Deciphering the Genes for Resilience

Jeffrey Bland, PhD
Chairman Emeritus
The Institute for Functional Medicine
Founder & President
The Personalized Lifestyle Medicine Institute
“Understanding of the biochemical individuality of each human being, based on the concepts of genetic and environmental uniqueness seems custom-made to cater to the belief among some of the woo-prone that they are special snowflakes, so utterly unique that treatment must be tailored to their finest uniqueness”.

David Gorski, M.D.
Science-based Medicine Blog
Third most viewed medical blog
Health is personal.
Wellness versus Health

- “Disease is incompatible with health, but not with wellness”
- “Less is known about what contributes to wellness than what causes disease”
- The time is ripe for engaging people in the promotion of their own wellness

Evaluation of Wellness Determinants and Interventions by Citizen Scientists

Most medical research focuses on disease rather than health. Yet people are interested in contributing to health and wellness. Wellness refers to diverse and interconnected dimensions of physical, mental, and social well-being that extend beyond the traditional definition of health. It includes choices and activities aimed at achieving physical vitality, mental acuity, social satisfaction, a sense of accomplishment, and personal fulfillment. Equally healthy people may differ in terms of their wellness, whether their life is filled with creativity, autonomy, friendship, and physical and intellectual achievement. Disease is incompatible with health, but not with wellness. For example, a dying patient who has led a rewarding life is surrounded by a loving family and friends may still enjoy high wellness.

Little is known about what affects wellness, as opposed to what causes disease. Lifestyle choices and behaviors (eg, physical activity, meditation, nutrition), technology, social participation, and engagement, genetics, work, school, neighborhood, and other environmental exposures may shape wellness. Most medical research evaluates the effectiveness of drugs, rather than nondrug interventions, even for indications for which nondrug alternatives such as exercise may be excellent choices. This creates a vacuum of evidence, which is subsequently filled by unfounded claims of a wellness market that is not driven by rigorous science. For example, popular talk shows and celebrities create theories of diets and treatments that produce miraculous outcomes despite the lack of credible scientific support.\

The current body of scientific evidence on lifestyle choices and other interventions that may affect wellness has significant limitations. Many interventions are complex and not well understood, and research evaluating their effectiveness consists of small and underpowered studies, with heterogeneous and inconclusive findings. Study registration is uncommon, and reporting of intervention and population characteristics remains inadequate. There is a clear need for rigorous research evaluating wellness and wellness-enhancing interventions. The choice of study design has significant implications for the validity and relevance of the research. Theorists state that the best way to establish whether an intervention is effective is to perform a randomized trial. Randomized trials are generally complicated and expensive and often take a long time to recruit participants and complete. However, randomized trials can become simpler, cost less, and have external validity similar to that of observational large population studies. Such trials should be the default option for evaluating wellness interventions.

Indeed, it is possible to leverage the strengths of both randomized and nonrandomized population studies, while minimizing their oft-cited limitations, as so-called hybrid designs. The general premise of hybrid designs is to couple randomized trials in large observational cohorts and biobanks, which collect longitudinal information on target populations. Hybrid designs could allow for performing intervention research on large numbers of real-world participants at low cost with long follow-up.

Population cohorts and biobanks could simultaneously provide a real-world view of lifestyle behaviors, exposures, and outcomes. Investment in collecting standardized data for large samples recruited from the general population with long-term follow-up has gained momentum over time. For example, the Ontario Health Study in Canada is a population cohort of more than 225,000 participants with data collection efforts focusing on key risk factors for chronic diseases. The biobank, biologic, and genetic data are also collected for a subset of the population.

With health consciousness at an all-time high, motivated people with a genuine interest in health and wellness represent an unfulfilled potential in research. Engaging people in the promotion of their own wellness requires thoughtful evaluation of the interventions they are using. A comprehensive approach to wellness would consider the complex interplay of lifestyle, environment, and health outcomes. This would require a broad interdisciplinary perspective, including experts in medicine, psychology, public health, and biotechnology. The ultimate goal is to foster a culture of wellness, where individuals take an active role in improving their overall well-being.
“Medicine is for Real People: Statistical Humans are of Little Interest”
The Gene-Environment Age

Genotype–Phenotype Correlation — Promiscuity in the Era of Next-Generation Sequencing
James T. Lu, Ph.D., Philippe M. Campeau, M.D., and Brendan H. Lee, M.D., Ph.D.

Ever since Mendel observed the varied phenotypes of peas — green or yellow, smooth or wrinkled — phenotypes have been used to systematically identify the genetic causes of disease. Similarly, genotype–phenotype relationships in humans could be dissected only if there were clearly recognizable, and relatively homogeneous, phenotypes. Since broad searches of genetic information were not technically feasible or cost-effective before the advent of next-generation sequencing (NGS), scientists studied well-characterized families to narrow the list of plausible genetic causes. However, being restricted to this set of “solvable” genetic problems led to ascertainment biases that favored highly penetrant mutations with straightforward functional consequences — that is, loss of function, gain of function, or dominant negative mutations dramatically affecting protein function. Thus, genetic studies before NGS systematically underestimated the true amount of genetic variation.

