# Framework for Developing a New Taxonomy of Disease

Tuesday and Wednesday, March 1st and 2nd, 2011  
The House of Sweden – Alfred Nobel Hall  
Washington, DC

## AGENDA  
Day 1

*Breakfast available at 7:15 am in the Atrium Lounge*

<table>
<thead>
<tr>
<th>Time</th>
<th>Session Title</th>
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<tbody>
<tr>
<td>8:00 AM</td>
<td><strong>SESSION 1: WELCOME AND OPENING TALKS</strong></td>
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<td>• Committee co-chairs:</td>
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<td></td>
<td>o Susan Desmond-Hellmann, Chancellor, UCSF</td>
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<td></td>
<td>o Charles Sawyers, Director of HOPP, Memorial Sloan-Kettering Cancer Center:</td>
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<td></td>
<td>• Chris Chute: Professor of Medical Informatics, Mayo Clinic College of Medicine – Current Taxonomy: importance, process of updating ICD</td>
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<td></td>
<td>• Atul Butte: Assistant Professor of Medicine, Stanford center for Biomedical Informatics Research – Current Taxonomy transitioning to New Taxonomy</td>
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<tr>
<td>9:20 AM</td>
<td>Break</td>
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<tr>
<td>9:35 AM</td>
<td>A NEW TAXONOMY NETWORK – Keith Yamamoto A proposal for consideration and further development.</td>
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<tr>
<td>10:00 AM</td>
<td><strong>SESSION 2: DO WE NEED AN AMERICAN GENOMES PROJECT?</strong></td>
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<td></td>
<td>A panel discussion – David Goldstein; Moderator</td>
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<td>Is genomic information central to a New Taxonomy of Disease? What are the opportunities and concerns? What is happening now with whole genome sequencing? What are the goals in near/long term?–Define productive pathways.</td>
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<td>• Andrew Conrad: Chief Scientific Officer, LabCorp's NGI</td>
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<td>• Aaron Brown: Senior Product Manager, Google Health (tentative)</td>
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<td>Panel discussion: ~30 min</td>
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### SESSION 3: BEYOND THE GENOME – INFORMATION FOR A NEW TAXONOMY

A panel discussion – Manuel Llinas; Moderator

In addition to genome sequence, other information could be leveraged to improve health and research, as part of a New Taxonomy of Disease Network. What information could/should be included in the network? Would this enable longitudinal studies?

- **Lewis Cantley:** Chief, Division of Signal Transduction, Harvard Medical School – Metabolome, proteome
- **Martin Blaser:** Frederick H. King Professor of Internal Medicine and Chairman of the Department of Medicine, NYU School of Medicine – Microbiome
- **Jason Lieb:** Professor, Department of Biology, UNC – Epigenetics; ENCODE project
- **Helmut Zarbl:** UMDNJ-Robert Wood Johnson Medical School, Environmental & Occupational Medicine, Rutgers University – Environmental Health, toxicology
- **Erin Ramos:** Epidemiologist, National Human Genome Research Institute – Sociological contributions, PhenX

#### Panel discussion: ~30 min

### 12:45 PM  
**Lunch**

### 1:30 PM  
**SESSION 4: ETHICS AND PRIVACY**

A panel discussion – Bernie Lo; Moderator

- **Alta Charo:** Professor of Law and Bioethics, University of Wisconsin Law School – (FDA) Informed Consent
- **Marc Rotenberg:** Executive Director, EPIC – Privacy; criminal justice concerns
- **Sanford Schwartz:** Professor of Medicine, Health Care Management, and Economics, University of Pennsylvania – Clinical validation issues
- **Debra Lappin:** President, Council for American Medical Innovation – Patient Advocate

#### Panel discussion: ~30 min
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<tr>
<td>3:00 PM</td>
<td>Break</td>
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<tr>
<td>3:30 PM</td>
<td><strong>SESSION 5: PRODUCT DEVELOPMENT – PHARMA; BIOTECH</strong></td>
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<td>A panel discussion – David Cox; Moderator</td>
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<td></td>
<td>1. How would a new taxonomy of human disease enable more cost effective and rapid development of new, effective and safe drugs in the pharma/biotech setting?</td>
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<td>2. How would a new taxonomy of human disease promote integration of clinical and research cultures in the pharma/biotech industry?</td>
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<td>3. How would a new taxonomy of human disease promote public/private partnerships between industry and academia?</td>
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<td>4. What are key factors that would limit the implementation of a new taxonomy of human disease in the pharma/biotech setting?</td>
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<td>• Klaus Lindpaintner: <em>Vice President of R&amp;D, SDI</em></td>
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<td>• Charles Baum: <em>Vice President of Global R&amp;D, Pfizer</em></td>
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<td>• Corey Goodman: <em>Managing Director and Co-Founder, venBio</em></td>
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<td>Panel discussion: ~30 min</td>
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<tr>
<td>5:00 PM</td>
<td>Summary of the day; overview of tomorrow, discussion: Susan Desmond-Hellmann and Charles Sawyers</td>
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<tr>
<td>6:30 PM</td>
<td>Committee will reconvene for closed session discussion over dinner</td>
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### AGENDA

**Day 2**

*Breakfast available at 7:15 am in the Atrium Lounge*

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<tr>
<td>8:00 AM</td>
<td>Opening Remarks: Susan Desmond-Hellmann and Charles Sawyers</td>
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<td>8:10 AM</td>
<td><strong>SESSION 6: PRAGMATIC CONSIDERATIONS – THE END USER</strong></td>
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<td>A panel discussion – David Hunter &amp; David Nichols; Moderators</td>
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<td></td>
<td>1. What taxonomy framework would be most useful for your end user group? (Why?)</td>
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<td>2. What characteristics of a taxonomy framework might harm your end user group? (Why?)</td>
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<td>3. What criteria should be used to assess the value of a new taxonomy? (cost, ethics, practicality, healthcare outcomes, etc.?)</td>
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<td>4. Should the lay public be able to comprehend a new taxonomy of disease?</td>
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<td>• <strong>Janet Woodcock:</strong> Director, CDER at the FDA</td>
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<td>• <strong>Jon Lorsch:</strong> Professor of Biophysics and Biophysical Chemistry, Johns Hopkins University, School of Medicine – Graduate and Medical Education Program Director</td>
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<td>• <strong>Brian Kelly:</strong> Head of Informatics and Strategic Alignment, Aetna</td>
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<td>Panel discussion: ~30 min</td>
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<tr>
<td>10:00 AM</td>
<td>Break</td>
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<td>10:15 AM</td>
<td><strong>SESSION 7: INSTRUMENTING THE HEALTHCARE DELIVERY SYSTEM TO DEFINE AND LEVERAGE A NEW TAXONOMY</strong></td>
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<td>A panel discussion – Isaac Kohane; Moderator</td>
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<td>Considerations for cognition, data handling, visualization and user interface.</td>
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<td>• <strong>Daniel Masys:</strong> Chair of the Department of Biomedical Informatics, Vanderbilt University Medical Center – eMERGE consortium (using healthcare data to run genomic studies)</td>
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<td>• <strong>John Brownstein:</strong> Instructor, Harvard Medical School – Informal data sources - Health map.org</td>
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<td>12:00 PM</td>
<td>Lunch</td>
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| 12:45 PM     | **SESSION 8: A CLINICAL PERSPECTIVE ON A NEW TAXONOMY** Case Studies – Charles Sawyers; Moderator

Physician/Scientists consider what a New Taxonomy of Disease would mean for the disease they study.

- **William Pao**: Director, Personalized Cancer Medicine at the Vanderbilt-Ingram Cancer Center – Lung Cancer
- **Ingrid Scheffer**: Professor of Paediatric Neurology Research, University of Melbourne – Epilepsy
- **Elissa Epel**: Associate Professor in Residence, Department of Psychiatry at UCSF – Chronic Stress/Obesity

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| 2:15 PM      | Final discussion and Closing Remarks: Susan Desmond-Hellmann and Charles Sawyers

(Committee may meet for an hour in closed session)

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<td>3:00 PM</td>
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Statement of Task

At the request of the Director’s Office of NIH, an ad hoc committee of the National Research Council will explore the feasibility and need, and develop a potential framework, for creating a “new taxonomy” of human diseases based on molecular biology. As part of its deliberations, the committee will host a large two-day workshop that convenes diverse experts in both basic and clinical disease biology to address the feasibility, need, scope, impact, and consequences of defining this new taxonomy. The workshop participants will also consider the essential elements of the framework by addressing topics that include, but are not limited to:

- Compiling the huge diversity of extant data from molecular studies of human disease to assess what is known, identify gaps, and recommend priorities to fill these gaps.
- Developing effective and acceptable mechanisms and policies for selection, collection, storage, and management of data, as well as means to provide access to and interpret these data.
- Defining the roles and interfaces among the stakeholder communities—public and private funders, data contributors, clinicians, patients, industry, and others.
- Considering how to address the many ethical concerns that are likely to arise in the wake of such a program.

The committee will also consider recommending a small number of case studies that might be used as an initial test for the framework.

The ad hoc committee will use the workshop results in its deliberations as it develops recommendations for a framework in a consensus report. The report may form a basis for government and other research funding organizations regarding molecular studies of human disease. The report will not, however, include recommendations related to funding, government organization, or policy issues.
FRAMEWORK FOR DEVELOPING A NEW TAXONOMY OF DISEASE

Committee Member Roster

SUSAN DESMOND-HELLMANN, (CO-CHAIR), Chancellor, University of California, San Francisco

CHARLES SAWYERS, (CO-CHAIR), Director of HOPP, Memorial Sloan-Kettering Cancer Center

DAVID R. COX, Senior Vice President and Chief Scientific Officer, AQG, Pfizer Inc.

CLAIRE FRASER-LIGGETT, Director of the Institute of Genome Sciences; Professor of Medicine, University of Maryland, School of Medicine

STEPHEN J. GALLI, Chief of Pathology at Stanford Hospital & Clinics and Professor of Pathology and of Microbiology and Immunology, Stanford University

DAVID B. GOLDSTEIN, Faculty and Director, Center for Human Genome Variation, Duke University School of Medicine

DAVID J. HUNTER, Dean of Academic Affairs, the Harvard School of Public Health

ISAAC S. KOHANE, Director at Children’s Hospital Informatics Program, Harvard Medical School

MANUEL LLINAS, Assistant Professor of Molecular Biology, Princeton University

BERNARD LO, Professor of Medicine; Director of Program in Medical Ethics, University of California, San Francisco

TOM MISTELI, Senior Investigator and Head of the Cell Biology of Genomes, National Cancer Institute

SEAN J. MORRISON, Investigator, HHMI; Director of University of Michigan’s Center for Stem Cell Biology Research

DAVID G. NICHOLS, Vice Dean of Education, the Johns Hopkins University School of Medicine

MAYNARD V. OLSON, Professor of Genome Sciences and of Medicine, University of Washington

CHARMAINE ROYAL, Associate Research Professor at the Institute for Genome Sciences and Policy, Duke University

KEITH YAMAMOTO, Executive Vice Dean of the School of Medicine, University of California, San Francisco

STAFF

INDIA HOOK-BARNARD, Study Director, Program Officer

AMANDA MAZZAWI, Senior Program Assistant
Toward a New Taxonomy of Disease: Workshop Panelists

Session 1: Welcome and Opening Talks

Susan Desmond-Hellmann

Dr. Susan Desmond-Hellmann, MD, MPH, is chancellor of the University of California, San Francisco. She assumed the post August 3, 2009. UCSF is a leading university dedicated to promoting health worldwide through advanced biomedical research, graduate-level education in the life sciences and health professions, and excellence in patient care. UCSF is the only campus in the 10-campus UC system devoted exclusively to the health sciences.

Desmond-Hellmann previously served as president of product development at Genentech, a position she held from March 2004 through April 30, 2009. In this role, she was responsible for Genentech’s pre-clinical and clinical development, process research and development, business development and product portfolio management. She also served as a member of Genentech’s executive committee, beginning in 1996. She joined Genentech in 1995 as a clinical scientist, and she was named chief medical officer in 1996. In 1999, she was named executive vice president of development and product operations. During her time at Genentech, several of the company’s patient therapeutics (Lucentis, Avastin, Herceptin, Tarceva, Rituxan and Xolair) were approved by the U.S. Food and Drug Administration, and the company became the nation’s No. 1 producer of anti-cancer drug treatments. She completed her clinical training at UCSF and is board-certified in internal medicine and medical oncology. She holds a bachelor of science degree in pre-medicine and a medical degree from the University of Nevada, Reno, and a master’s degree in public health from the University of California, Berkeley.

Prior to joining Genentech, Desmond-Hellmann was associate director of clinical cancer research at Bristol-Myers Squibb Pharmaceutical Research Institute. While at Bristol-Myers Squibb, she was the project team leader for the cancer-fighting drug Taxol.

Desmond-Hellmann also has served as associate adjunct professor of epidemiology and biostatistics at UCSF. During her tenure at UCSF, she spent two years as visiting faculty at the Uganda Cancer Institute, studying HIV/AIDS and cancer. She also spent two years in private practice as a medical oncologist before returning to clinical research.

In January 2009, Desmond-Hellmann joined the Federal Reserve Bank of San Francisco’s Economic Advisory Council for a three-year term. In July 2008, she was appointed to the California Academy of Sciences board of trustees. Dr. Desmond-Hellmann was named to the Biotech Hall of Fame in 2007 and as the Healthcare Businesswomen’s Association Woman of the Year for 2006. She was listed among Fortune magazine’s “top 50 most powerful women in business” in 2001 and from 2003 to 2008. In 2005 and 2006, the Wall Street Journal listed Desmond-Hellmann as one of its “women to watch.” From 2005 to 2008, Desmond-Hellmann served a three-year term as a member of the American Association for Cancer Research board of directors, and from 2001 to 2009, she served on the executive committee of the board of directors of the Biotechnology Industry Organization. She served on the corporate board of Affymetrix from 2004-2009.

Charles Sawyers

Dr. Charles Sawyers, M.D., is an Investigator of the Howard Hughes Medical Institute and the inaugural Director of the Human Oncology and Pathogenesis Program (HOPP) at Memorial Sloan-Kettering Cancer Center (MSKCC), where he is building a program of lab-based translational researchers across various clinical disciplines and institutional infrastructure to enhance the application of global genomics tools to clinical trials.
Sawyers’ laboratory is currently focused on characterizing signal transduction pathway abnormalities in prostate cancer, with an eye toward translational implications. His research is best demonstrated through his earlier studies of BCR-ABL tyrosine kinase function in chronic myeloid leukemia, his work with Brian Druker and Novartis in the development of the kinase inhibitor imatinib/Gleevec as primary therapy for CML, and his discovery that imatinib resistance is caused by BCR-ABL kinase domain mutations. This discovery led Dr. Sawyers to evaluate second generation Abl kinase inhibitors, such as the dual Src/Abl inhibitor dasatinib, which received fast track approval at the FDA in June 2006.

Dr. Sawyers’ work in prostate cancer has defined critical signaling pathways for disease initiation and progression through studies in mouse models and humane tissues. This preclinical work led to the development of a novel antiandrogen MVD3100, a small molecule inhibitor discovered in collaboration with UCLA Chemist Michael Jung, which targets the increased levels of androgen receptor found in the hormone refractory disease. Based on impressive clinical results in a phase I/II study, MDV3100 is currently in phase III registration trial. Dr. Sawyers is past President of the American Society of Clinical Investigation and served on the National Cancer Institute’s Board of Scientific Counselors. He has won numerous honors and awards, including: the Richard and Hinda Rosenthal Foundation Award; the Dorothy Landon Prize from the American Association of Cancer Research and the David A. Karnofsky Award from the American Society of Clinical Oncology; and the 2009 Lasker DeBakey Clinical Medical Research Award. He is a member of the Institute of Medicine and in 2010 was elected to the National Academy of Sciences.

Christopher Chute

Dr. Chute received his undergraduate and medical training at Brown University, internal medicine residency at Dartmouth, and doctoral training in Epidemiology at Harvard. He is Board Certified in Internal Medicine, and a Fellow of the American College of Physicians, the American College of Epidemiology, and the American College of Medical Informatics. He became founding Chair of Biomedical Informatics at Mayo in 1988, stepping down after 20 years in that role. He is now Professor of Medical Informatics, and is PI on a large portfolio of research including the HHS/Office of the National Coordinator (ONC) SHARP (Strategic Health IT Advanced Research Projects) on Secondary EHR Data Use, the ONC Beacon Community (Co-PI), the LexGrid projects, Mayo's CTSA Informatics, Mayo's Cancer Center Informatics including caBIG, and several NIH grants including one of the eMERGE centers from NGHRI, which focus upon genome wide association studies against shared phenotypes derived from electronic medical records. Dr. Chute serves as Vice Chair of the Mayo Clinic Data Governance for Health Information Technology Standards, and on Mayo’s enterprise IT Oversight Committee. He is presently Chair, ISO Health Informatics Technical Committee (ISO TC215) and Chairs the World Health Organization (WHO) ICD-11 Revision. He also serves on the Health Information Technology Standards Committee for the Office of the National Coordinator in the US DHHS, and the HL7 Advisory Board. Recently held positions include Chair of the Biomedical Computing and Health Informatics study section at NIH, Chair of the Board of the HL7/FDA/NCI/CDISC BRIDG project, on the Board of the Clinical Data Interchange Standards Consortium (CDISC), ANSI Health Information Standards Technology Panel (HITSP) Board member, Chair of the US delegation to ISO TC215 for Health Informatics, Convener of Healthcare Concept Representation WG3 within the (TC215), Co-chair of the HL7 Vocabulary Committee, Chair of the International Medical Informatics Association (IMIA) WG6 on Medical Concept Representation, American Medical Informatics Association (AMIA) Board member, and multiple other NIH biomedical informatics study sections as chair or member.

