Part V

VARIABILITY AND DIVERSITY
In Search of a Definition

There are two prevalent characterizations of “personalized” or “precision” medicine (PM; the abbreviation “PM” will refer to both of these terms, as they describe the same or very similar ideas, and whatever difference might exist between them will not matter for the purposes of this chapter). Their common core is the idea that medical treatment should be tailored to the individual characteristics of each patient in order to be maximally effective, precise, and free of side effects. Where they differ is in their view regarding which kind of patient characteristics should determine the choice of treatment. There is a broad definition that considers any kind of feature of an individual—biological, psychological, environmental—as potentially valuable in guiding treatment decisions (Anonymous, 2012; Buford and Pahor, 2012; Wolpe, 2009). The more typical view, however, is that it is essentially the molecular biology and, within that, the genetic profile of a person, which determines the optimal treatment (Ginsburg, 2001; Meyer, 2012; Personalized Medicine Coalition, 2015; Sweet and Michaelis, 2011). In this view, medical interventions can be tailored to individuals by tailoring them to their genetic constitution.

The difference between these two characterizations matters because the “genetic” version makes a strong assumption that the broad version doesn’t: that a person’s genome in principle contains all the disease information necessary to derive an optimal treatment. Because this assumption may not hold, the definition of PM is sometimes extended into the broad version, which includes all kinds of non-genetic disease predictors. However, when asking which version of PM should be the subject of analysis, we must consider the fact that, whereas broad PM may sometimes be advertised, it is genetic PM that is practiced. In other words, the broad version may be upheld as the image of PM, but what is actually done in labs around the world is primarily molecular biology and bioinformatics, the software-based management and analysis of genomic data (Ginsburg, 2001; Lesko, 2007; Schleidgen et al., 2012). PM should be evaluated according to the principle “actions speak louder than words.” If PM is what PM does, we should go with the genetic version.

This raises the question of the ontological status of (genetic) PM. Some have described it as a new model (Hudis, 2007; Wikipedia, 2015), philosophy (Anonymous, 2012; Buford and Pahor, 2012; Wolpe, 2009), or even paradigm (Ginsburg, 2001; Lesko, 2007) of medicine. These terms seem a bit overblown. The best that can be said about PM is that it is a vision for an improved medicine, whose plausibility is to be evaluated. It must therefore be treated as something other than a medical reality, as is for example the treatment of bacterial infections by antibiotics or
the prevention of viral diseases by vaccination. In its present state, it consists of a few successes and many more promises. Thus, the worst that can be said about it is that it is a hype.

The next two sections will compare the vision, or hype, to reality. What does PM promise and what can it deliver?

The Vision

Today's PM has arisen from a discipline called “pharmacogenetics,” which is based on the fact that interindividual differences in drug response depend on which variants of drug-metabolic enzymes are present in the body. There are slow and rapid metabolizing variants that are coded for by genetic polymorphisms. “Slow metabolizers” are at risk of being overdosed by a particular drug because they keep more of the drug in the body for a longer time, while “rapid metabolizers” are at risk of being underdosed. Both conditions can have potentially dangerous consequences. Knowing a patient's specific gene variant can therefore help determine their optimal dose regimen. Today, much is known about which drugs are metabolized by which enzymes and whether slow or rapid metabolic variants exist and how frequently they occur. This information is usually included in drug labels to potentially allow doctors to make better decisions about what drugs to give in what doses.

