, York, and their laboratory students collaborated with an expert in precision medicine to conduct a hands-on STS analysis and collaboratively ''co-imagine,'' and critically interrogate, futures in precision medicine (York et al., 2019a).

Scenario analysis of emerging technologies

In addition to students working on their own independent projects in the Futures Lab (ranging from topics in reproductive technologies to autonomous vehicles) and participating in STS seminar-style laboratory meetings, they, students, also serve as collaborators on York and Conley's research project ''Co-Imagining Futures with Experts Across Disciplines.'' This research project is oriented around examining the ways in which experts from different disciplines (such as STS and Biotechnology) can establish collaborative ''trading zones'' (Collins, et al., 2007) across disciplinary boundaries and foster interactional competence (Conley and Fisher, 2019) in each other's domains to collaboratively engage in imagining plausible futures in the invited expert's realm of expertise.

To do so, York and Conley have adapted scenario analysis, an approach used in industry that has traditionally been used as a planning tool to flesh out and anticipate plausible futures in a particular realm, about 25–30 years out (Wade, 2012). The process of scenario analysis as adapted in the laboratory context (using the example of precision medicine as elaborated on in York et al., 2019a) is as follows: the expert in precision medicine, Dr. Anne Henriksen (professor Emeritas at JMU), provided readings for York, Conley, and the students in her area of expertise. During this time period, York and Conley conducted a videotaped interview with Dr. Henriksen focused on topics such as how she became interested in precision medicine, what her concerns and hopes for the field are, and how she defined responsible innovation in her field.

Leading up to the Co-Imagining Futures workshop, student teams developed drivers (events, issues, and topics) based on the readings that can later be placed on a scenario cross. Examples of drivers might include high regulation/low regulation and high public acceptance/low public acceptance. Students drafted scenario crosses, plotting the drivers to create distinct quadrants, which they then presented at the workshop. They then worked collaboratively with Dr. Henriksen and York and Conley during the workshop to further refine the crosses, and Henriksen chose additional drivers to be plotted on the scenario cross. Students and faculty worked with Henriksen to flesh out each of the scenario crosses. For example, they collaboratively imagined how, in 25–30 years, there would be a scenario in which there might be low regulation and high public acceptance for precision medicine. Conley and York have found that the student/pedagogical aspect has been crucial elements of maintaining a collegial, friendly environment in which critiques can be made in a nonconfrontational way—in a sense, the students serve as important mediators and the teaching element of the workshop breaks down a siloed ''us versus them'' mindset between the experts. This environment, as noted by York (2018), enables an element of ''critical participation,'' for those involved. Downey and Zhang (2015), as quoted in York 2018, describe critical participation as ''figuring out ways of doing STS analysis so it maximally inflects the knowledge, expertise, identities, and commitments of those we study and with whom we work. It also means being willing to accept the risks of having our practices of knowledge production, knowledge expression, and knowledge travel inflected by them as well.'' (For in-depth additional details on this engagement, please see York et al., 2019a)

"Design fiction" to map the societal context of new technologies

Following the scenario analysis component of the workshop, Dr. Henriksen selected a quadrant from each student team that she wanted to explore more in depth. Student teams were then tasked with creating a ''design fiction.'' Design fiction blends science fiction, art, and design thinking to create a two-dimensional or three-dimensional (3D) representation of a particular technology as an everyday object in a particular future (Bleecker, 2009). This approach invokes Winner's notion of ''technologies as forms of life,'' (2014) in which technologies interact with, shape, and inform human interaction and sociotechnical outcomes. Design fictions can be anything as a quick sketch of stick figures to elaborate 3D dioramas. After the students, expert, and faculty sketched out their design fictions, they engaged in a conversation and unpacking of the future that each design fiction might evoke. Topics such as socioeconomics, fairness, privacy, governance, and others were discussed.

Indeed, the design fiction is not an end to the conversation, but serves as a conversation starter to deeply interrogate what sorts of futures we might want to live in (York et al., 2019a). As a component of the iterative Co-Imaging Futures collaborative ethos, we intend to follow up with Dr. Henriksen, building on our collaboration around precision medicine, regarding the role of carbohydrates and the sugar code in this domain of inquiry.

