The Future of Genomic Medicine IV

Thursday, March 3 and Friday, March 4, 2011 • Scripps Institution of Oceanography • La Jolla, California

Scripps Translational
Science Institute

Scripps Translational Science Institute

SCRIPPS GENOMIC MEDICINE
A Collaboration of Scripps Health and The Scripps Research Institute

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5:30 – 7:30 p.m.

Thursday Evening Welcome Reception at Scripps Institution of Oceanography
Location: 8610 Kennel Way
La Jolla, California 92037

Friday, March 4, 2011

7:30 a.m.	Registration and Breakfast
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5:50 p.m.	**Afternoon Panel Discussion/Q&A** Afternoon Session Speakers and Moderators
6:00 p.m.	*Wrap Up & Adjourn*

Helpful Information

Parking and Transportation during the conference

There will be a looping shuttle on Thursday, Mar. 3 and Friday, Mar. 4 between The Estancia Hotel & Spa, The La Jolla Shores Hotel, Kellogg Park and Scripps Institution of Oceanography. The shuttle will run from 6:15 a.m. to 7:45 p.m. on Thursday and from 6:30 a.m. to 6:30 p.m. on Friday.

Parking is available in the following locations:

- Parking is available in the underground parking lot at The La Jolla Shores Hotel ($5/day, $14 overnight) and at Kellogg Park (free). Street parking is also available.
- There will be a looping shuttle on Thursday, Mar. 3 and Friday, Mar. 4 between Estancia La Jolla Hotel & Spa, La Jolla Shores Hotel, Kellogg Park and Scripps Institution of Oceanography.
- You may also park and walk to/from La Jolla Shores Hotel and Kellogg Park to Scripps Institution of Oceanography (approximately 10 minutes).
- UCSD Employees/Faculty/Students are encouraged to park in a UCSD parking lot and take the SIO shuttle to/from Scripps Institution of Oceanography.

Important Note for those who park in The La Jolla Shores Hotel underground parking structure: Please see the front desk and mention you are attending the Scripps Genomic Medicine Conference in order to receive a parking pass.

Thursday Evening Welcome Reception

The welcome reception will take place on Thursday from 5:30 p.m. to 7:30 p.m. at Scripps Institution of Oceanography. Refreshments and light hors d'oeuvres will be provided.

Poster Presentations

Poster presentations will take place on Friday from 7:30 a.m. to 2:35 p.m. in the Charles E. Scripps room. The winners will be announced at 2:55 p.m.

The Future of Genomic Medicine Online Learning Module

This educational component is designed to assist conference participants in three ways:

- To provide online resources for furthering genomics knowledge;
- To provide reference materials and tutorial guides to prepare participants for the 2 day 'immersion' into the field of genomics;
- To make available topic-specific publications to prepare participants for the main discussion themes of the conference.

The Future of Genomic Medicine IV Online Learning Module can be accessed at: http://www.stsiweb.org/index.php/FoGM/

Internet Access during the conference

Wireless Internet is available during the conference. Upon accessing the internet you will be directed to a page that requests your email. Upon entering your information you will be registered automatically.

Social Networking

Visit our Scripps Health Facebook 2011 Future of Genomic Medicine IV events page at: http://on.fb.me/huXCjL to interact with colleagues before arriving to the conference. This is a great opportunity to connect with other attendees in your specialty from all over the country.

We are on Twitter! Connect with like-minded members on topics of interest and expand your professional contacts. Follow the conversation with the following hash tag: **#FOGM11.**

Conference Evaluation

Your feedback is very important! Please be sure to complete the online conference evaluation at: http://www.surveymonkey.com/s/futureofgenomicmedicineIV following your participation in the conference.

Questions?

Please contact Scripps Conference Services & CME at: (P) 858-652-5400 (E) Med.Edu@Scrippshealth.org

Industry Support

We would like to thank the following companies for providing generous support for this educational activity. Their support helps make this conference possible.

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Agilent Technologies
Genentech
Millenium: The Takeda Oncology Company
RainDance Technologies
Amgen
AstraZeneca
Complete Genomics
Genomic Health
BGI Americas

Scripps Translational Science Institute

Scripps Translational Science Institute (STSI), a collaborative, bridge initiative between the Scripps Health organization and The Scripps Research Institute, is transforming and integrating clinical and basic research by promoting interdisciplinary omics-based translational research efforts which advance the field of individualized medicine. STSI is supported by the NIH flagship program, Clinical and Translational Science Award (CTSA). Besides Scripps, there are collaborations with the Sanford-Burnham Institute for Medical Research, Children's Hospital of Philadelphia, Genomics Institute of the Novartis Research Foundation, J. Craig Venter Institute, Salk Institute for Biological Studies, San Diego State University, San Diego Supercomputer Center and The Neurosciences Institute on the San Diego Mesa. The Institute emphasizes all three dimensions of translation: *i)* traditional bench-to-bedside, *ii)* bedside-to-bench and back-to-bedside, and *iii)* bedside to the community medicine. STSI harnesses the excitement of today's scientific advances to catapult tomorrow's preventions, betterment of health, and the training of future leaders of academic medicine.

For more information on The Scripps Translational Science Institute (STSI), visit **www.stsiweb.org**.

Scripps Health, a nonprofit health care system based in San Diego, California, includes more than 2,600 affiliated physicians and over 13,000 employees at five acute-care hospital campuses, home health care services and a network of clinics, physician offices and outpatient centers. Scripps is committed to contributing to the future of medicine through its clinical research trials, graduate medical education and continuing medical education programs. More information can be found at www.scripps.org.

For more information on Scripps Health, visit **www.scripps.org**.

Conference Faculty

Course Director

Eric J. Topol, MD
Director, Scripps Translational Science Institute
Chief Academic Officer, Scripps Health
Professor of Translational Genomics, The Scripps Research Institute
The Gary and Mary West Chair of Innovative Medicine
La Jolla, California

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Duke University
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Associate Dean for Health Sciences
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La Jolla, California

Kevin Davies, PhD
Chief Editor, *Bio-IT World*
Author of ***The $1,000 Genome***

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Managing Director, Excel Venture Management
Chairman and CEO, Biotechonomy LLC
Co-founder, Synthetic Genomics Inc.
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Chair of the Department of Genomics of
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Director, Center for Genomic Medicine
Executive Director, Personalized Medicine
Duke Institute for Genome Science & Policy
Durham, North Carolina

Thomas Goetz, MPh
Executive Editor, WIRED Magazine
Author of ***The Decision Tree****: Taking Control of Your Health in the New Era of Personalized Medicine*

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Associate Professor of Pediatrics
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Daniel D. Von Hoff, MD, FACP
Physician-in-Chief, Senior Investigator
Translational Genomics Research Institute
Clinical Professor of Medicine
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Chief Scientific Officer
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Phoenix, Arizona

Bradley A. Patay, MD

Assistant Professor
Scripps Translational Science Institute
Head, Section of Internal Medicine
Scripps Clinic Torrey Pines
La Jolla, California

Biography

Head of the internal medicine section at Scripps Torrey Pines since 2008, Bradley A. Patay, M.D., is Assistant Professor at STSI, where he is the principal investigator of a novel clinical trial to evaluate whether intensive monitoring and genomic analysis improve blood pressure control. Brad, who also assists with the ***Wellderly*** study, is a Diplomate in Internal Medicine in the American College of Physicians and a Diplomate in Pediatrics in the American Academy of Pediatrics.

Dedicated to improving health by integrating genomic knowledge into primary care settings, he is a member of the board and vice president of the College of Genomic Medicine, established in 2010 to educate physicians and other health care professionals about genomic medicine.

His diverse clinical experience prior to joining Scripps Clinic in 2005 includes four years as an internist and pediatrician at both Neighborhood Healthcare, a private, nonprofit community healthcare practice, and Palomar Hospital. At these two institutions in Escondido, CA, he cared for a wide range of patients, from neonates to the elderly, in both intensive care and the general wards. Through his service on several committees, including patient safety, he helped improve the health care institutions' systems.

He graduated with honors in economics and molecular cell biology from the University of California at Berkeley, where he was elected to Phi Beta Kappa. After receiving his M.D. degree at UC San Diego in 1997, he completed a medical residency at Banner Health in Phoenix Arizona and earned board certifications in internal medicine and pediatrics.

Notes

Rejection after Cardiac Transplant

Hannah A. Valantine, MD, MRCP, FACC

Senior Associate Dean
Professor of Medicine, Cardiovascular Medicine
Stanford University School of Medicine
Stanford, California

Biography

Dr. Hannah Valantine is a recipient of the NIH Director's Pathfinder Award for diversity in the biomedical workforce, 2010. Originally from the Gambia, West Africa, she grew up in England, and is a graduate of St. George's Hospital, London University. She completed her residency at St. George's Hospital, Brompton Hospital and Guys Hospital London, and her cardiology fellowship training at Royal Postgraduate Medical School in Hammersmith London. For her post-doctoral research fellowship training she moved to Stanford University, and undertook research focused on Echocardiography for the diagnosis of acute rejection. During this time she also conducted clinical research to determine the role of conventional risk factors in transplant coronary artery disease, and the application of intravascular ultrasound for monitoring of the disease process.

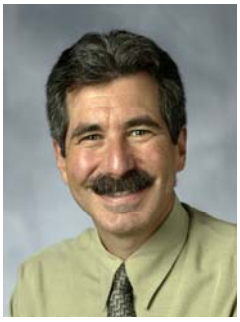
Dr. Valantine is a Professor of Cardiovascular Medicine and Senior Associate Dean for Diversity and Leadership at Stanford school of Medicine, a leadership position to which she was appointed in November 2004. In this role she has developed innovative approaches to faculty development, leadership and diversity. Her trans formative approach was recently recognized by the NIH Director, by awarding her the Pathfinder Award for diversity in the biomedical workforce. Not withstanding her leadership and administrative roles, Dr. Valantine maintains an active clinical research program that continues to yield high impact results in patient care. Most recently, she reported in the *New England Journal of Medicine, (April 2010)* on the effectiveness of a novel non-invasive approach for the diagnosis of acute heart transplant rejection, an innovation that represents a major paradigm shift in the way heart transplant patients will be managed in the future. This but one of Dr. Valantine's many innovations that often challenge conventional dogma. She hopes to bring this same level of rigorous enquiry to the challenging issue of faculty career flexibility. Dr. Valantine is Co-Director of heart transplantation, and Director of Clinical Transplant Research. Her current research interests include pathophysiology of transplant related atherosclerosis, with a focus on the role of infection and lipids; non-invasive diagnosis of acute rejection, with a current focus on the application of high-throughput genomic methods; and new approaches to the conduct of clinical trials. She is an nationally recognized clinical investigator, and has been the recipients of several research grants from the NIH and AHA, including being the Co-Principal Investigator for an NIH- funded Program Project Grant in transplant arteriosclerosis. Dr. Valantine is author of 160 peer-reviewed publications, 10 book chapters, and has been invited to be a presenter at over 100 lectures. She has served on many editorial boards including Journal of Heart & Lung Transplant, Transplantation and Circulation. She is a Past President of the American Heart Association Western States Affiliate Board of Directors.

She is married to Denis von Kaeppler whose background is in information technology. They have two daughters, a college sophomore and a high school senior. Aside from research and diversity, Dr. Valantine has a passion for travel, especially cruising, fine dining, visits to spas, and exercise.

Molecular Signatures to Classify Health and Disease

Geoffrey S. Ginsburg, MD, PhD
Director, Center for Genomic Medicine
Executive Director, Personalized Medicine
Duke Institute for Genome Sciences & Policy
Durham, North Carolina

Biography



Dr Ginsburg, the founding director of the Center for Genomic Medicine and assumed his current position in the Duke Institute for Genome Sciences and Policy in 2004 and was also appointed as a co-director of the Duke Translational Medicine Institute in 2006. He is also the founding executive director of the Center for Personalized Medicine established in 2010.

While at Duke, Dr Ginsburg has pioneered translational genomics, initiating the first genomic-guided clinical trials as well as developing novel practice models and implementation research for the integration of genomic tools in heath care systems. The centers focus on oncology, infectious diseases, cardiovascular disease and metabolic disorders.

In 1990, he joined the faculty of Harvard Medical School, where he was director of preventive cardiology and led a laboratory in applied genetics of cardiovascular disease. In 1997 he joined Millennium Pharmaceuticals Inc, as senior program director for cardiovascular diseases and was eventually appointed vice president of Molecular and Personalized Medicine at Millennium, where he was responsible for developing pharmacogenomic strategies for therapeutics, as well as biomarkers for disease and their implementation in the drug development process.

Dr Ginsburg's research interests are in the development of novel biomarkers that inform medical decisions, the paradigms for translating genomic information into medical practice, and the integration of personalized medicine into health care. He has received a number of awards for his research accomplishments, including the Innovator in Medicine Award from Millennium in 2004 and the Basic Research Achievement Award in Cardiovascular Medicine from Duke in 2005. He is a founding member and on the Board of Directors of the Personalized Medicine Coalition, a senior consulting editor for *The Journal of the American College of Cardiology,* editor-in-chief for *The HUGO Journal*, and an editorial advisor for *Science Translational Medicine*. In addition he is the editor of *Genomic and Personalized Medicine* (Elsevier) whose first edition was published in 2009.

He has been an international expert panel member for Genome Canada and the Secretary of Veterans Affairs Advisory Council on Genomic Medicine. He is currently a member of the Board of External Experts for the National Heart, Lung and Blood Institute, the Institute of Medicine's Roundtable on Genome-Based Research to Human Health, the National Advisory Council for Human Genome Research, and a member of the External Scientific Panel for the Pharmacogenomics Research Network.

He received his MD and PhD in biophysics from Boston University and completed an internal medicine residency at Beth Israel Hospital in Boston, MA. Subsequently, he pursued postdoctoral training in clinical cardiovascular medicine at Beth Israel Hospital and in molecular biology at Children's Hospital as a Bugher Foundation Fellow of the American Heart Association.

Notes

Breast Cancer Gene Expression

Steve Shak, MD
Chief Medical Officer,
Genomic Health
Redwood City, California

Biography

Steve Shak, M.D. has served as Chief Medical Officer since December 2000. From July 1996 to October 2000, Steve served in various roles in Medical Affairs at Genentech, Inc., most recently as Senior Director and Staff Clinical Scientist. From November 1989 to July 1996, Steve served as a Director of Discovery Research at Genentech, where he was responsible for Pulmonary Research, Immunology and Pathology. Steve led the clinical team that gained approval for Herceptin®, a targeted biologic treatment for breast cancer. He also initiated the cancer clinical trials of the anti-angiogenesis agent, anti-VEGF (Avastin®). In addition, Steve discovered Pulmozyme®, a mucus-dissolving enzyme that is approved worldwide for the treatment of the genetic disease cystic fibrosis. Prior to joining Genentech, Steve was an Assistant Professor of Medicine and Pharmacology at New York University School of Medicine. Steve holds a Bachelor of Arts degree in Chemistry from Amherst College and an M.D. from New York University School of Medicine, and completed his post-doctoral training at University of California, San Francisco.

Notes

Consumer Genome -Wide Disease Risk Profiling

Cinnamon S. Bloss, PhD
Assistant Professor
Scripps Translational Science Institute Scripps Health & The Scripps Research Institute
La Jolla, California

Biography
A genomics scientist as well as a licensed clinical psychologist, Cinnamon Bloss, Ph.D., is a lead investigator of the Scripps Genomic Health Initiative (SGHI) and the principal investigator of a National Institutes of Health/NHGRI-funded R21 grant to investigate individuals' behavioral and psychological responses to disclosure of genomic risk information for common, complex diseases. These studies reflect her strong interest in improving scientific understanding about the impact of predictive genomic testing and risk-disclosure on healthy individuals, families and patients.

Her other research interests include developing ways of combining genomics with traditional disease risk factors to make predictions about disease development, progression and response to treatment, as well as designing effective health interventions that leverage genomic information. She also conducts genetic association studies and has many collaborations investigating the genetic underpinnings of neurological, behavioral, and other health-related phenotypes.

After receiving a B.A. degree in psychology from Smith College, she was awarded a Ph.D. in clinical psychology with an emphasis in neuropsychology from the joint doctoral program at UC San Diego and San Diego State University (SDSU). She completed a predoctoral internship in clinical neuropsychology at the University of Florida. In 2005, she received the Outstanding Doctoral Student Teaching Award for SDSU's Department of Psychology.

Cinnamon completed a post-doctoral fellowship in statistical genetics and genomic medicine at TSRI before joining STSI in 2008. Soon after her appointment to a research position at STSI, she received a Scripps Clinical Research Development Award grant to identify biomarkers of cognitive decline in Parkinson's disease. At STSI, she directs the Summer Undergraduate Research Internship (SURI) Program.

As a clinical psychologist, she has worked with adults and children with a wide range of neurological, developmental and psychiatric conditions. While continuing her research at STSI, this year she will join the Scripps Clinic Medical Group Division of Neurology as a staff neuropsychologist.

Notes

Clopidogrel and rapid point of care genotyping

Matthew J. Price, MD, FACC, FSCAI
Assistant Professor,
Scripps Translational Science Institute
Director, Cardiac Catheterization Laboratory
Division of Cardiovascular Diseases
Scripps Clinic
La Jolla, California

Biography

Dr. Matthew Price is the Director of the Cardiac Catheterization Laboratory at Scripps Clinic and Assistant Professor at the Scripps Translational Science Institute in La Jolla, California. He graduated from Cornell University with *Distinction in All Subjects.* He earned his MD at the University of California, Los Angeles (UCLA) School of Medicine and completed his internship and residency in Internal Medicine at the UCLA Center for Health Sciences. He subsequently completed a fellowship in Cardiovascular Diseases at Cedars-Sinai Medical Center in Los Angeles, where he served as Chief Fellow. Dr Price completed his training in Interventional Cardiology at Scripps Clinic.

Dr Price is certified by the American Board of Internal Medicine in Internal Medicine, Cardiovascular Disease, and Interventional Cardiology. His clinical and research focus includes high-risk percutaneous coronary intervention (PCI), interventional approaches to congenital and structural heart disease, and antiplatelet therapy. Dr Price is involved in the leadership of several clinical trials examining the effectiveness of antiplatelet therapy during, and was the principal investigator of GRAVITAS, a randomized clinical trial that examined the safety and efficacy of individualized thienopyrdine therapy after PCI. He serves on the Editorial Board of the Journal of the American College of Cardiology and as an ad hoc reviewer for several professional journals, including the *American Heart Journal,* the *American Journal of Cardiology, Circulation,* and the *New England Journal of Medicine.*

Notes

Consumers and the $1,000 Genome

Kevin Davies, PhD

Chief Editor, *Bio-IT World*

Author of ***The $1,000 Genome***

Biography

Kevin Davies is the founding editor of *Bio-IT World* and *Nature Genetics*, and the author most recently of *The $1,000 Genome* (Free Press, 2010), an account of the revolution in DNA sequencing technologies, personal genomics, and the road to personalized medicine.

Davies previously penned *Cracking the Genome*, the first published account of the race for the Human Genome Project, praised by one savvy reviewer as "a rollicking good tale about an enduring intellectual monument" and translated into 15 languages. His first book, co-authored with Michael White, was entitled *Breakthrough*, about the race to isolate the *BRCA1* breast cancer gene.

Born and educated in England, Kevin read biochemistry at Oxford University and took a Ph.D in human genetics from St Mary's Hospital Medical School (University of London), working on the genetics of cystic fibrosis. Davies moved to the United States in 1987, but after two postdoctoral fellowships at MIT and Harvard Medical School, he sought refuge from the lab bench in the editorial offices of the journal *Nature*. In 1992, he was appointed editor of *Nature*'s first spin-off journal in 20 years, and quickly established *Nature Genetics* as one of the most influential and highly cited research journals.

After stints at the Howard Hughes Medical Institute, the largest medical philanthropy in the United States, and editorial director of Cell Press, where he conceived and developed the journal *Cancer Cell,* Davies was appointed the chief editor of *Bio-IT World*, a trade magazine covering the management of life sciences data. Launched in 2002 by IDG, the magazine is now owned and published by Cambridge Healthtech Institute.