Although pharmacogenetics has raised hopes for an increased personalization of medicine, one success story in particular inspired the vision of PM. In the late 1990s, the biotech firm Genentech developed the breast cancer drug trastuzumab (trade name “Herceptin”), for which it later gained approval from the U.S. Food and Drug Administration (FDA). Trastuzumab was different from the typical pharmacogenetic drug in two regards: its use was not determined by a patient's drug metabolic genotype, but by a different molecular feature, and this feature allowed for a stratification of patients into subgroups of responders and non-responders. Specifically, it turned out that trastuzumab only worked in a subgroup of women, whose breast cancer cells expressed high levels of a receptor molecule called HER2, which is involved in regulating cell growth. Thus, overexpression of HER2 could be used as what has come to be called a “biomarker” that indicated the likely effectiveness of treatment with trastuzumab. Indeed, clinical trials went on to show that women with HER2-positive breast cancer treated with this drug had a lower overall mortality and higher chances of disease-free survival than comparable women without the treatment (Hudis, 2007). To many, this seemed like a proof of principle for a vision of personalized medicine, in which the reality of individualized drug dosing based on drug-metabolic enzyme genotypes was extended into the possibility of individualizing any kind of medical treatment based on any kind of genetic or molecular information.

When, for example, Danielle seeks treatment for her type-2 diabetes mellitus, the genetic version of PM implies that a genome scan should, in principle, suffice to “read out” the specifics of her illness and find a tailored treatment, perhaps in the form of a drug that targets her body's insulin receptors. When Danielle goes to the doctor today, he or she won't be able to help her in this way, but for proponents of genetic PM, this is only a temporary limitation. A future Danielle, in a world where PM is perfected, would just give a drop of blood (or saliva) on a microchip, wait a few hours, and then pick up medicine targeted precisely to her specific variant of the disease.

But the emerging vision for PM is even more ambitious: it includes a vastly increased ability not just to tailor treatments to patients but also to understand the causes of disease, to predict and prevent disease in (as yet) unaffected individuals, and to make treatments more precise, effective, and less harmful. Medicine would shift to a new paradigm: from reactive to preventive, and from crude treatments found by trial-and-error to precise interventions on the molecular level (Chan and Ginsburg, 2011; Henney, 2012).
Excitement about the potential of a genomic medicine already started with the Human Genome Project. On the day of the announcement of the completed first draft of the human genome, then U.S. president Bill Clinton asserted that

with this profound new knowledge, humankind is on the verge of gaining immense, new power to heal. . . . Genome science . . . will revolutionize the diagnosis, prevention, and treatment of most, if not all, human diseases.

(cited in Collins, 2010)

Ever since, and especially with the unfolding success story of trastuzumab, the rhetoric of promised revolutions and imminent breakthroughs has never ceased to surround PM (Desiere and Spica, 2012; Ginsburg, 2001; Personalized Medicine Coalition, 2015). Not only the sensation-hungry mass media, but also researchers and university public relations offices have fueled the hype of the coming transformation of health care. Given this excitement, it can be a bit of a shock to learn that none of these fruits of PM have materialized. Instead, there is a modest number of personalized treatments, none of which have revolutionized anything.

The Reality

Most of what PM is today is still pharmacogenetics. The doses of a number of medications can be adapted to a patient’s specific enzyme variants, but the extent to which actual drug responses are predictable from the genotype is highly limited because they are also affected by many non-genetic factors (Shah and Shah, 2012). Even the most celebrated success of pharmacogenetics, a drug with the romantic name “warfarin,” is not an unambiguous example of tailoring a drug to a patient’s genetics. Warfarin is widely used as a blood-thinning drug, but the dose needed to achieve the required clinical effect varies greatly, and apparently unpredictably, from patient to patient. This unpredictable variability is very problematic, as too much or too little warfarin can lead to dangerous over- or undercoagulation. Consequently, much research has looked into the genetic basis of its pharmacology. As it turns out, however, genetic factors do not explain more than 50% of the variation in drug response, and genotype-based dosing offers little added benefit to clinically guided dosing (Kimmel et al., 2013; Shah and Shah, 2012).

Subsequently, the same has been found for many other drugs, showing that the seemingly simple causal pathway “gene → drug enzyme → drug blood level → drug effect” is neither simple nor deterministic (Shah and Shah, 2012). A patient’s drug response is determined not only by his or her genotype but also by a complicated network of metabolic pathways and by interactions with non-genetic factors such as age, sex, body weight, lifestyle, time of intake, amount of food in the stomach, renal/hepatic clearance, treatment duration, and ethnicity (Gamma, 2013). A comprehensive individualization of drug dosing using genetic information alone is therefore not possible.