Understanding the extent and sources of this variation is critical in diagnostic applications, since clinical care and treatment options rely heavily on predicting phenotypes from genetic polymorphisms. For many mendelian diseases, single genetic variations (e.g., single-nucleotide polymorphisms, frameshift insertions and deletions, triplet repeats, and copy-number variants) are often good predictors of clinical disease. Yet for most diseases (both common and complex disorders), prediction of clinical and treatment prognosis is challenging because of complex genetic mechanisms and variable expressivity and penetrance.

The advent of cost-effective NGS (see graph) — especially whole-exome sequencing (WES) —

• Much more genetic variation among “healthy people” than expected
• More than 3 million single nucleotide polymorphisms discovered
• Not sure how many have significant influence on how lifestyle and environment influence phenotype

NEJM 2014; 371 503-05.
ENVIRONMENTAL AND HERITABLE FACTORS IN THE CAUSATION OF CANCER

Analyses of Cohorts of Twins from Sweden, Denmark, and Finland

Paul Lichtenstein, Ph.D., Niels V. Holm, M.D., Ph.D., Pia K. Verkasalo, M.D., Ph.D., Anastasia Iliadou, M.Sc., J the Kaprio, M.D., Ph.D., Markku Koskenvuo, M.D., Ph.D., Eero Pukkala, Ph.D., Axel Skytté, M.Sc., and Kari Hemminki, M.D., Ph.D.

Conclusions  Inherited genetic factors make a minor contribution to susceptibility to most types of neoplasms. This finding indicates that the environment has the principal role in causing sporadic cancer. The relatively large effect of heritability in cancer at a few sites (such as prostate and colorectal cancer) suggests major gaps in our knowledge of the genetics of cancer. (N Engl J Med 2000;343:78-85.)
©2000, Massachusetts Medical Society.
THE ANGELINA EFFECT

Angelina Jolie’s double mastectomy puts genetic testing in the spotlight. What her choice reveals about calculating risk, cost and peace of mind

BY JEFFREY KLUGER & ALICE PARK
“The lifetime risk of breast cancer among female mutation carriers is presently 82%. Risks appear to be increasing with time. Before 1940 it was 24%. Lack of physical exercise and obesity in adolescence may be important modulating factors for risk in carriers”. Science 2003; 302: 643-50.
Incidence of Breast Cancer in Women with BRCA1/2 mutations

Cumulative breast cancer incidence vs. age for women born before and after 1940.
Natural Variation in Gene Expression
Modulates the Severity of Mutant Phenotypes

Many mutations cause genetic disorders. However, two people inheriting the same mutation often have different severity of symptoms, and this is partly genetic. The effects of genetic background on mutant phenotypes are poorly understood, but predicting them is critical for personalized medicine.

Cell 2015; 162: 391-401
Human Genome Project Reality

Single Nucleotide Polymorphisms (SNPs) are not the whole story (insertions/deletions, copy number variants, mosaicism)

• What we have learned from GWAS studies
  ▪ Exome only 1.5% of whole genome
  ▪ >80% of traits in non-coding regions of genome
  ▪ Cell specificity (more than 200 different cell types)

• How epigenetics/post-translation shapes our phenotype
  ▪ Methylation
  ▪ Acetylation
  ▪ Phosphorylation (kinases)
  ▪ Small inhibitory RNAs (siRNA)
    ➢ Oral oligonucleotide SMAD7 inhibitor (Mongersen) and Crohn’s Disease/Ulcerative Colitis
  ▪ Oxidation, Glycation, and Amino Acid Conjugation
21st Century Cures Act progresses through US Congress

A bill to speed up the translation of biomedical discoveries is getting wide support, but some argue that it is not adequately funded. The Lancet’s Washington correspondent Susan Jaffe reports.

• Patient-Focused Drug Development
• Biomarker Development
• Accelerated Approval
• Precision Medicine
  – Genetically Targeted
• Clinical Trials
  – Innovative Statistical Methods
• Expedited Patient Access and Input

• Treatments based upon the genetic, biomarker, phenotype and psychosocial characteristics

• Differentiation of a given patient from other patients with similar diagnosis or clinical presentation

• Minimizing adverse side-effects and maximizing clinical outcome

NEJM 2015; 372: 2229-34.
ClinGen — The Clinical Genome Resource

Heidi L. Rehm, Ph.D., Jonathan S. Berg, M.D., Ph.D., Lisa D. Brooks, Ph.D., Carlos D. Bustamante, Ph.D., James P. Evans, M.D., Ph.D., Melissa J. Landrum, Ph.D., David H. Ledbetter, Ph.D., Donna R. Maglott, Ph.D., Christa Lese Martin, Ph.D., Robert L. Nussbaum, M.D., Sharon E. Plon, M.D., Ph.D., Erin M. Ramos, Ph.D., Stephen T. Sherry, Ph.D., and Michael S. Watson, Ph.D., for ClinGen

Table 1. Goals of the Clinical Genome Resource (ClinGen).