Atul Butte

Atul Butte, M.D., Ph.D. is Chief of the Division of Systems Medicine in the Department of Pediatrics, and an Assistant Professor in Pediatrics, Medicine (Medical Informatics), and by courtesy, Computer Science, at Stanford University and the Lucile Packard Children's Hospital, and is a pediatric endocrinologist. Dr. Butte’s lab builds and applies tools that convert the billions of points of molecular, clinical, and epidemiological data measured by researchers and clinicians over the past decade into new diagnostics,
therapeutics, and new insights into disease. The Butte Laboratory currently has been funded by HHMI and under fifteen NIH grants, across 8 institutes of NIH. Dr. Butte has authored nearly 100 publications and delivered more than 120 invited presentations in personalized and systems medicine, biomedical informatics, and molecular diabetes, including 20 at the National Institutes of Health or NIH-related meetings. Dr. Butte is on the Board of Directors of the American Medical Informatics Association (AMIA). Dr. Butte has co-authored one of the first books on microarray analysis titled "Microarrays for an Integrative Genomics" published by MIT Press. Dr. Butte's research has been featured in the New York Times Science Times and the International Herald Tribune (2008), Wall Street Journal (2010), and San Jose Mercury News (2010).
Session 2: Do We Need an American Genomes Project?

David B. Goldstein

Dr. David B. Goldstein is currently Professor of Molecular Genetics & Microbiology and Director of the Center for Human Genome Variation at Duke University. He received his Ph.D. in Biological Sciences from Stanford University in 1994, and from 1999 to 2005 was Wolfson Professor of Genetics at University College London.

Dr. Goldstein is the author of over 150 scholarly publications in the areas of population and medical genetics. His work focuses on the genetics of human disease and treatment response, with a concentration on neuropsychiatric disease and host determinants of response to infectious diseases. He is the recipient of one of the first seven nationally awarded Royal Society/Wolfson research merit awards in the UK for his work in human population genetics and was awarded the Triangle Business Journal Health Care Heroes Award in 2008 for his work on host determinants of control of HIV-1. Most recently, he was appointed the co-chair and chair of the Gordon Research Conference meeting on human genetics and genomics for 2011 and 2013.

Andrew Conrad

Andrew Conrad, Ph.D. is the Chief Scientific Officer of Laboratory Corporation of America (LabCorp), Executive Director of Oncology and Pathology for DIANON/US LABS, and Executive Head of Clinical Trials Services for Esoterix Clinical Trials, Inc. He is also the Co-Founder and Chief Scientific Officer of LabCorp's National Genetics Institute.

National Genetics Institute (NGI) performs over three million PCR reactions per year and is one of the largest genetics laboratories in the world. The primary focus of Dr. Conrad's research has been on the effects and manifestations of chronic viral illnesses as measured by the polymerase chain reaction (PCR). He also conducts research on the role of gene expression in cancer and is the Responsible Head for the FDA Product License for The UltraQual Assay, a Nucleic Acid Test (NAT) for the detection of HIV-1, and HCV in plasma from large numbers of donors. Dr. Conrad has more than eighty-five publications in scientific and medical journals.

Dr. Conrad graduated with a B.S. in Neurobiology and a Ph.D. in Cell Biology from the University of California Los Angeles.

Aaron Brown
Session 3: Beyond the Genome – Information for a New Taxonomy

**Manuel Llinás**

Dr. Manuel Llinás is an Assistant Professor of Molecular Biology and a member of the Lewis-Sigler Institute for Integrative Genomics at Princeton University. Dr. Llinás earned a Ph.D. in molecular and cell biology from the University of California-Berkeley and did postdoctoral work in the lab of Joseph DeRisi at the University of California-San Francisco. He joined the Princeton faculty in 2005. Dr. Llinás' laboratory studies the deadliest of the four human Plasmodium parasites, *Plasmodium falciparum*. His research combines tools from functional genomics, molecular biology, computational biology, biochemistry, and metabolomics to understand the fundamental molecular mechanisms underlying the development of this parasite. The focus is predominantly on the red blood cell stage of development, which is the stage in which all of the clinical manifestations of the malaria disease occur. His research has focused on two major areas: the role of transcriptional regulation in orchestrating parasite development, and an in-depth characterization of the malaria parasite's unique metabolic network. On the transcription side, Dr. Llinás' lab works on the characterization of the first family of DNA binding proteins to be identified in the *Plasmodium falciparum* genome, the Apicomplexan AP2 (ApiAP2) proteins. The metabolomics work has begun to identify unique biochemical pathway architectures in the parasite including a novel branched TCA cycle. These two approaches explore relatively virgin areas in the malaria field with the goal of identifying novel strategies for therapeutic intervention.

**Lewis Cantley**

Lewis Cantley, Ph.D. is the William Bosworth Castle Professor of Medicine at Harvard Medical School and Director of the Cancer Center at Beth Israel Deaconess Hospital. In the course of investigations into how growth factors and oncogenes stimulate cell growth, Dr. Cantley discovered Phosphoinositide 3-Kinase (PI3K), a central regulator of cell growth and survival. His discoveries have led to the development of drugs to target this pathway for treating cancers. In recognition of his contributions to the understanding of human diseases, Dr. Cantley was elected to the American Academy of Arts and Sciences (1999) and the National Academy of Sciences (2001).

**Martin J. Blaser**

Since April 2000, Martin Blaser has served as the Frederick H. King Professor of Medicine and Chair of the Department of Medicine and as Professor of Microbiology at the New York University School of Medicine. Dr. Blaser’s research has focused on bacterial pathogenesis. He has worked for more than 30 years on the role of *Campylobacter* and *Helicobacter* species, among other organisms, in human disease. After early studies on the pathogenic *Campylobacter* species, much work since 1985 has involved the gastric bacterium *H. pylori*. His work linked the relation of colonization to inflammation, and to gastric cancer. His studies identified vacA and cagA, the two major virulence genes, and showed differential disease risk associated with particular alleles. Dr. Blaser developed a conceptual framework involving unique dynamic equilibria between *H. pylori* populations and colonized hosts, which has become a general model of persistence for co-adapted microbes. His explorations of *H. pylori* diversity have shown the intercontinental spread of these organisms in pre-historic times, and he is increasingly interested in the role of *H. pylori* in human health, including a protective role against adenocarcinoma of the esophagus, and allergic disorders such as asthma. Work with *H. pylori* has in turn led to studies of the composition and function of the human microbiome. He holds 24 U.S. patents relating to his research, and has authored over 470 original articles.

**Jason Lieb**

Jason Lieb is the Beverley W. Long Chapin Distinguished Professor of Biology in the UNC College of Arts and Sciences, and is Director of the Carolina Center for Genome Sciences. He is also an active member
of the UNC Lineberger Comprehensive Cancer Center. His research is primarily in the field of epigenetics. While people generally think about DNA as a hereditary code that only occasionally changes through mutation - the basis of the evolutionary process - the field of epigenetics focuses on DNA and its associated proteins, called chromatin. In particular, Lieb focuses on how information is encoded and used in the genome, specifically during transcription, DNA replication and repair, recombination, and chromosome segregation. While studying how these processes work in simple organisms, Lieb is also working to develop new technologies and concepts that can be applied to the treatment of patients. Using FAIRE (Formaldehyde-Assisted Isolation of Regulatory Elements), a method developed by his laboratory, his group can isolate and identify unpackaged regions of DNA across the whole genome. This information is valuable because when DNA is unpackaged, or "open" it indicates that the underlying regulatory information is being used by the cell. This is a promising method for typing breast cancers, or cancers in general, a process that is the first step to more targeted, personalized treatment. Lieb came to UNC in 2002 after completing a postdoctoral fellowship at Stanford University. He earned his undergraduate degree in biology at the University of North Carolina at Chapel Hill and his PhD in genetics at the University of California at Berkeley. He is a winner of the Phillip and Ruth Hettleman Prize for Artistic and Scholarly Achievement at UNC Chapel Hill and, has received a number of additional awards and honors.

Erin Ramos

Dr. Erin Ramos is an epidemiologist in the Office of Population Genomics, National Human Genome Research Institute (NHGRI). She received her M.P.H. and Ph.D. in the multidisciplinary field of public health genetics from the University of Washington where her research focused on the genetic epidemiology of Alzheimer's disease and the ethical, legal, and social implications (ELSI) that surround genomics research.

Dr. Ramos manages a portfolio of research in population genomics including a collaborative project to develop a set of standardized phenotypic and exposure measures for use in genome-wide association studies and related genomics research (www.phenxtoolkit.org). She serves as the chair of the Data Access Committee (DAC) for the Genetic Association Information Network (GAIN) and as a member of NHGRI's DAC. Her research interests include the genetic epidemiology of complex disease, genome-wide association studies and gene-environment interactions, and ELSI research including informed consent for large-scale genomic studies.

Helmut Zarbl

Helmut Zarbl is Professor of Environmental and Occupational Medicine at the Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey (UMDNJ). He is a member of the Environmental & Occupational Health Sciences Institute (EOHSI), a joint Institute of UMDNJ and Rutgers, The State University of New Jersey. He is also the Director of the NIEHS Center for Environmental Exposures and Disease at EOHSI, is the Associate Director for Public Health Science at the Cancer Institute of New Jersey. Previously, he was a member of the Divisions of Human Biology and Public Health Sciences at the Fred Hutchinson Cancer Research Center (FHRCC), where he was Director and a Principal Investigator for the NIEHS sponsored FHRCC/University of Washington Toxicogenomics Research Consortium. Dr. Zarbl's research has focused largely on toxicogenomics and functional genomics, carcinogenesis, molecular and cellular biology, and toxicology. Specifically this has included work to understand molecular mechanisms of chemical carcinogenesis, chemoprevention, and the genetic basis for differential susceptibility to mammary carcinogenesis using both animal and in vitro model systems. Recent studies include the role of circadian rhythm in cancer risk and prevention. His studies in the area of toxicogenomics include the development and application of standards for DNA microarray experiments, and phenotypic anchoring of response of human cells, model organisms (yeast) and target organs (rodents) to toxicants, providing insights into dose and temporal responses, as well as mechanisms of action. Dr. Zarbl is also actively involved in technology development, including his patented work on RNAi and its application to the development of novel platforms for functional genomics (with Engineering Arts, Inc). Dr. Zarbl served on the NRC committee that produced Application of
Toxicogenomic Technologies to Predictive Toxicology and Risk Assessment. Previously he was an Assistant and Associate Professor at M.I.T. He earned his Ph.D. in Biochemistry from McGill University.
**Session 4: Ethics and Privacy**

**Bernard Lo**

Bernard Lo, M.D., is Professor of Medicine and Director of the Program in Medical Ethics at UCSF. He is also National Program Director for the Greenwall Faculty Scholars Program in Bioethics, a career development award for bioethics researchers. He directs the Regulatory Knowledge Support Component of the NIH-funded Clinical and Translational Science Institute at UCSF and is co-Director of the Policy and Ethics Core of the Center for AIDS Prevention Studies. He chairs the UCSF Stem Cell Research Oversight Committee. He is co-chair of the Standards Working Group of the California Institute of Regenerative Medicine, which recommends regulations for stem cell research funded by the state of California. He is a member of the Centers for Disease Control and Prevention (CDC) Ethics Subcommittee of the Advisory Committee to the Director. He serves on DSMBs for NIH-sponsored HIV vaccine trials and for the Long-Term Oxygen Treatment Trial (LOTT) and on the Ethics Working Group of the HIV Prevention Trials Network. He also serves on the Board of Directors of the Association for the Accreditation of Human Research Protection Programs. He is a member of the Institute of Medicine (IOM), served on the IOM Council and as chair of the IOM Board on Health Sciences Policy. He chaired a 2009 IOM committee on conflicts of interest in medicine and several earlier reports. Dr. Lo is author of Resolving Ethical Dilemmas: A Guide for Clinicians (4th ed., 2010) and of Ethical Issues in Clinical Research (2010).

**Alta Charo**

R. Alta Charo is the Warren P. Knowles Professor of Law and Bioethics at the University of Wisconsin at Madison, where she is on the faculty of the Law School and the Department of Medical History and Bioethics. She writes on reproductive health, medical genetics, stem cell research, science funding, and research ethics. Professor Charo served on President Obama's transition team, where she was a member of the HH S review team, focusing her attention particularly on transition issues related to NIH, FDA, bioethics, stem cell policy, and women's reproductive health. She is on leave 2009-2011 to serve as a senior policy advisor on emerging technology issues in the Office of the Commissioner at the US Food & Drug Administration.

Charo's advisory committee service for the federal government includes the 1994 NIH Human Embryo Research Panel, and (1996-2001) President Clinton's National Bioethics Advisory Commission where she worked on studies related to cloning, stem cells, use of biological materials, and standards for human subjects research. Alta Charo also has extensive service at the National Academies, where she has served on committees related to bioterrorism, AIDS research and drug safety, co-chaired the National Academies' Human Embryonic Stem Cell Research Advisory Committee, and helped to draft the NAS guidelines for embryonic stem cell research. In 2006 she was elected to membership in the National Academies' Institute of Medicine.

**Marc Rotenberg**

**Sanford Schwartz**
Debra Lappin

Debra Lappin is recognized across government, academic and non-profit sectors as a public servant and leading strategist in public health and science policy. She consults on innovative public-private partnerships and other alliances to drive translation research and public health promotion and prevention. Calling upon her experiences as former national chair of the Arthritis Foundation, she is a recognized national spokesperson on public engagement in the nation's public health and scientific enterprise.

Debra's practice focuses on the increasingly influential role of non-profit patient organizations as partners with government in research, development and prevention, where she orchestrates coalitions, global consortia, and other strategic alliances among academic research institutions, voluntary health agencies, government and industry. Areas of focus for such collaborative agreements has included work with the leading causes of disability, Arthritis and Alzheimer's Disease, and rare diseases, such as Duchenne muscular dystrophy. Most recently, she has orchestrated science policy campaigns on issues of open access and genetic non-discrimination. Drawing upon her understanding of health agency trends, law, ethics, and practical business challenges, she advises on the development of a broad range of emerging, complex tools to enable translation, such as disease registries, large integrated databases, bio-specimen repositories and cross-institution affiliations to share data.

Debra serves or has served as an advisor to the leading agencies in public health, including the Centers for Disease Control and Prevention and the National Institutes of Health, and has participated on a number of committees at the National Academy of Sciences, including the Committee on the Organizational Structure of the NIH which led to a number of directions incorporated in the 2006 NIH Reform Act. She is President of the Council for American Medical Innovation, and a member of the Board of Research!America.
Dr. David R. Cox M.D. Ph.D. serves as Chief Scientific Officer for the Applied Quantitative Genotherapeutics Unit of Pfizer’s Worldwide Research & Development. This new unit brings together human genetics, systems biology, and cell biology, combining internal capabilities with outside collaborations, to focus on increasing preclinical target validation with the aim of significantly improving clinical survival. David is a co-founder of Perlegen, and was most recently Chief Scientific Officer of the company since its formation in 2000. David was Professor of Genetics and Pediatrics at the Stanford University School of Medicine as well as the co-director of the Stanford Genome Center. He obtained his A.B. and M.S. degrees from Brown University in Rhode Island and his M.D. and Ph.D. degrees from the University of Washington, Seattle. He completed a Pediatric Residency at the Yale-New Haven Hospital in New Haven, Connecticut and was a Fellow in both genetics and pediatrics at the University of California, San Francisco. David is certified by the American Board of Pediatrics and the American Board of Medical Genetics. He was an active participant in the large scale mapping and sequencing efforts of the Human Genome Project while carrying out research involving the molecular basis of human genetic disease. David has been a member of several commissions and boards, including the National Bioethics Advisory Commission (NBAC) and the Health Sciences Policy Board of the Institute of Medicine. He has also served on a number of international committees, including the Council of the Human Genome Organization (HUGO). He has authored over 100 peer-reviewed scientific publications and has served on numerous editorial boards. Dr. Cox’s honors include election to the Institute of Medicine of the National Academy of Sciences.

Klaus Lindpaintner

Dr. Charles Baum is Senior Vice President for BioTherapeutics Clinical Research within Pfizer’s Worldwide Research & Development division. His responsibilities include clinical trial planning, execution, and oversight of the biologics and therapeutic vaccine clinical portfolio. Dr. Baum has worked at Pfizer since 2003, serving in roles of increasing responsibility including as Vice President and Head of Oncology Development and as Chief Medical Officer for Pfizer’s Biotherapeutics and Bioinnovation Center. He has been responsible for the development of the oncology portfolio, including the approval of Sutent® for the treatment of gastrointestinal stromal tumor (GIST) and advanced kidney cancer. Prior to joining Pfizer, Dr. Baum was responsible for the Phase I-IV development of several oncology compounds at Schering-Plough, including the development of temozolomide which was approved for the treatment of patients with advanced brain tumors. His career has included academic and hospital positions at Stanford and Emory universities, as well as positions of increasing responsibility within the pharmaceutical industry (Systemix, Searle, and Schering-Plough).

Dr. Baum is a medical doctor and scientist having received his M.D. and Ph.D. (Immunology) from Washington University School of Medicine in St. Louis, Missouri. He completed his post-graduate work at Stanford University in Palo Alto, California, where he also completed his medical residency and conducted research on human bone marrow stem cells with Dr. Irving Weissman. Dr. Baum has received research grants from the National Institutes of Health and the American Cancer Society, published a number of peer-reviewed manuscripts, and patents.

Corey S. Goodman

Dr. Goodman is Managing Director and co-founder of venBio, a venture capital-private equity firm based on a new model of strategic collaboration with pharmaceutical and biotechnology companies. With a B.S. from Stanford University and Ph.D. from U.C. Berkeley, he spent 25 years as professor of neurobiology at
Stanford and Evan Rauch Chair at Berkeley, where he was Howard Hughes Medical Institute Investigator and co-founder and director of the Wills Neuroscience Institute. He is currently adjunct professor at U.C. San Francisco. He is an elected member of the National Academy of Sciences, American Academy of Arts and Sciences, and American Philosophical Society, and recipient of many honors including the Alan T. Waterman Award, Canada Gairdner Award, March-of-Dimes Prize, and Reeve-Irvine Research Medal.

Dr. Goodman co-founded Exelixis and Renovis, and led Renovis as President and CEO from a private to public company until its acquisition by Evotec. In 2007, he was recruited to be President and founder of Pfizer’s Biotherapeutics and Bioinnovation Center, a new division focused on biologics, and a member of Pfizer’s Executive Leadership Team. More recently, Dr. Goodman co-founded Second Genome and Ossianix. He is Chair of the Board of six biotech companies (iPierian, Limerick, Second Genome, Oligasis, Ossianix, & NuMedii), Board member of two others (Mirna & NeuroTherapeutics), and advises others.