The most advanced applications of PM are found in cancer research. A procedure called immunotherapy currently offers the greatest hope for effective treatment. It requires the administration of drugs such as trastuzumab, which are antibodies that block certain molecular receptors involved in the proliferation of cancer cells. These drugs are typically given in combination with conventional radio- or chemotherapy. They can be very effective in certain settings, but they are not the magic bullets they are often portrayed to be.

Trastuzumab, for example, reduces death and recurrence rates in early-stage HER2-positive breast cancer by 40% over a period of three years (Moja et al., 2012). In metastatic cancer, corresponding rates are 20% and 40%, which translates into a prolongation of life by an average of half a year (Balduzzi et al., 2014). However, the drug helps only about 25% of women with
breast cancer, and of those, fewer than 50% respond to the treatment (Bartsch et al., 2007). In fact, even in responders, resistance to the treatment develops rapidly, usually within a year (Nahta and Esteva, 2006).

Although these facts qualify the efficacy of the drug, others challenge another of PM’s claims: that new personalized treatments will have fewer adverse effects. In the case of trastuzumab, the opposite is true. The drug has been found to cause rare but serious cardiac dysfunction, sometimes leading to death by congestive heart failure (Dahabreh et al., 2008). This happens in about 2% of treated patients. In general, existing personalized therapeutics can have side effects as severe as those of any other drugs. Although the idea that more specific treatments will tend to have fewer side effects is plausible, the biological basis of undesired effects is not understood well enough to support general claims about a systematic reduction in adverse drug effects.

PM is a field of many activities and ambitions, but its overall clinical impact is minimal. Available treatments are mostly for rare diseases, and their benefits are rather small. PM has little to offer for the major health issues facing the world today, including common, complex diseases such as diabetes, heart disease, obesity, dementia, stroke, and affective disorders. Although countless studies searching the genome for gene-disorder associations (so-called GWAS = genome-wide association studies) have been performed, findings have been disappointing: many results have not been reproducible, and most genes that turn up contribute only a tiny risk to the overall phenotype (Hirschhorn and Gajdos, 2011). Disease prevention and prediction have generally not benefited from PM. Most illnesses are determined by a complex interplay of genetic and non-genetic factors, so that genetic tests are usually not of clinical value. Only for (rare) monogenic disorders, in which single genetic defects predict disease outcomes relatively reliably, have genetic tests been useful (e.g., screening for PKU or for BRCA variants in breast cancer). Add to that the important fact that diagnostic tests are of questionable use without concomitant therapeutic options, which are in many cases lacking.

When Danielle researches her disease on the internet, she finds that genetic information currently improves the prediction of diabetes risk achieved by non-genetic information by less than 1% (Vassy and Meigs, 2012). Like many diabetes patients, she was diagnosed late, when substantial damage to the cells in her pancreas had already occurred. But since the disease progressed imperceptibly slowly and there are no biomarkers for reliable early detection, she did not know until she was 50. Since she had normal cholesterol and blood pressure, the doctor first prescribed her a diet low in sugar and saturated fat plus moderate daily exercise to reduce her body weight. These changes helped a lot while she stuck to them, but maintaining them proved difficult. Not only was her self-discipline not the best, but there were few places in her neighborhood that made exercising really fun, and she had to drive quite far to get some of the foods she was supposed to eat. When her blood sugar levels increased, her doctor prescribed her an oral drug called Metformin, which worked well in the beginning, but finally the disease progressed to a point where her feet started hurting and feeling numb. Unfortunately, there are no known pharmacogenetic or other biomarkers to help personalize her drug treatment and reduce its side effects.

Comparing the hype of genetic PM with its clinical reality reveals a huge mismatch. How did it arise? The remainder of this chapter focuses on the epistemic challenges that generated the current situation. It will be argued that due to the particular history of genetics and the nature of modern knowledge economies in the life sciences, PM makes promises without having a principled strategy to keep them.