<table>
<thead>
<tr>
<th>Goals</th>
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<tbody>
<tr>
<td>Share genomic and phenotypic data provided by clinicians, researchers, and patients through centralized databases for clinical and research use</td>
</tr>
<tr>
<td>Standardize the clinical annotation and interpretation of genomic variants</td>
</tr>
<tr>
<td>Implement evidence-based expert consensus for curating genes and variants</td>
</tr>
<tr>
<td>Improve understanding of variation in diverse populations to realize interpretation of genetic testing on a global scale</td>
</tr>
<tr>
<td>Develop machine-learning algorithms to improve the throughput of variant interpretation</td>
</tr>
<tr>
<td>Assess the “medical actionability” of genes and variants</td>
</tr>
<tr>
<td>Structure and provide access to genomic knowledge for use in electronic health records ecosystems</td>
</tr>
<tr>
<td>Disseminate the collective knowledge and resources for unrestricted use in the community</td>
</tr>
</tbody>
</table>

NEJM 2015; 373:2235-42.
Pharmacogenomics and Drug Toxicity
Yusuke Nakamura, M.D., Ph.D.

In the United States alone, it is estimated that adverse drug reactions affect nearly 2 million patients and kill about 100,000 people each year.\(^1\) Adverse drug reactions are often classified into two groups. The first group can be explained by the mode of action of the therapeutic drug. Examples of adverse drug reactions in this group include hypoglycemia induced by diabetic drugs, leukopenia induced by cytotoxic anticancer drugs, and bleeding induced by warfarin, an oral anticoagulant.

- > 2 million annual adverse drug reactions
- > 100,000 deaths in the USA annually
- Individual response to drugs strongly related to pharmacogenomic uniqueness

N Engl J Medicine 2008; 359: 856-58
Personalized Cancer Care
Genetic Variation Determines PPARγ Function and Anti-diabetic Drug Response In Vivo

Many such SNPs alter binding motifs for PPARγ or cooperating factors and functionally regulate nearby genes whose expression is strain selective and imbalanced in heterozygous F1 mice. Other metabolic syndrome parameters. Thus, natural genetic variation in PPARγ genomic occupancy determines individual disease risk and drug response.

Cell 2015; 162: 33-44
### My 23andMe Statin Response Genotype

#### Drug Response > Statin Response

**Overview**

**Community (30)**

**Statin Response**
Statin drugs are prescribed to reduce cholesterol levels in people who have a high risk of cardiovascular disease. Though generally very safe, statins can cause some adverse effects, including liver problems, muscular soreness and an extremely rare condition known as rhabdomyolysis in which the muscles begin to disintegrate. Physicians can use blood tests to detect the drugs’ most serious adverse effects.

The following results are based on **Preliminary Research** for 2 reported markers.

**Printable Version**

#### Statin-related myopathy

<table>
<thead>
<tr>
<th>Journal/Study Size</th>
<th>Replications</th>
<th>Contrary Studies</th>
<th>Applicable Ethnicities</th>
<th>Markers</th>
<th>Who</th>
<th>Genotype</th>
<th>Genetic Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipids Health Dis</td>
<td>Replications</td>
<td>None</td>
<td>European</td>
<td>rs4693596</td>
<td>Stewart J Bland</td>
<td>CC</td>
<td>Moderately higher odds of myopathy while on statin therapy.</td>
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<td>None</td>
<td>None</td>
<td></td>
<td></td>
<td>CT</td>
<td>Typical odds of myopathy while on statin therapy.</td>
<td></td>
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<tr>
<td></td>
<td>None</td>
<td>None</td>
<td></td>
<td></td>
<td>TT</td>
<td>Typical odds of myopathy while on statin therapy.</td>
<td></td>
</tr>
</tbody>
</table>

About one person in 10,000 who takes statin drugs experiences muscle pain and/or weakness in a given year, a condition known as myopathy. It appears that higher doses increase the condition’s likelihood. This study compared 133 patients who experienced myopathy while taking statins to 158 patients who did not. All patients were taking a single statin (including atorvastatin, rosuvastatin and other statins) at varied doses. The authors found an association between myopathy and a SNP in the COX2 gene, which is involved in cellular energy production. Patients who had a C at both copies of rs4693596 had more than twice the odds of myopathy as those with the CT or TT genotype.