Amongst his many public policy roles, Dr. Goodman is on the Board of the California Council on Science and Technology, Pacific Institute, Bay Area Science and Innovation Consortium, and is former Chair of the National Research Council's (NAS) Board on Life Sciences and past President of the McKnight Endowment Fund for Neuroscience. He is also a member of the board of BayBio, QB3 (UCSF-UCB-UCSC) Industry Advisory Board, Stanford’s BioX Biosciences Advisory Council, Spinal Muscular Atrophy Foundation, and Stanley Center for Psychiatric Research (Harvard/MIT). He is on the Editorial/Advisory Board of the journals Science Translational Medicine and Neuron.
Session 6: Pragmatic Considerations – The End User

David J. Hunter

Dr. David J. Hunter is currently the Dean for Academic Affairs at the Harvard School of Public Health and the Vincent L. Gregory Professor in Cancer Prevention in the Departments of Epidemiology and Nutrition. His research interests include cancer epidemiology and molecular and genetic epidemiology. Dr. Hunter analyzes inherited susceptibility to cancer and other chronic diseases using molecular techniques and studying molecular markers of environmental exposures. He is Co-Chair of the NCI Breast and Prostate Cancer Cohort Consortium and Co-Director of the NCI Cancer Genetic Markers of Susceptibility (CGEMS) Special Initiative.

David G. Nichols

Dr. Nichols is a professor of anesthesiology/critical care medicine and pediatrics and the Mary Wallace Stanton Professor of Education. Since joining the School of Medicine faculty in 1984, he has held numerous leadership posts in both the Department of Anesthesiology and Critical Care Medicine and school-wide. Named vice dean for education in 2000, Dr. Nichols oversees undergraduate, graduate, residency, postdoctoral and continuing medical education programs, as well as the Welch Medical Library. He has led a wide variety of significant initiatives to improve the school of medicine's innovative use of technology in education; update the medical school's curriculum; improve faculty development by revising tenure and promotion guidelines; restructure graduate medical education; oversee the design of a new $50 million medical education building; and enhance diversity throughout Johns Hopkins Medicine.

From 1984 to 1987, Dr. Nichols was associate director of the residency education program in the Department of Anesthesiology and Critical Care Medicine. He became director of the Division of Pediatric Critical Care and of the pediatric intensive care unit (PICU) in 1988. The division was merged with pediatric anesthesiology under Dr. Nichols' leadership in 1997. During this period, he trained and mentored more than 50 postdoctoral fellows, many of whom now are professors or directors of PICUs in the United States and abroad. Dr. Nichols became a full professor of anesthesiology/critical care medicine and pediatrics in 1998 and became the recipient of the Mary Wallace Stanton Professorship for Education in 2005. He has written more than 80 professional journal articles and abstracts, held 17 guest professorships, headed more than 20 symposia and delivered more than 115 guest lectures. He also has been editor in chief of the leading textbooks in pediatric critical care medicine and edited Rogers Textbook of Pediatric Intensive Care and Critical Heart Disease in Infants and Children.

Janet Woodcock

Janet Woodcock, M.D. is the Director, Center for Drug Evaluation and Research, Food and Drug Administration (FDA). Dr. Woodcock held various leadership positions within the Office of the Commissioner, FDA including Deputy Commissioner and Chief Medical Officer, Deputy Commissioner for Operations and Chief Operating Officer and Director, Critical Path Programs. Previously, Dr. Woodcock served as Director, Center for Drug Evaluation and Research from 1994-2005. She also held other positions at FDA including Director, Office of Therapeutics Research and Review and Acting Deputy Director, Center for Biologics Evaluation and Research. A prominent FDA scientist and executive, Dr. Woodcock has received numerous awards, including a Presidential Rank Meritorious Executive Award, the American Medical Association's Nathan Davis Award, and Special Citations from FDA Commissioners. Dr. Woodcock received her M.D. from Northwestern Medical School, completed further training and held teaching appointments at the Pennsylvania State University and the University of California in San Francisco. She joined FDA in 1986.
Jon Lorsch

Jon Lorsch serves as the Director of Scientific Foundations of Medicine for first year medical students, and is currently Professor of Biophysics and Biophysical Chemistry at Johns Hopkins University School of Medicine. His educational focus is on the integration of basic and clinical sciences as well as the principles of biomedical education during an age of exponential information growth. Dr. Lorsch’s research focuses on the molecular mechanics of protein synthesis. His research is currently shedding light on how protein synthesis operates in normal cells and how it can be corrected when it goes awry in diseases such as cancer.

Dr. Lorsch has received many awards including the W. Barry Wood Award for Excellence in Preclinical Teaching and Graduate Student Association Teacher of the Year. He also serves as a current member of an NIH study section, Molecular Genetics A, and is the editor of an online basic biomedical methods resource, the Biomedical Methods Navigator. Dr. Lorsch earned his Ph.D. from Harvard University in 1995 and was a Post-doctoral Fellow at Stanford University from 1995 until 1999.

Brian Kelly

Brian J. Kelly, M.D., is the Head of Informatics and Strategic Alignment at Aetna. Brian leads the Informatics and Strategic Alignment team of approximately 160 people who work with the Chief Medical Officer and Aetna's clinical teams to define and measure the quality and affordability of healthcare. He also develops strategies to build market-leading business and system capabilities that allows Aetna to deliver on its strategy of helping members improve their health by accessing cost effective, high quality care. Brian joined Aetna in 2008 as the National Medical Director for National Accounts, where he provided clinical support for sales and retention efforts and helped lead the development of the Benefit, Engagement and Network Strategy (BEN) program.

A former Navy neurologist and intensive care medicine specialist, Brian retired from the Navy in 2003 and spent five years at Accenture consulting for a large number of health plans, hospitals, and governments with a primary focus on using information technology to improve health care. He has worked on care management initiatives with a variety of health plans and led Accenture’s global electronic health record practice.
Session 7: Instrumenting the Healthcare Delivery System to Define and Leverage a New Taxonomy

Isaac S. Kohane

Isaac (Zak) S. Kohane is the director of the Children's Hospital Informatics Program and is the Henderson Professor of Pediatrics and Health Sciences and Technology at Harvard Medical School (HMS). He is also co-director of the HMS Center for Biomedical Informatics and Director of the HMS Countway Library of Medicine. Dr. Kohane leads multiple collaborations at Harvard Medical School and its hospital affiliates in the use of genomics and computer science to study diseases (particularly cancer and autism). He has developed several computer systems to allow multiple hospital systems to be used as "living laboratories" to study the genetic basis of disease while preserving patient privacy. Among these, the i2b2 (Informatics for Integrating Biology and the Bedside) National Computing Center has been deployed at over 52 academic health centers internationally.

Dr. Kohane has published over 180 papers in the medical literature and authored a widely used book on microarrays for Integrative Genomics. He has been elected to multiple honor societies including the American Society for Clinical Investigation, the American College of Medical Informatics, and the Institute of Medicine. He leads a doctoral program in genomics and bioinformatics at the Division of Health Sciences and Technology at Harvard and MIT. He is also a practicing pediatrics endocrinologist and father of three energetic children.

Daniel Masys

Dr. Daniel R. Masys is Professor and Chair of the Department of Biomedical Informatics. An honors graduate of Princeton University (biochemistry and molecular genetics) and the Ohio State University College of Medicine, he completed postgraduate training in Internal Medicine, Hematology and Medical Oncology at the University of California, San Diego (UCSD), and the Naval Regional Medical Center, San Diego. Dr. Masys served as chief of the International Cancer Research Data Bank of the National Cancer Institute, National Institutes of Health, and from 1986 through 1994 was director of the Lister Hill National Center for Biomedical Communications, which is a computer research and development division of the National Library of Medicine. In this capacity, he served as principal program architect of the National Center for Biotechnology Information (NCBI), which hosts the data from the Human Genome Project and other molecular biology information resources and analysis tools. Prior to joining Vanderbilt, Dr. Masys was director of Biomedical Informatics and professor of Medicine at UCSD, and medical director of UCSD's Human Research Protections Program (IRB).

Dr. Masys is an elected member of the Institute of Medicine of the National Academies. He is board certified in hematology and medical oncology, a Fellow of the American College of Physicians, and a Fellow and past President of the American College of Medical Informatics. He was a founding associate editor of the *Journal of the American Medical Informatics Association*, and has received numerous awards including the NIH Director's Award and the US Surgeon General's Exemplary Service Medal.

John Brownstein

Dr. Brownstein is an Assistant Professor at Harvard Medical School and research faculty the Children's Hospital Boston Informatics Program. He was trained as an epidemiologist at Yale University. Overall, his research agenda aims is to have translation impact on the surveillance, control and prevention of disease through better epidemiologic understanding of risk factors, improved practice of public health and engaging the public around important health issues. This research has focused on a variety of infectious disease systems including malaria, HIV, dengue, West Nile virus, Lyme disease, RSV, salmonella, and influenza. He directs the Computational Epidemiology Group at the Children’s Hospital Informatics
Program where he oversees a 20-person team, including postdoctoral fellows, epidemiologists, computer scientists and engineers. He has been at the forefront of the development and application of public health surveillance including HealthMap.org, an internet-based global infectious disease intelligence system. The system is in use daily by over a million people a year including the CDC, WHO, DHS, DOD, HHS, and EU, and has been recognized by the National Library of Congress and the Smithsonian. Dr. Brownstein has advised the World Health Organization, Institute of Medicine, the US Departments of Health and Human Services and Homeland Security, and the White House on real-time public health surveillance. He plays a leading role in a number of international committees including Vice President of the International Society for Disease Surveillance and member of the IOM committees on disease surveillance, as well as a number of standing WHO advisory panels. He has authored over sixty peer-reviewed articles on epidemiology and public health. This work has been reported on widely including pieces in the New England Journal of Medicine, Science, Nature, New York Times, The Wall Street Journal, CNN, National Public Radio and the BBC.
Session 8: A Clinical Perspective on a New Taxonomy

Charles Sawyers

Dr. Charles Sawyers, M.D., is an Investigator of the Howard Hughes Medical Institute and the inaugural Director of the Human Oncology and Pathogenesis Program (HOPP) at Memorial Sloan-Kettering Cancer Center (MSKCC), where he is building a program of lab-based translational researchers across various clinical disciplines and institutional infrastructure to enhance the application of global genomics tools to clinical trials.

Sawyers’ laboratory is currently focused on characterizing signal transduction pathway abnormalities in prostate cancer, with an eye toward translational implications. His research is best demonstrated through his earlier studies of BCR-ABL tyrosine kinase function in chronic myeloid leukemia, his work with Brian Druker and Novartis in the development of the kinase inhibitor imatinib/Gleevec as primary therapy for CML, and his discovery that imatinib resistance is caused by BCR-ABL kinase domain mutations. This discovery led Dr. Sawyers to evaluate second generation Abl kinase inhibitors, such as the dual Src/Abl inhibitor dasatinib, which received fast track approval at the FDA in June 2006.

Dr. Sawyers’ work in prostate cancer has defined critical signaling pathways for disease initiation and progression through studies in mouse models and humane tissues. This preclinical work led to the development of a novel antiandrogen MVD3100, a small molecule inhibitor discovered in collaboration with UCLA Chemist Michael Jung, which targets the increased levels of androgen receptor found in the hormone refractory disease. Based on impressive clinical results in a phase I/II study, MDV3100 is currently in phase III registration trial. Dr. Sawyers is past President of the American Society of Clinical Investigation and served on the National Cancer Institute’s Board of Scientific Councilors. He has won numerous honors and awards, including: the Richard and Hinda Rosenthal Foundation Award; the Dorothy Landon Prize from the American Association of Cancer Research and the David A. Karnofsky Award from the American Society of Clinical Oncology; and the 2009 Lasker DeBakey Clinical Medical Research Award. He is a member of the Institute of Medicine and in 2010 was elected to the National Academy of Sciences.

Ingrid Scheffer

Professor Ingrid Scheffer is a paediatric neurologist and epileptologist at the University of Melbourne, Australia. Her work together with Professor Sam Berkovic, and with the Women’s and Children’s Hospital, Adelaide, has led the field of epilepsy genetics research over the last 19 years. This collaboration resulted in identification of the first epilepsy gene and ten of the twenty genes currently known. Professor Scheffer has described five new epilepsy syndromes and continues to work on genotype–phenotype correlation.

Professor Scheffer’s research interests include the genetics of epilepsy, epilepsy syndrome classification, novel antiepileptic therapies and autism spectrum disorders. She was awarded the 2007 American Epilepsy Society Clinical Research Recognition Award and the 2009 Eric Susman Prize from the Royal Australasian College Of Physicians. Professor Scheffer is currently Chair of the International League Against Epilepsy Commission for Classification and Terminology, the body that determines how the epilepsies are classified.

William Pao

Dr. William Pao is Associate Professor of Medicine, Cancer Biology, and Pathology at Vanderbilt University. He is also the Ingram Associate Professor of Cancer Research and Director of Personalized Cancer Medicine at Vanderbilt-Ingram Cancer Center. Dr. Pao obtained his MD and PhD degrees at Yale University, did his housestaff training in Internal Medicine at New York Presbyterian Hospital-Weill Cornell Campus and completed his medical oncology fellowship training at Memorial Sloan-Kettering Cancer Center. In his laboratory, he has developed a basic and translational research program that made seminal contributions to the understanding of molecular mechanisms in lung cancer pathogenesis.
His work has identified new molecular mechanisms of sensitivity and resistance of lung cancers to EGFR tyrosine kinase inhibitors and has yielded important insights into a molecular understanding of lung adenocarcinoma in never smokers. Based on these discoveries, he has developed and successfully tested new anti-cancer therapies in animal models and humans. His work has helped change the standard of care in lung cancer. More recently, his laboratory has established a high-throughput screen to identify kinase fusions in cancers, using next-generating sequencing technologies.

Dr. Pao has received multiple honors and awards, including an ASCO Young Investigator Award, a Clinical Scientist Development Award from the Doris Duke Charitable Foundation, a V Foundation grant, the Hope Now Award from the Joan's Legacy Foundation, and an SU2C Innovative Grant Award from the AACR.

Elissa Epel

Elissa Epel, Ph.D., is national leader in the field of health psychology and behavioral medicine, focusing on stress pathways. For the past 15 years, she has studied stress in the lab (using standardized stressors) and in the field, using common naturalistic stressors, and examined associations with an early aging syndrome. She has done seminal work showing stress pathways to disease precursors, focusing on eating behavior, abdominal obesity, and immune cell aging. She has shown that people's propensity to be stress reactive, psychologically or in terms of cortisol reactivity, is a predictor of overeating, of abdominal obesity, and in current work, of accelerated cell aging. With UCSF colleagues Elizabeth Blackburn and Jue Lin, she showed that stress perceptions as well as stress arousal are related to telomere shortness and dampened telomerase activity. This work has now been replicated and there are many lines of complementary research internationally. The UCSF group has many collaborations from animal models to population studies. Epel and colleagues are also examining how stress reduction interventions may enhance functioning of the telomere/telomerase maintenance system. This early work shows promise in understanding biochemical and behavioral (lifestyle) modulators of cell aging in people.

Epel studied psychology and psychobiology at Stanford University (1990, BA, with Distinction), and then clinical and health psychology at Yale University (PhD, 1998, with Distinction). She completed an NIMH funded postdoctoral fellowship at UCSF, where she has stayed on as faculty, in the Department of Psychiatry. Epel has received awards from the American Psychological Association, for her research conducted as a student (1996, 1998), a junior investigator (2005), and more recently, the Early Career Award (2008). She also was awarded the Academy of Behavioral Medicine Research Neal Miller Young Investigator Award and the International Society for Psychoneuroendocrinology's Young Investigator Award.

At UCSF, she plays several leadership and mentorship roles. In her research and teaching, she focuses on the important role that stress and lifestyle factors have on health and longevity. She is the Assistant Director of the Center for Health and Community, a center promoting interdisciplinary research, faculty in the Robert Wood Johnson Health and Society Scholar Postdoctoral Fellowship on population health, and for the NIMH funding Psychology and Medicine Postdoctoral Fellowship. She is involved in several clinical trials at the UCSF Osher Center for Integrative Medicine, where she helps examine how mindfulness meditation affects stress pathways and cell aging. She was a founder and a now Director of the UCSF Center for Obesity Assessment, Study, and Treatment (COAST), which focuses on how socio-economic status and stress pathways play a role in the obesity epidemic.
Common diseases are currently defined by their clinical appearance, with little reference to mechanism. Molecular genetics may provide the tools necessary to define diseases by their mechanisms. This is likely to have profound effects on clinical decisions such as choice of treatment and on our ability to characterise more clearly the course of disease and contributory environmental factors. This information also raises the possibility that new therapeutic interventions can be obtained rationally, based on a clear understanding of pathogenesis. Most of these genetic factors will act as “risk factors” and should be managed ethically and practically, as would other risk factors (in hypertension or hypercholesterolaemia, for example).

The rapid advances in human molecular genetics seen over the past five years indicate that within the next decade genetic testing will be used widely for predictive testing in healthy people and for diagnosis and management of patients.

Molecular genetics was originally used in medicine to map and identify the major single gene disorders, such as cystic fibrosis and polycystic kidney disease. The excitement in the field has shifted to the elucidation of the genetic basis of the common diseases. With the help of very large, well characterised family collections, genetic linkages for many of the major causes of morbidity and mortality in Western populations have been identified. The genes and DNA variants responsible for these disorders are now being cloned at an ever increasing pace. Large scale genotyping, increasingly integrated genetic and expressed sequence maps, and large scale sequencing programmes have all contributed to this remarkable evolution in our understanding of how genes might modify our susceptibility to disease.

Considering the current rapid acquisition of genetic information relating to common disease and the dramatic technological developments that continue to fuel the field, it would be surprising if most of the major genetic factors involved in human disease were not defined over the next 5-10 years. This information will form an important template for redefining disease, clarifying biological mechanisms responsible for disease, and developing new treatment for most disorders.

