CONVERGENCE

News, Links, and Insights
by JEFFREY BLAND, PHD

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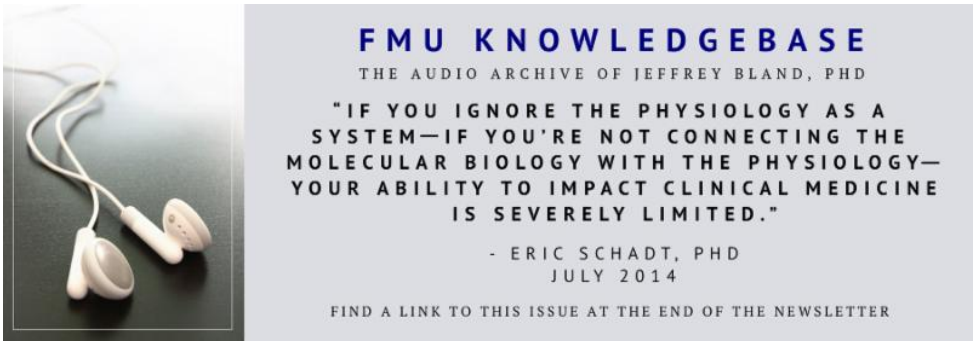

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"Deep Phenotyping" to Create N=1 Study Standard

For many years, ethical, financial, and practical considerations have required the use of non-human research models in the pursuit of medical and scientific knowledge, but with technological advances, human research—and even the N=1-person study—may be on the way to becoming the standard. "Phenomics" comprises all manifestations of individual physical and metabolic traits, including one's appearance, -omics (epi/genome, microbiome, metabolome, proteome, etc.), biological/functional age, and level of health and function.

Phenotyping increasingly involves investigating phenomics across broad populations to discover previously hidden functional relationships, and "deep phenotyping" refers to highly detailed examination of phenomics under controlled conditions. This occurs on a limited basis as yet, as these research methods have not yet been scaled for greater feasibility. Deep phenotyping has the potential to characterize wellness as well as illness on an individual basis and to help answer the following types of questions:

- What is unique about each person with a given health condition, and how can that be applied to personalize his/her treatment?
- Are there recognizable phenomic subtypes of a given condition? What do atypical disease presentations look like, at the phenome level?
- Who will respond, not respond, or adversely respond to a particular treatment?
- What characterizes wellness in those at risk for a given illness who do not manifest it?
- Which traits characterize resilience in those who are able to recover from a certain health condition, and can these qualities be cultivated in others?

Clearly, deep phenotyping encompasses broad physiologic and biochemical territory, and necessitates extensive cooperation among medical and technological disciplines. This article describes the need for a broader consideration of genotype-phenotype relationships, and suggests ways in which this may be explored within cardiovascular medicine. The future challenge is to close the gaps between previously defined areas of medical expertise with aspects of the exposome to truly address health and wellness at the N=1 level—each individual human being.

Food for Thought Video Episode

Afraid of Hearing Your Genomics Test Results?

Listen to Dr. Bland's take on the positive messages your genes are waiting to tell, and what kind of environment and lifestyle they prefer.

Video Link: https://vimeo.com/291992413

Video is one of Dr. Bland's favorite communication tools. Subscribe to his YouTube channel to never miss an update, and also find many additional videos on the Personalized Lifestyle Medicine Institute Vimeo page.

Gut-Brain Gateways to Parkinson's

Once it was thought that Parkinson's disease (PD) was primarily a central nervous system condition that impinges upon motor function, but now we know that it entails critical inputs from the enteric nervous system (ENS), intestinal and brain barriers, exposome, enteric immune response, and

microbiome. Deeper digging into the founding mechanisms of Parkinson's suggests that it could actually originate in the intestines, employing immune dysregulation and the resulting inflammation as a chronic distress signal for recruiting the broader whole-body response; even the concept of the vagus nerve serving as a direct physical vector for conveying substances between the brain and gut is no longer revolutionary,