The Information Metaphor
The privileged position of genes in ontogeny (an organism’s development from conception to death) is a basic tenet of biomedicine that hardly ever requires justification. When the question
comes up, the only explanation usually given is a vague reference to the information-carrying function of DNA, what philosophers of science have called the “information metaphor.” The information metaphor is the belief that genes carry information in the form of instructions that control the development of an organism (Griffiths, 2001). They are the main determinants of a creature’s traits and, particularly in humans, also of its disposition for disease.

This belief in the primacy of genes in development has dominated the course of biomedicine into the 21st century. But where does it come from, and is it true? Let’s tackle these questions one at a time.

A one-sentence summary of the history of biology as it relates to genes might run as follows. Scientists had always believed that seeds and germs carry the potential to form a new organism, and by the middle of the 20th century they had convinced themselves that this potential was located in the DNA of biological cells. The concept of “information” that was afloat at that time in communications theory was quickly appropriated by molecular biologists as a convenient description of what they believed genes do: passing instructions to the cell for making proteins and regulating the expression of other genes. Soon enough, the term “information” had assumed a life of its own, divorced from its original meaning of the amount of signal transmissible by a communications device. The information in genes came to be understood in semantic terms, as instructions, programs, and blueprints, and later even as a history book, user manual, and operating system of the human organism (Keller, 1995).

The deep belief that genes represent and determine traits, whereas non-genetic factors mostly provide unspecific variation, has ultimately been the driver behind the big biology projects of our time, starting with the Human Genome Project (HGP) and continuing to today’s Personalized Medicine. Among other things, it has given us the idea that most diseases are ultimately genetic (see Chapter 14) and that, therefore, the cleanest, most specific, and effective treatment would be to correct the faulty genes. Another corollary is that genes hold the information about future risk for disease that can be used to predict and possibly prevent its occurrence.

Unfortunately, there is no reason to think that this belief is true. Both empirical evidence as well as conceptual considerations militate against it (Griffiths, 2001; Nijhout, 1990; Sarkar, 1996). On the conceptual side, the information metaphor posits a rich semantics of genes and their molecular entourage that has been adopted from the realm of human minds without warrant. The concept of information as meaning (e.g., conversations, messages, news), the ability to both give instructions and to understand and execute them, and the capacity to represent things (objects, states, goals) are all inherent to creatures with minds and their interactions. That is where these phenomena have their natural homes and the only place we encounter them. To ascribe them to inanimate objects like molecules is simply unjustified, unless there is compelling evidence to do so, but there is not.

A first clue is the simple but powerful observation that the DNA of genes is just an ordinary molecule, whose effects, like those of any protein, sugar, or fatty acid, depend on the specificity of its spatial, mechanical, and electromagnetic interactions with other molecules. It is hard to see where any special informational powers of genes should come into the picture.

Next, studies of the relationship between genes and phenotypic outcomes show, without exception, that genes alone do not determine outcomes. We have seen this already in the case of pharmacogenetics, where genes for drug-metabolic enzymes contribute to, but do not determine, drug response. Another example are so-called monogenic disorders, where a single gene defect is the origin of a disease. Even in such cases, one and the same mutation does not systematically “bring forth” the same disease outcome in different individuals. This is true, for example, for diseases such as phenylketonuria (PKU; Bercovich et al., 2008; Kayaalp et al., 1997; Pérez et al., 1993) and cystic fibrosis (Cutting, 2006; Schaedel et al., 2002). There are
countless examples like these, and interested readers can find a rich literature on the subject (e.g., Neumann-Held and Rehmann-Sutter, 2006).