Summary points

- Genetic information is likely to transform the practice of clinical medicine
- Genetics will provide a taxonomy of disease that is based on biochemical mechanisms rather than phenotype
- Genetic information will be used to identify individuals who are likely to respond to or suffer toxicity from drugs
- Genetic variation will be another form of "risk factor" and will permit early treatment and directed screening

The rapid developments in human molecular genetics have often been underestimated, largely due to a failure to recognise the power of new technologies being applied to the problem. The use of information encoded within the genome for clinical practice has previously been limited by problems of scaling up accurate detection of DNA variation for rapid and inexpensive analysis. The problem will soon be resolved, perhaps by the use of oligonucleotide array technology or "chips." The ease with which this can be accomplished will determine how widespread DNA diagnostics will become, but there is little doubt...
that the problem is likely to be solved, technologically, in the near future.

The role of genes for susceptibility to disease has been emphasised in clinical medicine; it is now clear that this represents too narrow a perspective for the genetics of the future. Although such genes will be critical for redefining diseases and understanding their pathogenesis, equally important will be loci that determine disease progression, disease complications, and response to treatment.

A new taxonomy of disease

Perhaps the most important single contribution of the new genetics to health care is that it will create a biological rather than a phenotypic framework with which to categorise diseases. Clinical physiology and biochemistry have provided many insights into the biological disturbances that accompany disease, but it is genetics that is able to identify the pathways that are unambiguously involved in pathogenesis. Such genetic information will eventually lead to the redefinition of disease on the basis of biochemical events rather than phenotype; on molecular events driving biological processes rather than a correlation of clinical syndromes and outcomes.

The ability to redefine common human disease, using genetics to define the biochemical processes responsible for disease, will allow the subdivision of heterogeneous diseases such as hypertension or diabetes into discrete entities. Such subdivision is likely to help explain the wide variation of these diseases, including apparent differences in physiology, clinical course, and response to treatment, and it might also provide a basis for identifying environmental factors that contribute only to certain subtypes of disease. This has already begun in diabetes, where definition of the involvement of HLA genes suggested an immune mechanism in a subset of patients, leading to the subdivision into type I and type II diabetes.6 More recently, type II diabetes has been subdivided further on the basis of distinct mechanisms involving glucose phosphorylation and insulin (glucokinase) secretion, transcriptional regulation (HNF), and insulin receptor dysfunction.

Understanding of how genes might modify our susceptibility to disease is evolving

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A new taxonomy of disease: diabetes

Type I Autoimmune (HLA, INS) Type II Insulin resistant (INS receptor) Insulin secretion (glucokinase) Insulin transcription (?) (HNF1α, HNF4α, IPF)

Disease mechanisms have led to clear definitions of infectious diseases. For example, our understanding of hepatitis has progressed: it used to be viewed as a clinical syndrome with a wide variety of outcomes, and is now seen as a set of quite specific diseases defined by the aetiological agent, each with its own clinical course, prognosis, and (perhaps) response to treatment. An understanding of the biological process underlying the clinical phenotype has been of unquestionable benefit in defining and managing disease, and doctors are unlikely to attempt to manage a jaundiced patient with hepatitis without attempting to define the specific viral agent involved. Similarly, pharmaceutical companies are unlikely to attempt to develop novel vaccines or therapies without precise information about the disease type. Even in a well defined disease such as viral hepatitis, aspects of disease progression such as viral persistence will need to await genetic clarification.

Understanding the biological events and pathways identified by genetics as contributing to disease will lead to clear definition of disease. Such information may become the starting point in the management of most patients.

A new taxonomy of disease based on genetics is already being developed. The first examples of disease definition have come from the loci in common disease that seem to resemble autosomally inherited traits in families. Although these contribute to disease in only a small proportion of affected people, they provide considerable insights into disease mechanisms. Breast cancer (BRCA1, BRCA2), 7 8 colon cancer (FAP, HNPCC),9 and diabetes (MODY 1, 2 and 3)10-12 all have such highly penetrant loci, and their elucidation has provided some of the first insights into disease pathogenesis. The
The new genetics: The new genetics in clinical practice -- Bell 316...

An indication of how important genetic information will be in defining disease and predicting outcome.

Genetic screening by indication will go hand in hand, and lifelong treatment on the basis for severe side effects of drugs and not giving individuals from receiving a drug if they are unlikely to benefit or those managing the disease and will need to be tested for. Even relatively simple management decisions regarding individuals at risk of deep venous thrombosis (patients with total hip replacement, or those taking the oral contraceptive pill) may benefit from evaluation of their factor V Leiden status. Decisions about the best treatment (CETP alleles and statins, 5'-lipooxygenase inhibitors) or the side effects of drugs (cytochrome P-450 and flecanide) may rely on genetic stratification.

Clinical benefit accruing from genetic studies of disease

- A new taxonomy of disease based on mechanisms, not phenotype
- New drugs developed rationally from our understanding of pathogenesis
- Drug development and utilisation focused on disease subtypes likely to respond to treatment
- Adverse effects of drugs avoided by genetic screening
- "Risk factor" analysis will facilitate environmental modification, screening, and therapeutic management of people before they develop symptoms

Discovery and development of drugs

One of the earliest applications of this genetic information will be in the discovery and development of new drugs. Genetics is now widely used to identify new targets for drug designs, and it is increasingly recognised that defining disease populations by genotype will probably correlate with response to drug treatment. The variety of mechanisms that underlie complex disease may account for the wide variations in response seen in clinical practice and the difficulty often encountered in drug development of showing consistent large benefits in trial populations. Wise pharmaceutical companies are already introducing genotyping in their trials to predict response, and eventually this information will be needed to move toward a refined taxonomy in medicine that is based on biochemical mechanisms and driven by genetics.

Genes as risk factors

An indication of how important genetic information will be in defining disease and predicting outcomes in complex diseases can be gained from our knowledge of Apo E4 and Alzheimer's disease. Homozygosity for this allele is associated with a shift of about 20 years in the average age of onset of Alzheimer's disease. These effects are at least as great as other more...
conventional risk factors in common disease (such as hypertension in hypercholesterolaemia). Although current recommendations suggest that Apo E genotyping be used as an adjunct to diagnosis in cognitively impaired people, it is likely that genetic stratification by Apo E genotype will define drug response, and hence such genotyping may soon be applied in clinical trials and eventually will be more relevant to daily clinical practice.

Examples such as Apo E4 raise the question of whether a genetic susceptibility factor might best be treated as another "risk factor." Other risk factors (blood pressure or cholesterol concentrations) show similar patterns of incomplete penetrance and have been considered for population screening. There is little reason that risk factors based on DNA should not be treated in the same way. Genetic factors that can be used to predict the risk of a population rather than an individual should be viewed in the same way as other risk factors, particularly if safe treatment or environmental modification were available.

This raises the possibility of population screening to detect important susceptibility loci when intervention becomes available. The obvious requirement for such screening would be validation by large scale trials on the benefits of such early detection and treatment. A combination of conventional and genetic risk factors may be optimal for identifying populations at risk. In hypertension or hypercholesterolaemia, risks vary greatly. Treating the extremes of variation has the most favourable cost benefit ratio, but most "at risk" patients fall within the normal range. Genetics could be used to identify those who have additional genetic risks and in whom reduction of these variables might be beneficial, even where such variables might be in the "normal" range. There are some trial data to support such an approach. 19

### Conclusion

The widespread redefinition of disease through genetics will be accompanied by the use of genetics for prediction and diagnosis and to optimise treatment in most common diseases. This is likely to occur within the next decade. Testing for genetic "risk factors," even in people without symptoms, may develop (as it has for other risk factors), and this information may be used to identify people at increased risk, for early intervention. There is a possibility, however, that DNA diagnostics and pharmacogenomics will be used without proper evaluation—especially as few resources are available for rigorous evaluation and pressure continues to introduce this information in routine clinical practice.

### Acknowledgments

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Conflict of interest: JB sits as a non-executive member on the board of Oxagen, a genomic biotechnology company, but holds no equity.

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Redefining Disease, Genes and All

By ANDREW POLLACK

Correction Appended

Duchenne muscular dystrophy may not seem to have much in common with heart attacks. One is a rare inherited disease that primarily strikes boys. The other is a common cause of death in both men and women. To Atul J. Butte, they are surprisingly similar.

Dr. Butte, an assistant professor of medicine at Stanford, is among a growing band of researchers trying to redefine how diseases are classified — by looking not at their symptoms or physiological measurements, but at their genetic underpinnings. It turns out that a similar set of genes is active in boys with Duchenne and adults who have heart attacks.

The research is already starting to change nosology, as the field of disease classification is known. Seemingly dissimilar diseases are being lumped together. What were thought to be single diseases are being split into separate ailments. Just as they once mapped the human genome, scientists are trying to map the “diseasome,” the collection of all diseases and the genes associated with them.

“We are now in a unique position in the history of medicine to define human disease precisely, uniquely and unequivocally,” three scientists wrote of the new approach last year in the journal Molecular Systems Biology. Such research aims to do more than just satisfy some basic intellectual urge to organize and categorize. It also promises to improve treatments and public health.

Scientists are finding that two tumors that arise in the same part of the body and look the same on a pathologist’s slide might be quite different in terms of what is occurring at the gene and protein level. Certain breast cancers are already being treated differently from others because of genetic markers like estrogen receptor and Her2, and also more complicated patterns of genetic activity.

“In the not too distant future, we will think about these diseases based on the molecular pathways that are aberrant, rather than the anatomical origin of the tumor,” said Dr. Todd Golub, director of the cancer program at the Broad Institute in Cambridge, Mass.

The reclassification may also help find drugs. “There are 40 drugs to treat heart attacks, but none to treat muscular dystrophy,” Dr. Butte said. If the diseases are similar in some molecular pathways, perhaps the heart attack drugs should be tested against muscular dystrophy.

Dr. Golub and colleagues at the Broad Institute have developed a “Connectivity Map,” which profiles drugs by the genes they activate as a way to find new uses for existing drugs.

The research will also improve understanding of the causes of disease and of the functions of particular genes. For instance, two genes have recently been found to influence the risk of both diabetes and prostate cancer.

“I’m shaking my head with disbelief that two genes would pop up in these two diseases that have absolutely nothing in common,” said Dr. Francis S. Collins, the director of the National Human Genome Research Institute. He said another gene, cyclin-dependent kinase inhibitor 2A, seemed to be involved in cancer, diabetes and heart disease.

A consistent way to classify diseases is also essential for tracking public health and detecting epidemics. The World Health Organization takes pains to periodically revise its International Classification of Diseases, which is used, among
other ways, to tally the causes of death throughout the world. The classification is also the basis of the ICD-9 codes used for medical billing in the United States.

The first international classification, in the 1850s, had about 140 categories of disease, according to Dr. Christopher G. Chute, chairman of biomedical informatics at the Mayo Clinic. The 10th edition, in 1993, had 12,000 categories, said Dr. Chute, chairman of the committee developing the 11th version, due in 2015.

The increase stems mainly from better knowledge and diagnostic techniques that allow diseases to be distinguished from one another. For most of human history, diseases were named and classified by symptoms, which was all people could observe.

Linnaeus, the 18th-century Swedish scientist known for categorizing creatures into genus and species, also developed a taxonomy of disease. He had 11 classes — painful disease, motor diseases, blemishes and so on — that were further broken down into orders and species. But not knowing about viruses, for instance, he classified rabies as a mental disease, Dr. Chute said.

In the 19th century, a big shift occurred. Doctors began learning how to peer inside the body. And diseases began to be classified by their anatomic or physiological features.

The stethoscope let doctors realize that what had been thought of as 17 conditions — like coughing up blood and shortness of breath — could all be different symptoms of the same disease, tuberculosis.

“The advent of the stethoscope made it possible to unify tuberculosis,” said Dr. Jacalyn Duffin, a professor of the history of medicine at Queen's University in Ontario.

The shift from symptoms to anatomical measurements had big implications for patients, said Dr. Duffin, who is also a hematologist.

“Up until the 18th century, you had to feel sick to be sick,” she said. But now people can be considered sick based on measurements like high blood pressure without feeling ill at all.

Indeed, Dr. Duffin said, people who feel sick nowadays “don’t get to have a disease unless the doctor can find something” and instead might be told that it’s all in their head. Doctors argue, for instance, about whether fibromyalgia or chronic fatigue syndrome, which have no obvious anatomical causes, are really diseases.

Genes might allow the study of diseases at a finer level than even physiological tests. Genes are the instructions for the production of proteins, which interact in complex ways to carry out functions in the body. Disruptions in these molecular pathways can cause disease.

“It gives you a direct connection to what the root causes are,” said Dr. David Altshuler, a professor of medicine and genetics at Harvard and Massachusetts General Hospital, and a researcher at the Broad Institute. “That is different from listening to a stethoscope.”

Some of the earliest work has until now been with inherited diseases caused by mutations in a single gene. Diseases have been subdivided by the type of mutation. Hemophilia was divided into hemophilia A and B, caused by mutations in different genes for different clotting factors. And what was once considered a mild form of hemophilia was later identified as a variant of a different clotting disorder, von Willebrand disease, caused by mutations in a different gene and requiring a different clotting factor as treatment.

Diseases are being lumped, as well as split. Researchers at Johns Hopkins reported in the April issue of Nature Genetics that two rare syndromes with different symptoms might represent a continuum of one disease. One syndrome, Meckel-Gruber, is tied to neural defects and death in babies. The other, Bardet-Biedl, is marked by vision loss, obesity, diabetes and extra fingers and toes.

The techniques are being applied to diseases for which the genetic cause is not as clearly known and which might be a
result of multiple genes.

Dr. Butte uses data from gene chips that measure which genes are active, or expressed, in a cell. Amid thousands of studies using such chips, many compared the gene activity patterns in diseased tissue with that of healthy tissue.

Much of the raw data from such studies are deposited in a database. So Dr. Butte can gather data on gene activity for scores of diseases without leaving his desk. He then performs statistical analyses to map diseases based on similarities in their patterns of gene activity.

Other scientists use data on which genes appear to cause disease or contribute to the risk of contracting it.

Using such data, Marc Vidal, a biologist at Harvard, and Albert-Laszlo Barabasi, now a physicist at Northeastern University, created a map of what they called the “diseasome” that was published last year in The Proceedings of the National Academy of Sciences.

Diseases were represented by circles, or nodes, and linked to other diseases by lines that represent genes they have in common — something like the charts linking actors to one another (and ultimately to Kevin Bacon) based on the movies they appeared in together.

The number of genes associated with diseases is expanding rapidly because of so-called whole genome association studies. In these studies, gene chips are used to look for differences between the genomes of people with a disease and those without.

Multiple techniques can be combined. In a paper published online in Nature in March, scientists at Merck reconstructed the network of genes involved in obesity.

One area that might benefit from genetic disease classification is psychiatry. Because of the difficulty of measuring the brain, psychiatric diagnoses are still mainly based on symptoms. The Diagnostic and Statistical Manual of Mental Disorders contains descriptions of conditions as diverse as acute stress disorder and voyeurism.

Scientists have found that certain genes appear to be associated with both schizophrenia and bipolar disorder. Those links, and the fact that some drugs work for both diseases, have prompted a debate over whether they are truly distinct disorders. “The way we categorize these into two separate entities is almost certainly not correct,” said Dr. Wade H. Berrettini, a professor of psychiatry at the University of Pennsylvania.

But Dr. Kenneth S. Kendler, a professor of psychiatry and human genetics at Virginia Commonwealth University, said that even if the two diseases shared genes, the diseases remained distinct. Schizophrenia is marked by hallucinations and impaired social functioning, and bipolar disorder by mood swings.

“It’s extremely naïve to think that psychiatric illnesses will collapse into categories defined by a gene,” he said. “Each gene at most has a quite modest effect on the illness.”

Some experts say that such limitations may hold true for other diseases, as well, and that genetics will not be able to unequivocally define and distinguish diseases. “We shouldn’t expect, nor will we get, this decisive clarity,” said Fiona A. Miller, associate professor of health policy, management and evaluation at the University of Toronto.

She and others said genetic classification could bring its own ambiguities. Newborns are now often screened for cystic fibrosis with the idea that they can be treated early to help avoid complications. But some infants with a mutation in the gene responsible for the disease are unlikely ever to have symptoms. Do they have the disease?

“We don’t know what to call these infants,” said Dr. Frank J. Accurso, a professor of pediatrics at the University of Colorado. “We don’t even have a good language for it yet.”

Still, Dr. Butte said nosology based on genes would one day make today’s classifications look as quaint as ones from 100 years ago look now. One category in the 1909 listing of the causes of death, for instance, was “visitation of God.”
“Imagine how they are going to be laughing at us,” he said. “Not 100 years from now, but even 50 or 20 years from now.”

This article has been revised to reflect the following correction:

**Correction: May 9, 2008**

An article on Tuesday about changes in the way diseases are classified misspelled the university where Dr. Jacalyn Duffin works as a professor of the history of medicine. It is Queen’s University, not Queens.
The human disease network

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A network of disorders and disease genes linked by known disorder–gene associations offers a platform to explore in a single graph-theoretic framework all known phenotype and disease gene associations, indicating the common genetic origin of many diseases. Genes associated with similar disorders show both higher likelihood of physical interactions between their products and higher expression profiling similarity for their transcripts, supporting the existence of distinct disease-specific functional modules. We find that essential human genes are likely to encode hub proteins and are expressed widely in most tissues. This suggests that disease genes also would play a central role in the human interactome. In contrast, we find that the vast majority of disease genes are nonessential and show no tendency to encode hub proteins, and their expression pattern indicates that they are localized in the functional periphery of the network. A selection-based model explains the observed difference between essential and disease genes and also suggests that diseases caused by somatic mutations should not be peripheral, a prediction we confirm for cancer genes.

Results

Constructions of the Diseasome. We constructed a bipartite graph consisting of two disjoint sets of nodes. One set corresponds to all known genetic disorders, whereas the other set corresponds to all known disease genes in the human genome (Fig. 1). A disorder and a gene are then connected by a link if mutations in that gene are implicated in that disorder. The list of disorders, disease genes, and associations between them was obtained from the Online Mendelian Inheritance in Man (OMIM; ref. 18), a compendium of human disease genes and phenotypes. As of December 2005, this list contained 1,284 disorders and 1,777 disease genes. OMIM initially focused on monogenic disorders but in recent years has expanded to include complex traits and the associated genetic mutations that confer susceptibility to these common disorders (18). Although this history introduces some biases, and the disease gene record is far from complete, OMIM represents the most complete and up-to-date repository of all known disease genes and the disorders they confer. We manually classified each disorder into one of 22 disorder classes based on the physiological system affected [see supporting information (SI) Text, SI Fig. 5, and SI Table 1 for details].