Married with two children, Kevin makes his home in Lexington, Massachusetts.

Notes

Consumers and the $1,000 Genome

Kevin Davies, PhD

2011 marks the tenth anniversary of the publication of the first draft of the Human Genome Project. It is also about ten years ago that researchers coined the catchphrase "the $1,000 genome," as the ambitious target to fully realize the fruits of human genomic research. Remarkably, thanks to astonishing progress in the development of "next-generation" sequencing technologies that are outstripping Moore's Law, that goal is almost a reality. Companies are already sequencing and annotating complete human genomes for less than $10,000, and personal genome sequencing is available to the public for less than twice that sum. Several encouraging examples of whole-genome (or exome) sequencing in the clinic, particularly in the fields of paediatrics and oncology, have already been published. These suggest a bright future for genomic medicine while accentuating the downstream informatics challenges, what some refer to as "the $1-million interpretation." In this talk, I will review the latest progress and prospects in next-generation sequencing technologies with a focus on their clinical applications, and discuss some of the issues surrounding the delivery of that information to the public.

Notes

DNA and the DECISION TREE

Thomas Goetz, MPh

Executive Editor, WIRED Magazine

Author of ***The Decision Tree:*** *Taking Control of Your Health in the New Era of Personalized Medicine*

Biography

Thomas Goetz is author of ***The Decision Tree:*** *Taking Control of Your Health in the New Era of Personalized Medicine*. Former FDA commissioner Dr. David Kessler calls The Decision Tree "a game changer," and Dr. Dean Ornish says that Goetz "writes more clearly and presciently about the future of health care than anyone on the planet."

The executive editor of WIRED Magazine, Goetz writes frequently on the confluence of medicine, health and technology. His cover stories at WIRED have covered the early detection of cancer, the advent of personal genomics, and the controversial diagnosis of metabolic syndrome. His work has been selected for both the Best American Science Writing and the Best Technology Writing anthologies. Since Goetz joined WIRED in 2001, the magazine has been nominated for 12 National Magazine Awards and has won six times, including the top award for general excellence three times, including in 2009.

Prior to joining WIRED, Goetz was a staff reporter at The Wall Street Journal and the Village Voice. His writing has also appeared in The New York Times Magazine, The New York Times op-ed page, Rolling Stone, and other publications. He has been a commentator for BBC Radio and appeared many times on CNN, CNBC, ABC, and other television outlets.

Goetz earned a Master of Public Health degree at University of California, Berkeley. An English major at Bates College, he also holds a Master's degree in American literature from the University of Virginia.

Notes

Patient-Organized Genomic Research Studies

Melanie Swan, MBA

Founder, DIYgenomics

Palo Alto, California

Biography

Melanie Swan is a Research Fellow at DIYgenomics, a citizen science organization she founded in March 2010. Ms. Swan has a quantitative risk assessment background and became interested in the predictive risk modeling and practical applications of personal genomics in 2008. Her educational background includes an MBA in Finance and Accounting from the Wharton School of the University of Pennsylvania, a BA in French and Economics from Georgetown University, and recent coursework in bioscience, nanotechnology, physics, and computer science. She is a faculty member at Singularity University and an Affiliate Scholar at the Institute for Ethics and Emerging Technologies.

Ms. Swan's career has focused on research, finance, and entrepreneurship, including founding an option-trading hedge fund and a technology startup company, GroupPurchase, which aggregated small business buying groups. She was Director of Research at Telecoms Consultancy Ovum RHK and previously held management and finance positions at iPass in Silicon Valley, J.P. Morgan in New York, Fidelity in Boston, and Arthur Andersen in Los Angeles.

Ms. Swan serves as an advisor to research foundations, government agencies, corporations, and startups and is active in the community promoting science and technology, and opportunities for women. She designs professional and educational simulations, including "Discontinuity Futures," "Being an Entrepreneur" and "The Trader's Pit." Ms. Swan is the former Treasurer of San Francisco-based non-profit Equal Rights Advocates, an Advisory Board member of the Foundational Questions Institute, Lifeboat Foundation, and Accelerating Studies Foundation, a presenter at the Expanding Your Horizons math and science conference, and co-moderator of the Philadelphia and Boulder Future Salons, free monthly events discussing science and technology innovations and their implications. Ms. Swan speaks French, Spanish, and Portuguese, and enjoys reading, international travel, and kick-boxing.

Notes

Patient-Organized Genomic Research Studies

Melanie Swan, MBA

Abstract

The hundreds of genome-wide association studies (GWAS) that have linked specific genes and variants to conditions can be synthesized and applied comprehensively to the personal genomic data of individuals. Carrier status has been a long-established application area. Health condition risk, drug response, athletic performance, and mental performance are other application areas, with differing levels of validity and utility. One broader goal of using genomic data is to realize personalized medicine by establishing individual susceptibilities and baseline measures and intervening at pre-clinical stages. Towards this end, wellness profiling is another potential area for applied genomics, both for disease: cancer, aging, and immune system profiling, and organ wellness: liver, kidney, heart, and lung profiling. DIYgenomics has developed a methodology for the conduct of patient-organized genomic research studies, obtaining outcomes by linking genomic data to phenotypic data and intervention. The general hypothesis is that individuals with one or more polymorphisms in the main variants associated with conditions may be more likely to have baseline out-of-bounds phenotypic biomarker levels, and could benefit the most from targeted intervention. A MTHFR/Vitamin B deficiency pilot study has been completed ("Citizen science genomics as a model for crowdsourced preventive medicine research"), an aging study is in open enrollment, and additional studies are in design for Vitamin D deficiency, metabolism, lymphocyte strength, mental performance, and retinitis pigmentosa/macular degeneration.

DIYgenomics is a non-profit research organization founded in March 2010 focused on the design of crowdsourced clinical trials and open-source personal genome applications (there have been over 3,000 downloads of the iPhone/Android mobile apps as of January 2011).

Press

- "A group called DIYgenomics has banded together to analyse their genomes, and even conduct and participate in small clinical trials" – *Nature, October 2010*
- "...early adopters are showing how empowering and beneficial to science personal genetic information can be" – *Nature Medicine, September 2010*
- "Many people who have discovered some or all of their genetic information are sharing it" – *Nature, December 22, 2010*

Publications (slides: http://www.slideshare.net/lablogga)

- Swan, M., Hathaway, K., Hogg, C., McCauley, R., Vollrath, A. Citizen science genomics as a model for crowdsourced preventive medicine research. *J Participat Med.* **2010** Dec 23; 2:e20.
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Notes

- Journal of Participatory Medicine - http://www.jopm.org -

Citizen Science Genomics as a Model for Crowdsourced Preventive Medicine Research

Posted By Melanie Swan On December 23, 2010 @ 4:45 pm In Research,Vol. 2, 2010 | No Comments

Abstract

Summary: A research model for the conduct of citizen science genomics is described in which personal genomic data is integrated with physical biomarker data to study the impact of various interventions on a predefined endpoint. This research model can be used for large-scale preventive medicine studies by both institutional researchers and citizen science groups. The genome-phenotype-outcome methodology comprises seven steps: 1) identifying an area of genotype/phenotype linkage for study, 2) conducting a thorough literature review of data supporting this genotype/phenotype linkage, 3) elucidating the underlying biological mechanism, 4) reviewing related studies and clinical trials, 5) designing the study protocol, 6) testing the study design and protocol in a small pilot study, and 7) modifying study design and protocol based on information from the pilot study for a large-scale prospective study. This paper describes a real-world example of the methodology implemented for a proposed study of polymorphisms in the MTHFR gene, and how these polymorphisms may influence homocysteine levels and vitamin B deficiency. The current study looks at the possibility of optimizing personalized interventions per the genotype-phenotype profiles of individuals, and tests the hypothesis that simple interventions may be effective in reducing homocysteine in individuals with high baseline levels, particularly in the presence of a polymorphism in the MTHFR variant rs1801133.
Keywords: MTHFR, homocysteine, genomics, polymorphism, variant, citizen science, patient-driven clinical trial, crowdsourced clinical trial, research study, self-experimentation, intervention, personalized medicine, preventive medicine, participatory medicine, quantified self, genome-phenotype-outcome study, citizen science genomics.
Citation: Swan M, Hathaway K, Hogg C, McCauley R, Vollrath A. Citizen science genomics as a model for crowdsourced preventive medicine research. J Participat Med. 2010 Dec 23; 2:e20.
Published: December 23, 2010.
Competing Interests: The authors have declared that no competing interests exist.

Introduction

Continually decreasing costs in genomic sequencing have made it possible for individuals to obtain their own genomic data. An estimated 80,000 individuals have subscribed to consumer genomic services. Genotyping provider 23andMe counted 50,000 subscribers as of June 2010.1 [1]] Navigenics and deCODEme had an estimated 20,000 and 10,000, respectively, as of March 2010.2 [2]] Others may be clients of Pathway Genomics or other services. Today, individuals can view the 200 or so variants analyzed by consumer genomic companies for a variety of disease, drug response, trait, and carrier status conditions via a web-based interface, and a question naturally arises as to what else can be done with the data.

Tools do not yet exist to identify and prevent disease before clinical onset. Integration of genomic, phenotypic, environmental, and microbiometric health data streams will be required to create reliable predictive tools. The potential volume of this data is staggering, numbering, perhaps, a billion data points per person,3 [3]] which may routinely generate zettabytes of medical data.4 [4]]

The combination of multiple health data streams, the anticipated data deluge, and the challenges and expense of recruiting subjects for studies all suggest that there could be a benefit to supplementing traditional randomized clinical trials with other techniques.5 [5]] Crowdsourced cohorts of citizen scientists (eg, patient registries) could be a significant resource for testing multiple hypotheses as research could be quickly and dynamically applied in various populations. Engaged citizen scientists could collect, synthesize, review, and analyze data. They could interpret algorithms, and run bioinformatic experiments. This paper proposes a research model that could be used in conducting citizen science genomics, that integrates personal genomic data with physical biomarker data and interventions, and that could be applied in large-scale preventive medicine studies by both institutional researchers and citizen science groups.

Methods

An increasing number of individuals have access to their own genomic data, would like to contribute this data to scientific research, and would like to put it to use in managing their own health. Scalable models for conducting citizen science studies are needed. The authors designed a methodology for the conduct of citizen science genomics which links genomic data to corresponding phenotypic measures and relevant interventions. The purpose is to create mechanisms for establishing and monitoring baseline measures of wellness, and tools for the conduct of preventive medicine. The key steps in the methodology include:
1. Selecting a specific area of genotype/phenotype linkage for potential study and generating a testable hypothesis
2. Conducting a literature review to validate the selected study area
3. Analyzing the underlying biological pathway and mechanism
4. Reviewing related studies and clinical trials
5. Designing the study protocol
6. Testing the study design in a small non-statistically significant pilot
7. Identifying the next steps for a full-scale launch of the study

Results

The results are presented as a detailed outline of the seven-step methodology for operating citizen science genomic studies. The methodology is implemented in the specific case of a proposed study looking at polymorphisms in the MTHFR gene and how these polymorphisms relate to homocysteine levels and vitamin B deficiency.

1. Select a specific area of genotype/phenotype linkage for potential study and generate a testable hypothesis.

For the inaugural citizen science genomic study, 40 potential ideas were identified in a variety of health and behavioral genomic areas in recently published research (http://diygenomics.pbworks.com). One area that seemed conducive to study was the potential association of the MTHFR gene and vitamin B deficiency. MTHFR polymorphisms may keep vitamin B-9 (folic acid) from being metabolized into its active form, folate. This may lead to the potentially harmful accumulation of homocysteine. There is a strong research-supported association between the principal MTHFR variant (rs1801133) and homocysteine levels.6 [6]] Genotyping data for MTHFR variants are available in 23andMe data. Furthermore, blood tests for homocysteine, vitamin B-12, and vitamin B-9 are readily obtainable, as are over-the-counter vitamin supplement interventions. A testable hypothesis was generated that supplements may be effective in reducing homocysteine levels, particularly for those with a genetic polymorphism.

Studying MTHFR and vitamin B deficiency could have an important public health benefit since approximately half of the US population is estimated to have one or more MTHFR polymorphisms. The distribution of genotypes in the US for rs1801133 is 49% CC (homozygous normal), 40% CT (heterozygous), and 11% TT (homozygous risk).7 [7]] In addition, vitamin B-12 deficiency is a common nutritional deficiency in both the US and the developing world,8 [8]] particularly for the elderly and vegetarians (approximately 3% of the US population).9 [9]]

2. Conduct a literature review to validate the selected study area

Numerous observational and prospective studies have found correlations between elevated plasma homocysteine levels and cardiovascular disease, renal disease, depression, anxiety, Alzheimer's disease, and colorectal cancer.10 [10]]11 [11]]12 [12]]13 [13]]14 [14]]

The majority of published literature relates to cardiovascular disease. A meta-analysis of 30 prospective and retrospective studies (involving a total of 5,073 ischemic heart disease (IHD) events and 1,113 stroke events) showed that a 25% lower homocysteine level was independently associated with an 11% lower risk of coronary heart disease and a 19% lower risk of stroke.10 [10]] Despite this, the causal relationship between elevated homocysteine and cardiovascular outcomes has not been conclusively proven. A large (n=12,064), recently published (June 2010), prospective, randomized study of patients with a prior myocardial infarction provided either folic acid or vitamin B-12 supplementation compared to placebo. The authors tracked coronary events over an average of 6.7 years. They found an average reduction of 28% in plasma homocysteine levels, but no difference

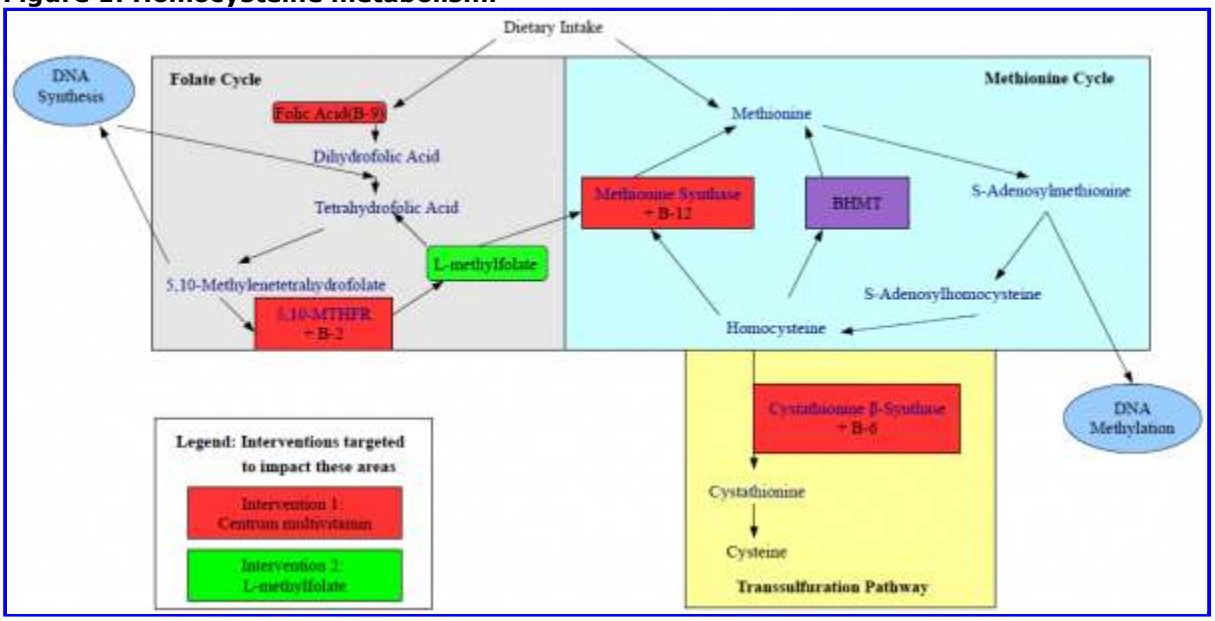
between the vitamin group and placebo group in the occurrence of coronary events or death.15 [15]] However a prospective, randomized study of the impact of homocysteine levels on the progression of atherosclerosis showed that folic acid supplementation led to reduced homocysteine levels and a regression in carotid intima-media thickness (CIMT) compared to an increase in CIMT for the placebo group.16 [16]]

Although more research is needed, there appears to be adequate evidence that low homocysteine levels are desirable, and may reduce risk for a number of conditions.

3. Analyze the underlying biological pathway and mechanism

The MTHFR pathway and homocysteine metabolism are the underlying biological mechanisms in this study. There are a number of ways in which genetic variation and intervention may impact homocysteine metabolism. Homocysteine is a naturally-occurring amino acid in the blood which is broken down (metabolized) through three interconnected pathways: the folate cycle, methionine cycle, and transsulfuration pathway (Figure 1).17 [17]] A detailed explanation of homocysteine metabolism is presented in the Supplementary Material. The pathways are fairly complex and involve two other enzymes in addition to MTHFR. It is possible that different interventions could impact overall homocysteine metabolism in different ways. In Figure 1, the red boxes show the different places where the first intervention (the inactive form of B-9, further described below) may impact the pathway; the green box shows where the second intervention (the active form of B-9) may impact the pathway.

Figure 1: Homocysteine metabolism.



[18]

4. Review related studies and clinical trials

Several clinical trials have been conducted to investigate the ability of interventions to lower homocysteine levels. A detailed review of nine studies was conducted and is presented in the 18 [19]]19 [20]] specifically compared folic acid with the active form of folate, 5-MTHF (5-methyltetrahydrofolate). Both found that the active formulation was most effective in reducing homocysteine levels (Akoglu 37% versus 24%;18 [19]] Lamers 19% versus 12%19 [20]]).

The existing clinical trials suggest that several factors may influence baseline homocysteine levels, in particular, age, health status, and genotype. Individuals who were older (especially over 50), had just experienced a major health disruption, or had one or more polymorphisms in the main MTHFR variant rs1801133, were more likely to have higher baseline homocysteine levels than those that did not (Supplementary Material: Figure 2). Further, the reduction proportion from the baseline level was greater for those individuals with higher initial levels of homocysteine.

5. Design the study protocol

The required genomic and phenotypic data were identified. Approximately 20 variants have been linked with homocysteine in genome-wide association studies.20 [21] MTHFR 677C>T (rs1801133) was selected as the variant with the strongest association to mild enzyme deficiency, and MTHFR 1298A>C (rs1801131) as the leading secondary variant.6 [6] The corresponding phenotypic measures selected were blood tests for homocysteine, vitamin B-12, and folate (vitamin B-9).

The type and timing of interventions were determined based on published literature. The background research on the MTHFR mechanism suggests that individuals with one or more polymorphisms may not be able to metabolize folic acid (the inactive form of B-9) into its active form (tetrahydrofolate or folate), as efficiently as individuals without a polymorphism. Therefore, the first intervention selected was administration of the inactive form of B-9, which is commonly present in over the counter B vitamin products such as Centrum multivitamins. The second intervention involved administration of the active form of folate (L-methylfolate), and the third was administration of the inactive and active forms together (also being tested by a current clinical trial).21 [22] The supplement contents were as follows: the Centrum multivitamin contained 2 mg of pyridoxine hydrochloride (B-6), 400 mcg of folic acid (B-9), and 6 mcg of methylcobalamin (B-12); the Life Extension Foundation L-methylfolate contained 1,000 mcg of L-methylfolate. The interventions were to be taken on a daily basis, at the same time of day, with food.

For this pilot phase of the study, the authors opted to use a crossover study design. Each individual tried each intervention, in sequence, essentially serving as his or her own control. While other homocysteine clinical trials typically had at least four-week periods for testing interventions, two representative trials confirmed that most of the observed effect occurred within the first two weeks.18 [19]19 [20] Therefore in the pilot study, two-week minimum intervention periods were selected with a two-week washout period at the beginning.

Participant recruitment was accomplished by talking about the study in public speaking engagements and targeting special interest groups such as the DIYbio, Quantified Self, Health 2.0, Singularity University, futurist, and life extension communities, particularly 23andMe clients. Some potential participants were motivated to sign up for 23andMe in order to participate in citizen science genomic studies. Many potential participants were interested, but did not join the study for a variety of reasons. The biggest barrier was the self-supported cost of blood tests and supplement interventions ($291). In a full-scale launch, other strategies will be necessary to target a more representative segment of the population.