The relative and absolute makeup of gut microbe metabolites (fatty acids, neurotransmitters, peptides, hormones, etc.) affects immune cell metabolism and cytokine production, and the microbiome is, in turn, profoundly influenced by dietary inputs and environmental exposures. Consistent changes in relative abundance of several bacterial phyla has been noted in the PD microbiome, and may relate to inflammation and altered production of ghrelin (a hormonal factor in brain dopamine function), B vitamins, and short-chain fatty acids, especially butyrate (a crucial energy substrate for enteric health); some scientists feel that smoking and coffee drinking may impact PD through the microbiome. One well-known microbial candidate, *Helicobacter pylori*, may contribute to PD through multiple mechanisms, including altering gut microbiota composition, exacerbating inflammation, altering dopamine metabolism, worsening motor symptoms, and producing neurotoxic substances. Intestinal bacterial overgrowth is more common in those with PD, and PD patients with dysbiosis have shown greater symptomatology that improves with antimicrobial treatment. Animal models additionally present evidence for negative effects of microbiome transplants from PD patients on motor function.

Gastrointestinal difficulties like constipation and reduced motility characterize early Parkinson's disease to some degree, and overexpression and aggregation of the distinctive Parkinson's protein alpha-synuclein occurs in the intestines as well as the brain. The enteric nervous system (and particularly the inflammation-sensitive dopaminergic neurons in the intestinal musculature), which interacts in a profusely intimate fashion with the microbiome, appears to be a focal point in Parkinson's pathology. Heightened intestinal permeability can additionally compromise the blood-brain and blood-cerebrospinal fluid barriers, introducing or aggravating neuroinflammatory processes, and the presence of pesticides in the individual exposome clearly contributes to PD risk.

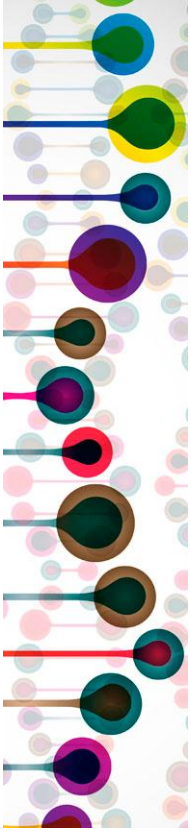
SNiPpets

How significant to health are certain single nucleotide polymorphisms, also known as SNPs? SNiPpets is an ongoing exploration of this topic. This column is produced by Jeffrey Bland, PhD and the Personalized Lifestyle Medicine Institute.

In Men, These Nutrient-Sensitive Gene Networks Influence Heart Health

Gene variants that influence folate metabolism are among the best-known polymorphisms, and research is opening up understanding of folate's broad genetic networks. A study examining these networks in men's heart disease risk discovered new associations with pathways that are responsive to B-vitamin family nutrition.

- The CBS gene codes for proteins related to homocysteine metabolism, and men with a C-to-T switch at locus rs6586282 or a G-to-A switch at locus rs6586281 of this gene enjoyed 27-29% reduced risk for heart disease, and this relationship is



strengthened by better folate nutritional status.
- The BHMT gene codes for methylation function, and men with a TA genotype at locus rs585800 of this gene showed greater cardiovascular risk with either low or median vitamin B12 levels.
- The TCN1 gene influences vitamin B12 transport, and men with a T-to-C switch at the rs17154234 locus of this gene showed a 62% increased heart disease risk, and this association was stronger among those with poor folate or vitamin B6 or B12 nutritional status.
- The MTHFS gene relates to bioactivation of folate, and men with a G-to-A switch at locus rs7177659 enjoy a 29% lower risk for heart disease, an association which is strengthened by better nutritional status with folate and vitamins B6 and B12.
- The SLC25A32 gene relates to mitochondrial folate transport, and men with a GA genotype at the rs1061196 locus of this gene showed greater cardiovascular risk when they had high (yes, high) vitamin B12 levels.
- The study confirmed previous findings related to the MTHFR gene, which influences folate activation and methylation. Men with a TT genotype at locus rs1801133 of this gene showed a 71% increased heart risk, especially in those with worse folate or vitamin B6 or B12 nutritional status.

The study also noticed differences in an area containing two chymotrypsin genes that, interestingly, are read in opposite directions during gene transcription, and found that the presence of a C allele at *CTRB1-CTRB2* locus rs8055167 increased pancreatitis risk for non-alcoholics as well as alcoholics.

Men with these gene variants may wish to discuss their overall methylation function and genomic stability with a Functional Medicine practitioner to devise an optimal long-term health strategy.