Starting from the diseasome bipartite graph we generated two biologically relevant network projections (Fig. 1). In the “human disease network” (HDN) nodes represent disorders, and two disorders are connected to each other if they share at least one gene in which mutations are associated with both disorders (Figs. 1 and 2a). In the “disease gene network” (DGN) nodes represent disease genes, and two genes are connected if they are associated with the same disorder (Figs. 1 and 2b). Next, we discuss the potential of these networks to help us understand and represent in a single framework all known disease gene and phenotype associations.

Properties of the HDN. If each human disorder tends to have a distinct and unique genetic origin, then the HDN would be disconnected into many single nodes corresponding to specific disorders or grouped into small clusters of a few closely related disorders. In contrast, the obtained HDN displays many connections between both individual disorders and disorder classes (Fig. 2a). Of 1,284 disorders, 867 have at least one link to other disorders, and 516 disorders form a giant component, suggesting that the genetic origins of most diseases, to some extent, are shared with other diseases. The number of genes associated with a disorder, s, has a broad distribution (see SI Fig. 6a), indicating that most disorders relate to a few disease genes, whereas a handful of phenotypes, such as deafness ($s = 41$), leukemia ($s = 37$), and colon cancer ($s = 34$), relate to dozens of genes (Fig. 2a). The degree ($k$) distribution of HDN (SI Fig. 6b) indicates that most disorders are linked to only

Author contributions: D.V., B.C., M.V., and A.-L.B. designed research; K.-I.G. and M.E.C. analyzed data; and K.-I.G., M.V., and A.-L.B. wrote the paper.

The authors declare no conflict of interest.

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Abbreviations: DGN, disease gene network; HDN, human disease network; GO, Gene Ontology; OMIM, Online Mendelian Inheritance in Man; PCC, Pearson correlation coefficient.

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a few other disorders, whereas a few phenotypes such as colon cancer (linked to $k = 50$ other disorders) or breast cancer ($k = 30$) represent hubs that are connected to a large number of distinct disorders. The prominence of cancer among the most connected disorders arises in part from the many clinically distinct cancer subtypes tightly connected with each other through common tumor suppressor genes such as $TP53$ and $PTEN$.

Although the HDN layout was generated independently of any knowledge on disorder classes, the resulting network is naturally and visibly clustered according to major disorder classes. Yet, there are visible differences between different classes of disorders. Whereas the large cancer cluster is tightly interconnected due to the many genes associated with multiple types of cancer ($TP53$, $KRAS$, $ERBB2$, $NFI$, etc.) and includes several diseases with strong predisposition to cancer, such as Fanconi anemia and ataxia telangiectasia, metabolic disorders do not appear to form a single distinct cluster but are underrepresented in the giant component and overrepresented in the small connected components (Fig. 2a). To quantify this difference, we measured the locus heterogeneity of each disorder class and the fraction of disorders that are connected to each other in the HDN (see SI Text). We find that cancer and neurological disorders show high locus heterogeneity and also represent the most connected disease classes, in contrast with metabolic, skeletal, and multiple disorders that have low genetic heterogeneity and are the least connected (SI Fig. 7).

Properties of the DGN. In the DGN, two disease genes are connected if they are associated with the same disorder, providing a complementary, gene-centered view of the diseasome. Given that the links signify related phenotypic association between two genes, they represent a measure of their phenotypic relatedness, which could be used in future studies, in conjunction with protein–protein interactions (6, 7, 19), transcription factor-promoter interactions (20), and metabolic reactions (8), to discover novel genetic interactions.

In the DGN, 1,377 of 1,777 disease genes belong to a giant component (Fig. 2b). Whereas the number of genes involved in multiple diseases decreases rapidly (SI Fig. 6f; light gray nodes in Fig. 2b), several disease genes (e.g., $TP53$, $PAX6$) are involved in as many as 10 disorders, representing major hubs in the network.

Functional Clustering of HDN and DGN. To probe how the topology of the HDN and GDN deviates from random, we randomly shuffled the associations between disorders and genes, while keeping the number of links per each disorder and disease gene in the bipartite network unchanged. Interestingly, the average size of the giant component of 10$^4$ randomized disease networks is 643 ± 16, significantly larger than 516 ($P < 10^{-4}$; for details of statistical analyses of the results reported hereafter, see SI Text), the actual size of the HDN (SI Fig. 6c). Similarly, the average size of the giant component from randomized gene networks is 1,087 ± 20 genes, significantly larger than 903 ($P < 10^{-4}$), the actual size of the DGN (SI Fig. 6e). These differences suggest important pathophysiological clustering of disorders and disease genes. Indeed, in the actual networks disorders (genes) are more likely linked to disorders (genes) of the same disorder class. For example, in the HDN there...
Fig. 2. The HDN and the DGN. (a) In the HDN, each node corresponds to a distinct disorder, colored based on the disorder class to which it belongs, the name of the 22 disorder classes being shown on the right. A link between disorders in the same disorder class is colored with the corresponding dimmer color and links connecting different disorder classes are gray. The size of each node is proportional to the number of genes participating in the corresponding disorder (see key), and the link thickness is proportional to the number of genes shared by the disorders it connects. We indicate the name of disorders with more than 10 associated genes, as well as those mentioned in the text. For a complete set of names, see SI Fig. 13. (b) In the DGN, each node is a gene, with two genes being connected if they are implicated in the same disorder. The size of each node is proportional to the number of disorders in which the gene is implicated (see key). Nodes are light gray if the corresponding genes are associated with more than one disorder class. Genes associated with more than five disorders, and those mentioned in the text, are indicated with the gene symbol. Only nodes with at least one link are shown.
shown for comparison. To investigate the validity of this hypothesis, we measured the GO (24). If the HDN shows modular organization, then a group and functional characteristics, as annotated in the Gene Ontology interactome mapping (6, 7) and literature curation (6). We found that disease genes encoding proteins that interact in functionally distinguishable modules, then the proteins within such disease modules should tend to participate in the same cellular pathway, molecular complex, or functional module (21, 22). For example, Fanconi anemia arises to encode hubs in the cellular network in human diseases? Are disease genes more likely result in an important mystery: what is the role, if any, of the 8688/H20841 genes have a 32% larger number of interactions (6, 7) with other proteins (average degree) than the nondisease proteins (see SI Fig 9) and that high-degree proteins are more likely to be encoded by genes associated with diseases than proteins with few interactions (P = 1.6 × 10^{-17}; Fig. 4a). Next, we show, however, that despite this component, finding significant elevation of GO homogeneity with respect to random controls in all three branches (SI Fig 8).

Disease genes encoding proteins that interact within common functional modules should tend to be expressed in the same tissue. To measure this, we introduced the tissue-homogeneity coefficient of a disorder, defined as the maximum fraction of genes among those belonging to a common disorder that are expressed in a specific tissue in a microarray data set obtained for 10,594 genes across 36 healthy tissues (25). We found that 68% of disorders exhibited almost perfect tissue-homogeneity (Fig. 3b), compared with 51% expected by chance (P < 10^{-3}).

Finally, disease genes that participate in a common functional module should also show high expression profiling correlation (26). The distribution of Pearson correlation coefficients (PCCs) for the coexpression profiles of pairs of genes associated with the same disorder was shifted toward higher values compared with that of a random control (Fig. 3c; P < 10^{-6}, χ^2 test). Similarly, the average PCC over all pairs of genes within a given disorder shows a significant shift from the random reference (Fig. 3d), with a small but clearly distinguishable peak in the distribution around PCC ≈ 0.75. This peak corresponds to ~33 disorders with average PCC > 0.6 for which all genes are highly coexpressed in most tissues, including Heinz body anemia (PCC = 0.935), Bethlem myopathy (PCC = 0.835), and spherocytosis (PCC = 0.656).

In summary, genes that contribute to a common disorder (i) show an increased tendency for their products to interact with each other through protein–protein interactions, (ii) have a tendency to be expressed together in specific tissues, (iii) tend to display high coexpression levels, (iv) exhibit synchronized expression as a group, and (v) tend to share GO terms. Together, these findings support the hypothesis of a global functional relatedness for disease genes and their products and offer a network-based model for the diseasome. Cellular networks are modular, consisting of groups of highly interconnected proteins responsible for specific cellular functions (21, 22). A disorder then represents the perturbation or breakdown of a specific functional module caused by variation in one or more of the components producing recognizable developmental and/or physiological abnormalities.

This model offers a network-based explanation for the emergence of complex or polygenic disorders: a phenotype often correlates with the inability of a particular functional module to carry out its basic functions. For extended modules, many different combinations of perturbed genes could incapacitate the module, as a result of which mutations in different genes will appear to lead to the same phenotype. This correlation between disease and functional modules can also inform our understanding of cellular networks by helping us to identify which genes are involved in the same cellular function or network module (21, 22).

Centrality and Peripherality. An early indication of the connection between the structure of a cellular network and its functional properties was the finding that in Saccharomyces cerevisiae highly connected proteins or “hubs” are more likely encoded by essential genes (15, 16). This prompted a number of recent studies (27, 28) to formulate the hypothesis that human disease genes should also have a tendency to encode hubs. Yet, previous measurements found only a weak correlation between disease genes and hubs (29), resulting in an important mystery: what is the role, if any, of the cellular network in human diseases? Are disease genes more likely to encode hubs in the cellular network?

Our initial analysis appears to support the hypothesis that disease genes, given their impact on the organism, display a tendency to encode hubs in the interactome (27, 28), finding that disease related proteins have a 32% larger number of interactions (6, 7) with other proteins (average degree) than the nondisease proteins (see SI Fig 9) and that high-degree proteins are more likely to be encoded by genes associated with diseases than proteins with few interactions (P = 1.6 × 10^{-17}; Fig. 4a). Next, we show, however, that despite this.
orthologs of mouse genes that result in embryonic or postnatal lethality when disrupted by homologous recombination (Mouse Genome Informatics; www.informatics.jax.org). All together, we find 1,267 such mouse lethal orthologs of human genes, of which 398 are associated with human diseases, representing 22% of all known human disease genes. This allows us to distinguish between two classes of human genes: 1,267 “essential genes” and 1,379 “nonessential disease genes,” the latter obtained by removing from the full list of 1,777 OMIM disease genes the 398 that are also essential (Fig. 4b). Next, we show that these two classes of genes play quite different roles in the human interactome.

First, we find that essential proteins show a tendency to be associated with hubs ($P = 1.3 \times 10^{-17}$; Fig. 4c), displaying a much stronger trend than the one observed for all disease proteins (Fig. 4a). This raises an important question: Could the observed correlation between disease genes and hubs (Fig. 4a) be the sole consequence of the fact that a small fraction (22%) of disease genes is also essential? To address this question we measured the degree dependence of the nonessential disease proteins (Fig. 4d). Surprisingly, the correlation between hubs and disease proteins entirely disappears. Thus, the vast majority of disease genes (78%), those that are nonessential, do not show a tendency to encode hubs, indicating that the observed weak correlations between hubs and disease genes (Fig. 4a) was entirely due to the few essential genes within the disease gene class.

To carry on its basic functions, the cell needs to maintain the coordinated activity of important functional modules, driving in a relatively synchronized manner the expression patterns of the most important genes. Therefore, one expects that the expression pattern of both essential and disease genes will be synchronized with a significant number of other genes. To test this, we determined the average gene coexpression coefficient $\hat{r}_{ij} = \Sigma \hat{PCC}_{i}$ between an essential (or nonessential disease) gene $i$ and all other genes in the cell, calculating the $\hat{PCC}_{i}$ values from healthy human tissue microarray measurements (25). Confirming our expectation, for essential genes we find that genes that display high average coexpression $\rho$ with all other genes are more likely to be essential than those that show small or negative $\rho$ ($P = 1.7 \times 10^{-4}$; Fig. 4e). Surprisingly, however, nonessential disease genes show the opposite effect, being associated with genes whose expression pattern is anticorrelated or not-correlated with other genes, and underrepresented among the genes that are highly synchronized ($\rho > 0.2$) ($P = 2.6 \times 10^{-4}$; Fig. 4f). Thus, the expression pattern of nonessential disease genes appears to be decoupled from the overall expression pattern of all other genes, whereas essential genes have a tendency to be coupled to the rest of the cell.

Finally, we asked whether housekeeping genes, expressed in all tissues, have a tendency to encode disease genes. We find that the more tissues in which a gene is expressed, the higher the likelihood that it will be essential ($P = 2.8 \times 10^{-16}$; Fig. 4g). The opposite is true for nonessential disease genes: they have a tendency to be expressed in a few tissues ($P = 1.4 \times 10^{-4}$; Fig. 4h). Similarly, we found that only 9.9% of housekeeping genes correspond to disease genes, compared with 13.5% of nonhousekeeping genes, a significant 36% difference ($P = 3.6 \times 10^{-4}$). In contrast, 59.8% of housekeeping genes annotated with mouse phenotype were essential, compared with 40.5% for nonhousekeeping genes ($P < 10^{-4}$).

These results support the somewhat unexpected conclusion that nonessential disease genes are not associated with hubs (27, 28), show smaller correlation in their expression pattern with the rest of the genes in the cell than expected from random, and have a tendency to be expressed in only a few tissues. Therefore, contrary to earlier hypotheses and our expectations, the vast majority of nonessential disease genes occupy functionally peripheral and topologically neutral positions in the cellular network. In stark contrast, essential genes are likely to encode hubs, show highly synchronized expression with the rest of the genes, and are expressed in most tissues, being overrepresented among housekeep-
ing genes. Thus, essential genes are topologically and functionally central.

This unexpected peripherality of most disease genes can be best explained by using an evolutionary argument. Mutations in topologically central, widely expressed genes are more likely to result in severe impairment of normal developmental and/or physiological function, leading to lethality in utero or early extraterrestrial life and to eventual deletion from the population. Only mutations compatible with survival into the reproductive years are likely to be maintained in a population. Therefore, disease-related mutations in the functionally and topologically peripheral regions of the cell give a higher chance of viability.

Disease genes whose mutations are somatic should not be subject to the selective pressure discussed above. Instead, somatic mutations that lead to severe disease phenotypes should more likely affect the functional center. To test the predictive power of this selection-based argument, we studied separately the properties of somatic cancer genes (Cancer Genome Census; www.sanger.ac.uk/genetics/CGP/Census) and found that they (i) are more likely to encode hubs, (ii) show higher coexpression with the rest of the genes in the cell, and (iii) are more represented among housekeeping genes (SI Fig. 10). The observed functional and topological centrality of somatic cancer genes fits well with our current understanding that many cancer genes play critical roles in cellular development and growth (11).

Discussion
Throughout history, clinicians and medical researchers have focused on a few disorder(s) sharing commonalities in etiology or pathology. Recent progress in genetics and genomics has led to an appreciation of the effects of gene mutations in virtually all disorders and provides the opportunity to study human diseases all at once rather than one at a time (4, 30). This unique approach offers the possibility of discerning general patterns and principles of human disease not readily apparent from the study of individual disorders.

An important tool in this quest is the HDN that represents a genome-wide roadmap for future studies on disease associations. The accompanying detailed diseasome map (SI Fig. 13), showing all disorders and the genes associated with different disorders, offers a rapid visual reference of the genetic links between disorders and disease genes, a valuable global perspective for physicians, genetic counselors, and biomedical researchers alike.

To test whether the conclusions obtained in this work are robust to the incompleteness of the OMIM coverage, we expanded our study to include not only genes with identified mutations linked to the specific disease phenotype, but also those that satisfy the less stringent criterion that the phenotype has not been mapped to a specific locus (18). This expansion increased the number of disease-associated genes from 1,777 to 2,765, but also introduced noise in the data, because the link between many of the newly added genes and diseases is less stringent. Yet, the overall organization of the expanded diseasome map remains largely unaltered (SI Fig. 11), and none of the trends uncovered in Fig. 4 are affected by this extension (SI Fig. 12), supporting the robustness of our findings to further expansion of the OMIM database. Thus, although the maps shown in Fig. 2 and SI Fig. 13 will inevitably undergo local changes with the discovery of new disease genes, this will not change the overall organization and layout of the HDN significantly, because the HDN reflects the underlying cellular-network-based relationship between genes and functional modules.

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Molecular Profiling of Lung Cancer

Lung cancer is the leading cause of cancer-related mortality in the United States, with an estimated 222,520 new cases and 157,300 deaths anticipated in 2010 (Jemal, 2010). Classically, treatment decisions have been empiric and based upon histology of the tumor. Platinum-based chemotherapy remains the cornerstone of treatment. However, survival rates remain low. Novel therapies and treatment strategies are needed.

Lung cancer is comprised of two main histologic subtypes: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Over the past decade, it has become evident that subsets of NSCLC can be further defined at the molecular level by recurrent ‘driver’ mutations that occur in multiple oncogenes, including EGFR, KRAS, BRAF, NRAS, PIK3CA, MEK1, AKT1, HER2, and ALK (Fig. 1). Such ‘driver’ mutations lead to constitutive activation of mutant signaling proteins that induce and sustain tumorigenesis. These mutations are rarely found concurrently in the same tumor. Mutations can be found in all NSCLC histologies (including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma) and in current, former, and never smokers (defined by individuals who smoked less than 100 cigarettes in a lifetime). Never smokers with adenocarcinoma have the highest incidence of EGFR, HER2, and ALK mutations. Importantly, targeted small molecule inhibitors are currently available or being developed for specific molecularly defined subsets of lung cancer patients.

The following text is meant to provide a broad overview of several of the oncogenes known to be important for lung cancer pathogenesis. Where possible, the presence of a specific mutation is correlated to clinical parameters as well as response to both conventional chemotherapy and targeted agents. At present, only data for treatment of advanced (stage IIIB/IV) disease is presented.