6. Test the study design in a small non-statistically significant pilot

To test the study design, a small non-statistically significant pilot study was conducted in three phases: execution, results collection, and results analysis. The type of analysis that could be conducted on data results is presented here, realizing that the pilot cohort sample size (n=7) is not statistically significant.

Seven healthy men and women, ages 26-47, who had not taken any vitamin supplements for two weeks or more and met other usual study exclusion criteria, were enrolled in the study. The study was conducted from June to December 2010. Three participants cycled through the study at nearly exact two-week intervals. Three participants went through the study in two- to three-week periods on average, and one participant specifically tested three-week intervals. Six participants ordered blood tests from the Life Extension Foundation as they offered the lowest cost, and lab work orders were fulfilled at local LabCorp (standardized testing) facilities in the US. The remaining participant had homocysteine levels tested at a Japanese medical facility in Tokyo. The L-methylfolate supplement was mail-ordered by the group from the Life Extension Foundation. The Centrum multivitamin was purchased individually at local drug stores. All seven of the study participants collaborated in the study design or an active review of the protocol.

The study relied on self-reporting that the supplement protocol was followed. Participants tried to avoid unusual variance in nutrition, exercise, stress levels, sleep, and other behaviors. Participants looked up their genotype data for the relevant MTHFR variants in their 23andMe data files (genotyping is assumed to be accurate22 [23]), and recorded them in the study's public wiki (http://diygenomics.pbworks.com/MTHFR_Results). Blood test measurements from LabCorp PDFs or other reports were entered similarly in the public wiki. All participants were interested in full transparency and public accessibility of their genotypic and phenotypic study results, and allowed their names to be associated with the study. Participants were enumerated as Citizen 1, 2, etc with their initials.

Genotype results: Table 1 lists the pilot study participants and their genotype data for the two reviewed variants. For the main associated variant, rs1801133, three participants are homozygous normal (GG) and four are heterozygous (AG). Two of the heterozygous participants are also vegetarians/vegans which further increases their potential risk of vitamin B deficiency. For the secondary variant, rs1801131, two participants are homozygous normal (TT), four are heterozygous (GT), and one is homozygous for the polymorphism (GG). The table then includes maternal and paternal haplotype group information from 23andMe and demographic information regarding participant ethnicity, gender, age, and vegetarian status.

23andMe's genotype reporting method (all genotypes are listed as their forward strand values) means that sometimes their genotyping values need to be mapped to other conventions for interpretation. Commonly used resources for obtaining major/minor allele mappings indicate C/T as the major/minor alleles for rs1801133, and A/C for rs1801131 (dbSNP;23 [24]] SNPedia;24 [25]] HuGE Navigator7 [7]]). The mapping of the alleles from the standard resources to 23andMe would be that rs1801133 C/T is G/A in 23andMe data, and rs1801131 A/C is T/G in 23andMe data (C maps to G and vice versa; A maps to T and vice versa). The mapping was confirmed by comparing deCODEme, Navigenics, and 23andMe data files for the same individuals, and by reviewing genotype prevalence across multiple 23andMe files.

Table 1: Genotype results and demographic profiles.

Participant	rs1801133 (Normal/Risk: G/A)	rs1801131 (Normal/Risk: T/G)	Maternal haplogroup	Paternal haplogroup	Ethnicity	Gender	Age	Vegetarian status
Citizen 1 (AV)	AG	TT	J1b1a	R1b1b2a1a2	European	Male	36	Vegan
Citizen 2 (RM)	GG	GG	K1c2	R1b1b2a1a2*	European	Male	44	n/a
Citizen 3 (MS)	AG	GT	K1a	n/a	European	Female	42	Vegetarian
Citizen 4 (KH)	GG	GT	K1b2a	n/a	European	Female	47	n/a
Citizen 5 (CH)	GG	GT	K1b2a	R1b1b2a1a2f2	European	Male	35	n/a
Citizen 6 (TK)	AG	GT	n/a	n/a	Japanese	Male	38	n/a
Citizen 7 (WR)	AG	TT	J2a1a1	R1a1a*	European	Male	26	n/a

[26]

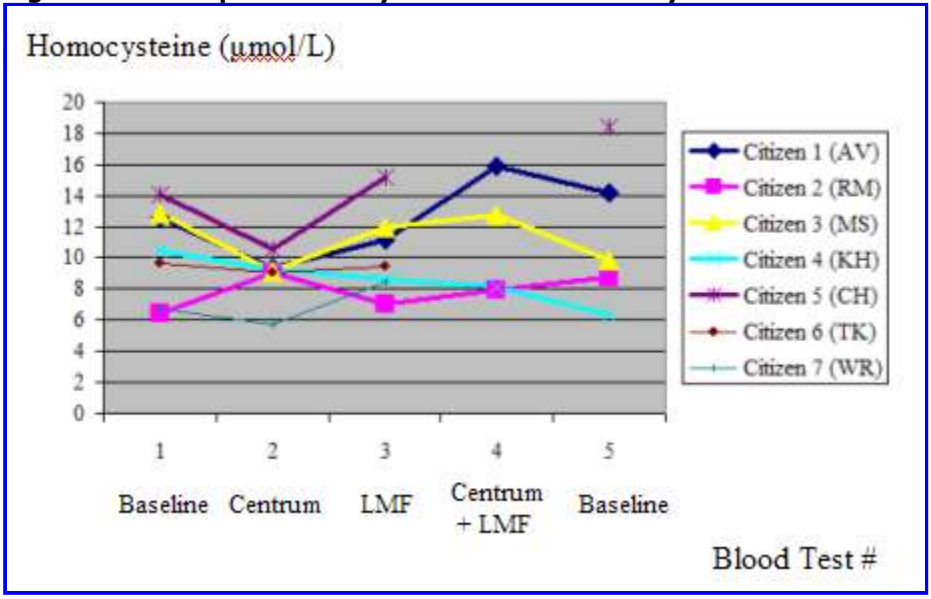
Phenotype results: Figure 2 and Table 2 illustrate how homocysteine levels shifted during the pilot study. Table 3 contains the blood test data for vitamin B-12. At baseline, homocysteine levels ranged from 6.4 – 14.1 µmol/L. The cohort mean was 10.4 (SD (standard deviation) 3.03), and was higher for vegan/vegetarian individuals with a polymorphism in rs1801133 (12.8 versus 9.5). After the first intervention (Centrum multivitamin), homocysteine went down for six individuals and up for one individual, and had a tighter range (5.7-10.6; mean 8.8; SD 1.50).

After the second intervention (L-methylfolate), homocysteine was higher for five individuals, including the four with a polymorphism, and lower for two (mean 10.3; SD 2.77). For the four individuals that included a plasma folate test, levels were at or above the high point of the test reference range (19.9 mg/mL) (Supplementary Material – Table 3) after the second intervention. After the third intervention (Centrum multivitamin + L-methylfolate), for three of the four participants who tried it, homocysteine was higher than with L-methylfolate alone. In the final step, five individuals completed an ending washout blood test, with three participants, including two with a polymorphism, having lower homocysteine levels than after the third intervention. The fourth participant had slightly higher homocysteine, and the fifth participant had markedly higher homocysteine as compared with the last intervention tried, the L-methylfolate. For three out of four participants that included the vitamin B-12 test (Table 3), B-12 levels went up an average of 17.5% after the first intervention, and one participant's went down 17%. B-12 movement then generally progressed flat or with a slight increase for the duration of the study.

An analysis of the test data results was performed to calculate the percent declines for each period from baseline and for each period relative to the prior period (smoothing was employed for one missing value). There was a 19% average decline in homocysteine for the best solution in any period versus the baseline (Table 2) and a 21% average decline in homocysteine for the best solution in any period versus the prior period. There was not a significant difference between homozygous normal

individuals (GG) for the main variant rs1801133 (18% average reduction) and heterozygous individuals (AG) (19% reduction), but the two vegan/vegetarian heterozygous individuals experienced a 28% average reduction. In a larger study that investigated genotype polymorphisms, a difference was found in having greater reduction in heterozygous subjects (12% versus 9%).25 [27]] The secondary variant, rs1801131, did not seem to have an impact, either in isolation or when considered together with rs1801133.

Figure 2: Participant homocysteine levels at study intervals.



[28]

Table 2: Participant homocysteine levels (µmol/L) and statistics at study intervals.

Participant	Study Interval					Greatest Decline
	1	2	3	4	5	
Citizen 1 (AV)	12.6	9.3	11.2	15.9	14.2	-26%
Citizen 2 (RM)	6.4	9	7	7.9	8.7	-22%
Citizen 3 (MS)	12.9	9.1	12	12.8	9.8	-29%
Citizen 4 (KH)	10.5	9.2	8.6	8.1	6.3	-40%
Citizen 5 (CH)	14.1	10.6	15.2	n/a	18.4	-25%
Citizen 6 (TK)	9.6	9.0	9.4	n/a	n/a	-6%
Citizen 7 (WR)	6.7	5.7	8.4	n/a	n/a	-15%
Average	*10.4*	*8.8*	*10.3*	*12.3*	*11.5*	*-19%*
Avg: rs1801133 GG (n=3)	*10.3*	*9.6*	*10.3*	*10.9*	*11.1*	*-18%*
Avg: rs1801133 AG (n=4)	*10.5*	*8.3*	*10.3*	*14.4*	*12.0*	*-19%*
Avg: rs1801133 AG & Vegetarian/Vegan (n=2)	*12.8*	*9.2*	*11.6*	*14.4*	*12.0*	*-28%*

[29]

Table 3: Participant vitamin B-12 levels (pg/mL) at study intervals.

Participant	Study interval				
	1	2	3	4	5
Citizen 1 (AV)	482	527	501	493	562
Citizen 2 (RM)	715	594	625	661	n/a
Citizen 3 (MS)	253	329	312	318	311
Citizen 5 (CH)	185	209	186	n/a	198

[30]

Discussion

The overall result seen in this was a 19% average reduction in homocysteine levels. While not statistically significant, this is consistent with the 23% average reduction achieved in reported clinical trials.

While a homocysteine range of 0.0-15.0 µmol/L is considered clinically normal, many scientists contend that lower levels are preferable. Suggested preferred levels are less than 11.4 µmol/L for men and less than 10.4 µmol/L for women in one paper cited.26 [31]] According to these measures, four out of the seven pilot participants had high baseline homocysteine levels which they were able to meaningfully reduce with supplement interventions.

The best intervention for five out of seven individuals was the regular B vitamin as opposed to the active form of B-9 (folate). The active form of B-9 worked better for one individual. The remaining individual, having a homozygous minor variant form of rs1801133, did not have high initial homocysteine and found that the active form of B-9 was better than the regular B vitamin, but that no intervention was best. This suggests that targeted solutions may be optimum for groups of individuals with certain profiles.

The biggest question was why the blood test values for homocysteine increased in five individuals (three with high baseline homocysteine; four with a polymorphism) after B-9 when other clinical trials found the active form of B-9 to be the superior intervention for lowering homocysteine. Participant behavior was generally consistent, and the reproducibility of testing results (within-person, between-person, and in labs) was also confirmed (Supplementary Material: Variability in homocysteine test results). Variation could have been introduced by a number of factors including the natural variability in homocysteine levels, variability in the active ingredient amounts in the intervention supplements, carryover effects between interventions (also evidenced by the lack of homocysteine levels returning to baseline levels in the final washout cases), or other complexities related to the homocysteine pathway.

This pilot study represents an example of how genomic-phenotypic-outcome research can be conducted in the era of personalized genetic data availability. It also illustrates the potential importance of including genomics as a data element in preventive medicine research, and illustrates the potential of using motivated individuals in citizen science genomic studies. Several participants also indicated the value of their experience and how it translated into post-study behavioral changes (Supplementary Material: Personal statements from study participants).

7. Identify the next steps for a full-scale launch of the study

There are a number of steps required for a full-scale cohort launch including implementing an independent ethical review and informed consent process, adjusting the study protocol, forming strategies for study financing and representative population targeting, and creating a data collection and analysis platform:

Independent Ethical Review and Informed Consent
Citizen science genomics is human subjects research and as such, should have independent ethical review and oversight. There are at least two independent review boards in the US which have indicated their willingness to discuss the potential review of citizen science studies: IRC, Independent Review Consulting, Inc., in Corte Madera, CA (http://www.irb-irc.com) and WIRB, the Western Institutional Review Board, in Olympia, WA (http://www.wirb.com). A related model of consumer genomic research conducted by 23andMe27 [32]] brought up a number of ethical issues,28 [33]] and ultimately IRC reviewed their study. As citizen science models develop, oversight models could evolve to include citizen ethicists, citizen review boards, health advisors (analogous to financial advisors), and insurance mechanisms for personal health experimentation communities. Informed consent would be an obviously required process to include in any full-scale human subjects research study.

Protocol Adjustment
The pilot study confirmed that the central point for investigation in a full-size cohort is whether interventions can be optimized according to the genotype-phenotype profiles of individuals. The pilot study also suggested that a regular B vitamin may be most effective in lowering homocysteine in individuals with high baseline homocysteine levels, especially in the presence of one or more rs1801133 polymorphisms. A number of structural changes could be made to improve scientific rigor in a broader launch, including participant blinding, inclusion of a placebo arm, and standardized

monitoring, testing, and interventions.

Strategies for Funding and Representative Population Targeting

To date, citizen science genomics has relied on the study recruitment pool being the limited number of individuals (approximately 100,000) who have subscribed to personal genotyping services. These individuals may not be representative of the population at large; the literature characterizes direct-to-consumer genomic customers as early adopters and self-driven information seekers.29 [34]]30 [35]] For widespread public health studies, it will be necessary to target a broad diversity of participants across multiple dimensions including information-seeking and action-taking propensity, ethnicity, and socioeconomic background. To accomplish this, traditional recruitment techniques could be used together with new patient-centered social media strategies.

Conclusion

This paper presents citizen science genomics, a research model contemplated for large-scale execution of preventive medicine research in crowdsourced cohorts. The model integrates personal genomic data with physical biomarker data to study the impact of various interventions on a predefined endpoint. Citizen science genomics could allow both traditional researchers and citizen scientists to access crowdsourced subjects who are ready to engage in research studies. Citizen scientists could be important resources as they increasingly have access to their health information, may be willing to contribute their data to various studies, have the interest and motivation to investigate conditions of personal relevance, and can leverage crowdsourced labor for data collection, monitoring, synthesis, and analysis, and new tool development.

Preventive medicine is a key public health challenge in the coming decades. New models like citizen science genomics are needed to answer important questions. Dropping prices and new technologies for collecting data regarding microbiomes, proteomics, imaging, personal tracking, and other information streams will increase the feasibility of this approach. Preventive medicine has the potential to take on new relevance and meaning through the use of citizen science genomic studies, as crowdsourced participants establish baseline and ongoing longitudinal measures for wellness, health maintenance, and customized intervention.

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Acknowledgments

We would like to acknowledge Takashi Kido and William Reinhardt for sharing their genotypic and phenotypic data, and many individuals who shared their genetic data for research purposes including David Orban, Geoffrey Shmigelsky, Eri Gentry, Todd Huffman, Fadi Bishara, Richard Leis, Jr., Mark Even Jensen, Misha Angrist, and several parties whom wish to remain anonymous. We would like to acknowledge Lyn Powell and Lucymarie Mantese for their advisory contribution and study support.

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Icelandic Population

Kári Stefánsson, MD

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Biography

Kári Stefánsson, MD, Dr. Med., founded deCODE in 1996 and serves as the company's President and CEO. Prior to deCODE, he was a Professor of Neurology, Neuropathology and Neuroscience at Harvard University and Director of Neuropathology at Beth Israel Hospital in Boston. During 1983 to 1993, he held faculty positions in Neurology, Neuropathology and Neurosciences at the University of Chicago.

Dr. Stefánsson, who received his M.D. and Dr. Med. at the University of Iceland, is board-certified in neurology and neuropathology in the U.S.

Author and co-author of over 250 papers, reviews and correspondence, Dr. Stefánsson was one of *Time* magazine's 100 most influential people of 2007. Also that year, *Newsweek* named him as one of 10 most important biologists of the 21 century. In addition, he was honored with the 2007 World Glaucoma Association Award. In 2009, he received the European Society of Human Genetics Award.

Notes

Extremes

Aravinda Chakravarti, PhD

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Biography

Aravinda Chakravarti, PhD is Director, Center for Complex Disease Genomics and Professor of Medicine, Pediatrics, Molecular Biology & Genetics, and, Biostatistics at the Johns Hopkins University School of Medicine and the Bloomberg School of Public Health. He is a Past-President of the American Society of Human Genetics, a member of the US National Academy's Institute of Medicine and an Honorary Fellow of the Indian Academy of Sciences. He has been a key participant and architect of the Human Genome, HapMap and 1000 Genomes project.

He received his doctoral degree in human genetics from the University of Texas Health Science Center in Houston in 1979 and continued postdoctoral training at the University of Washington in Seattle during 1979-80. He started his faculty career at the University of Pittsburgh (1980 – 1993), was the James H. Jewell Professor of Genetics at Case Western Reserve University (1994-2000), and the inaugural Director and Henry J. Knott Professor of the McKusick-Nathans Institute of Genetic Medicine at Johns Hopkins (2000-2007). Dr. Chakravarti is one of the founding Editors-in-Chief of *Genome Research* and *Annual Reviews of Genomics & Human Genetics,* serves on the Advisory and Editorial Boards of numerous international journals, boards, academic societies, the NIH and biotechnology companies. His research is aimed at genome-scale analysis of humans and computational analysis of gene variation and function to understand the molecular genetic basis of human disease.

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Notes

Bringing Genomic Sequence into the Clinic: Just Another Lab Value?

Howard J. Jacob, PhD

Director, Human and Molecular Genetics Center
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Professor, Department of Physiology & Pediatrics
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Biography

Professor Jacob received his Ph.D. in Pharmacology from University of lowa in 1989. He completed two parallel post-doctoral fellowships in functional genomics and molecular genetics/genomics at Harvard, Stanford and MIT with Victor J. Dzau, M.D. and Eric S. Lander, Ph.D. In 1992 he was appointed an Assistant Professor at Harvard Medical School at Massachusetts General Hospital. He joined the Medical College of Wisconsin in 1996 as an Associate Professor, Department of Physiology with full Professorship and Tenure in 2001. He was appointed the Founding Director of the Human and Molecular Genetics Center (HMGC) and awarded the Warren P. Knowles Chair of Genetics in 1999. Dr. Jacob along with Drs. Reza Shaker (PI) and Ellis Avner developed the Clinical Translational Science Institute at MCW. In 2009, he became the Vice Chair of Research in Pediatrics. Dr. Jacob is also an entrepreneur having co-founded the company, PhysioGenix Inc. in 1997 and Primary Genetics in 2010.

Under his leadership the Human and Molecular Genetics Center (HMGC) has grown from two faculty members to 30 and is one of the top funded genetic programs based on NIH funding. In 2009, the grant support for the HMGC grew by 46%, including a Center of Excellence in Genomic Sciences, and winning a Grand Opportunities (ARRA) grant. The HMGC has faculty from 9 different departments and has initiated numerous novel research programs. The HMGC also provides clinical services with faculty providing clinical genetics, pre-implementation genetic diagnosis, molecular diagnostics and recently genomic sequencing.

His research interests center on physiological genetics, genetic dissection of and analysis of common, complex disease, especially target organ damage associated with diabetes mellitus and hypertension. His laboratory is known for applying genomics, and high through-put phenotyping, genomic sequencing as well as comparative genomics and bioinformatics. Dr. Jacob previously chaired the Coordinating Committee for the Program for Genomic Applications (PGA), which consisted of 11 institutions and $33M annual budget funded by the National Heart, Lung and Blood Institute. Dr. Jacob currently participates in 8 NIH grants and 2 European Union grants. He has published 196 scientific papers, and 11 book chapters.

Notes

Bringing Genomic Sequence into the Clinic: Just Another Lab Value?