In the context of ontogeny, genes are not privileged. There is a fundamental parity of the causal roles and effects of genes and other developmental resources, such as an organism's non-genetic biochemical constituents and its physical, biological, and social environments (Griffiths, 2001). Thus, while genes may turn out empirically to contribute more to a given trait or disease (e.g., by causing more of its observable variability), they do not contribute more in principle. There is therefore no a priori reason to assume that diseases are ultimately genetic or that an intervention at the genetic level would always be the ideal treatment. Biological research has time and again confirmed the view that development is a matter of complex interactions between many players, genetic and non-genetic, on a level playing field. Modulation at any causal nexus can alter the outcome, and it is not usually possible to identify an unambiguous beginning of a developmental process. Genes are neither privileged origins of diseases nor privileged intervention points. It is a purely empirical question what kind of causal factor gives us the most useful information for diagnosis, prediction, prevention, or treatment, in any given situation.

For type-2 diabetes, likely causes are age, body weight, birth weight, family history, genes, diet, physical activity, and possibly serum biomarkers such as adiponectin, HDL-Cholesterol, CRP-, and HBA1c-levels. A positive family history alone more than doubles the odds of developing type-2 diabetes (Chan and Ginsburg, 2011), which is more than what single known susceptibility genes contribute (Vassy and Meigs, 2012). The same is true for other non-genetic factors such as diet and exercise. The general point is that PM is never going to be able to extract from the genome all the information it needs for its diagnostic and therapeutic vision, because this information is simply not there.

Finally, there is one important point to make about what Germans call Etikettenschwindel ("false labeling"). Therapeutic successes, such as new drugs against cancer and cystic fibrosis (Wainwright et al., 2015), may be claimed for personalized medicine, but that doesn’t mean they are the result of its presumed success strategy, that of transforming genetic information into treatments. In fact, the opposite will usually be the case: the mechanism of action of the cancer drug Gleevec, for example, is to inhibit an enzyme in one of the cell's signaling pathways; it could not have been discovered without substantial knowledge of non-genetic metabolic processes. The same is true for other “personalized” drugs, which usually work by binding to certain receptor molecules in the cell. There is a danger that PM will allow therapeutic successes to be attributed to its gene-centered vision when in fact they are indicators of its shortcomings. This would unfortunately make it hard to learn from the present situation in biomedicine.

The Challenge of Scientific Inference

PM also faces formidable challenges of scientific inference, and it has yet to come up with a systematic and realistic way of addressing them.

Epistemically, knowledge relevant to PM sits uneasily between the opposing goals of generalization and individualization of inference. On the one hand, PM wants evidence that is valid beyond the contingent samples from which it is obtained; on the other hand, it wants evidence that, in the limit, is valid only for the individual patient from whom it is obtained. These two goals are conflicting in ways that are not yet fully understood, and each of them also has its own challenges.

The problems of the generalizability of evidence are relatively well known but nevertheless seemingly intractable. The first problem concerns representativeness: theoretically, a perfectly
representative sample, obtained by random sampling from a population, would allow an accurate estimation of population effects. The effect of a drug, or the association between a gene and a disorder, found in the sample could be generalized to the population that it represents. However, in the real world, random sampling almost never holds, and samples are almost never representative. This means that drug effects and gene-disease associations will often be unreliable and replicate poorly.

Genome-wide association studies (GWAS) have been struck particularly hard by this problem, because, in their case, it is compounded by two further issues: first, by their nature, these studies test huge numbers of genes as possible predictors of disease, thereby incurring a severe multiple-testing problem (i.e., the fact that many gene-phenotype associations will reach statistical significance by mere chance). Second, because the number of predictors is so much larger than the number of subjects, the “curse of dimensionality” strikes. This term refers to the fact that in such “high-dimensional” settings, it will almost always be possible to find a combination of predictors (genes) that can discriminate well between healthy and diseased individuals, but the particular combination found in one study will not be the same as that found in the next (James et al., 2013). This is probably the main reason why many GWAS, particularly in the early years, failed to be replicated (Hirschhorn et al., 2002).