<table>
<thead>
<tr>
<th>Gene</th>
<th>AKT1</th>
<th>ALK</th>
<th>BRAF</th>
<th>EGFR</th>
<th>HER2</th>
<th>KRAS</th>
<th>MEK1</th>
<th>NRAS</th>
<th>PIK3CA</th>
<th>PTEN</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>1%</td>
<td>3-7%</td>
<td>1-3%</td>
<td>10-35%</td>
<td>2-4%</td>
<td>15-25%</td>
<td>1%</td>
<td>1%</td>
<td>1-3%</td>
<td>4-8%</td>
<td>~50%</td>
</tr>
</tbody>
</table>

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SUMMARY

The International League Against Epilepsy (ILAE) Commission on Classification and Terminology has revised concepts, terminology, and approaches for classifying seizures and forms of epilepsy. Generalized and focal are redefined for seizures as occurring in and rapidly engaging bilaterally distributed networks (generalized) and within networks limited to one hemisphere and either discretely localized or more widely distributed (focal). Classification of generalized seizures is simplified. No natural classification for focal seizures exists; focal seizures should be described according to their manifestations (e.g., dyscognitive, focal motor). The concepts of generalized and focal do not apply to electroclinical syndromes. Genetic, structural–metabolic, and unknown represent modified concepts to replace idiopathic, symptomatic, and cryptogenic. Not all epilepsies are recognized as electroclinical syndromes. Organization of forms of epilepsy is first by specificity: electroclinical syndromes, nonsyndromic epilepsies with structural–metabolic causes, and epilepsies of unknown cause. Further organization within these divisions can be accomplished in a flexible manner depending on purpose. Natural classes (e.g., specific underlying cause, age at onset, associated seizure type), or pragmatic groupings (e.g., epileptic encephalopathies, self-limited electroclinical syndromes) may serve as the basis for organizing knowledge about recognized forms of epilepsy and facilitate identification of new forms.

KEY WORDS: Epilepsy, Classification, Syndrome, Seizure, Organization.

The history of classification has rested largely upon astute observations and expert opinions. First published in 1960 and last updated officially in 1981 for seizures (Commission on Classification and Terminology of the International League Against Epilepsy [ILAE], 1981) and 1989 for epilepsies (Commission on Classification and Terminology of the International League Against Epilepsy, 1989), the ILAE classifications are based on concepts that, for the most part, predate modern neuroimaging, genomic technologies, and concepts in molecular biology. The original authors foresaw that changes to the classification would be needed as new information was acquired and as new investigative technologies were developed. This is no simple task. Attempts have been made to update the 1989 and 1981 documents (Engel, 2001, 2006); however, no new proposal has been forthcoming.

A primary motivation for revising the classification in the 2005–2009 Commission term and to continue revising it in the future is to bring epilepsy out of the
shadows of expert opinion and assertion-dominated arguments so that the classification of the epilepsies fully reflects and profits from all of the other advances being made in basic and clinical neurosciences and so that those advances can be incorporated into clinical practice. In the following report we present the main findings and recommendations of the Commission’s deliberations during the 2005–2009 term accompanied by comments interleaved with the main text. The comments provide background, explanations, and justifications for these decisions and provide some insight into the variety of considerations that were addressed and why specific decisions were made.

Although changes have been made to terminology and concepts, we emphasize that no changes (other than to nomenclature) are being made to the list of epilepsy entities (“syndromes”) already recognized and updated in the 2006 Task force report (Engel, 2006). Furthermore, the revisions made to terminology and concepts in epilepsy do not have any tangible impact on how clinicians use the electroclinical syndromes that have been internationally recognized and that are applied to people with epilepsy around the world every day.

Terminology and Concepts for Classification of Seizures and Epilepsies

Mode of seizure onset and classification of seizures

Generalized epileptic seizures are conceptualized as originating at some point within, and rapidly engaging, bilaterally distributed networks. Such bilateral networks can include cortical and subcortical structures, but do not necessarily include the entire cortex. Although individual seizure onsets can appear localized, the location and lateralization are not consistent from one seizure to another. Generalized seizures can be asymmetric.

Focal epileptic seizures are conceptualized as originating within networks limited to one hemisphere. They may be discretely localized or more widely distributed. Focal seizures may originate in subcortical structures. For each seizure type, ictal onset is consistent from one seizure to another, with preferential propagation patterns that can involve the contralateral hemisphere. In some cases, however, there is more than one network, and more than one seizure type, but each individual seizure type has a consistent site of onset. Focal seizures do not fall into any

Comments: Introduction

Within the context of epilepsies and seizures, the word “classification” has been used to refer to at least three concepts:

1. The list of entities that are recognized as distinct forms of epilepsy: Nothing has changed in the elements of this list for specific types of electroclinical syndromes, although the list of seizures has been simplified from previous versions.

2. The concepts and structure underlying the organization and presentation of that list: The 1989 classification (Commission, 1989) was an organization built on concepts that no longer correspond to or accurately describe our increasing knowledge of seizures and the epilepsies. Consequently, the current organization and the concepts on which it is based are abandoned or revised. The dimensions by which we characterize seizures and epilepsies should represent useful, natural classes. Furthermore, the order and organization of the list of recognized syndromes need not be singular, constrained, or rigid but should be flexible to reflect our best current understanding of the neurobiology, the clinical features, prognostic implications, and any other features relevant to clinical practice or research.

3. The methods and process that determine which entities are recognized and those features by which those entities are organized: The expert-opinion review process for “admitting” a syndrome to the list will need to be replaced by a system based upon objective analysis and assessment of relevant evidence. This will be required to provide leads for new potential syndromes and some guidance into the natural classes and dimensions by which a scientific classification could be constructed (Berg & Blackstone, 2006). We intend to initiate such a process in the future.

In reviewing the current classifications, such as they are, and in modifying terminology and concepts, the Commission’s work was aided by proceedings of the Monreale workshop (Capovilla et al., 2009). Although we set forth a revised, simplified classification for seizures, we did not find that there was an adequate knowledge base currently to propose a new classification (in the sense of organization) of epilepsies. Rather we have provided new terminology and concepts that better reflect the current understanding of these issues. A guiding principle has been to strive for clarity and simplicity so that terms refer to single qualities and are not a mixture of different concepts and dimensions. Another guiding principle has been, to the greatest extent possible, not to accept assumptions and assertions as the basis for classification and to acknowledge areas for which we do not have good information for making decisions. We present new concepts, but acknowledge them as concepts in need of further development and evidence (e.g., for generalized and focal seizures).
Comments: Classification and terminology as it relates to seizures:

The Commission accepted the ILAE definition of epileptic seizure (Fisher et al., 2005): “a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.” Therefore, the comments are limited to describing epileptic seizures and are not designed to assist the clinician in distinguishing epileptic seizures from nonepileptic events. This will be treated separately in a diagnostic manual.

The terms “focal” and “generalized” have been used to express a dichotomous classification for both seizures and the epilepsies. In fact in the late 1800s, Hughlings-Jackson wrote that focal discharging lesions caused both focal and generalized seizures (see York & Steinberg, 2009). For seizures, based on current electroclinical evidence, the Commission felt that it was still of some pragmatic utility to maintain the terminology, although it was generally acknowledged that these terms likely did not represent a clear dichotomy.

The conceptualization of generalized seizures as arising in and rapidly engaging bilaterally distributed networks was, in part, an attempt to address the apparently generalized nature of spasms in the context of a focal lesion. This could represent a paradigmatic breakthrough in thinking about manifestations versus underlying pathology. There was much lively discussion and at times bitter disagreement over how best to classify spasms, as generalized or focal or both. In the end, the considerable collective knowledge of spasms represented by the various Commission members was still not up to the task of resolving this issue precisely because of inadequate information. Spasms are thus left on their own.

The 1981 seizure document used the terms simple partial, complex partial, and partial seizures secondarily generalized (Commission, 1981). This terminology was imprecise, as the terms “simple” and “complex” were often misused or misunderstood. Moreover, the distinction based on impairment of consciousness or awareness, although of great pragmatic social importance (e.g., for driving), was impossible to define precisely (Gloor, 1986). The term “secondarily” generalized is poorly understood and inconsistently used. Currently, we have inadequate information to create a scientific classification within focal seizures. Instead, we recommend that focal seizure be described according to features that are the most useful for a given specific purpose. For example, in many circumstances such as the differential diagnosis of epileptic versus nonepileptic events or in presurgical evaluation it is often useful to describe the specific elemental features of seizures and their sequence of occurrence (Luders et al., 1993). Others may wish to recognize terms to describe degree of disability caused by the seizures. We encourage those interested to consult the Glossary of Ictal Semiology (Blume et al., 2001) for well-defined descriptive terms.

<table>
<thead>
<tr>
<th>Table 1. Classification of seizures*</th>
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<tbody>
<tr>
<td>Generalized seizures</td>
</tr>
<tr>
<td>Tonic–clonic (in any combination)</td>
</tr>
<tr>
<td>Absence</td>
</tr>
<tr>
<td>Typical</td>
</tr>
<tr>
<td>Atypical</td>
</tr>
<tr>
<td>Absence with special features</td>
</tr>
<tr>
<td>Myoclonic absence</td>
</tr>
<tr>
<td>Eyelid myoclonia</td>
</tr>
<tr>
<td>Myoclonic</td>
</tr>
<tr>
<td>Myoclonic</td>
</tr>
<tr>
<td>Myoclonic astatic</td>
</tr>
<tr>
<td>Myoclonic tonic</td>
</tr>
<tr>
<td>Clonic</td>
</tr>
<tr>
<td>Tonic</td>
</tr>
<tr>
<td>Atonic</td>
</tr>
<tr>
<td>Focal seizures</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>Epileptic spasms</td>
</tr>
</tbody>
</table>

*Seizure that cannot be clearly diagnosed into one of the preceding categories should be considered unclassified until further information allows their accurate diagnosis. This is not considered a classification category, however.
Comments: Terminology and concepts for underlying cause:

The terms idiopathic, symptomatic, and cryptogenic have taken on a variety of meanings and connotations laden with presumptions which, at times, conflate multiple concepts into a single word. This has resulted in considerable contradiction and confusion. The term idiopathic was defined in the 1989 document: “There is no underlying cause other than a possible hereditary predisposition. Idiopathic epilepsies are defined by age-related onset, clinical and electrographic characteristics, and a presumed genetic etiology.” We now state a minimum threshold for presuming a form of epilepsy does in fact have a genetic basis. Undocumented assertions are not accepted. Examples of epilepsy syndromes that would be classified as genetic epilepsies include childhood absence epilepsy, autosomal dominant nocturnal frontal lobe epilepsy, and Dravet syndrome. Note that in the 1989 classification, Dravet syndrome was not classified as idiopathic epilepsy. Dravet is now considered as a genetic epilepsy.

The term “idiopathic” was also used to convey the idea of a highly pharmacoresponsive form of epilepsy. Many, although not all, of the traditional “idiopathic” epilepsies also spontaneously remit during a predictable age range (a separate quality or dimension) and were generally thought to be unaccompanied by other consequences or disabilities, although this is clearly not the case, as a variety of subtle cognitive and behavioral disorders are seen in association with these epilepsies.

The new terminology and concepts require that the concept of cause contain only one dimension and not be used to imply others. Cause is no longer equated with prognosis, and the implication that “idiopathic” confers the quality of “benign” is intentionally discarded. It is possible that the genetic defect may have other effects in addition to the seizures but, as best we can tell, these other effects are not interposed between the genetic effect and the seizures.

The term “symptomatic” is a truism; all epilepsy is symptomatic of something. It is often substituted for the concept of a poor prognosis. The term “structural and metabolic” is intended to highlight that there is a separate disorder the relationship of which to epilepsy is not as direct. The grouping of structural and metabolic disorders together is only to distinguish this concept from that of genetic (i.e., genetic vs. all else). Depending on the purposes, it will be necessary to subdivide these heterogeneous causes further starting with separate groups for structural and for metabolic. Within each of these subdivisions, further taxa will be elaborated (e.g., for malformations, gliomas, and mitochondrial disorders). Other ILAE Commissions and other groups around the world are tackling these very issues.

“Cryptogenic” was defined in 1989 as “presumed symptomatic,” apparently meaning “lesional.” It is, however, from among these “cryptogenic” epilepsies that genetic electroclinical syndromes such as autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) and autosomal dominant epilepsy with auditory features (ADEAF) have been discovered (Scheffer et al., 1995; Ottman et al., 1999). In replacing the term “Cryptogenic” with “unknown,” the Commission discarded the notion that a clinical hunch should be the basis of a scientific classification.

Examples of syndromes that would be classified as “of unknown cause” include epilepsy of infancy with migrating focal seizures and myoclonic epilepsy in infancy [formerly benign myoclonic epilepsy of infancy, (Engel, 2006)]. At the present time, it might be reasonable to include some of the traditional electroclinical syndromes previously classified as “idiopathic” in the unknown category as well. These include benign rolandic epilepsy (Vadlamudi et al., 2006), Panayiotoopoulos syndrome, and benign occipital epilepsy of the Gastaut type (Taylor et al., 2008). It is likely that genetic factors are involved in these syndromes. Current evidence (e.g., low or absent concordance in siblings) does not suggest that genetic factors are paramount. This issue will be revisited if high quality evidence supporting the hypothesis of a genetic contribution comes to light.

As new genetic contributions to epilepsy are recognized, it may often be difficult to know how best to characterize them with respect to the preceding distinctions. For example, ARX, a homeobox gene, is associated with phenotypic heterogeneity including West syndrome and lissencephaly (Stromme et al., 2002). STXB1 encodes a protein involved in synaptic vesicle release and is associated with Ohtahara syndrome (Saitou et al., 2008). Both syndromes involve severe encephalopathic forms of epilepsy. In the first case, one might consider the ARX mutation in the structural/metabolic category. In the case of STXB1, because of the function of the protein product, one might associate this with the concept of genetic epilepsy. No determination has been made in either case at this time. Instead the role of the specific genetic error should be recognized, but it is not necessary to pigeon-hole the cause of the disorder further unless there is an adequate basis for doing so. We advocate a focus on mechanisms. This focus should ultimately reveal the natural classes. The overly simplistic designation of “genetic” versus “structural-metabolic” will then be replaced by a more precise characterization of the underlying cause.
patients and for specific purposes (e.g., differential diagnosis of nonepileptic events from epileptic seizures, randomized trials, surgery). Nothing in this recommendation precludes describing focal seizures according to these or other features.

5. Myoclonic atonic (previously called “myoclonic astatic”) seizures are now recognized.

Table 1 presents the list of recognized seizure types.

Descriptors of focal seizures

For pragmatic reasons and to facilitate continuity with the 1981 classification of seizures, descriptors of focal seizures may be used, individually or in combination with other features depending on the purpose. We have listed examples chosen to facilitate continuity with the 1981 seizure document and which have been drawn from the glossary of ictal semiology (Blume et al., 2001) (Table 2).

The classification of status epilepticus will be the subject of a separate report in the future.

Underlying type of cause (etiology)

Instead of the terms idiopathic, symptomatic, and cryptogenic, the following three terms and their associated concepts are recommended:

1. Genetic: The concept of genetic epilepsy is that the epilepsy is, as best as understood, the direct result of a known or presumed genetic defect(s) in which seizures are the core symptom of the disorder. The knowledge regarding the genetic contributions may derive from specific molecular genetic studies that have been well replicated and even become the basis of diagnostic tests (e.g., SCN1A and Dravet syndrome) or the evidence for a central role of a genetic component may come from appropriately designed family studies. Designation of the fundamental nature of the disorder as genetic does not exclude the possibility that environmental factors (outside the individual) may contribute to the expression of disease. At the present time, there is virtually no knowledge to support specific environmental influences as causes of or contributors to these forms of epilepsy.

2. “Structural/metabolic”: Conceptually, there is a distinct other structural or metabolic condition or disease that has been demonstrated to be associated with a substantially increased risk of developing epilepsy in appropriately designed studies. Structural lesions of course include acquired disorders such as stroke, trauma, and infection. They may also be of genetic origin (e.g., tuberous sclerosis, many malformations of cortical development); however, as we currently understand it, there is a separate disorder imposed between the genetic defect and the epilepsy.

3. “Unknown cause”: Unknown is meant to be viewed neutrally and to designate that the nature of the underlying cause is as yet unknown; it may have a fundamental genetic defect at its core or it may be the consequence of a separate as yet unrecognized disorder.

Diseases, syndromes, and epilepsies

Disease versus syndrome

Although there is reason to distinguish the concepts of disease and syndrome, these terms are not consistently used in medicine. Ultimately, it was decided not to insist on the disease–syndrome distinction in referring to the epilepsies at this time, although either or both terms have been and will continue to be used depending on the context and custom. Instead, there are at least three or four groupings that may be invoked in this context and as described below:

Electroclinical syndromes: Henceforth, the use of the term “syndrome” will be restricted to a group of clinical entities that are reliably identified by a cluster of electroclinical characteristics. Patients whose epilepsy does not fit the criteria for a specific electroclinical syndrome can be described with respect to a variety of clinically relevant factors (e.g., known etiology and seizure types). This does not, however, provide a precise (syndromic) diagnosis of their epilepsy.

Constellations: In addition to the electroclinical syndromes with strong developmental and genetic components to them, there are a number of entities that are not exactly electroclinical syndromes in the same sense but which represent clinically distinctive constellations on the basis of specific lesions or other causes. These are diagnostically meaningful forms of epilepsy and may have implications for clinical treatment, particularly surgery. These include mesial temporal lobe epilepsy (with hippocampal sclerosis), hypothalamic hamartoma with gelastic seizures, epilepsy with hemiconvulsion and hemiplegia, and Rasmussen “syndrome.” Age at presentation is not a defining feature in these disorders, as we understand them; however, they are

<table>
<thead>
<tr>
<th>Table 2. Descriptors of focal seizures according to degree of impairment during seizurea</th>
</tr>
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<tbody>
<tr>
<td>Without impairment of consciousness or awareness</td>
</tr>
<tr>
<td>With observable motor or autonomic components. This roughly</td>
</tr>
<tr>
<td>corresponds to the concept of “simple partial seizure.”</td>
</tr>
<tr>
<td>“Focal motor” and “autonomic” are terms that may adequately</td>
</tr>
<tr>
<td>convey this concept depending on the seizure manifestations).</td>
</tr>
<tr>
<td>Involving subjective sensory or psychic phenomena only. This</td>
</tr>
<tr>
<td>corresponds to the concept of an aura, a term endorsed in the</td>
</tr>
<tr>
<td>2001 Glossary.</td>
</tr>
<tr>
<td>With impairment of consciousness or awareness. This roughly</td>
</tr>
<tr>
<td>corresponds to the concept of complex partial seizure.</td>
</tr>
<tr>
<td>“Dyscognitive” is a term that has been proposed for this</td>
</tr>
<tr>
<td>concept (Blume et al., 2001).</td>
</tr>
<tr>
<td>Evolving to a bilateral, convulsiveb seizure (involving tonic,</td>
</tr>
<tr>
<td>or tonic and clonic components). This expression replaces the</td>
</tr>
<tr>
<td>term “secondarily generalized seizure.”</td>
</tr>
</tbody>
</table>

aFor more descriptors that have been clearly defined and recommended for use, please see Blume et al., 2001.

bThe term “convulsive” was considered a lay term in the Glossary; however, we note that it is used throughout medicine in various forms and translates well across many languages. Its use is, therefore, endorsed.
sufficiently distinctive to be recognized as relatively specific diagnostic entities. Whether or not they are considered “electroclinical syndromes” now or in the future is less important than that they be recognized by clinicians who are treating patients.