Howard J. Jacob, PhD

Ten years ago the human genomic sequence was released, followed by the mouse, then rat, and practically the entire zoo. Many species were selected to bridge evolutionary niches to provide important information about speciation and offering the ability to look at gene conservation to help identify which nucleotides were critical (these are unchanged across species). Other species were selected because they had key phenotypes that reflect a human disease, symptom or trait. The 1000 genome project and the increased capacity of the NextGen sequencers have made the prospect of individualized medicine a reality.

In July of 2009, the Medical College of Wisconsin embarked on personalized medicine to try and save the life of a young boy with severe Crohn's like symptoms that had resulted in over 100 surgeries and the loss of his colon. All standard therapeutic interventions had been deployed by clinical care team without success. As a last ditch effort, the lead physician Alan Mayer requested to have the patients genome sequenced. At the time, only an exome (all exons) was affordable. This was done, the sequenced analyzed, largely by Drs. Liz Worthey and David Dimmock. The mutation was found in the gene XIAP, previously not identified with GI, rather XLP2 a disease that is lethal without a bone marrow or cord blood transplant (1,2). The mutation was validation by Dr. James Verbsky using cells from the patient. The transplant was done by Dr. David Margolis and 7 months later the patient is doing remarkably well with no gut symptoms. We have since developed a clinical protocol, "the Milwaukee Approach" that is being used to end diagnostic odysseys. This program and what we have learned by applying genomic sequence in the clinic will be discussed.

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Notes

Wellderly Exomes

Sarah S. Murray, PhD

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Biography

Sarah Shaw Murray, PhD is Director of Genetics at Scripps Genomic Medicine, and Associate Professor of Translational Genomics at The Scripps Research Institute. Dr. Murray directs a high-throughput genotyping laboratory aimed at discovering genetic components of both various diseases and health, and determining risk profiles based on combinations of specific risk alleles in large prospective studies. Before her position at Scripps Genomic Medicine, Dr. Murray was the staff geneticist at Illumina, a San Diego biotech, where she played a large role in developing the technology that has enabled large-scale genome-wide genetic studies. Dr. Murray has a long history in both theoretical and applied genetics research. She has published over 60 articles in the human genetics literature that focus on the discovery and analysis of DNA sequence polymorphism. Dr. Murray received her Ph.D. from the University of Pittsburgh's Department of Human Genetics, and was a postdoctoral fellow at Case Western Reserve's Department of Genetics.

Notes

Rare Mendelian Traits

James R. Lupski, MD, PhD

Cullen Professor and Vice Chairman
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and Professor of Pediatrics
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Biography

James Lupski, MD, PhD, a physician-scientist at Texas Children's Hospital, is vice chair and professor of Baylor College of Medicine's Department of Molecular and Human Genetics.
Dr. Lupski, who also holds the Cullen Endowed Chair in Molecular Genetics at Baylor, trained to be a clinical scientist so that he could investigate the genetic origins of Charcot-Marie Tooth, a neurological disease that afflicted him as well as four of his siblings.

While an undergraduate at New York University (NYU), he spent two summers working with Nobel laureate James Watson, Ph.D., at the Cold Spring Harbor Laboratory. He subsequently was awarded both the B.A. and the Ph.D., at NYU. After receiving the M.D. degree at NYU School of Medicine, he completed postdoctoral studies at NYU and then a residency and medical genetics fellowship at Baylor.

In 1991, Dr. Lupski and colleagues identified the genetic cause, a copy number variation, in the most common variant of Charcot-Marie Tooth that affects 70% of patients, but not Dr. Lupski or his siblings, according to a 2010 Houston Chronicle article. Nine years later, however, he and his collaborators identified the genetic variation that triggered his and his siblings' disease in a paper published in the *New England Journal of Medicine*.

He was elected to the Institute of Medicine of the National Academies of Science in 2002.

Notes

Making sense of genomes

Nicholas J. Schork, PhD
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Scripps Health
Director of Biostatistics and Bioinformatics
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Dr. Schork is Director of Bioinformatics and Biostatistics at the Scripps Translational Science Institute; Director of Research, Scripps Genomic Medicine; and Professor, Department of Molecular and Experimental Medicine at The Scripps Research Institute. Dr. Schork's interest and expertise are in the areas of quantitative human genetics and genomics, especially the design and implementation of methodologies used to dissect the genetic basis of complex traits and diseases.

Prior to his appointments at Scripps, Dr. Schork was a Professor of Biostatistics and Psychiatry, and Co-Director of the Center for Human Genetics and Genomics at the University of California, San Diego from 2000-2007. From 1994-2000 Dr. Schork was an Associate Professor of Epidemiology and Biostatistics at Case Western Reserve University in Cleveland, Ohio and an Associate Professor of Biostatistics at Harvard University. Between 1999 and 2000 Dr. Schork took a leave of absence to conduct research as the Vice President of Statistical Genomics at the French Biotechnology company, Genset, where he helped guide efforts to construct the first high-density map of the human genome. Dr. Schork has been selected as a member of a number of scientific journal editorial boards, is a frequent participant in U.S. National Institutes of Health-related steering committees and review boards, and has also been on the advisory board of five companies.

Dr. Schork is currently Director of the Bioinformatics and Biostatistics Core of the NIA-sponsored Longevity Consortium and a member of the NHGRI's Genetic Association Information Network (GAIN) data analysis committee. He has published over 300 scientific articles and book chapters on the analysis of complex, multifactorial traits and diseases. Dr. Schork earned a B.A. in Philosophy, an M.A. in Philosophy, an M.A. in Statistics, and a Ph.D. in Epidemiology all from the University of Michigan in Ann Arbor, Michigan.

Notes

Making sense of genomes
Nicholas J. Schork, PhD

Modern DNA sequencing technologies have made it possible to sequence large portions of, if not entire, individual human genomes. This fact raises very thorny questions about how to interpret the differences between individual genomes with respect to phenotypic differences between individuals. In this talk, an overview of some of the complexities of the human genome are discussed as well as how one can approach the identification of important, phenotypically-relevant variants in the human genome.

Important concepts to be discussed include:

- Certain problems plague the sequencing of entire individual human genomes.
- There are limits to what one can identify in the human genome as influencing disease susceptibility with certain strategies, suggesting new strategies are needed.
- Rare variants in the genome can influence phenotypic expression.
- Humans are diploid and hence actually possess two genomes: one inherited from the mother and one from the father.
- Many elements in the human genome, when perturbed, can influence, e.g., disease susceptibility.
- The future will clearly be one in which individual human genome sequencing is routine and this raises important questions about how that sequence information will be used.

Notes

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Notes

The Genetics of Multiple Sclerosis: SNPs to Pathways to Pathogenesis

Stephen L. Hauser, MD
Professor and Chair, Department of Neurology
University of California, San Francisco
San Francisco, California

Biography

Stephen L. Hauser, MD is the Robert A. Fishman Distinguished Professor and Chair of the Department of Neurology at UCSF. He is a graduate of MIT (Phi Beta Kappa) and Harvard Medical School (Magna Cum Laude). He trained in internal medicine at the New York Hospital–Cornell Medical Center, in neurology at the Massachusetts General Hospital (MGH), and in immunology at Harvard Medical School and the Institute Pasteur in Paris, France, and was a faculty member at Harvard Medical School before moving to UCSF.

A neuroimmunologist, Dr. Hauser's research has advanced our understanding of the genetic basis, immune mechanisms, and treatment of multiple sclerosis. Dr. Hauser is a fellow of the American Academy of Arts and Sciences and the American Academy of Physicians, a member of the Institute of Medicine of the National Academy of Sciences (currently Chair of the Committee on Gulf War and Health Outcomes), an editor of the textbook Harrison's *Principles of Internal Medicine*, and editor-in-chief of *Annals of Neurology*. He is a former President of the American Neurological Association and President of the Medical Staff at UCSF. He also serves on several scientific advisory boards for nonprofit organizations. Dr. Hauser has received numerous awards and honors for his work, including the Jacob Javits Neuroscience Investigator Award and the John Dystel Prize for Multiple Sclerosis Research. In April 2010 Dr. Hauser was appointed by President Obama to the Presidential Commission for the Study of Bioethical Issues charged with advising the President on issues that may emerge from advances in biomedicine and related areas of science and technology.

Notes

Tumour Genome Sequencing: a Path to Personalized Medicine

David R. Bentley, DPhil, FMedSci
Vice President and Chief Scientist
Illumina Cambridge
United Kingdom

Biography
David Bentley is Vice President and Chief Scientist at Illumina Inc., developing new DNA sequencing technology for fast, accurate sequencing of complex genomes. His research interests include the study of human sequence variation and its impact on health and disease.

David was previously the Head of Human Genetics and a founder Member of the Board of Management at the Wellcome Trust Sanger Institute. He played a leading role in the Human Genome Project, The SNP Consortium, the International HapMap Project, and initiation of the Wellcome Trust Case-Control Consortium multi-disease Genome-Wide Association Study.

David graduated with an M.A. in Natural Sciences from Cambridge and a D.Phil from Oxford. During his career, he has been Senior Lecturer at London University and has published over 150 articles in peer-reviewed journals.

Notes

Understanding Life Codes and Changing Medicine

Juan Enriquez, BA, MBA
Managing Director, Excel Venture Management
Chairman and CEO, Biotechonomy LLC
Co-founder, Synthetic Genomics Inc.
Boston, Massachusetts

Biography

Mr. Enriquez is an experienced business leader, author, and academic who is recognized as one of the world's leading authorities on the economic and political impacts of life sciences. He is a Managing Director in Excel Venture Management, a venture capital firm that invests in life science companies whose products/services significantly change their field.

He was the founding director of Harvard Business School's Life Sciences Project. He then founded Biotechonomy LLC, a life sciences research and investment firm, where he remains as Chairman and CEO. In July of 2005, he co-founded Synthetic Genomics, Inc., a synthetic biology company focused on developing and commercializing genomic-driven solutions to address global energy and environmental challenges. He has been an active investor in early-stage private companies in the biotechnology and information sciences sectors. While at Harvard, he wrote various articles and case studies, won a McKinsey Prize, and published the best-selling *As the Future Catches You*, an analysis of the impact of genomics on business and society. His most recent publication is an eBook co-authored with Dr. Steve Gullans, *Homo Evolutis: A Short Tour of our New Species*, which describes a world where humans increasingly shape their environment, themselves, and other species. Mr. Enriquez serves on a number of boards including Cabot Corporation, Synthetic Genomics, Catch.com, Shape Up The Nation, the Public Interfaces Steering Committee of the Division of Earth & Life Sciences of the National Academy of Sciences, The Chairman's International Council of the America's Society, and the Visiting Committee of Harvard's David Rockefeller Center.

He earned a BA and MBA from Harvard, with Honors.

Cancer Genomics: Future Directions

Robert L. Strausberg, PhD

Executive Director of Collaborative Sciences
Ludwig Institute for Cancer Research Ltd
New York, New York

Biography

Dr. Bob Strausberg is Executive Director of Collaborative Sciences for the Ludwig Institute for Cancer Research. He also serves as Adjunct Professor in the Neurological Surgery Department at Johns Hopkins University, where he is co-Director of the Ludwig Collaborative Laboratory for Cancer Biology and Therapy.

Previously, he was Deputy Director of the J. Craig Venter Institute (JCVI), overseeing the daily operations of the Institute. He also led the Human Genomic Medicine group at the JCVI where he conducted studies of human genomes based on whole genome analysis, as well as the exome, transcriptome, and the epigenome. Dr. Strausberg served as Principal Investigator for NIAID funded centers at the JCVI including the Microbial Sequencing Center, as well as for the Human Microbiome Project. In 2004, he was recruited from the NCI to become Vice President for Research at The Institute for Genomic Research (TIGR) subsequently merged with the JCVI.

Prior to joining TIGR, Dr. Strausberg was Director of the National Cancer Institute's Cancer Genomics Office, where he led the NCI Cancer Genome Anatomy Project and NIH Mammalian Gene Collection, programs that have served as platforms for the international biomedical research community. At the NIH, Dr. Strausberg also was Chief of the DNA Sequencing Technology Development Branch for National Center for Human Genomic Research (now the NHGRI). Dr. Strausberg received his Ph.D. in Developmental Biology from Ohio State University and performed post-doctoral research at the University of Texas Southwestern Medical Center at Dallas.

Notes

Cancer Genomics: Future Directions

Robert L. Strausberg, PhD

Over the past several decades genetic and genomic analysis has revealed alterations that contribute to the development and progression of cancer. Spurred by advances in human genomics, and with rapid advances in DNA sequencing technologies and methodologies, new opportunities have emerged to look more comprehensively at the multitude of changes that occur in cancers. With those technologies and methods accessible, and together with advancing knowledge of the coding potential of the human genome, scientists have widened their searches for genomic alterations that might be causative to cancers.

Initially, these more comprehensive approaches focused on gene families. For example, based on successes in targeting tyrosine kinases, several studies focused on identification of additional members of that family that might serve as new targets for cancer intervention.

Even bolder strategies have recently been pursued, such that thousands of genes (and most recently the entire set of protein-encoding genes) have been sequenced in various forms of cancer. These studies have focused on comparisons of tumor and normal DNA from the same patient, thereby revealing somatic alterations that are cancer-specific. Such approaches have already provided much insight to the genomic basis of cancers. In a limited number of cases, frequently occurring gene mutations that are drivers of cancer have been revealed, suggesting potential new opportunities for intervention. These studies have also revealed the complexity of cancers, and that there are various genomic paths to cancers that may appear to be very similar, but are actually quite distinct at the molecular level. Moreover, many genomic changes occur in only a small subset of tumors, and often it remains a challenge to determine which of those alterations actually contribute to cancer development, and how the multitude of changes might act in a synergistic manner.

With the introduction of NextGen sequencing technologies and beyond, the opportunity for cancer genome-based discovery has increased much further to include, for example, comprehensive analysis of complete genomes, as well as epigenomes, and transcriptomes. An opportunity and challenge is the integration of such datasets to reveal drivers of cancer, including genetic and environmental components, and to learn how intervention might be improved.

This overview presentation will discuss features of cancer that are being revealed through genomic analysis of cancer, how this new data has the potential to inform cancer intervention, as well as the challenges that remain to be addressed.

Suggested reading for this presentation is the following review article that is accessible online:

Strausberg RL and Simpson, AJG (2010) Whole-genome cancer analysis as an approach to deeper understanding of tumour biology. Br J Cancer 102(2):243-8. PMID: 20029419

Notes

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Notes

Whole Genome Sequencing in Breast Cancer

Elaine R. Mardis, PhD
Associate Professor, Genetics and Molecular Microbiology
Co-Director of The Genome Center
Washington University
Washington University School of Medicine at Washington University Medical Center
St. Louis, Missouri

Biography

Dr. Elaine Mardis graduated Phi Beta Kappa from the University of Oklahoma with a B.S. degree in zoology. She then completed her Ph.D. in Chemistry and Biochemistry in 1989, also at Oklahoma. Following graduation, Dr. Mardis was a senior research scientist for four years at BioRad Laboratories in Hercules, CA.

In 1993, Dr. Mardis joined The Genome Center at Washington University School of Medicine. As Director of Technology Development, she helped create methods and automation pipelines for sequencing the Human Genome. She currently orchestrates the Center's efforts to explore next generation and third generation sequencing technologies and to transition them into production sequencing capabilities.

Dr. Mardis has research interests in the application of DNA sequencing to characterize cancer genomes. She also is interested in facilitating the translation of basic science discoveries about human disease into the clinical setting.

Dr. Mardis serves on several NIH study sections, is an editorial board member of *Genome Research,* and acts as a reviewer for *Nature* and *Genome Research*. She serves as chair of the Basic and Translational Sciences Committee for the American College of Surgeons Oncology Group, an NCI funded cooperative group. She serves on the scientific advisory boards of Pacific Biosciences, Inc. and Edge Biosciences, Inc. Dr. Mardis received the Scripps Translational Research award for her work on cancer genomics in 2010, and has been named a Distinguished Alumni of the University of Oklahoma College of Arts and Sciences for 2011.

Notes

Whole Genome Sequencing in Breast Cancer

Elaine R. Mardis, PhD

Our laboratory has adapted next-generation DNA sequencing methods and comprehensive bioinformatic analysis to compare the genomes of matched tumor and normal samples in pursuit of identifying those somatic mutations potentially important in the disease development and course. In solid tumors of heterogeneous nature, such as breast cancer, these analyses pose specific challenges but can yield incredibly insightful results. One study is examining pre- and post-treatment samples from a clinical trial that evaluated the impact of aromatase inhibitors on estrogen-receptor positive breast tumors relative to surgical outcome. Whole genome studies of these samples have begun to reveal how patients who respond to the drug by tumor mass reduction differ from those whose tumors remain unchanged or grow in size. Evaluating the allelic frequency changes of specific mutations between pre- and post-treatment samples also indicates the impact of the drug on tumor heterogeneity. A second type of study evaluates the alterations in heterogeneity that occur upon the development of metastatic disease. These studies build on our existing work in tumor progression by comparing the primary tumor genome with those of coincident metastatic sites. Taken together, the range of genomic motifs in breast cancer is striking, and indicates to some extent the diversity in outcomes across the disease spectrum.

Notes

Cancer Genomics

Thomas J. Kipps, MD, PhD

Evelyn and Edwin Tasch Chair in Cancer Research
Professor of Medicine and Deputy Director, Research
Moores UCSD Cancer Center
University of California, San Diego
La Jolla, California

Biography

Thomas Kipps, M.D., Ph.D., is Professor of Medicine and the Evelyn and Edwin Tasch Chair in Cancer Research at UC San Diego and Deputy Director for Research Operations at the Moores Cancer Center at UCSD.

A major focus of Dr. Kipps' research is chronic lymphocytic leukemia (CLL). His laboratory was the first to define a role for microRNA or ultra-conserved non-coding RNA in any malignancy. He and his collaborators reported the results in 2007 paper in *Blood*. The investigation involved in the CLL Research Consortium, which he established and currently directs.

After receiving the Ph.D. in Immunology and the M.D. at Harvard University, he completed residency and fellowship training in Internal Medicine, Hematology and Genetics at Stanford University.

Notes

New Insights from Cancer Sequencing

Samuel Levy, PhD
Director of Genomic Sciences
Scripps Translational Science Institute
Scripps Health and The Scripps Research Institute
La Jolla, California

Biography

Samuel Levy, PhD, Director of Genomic Sciences, has an ongoing interest in characterizing and refining the structure and function of the genome and epigenome in human populations. His work at the Scripps Translational Sciences Institute involves characterizing genomic changes in tumors to enable the development of specific treatment regimens and determining how genomic modifications impact our response to different drug therapies.

During his tenure as Director and Professor in Human Genomics at the J. Craig Venter Institute, Dr. Levy was the leading scientist on the first published diploid genome sequence of a human, J. Craig Venter, Ph.D., additionally he led studies involving the functional characterization of DNA variants in protein coding and cis-regulatory regions prior to joining STSI in 2009. Dr. Levy also provided a clinical sequencing pipeline for the National Heart, Lung and Blood Institute (NHLBI) and has worked with over 15 different research groups over the last five years providing high throughput discovery of DNA variants on clinical samples for disease association studies.

Prior to joining JCVI in 2002, Dr Levy worked at Celera Genomics for a three-year period and was involved in developing computational tools for gene discovery and functional annotation in the *Drosophila* and human genome sequences. Prior to his work at Celera Genomics, from 1989-1999, Dr. Levy was a postdoctoral worker and then independent investigator in the Molecular, Cellular and Developmental Biology (MCDB) Department at the University of Colorado at Boulder. At MCDB, he worked on a variety of projects ranging from extracellular Golgi-based trafficking in plants, plant cell wall development and structure-function relationship in complex carbohydrates using a range of approaches involving biochemistry, cell biology and computational chemistry.

In 1982, Dr. Levy received a B.Sc. in Molecular Biophysics at the University of Leeds, UK, in 1986 was awarded the Ph.D., in cell and computational biology at the University of Bristol, UK. He was in receipt of a NATO/SERC postdoctoral fellowship for a two-year period studying structural and biochemical changes in plant cell walls at the École Normale Supérieure, France.