Thinking AI and human intelligence (HI) together

The introduction of AI technologies into medicine has been decades in the making (Garvey and Maskal, 2020). Yet with the convergence of Big Data, cloud computing, and machine learning (ML) algorithms, contemporary AI appears poised to succeed where earlier paradigms, such as ''expert systems,'' have failed (Garvey, 2018). Today, AI is transforming virtually every area of health care (Topol, 2019) and promises to facilitate personalized medicine by extracting insights about individual patients from large datasets, potentially accelerating the development of glyco-theranostics (Özdemir, 2020b) by providing tools for multiomics data integration.

One thing AI technologies cannot do, however, is eliminate the need for human intelligence (HI) (Özdemir, 2019b). Rather, HI will be in greater demand because the adoption of AI into health care introduces many potential risks requiring careful sociomaterial study, a few of which we touch on here.

It is now widely acknowledged that AI technologies can absorb harmful biases from the data used to train ML

algorithms (Char et al., 2018). However, biases can also arise from data practices like relying on proxies to estimate the state of the world. For example, Obermeyer et al. (2019) demonstrated how an algorithm that used the cost of health care, rather than illness, as a proxy for health significantly discriminated against black patients, potentially affecting millions of people. If the error was corrected, almost 30% more black patients would receive additional care. The study suggests, ''the choice of convenient, seemingly effective proxies for ground truth can be an important source of algorithmic bias in many contexts'' (Obermeyer et al., 2019).

Third, however impressive, the superhuman performance of AI systems on specific tasks, for example, object recognition in radiology, does not necessarily translate into clinically meaningful outcomes (Parikh et al., 2019). Recognition of a tumor in an image is only one step in a multistage process. Moreover, AI diagnostics can introduce new classes of risk, such as ''hidden stratification,'' wherein the high accuracy of a given AI system on large datasets obscures its poor performance on clinically important subsets of cases (Oakden-Rayner et al., 2019). Given the medical truism that serious diseases are generally less common than mild diseases—and may therefore be underrepresented in training data—the potential for misdiagnosis is nontrivial.

More could be said about the cybersecurity risks arising from data privacy issues in medical AI (Pesapane et al., 2018) or the dangers of ''black box'' algorithms and the need for ''explainability'' in AI systems more generally (Wachter et al., 2017), but we close this section by noting that AI is not yet contributing to health in resource-poor settings (Wahl et al., 2018). Like many medical technologies before it, AI risks exacerbating social inequality by providing services such as personalized medicine to wealthier nations in the Global North long before humankind elsewhere benefits (Sarewitz and Woodhouse, 2003).

Regardless of the domain, however, AI systems are sociotechnical systems, products of contingent history and human values as much as technical potentials (Garvey, 2019). Therefore, responsible innovation and other sociomaterial approaches to risk anticipation that make use of HI, such as STIR and scenario analysis, will be necessary to protect against or otherwise mitigate AI risks in personalized glycomedicine.

That said, if the technical community continues to resist critical public engagement with AI (Garvey, 2019), these and other risks could go unaddressed in transitioning glycotheranostics from the laboratory to the marketplace, the promise of AI for personalized medicine could be broken, repeating a pattern seen elsewhere in AI history.

Responsible Innovation in the European Union

What to anticipate after Horizon 2020?

Responsible research and innovation require a form of governance that will direct innovation toward societally desirable outcomes. The specific program for implementing the new European Framework for Research and Innovation (Horizon Europe), which will run from 2021 to 2027, will foresee responsible research and innovation as an operational objective.

Generally, the Horizon Europe will operationalize some key features of responsible innovation across the program: co-creation and co-design of research agendas with Member States of the European Union and stakeholders, including citizen and end users, are part and parcel of the overall design of the Horizon Europe. The sustainable development goals have been identified as consensual societally desirable outcomes of research. More importantly, the program will feature mission-oriented research as one possible mechanism to operationalize responsible innovation for democratically legitimized objectives (e.g., European Parliament, stakeholders and member states were involved in defining the first set of 'missions'), such as climate change and cancer research.

The co-creation and co-design of such missions with stakeholders and citizens with a view on achievable objectives during overseeable timescales will be a challenging endeavor and practiced on a scale that was never demonstrated under previous research and innovation programs.