**Citations**


#### Statin-related myopathy

<table>
<thead>
<tr>
<th>Journal/Study Size</th>
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<th>Applicable Ethnicities</th>
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<th>Genetic Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>N Engl J Med</td>
<td>Replications</td>
<td>None</td>
<td>European</td>
<td>rs4149056</td>
<td>Stewart J Bland</td>
<td>CC</td>
<td>Greatly increased odds of myopathy while on simvastatin.</td>
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<tr>
<td></td>
<td>None</td>
<td>None</td>
<td></td>
<td></td>
<td>CT</td>
<td>Substantially increased odds of myopathy while on simvastatin.</td>
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<tr>
<td></td>
<td>None</td>
<td>None</td>
<td></td>
<td></td>
<td>TT</td>
<td>Typical odds of myopathy while on simvastatin.</td>
<td></td>
</tr>
</tbody>
</table>

About one person in 10,000 who takes statin drugs experiences muscle pain and/or weakness in a given year, a condition known as myopathy. It appears that higher doses increase the condition’s likelihood. This study compared 85 patients who experienced myopathy to 90 patients who did not. All were taking 80 mg of simvastatin daily – a relatively high dose – as part of a much larger study involving 12,000 patients who were taking the drug after experiencing a heart attack. The authors found that having one C at rs4149056, a SNP in the SLC01B1 gene, increased a person's odds of having myopathy 4.5 times compared to the TT genotype. Having two C copies of the SNP increased a person's odds of myopathy by about 17 times. The authors of the study succeeded in detecting a similar effect in individuals taking 40 mg of simvastatin daily, but the effect was much less extreme. Please note...
SLCO1B1 Variants and Statin-Induced Myopathy — A Genomewide Study

The SEARCH Collaborative Group∗

We have identified common variants in SLCO1B1 that are strongly associated with an increased risk of statin-induced myopathy. Genotyping these variants may help to achieve the benefits of statin therapy more safely and effectively. (Current Controlled Trials number, ISRCTN74348595.)

Weighing the Benefits of High-Dose Simvastatin against the Risk of Myopathy

Amy Egan, M.D., M.P.H., and Eric Colman, M.D.

Key Components of Recent Safety-Labeling Changes for Simvastatin

1. Use of the 80-mg dose of simvastatin should be restricted to patients who have been taking it for a long time (e.g., 12 months or more) without signs or symptoms of clinically significant toxic effects on muscle.

2. Patients who are currently taking an 80-mg dose of simvastatin without adverse effects but who need to begin taking an interacting drug that is contraindicated or is associated with a dose cap for simvastatin should be switched to an alternative statin with less potential for a drug–drug interaction.

3. Patients in whom the LDL cholesterol goal cannot be achieved with a 40-mg dose of simvastatin should instead be given other appropriate LDL cholesterol-lowering therapy (e.g., a more potent statin that poses a lower risk of myopathy, such as atorvastatin or rosuvastatin).

Drug Interactions Associated with Increased Risk of Myopathy and Rhabdomyolysis

<table>
<thead>
<tr>
<th>Interacting Agents</th>
<th>Prescribing Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole</td>
<td>Contraindicated with simvastatin</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td></td>
</tr>
<tr>
<td>Posaconazole</td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td></td>
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<tr>
<td>Clarithromycin</td>
<td></td>
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<tr>
<td>Telithromycin</td>
<td></td>
</tr>
<tr>
<td>HIV protease inhibitors</td>
<td></td>
</tr>
<tr>
<td>Nefazodone</td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>Do not exceed 10 mg of simvastatin daily</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Do not exceed 20 mg of simvastatin daily</td>
</tr>
<tr>
<td>Danazol</td>
<td></td>
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<tr>
<td>Amiodarone</td>
<td></td>
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<tr>
<td>Verapamil</td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td></td>
</tr>
<tr>
<td>Ranolazine</td>
<td>Avoid large quantities of grapefruit juice (&gt;1 qt daily)</td>
</tr>
</tbody>
</table>

Statin Adverse Effects: A Review of the Literature and Evidence for a Mitochondrial Mechanism

We hypothesize, and provide evidence, that the demonstrated mitochondrial mechanisms for muscle AEs have implications to other nonmuscle AEs in patients treated with statins. In meta-analyses of randomized controlled trials (RCTs), muscle AEs are more frequent with statins than with placebo. A number of manifestations of muscle AEs have been reported, with rhabdomyolysis the most feared. AEs are dose dependent, and risk is amplified by drug interactions that functionally increase statin potency, often through inhibition of the cytochrome P450 (CYP)3A4 system. An array of additional risk factors for statin AEs are those that amplify (or reflect) mitochondrial or metabolic vulnerability, such as metabolic syndrome factors, thyroid disease, and genetic mutations linked to mitochondrial dysfunction. Converging evidence supports a mitochondrial foundation for muscle AEs associated with statins, and both theoretical and empirical considerations suggest that mitochondrial dysfunction may also underlie many non-muscle statin AE.