Notes

The Oncologists' 6th Vital Sign – A Context of Vulnerability

Daniel D. Von Hoff, MD, FACP
Physician-in-Chief, Senior Investigator
Translational Genomics Research Institute
Clinical Professor of Medicine
University of Arizona
Chief Scientific Officer
Scottsdale Healthcare
Phoenix, Arizona

Biography

Daniel Von Hoff, M.D., F.A.C.P., Physician-in-Chief and Distinguished Professor at the Translational Genomics Research Institute (TGen) and Chief Scientific Officer at Scottsdale Healthcare, also is Professor of Medicine at both Mayo Clinic in Arizona and the University of Arizona College of Medicine. Dr. Von Hoff's research concentrates on the development of targeted therapies for patients with pancreatic and other advanced cancers. He and his colleagues have been involved in the early stages of the development of many current agents against cancer including mitoxantrone, fludarabine, paclitaxel, docetaxel, gemcitabine and CPT-11.

Currently serving a six-year term on the National Cancer Advisory Board, Dr. Von Hoff has been a member of the FDA's Oncology Advisory Committee and is a past President of the American Association for Cancer Research (AACR). He also is a former member of the Board of Directors of both the AACR and the American Society of Clinical Oncology.

Dr. Von Hoff, a Fellow of the American College of Physicians, founded and is Editor Emeritus of *Investigational New Drugs - The Journal of New Anticancer Agents* and is Editor-in-Chief of *Molecular Cancer Therapeutics*. He was the Associate Editor for two AACR journals, *Clinical Cancer Research* and *Cancer Research*.

After receiving the M.D. degree at Columbia University College of Physicians and Surgeons, he completed his internship and residency at the University of California, San Francisco and then a fellowship at the National Cancer Institute. While a Professor in the Departments of Medicine and Cellular and Structural Biology at the University of Texas Health Science Center, San Antonio, he was the Founding Director of the Institute for Drug Development at the Cancer Therapy and Research Center in San Antonio.

Dr. Von Hoff, who has published over 515 papers and 125 book chapters, is a founder of ILEXTM Oncology, Inc., which was acquired by Genzyme.

Notes

Genomics and Drug Development

Dennis A. Carson, MD

Director, Moores Cancer Center
Chugai Pharmaceutical Chair in Cancer
Associate Dean for Health Sciences
University of California, San Diego
La Jolla, California

Biography

Carson earned his medical degree at Columbia University, completed his residency at UCSD, and received post-doctoral training at the Salk Institute, the National Institutes of Health and UCSD. He has published over 485 scientific papers, is an inventor on more than 70 issued U.S. patents, and has founded six biotechnology companies working in the oncology field (Vical, Triangle Pharmaceuticals, Dynavax, Salmedix, Telormedix and Wintherix). He is a member the National Academy of Sciences, the Institute of Medicine, and the American Academy of Arts and Sciences.

Carson is perhaps best known for developing 2-chlorodeoxyadenosine, or 2-CdA, for the treatment of hairy cell leukemia. This drug is the treatment of choice for this disease and has resulted in long term, complete remissions in about 75 percent of patients.

Carson is convinced that novel partnerships between the public and private sectors are necessary to develop the next generation of anticancer treatments.

As Cancer Center Director his priorities are to develop strong, formalized relationships with the biotechnology and pharmaceutical communities, to speed the translation of basic science discoveries into new treatments for cancer patients.

Notes

Eric J. Topol, MD

Director, Scripps Translational Science Institute
Chief Academic Officer, Scripps Health
Professor of Translational Genomics, The Scripps Research Institute
The Gary and Mary West Chair of Innovative Medicine
La Jolla, California

Biography

Eric J. Topol, MD is the Director of the Scripps Translational Science Institute, a National Institutes of Health funded program of the Clinical and Translational Science Award (CTSA) Consortium focused on advancing individualized medicine. He is the Chief Academic Officer of Scripps Health, a Senior Consultant cardiologist practitioner at Scripps Clinic, and Professor of Translational Genomics at The Scripps Research Institute.

He received his BA degree with highest distinction from the University of Virginia in 1975, his MD with Honor from the University of Rochester School of Medicine and Dentistry in 1979, and completed internal medicine residency at University of California, San Francisco and cardiology fellowship at Johns Hopkins. He then was on the faculty at the University of Michigan from 1985-1991 and was a tenured Professor of Medicine before moving to Cleveland.

In Cleveland, he chaired the Department of Cardiovascular Medicine at Cleveland Clinic for 15 years and raised its status to rank #1 by US News and World Report for 11 consecutive years, served on the faculty of Case Western as a professor in genetics, and was Founder and Provost of the Cleveland Clinic Lerner College of Medicine. His work in the genomics of heart attack has led to discovery of key genes recognized by the American Heart Association twice as top 10 research advances. As a leader in clinical trials of novel therapeutics, he administered recombinant t-PA to the first patient in 1984, pioneered and led the clinical development of clopidogrel (Plavix), bivalirudin (Angiomax), and abciximab (ReoPro). He was the first physician to publish safety concerns on the cardiovascular risk of Vioxx. He has over 1000 original peer reviewed publications, and has edited over 30 books, including the Textbook of Interventional Cardiology (6^{th} ed), and the Textbook of Cardiovascular Medicine (3^{rd} ed), and a new book for consumers entitled Digitizing Man due out in 2011. He has been a medical innovator in wireless medicine, including wireless ECG telemetry, vital signs, and as a Founder and Vice-Chairman of the West Wireless Health Institute. Dr. Topol has been elected to the Institute of Medicine of the National Academy of Sciences, the American Association of Physicians and recognized by the Institute of Scientific Information (ISI) to be in the top 10 cited biomedical researchers in medicine in the past decade.

Notes

View from the Outside II
Brook Byers

Partner
Kleiner Perkins Caufield & Byers
Menlo Park, California

Biography

Brook Byers has been a venture capital investor since 1972. He has been closely involved with more than fifty new technology based ventures, over half of which have already become public companies. He formed the first Life Sciences practice group in the venture capital profession in 1984 and led KPCB to become a premier venture capital firm in the medical, healthcare, and biotechnology sectors. KPCB has invested in and helped build over 110 Life Sciences companies which have already developed hundreds of products to treat major underserved medical needs for millions of patients.

Brook was the founding President and then Chairman, of four biotechnology companies which were incubated in KPCB's offices and went on to become public companies with an aggregate market value over $8 Billion. He is currently on the Board of Directors of nine companies, most recently joining CardioDX, Crescendo, Genomic Health Incorporated, Five Prime Therapeutics, OptiMedica, Pacific Biosciences, Inc., Tethys, Veracyte and XDx, Inc. He was formerly a Director of Idec Pharmaceuticals (Chairman), Athena Neurosciences (Chairman), Signal Pharmaceuticals, Arris Pharmaceuticals, Onyx Pharmaceuticals, Hybritech (Chairman), Genprobe and others. These companies have pioneered the medical use of molecular biology, monoclonal antibodies, personalized medicine, molecular diagnostics, genomics and sequencing.

Brook was President and a Director of the Western Association of Venture Capitalists. He is a currently a Board member of the University of California at San Francisco Medical Foundation, the New Schools Foundation, Stanford's Bio-X Advisory Council and the Stanford Eye Council. He was Co-Chair of the five year, $1.4 billion, UCSF Capital Campaign. In 2007, he was awarded the "UCSF Medal" as their honorary degree equivalent. In 2008, he was elected a Fellow of the American Academy of Arts and Sciences. In 2009, he received the Lifetime Achievement Award from the National Venture Capital Association. In May, 2010, he received an Honorary Ph.D. from Georgia Tech.

He was formerly a Director of the Entrepreneurs Foundation, the California Healthcare Institute, the Asian Art Museum in San Francisco, the Stanford Graduate School of Business Advisory Council, That Many May See (UCSF) Vision Research Foundation (Chairman), the Georgia Tech Advisory Board and was a founder of TechNet.

Raised in Atlanta, Georgia, Brook graduated in Electrical Engineering from Georgia Tech and received an MBA from Stanford.

Notes

Scientists and the public: communication breakdown?

Amy Harmon
Pulitzer Prize-winning National Correspondent
The New York Times
New York, New York

Biography
Amy Harmon is a New York Times national correspondent and two-time Pulitzer Prize winner who covers the impact of science and technology in American life. In 2008, Ms. Harmon won a Pulitzer for her series, "The DNA Age," which explored the rise of new genetic technology through the personal stories of people who were grappling with its myriad benefits and burdens.

Among other subjects, Ms. Harmon has written about a high school biology teacher teaching evolution to students who believe the Bible's creation story is fact, how webcams are changing relationships between grandparents and grandchildren, the genetic children of sperm donors, and the embrace of robotic companions among the elderly.

Ms. Harmon's journalism career began at The Michigan Daily, the student newspaper at the University of Michigan, where she earned a B.A. in American Culture in 1990. After graduation, her prowess at tabulating auto sales in the Los Angeles Times' Detroit bureau earned her a transfer to Los Angeles, where she wowed her editors with an incredible skill she had picked up in college: how to send e-mail. She somehow parlayed that into a beat she called the sociology of technology, and in 1997, The New York Times hired her to expand on it. Ms. Harmon's article about two Internet entrepreneurs, one white and one black, was part of a Times series on race relations that won a Pulitzer in 2001.

That was her first experience with long-form narrative writing, which she continues to labor over despite research proving that it is futile to try to hold the attention of Web readers for more than three sentences. (She holds out hope for the infinitely more patient mobile device user). Ms. Harmon's story, "Facing Life with a Lethal Gene," is included in "The Best American Science Writing 2008." She lives with her husband and their daughter in New York City.

Notes

The New York Times

NEW YORK, MONDAY, FEBRUARY 22, 2010

Urgent Chase for a Cure

Doggedly Testing a New Drug to Treat Melanoma

By AMY HARMON

PHILADELPHIA — His patient, a spunky Italian-American woman in her 60s, was waiting in an exam room down the hall for the answer: Was the experimental drug stopping her deadly skin cancer?

But as Dr. Keith Flaherty read out the measurements of her tumors from the latest CT scan, he could not keep the distress from his voice.

"She's worse," he said to the clinical trial nurse at the University of Pennsylvania's melanoma clinic.

Like the 17 other patients on the drug trial — the corporate lawyer, the receptionist with young children, the Philadelphia philanthropist — the woman known in the trial as Patient 18 was going to die, most likely within months.

In the exam room, her gratitude for his failed efforts to save her tore at his heart.

He had been so optimistic. A radical departure from standard chemotherapy, the drug was designed to reverse the effect of a genetic mutation particular to the patient's tumors. The approach represented what some oncologists see as the best bet for attacking all types of cancer.

ÁNGEL FRANCO/THE NEW YORK TIMES

Dr. Keith Flaherty

And as he returned to his office that autumn afternoon two years ago, Dr. Flaherty was already calculating the next step: he wanted to test the drug at a more potent dose before giving it to more patients in a larger trial. It would require retooling the drug in a costly and complicated task that might not work, and he would have to make his case to two companies that had already poured hundreds of millions of dollars into the drug and were eager to move it forward.

"This," he insisted to colleagues, "is the best drug we're going to get."

Dozens of such "targeted" drugs are emerging from the laboratory, rooted in decades of research and backed by unprecedented investment by pharmaceutical companies, which stand to profit from drugs that prolong life even by weeks.

But putting them to their truest

Continued on Page A12

TARGET CANCER

A Doctor's Trial

First of three articles.

From Page 1

test falls to a small band of doctors committed to running experimental drug trials for patients they have no other way to heal.

At a time when cancer still kills one in four Americans, it is a job that requires as much hubris as heart. To chronicle the trial of the drug known as PLX4032 is to ride a roller coaster of breakthroughs and setbacks at what many oncologists see as a watershed moment in understanding the genetic changes that cause cancer.

Over three tumultuous years, Dr. Flaherty saw patients who drove hundreds of miles for their monthly dose, and one who arrived barely able to walk. Some took 32 pills a day. When it became clear they were not absorbing the drug, he asked them to take the pills with high-fat foods like hamburgers and eggs, which might help dissolve them.

At academic conferences, he clashed with other oncologists who warned that targeted therapy had almost never had long-lasting results. At Penn, he badgered laboratory researchers whose animal tests might provide early clues for how a drug would behave in his patients.

And always, he ended up on his BlackBerry, e-mailing, calling, cajoling the drug makers to commit even more resources to the new category of drugs he so deeply believed in.

A five-and-a-half-foot streak of outsize energy, Dr. Flaherty, 39, seemed buoyed by an innate optimism and a faith in the scientific logic underlying the approach.

But at his clinic, where he gave vials of pills to patients whose tumors were often erupting, black and bumpy across their arms and legs, he told them only what he believed to be true.

"This," he said, "is our best shot."

The Driver Gene

In many ways, Keith Flaherty had been training to run the trial of this drug since his residency in the late 1990s at Brigham and Women's Hospital in Boston.

There he grew to despise chemotherapy, which rarely cured cancer in its advanced stages, even as he learned to dispense it. The mainstay of cancer treatment for half a century, the chemotherapy drugs attacked all fast-growing cells, poisoning those that grow fast normally as well as the cancerous ones.

Drawn to oncology for the reason other residents often rejected it, Dr. Flaherty found strength in the intensity of treating patients who knew that they, and he, were fighting for their lives.

But he also chose the field because advances in understanding cancer's molecular biology convinced him it might finally be possible to cure the disease — and he wanted to have a hand in it.

Healthy cells turned cancerous, biologists knew, when certain genes that control their growth were mutated, either by random accidents or exposure to toxins like tobacco smoke and ultraviolet light. Once altered, like an accelerator stuck to the floor, they constantly signaled cells to grow.

What mattered in terms of treatment was therefore not only where a tumor originated, like the lungs or the colon, but also which set of these "driver" genes was fueling its growth. Drugs that blocked the proteins that carried the genes' signals, some believed, could defuse a cancer without serious side effects.

Dr. Flaherty arrived at Penn for a fellowship in the fall of 2000 just as one of the first such drugs, Gleevec, was inducing complete remission in patients with a rare leukemia. Yet many oncologists remained skeptical that its success could be replicated in common cancers that were more aggressive and genetically complex.

And there was no guarantee that the pharmaceutical industry, which already viewed cancer as too fragmented a market, would invest in developing drugs tailored to what were probably dozens of driver genes that had yet to be identified.

Dr. Flaherty, however, was convinced that what he called the "targeted therapy revolution" was around the corner. It was the only real hope, he told friends, colleagues, medical students and whoever would listen, "because it is based on what makes cancer tick."

A career that combined treating patients with testing drugs would be far less lucrative than private practice. Such doctors are not allowed to have a financial stake in a drug, for obvious reasons. But Dr. Flaherty, the son of two medical researchers, had always wanted to pursue research.

He accumulated an encyclopedic knowledge of the targeted drugs in development and gravitated to melanoma, where the absence of reliable treatments made patients eager to try experimental ones.

The cancer, which struck 70,000 Americans last year, is easily treatable in its earliest stages, but almost always fatal within a year once it spreads beyond the skin.

In early 2002, when Dr. Flaherty started seeing patients on his own, the available trials still centered on chemotherapy drugs, and he sought to soften recitation of their toxic side effects — nausea, anemia, infection, hair loss — by mocking his own lack of hair.

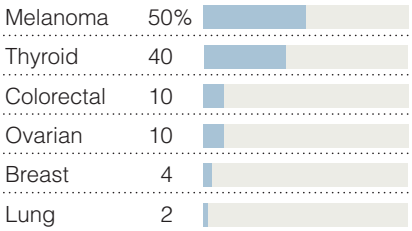
"I've got bigger problems than hair loss," many patients said.

"Tell me about it," the doctor replied, invariably eliciting laughter.

He wore bow ties under his lab coat, and told patients to leave their health to him. Yet when grateful families gave him money for research, or sent him bow ties to add to his collection, he felt like a fraud. "What I do is palliative care," he told his wife, a primary-care physician, in a form of self-indictment.

Cancer Patients With a B-RAF Mutation

The B-RAF mutation is most common in melanoma patients but can also be found in other cancers.



Sources: Plexxikon; Wellcome Trust Sanger Institute THE NEW YORK TIMES

So when an article in the journal Nature brought news of what was almost surely one of the driver genes in melanoma in the spring of 2002, Dr. Flaherty could hardly contain himself. British scientists analyzing hundreds of tumor samples, he read, had found the same gene mutated in more than half of melanomas, and smaller numbers of other cancers as well. It was called B-RAF.

Dr. Flaherty, who has a near-photographic memory, was not accustomed to rereading. But in his campus office that morning, he scrolled through the article on his computer again to be sure he had understood. The presence of the same B-RAF mutation in so many cancers, he thought, meant it was one of the biggest genetic smoking guns yet identified in cancer. A drug that blocked the protein made by the defective gene might have enormous consequences for patients — and he knew of one that just might work.

Dr. Flaherty raced to the melanoma clinic. "We have to jump on this," he urged his mentor, Dr. Lynn Schuchter.

For a junior faculty member, he was more confident than he had a right to be, Dr. Schuchter thought. Yet his optimism was infectious.

She would make trials of drugs that homed in on B-RAF a top priority, she told him.

That first effort, however, was destined to fail.

Dashed Hopes

Possessed of an energy that even friends called manic, Dr. Flaherty was used to finding diffuse outlets for it. In medical school at Johns Hopkins, he had read the entire works of Proust and cultivated bonsai. In Philadelphia, he collected a library of first edition books; copied the entire works of Mozart, Bach and Beethoven onto CD; and restored by hand the 150-year-old home he had bought with his wife, Dr. Mira Kautzky.

Raised in an affluent part of Baltimore, an A- student who had avoided

exerting himself for the extra grade at boarding school at Phillips Andover and as an undergraduate at Yale, he now told his wife, “I feel like I’m applying myself for the first time.”

And if she wished that his version of taking care of their two young daughters did not so often involve settling them in front of golf tournaments on TV while he pored over patient charts and wrote trial protocols — the girls became avid fans of the sport — she also understood what drove him.

Over the next four years, with the backing of his superiors at Penn, Dr. Flaherty enrolled several hundred patients in trials of the drug, developed by an academic pioneer in targeted therapy and now owned by Bayer.

He asked the trial nurses to work weekends processing blood and tissue samples. And he evangelized the targeted approach at scientific conferences, where he invariably found himself outnumbered by melanoma researchers devoted to a class of drugs that sought to harness the immune system to attack cancer.

While a single targeted drug was likely to hold off cancer for only a limited time, immunotherapy can be curative. But after decades of effort, the only such treatment approved for use in melanoma helped just a tiny fraction of patients.

“You’re swinging for the fences on every pitch,” Dr. Flaherty told the immune therapists. And, he thought to himself, they were mediocre batters at best.

But for all his self-confidence, Dr. Flaherty found himself sobbing uncontrollably one evening in late 2004 over a letter from the wife of a patient who had died, the latest of several patients on the targeted drug whom he had lost in recent weeks. The reminders of the hope and trust that people put in him, he told his wife that night, “can be overwhelming.”

To many of Dr. Flaherty’s colleagues, the failure of the Bayer drug indicated that melanoma would prove impervious to targeted therapy. And to many other oncologists, it was a blow to the notion that targeted therapy would work in any cancer as its proponents envisioned.

Dr. Flaherty brushed them off.

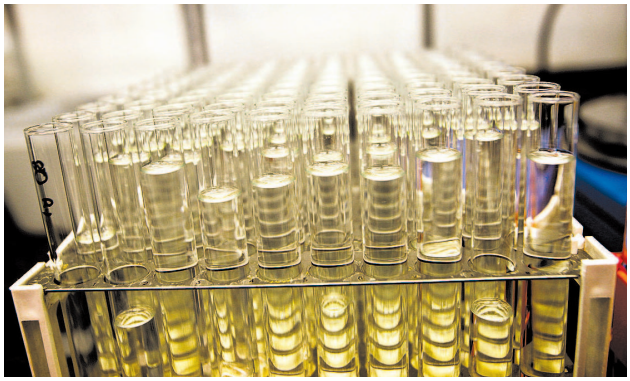
“We just had the wrong drug,” he insisted whenever he could. “The principle holds.”

But more often than not, when he gave his targeted therapy pep talks, he found himself talking to half-empty rooms, waiting, in awkward silence, for questions no one cared enough to ask.