Yet, we have to understand the distinctive nature of responsible research and responsible innovation and their relationship (Von Schomberg, 2019a, 2019b). In the case of personalized medicine, without doubt, a subject matter of the Horizon Europe, one has to reflect on the reasons for its emergence. In the innovation dimension, the industrial production of medicine is thus far favored by an universalistic, uncustomized, approach (Chinese Traditional Medicine is based on the paradigm of a personalized approach, but it was considered far more easier to market and produce aspirin as a painkiller for all people on earth by the industry). Hence, the shaping of ''personalized'' medicine is likely to be affected by these macroeconomic considerations. Interestingly, this may as well be part of the explanation for the focus in the research dimension on universal principles, such as the template-driven code of DNA that ''conveniently'' ignores the complexity of the open-endedness of the sugar code. With the rise of data science, we may well be able to deal with increased complexity and address the subject matter in more adequate interdisciplinary settings, yet nonuniversal outcomes are not on the radar screen of the pharmaceutical industry and the first products of 'personalized' medicine may well turn out to be disappointing and the employment of data science again may well favor universalistic (blockbuster) outcomes, which, as with current medicine, do not adequately deal. Notably, Edwards et al. (2011) reported that researcher interest has concentrated on fewer than 50 of the 500 known kinases relevant for potential cure of human disease. As these very few kinases promise better economic outcomes, the pharmaceutical industry competes on this narrow range, while neglecting the broader range of kinases that may be fruitful for treatment of human diseases. Open scholarship, by which researchers share knowledge and data as early as possible in the research process with all relevant knowledge actors, is therefore required to enable break-through personalized medicines, as demonstrated, for example, by the Structural Genome Consortium (https://www.thesgc.org/), an Oxford-based non-for-profit organization, which focused its research on those kinases ignored by the industry and brought, since its start in 2004, molecules into more than 25 clinical trials in short time lines.

Open scholarship should not be the exemption, but the rule. The Horizon Europe will promote open scholarship practices, in the expectation that science will become more effective (as we can share resources), reliable (as we collectively verify

data at early stages), and more responsive to societal challenges through the inclusion of stakeholder involvement and citizens.

Conclusions

Decisions made on a day-to-day basis in a scientific laboratory have many unchecked assumptions, human values, and preferences that go unnoticed and unconsciously built into how new technologies emerge, some rapidly, while others do not at all. This has consequences not only for broader social outreach and impacts of science but also how we design and implement science and technology in the laboratory space. These laboratory outputs or iterations are only as useful to the extent they relate to broader societal concerns and values. A good example is the inadequate attention paid to carbohydrate-based diagnostics within personalized medicine over the past decades.

Carbohydrates matter for personalized medicine. Glycotheranostics refers to a new generation of diagnostics to individually tailor drug treatment and other health interventions (Özdemir, 2020b). Despite its importance on par with genomics and proteomics, the unraveling of the sugar code or the third alphabet of life has lagged behind the DNA and the protein codes. This article makes a theoretical contribution by providing a new explanation through a sociomaterial conceptual lens that builds on both social constructivism and the material differences of carbohydrates from other molecules such as nucleic acids, thus calling attention to the sociomateriality of the cell.

The article also makes a practical contribution by bringing together experts in systems sciences with scholars in critically informed social sciences and humanities, which should bode well for responsible innovation as the new field of personalized glycomedicine evolves and advances.

Traditionally, the concepts and practical examples discussed in this article have been considered and published either in science and technology journals or social sciences and humanities journals, thus contributing to knowledge silos or what has been noted as the ''two cultures divide'' (Snow, 1993). As it should be evident to the reader at this stage, a broader perspective on science and technology is not a distraction, but an important remedy to bridge such gaps in science education and framing of knowledge and scholarship in the 21st century. This is not only the opinion of the authors but also, many science and research funding agencies now require formal consideration of the broader social and political dimensions of a research proposal, not separately, but in ways uniquely integrated in a science, engineering, and biomedical project proposal. To this end, the article also provides some of the prominent tools and practical approaches to integrate new technologies with their societal contexts.

