

Microbiome-Based Precision Medicine

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Abstract

The Precision Medicine Initiative announced in 2015 offers the promise of improved, highly individualized healthcare. But missing as a central focus is the microbiome. In this opinion article, I discuss the ramifications of casting future medicine under an outdated 20th century rubric of human, single-species biology (i.e., driven almost exclusively by the human mammalian genome) vs. the 21st view of humans as a multi-species super organism (i.e., driven largely the microbiome.)

Background

The Precision Medicine Initiative (PMI) announced by the U.S. President in concert with federal agencies early in 2015 promises to usher in a new, individualized approach to patient care. It brings the hope that medical approaches including the prevention and treatment of disease will account for individual patient variation [1,2].

On the surface, the PMI is very good news. Chronic diseases (non communicable diseases, NCDs) are the number one killer globally [3]. To date treatment of NCDs often involves managing the diseases across a lifetime rather than curing the diseases. NCDs are extensively interlinked in underlying causes and co-morbid risks [4]. Finally, once an initial disease such as childhood asthma, obesity, celiac disease, or type 1 diabetes has been diagnosed, the risk of additional, co-morbid NCDs is significantly increased. Additionally, the overall epidemic of NCDs has risen to a level that it is threatening the stability of global economies and healthcare systems [3,5].

A statement from President Obama on the White House website captured the PMI focus: “You can match a blood transfusion to a blood type — that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard?” [1]. The initiative will begin with cancer and then expand to include other priority diseases. The designation of “individual variation” is the key to the eventual track that precision medicine takes. But the key phrase that will determine whether this initiative fulfills its promise is “genetic code,” and more specifically we should ask, which genetic code. Will it be the human mammalian code as traditional medicine dictates or the human microbial genetic code as the newly-envisioned paradigm of fundamental human biology requires? Or both? As the PMI has taken form during 2015 there are serious doubts whether the microbiome will be the center piece of the PMI or merely window dressing.

For example, a PMI Working Group, established by the director of the U.S. National Institutes of Health, issued a report on plans for a program of human cohort studies on September 15, 2015 [6]. Not only did the report have no plans for collecting samples for analysis of the microbiome of patients, but also raised serious doubts as to whether patient genetic and metabolomic analyses would extend beyond the mammalian-centric focus of the 20th century. In fact, the word microbiome appears only three times in the entire document and not in any significant context. Here is why this is a major problem.

Opinion

By several measures, humans are majority-microbial organisms with approximately 90% of our cells and 99% of our genes coming from our microbiome rather than the mammalian part of our body [7,8]. This translates directly into significant metabolic activity, some of which is required for our very survival, since the microbes produce needed vitamins that our mammalian cells cannot synthesize [9]. Additionally, our microbes exert exquisite control over the development and function of our physiological systems (e.g., immune, gastrointestinal and neurological) to the extent of significantly affecting human behavior and health status [10-12]. Finally, the microbiome filters virtually everything (e.g., environmental chemicals, drugs, foods) our mammalian cells see by virtue of occupying the portals of entry to our bodies (e.g., skin and the respiratory, gastrointestinal, and urogenital tracts) [13]. Besides being the majority source of our genes, the microbiome is more accessible and easily manipulated using rebiosis-based gene and metabolic therapies than is the human mammalian genome. It is a simple question whether it is better to focus on medically managing the comparatively inaccessible 1% of our genetic code or the more easily accessible 99% of our genes?

The PMI is in danger of producing grossly underwhelming results given its apparent focus on the wrong human patient, the human mammal, and not the complete human-microbial super organism. Managing the health of the human mammal has been largely about treating presenting symptoms within a single-species perspective. In fact keeping the patient biologically pure and free of microbes has been a major 20th century health strategy. In contrast, managing the health of the human super organism is more analogous to ecological management with all the considerations that surround multi-species interactions and the surrounding environment. To be truly effective, the PMI might be better cast as Precision Ecological Management.

With the human microbiome occupying the major portals of entry from the environment (skin, mouth-gastrointestinal tract, urogenital tract), environmental and drug-based therapies are filtered through the microbiome before even reaching human mammalian cells and tissues [13,14]. The issue of needing to put the microbiome front and center in future medicine is driven home by the evidence that the pharmacological and toxicological aspects of medicine are about to change in a major way. The efficacy and safety of existing drugs and safety of environmental chemicals and food additives is dependent upon the microbiome. For example, cardiac glycosides such as digoxin are metabolized by bacteria in the microbiome, and the composition of the microbiome in the individual determines the effective vs. toxic dose [15]. Similarly, many of the most prescribed and used drugs including statins [16], non-steroidal anti-inflammatory drugs (NSAIDs) [17], proton pump inhibitors [18], and anti-cancer drugs [19] either damage the patient's microbiome or require specific microbial metabolism to be effective in the patient. In the absence of information on the individual patient's microbiome, the risk of ineffective or dangerous long-term adverse outcomes resulting from treatments is high. In short, a patient's microbiome status is probably the single most important biomarker needed before prescribing drugs.

Conclusions

If Precision Medicine is to attain the goal of improved individually-tailored healthcare, it first must embrace the new biological paradigm, the human patient as a multi-species super organism. Preventive strategies and treatment of diseases need to work with and through the individual's microbiome. It is time to put the microbiome front-and-center in our healthcare initiatives.

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