ONLINE: A PATIENT, A PIONEER

After surgeries and chemotherapies fail, Sam Spero’s last hope is an experimental drug. Also, Amy Harmon, the series reporter, answers readers’ questions:

nytimes.com/health



HEIDI SCHUMANN FOR THE NEW YORK TIMES

ÁNGEL FRANCO/THE NEW YORK TIMES

THE INVESTIGATOR

Dr. Keith Flaherty oversees the testing of a drug known as PLX4032, upper left, calling it the best hope against melanoma "because it is based on what makes cancer tick."

The New York Times

NEW YORK, TUESDAY, FEBRUARY 23, 2010

After Long Fight, Drug Gives Sudden Reprieve

By AMY HARMON

TARGET CANCER

A Dose of Hope

Second of three articles.

For the melanoma patients who signed on to try a drug known as PLX4032, the clinical trial was a last resort. Their bodies were riddled with tumors, leaving them almost certainly just months to live.

But a few weeks after taking their first dose, nearly all of them began to recover.

Lee Reyes, 30, of Fresno, Calif., who had begun using a feeding tube because of a growth pressing against his throat, bit into a cinnamon roll.

Nothing, he told his mother, had ever tasted as good.

Rita Quigley, who had been grateful just to find herself breathing each morning since learning she had the virulent skin cancer, went shopping for new clothes with her daughters at a mall in Huntsville, Ala.

Randy Williams, 46, who drove 600 miles from his home in Jonesboro, Ark., to the M. D. Anderson Cancer Center in Houston to get the experimental drug, rolled out of bed. "Something's working," he thought, "because nothing's hurting."

It was a sweet moment, in autumn 2008, for Dr. Keith Flaherty, the University of Pennsylvania oncologist leading the drug's first clinical trial. A new kind of cancer therapy, it was tailored to a particular genetic mutation that was driving the disease, and after six years of disappointments his faith in the promise of such a "targeted" approach finally seemed borne out. His collaborators at five other major cancer centers, melanoma clinicians

Continued on Page A16

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who had tested dozens of potential therapies for their patients with no success, were equally elated.

In a kind of "pinch me" exercise, the six doctors sent one another "before and after" CT scans of their patients.

One was of Mark Bunting, 52, an airline pilot in Sandy, Utah. His initial scan in early October showed the cancer in his bones, an incursion considered virtually impossible to reverse. After two months on the drug, it had all but disappeared.

"Holy Cow!" Dr. Flaherty typed in reply to the slide from Dr. Antoni Ribas at the University of California, Los Angeles, that Dec. 17.

"Are you sure it is the same patient??" added Dr. Jeffrey A. Sosman at the Vanderbilt-Ingram Cancer Center in Nashville.

From New York, Dr. Paul B. Chapman of Memorial Sloan-Kettering Cancer Center, perhaps the most determined skeptic of the group, acknowledged, "This looks impressive."

The trial of PLX4032 offers a glimpse at how doctors, patients and drug developers navigate a medical frontier as more drugs tailored to the genetic profile of a cancer are being widely tested on humans for the first time.

Throughout the fall, the only two patients on the trial whose tumors continued to grow were the ones who did not have the particular gene mutation for which the drug had been designed. They were removed from the trial. By late December, tumors in the 11 patients who did have the mutation had shrunk. Those involved in the trial held their collective breath waiting to see how long the remissions would last.

It was a far cry from where they had been a year earlier, when a previous incarnation of the drug had no effect. Urged on by Dr. Flaherty and Dr. Chapman, the companies that owned it had spent months devising a new formulation that could be absorbed at higher doses.

But the new drug, still in the earliest phase of testing, had to pass several more hurdles before federal regulators would determine whether it was safe and effective enough for widespread use.

In December, as the doctors added more patients to the Phase 1 trial, looking for the highest dose they could give without intolerable side effects, they scrambled to prepare slides with graphs and statistics to convince the Food and Drug Administration that the drug should be tested in a larger Phase 2 trial. The agency required a summary of any and all side effects — there had been only a few — and any deaths of patients on the study; thankfully, there had been none since the drug was reformulated. In a matter of days they needed to submit their findings for a prestigious meeting of clinical oncologists in June.

First, though, Dr. Flaherty, 39, needed to respond to a desperate phone message from a patient named Christopher Nelson. It came the day after Christmas.

"Dr. Flaherty," the message said, "I need to get onto your trial."

Hoping for a Match

The doctor had expected the call.

Mr. Nelson, 42, and his wife, Sharlene, had come to see him just before Thanksgiving. They were planning to travel to Bethesda, Md., so Mr. Nelson could enroll in a trial for a different melanoma drug. But the couple, from Jackson, N.J., had learned of Dr. Flaherty's trial, and wanted to cover all their bases.

He liked them: Sharlene, a real estate broker who peppered him with questions, and Chris, a furniture installer around his own age with a penchant for low-stakes poker and the Grateful Dead. Both were quick to make light of a grim situation.

"I've gained the 60 pounds he's lost from the cancer," Mrs. Nelson observed. "Stress eating."

They had met after high school, at Levitz, the furniture store where they both worked. Like Dr. Flaherty, they had two children.

"He was never sick a day in his life," Mrs. Nelson told Dr. Flaherty. "Never had a headache, never took a sick day. I mean, can't you give me the common cold first? It had to be cancer?"

The trial in Bethesda, run by the National Cancer Institute, involved coaxing immune cells to grow in a test tube in a procedure that worked for only a small fraction of patients, Dr. Flaherty knew.

But there would be no point in Mr. Nelson taking PLX4032 if his tumor did not carry the right mutation. For now, the doctor had a slot for only one more patient on the trial, and he and his collaborators had agreed it was almost unethical to give the drug to people without that mutation.

He wished, not for the first time, that he could snap his fingers and know the genetic profile of his patient's cancer cells. But getting a hospital that had operated on a patient months earlier to retrieve a tumor sample from storage could take days or weeks; the test for the gene mutation could take even longer. To speed the process, Mr. Nelson drove his tumor sample himself from Robert Wood Johnson University Hospital in New Brunswick, N.J., where it had been removed from his lymph nodes, to the laboratory at the University of Pennsylvania.

Dr. Flaherty agreed that while they waited, Mr. Nelson should proceed with the trial in Bethesda, which first required the removal of his tumor-laden spleen. Either way, that needed to go.

Mrs. Nelson thought her husband had died when she saw the stricken look on the face of the surgeon after the operation. Normally 2 pounds, the spleen had weighed 10. Mr. Nelson's liver was so enlarged that maneuvering around it had been almost impossible. And then, on Dec. 23, Mr. Nelson learned that the doctors running the trial had been unable to grow his immune cells.

On the phone, Dr. Flaherty assured him he would let them know his genetic status as soon as he found out. "If it's positive," Dr. Flaherty told him, "the spot is yours."

Checking, Checking

No one knows just what causes the single change in a single gene in a single cell that fuels a malignant melanoma.

Randy Williams, now in recovery, had gone over in his mind a million times the day he fell asleep in the sun at the lake when he was 16. His feet were so badly burned, he could not walk for a week. Twenty years later, a mole inside the arch of his left foot turned cancerous.

Was that it? Was that the moment his fate was set? Because melanoma has been linked to sunburn, especially in childhood, many of the trial's participants relived such memories. Almost certainly, each had accumulated mutations in many other genes, at other moments, over the course of their lives. Some may have inherited a gene that was already damaged.

Once unleashed, however, any cancer seemed to rely on the protein made by a particular mutated gene to fuel its wild growth. In all of the PLX patients, that gene was B-RAF. And whatever the cause, they came to consider themselves, so far as it was possible with what has always been a virtually untreatable cancer, charmed.

SARAH PHIPPS FOR THE NEW YORK TIMES

FINGERS CROSSED Kerri Adams at home near Oklahoma City. After seeing an improvement from her treatment, she tried not to jinx it, declining to seek new information about the drug, the gene or the cancer.

NEEMAH A. ESMAEILPOUR FOR THE NEW YORK TIMES

ALWAYS WATCHING Randy Williams drove from Jonesboro, Ark., to Houston for treatment. Even after tumors disappeared, he says of his cancer, "I don't think I'll ever believe that it's not coming back."

ÁNGEL FRANCO/THE NEW YORK TIMES

LEADING THE PACK Mark Bunting in Sandy, Utah, with his wife, Trish, and children, Koda, Kylee and Kaila. He had cancer in his bones, seen as irreversible. After two months of treatment, it had nearly vanished.

COURTESY OF THE NELSON FAMILY

NEW APPETITE Christopher Nelson of Jackson, N.J., could barely eat or walk when he began a drug trial. Soon, he was out enjoying meals with his wife, Sharlene, and children, Julia and Dylan.

The New York Times

NEW YORK, WEDNESDAY, FEBRUARY 24, 2010

Cycle of a Drug Trial: Recovery and Relapse, Then Reinvention

By AMY HARMON

ORLANDO, Fla. — On a sunny afternoon last June, Dr. Keith Flaherty stood before a large room packed with oncologists from around the world and described the extraordinary recovery of the melanoma patients in the experimental drug trial he was leading.

It was a moment he had looked forward to for months. Beyond a breakthrough for melanoma, the results were a promising sign for an approach to treatment for all forms of cancer that he and others had championed as more effective and less toxic than standard chemotherapy.

TARGET CANCER

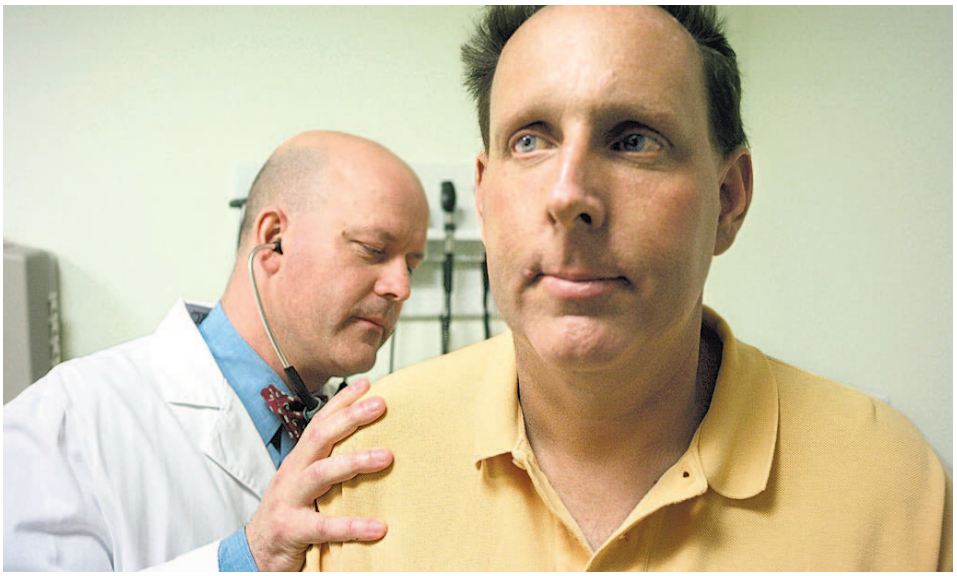
The Next Hurdle

Last of three articles.

But even as he flashed the slide of his favorite graph, showing tumors shrinking in nearly every patient, his mind was on what had happened to them since.

In the weeks leading up to the annual oncologists' conference here, several of the patients on the trial of the drug known as PLX4032 had relapsed. One had died. Another, Christopher Nelson, who had made what seemed like a miraculous recovery in March, had lost his appetite again. Dr. Flaherty feared what he might see on Mr. Nelson's scan when he returned to his office at the University of Pennsylvania.

The drug's ability to stop the melanoma, on average, he told the crowd, "appears to be approximately six months."



ÁNGEL FRANCO/THE NEW YORK TIMES

Dr. Keith Flaherty with Christopher Nelson, a patient in his melanoma drug trial.

"I was hoping we'd get more time," said Dr. Grant McArthur, one of the six oncologists on the trial team, voicing the thought on everybody's mind when the group met at the conference. None of them had a financial stake in the drug.

Dr. Flaherty, whose perpetual optimism about this kind of treatment, known as targeted therapy, raised eyebrows among some colleagues, declined to dwell on the drug's limitations. However briefly, PLX4032 had held off the cancer by blocking a particular protein in its cells that was spurring them to multiply. If such targeted drugs were ever to provide a lasting benefit, many oncologists believed they would need to be combined with others, much as cocktails of protease inhibitors have worked against H.I.V.

"We just need," Dr. Flaherty said, "to find

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the right combination."

If they acted quickly enough, they might even be able to help the trial's participants. Many were still in remission. Those who had relapsed were searching for another treatment, acutely aware that their time was running out: most melanoma patients die within a year after the cancer spreads.

The problem, which had bedeviled targeted therapies for other cancers, was that while PLX4032 blocked the protein made by one mutated gene, a second mutation now seemed to be driving the cancer's growth. If that mutation could be identified, they believed, its protein could also be blocked, in a game of biological Whac-a-Mole that just might be possible to win.

The most expedient approach would be to test PLX4032 in combination with other experimental drugs that targeted other mutations, including those seen in Dr. Flaherty's relapsing patients.

But a drug that gave a patient even a few months of life could generate billions in revenue. And the standard practice among pharmaceutical companies, which say they typically invest nearly a billion dollars developing and testing a single drug, is to get each drug approved individually before testing it with others, especially those of competitors that are still experimental. Even small Phase 1 trials can cost over a million dollars. And one drug that was safe and effective, they worried, might be tainted by association with another that proved to have toxic side effects.

As Roche, the pharmaceutical giant that had licensed PLX4032, made plans to test the drug in larger trials in hopes of quick Food and Drug Administration approval, Dr. Flaherty's colleagues in the laboratory would search for the new mutation in the tumor samples of patients who had relapsed, trying to understand why the drug had stopped working.

For his part, the doctor would try to keep his patients alive. And he would work to convince the pharmaceutical industry that the fastest path to finding a combination that really worked would require changing their standard operating procedure.

A Bitter Pill

At 4:40 p.m. June 25, Mr. Nelson, 43, waited with his wife, Sharlene, in the melanoma clinic at Penn. Dr. Flaherty was running late.

Mr. Nelson credited Dr. Flaherty with snatching him from the jaws of death four months earlier. The name of the protein fueling his cancer had become part of his personal lexicon: it was called B-RAF, he told his poker buddies. Mrs. Nelson had recounted dozens of times the story of his turnaround on the Roche drug that blocked it.

"It's a miracle drug," she would say.

They sat side by side. To pass the time, Mr. Nelson tried to remember all the adjectives their 10-year-old daughter, Julia, had come up with for her Father's Day card the week before, each starting with one of the letters in "Christopher."

"C" was for caring, "H" was for helpful. "E" was for 'elderly person,'" Mr. Nelson recalled. "I'm like, 'Thanks.'"

As he finished with other patients, Dr. Flaherty found himself rehearsing what to say to the Nelsons. He relayed bad news almost daily; it was part of his job. But this, somehow, was worse.

When he arrived, he sat and faced them, meeting Mr. Nelson's eyes.

"The cancer," he said, "is starting to wake up again."

Mr. Nelson, always ready with a quip, said nothing.

"But this drug," Mrs. Nelson started, her voice breaking. "This drug could push it back just in the first two weeks — you would think it would just keep pushing!"

Then Dr. Flaherty gave them a new hope. One theory, he told them, was that the mutant B-RAF protein was managing to activate another protein on the same pathway in the cancer's cells. And a space was about to open up in the trial of a new drug designed to block the second protein.

Its developer, GlaxoSmithKline, required Mr. Nelson to wait at least a month to clear his system of the Roche medication. And Dr. Flaherty himself was moving to Boston the next month, where he would oversee targeted therapy development across all cancer types at Massachusetts General Hospital at Harvard. He was entrusting Mr. Nelson's care to a colleague, and would be in close touch.

Mrs. Nelson took her husband's hand.

"O.K.," she said. "We have a plan."

Pressuring the Industry

He had done his best for the Nelsons, Dr. Flaherty thought as he hailed a cab to the airport that evening to fly to Chicago, where he would give a talk on targeted therapy.

But over dinner alone near his hotel, he second-guessed himself. What if Mr. Nelson's cancer was not being fueled by the protein the Glaxo drug was trying to block? There were other likely drivers, which lay on a different pathway. And many cancer biologists suspected that both pathways needed to be blocked to stamp out the melanoma.

What bothered him more than anything was that he had to guess. The scientists studying the tumor samples were proceeding slowly. Without the cooperation of the drug companies, it was impossible to know which was the best therapy for his patient.

Even if some combination of targeted drugs could put melanoma into a long hibernation — and that was still not clear, he knew — it might take a cocktail of five or more such drugs to treat any given case. And it can take 10 years for even one drug to reach the market.

"If they do it the way they've always done it," Dr. Flaherty complained in e-mail messages and calls to colleagues, "it will delay by years how quickly we can figure this out."

Such frustration, he knew, went beyond melanoma specialists, especially as it grew clear that there were so many new targeted drugs to be tested and that no single one was likely to hold off any given cancer for more than a limited time.

Unable to obtain drugs from the companies themselves, some researchers were paying to have the equivalent of designer knockoffs made so they could test the most logical combinations in laboratory animals. One such experiment had arrested the growth of lung cancer in mice, and clinical researchers were "climbing the walls," a colleague told him, because the companies who owned the two drugs had no plans yet to combine them in a human trial.

Over the summer, Dr. Flaherty urged the leading melanoma researchers to form an alliance to make it easier and cheaper for drug companies to conduct several trials at one time, advising them which were the most promising.

Years earlier, he had secured the backing of a patient advocacy group, the Melanoma Research Foundation, for the idea. Forging cooperation among academic researchers had been more difficult, given that they compete for jobs and grant money. And many still believed that a different approach, which boosted patients' immune systems, was more likely to produce a cure.

But the results of the PLX4032 trial offered the most substantial support to date for the targeted approach in an aggressive and common cancer. For many oncologists, it seemed to add a moral imperative to the demand for swift testing of the drugs in combination. And on a steamy morning in August, leading melanoma researchers from across the country gathered at a meeting in Boston to discuss it.

"This is the most important meeting for melanoma patients that's happened in years," said Dr. Lynn Schuchter, chief of oncology at the University of Penn-

ONLINE: UNCHARTED WATERS, FRAGILE HOPES

Patients and doctors in a cancer drug trial face the uneasy task of managing expectations in this new scientific frontier. The series reporter, Amy Harmon, answers readers' questions.

nytimes.com/health

sylvania.

The stories of those who had recovered and relapsed on the Roche drug gave the meeting its momentum. An avid golfer in New Jersey had played three rounds in the rain when the tumor under his arm receded enough to let him swing a club. One woman, 30, who had been told before joining the trial that she should "focus on the quality, not the quantity" of her days, was informed that her scans were cancer-free.

The average time the drug halted tumor growth had stretched to almost nine months. Yet Mark Bunting, the airline pilot who had once declared himself the trial's "leader of the pack," had been rushed into emergency surgery when a new tumor had pierced his bowel. And Mr. Nelson's initiation to the Glaxo trial had been delayed while he received radiation for tumors that had appeared in his brain.

The doctors agreed to hammer out the legalities of pooling resources among institutions, and Dr. Flaherty agreed to approach the companies on behalf of the alliance.

Their first choice would be to test Roche's B-RAF drug with another one the company owned. Glaxo had two drugs designed to block the same proteins. Novartis, Pfizer and Bristol-Myers Squibb also had drugs that might work best with a competitor's. If they had needed any more incentive, the doctors were increasingly urged on by the frustrations of their patients.

"Why can't they put them together and do it in one shot?" Mrs. Nelson wanted to know when she and her husband arrived at Penn in early October to start the Glaxo trial. "Wouldn't that give him a better chance?"

Mr. Nelson's latest CT scan showed the cancer throughout his body. Twelve tumors, though inactive, remained in his brain. Another protruded from his neck. Because of a concern that the drug could cause vision problems, he had been examined by an ophthalmologist.

"My eyes are perfect, by the way," he told his wife, trying to make light.