Structural/metabolic epilepsies: The next group includes epilepsies secondary to specific structural or metabolic lesions or conditions but which do not, given our current understanding, fit a specific electroclinical pattern, although that may change in the future. Therefore, these entities represent a lower level of specificity than the two previous groups.

Epilepsies of unknown cause: Those epilepsies, which in the past were termed “cryptogenic,” will now be referred to as being of “unknown” cause.

Dimensions for classifying epilepsies and organizing information

In referring to syndromes, the dichotomy of focal versus generalized will be abandoned, that is, “the focal or generalized epilepsies.” This is intended to separate the manifestations from the underlying pathology that produced them.

Each syndrome and each patient can be characterized according to a large number of other features, which are often routinely part of any patient’s evaluation and which are essential features in distinguishing among established syndromes. These include the age at onset, cognitive and developmental antecedents and consequences, motor and sensory examinations, EEG features, provoking or triggering factors, and patterns of seizure occurrence with respect to sleep.

Comments: Reestablishing the concept of “electroclinical syndrome” and recognizing the precision or imprecision of diagnosis.

Electroclinical syndromes: The 1989 report used the terms “syndromes” and “epilepsies” almost interchangeably. The result was that the term “syndrome” took on a broad and very imprecise meaning to the point where very specific and highly recognizable entities (such as childhood absence epilepsy) and poorly differentiated and not well-described epilepsies (such as cryptogenic parietal lobe epilepsy) tended to be treated as though they represented the same level of diagnostic precision. The result was a veneer of equivalency bestowed upon all entities identified within that document.

An electroclinical syndrome, however, is a complex of clinical features, signs, and symptoms that together define a distinctive, recognizable clinical disorder. These often become the focus of treatment trials as well as of genetic, neuropsychological, and neuroimaging investigations (e.g., Scheffer et al., 1998, 2008; Guerrini et al., 2007; Ottman et al., 2008). These are distinctive disorders identifiable on the basis of a typical age onset, specific EEG characteristics, seizure types, and often other features which, when taken together, permit a specific diagnosis. The diagnosis in turn often has implications for treatment, management, and prognosis. It would be inappropriate to refer to, for example, epilepsy with a frontal lobe focus and not otherwise specified as a “syndrome.” The currently recognized electroclinical syndromes are presented in the first part of Table 3 organized by typical age at onset, as this is one of the most distinctive and clinically salient dimensions for organizing these entities, but this is just an example of one way to organize them.

Constellations: Whether these entities should be considered syndromes or nonsyndromic epilepsies was the subject of considerable disagreement. Ultimately, these conditions can and should be recognized based on their clinical features. What they are called as a group in no way detracts from their clinical importance.

Epilepsies associated with structural or metabolic conditions: Previously, many such epilepsies were grouped together as “symptomatic focal epilepsies” and distinguished on the basis of localization. We recommend less emphasis be given to localization and more to the underlying structural or metabolic cause. Terms such as “symptomatic temporal lobe epilepsy” are replaced by longer but more precise expressions such as “epilepsy with focal seizures secondary to cortical dysplasia in the temporal lobe.” Localization is not, based on current knowledge, the primary factor of importance for understanding the cause and prognosis of these epilepsies. Further organizations might consider type of lesion, age at onset, localization, seizure type, specific ictal and interictal EEG patterns, or other factors.

Epilepsies of unknown cause: These epilepsies account for one-third or more of all epilepsy, are the most poorly understood, and represent perhaps the most fertile area for future research in imaging and genetics. For such research to be feasible, however, it will require that the simple characterization by localization of interictal focus (e.g., cryptogenic parietal lobe epilepsy) be replaced with a detailed characterization of all relevant features (see next section). Among these poorly differentiated epilepsies are likely to be additional genetic electroclinical syndromes (such as ADNFLE and ADEAF); however, they cannot be recognized until they are adequately characterized. This approach should also facilitate identification of nongenetic determinants of epilepsy.
Natural evolution of the disorder
Among the many dimensions that may be used for organizing forms of epilepsy, “natural” evolution is highlighted here because of its considerable importance in reflecting our growing understanding of the full nature of the epilepsies.

Epileptic encephalopathy. The concept of epileptic encephalopathy has grown in acceptance and use. It was formally recognized in the 2006 report and is now defined within this document. Epileptic encephalopathy embodies the notion that the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone (e.g., cortical malformation), and that these can worsen over time. These impairments may be global or more selective and they may occur along a spectrum of severity. Although certain syndromes are often referred to as epileptic encephalopathies, the encephalopathic effects of seizures and epilepsy may potentially occur in association with any form of epilepsy.

Other concepts and terms. The terms catastrophic and benign are not recommended. The first has strong emotional overtones and thus is not considered an appropriate term for a diagnostic label or category. The second belies the growing understanding of the relationship between the epilepsies and a wide variety of brain disorders including cognitive, behavioral, and psychiatric illnesses as well as sudden death and suicide. “Benign” can be misleading and leave physicians, patients, and families unaware of and unprepared to address these associated disorders. That said, names of syndromes have not, at this time, been changed.

An interim organization (“classification”) of the epilepsies
In a departure from the 1989 classification of the epilepsies, there is no one specific organization proposed for the revised classification. Instead, the various forms of epilepsy (at all levels of specificity) will be organized according to those dimensions that are most relevant to a specific purpose. These may be comparable to those in the 1989 classification (seizure onset, “etiology,” and age at onset), a different hierarchical arrangement of these same dimensions, a more detailed version of these dimensions, or by entirely different dimensions as needed. For example, Table 3 provides a list of epilepsies from the Task Force on Classification and Terminology (Engel, 2006) according to level of specificity and within those designations, by age where meaningful.

### Acknowledgments

During the Commission’s 2005–2009 term, input was sought from experts in the genetics of epilepsy, neuroimaging, therapeutics, pediatric and adult epileptology, as well as statistics and research design. The results

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**Table 3. Electroclinical syndromes and other epilepsies**

<table>
<thead>
<tr>
<th>Electroclinical syndromes arranged by age at onset&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neonatal period</strong></td>
<td></td>
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<tr>
<td>Benign familial neonatal epilepsy (BFNE)</td>
<td></td>
</tr>
<tr>
<td>Early myoclonic encephalopathy (EME)</td>
<td></td>
</tr>
<tr>
<td>Ohtahara syndrome</td>
<td></td>
</tr>
<tr>
<td><strong>Infancy</strong></td>
<td></td>
</tr>
<tr>
<td>Epilepsy of infancy with migrating focal seizures</td>
<td></td>
</tr>
<tr>
<td>West syndrome</td>
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<td>Myoclonic epilepsy in infancy (MEI)</td>
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<td>Benign infantile epilepsy</td>
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<td>Benign familial infantile epilepsy</td>
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<td>Dravet syndrome</td>
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<td>Myoclonic encephalopathy in nonprogressive disorders</td>
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<td><strong>Childhood</strong></td>
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<td>Febrile seizures plus (FS+) (can start in infancy)</td>
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<td>Panayiotopoulos syndrome</td>
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<td>Epilepsy with myoclonic atonic (previously astatic) seizures</td>
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<td>Benign epilepsy with centrotemporal spikes (BECTS)</td>
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<td>Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFL)</td>
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<td>Late onset childhood occipital epilepsy (Gastaut type)</td>
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<td>Epilepsy with myoclonic absences</td>
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<td>Lennox-Gastaut syndrome</td>
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<td>Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Landau-Kleffner syndrome (LKS)</td>
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<td>Childhood absence epilepsy (CAE)</td>
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<td><strong>Adolescence – Adult</strong></td>
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<td>Juvenile absence epilepsy (JAE)</td>
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<td>Juvenile myoclonic epilepsy (JME)</td>
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<td>Epilepsy with generalized tonic–clonic seizures alone</td>
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<td>Progressive myoclonus epilepsies (PME)</td>
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<td>Autosomal dominant epilepsy with auditory features (ADEAF)</td>
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<td>Other familial temporal lobe epilepsies</td>
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<td><strong>Less specific age relationship</strong></td>
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<td>Familial focal epilepsy with variable foci (childhood to adult)</td>
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<td>Reflex epilepsies</td>
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<td><strong>Distinctive constellations</strong></td>
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<td>Mesiol temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)</td>
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<td>Rasmussen syndrome</td>
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<td>Gelastic seizures with hypothalamic hamartoma</td>
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<td>Hemiconvulsion–hemiplegia–epilepsy</td>
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<td>Epilepsies that do not fit into any of these diagnostic categories can be distinguished first on the basis of the presence or absence of a known structural or metabolic condition (presumed cause) and then on the basis of the primary mode of seizure onset (generalized vs. focal)</td>
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<td>Epilepsies attributed to and organized by structural-metabolic causes</td>
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<td>Malformations of cortical development (hemimegalencephaly, heterotopias, etc.)</td>
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<td>Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc.)</td>
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<td>Tumor</td>
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<td>Stroke</td>
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<td>Etc.</td>
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<td>Epilepsies of unknown cause</td>
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<td>Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se</td>
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<td>Benign neonatal seizures (BNS)</td>
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<td>Febrile seizures (FS)</td>
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<sup>a</sup>The arrangement of electroclinical syndromes does not reflect etiology.

<sup>b</sup>Sometime referred to as Electrical Status Epilepticus during Slow Sleep (ESES).
Comments: Other dimensions for classifying epilepsies and organizing information:

The commission decided to discard the terms generalized and focal for modifying the epilepsies themselves. “Generalized” spasms arising from a focal lesion as occurs in West syndrome and focal seizures arising from a diffuse genetic disorder as occurs in Dravet syndrome were some of the prime examples of why and how these terms do not adequately reflect the processes underlying the epilepsies.

In addition to the traditional dimensions and features, each syndrome and each patient can be characterized according to a large number of other features, which are often routine parts of any patient’s evaluation and essential features in distinguishing among established syndromes. These include the cognitive and developmental antecedents and consequences, motor and sensory examinations, EEG features, provoking or triggering factors, and patterns of seizure occurrence with respect to sleep. There is also an important traditional cluster of syndromes that might be convenient to maintain, the “idiopathic generalized epilepsies;” however, we recommend that they be called the “genetic generalized epilepsies.”

Natural evolution: Epileptic Encephalopathy. The term “epileptic encephalopathy” can be used to characterize syndromes and also be applied to individuals. As a domain for clustering and describing syndromes, an epileptic encephalopathy is an electroclinical syndrome associated with a high probability of encephalopathic features that present or worsen after the onset of epilepsy. Separately but important to note, as a group, they tend to be pharmacoresistant, but this is another quality or dimension. Inclusion of a specific syndrome in the domain of “epileptic encephalopathy” does not imply that all individuals with these disorders will appear encephalopathic; however, the risk is often quite high. Diagnosing an individual as having an encephalopathic course requires demonstration of a failure to develop as expected relative to same-aged peers or to regress in abilities. Note that it is not necessary for an individual to have a syndrome identified as being one of the “epileptic encephalopathies” (e.g., West, Dravet) in order to have an encephalopathic course. Epileptic encephalopathy can present along a continuum of severity and may occur at any age. The phenomenon is most common and severe in infancy and early childhood, where global and profound cognitive impairment may occur. Adults, however, can also experience cognitive losses over time from uncontrolled seizures (Hermann et al., 2006). Whether these involve similar or different mechanisms as those early in development remains to be seen, but the phenomenon should be recognized.

Inherent in the concept of epileptic encephalopathy is the notion that suppression of epileptic activity may improve cognition and behavior. Early effective intervention may in fact improve seizure control and developmental outcome in some cases (Jonas et al., 2004; Freitag & Tuxhorn, 2005; Jonas et al., 2005; Lux et al., 2005).

“Epileptic encephalopathy” should be viewed as a concept and a description of what is observed clinically with the recognition that, we are rapidly approaching a clearer understanding of the effects of epilepsy on brain function and the potential for lasting deleterious impact in the developing brain. We must, however, recognize that the source of an apparent encephalopathy is usually unknown. It may be the product of the underlying cause, the result of epileptic process, or a combination of both.

The argument against the term, “Benign”: One of the new research Benchmarks of the National Institutes of Health for epilepsy research is to understand the various comorbidities of epilepsy including cognitive, behavioral, and psychiatric disorders as well as mortality (Kelly et al., 2009). There are international efforts underway to understand the mechanisms of sudden death and to educate patients and families of this risk and how it may be mitigated. Increasingly, basic science and clinical studies are illuminating the shared mechanisms between epilepsy and these various other disorders.

Self-limited: The terms “idiopathic” and “benign” captured important features of clinical relevance. We recommend that, instead of designating a group of syndromes as “benign,” we recognize the different qualities that make up the concept of benign and apply them specifically and consistently to individual forms of epilepsy. One of these features is predictable spontaneous remission. Instead of benign, we recommend the descriptive term “self-limited” to mean having a high likelihood of spontaneously remitting at a predictable age. If a better term is devised, that can be considered in the future.

Pharmacoresponsive: In syndromes designated as idiopathic, most cases tend to be pharmacoresponsive. Diagnosis of one of these syndromes allows, within a reasonable certainty, the prediction that the seizures will rapidly come under control with appropriate medication. As yet, we do not have perfect prediction, so some patients diagnosed with a particular syndrome may not be pharmacoresponsive; however, clinical prognostication was never an exact science. Labeling these syndromes as pharmacoresponsive may be more meaningful to clinicians and provide anticipatory guidance to families better than the term “idiopathic,” which requires explanation.

Of note, the inclusion of features that are descriptive of the natural evolution of a form of epilepsy is not, strictly speaking, based upon natural classes but rather on repeated observations and impressions. They are included for pragmatic purposes.
Age at onset: For grouping syndromes or individuals, age at onset categories are recommended as per standard use: neonate (<44 weeks of gestational age), infant (<1 year), child (1–12 years), adolescent (12–18 years), and adult (>18 years). For some purposes, it may be helpful to distinguish a category for elderly (>60 or >65). The age ranges are approximate and meant to be used only for convenience in describing already characterized forms of epilepsy. For individual patients, the exact age at onset or best approximation should be used, and greater precision for electroclinical syndromes is encouraged when possible.

Other features: Many other dimensions and features will ultimately be used in describing, classifying, and grouping the different forms of epilepsies and may prove to be more useful for organizing the epilepsies than those used in the 1989 Classification. We may ultimately classify by specific cause, for example, ion channelopathies and by specific ion channel genes, as is being done with prolonged QT syndrome (Johnson et al., 2009). Alternatively, one could organize a subgroup of epilepsies by age at onset and association with specific types of cortical malformations (Lerner et al., 2009). Other dimensions would include but are not limited to detailed aspects of ictal and interictal EEG, structural neuroimaging findings, neurologic examination, and cognitive and psychiatric status.

A syndrome is characterized with respect to many factors. Knowing a given patient’s syndromic diagnosis, provides key information about that patient’s epilepsy, for example, likely age at onset, EEG patterns, likely responses to medications, and cognitive and developmental status. We can organize our information about these syndromes along the many dimensions by which they are characterized. The benefits of this approach for developing a diagnostic manual are considerable.

For epilepsies that do not fall into clear electroclinical syndromes and which are associated with structural–metabolic causes, the most natural and rational primary approach to organizing them seems to be by specific underlying cause or lesion. For epilepsies of unknown cause and predominately characterized by seizure onset, there is no natural class that validly sorts them into more homogeneous groups. The revised recommended approach explicitly acknowledges this. Forcing these partially or poorly characterized epilepsies into a system of classification for which they are not yet ready suggests greater knowledge than we currently have and impedes progress. Much greater effort should be invested in characterizing individual patients sufficiently to facilitate objective research into identifying previously unrecognized entities. This information can then be used as the basis for objective analyses to identify potential new “syndromes” (Berg & Blackstone, 2006). It will also greatly facilitate the use of the planned diagnostic manual, which will provide a guide with specific definitions and examples that will encourage clinicians to make the necessary, precise observations on all patients in order to make or exclude specific diagnoses.

Comments: Classification in the future:

The previous “classifications” of seizures and epilepsies were often treated as rigid doctrine. Epilepsy classification was dominated by expert opinion and assertion. Advances in all areas of investigation (epidemiology, electrophysiology, imaging, developmental neurobiology, genomics, computational neuroscience, and neurochemistry) have made it clear that such a simple and often autocratic approach does not do justice to the complexity of the underlying developmental and physiologic processes. Therefore, any classifications put forth by this Commission should be viewed as a guide to summarize our current understanding about seizures and epilepsies in a useful manner, one that is responsive to the needs to which it is put and flexible enough to incorporate new information as it develops.

Unfortunately, this remains an area where long-held beliefs and ignorance often clash with reason and evidence. For example, an overly melodramatic comment posted on the website stated that the Commission’s rejection of the term “benign” to characterize epilepsy was “…a stone of death to all of us, who have campaigned for year that on evidence, a significant number of patients and mainly children have some forms of epilepsies … that are entirely benign with little or no detrimental consequences as documented with long term prospective studies over the last 50 years (…). The main consequences … are psychosocial resulting from equating them with epilepsy.” Such emotional assertions actively ignore the last several years of very productive research in the neurosciences and represent the kind of arguments that are no longer acceptable.