Am J Cardiovasc Drugs 2008; 8: 373-418
Missense mutation of the COQ2 gene causes defects of bioenergetics and de novo pyrimidine synthesis

Coenzyme Q<sub>10</sub> (CoQ<sub>10</sub>) deficiency has been associated with an increasing number of clinical phenotypes that respond to CoQ<sub>10</sub> supplementation. In two siblings with encephalomyopathy, nephropathy and severe CoQ<sub>10</sub> deficiency, a homozygous mutation was identified in the CoQ<sub>10</sub> biosynthesis gene COQ2, encoding polyprenyl-pHB transferase.
• “We found that the majority of variations among the way people respond to various stimuli goes well beyond genetic variation: the regulation of genetic expression may arise from epigenetic differences due to environmental factors such as lifestyle, diet, the microbiome, drugs, and toxic exposures.”
Personalized Nutritional Pharmacology: Interleukin-1 genotype-selective inhibition of inflammatory mediators by a botanical: a nutrigenetics proof of concept.

- Kornman K et al.

At 12 wk of dosing with the botanical formulation, IL-1beta gene expression by stimulated peripheral blood mononuclear cells was significantly lower than at baseline and significantly lower than placebo in IL1(Pos) and IL1(Neg) subjects. Mean IL-1beta gene expression treatment effect over the 12-wk period was greater in IL1(Pos) than in IL1(Neg) subjects. At 12 wk of dosing the botanical mixture produced no mean change in serum CRP levels. However, in IL1(Pos) subjects, significantly more subjects achieved a reduction in CRP with the botanical mixture than with placebo. No CRP effect was observed in the IL1(Neg) subjects.

This study represents one of a few prospective clinical trials in which genetic variations were shown to differentially influence nutrient effects on outcomes.
OMICS: P4, Precision, and Personalized Medicine

The Functional Medicine Revolution

• Harnessing the “omics revolution” requires a systems biology operating system

• Functional Medicine is the systems biology operating system for all the “omics” related technologies
Objective: To personalize healthcare from a systems biology perspective
The Era of Predictive Analytics

- “Predictive analytics incorporates complex information about the patient into prognostic models that estimate the likelihood of a particular event”
- “Physicians must understand the limitations of the information that result in predicting risks or benefits of specific therapies”

JAMA 2015; 314: 25-26
Resilience versus Disease Risk

Eric Schadt, PhD

Stephen Friend, MD, PhD

The Resilience Project:
A Search for Unexpected Heroes
Converting the At Risk Patient to the Resilient Human

- 127 classical Mendelian single gene diseases
- Over 5000 non-Mendelian diseases with different susceptibilities
- Converting “at risk” to “resilient” is related to epigenetic effects
- Epigene is modified by lifestyle and environment exposure

Quantifying Wellness and Resilience

P4 Medicine:
- Predictive
- Preventive
- Personalized
- Participatory

Leroy Hood, MD, PhD

Learn more:
www.systemsbiology.org
www.p4mi.org
The Institute for Systems Biology
Pioneer 100 Wellness Project

AN EXAMINED LIFE
A nine-month study will collect data at daily and three-month intervals, and allow personalized interventions — such as changes in diet — as the study proceeds.

**BRAIN**
- What's measured:
  - Sleep patterns
- Frequency: Daily
- Method: Wrist sensor

**LIVER, LUNGS, BRAIN & HEART**
- 100 proteins to track organ health
- Every three months
- Blood sample

**HEART**
- Pulse, physical-activity level
- Daily
- Wrist sensor

**LYMPHATIC SYSTEM**
- Immune-cell activity
- Every three months
- Blood sample

**COLON**
- Microbiome ecology
- Every three months
- Stool sample

**INSULIN SENSITIVITY**
- Blood glucose
- Every three months
- Blood sample

**CHROMOSOMES**
- Whole-genome sequence
- At enrolment
- Blood sample

Source: Institute for Systems Biology
The First “Quantified Human”

Revolution in personalized medicine: First-ever integrative 'omics' profile lets scientist discover, track his diabetes onset

Geneticist Michael Snyder, PhD, has almost no privacy. For more than two years, he and his lab members at the Stanford University School of Medicine pored over his body’s most intimate secrets: the sequence of his DNA, the RNA and proteins produced by his cells, the metabolites and signaling molecules wafting through his blood. They spied on his immune system as it battled viral infections.

Finally, to his shock, they discovered that he was predisposed to type-2 diabetes and then watched his blood sugar shoot upward as he developed the condition during the study. It's the first eyewitness account — viewed on a molecular level — of the birth of a disease that affects millions of Americans. It's also an important milestone in the realization of the promise of truly personalized medicine, or tailoring health care to each individual's unique circumstances.

Source: med.stanford.edu/news
What is a “Comorbidity” or “Disease Adjacency” in the Age of Systems Medicine?