A Plea Rejected

Dr. Flaherty could tell by whom Roche sent to his first meeting with the company that he would make little headway. Any strategic decisions, he knew, would be made at a higher level.

Over sandwiches in a Midtown Manhattan office, a Roche official told him that the best interest of patients would be served by getting its B-RAF drug approved for sale as quickly as possible. "That has to be our focus right now," she insisted.

The request by Dr. Meenhard Herlyn, a prominent melanoma research scientist, to conduct preliminary tests of the drugs in the laboratory met with the same response.

"You know," Dr. Flaherty said finally, "other companies will be ready to do this."

But his habitual breakneck pace was slower as he walked toward Pennsylvania Station with Dr. Herlyn, who had traveled from Philadelphia.

"That was a waste," Dr. Herlyn said flatly. As they parted ways, Dr. Flaherty, for once, was at a loss for a more positive spin.

A Death in the Family

At an appointment in mid-November, the tumors on Mr. Nelson's neck and inside his heart had shrunk. "Aren't you excited?" Mrs. Nelson crowed.

Maybe, Mr. Nelson thought, he could make it to a poker tournament the next month after all. Or to his son's 17th birthday on Jan. 18. Or maybe not.

"I'm happy, Sharl," he said slowly. "But how long do you think it will last?"

A few weeks later, when Dr. Flaherty again made the pitch for a combination trial, this time at a meeting with Glaxo, an executive hinted that the company would sponsor such a trial soon. The company had a pragmatic reason: Roche was likely to get its B-RAF drug approved first, but Glaxo might take the lead if it had a combination that could do a better job. It was becoming clearer that some targeted drugs might find a market only if combined.

"The culture is changing," the Glaxo executive agreed.

It would be too late, however, for Mr. Nelson. On Jan. 5, Mrs. Nelson wheeled him on a stretcher to his appointment at Penn. Three days later, an ambulance took him to hospice at a local hospital.

"Take me to Atlantic City instead," Mr. Nelson joked with the driver. "I'll pay you extra."

At his wake, Mrs. Nelson told relatives she felt blessed that he had lived longer than expected. They had celebrated their 21st wedding anniversary. With the children, he had ridden every water ride at Six Flags Great Adventure.

"It's a year I would never trade in," she said.

One year, Dr. Flaherty thought, when he heard the news. Certainly no triumph. But it was something. Something to be built on.

Novartis and Bristol-Myers had agreed to schedule teleconferences for later in the month to talk about combination trials. He checked the dates on his electronic calendar. A meeting with Pfizer was also pending.

Stalling the Advance of a Deadly Cancer

Nearly all of the melanoma patients whose tumors carried a particular genetic mutation responded to an experimental drug, PLX4032, when it was given at a high enough dose. As of now, tumors of the 39 patients who responded in the drug's first human trial have stopped growing for nine months on average. Several patients are still in remission. Others have died, or are searching for another therapy.

Randy Williams, *Jonesboro, Ark.*

Mr. Williams, 47, a contractor, has responded to the drug for 18 months. He drives 1,200 miles round trip to appointments in Houston to get his monthly quota of pills.

Rita Quigley, *Huntsville, Ala.*

Over the last 19 months, Ms. Quigley's initial tumors disappeared, but earlier this month new ones appeared in her brain and her heart. On Monday she started radiation treatment for the brain tumors.

Mark Bunting, *Sandy, Utah*

Mr. Bunting, 53, an airline pilot, told friends he was "leading the pack" when his tumors shrank by more than 80 percent. After relapsing, he is trying chemotherapy for a second time.

Dezarae Dittmar, *Marietta, Ga.*

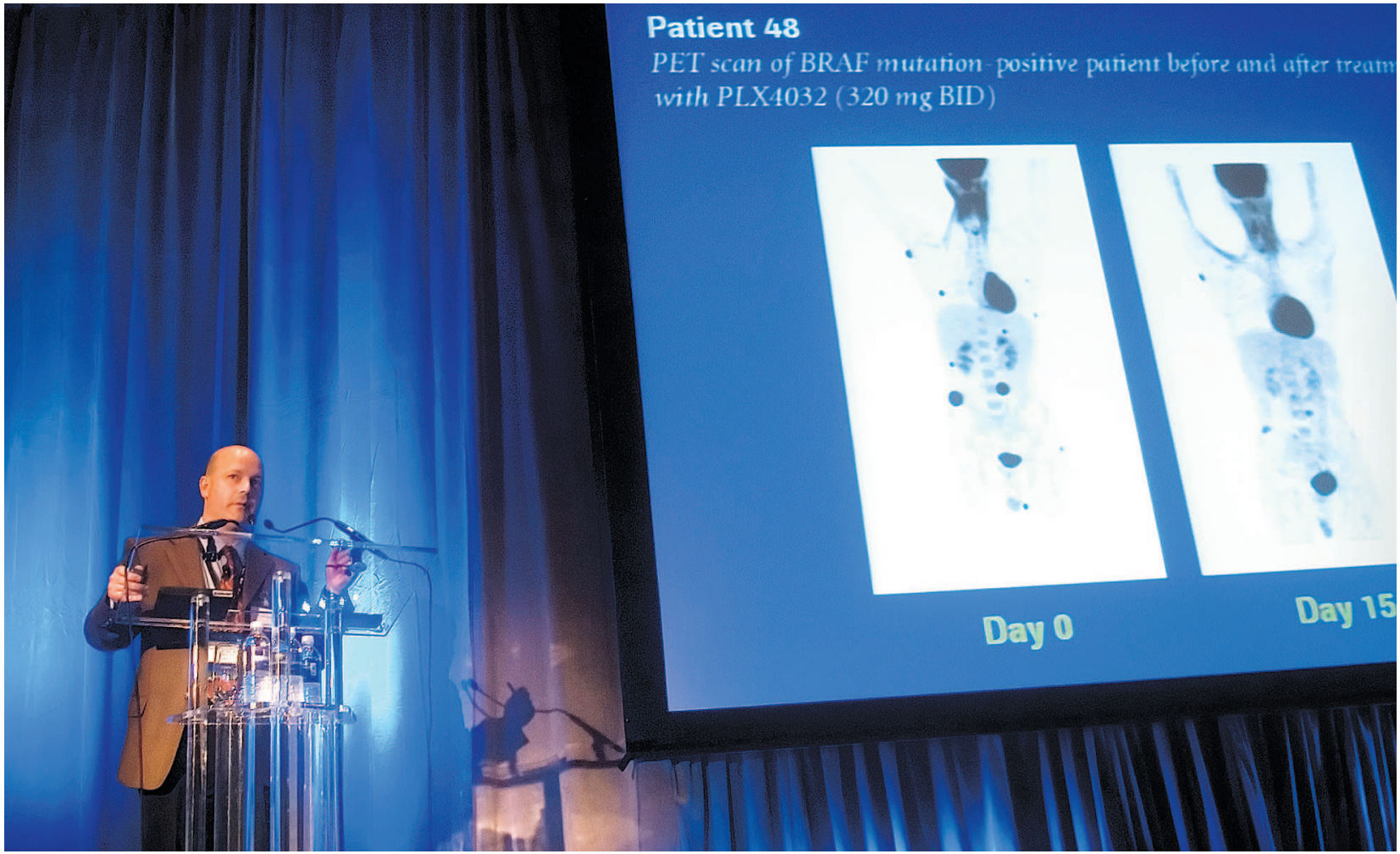
A tumor below her waistline, the size of a baseball, shrank to the size of a pea in the two months that she took the drug, but just as abruptly began to grow again. She died on Feb. 13 at age 46.

Lee Reyes, *Fresno, Calif.*

After months of using a feeding tube, Mr. Reyes began savoring food again after enrolling in the drug trial, but after a brief remission, his cancer came back. He died in September, 10 days after his 31st birthday.

Sources: ASCO 2009 presentation; New York Times reporting

THE NEW YORK TIMES



CHIP LITHERLAND FOR THE NEW YORK TIMES

OFFERING HOPE
Dr. Keith Flaherty, the lead investigator in a melanoma drug trial, discussing results at a conference last year.

ÁNGEL FRANCO/THE NEW YORK TIMES

SHARLENE NELSON

FACING REALITY

Dr. Flaherty with Christopher and Sharlene Nelson. Mr. Nelson quickly recovered on the trial, enjoying a trip to the Jersey Shore. After a relapse, then new treatment and another lift, he told his wife in November: “I’m happy, Sharl. But how long do you think it will last?” He died last month.

The New York Times

NEW YORK, SUNDAY, SEPTEMBER 19, 2010

When Testing a Drug Means Withholding It

By AMY HARMON

Growing up in California's rural Central Valley, the two cousins spent summers racing dirt bikes and Christmases at their grandmother's on the coast. Endowed with a similar brash charm, they bought each other matching hardhats and sought iron-working jobs together. They shared a love for the rush that comes with hanging steel at dizzying heights, and a knack for collecting speeding tickets.

And when, last year, each learned that a lethal skin cancer called melanoma was spreading rapidly through his body, the young men found themselves with the shared chance of benefiting from a recent medical breakthrough.

Only months before, a new drug had shown that it could safely slow the cancer's progress in certain patients. Both cousins had the type of tumor almost

TARGET: CANCER

Trial or Error?

sure to respond to it. And major cancer centers, including the University of California, Los Angeles, were enrolling patients for the last, crucial test that regulators required to consider approving it for sale.

"Dude, you have to get on these superpills," Thomas McLaughlin, then 24, whose melanoma was diagnosed first, urged his cousin, Brandon Ryan. Mr. McLaughlin's tumors had stopped growing after two months of taking the pills.

But when Mr. Ryan, 22, was admitted to the trial in May, he was assigned by a computer lottery to what is known as the control arm. Instead of the pills, he was to get infusions of the chemotherapy drug that has been the notoriously ineffective recourse in treating melanoma for 30 years.

Even if it became clear that the chemotherapy could not hold back the tumors advancing into his lungs, liver and, most painfully, his spine, he would not be allowed to switch, lest it muddy the trial's results.

"I'm very sorry," Dr. Bartosz Chmielowski, the U.C.L.A. oncologist treating both cousins, told Mr. Ryan's mother, Jan. He sounded so miserable that afternoon that Mrs. Ryan, distraught, remembers pausing to feel sorry for the doctor.

Controlled trials have for decades been considered essential for proving a drug's value before it can go to market. But the continuing trial of the melanoma drug, PLX4032, has ignited an anguished debate among oncologists about whether a controlled trial that measures a drug's impact on extending life is still the best method for evaluating hundreds of genetically targeted can-

Continued on Page 28

MONICA ALMEIDA/THE NEW YORK TIMES

TWO COUSINS, TWO PATHS

Thomas McLaughlin, left, was given a promising experimental drug to treat his lethal skin cancer in a medical trial; Brandon Ryan had to go without it.

From Page 1

cer drugs being developed.

Defenders of controlled trials say they are crucial in determining whether a drug really does extend life more than competing treatments. Without the hard proof the trials can provide, doctors are left to prescribe unsubstantiated hope — and an overstretched health care system is left to pay for it. In melanoma, in particular, no drug that looked promising in early trials had ever turned out to prolong lives.

PLX4032 shrinks tumors in the right patients, for a limited time. But would those who took it live longer? No one knew for sure.

"I think we have to prove it," said Dr. Paul B. Chapman, a medical oncologist at Memorial Sloan-Kettering Cancer Center who is leading the trial. "I think we have to show that we're actually helping people in the long run."

But critics of the trials argue that the new science behind the drugs has eclipsed the old rules — and ethics — of testing them. They say that in some cases, drugs under development, PLX4032 among them, may be so much more effective than their predecessors that putting half the potential beneficiaries into a control group, and delaying access to the drug to thousands of other patients, causes needless suffering.

"With chemotherapy, you're subjecting patients to a toxic treatment, and the response rates are much lower, so it's important to answer 'Are you really helping the patient?'" said Dr. Charles L. Sawyers, chairman of human oncology at Sloan-Kettering. "But with these drugs that have minimal side effects and dramatic response rates, where we understand the biology, I wonder, why do we have to be so rigorous? This could be one of those defining cases that says, 'Look, our system has to change.'"

Dr. Richard Pazdur, director of the cancer drug office at the Food and Drug Administration, said in a recent interview that the new wave of drugs in development — especially for intractable cancers like melanoma — might require individual evaluation. "This is an unprecedented situation that will, hopefully, be increasingly common, and it may require a regulatory flexibility and an open public discussion," he said.

And doctors say that for them, the new wave of cancer drugs is intensifying the conflict between their responsibility to their patients and their commitment to gathering scientific knowledge for generations of the critically ill.

Of course, no single pair of patients can fairly represent the outcomes of a trial whose results are not yet known. Rather, the story of Thomas McLaughlin and Brandon Ryan is one of entwined paths that suddenly diverged, with a roll of the dice.

At times beseeching and belligerent, Mr. McLaughlin argued his cousin's case to get the new drug with anyone he could find at U.C.L.A. "Hey, put him on it, he needs it," he pleaded. And then: "Who the hell is making these decisions?"

He believed he should trade places on the trial with Mr. Ryan, who was pursuing his contractor's license and had just bought a four-bedroom home in Bakersfield. "Brandon has everything going for him," he told his Aunt Jan.

But Mr. Ryan told his mother he was glad that Mr. McLaughlin, who has a young son and daughter, was the one getting the promising drug. "Tommy has the kids," he said. "They need him around."

Path to a Second Trial

The debate over the controlled testing of PLX4032 began in June 2009, around the time Mr. McLaughlin awakened with what felt like an explosion under his right armpit.

The drug, manufactured by Roche, the Swiss pharmaceutical giant, was designed for melanoma patients whose tumors carry a particular mutation, and the company reported that month that nearly all 32 such patients in the drug's first clinical trial, called Phase 1, had seen their tumors shrink.

The reprieve was all too brief: most saw their tumors begin to grow again within the year. Still, The New England Journal of Medicine called the drug "a major breakthrough" for people with advanced melanoma, whose median survival is eight months after diagnosis. A second, or Phase 2, trial, aiming to validate the results in more patients, was already in the works. And in meetings that summer, several oncologists urged Roche to seek accelerated approval from the F.D.A. The agency allows a manufacturer to sell a drug based on early promise so long as it proceeds with the traditional controlled trial comparing it with the standard treatment.

But with patients already begging doctors for the drug, it seemed unlikely that anyone would join a trial with only a 50-50 chance of getting PLX4032 once it was already on the market. Unless the trial was conducted before approval, it seemed, there would be no chance to get definitive data on its effectiveness.

Some melanoma specialists familiar with the drug would have traded the data for faster access to the drug. "I know all that I need to know based on the results we already have," said Dr. Keith Flaherty of Massachusetts General Hospital, who led the early clinical testing. "My use of this drug is not going to be informed by testing it against a drug we all hate and would rather never give a dose of again in our lives."

The standard chemotherapy used in melanoma, dacarbazine, slowed tumor growth in 15 percent of patients for an average of two months. By contrast, PLX4032 had halted tumor growth in 81 percent of patients for an average of eight.

It was conceivable that when the cancer started up again, it would progress much faster in patients who had taken the new drug, wiping out any extra time they might have gained. But even if so, many doctors believed that if the drug provided relief by shrinking tumors — like the one Mr. McLaughlin soon learned was pressing against a nerve in his arm — that would improve their patients' lives.

The trial, moreover, would cost $100 million and delay the possibility of F.D.A. approval by at least two years. To some doctors, it seemed a waste of time and resources that would be better used for trials testing what everyone most cared about: how to prolong the remissions.

There was reason to believe that combining PLX4032 with other drugs — some from competitors — would make it more effective. But researchers had to rely on Roche for permission until the drug was available for sale, and the company had not been forthcoming.

Dr. Chapman of Sloan-Kettering came up with a new tack: an unconventional bid to speed the drug's approval, rooted in the observation that patients weeks or days from death could get out of bed and off oxygen when given PLX4032, sometimes for months. The doctors working with the drug referred to this as the Lazarus effect; it was unheard of with dacarbazine.

A trial that cataloged PLX4032's effect on the well-being of the sickest patients, Dr. Chapman argued, would probably yield fast, tangible results. For him, it represented a chance to give patients symptomatic relief, even if the drug turned out not to prolong life.

"Even without a survival benefit, maybe we could show that it helps people," he urged. "If you could get Aunt Sadie to the wedding and off of oxygen, that would be great."

But company officials feared that might lead to approval for only a narrow group of the sickest patients. The surest way to get the F.D.A's endorsement for a broader market was a controlled trial. And with its competitors rushing to get similar drugs to market, the findings of such a trial might give Roche an advantage in marketing its version as the only one proven to prolong survival.

Target Cancer

Previous articles in this series chronicled the first human trial of an experimental melanoma drug, exploring the challenges that face the doctors and patients through early success, relapse and the push to collaborate on a cure.

ONLINE: *Previous articles and videos in this series:*

nytimes.com/health

On Sept. 1 last year, the company submitted its plan to the F.D.A. for the traditional, randomized, controlled trial of PLX4032. It would involve 680 patients, half of them in a control group. Dr. Chapman would be the lead investigator for more than 100 sites in the United States, Europe and Australia. Because of the different ways the drugs were dispensed — one by mouth and one by infusions — doctors and patients, it was decided, would both know who got which drug.

The following week was when Mr. Ryan learned that his cousin might have a health problem. He called Mr. McLaughlin from a job site in Colorado, to tell him about his new Dodge Ram, a truck he knew Mr. McLaughlin had long coveted.

He invited Mr. McLaughlin to come stay with him: there was plenty of welding work, and he could help break in the truck. But Mr. McLaughlin, who had no health insurance, had finally visited a doctor about the pain under his arm. It was melanoma, and he would need surgery to remove some lymph nodes.

"Wow," Mr. Ryan said, suddenly silent. "You have cancer?"

Two Men's Struggles

Mr. McLaughlin's surgery, it seemed, had come too late. In the weeks following, small tumors popped up across his body, including one on his collarbone and one on his triceps.

When Mr. Ryan discovered a swollen node under his own right armpit in October, his mother was not taking any chances. She begged him to go to the emergency room in Colorado. Even so, when the verdict was melanoma, both families were shocked.

Was it genes? Their mothers, after all, were sisters. But there was no history of cancer in the family.

Environment? The boys had fought, played and competed with each other since childhood: who could hold his breath the longest, do the highest cannonball dive, suck down a Slurpee fastest, win their grandfather's approval? They had ranged across California on iron-working jobs, eating the same food, drinking the same large quantities of beer, promising, in a rare moment of seriousness, that each would bury the other with his hardhat when the moment came. Coincidence?

Compared with most cancers, melanoma strikes a disproportionate number of young people; it is the sixth most common cancer in the United States.

There was no way to know.

Last Thanksgiving, Mr. McLaughlin greeted Mr. Ryan with the usual bear hug. "Looks like we're doing this together," he said.

Not ones for excessively talking things over, they left it at that.

Yet both cousins, like the other family members, believed then that Mr. Ryan stood a far better chance of surviving the disease than his cousin. His cancer was rated Stage 3, with no evidence yet that it had spread to distant parts of his body. Mr. McLaughlin, at Stage 4, had a tumor ominously near his liver. And Mr. Ryan had health insurance, while Mr. McLaughlin had none.

MONICA ALMEIDA/THE NEW YORK TIMES

A SHARED FIGHT Thomas McLaughlin, top, who received an experimental melanoma drug, and his cousin Brandon Ryan, in a control group, each thought the other more deserving of the treatment.

The New York Times

NEW YORK, MONDAY, DECEMBER 27, 2010

Enlisting the Dying for Clues to Save Others

By AMY HARMON

LOS ANGELES — They had told him on his last visit: the experimental drug that had so miraculously melted his tumors was no longer working. His legs were swollen, the melanoma erupting in angry black lumps. The patient, a computer consultant in his 40s, had little time left.

And now the man's doctor, Roger Lo of the cancer center at the University of California, Los Angeles, was calling to ask whether they could harvest a slice of one of his resurgent tumors for research he would almost certainly not be alive to benefit from. He would need to fly to Los Angeles from Northern California at his own expense, subject himself to an injection of anesthetic and the slight risk of infection, and spend yet another afternoon in the hospital.