Proponents of PM often enthusiastically embrace bioinformatics and big data as the solution to the problem of extracting diagnostically or therapeutically relevant knowledge from large amounts of patient data (Hood and Flores, 2012). The sheer mass of data in combination with advanced software algorithms is seen to virtually guarantee a greater understanding of disease. However, data science, while one of the fastest growing academic and industrial markets, is still in its infancy and has yet to live up to the hopes placed on it. Sober assessments indicate that the dream of gaining knowledge by brute data force will not generally work. Crunching numbers without well-motivated hypotheses is destined to produce a flood of false leads and spurious connections. Big data will drown in noise (Jordan, 2014). As in the case of GWAS, the perpetrators are the curse of dimensionality, multiple testing, and overfitting (i.e., the situation in which a statistical model “mistakes” the random noise in a data set as true effects, which severely limits the generalizability of its results). The push toward more data and computing power will be fruitless unless analyses are based on a solid foundation of empirical and theoretical work.

As one takes a step toward drawing scientific inferences about subgroups of—or even single—patients, different sets of problems arise. PM’s main epistemic approach to personalizing treatments has been to find drugs that are effective only in subgroups of patients exhibiting certain biomarkers. Although looking for subgroup-specific drugs may sound counterintuitive (“why not find drugs that work for all people?”), from the perspective of PM the excitement arose when trastuzumab, which initially was shown ineffective in the study sample as a whole, was later discovered to be effective, but only in a subgroup of patients. This success was seen as a proof of principle that the same strategy could generalize to many drugs and many diseases. Although this may or may not be true, subgroup analyses as currently practiced create as many problems as they solve because they are usually underpowered, lacking the necessary sample sizes to reliably detect subgroup effects (Pocock et al., 2002). The consequence is effects that are either spurious (false positives or type-I errors) or missed (false negatives, type-II errors). Widespread bad statistical practices aggravate the situation. Researchers do not always use the correct statistical methods, nor do they pre-plan their subgroup analyses, which invites post-hoc fishing for and selective reporting of statistically significant effects (Pocock et al., 2002; Smith, 2005). As about 50% of randomized clinical trials (RCTs) use subgroup analyses, the problem is substantial.

Note that despite constituting a step toward individualization, subgroup analysis still looks for results that are generalizable, namely to the entire population of patients exhibiting a
certain biomarker. Proponents of PM have begun to advocate an even more individualistic methodological approach (Schork, 2015). In so-called n-of-1 trials, single patients go through several cycles of different active treatments and appropriate control conditions. This design offers some statistical advantages, such as the ability to isolate patient-by-treatment interactions (DEcIDE Methods Center N-of-1 Guidance Panel, 2014; Senn, 2001). Participants have more palatable benefits than in other kinds of trial by being able to compare different therapeutic options directly relevant to them on outcome measures directly relevant to them. The design’s participatory nature is a welcome step toward a more patient-focused medicine, where treatment decisions are shared and centered on a patient’s preferences.

On the down side, n-of-1 trials are not feasible for treatments whose outcomes manifest in the long term. An individual cannot both receive a treatment and wait for decades for the outcome and also receive a placebo and again wait for decades to see the outcome. These trials will also be difficult to conduct in terminal illnesses like end-stage cancers, where time is limited. This makes n-of-1 trials unsuitable for some of the leading causes of morbidity and mortality.

A final epistemic challenge is risk prediction. PM promises the routine use of prognostic biomarkers to the extent of turning health care from a reactive into a preventive system. At the same time, it offers little clue about how to achieve this transformation, beyond just assuming that the few existing successes will generalize. The basic problem is that, due to the complexity of human biological, psychological, and social life, single, highly predictive markers for diseases will generally not be available (and even less so if restricted to genetic markers). The norm will rather be many weakly determining causes acting in non-additive ways. In such a situation, inferential statistics hits its limits. As discussed above, results from RCTs will not generalize, most variables will only be accessible in observational studies, which suffer from problems of confounding, and sample sizes affording enough power to avoid false positive and negatives become prohibitively large.