A Few Representative Clinical Examples
Clinical Implications of the Osteoprotegerin/RANKL/RANK System for Bone and Vascular Diseases

**A. Skeletal System**
- **RANKL Expression**
  - Increased by IL-1, IL-11, IL-17, TNF-α
  - PTH
  - Prostaglandin E2
  - Glucocorticoids
  - Decreased by IL-4
  - TGF-β
  - 17β-Estradiol

- **OPG Production**
  - Increased by IL-1, IL-10, IL-18, TNF-α
  - TGF-β, BMP-2
  - 17β-Estradiol
  - Leptin
  - Mechanical Strain

- **Stromal Cell or Osteoblast**
  - RANKL
  - TACE
  - OPG

- **Osteoclast Precursor**
  - NF-κB Pathway
  - c-Jun N-Terminal Kinase Pathway

- **Mature Osteoclast**
  - PKB/Akt Pathway

**B. Immune System**
- **RANKL Expression**
  - Increased by IL-1, IL-7, IL-17, TNF-α
  - Decreased by 17β-Estradiol

- **OPG Production**
  - Increased by CD40 Ligand

- **T Cell**
  - NF-κB Pathway
  - c-Jun N-Terminal Kinase Pathway

- **Dendritic Cell**
  - T Cell

**C. Vascular System**
- **RANKL Expression**
  - Increased by IL-1, TNF-α

- **OPG Production**
  - Increased by PDGF-BB
  - Decreased by Glucocorticoids
  - Cyclosporin A
  - Thrombomodulin

- **Endothelial Cell**
  - RANKL
  - RANK
  - OPG

- **Smooth Muscle Cell**
  - PKB/Akt Pathway

C. Lynn
Artificial sweeteners induce glucose intolerance by altering the gut microbiota

Jotham Suez, Tal Korem, David Zeevi, Gili Zilberman-Schapira, Christoph A. Thaiss, Ori Maza, David Israeli, Niv Zmora, Shlomit Gilad, Adina Weinberger, Yael Kuperman, Alon Harmelin, Ilana Kolodkin-Gal, Hagit Shapiro, Zamir Halpern, Eran Segal & Eran Elinav

Non-caloric artificial sweeteners (NAS) are among the most widely used food additives worldwide, regularly consumed by lean and obese individuals alike. NAS consumption is considered safe and beneficial owing to their low caloric content, yet supporting scientific data remain sparse and controversial. Here we demonstrate that consumption of commonly used NAS formulations drives the development of glucose intolerance through induction of compositional and functional alterations to the intestinal microbiota. These NAS-mediated deleterious metabolic effects are abrogated by antibiotic treatment, and are fully transferrable to germ-free mice upon faecal transplantation of microbiota configurations from NAS-consuming mice, or of microbiota anaerobically incubated in the presence of NAS. We identify NAS-altered microbial metabolic pathways that are linked to host susceptibility to metabolic disease, and demonstrate similar NAS-induced dysbiosis and glucose intolerance in healthy human subjects. Collectively, our results link NAS consumption, dysbiosis and metabolic abnormalities, thereby calling for a reassessment of massive NAS usage.

Nature 2014
Significance of the microbiome in obstructive lung disease

The composition of the lung microbiome contributes to both health and disease, including obstructive lung disease. Because it has been estimated that over 70% of the bacterial species on body surfaces cannot be cultured by currently available techniques, traditional culture techniques are no longer the gold standard for microbial investigation. Advanced techniques that identify bacterial sequences, including the 16S ribosomal RNA gene, have provided new insights into the depth and breadth of microbiota present both in the diseased and normal lung. In asthma, the composition of the microbiome of the lung and gut during early childhood development may play a key role in the development of asthma, while specific airway microbiota are associated with
GPCR41 Activation by Dietary Fiber Induces Lung Antiinflammation through GI Microbiota Short Chain Fatty Acid Production

Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis

Metabolites from intestinal microbiota are key determinants of host-microbe mutualism and, consequently, the health or disease of the intestinal tract. However, whether such host-microbe crosstalk influences inflammation in peripheral tissues, such as the lung, is poorly understood. We found that dietary fermentable fiber content changed the composition of the gut and lung microbiota, in particular by altering the ratio of Firmicutes to Bacteroidetes. The gut microbiota metabolized the fiber, consequently increasing the concentration of circulating short-chain fatty acids (SCFAs). Mice fed a high-fiber diet had increased circulating levels of SCFAs and were protected against allergic inflammation in the lung, whereas a low-fiber diet decreased levels of SCFAs and increased allergic airway disease. Treatment of mice with the SCFA propionate led to alterations in bone marrow hematopoiesis that were characterized by enhanced generation of macrophage and dendritic cell (DC) precursors and subsequent seeding of the lungs by DCs with high phagocytic capacity but an impaired ability to promote T helper type 2 (Th2) cell effector function. The effects of propionate on allergic inflammation were dependent on G protein–coupled receptor 41 (GPR41, also called free fatty acid receptor 3 or FFAR3), but not GPR43 (also called free fatty acid receptor 2 or FFAR2). Our results show that dietary fermentable fiber and SCFAs can shape the immunological environment in the lung and influence the severity of allergic inflammation.