In the future, the Classification of the Epilepsies will essentially be a database. The features discussed earlier and other essential pieces of information will form the basis for a diagnostic manual. In the interim, we encourage people to conceptualize a future classification as a flexible, multidimensional catalog of features for organizing information about different epilepsies (or seizures) as appropriate for purposes of drug development, clinical and basic research, and of course, clinical practice.
of those deliberations were presented at the ICE in Budapest, 2009. Following comments received at the meeting, a written report was disseminated to the many ILAE chapters with an invitation to respond with feedback. The report was also posted on the ILAE website, again with an invitation to comment, and comments were posted on the website. We owe a special debt of gratitude to the many colleagues around the world who took the time to consider our proposals and convey their thoughts, suggestions, and critiques to us throughout this process. We also thank our colleagues Pawel Matykievicz, Ruth Ottman, Philippe Kryvien, and Peter Wolf for their input into some of our meetings. The process for approving this report followed that outlined in the Commission Operations Manual of the ILAE, 2009.

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure
None of the authors has any conflict of interest to disclose.

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Telomeres in a Life-Span Perspective: A New “Psychobiomarker”?  

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ABSTRACT—In order to more fully understand associations between psychological stress and health, it is helpful for researchers to identify “psychobiomarkers,” or biological measures that are regulated in part by psychological function and that predict longevity. Telomere length appears to be such a measure. Telomeres, the protective caps at the tips of chromosomes, shorten with age, and this shortening predicts disease and longevity. Leukocyte telomere length may be best viewed through a life-span approach, as it reflects in part the cumulative number of cell divisions that have occurred and the long-term biochemical environment. Recently, a critical mass of studies demonstrated that telomeres appear to shorten with chronic stress, although the mechanisms are unknown. This paper reviews what appear to be malleable determinants of rate of telomere attrition, focusing on early life chronic stressors and metabolic adversity (poor nutrition during development, and obesity). The next generation of research will benefit from experimental and longitudinal models integrating genetic variation, social environments, life experience, and health behaviors.  

KEYWORDS—chronic stress; aging; telomeres; psychobiomarker; life-span approach  

TELOMERES AS A PSYCHOBIO MARKER?  

While chronological aging occurs at a constant predictable rate, biological aging, its related consequence, can in some cases have a course of its own. It is helpful to have biomarkers of age in order to predict health status and longevity. While true biomarkers change with age and predict mortality, many have no known relationship with psychological factors. “Psychobiomarker” might be a helpful label for a biomarker that is also known to be influenced by one’s psychological state and, thus, social and environmental context. In the search to understand the mechanistic links between how social environments and psychological processes impact how we age, validated psychobiomarkers are essential to provide a window into how our social environment gets under our skin.  

Telomeres may be such a measure. Telomeres are repeat sequences of DNA that cap the end of chromosomes and protect the cell’s genomic stability. The molecular structure of telomeres, discovered by Elizabeth Blackburn and colleagues, solves the end-replication problem, which is that the enzymes that replicate chromosomes cannot do so fully at the tips, which could cause us to lose parts of genes when cells replicate. Instead, the telomeres serve as a buffer of DNA at the ends of chromosomes, so that with cell replication, the telomeres shorten. The telomere caps have many other functions, including preventing recombinations and fusions of the ends of genes with fragments of DNA from broken chromosomes, which could typically lead to cancer. Telomeres that are shortened past a critical length cause the cell to enter a state of arrest (cell senescence) when cells can no longer divide. Senescent cells tend to underlie tissue aging and possibly organizational aging. Telomeres tend to shorten with age, although rate of shortening depends on levels of telomerase activity; telomerase is an enzyme that can lengthen and protect telomeres.  

In the last decade, there has been an explosion of epidemiological research on telomere length (TL) and disease. Shorter TL in leukocytes (white blood cells) has been consistently associated with chronic disease states, primarily cardiovascular-related diseases, and is predictive of clinical disease and, in several studies, of early mortality (Fuster & Andres, 2006).  

TELOMERES MAINTENANCE THROUGH A LIFE-SPAN PERSPECTIVE  

Telomeres appear to lengthen and shorten in response to sociobiological signals during critical developmental or
stRESSFUL PERIODS, DESCRIBED BELOW. Thus, it may be helpful to view TL maintenance through a theoretical framework of life-span development (Baltes, 1987). For example, TL adaptation shows plasticity—lengthening or shortening at different rates depending on stage of growth or aging—which occurs from conception to death. Adaptation over the life span involves changes in the allocation of resources used for growth, maintenance, and restoration. Last, adaptation is influenced by ontogenic and biopsychosocial forces. As described below, telomeres can lengthen in people as well as shorten, depending on the extent of the fluctuations of the dynamic biochemical environment as it responds to the demands of the external environment.

Although no prospective studies have been conducted from infancy to adulthood, given the small changes in TL over time within a cell, average leukocyte TL may prove to have a strong “tracking record” over the life span. While TL likely tracks over time, it does not change at a constant rate. For example, people have long telomeres in infancy (around 10,000 base pairs); show rapid loss early on, and then show slower loss during adulthood—roughly 30 to 60 base pairs a year (Zeichner et al., 1999). Life experience may also alter rate of loss, as I will describe. Thus, to understand the etiological forces that have shaped TL at any one point in time, it is helpful to consider both early developmental periods or events that influence TL trajectories, and current factors that modulate the rate of TL attrition versus TL lengthening.

A REVIEW AND RESEARCH AGENDA

In what follows, I list the presumed biochemical pathways regulating TL and review other influences, including early-life exposures, metabolic health, chronic stress, and sociodemographic factors.

Biochemical and Other Regulators of TL

Several factors, including genetic effects and immune challenges (antigen exposure leading to higher telomerase and T-cell turnover and thus telomere shortening), are known to influence TL and telomerase. Changes in telomere length may also be due to changes in hematopoietic stem cells, the precursor cells to leukocytes (Lansdorp, 2006). Recent research has pointed to a broad set of candidate biochemical factors. Oxidative stress is the best-established factor, as it causes telomere shortening in laboratory experiments and is associated with shorter telomeres in people. Several studies in adults have now linked telomere shortness or telomerase to the stress hormones cortisol and catecholamines, and to metabolic factors such as obesity and insulin (Epel et al., 2006; Gardner et al., 2005), and cortisol has been found to dampen telomerase in laboratory experiments (Choi, Fauce, & Effros, 2008). It is thought that certain immune-regulating proteins called cytokines promote telomere shortening. It is logical evolutionarily that this array of biochemical regulators ensures that signals about an organism’s state of stress (metabolic or psychological) can influence telomere maintenance and thus cell longevity versus early senescence. Unfortunately, most human studies are merely correlational, and there is little direct evidence that metabolic or other biochemical factors play a causal role in telomere shortening. While animal studies can provide the best models for elucidating causal pathways, this remains a largely untouched research area.

Metabolic Health in Childhood and Adulthood

Aspects of health are transmitted across generations, not just through genetics and health behaviors but also through the prenatal environment (fetal programming). For example, a woman’s nutritional status during pregnancy affects the birth weight of her infant, which in turn will affect the child’s catch-up growth and later obesity or metabolic disease. There are some hints that TL may be affected by similar early factors as well. In rodents, poor maternal nutrition during pregnancy (reduced protein), compared to poor nutrition after birth, leads to low birth weight, rapid catch-up growth later, and the development of shorter telomeres in kidney tissue (Jennings, Ozanne, Dorling, & Hales, 1999) and aortic tissue (Tarry-Adkins, Martin-Gronert, Chen, Cripps, & Ozanne, 2008) in early life. So far, one study compared leukocyte TL in preschool-age children who had been normal-birth-weight infants to that in children who had been low-birth-weight infants, and found that the low-birth-weight group had shorter TL (Raqib et al., 2007), possibly analogous to the rodent studies described above. The first 5 years of life (at least) are characterized by a dramatic rate of telomere attrition, thought to be due to anatomical and functional changes in the immune system (French, Blackburn, & Shannon, 1998). However, this period is largely unstudied in terms of nutrition or psychosocial factors. Figure 1 models these isolated effects, suggesting they may leave imprints on TL in later life. As described above, there are clues that telomere maintenance in adulthood may be similarly influenced by metabolic pathways (Gardner et al., 2005), and thus one would expect synergistic effects between early experience and later health on TL trajectories (not shown in Fig. 1).

Stress and TL

Given the malleability of TL, and its vulnerability to an adverse biochemical environment, my colleagues and I hypothesized that years of chronic stress and associated stress arousal would dampen telomerase and lead to prematurely shortened leukocyte telomeres in young adulthood. Chronic stress leads to dysregulation of allostatic systems (McEwen, 2007) and could affect rate of shortening through lifestyle, biochemical milieu, and/or greater vulnerability to immune challenges. In our first test of this hypothesis, we found that perceived stress and duration of a chronic stressor (parenting a child with a chronic condition) were associated with lower telomerase and shortened leukocyte telomeres (Epel et al., 2004). These findings have been extended by others,
Can telomeres lengthen in people? TL may not change in a unidirectional fashion, simply shortening over time. We still know little about telomere attrition in vivo, which has been determined almost solely by cross-sectional studies. One would assume TL could not change appreciably in adults over just a few years. But TL appears to be more dynamic than initially thought, when sampled over short periods. In the first mouse study examining stress effects, telomeres shortened as expected after mice were exposed to 4 months of stress, but actually lengthened in the control mice (Kotrschal, Ilmonen, & Penn, 2007). Our preliminary data across two samples of healthy older adults suggests that average TL increased over time in a sizable minority, and in one study, where stress was repeatedly measured, lengthening was correlated with decreases in life stress over the same time period. On the surface, it may seem counterintuitive that what appears to be a cumulative marker of aging doesn't move in just one direction, toward age-related shortening, but may actually lengthen. However, we must postpone assumptions about telomere dynamics until there is a critical mass of longitudinal data. Last, observed changes could be due to increases per cell or due to changes in a certain subset of circulating cells or in stem-cell dynamics.

Stress works indirectly through promoting smoking, obesity, and sedentariness, which have all been linked to shorter TL. Can behavioral interventions increase TL? So far, one pilot study found that intensive lifestyle modification was associated with a significant improvement in leukocyte telomerase activity levels in men with prostate cancer (Ornish et al., 2008). Although this study lacked a control group, the greater the reduction in intrusive thoughts and distress about cancer, the greater the increase in telomerase, suggesting a possible stress pathway. Smoking cessation, exercise, weight loss, and stress reduction all merit examination.

Thus, there now appears to be a critical mass of studies demonstrating effects of severe stress on TL and a suggestion that telomeres can lengthen. It will be helpful to know how individual differences and interventions affect TL, especially in interaction with stress exposure, and through which pathways.

Sociodemographic Contexts and TL.
The life-span perspective considers how people’s health is influenced by their environment, including neighborhoods, socioeconomic status (SES), and social changes. One would expect those of lower SES, which is a proxy for greater exposure to a range of stressors, to have shorter TL. Indeed, in one study, lower occupational status was linked to shorter TL in women, even after controlling for body mass index, smoking, and exercise (Cherkas et al., 2006), although replication is needed. This research opens up the possibility that a range of factors embedded in SES, such as neighborhood and childhood SES, may also have effects on TL.

Studies on racial differences are in progress, testing the hypothesis that telomere attrition is the biological mechanism for Arline Geronimus’ construct of “weathering”—stress-induced early aging that might underlie the persistent U.S. racial health inequity. It will be a challenge to parse out sources of observed differences (e.g., genetics or culturally or SES-patterned factors such as diet and stress exposure).

Gender differences can also be better understood through a developmental perspective. Although females do not have longer telomeres at birth than men, they are significantly longer by adulthood, and it is unclear when this sex difference emerges or how it may relate to gendered social experiences or biological differences over the life course. The gender gap in telomere length most likely reflects the greater rate of telomere attrition in men compared to women, at least in early adulthood. In later adulthood, after women experience menopause, women’s rate of attrition may become more similar to that of men.

Do Developmental Periods Affect Telomere Maintenance? A Life-Span Approach
Perinatal or early childhood influences on TL are a ripe area for research and possibly intervention. It is conceivable that

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Fig. 1. Hypothetical telomere length (TL) trajectories over the life span in three hypothetical individuals—one born in a high-stress environment (early stress; red), one born in a low-stress environment (black), and one having experienced poor fetal nutrition (metabolic adversity; blue). The high-stress person has equivalent TL at birth to the low-stress person but is exposed to greater stress arousal and possibly has greater antigen exposure, which result in accelerated attrition in the first 5 years of life, the most dynamic period of change. The person with metabolic adversity is both born with shorter TL and has a greater rate of attrition during catch-up growth. (The model does not take into account changing levels of stress throughout the life span.) By late life, the hypothesized effects from the early exposures has led to 15% shorter TL for the high-stress individual and 30% shorter TL for the individual who experienced metabolic adversity. These estimates of telomere size and rate of attrition are roughly based on several studies (e.g., Zeichner et al., 1999) but should be viewed as theoretical, since such estimates vary significantly from study to study.
common factors such as a mother’s obesity, stress, depression, or substance use could affect TL in utero. Animal studies show early life stressors (e.g., maternal separation) can alter stress response systems and immune function years later (McEwen, 2007). In turn, it is possible these factors may hasten telomere-induced cell senescence. Low SES is related to greater childhood infectious disease and later susceptibility to colds (Cohen, Doyle, Turner, Alper, & Skoner, 2004). Excessive childhood infections lead to T cell turnover, and such turnover, without sufficient telomerase, presumably leads to shorter TL. In this way, if tracking of telomere length is strong, early infections might also promote earlier replicative senescence of the immune system in adulthood. On the other hand, telomere length may be quite malleable even late in life. A recent study showed that in the elderly, over a mere 2.5-year period, some had telomere shortening as expected, but some also had telomere lengthening. Furthermore, greater rate of shortening predicted earlier mortality in men (Epel et al., 2009).

Early infancy may be a unique period, given the dramatic rate of telomere attrition, but it is likely not the only period of dynamic change. We need studies closely examining other potentially critical periods, such as later childhood, puberty, and menopause. Given the effects of estrogen exposure, which can increase telomerase in laboratory studies, it is conceivable that telomeres may show lengthening after puberty and accelerated attrition after menopause. This is speculative, and studies are needed to test these periods characterized by dramatic changes in hormones.

If a mother’s poor nutrition, depression, and damaging health behaviors during pregnancy prove to play a role in setting up a lifelong trajectory of rapid telomere attrition in her child, it will be warranted to test effects of interventions, such as enhanced prenatal care, parenting skills, and enrichment programs for preschoolers, during these critical developmental periods.

**SUMMARY AND CONCLUSIONS**

TL appears to be a promising psychobiomarker. It appears to reflect an individual’s recent past and cumulative history, possibly starting as early as the prenatal environment. Biochemical signals appear to shape telomere maintenance throughout the life span, making TL responsive to allostatic demands. Thus TL is best viewed through a life-span approach, which emphasizes life circumstances, adverse exposures, and health behaviors across time, as well as sociocultural context.

Given the novelty of research on TL in humans, there are numerous unanswered questions, such as the ones above. The first generation of human telomere research has examined cross-sectional relations in large cohorts. This led to novel information, showing that telomeres are associated with lifestyle and social context. Integrating findings from the studies available provides a tentative model to promote a longitudinal perspective and generate a research agenda that moves beyond correlations and serves as a starting point for a life-span perspective. Figure 1 shows hypothesized effects of extreme exposures to early chronic stress or adverse prenatal environments on TL, which will likely interact with later lifestyle and stress.

There is still much to learn from well designed cross-sectional studies in terms of identifying correlates that may serve as potential predictors and consequences of TL. However, an investigation of how nature interacts with nurture over time requires translational research models. Experimental studies that manipulate presumed regulators of telomerase and TL in people are necessary. A single level of analysis focusing on genetic variation or biological-, psychological-, or social-level factors will be limiting, as these factors do not work in isolation but rather in interaction. The next generation of studies should thus move toward longitudinal multilevel and experimental perspectives. Measuring the complex network of one’s social, biological, and genetic contexts over time will ultimately provide the most predictive models of telomere maintenance throughout the life span.

In the near future, however, the field requires answers to basic questions: What are the rates of telomere attrition in different developmental periods? In which cell types? And how do these differ by individual differences and across sociodemographic groups? Collaborations between basic, clinical, social, and epidemiological scientists can promote this type of research and deepen our understanding of TL maintenance throughout the life span.

**Recommended Reading:**


Gardner, J.P., Li, S., Srinivasan, S.R., Chen, W., Kimura, M., Lu, X., et al. (2005). (See References). One of the few published studies with longitudinal data on TL; it finds that a minority of people show increases over time and that insulin resistance tracks with TL.


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REFERENCES


A few quick reminders:
- Taxis are reimbursable! You must submit receipts of expenses $75 or more. Yellow Cab DC’s phone #: 202-544-1212.
- Rental Cars in DC are not reimbursable by the Academies.
- Please do not use limo services as they tend to be more expensive than taxis.
- Per Diem in DC in December is $71 for meals & incidentals. Please take into account that NAS will provide some of your meals at prices of: $12 for breakfast, $18 for lunch, $36 for dinner. Please do not exceed $71 in total for all three meals in 1 day.

If you booked your hotel room through me, then you will be staying at the hotel mentioned below:
- Georgetown Suites
  1111 30th Street, NW,
  Washington, D.C. 20007
  Phone: 1-877-784-6835

You should not have to provide a credit card (except for incidentals) since your room will be directly billed to us. If you have any problems please let me know.

Meeting Times & Location:

March 1st:
- Meeting Times: 8:00 a.m.-5:00 p.m.
  Breakfast will be available at 7:30 a.m. and lunch will be provided
- The House of Sweden,
  The Alfred Nobel Hall
  2900 K Street, NW
  Washington, DC 20007

March 2nd:
- Meeting Times: 8:00 a.m.-3:00 p.m.
  Breakfast will be available at 7:30 a.m. and lunch will be provided
- The House of Sweden,
  The Alfred Nobel Hall
  2900 K Street, NW
  Washington, DC 20007
Committee on a Framework for Developing a New Taxonomy of Disease

Point A is the House of Sweden and Point B is the Georgetown Suites Hotel. The closest metro stop is the Foggy Bottom – GWU Station, of the Blue and Orange lines.

Please feel free to contact me at 202-334-1957 or at amazzawi@nas.edu with questions or concerns. If you booked your flight through Kentlands and you have any emergency travel issues, please use their 24-hour emergency phone lines (1-888-565-9174). Have a safe trip to DC!