With the insight that there are no special instructive powers of genes, prediction becomes even harder. Genes represent a relatively stable aspect of organisms that at least potentially permits long-term predictions, as demonstrated by genetic tests for monogenic disorders. When the role of genes in ontogeny is appropriately qualified, the role of non-genetic, and potentially more variable, causal factors comes to the fore. Aspects of lifestyle and environment, for example, are crucial determinants of common, complex disorders such as diabetes, but are hard-to-impossible to predict. Accordingly, the predictive power achievable from single markers will be negligible, and even combining several markers may leave substantial portions of the variance unexplained. In type-2 diabetes, for example, reliable prediction would be highly valuable in order to detect the many non-symptomatic early cases. However, even a combination of known susceptibility genes explains only about 10% of the heritable risk for the disease (Imamura and Maeda, 2011).

A Biased Knowledge Economy

The specific nature of PM cannot be understood without reference to the cultural context in which it has grown. In the past three decades, the face of biomedicine has significantly changed. The HGP has brought the commercialization of biological research into the mainstream. A new breed of scientist-entrepreneur with stakes in the biotech and pharma industry has come to dominate the field, to the point where commentators have remarked that it is hard to find leading researchers without any economic investment in their field. Many stand to gain from consulting and collaborating with pharma companies and from patenting and marketing diagnostic and therapeutic products.
The invasion of the profit motive into biomedicine has radically altered the field. Researchers and universities alike have come under the rule of the market, with pressures to compete for financial and intellectual resources intensifying. High-ranking biomedical journals have become conduits for the pharmaceutical industry by uncritically publishing their trial data, which, not surprisingly, are overwhelmingly in favor of the industry’s products (Smith, 2005).

Essential to the mechanics of this new knowledge economy are media communications. Their logic of attention-grabbing headlines and dramatized reporting fits the needs of the industry to advertise its products. The result is a constant hype over ever-new claims of medical breakthroughs, with little pause to reflect critically on their basis and outcomes. The usual and almost inevitable failure of such claims therefore remains unacknowledged by most, lessons cannot be learned, and the cycle is bound to repeat.

In this context, PM can be seen as the latest in a sequence of gene-related hypes that started with the promises of the HGP and continued with the buzz surrounding gene therapy. Both of these eventually engendered disappointment (the HGP did not produce the predicted leap in our understanding and treatment of diseases, as evidenced by the failure of early gene therapy trials), but business interests were quickly restored with the vision of a genetics-driven personalized medicine.

In an environment driven by big business and the media, biomedical knowledge has become extremely biased. The strongest distortion stems from the heavy tilt toward genetics supported by the information metaphor. Then, most research on personalized treatments is industry-sponsored and biased toward exaggerating the efficacy of its products by selectively publishing positive findings or by subtly choosing outcome variables so as to make a positive result more likely (Smith, 2005). Due to their business entanglements, researchers and universities have become part of the problem as incentives shift toward competitiveness and profitability and away from finding the truth and serving patients’ needs.

Danielle has heard a lot about so-called personalized medicine and hopes its promises will one day come true. It would be nice to have a pill that just cures it all. But she also knows that there could be vast improvements in diabetes care if only people could be made to maintain a healthy lifestyle. She thinks that maybe, instead of pursuing expensive high-tech research, biomedicine should focus more on how to provide better opportunities and incentives for diabetics to lead healthy lives in ways that are sustainable.

Conclusion

Genetic PM is not a realistic vision, because it has inherited the faulty belief that genes contain all of the information about an organism and direct its translation into a phenotype. It has no answers to a number of problems that severely bias scientific inference and knowledge acquisition. PM as it is currently practiced therefore lacks any principled and credible strategy to achieve its goals. If it is to have any role in the future of medicine, it will have to greatly expand its purview in a way that takes it well beyond medicine’s current focus on the causal and predictive powers of genes.

References


Smith, R., 2005. Medical journals are an extension of the marketing arm of pharmaceutical companies. Plos Med 2, e138.

Further Reading

HealthNewsReview: http://www.healthnewsreview.org
The BMJ blogs: http://blogs.bmj.com/bmj/feed/ (RSS feed)