Nature Medicine 2014; 20: 139-163
Dietary Fiber, Microbiome, Gut Immune Response and Pulmonary Antiinflammation

Nature Medicine 2014; 20: 120-121
Gut Microbiota, the Genome, and Diet in Atherogenesis

Joseph Loscalzo, M.D., Ph.D.

The Galtonian distinction between the influence of genetics and environment on phenotype is now widely recognized as an overly simplistic dichotomy. Genes and environmental factors interact in myriad ways to modulate and modify the biology of all living organisms, challenging the notion that these two principal determinants of phenotype can ever truly act independently of each other.

The largest and most complex of these host-associated microbial communities is that contained within the gut. The metagenomic potential of this internal microbial community coevolved with the human host and has increasingly been shown to interact with the host genome in health and in diseases ranging from periodontal disease to rheumatoid arthritis to inflammatory bowel disease.
Cancer and the microbiota

Wendy S. Garrett

A host's microbiota may increase, diminish, or have no effect at all on cancer susceptibility. Assigning causal roles in cancer to specific microbes and microbiotas, unraveling host-microbiota interactions with environmental factors in carcinogenesis, and exploiting such knowledge for cancer diagnosis and treatment are areas of intensive interest. This Review considers how microbes and the microbiota may amplify or mitigate carcinogenesis, responsiveness to cancer therapeutics, and cancer-associated complications.

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Germs and joints: the contribution of the human microbiome to rheumatoid arthritis

Geraint B Rogers

Rheumatoid arthritis (RA) is a debilitating autoimmune disorder, the etiology of which is poorly understood. A new study reveals dysbiosis in gut and oral microbiomes of affected individuals, potentially providing a basis for patient stratification and clues to pathophysiological mechanisms of RA onset and progression.
The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment.

We carried out metagenomic shotgun sequencing and a metagenome-wide association study (MGWAS) of fecal, dental and salivary samples from a cohort of individuals with rheumatoid arthritis (RA) and healthy controls. Concordance was observed between the gut and oral microbiomes, suggesting overlap in the abundance and function of species at different body sites. Dysbiosis was detected in the gut and oral microbiomes of RA patients, but it was partially resolved after RA treatment. Alterations in the gut, dental or saliva microbiome distinguished individuals with RA from healthy controls, were correlated with clinical measures and could be used to stratify individuals on the basis of their response to therapy. In particular,
Multiple recent investigations have highlighted the promise of helminth-based therapies for the treatment of inflammatory disorders of the intestinal tract of humans, including inflammatory bowel disease and coeliac disease. However, the mechanisms by which helminths regulate immune responses, leading to the amelioration of symptoms of chronic inflammation are unknown. Given the pivotal roles of the intestinal microbiota in the pathogenesis of these disorders, it has been hypothesized that helminth-induced modifications of the gut commensal flora may be responsible for the therapeutic properties of gastrointestinal parasites. In this article, we review recent progress in the elucidation of host–parasite–microbiota interactions in both animal models of chronic inflammation and humans, and provide a working hypothesis of the role of the gut microbiota in helminth-induced suppression of inflammation.
Molecular Diagnostic Yield of Chromosomal Microarray Analysis and Whole-Exome Sequencing in Children With Autism Spectrum Disorder

CONCLUSIONS AND RELEVANCE Among a heterogeneous sample of children with ASD, the molecular diagnostic yields of CMA and WES were comparable, and the combined molecular diagnostic yield was higher in children with more complex morphological phenotypes in comparison with the children in the essential category. If replicated in additional populations, these findings may inform appropriate selection of molecular diagnostic testing for children affected by ASD.
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Reversal of cognitive decline: A novel therapeutic program

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Key words: Alzheimer's, dementia, mild cognitive impairment, neurobehavioral disorders, neuroinflammation, neurodegeneration, systems biology.

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Abstract: This report describes a novel, comprehensive, and personalized therapeutic program that is based on the underlying pathogenesis of Alzheimer's disease, and which involves multiple modalities designed to achieve metabolic enhancement for neurodegeneration (MEND). The first 10 patients who have utilized this program include patients with memory loss associated with Alzheimer's disease (AD), amnestic mild cognitive impairment (aMCI), or subjective cognitive impairment (SCI). Nine of the 10 displayed subjective or objective improvement in cognition beginning within 3-6 months, with the one failure being a patient with very late stage AD. Six of the patients had had to discontinue working or were struggling with their jobs at the time of presentation, and all were able to return to work or continue working with improved performance. Improvements have been sustained, and at this time the longest patient follow-up is two and one-half years from initial treatment, with sustained and marked improvement. These results suggest that a larger, more extensive trial of this therapeutic program is warranted. The results also suggest that, at least early in the course, cognitive decline may be driven in large part by metabolic processes. Furthermore, given the failure of monotherapeutics in AD to date, the results raise the possibility that such a therapeutic system may be useful as a platform on which drugs that would fail as monotherapeutics may succeed as key components of a therapeutic system.
Beyond the Pathology to the Functional Origin of the Disease