Reprogramming Multiple Sclerosis

Multiple sclerosis (MS) is a most challenging condition to treat, witness, live with, and survive. What if a therapy could address some of the underlying autoimmunity in MS? A basic characteristic in MS is loss of crucial neuronal myelination as a result of immune dysfunction, and recent animal research has identified a potential method for resetting the balance among T-helper cell populations (T-reg, Th17, and Th1 cells) in MS, effectively shifting immune function into less-inflammatory expression.

Perhaps the most exciting facet of this breakthrough is that it is achieved not through complex, costly, or risky means, but rather through a strategic change in eating behaviors. In lab animals with an induced form of MS, following a Fasting-Mimicking Diet (FMD) pattern reduced symptom severity in all animals tested and abolished symptoms in about one-fifth of them. FMD typically entails overall dietary modification (Mediterranean Diet-style) combined with strategic caloric restriction for several days each month, and FMD can be designed with limited crossover features of a ketogenic diet. Relative to more common therapies, FMD appears to be safe, effective, and inexpensive. In study animals, FMD was accompanied by significant shift in cytokine levels, regeneration of remyelinating stem cells, and remyelination, and preliminary study in humans with MS confirmed its safety and feasibility as a treatment. With stem cell regeneration and immune re-equilibration emerging as key aspects of FMD, it is being developed for application in a number of degenerative and neoplastic conditions.

Where in the World is Dr. Bland?

Every year, Dr. Jeff Bland speaks in front of audiences around the world.

Will this be the year your paths cross?

View Appearances Calendar

FMU KNOWLEDGEBASE

For more than three decades, Dr. Jeff Bland recorded and self-published a monthly audio journal called Functional Medicine Update (FMU). Although he is no longer recording new issues, an archive of content spanning 1997-2016 is free to explore on Dr. Bland's website, and this extraordinary collection is now known as the FMU Knowledgebase.

To access the **July 2014** issue, which is featured at the start of this newsletter, click here. That issue features an interview with Eric Schadt, PhD.

In research, why are healthy people only brought in as controls for studying illness? After many decades of investigating disease, we have some idea of what it looks like and who may end up with it—yet know relatively little about what enables people to withstand adversity and stay well—whether because of or in spite of their genetic inheritance. What are the physical, genetic, and epigenetic presentations (phenotypes and genotypes) of this resilience, and how can it be cultivated? What are 'perturbagens,' and are there beneficial as well as beneficial perturbagens? In this classic FMU interview, Dr. Jeffrey Bland talks with genomics researcher Eric Schadt, PhD, who helped usher in the collaborative era of sharing and analyzing complex Big Data datasets, and is investigating functional traits involved in stress resilience. They discuss the potential benefits of studying not only seemingly disadvantageous genetics (and how to counter them) but also "gain of function" mutations related to long-term wellness.

Classic FMU Top Ten Clinical Pearls From This Issue:

1. Science has long focused on disease physiology (and "bad" genes), and it's time to learn about wellness, including "good" genetics/epigenetics and how to counter "bad" genetics.
2. Health care providers will likely soon share responsibility for communicating -omics findings as health risk analyses and management opportunities to their patients.
3. Medical students should study their own -omics to gain practical knowledge in the integration and application of these datasets in an individualized and continuously updated manner.
4. Transcriptomics (real-time RNA analysis) can provide valuable insights into how one's environmental and lifestyle inputs (or exposome) impact an individual's physiology and trajectory towards health or disease.
5. Wearable devices and direct-to-consumer testing services are providing valuable data that is helping shape advanced methods of analyzing and applying extremely dense and complex datasets.
6. Health potential is always changing, and "perturbagens" are factors that shift

physiology towards a health or a disease trajectory.

7. Better prediction of health and disease necessitates understanding the ever-changing context of genetic input, epigenetic and proteomic modification, environmental influences, and cell-to-cell interactions.
8. -Omics will ultimately shift our view of what constitutes the root causes of disease versus what constitutes earlier or later perturbations in physiology as a result of these root causes.
9. The systems biology approach is deepening our understanding of chronic inflammatory conditions like obesity, joint dysfunction, and atopic disease—and how to individualize treatment.
10. Cross-functional thinking and cooperation is the key to the future of medicine, not only in researchers but also in health care practitioners.

Interview Link:
http://jeffreybland.com/knowledgebase/july-2014-issue-eric-schadt-phd/

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