A new approach to science and technology, responsible innovation, is emerging in the 21st century, building on a long legacy of critically informed social sciences and humanities. Science education for engineers, biologists, nurses, physicians, and health care workers is also changing, with the rise of ''T-shaped scholars'' schooled in both their subject matter (e.g., engineering) as well as social sciences and humanities (Fig. 5) (Arga, 2019; Conley, 2018; Dandara, 2019; Fisher, 2019c; Fisher et al., 2019b; Garvey, 2018; Özdemir, 2014).

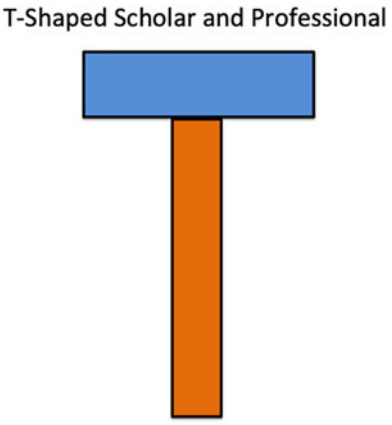

FIG. 5. The new T-shaped scholar: a new generation of scholars and intellectuals schooled in their primary chosen field of professional inquiry (the long and narrow arm of the T) seeking solutions to problems and questions in their specific field, and critically informed by social sciences and humanities (the short, but thick arm of the T) that examine the questions asked in that field of research and excavating the social dimensions, that is, human values, power, and politics, embedded in emerging technologies and scientific practices. For engineers, life scientists, nurses, and physicians, this means seeking the broader and often opaque societal and political contexts in which new technologies and scientific practices emerge. If overlooked, such broader context in which technologies are situated may stall veritable innovations as discussed in this article in relationship to the sugar code. For social scientists and humanists, the T-shaped scholarship invites them to learn about the material differences of new technologies and the built environment of the scientific laboratory so as to decipher the important interplay between social constructivism and materiality in co-production of knowledge.

OMICS has championed integrative science and building strong bridges between science and society for the past decade as a journal of integrative biology (Özdemir, 2013; Özdemir et al., 2009).

Thinking about technology and society in tandem and in real time demands critical systems thinking, however. Not any or uncritically framed technology ethics and policy research methodology will serve toward the goals of reflexive, responsive, responsible, inclusive, and robust science, engineering and medicine (Özdemir, 2019a). This article described some of the salient methodologies such as STIR, design fiction, and scenario analyses that serve as microfoundations for responsible innovation and integrative science education before students embark on their careers and professions.

Responsible innovation is also redefining what is ''part of the job'' of scientists, engineers, and physicians, not only in academia but also in industry, public health, and governmental institutions across the world (Flipse et al., 2013). Aligning the key performance indicators with social dimensions of technology is increasingly being considered useful and beneficial by industries as well (Flipse et al., 2014).

This article proposes that it is not enough to observe and describe the everyday laboratory life and that we ought to address the normative dimensions as well so as to make science democratic and responsible. In other words, questions of

politics and power and ''who and what gets excluded'' matter (Barad, 2011). It is indeed possible to engage with both science and science studies, which, in Karen Barad's words, is as follows:

> A part of that longstanding tradition in feminist science studies that focuses on the possibilities of making a better world, a livable world, a world based on values of coflourishing and mutuality, not fighting and diminishing one another, not closing one another down, but helping to open up our ideas and ourselves to each other and to new possibilities, which with any luck will have the potential to help us see our way through to a world that is more livable, not for some, but for the entangled wellbeing of all (Barad, 2011).

In all, the lessons learned from unraveling of the sugar code, responsible innovation, the history of systems science highlighted here, and sociomateriality of the cell and biomolecules are instructive in charting robust futures for personalized glycomedicine, and other emerging multiomics technologies.

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Abbreviations Used

3D = three dimensional
ADR = adverse drug reaction
AI = artificial intelligence
CI = confidence interval
CRI = Center for Responsible Innovation
HI = human intelligence
ISAT = Integrated Science and Technology
JMU = James Madison University
ML = machine learning
NSF = National Science Foundation
STIR = sociotechnical integration research
STS = science and technology studies
T2DM = type 2 diabetes mellitus
VIRI = Virtual Institute of Responsible Innovation