Epigenetics

- Trauma
- Stress
- Fear
- Anxiety
- Absence of “Locus of Control”
- Lack of attribution and love
- Poverty- Being “impoverished”
Environmental epigenomics and disease susceptibility

Randy L. Jirtle & Michael K. Skinner

Epidemiological evidence increasingly suggests that environmental exposures early in development have a role in susceptibility to disease in later life. In addition, some of these environmental effects seem to be passed on through subsequent generations. Epigenetic modifications provide a plausible link between the environment and alterations in gene expression that might lead to disease phenotypes. An increasing body of evidence from animal studies supports the role of environmental epigenetics in disease susceptibility. Furthermore, recent studies have demonstrated for the first time that heritable environmentally induced epigenetic modifications underlie reversible transgenerational alterations in phenotype. Methods are now becoming available to investigate the relevance of these phenomena to human disease.

Randy Jirtle, PhD

Michael Skinner, PhD

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The science of early adversity: is there a role for large institutions in the care of vulnerable children?

Anne E Berens, MSc, Prof Charles A Nelson, PhD
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Summary
It has been more than 80 years since researchers in child psychiatry first documented developmental delays among children separated from family environments and placed in orphanages or other institutions. Informed by such findings, global conventions, including the 1989 UN Convention on the Rights of the Child, assert a child's right to care within a family-like environment that offers individualised support. Nevertheless, an estimated 8 million children are presently growing up in congregate care institutions. Common reasons for institutionalisation include orphaning, abandonment due to poverty, abuse in families of origin, disability, and mental illness. Although the practice remains widespread, a robust body of scientific work suggests that institutionalisation in early childhood can incur developmental damage across diverse domains. Specific deficits have been documented in areas including physical growth, cognitive function, neurodevelopment, and social-psychological health. Effects seem most pronounced when children have least access to individualised caregiving, and when deprivation coincides with early developmental sensitive periods. Offering hope, early interventions that place institutionalised children into families have afforded substantial recovery. The strength of scientific evidence imparts urgency to efforts to achieve deinstitutionalisation in global child protection sectors, and to intervene early for individual children experiencing deprivation.
Moshe Szyf, Ph.D.

- Professor of Pharmacology and Therapeutics
- McGill University, Montreal
- The Szyf lab proposed two decades ago that epigenetic changes in DNA are a target in cancer and other diseases and has provided the first set of evidence that the “social environment” early in life can alter DNA epigenetics changing functional expression of the genes and launching the emerging field of “social epigenetics”.
Holocaust Exposure Induced Intergenerational Effects on FKBP5 Methylation

Rachel Yehuda, Nikolaos P. Daskalakis, Linda M. Bierer, Heather N. Bader, Torsten Klengel, Florian Holsboer, Elisabeth B. Binder

Results

Holocaust exposure had an effect on FKBP5 methylation that was observed in exposed parents as well as in their offspring. These effects were observed at bin 3/site 6. Interestingly, in Holocaust survivors, methylation at this site was higher in comparison with control subjects, whereas in Holocaust offspring, methylation was lower. Methylation levels exposed parents and their offspring were significantly correlated. In contrast to the findings at bin 3/site 6, offspring methylation at bin 2/sites 3 to 5 was associated with childhood physical and sexual abuse in interaction with an FKBP5 risk allele previously associated with vulnerability to psychological consequences of childhood adversity. The findings suggest the possibility of site specificity to environmental influences, as sites in bins 3 and 2 were differentially associated with parental trauma and the offspring's own childhood trauma, respectively. FKBP5 methylation averaged across the three bins examined was associated with wake-up cortisol levels, indicating functional relevance of the methylation measures.

Conclusions

This is the first demonstration of transmission of preconception parental trauma to a child associated with epigenetic changes in both generations, providing a potential insight into how severe psychological trauma can have intergenerational effects.
“Understanding of the biochemical individuality of each human being, based on the concepts of genetic and environmental uniqueness seems custom-made to cater to the belief among some of the woo-prone that they are special snowflakes, so utterly unique that treatment must be tailored to their finest uniqueness”.

David Gorski,M.D.
Science-based Medicine Blog
Third most viewed medical blog
SPECIAL SNOWFLAKE

Yes, you're special, just like all of the other snowflakes in the snowstorm who will be pushed aside by the snow plow of progress and turned into slush.
Treating the “Snowflake” in 21st Century Postgenomic Medicine

- Focus on the gene-environment connection
- Celebrating individuality
- Developing an integrative systems approach
- Unlocking resilience
- Quantifying wellness
- Redefining patient engagement
- Pharmacogenomics
- Recognizing the importance of epigenetics