"I was hoping," Dr. Lo said that day last spring, "you would come in for a biopsy."

The hope lies in a new breed of cancer drugs that work by blocking the particular genetic defect driving an individual tumor's out-of-control growth — in the case of Dr. Lo's patient, a single overactive protein. If researchers can pinpoint which new genetic alteration is driving the cancer when it evades the blockade — as it nearly always does — similarly tailored drugs may be able to hold it off for longer. The crucial evidence resides in the tumor cells of patients who, like Dr. Lo's, have relapsed.

But the need to ask those who know their time is short to undergo another invasive procedure in the name of science is just one obstacle to what many oncologists see as the best chance to give future cancer patients a more permanent reprieve.

A regulatory process that can take years to approve a drug for sale means that instead of thousands of patients to draw on, only the few hundred who receive the drug through clinical trials are available for such research. Ethical review boards frown on any procedure that exposes patients to unnecessary risk, like the rupturing of a blood vessel or puncturing of a lung. Some hard-won tumor samples prove unsuitable for research.

TARGET CANCER

A Winding Road to Hope

Then there is the question of who will pay for the biopsies, which cost as much as $5,000 and typically cannot be billed to insurance. Dr. Lo, for one, covered the costs when there was no other means to pay.

As drugs tailored to the genetics of particular tumors make their way through early clinical trials, similar quests to improve on them are being undertaken by researchers in the various forms of a disease that kills more than a half-million Americans and millions more people worldwide every year.

Dr. Lo's quest to understand how melanoma forges its resistance to the drug PLX4032, made by Roche, illustrates the Herculean effort required to take even a baby step toward a

Continued on Page A10

ANN JOHANSSON FOR THE NEW YORK TIMES

Dr. Roger Lo removing a tumor that he hopes will help researchers find drugs to treat relapsing cancer patients.

From Page A1

cure for cancer. Finding a single clue that could lead to the testing of one new drug that might help a small fraction of patients took two long years.

But it also shows how such progress emerges, from a complex mix of academic ambition, collaboration and competition among scientists, and, especially, the willing participation of dying patients.

When the man Dr. Lo had called arrived in his office a week later, tumors covered his legs from the bottom of his feet to his groin. Some of them were infected, their odor so overwhelming that the doctor put on a mask before administering an anesthetic and cutting into his left thigh.

A Researcher's Trials

Dr. Roger Lo, 38, was an unlikely player in the scramble to improve on the Roche drug, which had been given to only a handful of patients when its successes began to grab the field's attention in late 2008.

An assistant professor in dermatology, he had started his own laboratory only a few months earlier and had been advised by senior colleagues to avoid high-risk projects until he secured a steady source of financial support.

But like others in the field, he was galvanized by watching melanoma patients respond to the Roche drug, the first to reliably slow a disease that typically kills within a year of diagnosis, and rarely responds to chemotherapy.

Studying how to prevent a relapse, he argued in a grant proposal in early 2009, was "of paramount importance."

Impressed by his drive, and equally eager to realize the full promise of the drug's approach, Dr. Antoni Ribas, the melanoma oncologist running U.C.L.A.'s arm of the drug's clinical trial, agreed to collaborate with Dr. Lo. Bigger, better-financed laboratories pursuing the same question might reach an answer first, Dr. Ribas warned.

But Dr. Lo had reason to hope the results would be published in a leading journal if he was the first to find the culprit responsible for reigniting the cancer, among the many possibilities. That could prompt drug companies to speed the development of a new therapy.

Lacking tumor samples from patients in the Roche trial, Dr. Lo instead sought to replicate the cancer's resistance to the drug by feeding a steady diet of the drug to melanoma cells taken from three previous patients who had never received it. When the few cancer cells that survived the onslaught began to grow in their petri dishes, he used those, now resistant to the drug, to begin his search.

It could have been straightforward. Many researchers believed the answer would be that the gene whose mutation initially made the protein that drove the cancer's uncontrolled growth had mutated again, as had happened in other cancers. In a few cases, a new drug tailored to the new mutations had lengthened remissions.

But Dr. Lo found no evidence of this. Nor did he find the smoking gun in several other genes linked to the growth of other cancers.

Instead, he began the painstaking process of measuring the activity of hundreds of proteins that might have driven the cancer's uncontrolled growth. The experiments required modifying the levels of each protein in the drug-resistant cells, dosing them with the drug and checking every few hours to see how fast they were growing. With only two junior scientists and a technician in his laboratory, Dr. Lo performed much of the work himself.

Even so, he knew, nothing he found in the cells whose resistance he had artificially bred in the lab would matter unless he also found it in the patients who had relapsed.

One Patient's Contribution

Those who wonder whether a single patient can help cancer research should know the case of Lee Reyes.

Thirty years old when his advanced melanoma was diagnosed in early 2008, Mr. Reyes was distraught at how little he had accomplished. Introverted and a perfectionist, he had dropped out of college and lived with his parents in Fresno, Calif. He cycled through video game systems, favoring the Xbox. He loved flying and thought about getting a helicopter pilot's license, but never pursued it.

"For the better part of about 10 years I did close to nothing," he said two years ago. "I just always felt I had so much time."

One of Dr. Ribas's first patients in the trial of the Roche drug, Mr. Reyes was selected because he was among the half of melanoma patients whose tumors carried the overactive protein the drug blocked. As it would for nearly every patient in the trial, the drug held his cancer at bay for several months. But as would happen with the others, his response did not last.

With his life at immediate risk because of a melanoma tumor that had metastasized to his heart, Mr. Reyes traveled to U.C.L.A. for surgery in May 2009, agreeing to let his tumor be used for research.

On Dr. Ribas's instructions, a technician stood in Mr. Reyes's surgery room and, as soon as the surgeon extracted the tumor, ran with it to the nearby laboratory to reduce the chance of exposure to contamination. To coax the cancer cells to thrive so that Dr. Lo could run them through a battery of tests, it was sliced up with sterile knives and deposited, in a flask with sugar solution, in an incubator.

"Let's hope it grows," Dr. Ribas said to Dr. Lo.

On a visit to Mr. Reyes's room after the surgery, Dr. Ribas did not discuss the future with his patient. They both knew the options were limited. Instead, they talked of animals: Mr. Reyes's affinity for monkeys — he was clutching a stuffed one from a hospital gift shop — and Dr. Ribas's for sea otters.

When Mr. Reyes died a few months later, Dr. Ribas called his mother to offer his condolences, as is his custom. And then he told her something else.

"He said Lee is helping them," Ellen Reyes told her husband.

Mr. Reyes's cells were growing.

A Breakthrough

It would take months for Mr. Reyes's cells to multiply to the numbers Dr. Lo needed to perform his tests. And that summer, the foundation he had hoped would finance his research judged his grant proposal "too ambitious" for a junior investigator.

But by late September 2009, using the laboratory cells he had earlier bred to resist the Roche drug, he had narrowed his search. The cancer's new driver, he believed, was one of 42 proteins on the surface of the cell. A few weeks later, he closed in. An experiment that could detect all 42 found a single culprit, appearing as twin dots of black on the translucent background of the film: the resistant cells contained 10 times more of the protein than those that were still responding to the Roche drug in Dr. Lo's petri dishes.

And, he noted with excitement, a drug designed to block that protein was already being prescribed for other cancers. Perhaps a solution for patients was available already.

But as he prepared to see whether Mr. Reyes's cells bore out the observation, Dr. Lo tried to restrain his hopes.

"We have a likely candidate," he told Dr. Ribas carefully.

It was probable, he reminded himself, that this protein was not the source of the cancer's resistance in all patients. In fact, the cancer could reroute itself differently in every patient. Even if the theory was right, Mr. Reyes's tumor might not reflect it.

In October, as the precious cells grew close to the number required for the experiment, Dr. Ribas received a box in the mail. In it was a stuffed sea otter, and a note from Mr. Reyes's mother.

They had visited the Monterey Aquarium over the summer, she wrote. Mr. Reyes had bought the otter to take to Dr. Ribas on his next trip.

On a Saturday night in mid-November, Dr. Lo called Dr. Ribas. He was looking at the film showing the results of the experiment on Mr. Reyes's cells. On the translucent background, the same twin dots showed black.

The patient's cells, still living, harbored levels of the protein far higher than even Dr. Lo's laboratory models.

"Toni," he said. "You have to see this for yourself."

The Scramble for Donors

To be confident that his find was not a fluke, Dr. Lo needed more samples from other patients. Their goal would be 10, he and Dr. Ribas agreed in late-night e-mail exchanges. The best would be "before" and "after" snapshots from patients at the beginning of their treatment and after they had relapsed. But those were in short supply.

Only 48 patients had been treated in the drug's first trial, eight at each of six leading cancer centers. Many had not been biopsied when their cancer returned. Some of the biopsies had been sent to Roche, which had not yet shared its own research with the academic researchers.

Briefly, researchers at the six sites contemplated pooling the few samples in their possession, and sharing authorship of their results. But the tissues could be subjected to only so many tests before being used up. And success in academia can hinge on being listed as a paper's lead author. When several group discussions failed to yield even a complete accounting of who had how many samples, researchers agreed to stay in touch, but go it separately.

Still, in late 2009, Dr. Ribas approached two of the oncologists he knew to ask if they would share samples with Dr. Lo.

"I think he really has something," he told the two, Dr. Jeffrey Sosman and Dr. Grant McArthur.

Four tumor samples, two from each doctor, arrived a few days later by FedEx. One, from a retired math teacher in Tennessee, tested positive for high levels of Dr. Lo's protein.

The same protein was hyperactive in another sample, which came from a Croatian patient of Dr. Ribas's who had been commuting to Los Angeles for treatment. The patient had surgery in Croatia to remove a tumor in his abdomen and requested that it be sent to Dr. Ribas.

Like everyone treating the patients in the Roche trial, Drs. Lo and Ribas were growing increasingly tormented by the knowledge that they could not promise more than a few months' reprieve to the patients enrolled in the drug trial.

They also knew that other researchers were close to publishing their own findings. One had given a presentation at a conference, and there was a rumor that his paper had been tentatively accepted by Nature, a premier science journal.

Over the first six months of this year, the doctors renewed their efforts to perform biopsies. Dr. Lo sent gentle e-mail reminders to the other oncologists with patients on the Roche drug, who might forget to ask or sidestep the difficult conversation.

He juggled his schedule to be available whenever the opportunity arose, borrowing exam rooms to squeeze patients in. He scraped exposed tumor off the neck of a dance teacher in her 60s, and sliced into the lower back of a mortgage broker in her 50s.

Roche's rules for how biopsy samples would be stored in the next, larger trial of its drug made it impossible to perform many of the tests Dr. Lo wanted to try. So the U.C.L.A. doctors asked patients to sign a separate consent form, authorized by the university's ethical review board, for research that would be conducted independent of the drug company.

There were some biopsies they did not get. One patient's family volunteered an autopsy if it would help, but the timing made it impossible: Dr. Lo needed living tissue for the studies he was conducting. The doctors decided against asking another patient, a young mother whose tumor was in her liver. The risk of complications did not justify the benefit.

A prominent immunologist from San Diego was willing to subject himself to a biopsy of a tumor near his knee, but the U.C.L.A. surgeon turned him away on the operating table, judging it too painful to remove. Still, when the immunologist, Dr. Norman Klinman, underwent surgery in San Diego after relapsing, his son raced to deliver his tumor sample, strapped into the front seat of his car in a container of dry ice, to Dr. Ribas's laboratory.

By early May, they had nine samples. Dr. Lo's three lab workers had worked nearly every weekend for a year, and he lacked the money to hire more. Another of his grant proposals had been turned down because a reviewer said the Roche drug was too early in its testing to warrant a search for the cause of resistance to it.

When the machine they used to measure cell growth broke down that month and dozens of experiments had to be redone, Dr. Lo's postdoctoral trainee mentioned a long-postponed trip to see relatives on the East Coast.

"Put it on hold," Dr. Lo urged. "We're almost there."

An Elusive Target

When Dr. Lo submitted his paper to Nature last July, he had collected tumor samples from 12 patients. Of the four that contained his suspect protein, three of the patients had died by the time he had identified it in their biopsy.

But the last one came from a 54-year-old Canadian named Wes Coyle, who was alive, but barely, when Dr. Lo confirmed the protein's presence through a biopsy of a tumor in his pelvis. It was the first time that, using his and Dr. Lo's research, Dr. Ribas could try to help a patient who had relapsed. He warned Mr. Coyle's sister Peggy Coyle Seaver, who was caring for her brother, that it was a long shot. But he prescribed the drug, made by Pfizer, that was known to block the protein in some other cancers.

For two weeks, Ms. Seaver reported to the doctor, her brother was able to eat again. Yet he died soon after that.

Another opportunity arose with a fifth patient who contributed tumor samples to Dr. Lo's collection, an avid gardener in Los Angeles. Her sample carried a gene mutation that suggested a second possible escape route for the cancer. But on a clinical trial for a drug specifically designed to block it, she quickly deteriorated.

Most likely, the two doctors knew, single drugs would not alone block the resurgent cancer, even if they were hitting the right targets.

"Damn it!" Dr. Ribas exploded, calling Dr. Lo when he saw the tumors growing on her scans. Of the 12 patient samples, Dr. Lo had identified the likely source of the cancer's resurgence in five. In August, with a grant he received from the Melanoma Research Alliance, along with researchers at other institutions, Dr. Lo began to probe the rest.

And in late November, after requesting another round of experiments, Nature published his paper, along with one from a competing researcher.

Ms. Seaver scanned the copy Dr. Ribas sent her, her breath catching when she recognized her brother, listed in a table as the 54-year-old male who had a 78-day response. "It feels like Wesley is still alive," she told her husband.

Brian Lewis, a paramedic whose wife Dr. Lo had decided against asking for a liver biopsy, read about his paper on the Internet, and contacted the doctor to ask whether providing one now would help him. His wife was doing poorly, but they had two young children, he wrote, "and I would hate to see them fight the same battle their mom is fighting."

A researcher at Memorial Sloan-Kettering Cancer Center consulted his own batch of five tumor samples from patients who had relapsed. One of them, he told colleagues on a conference call, had the second mutation Dr. Lo had found.

In early December, Dr. Ribas visited Roche's offices in San Francisco. The data in the paper, he argued, made a case for clinical trials of combinations of drugs the company was already developing. Researchers would need to take biopsies from patients in those trials, too, they all agreed. Because the cancer, even if blocked a second time, might find another way through.

"We have a lot more to do," Dr. Lo tells his laboratory staff every day.

Target Cancer

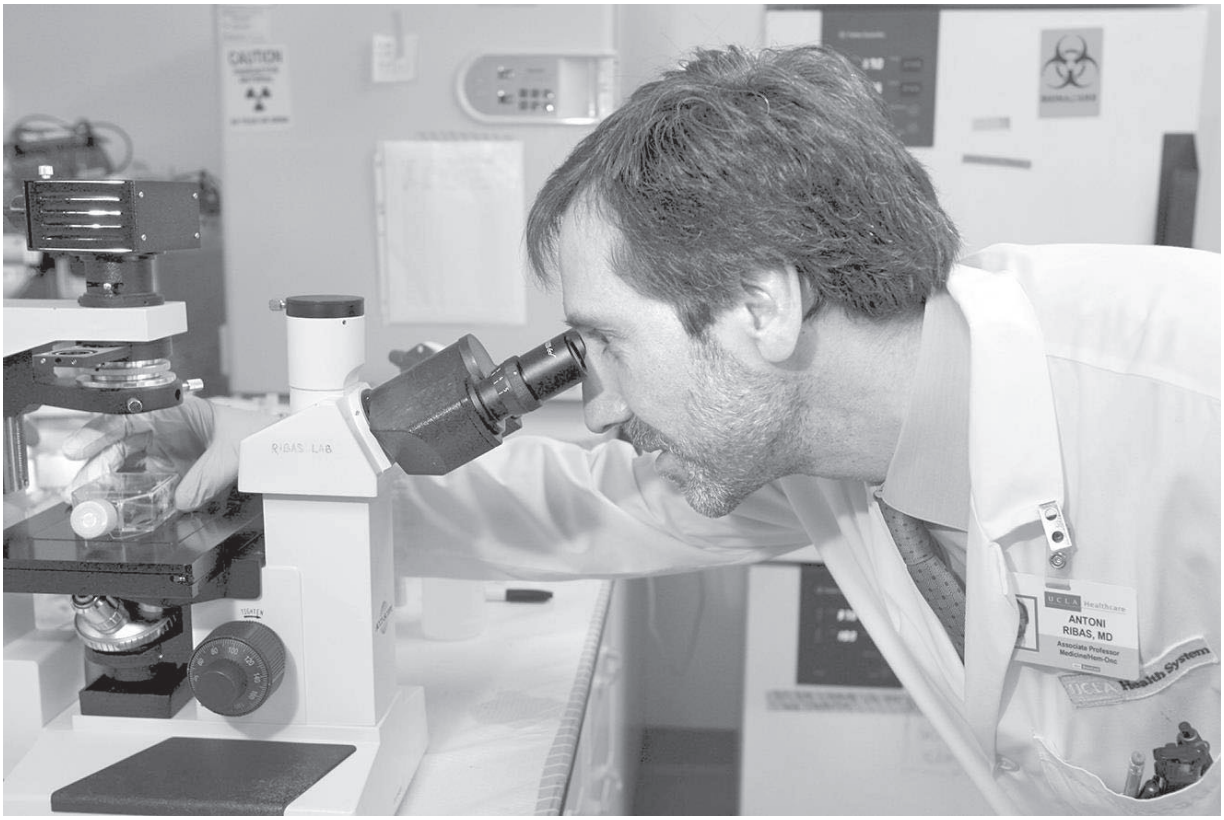
Articles in this series have chronicled the trial of an experimental melanoma drug through the eyes of doctors and patients.

ONLINE: *Previous articles in the series:*

nytimes.com/national

TRYING TO UNLOCK THE SECRETS

Above, a tumor from a patient is placed in a vial. Below, Dr. Antoni Ribas, the melanoma oncologist running a cancer drug trial at the University of California, Los Angeles.



PHOTOGRAPHS BY ANN JOHANSSON FOR THE NEW YORK TIMES

REYES FAMILY

A CRUCIAL ROLE

Lee Reyes, center, with his mother, Ellen, and brother, James. Cells from Lee Reyes, who relapsed after early progress, proved to be a central part of the cancer drug trial.

The Future Ain't What It Used to Be: Underpromising and Overdelivering on Postgenomic Health and Wellbeing

Misha Angrist, PhD
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Biography
Misha Angrist is Assistant Professor of the Practice in the Duke University Institute for Genome Sciences & Policy and a Visiting Lecturer at Duke's Sanford School of Public Policy. He trained as a genetic counselor and human geneticist, Recently he had his entire genome sequenced and made public. His new, intensely personal book about this experience and the emerging technology that made it possible is called *Here is a Human Being: At the Dawn of Personal Genomics (*Harper Books).

Notes

Lately there is much grumbling in the public sphere and defensive handwringing among geneticists and genomicists about the value of the latter's activities and the perceived failure to bring genomic discoveries to the clinic in a timely and powerful way. I argue that the anxieties surrounding the current state of clinically relevant genomic discovery and application could be mitigated, if not eliminated, by reimagining the relationship between investigators and research participants. Central to this new vision is an ethos of inclusiveness and partnership exemplified by return of genomic data to participants, easy access to publications, and cultivation of an ongoing connection between science and those who give of themselves for the sake of science.

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Notes

Type 1 DM

Hakon Hakonarson, MD, PhD

Director, Center for Applied Genomics
Associate Professor of Pediatrics
Department of Pediatrics and Division of Genetics
The Children's Hospital of Philadelphia
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

Biography

Hakon Hakonarson, M.D., Ph.D., is an associate professor of Pediatrics at The University of Pennsylvania School of Medicine. He is a physician-scientist and director of The Children's Hospital of Philadelphia's Center for Applied Genomics (CAG), a high-throughput highly automated genotyping facility founded to identify the genetic causes of complex medical disorders in children, such as autism and cancer, with the objective of developing new therapies. The Center represents a $40 million commitment from CHOP to genotype approximately 100,000 children a research undertaking that has gained nationwide attention, including news features in the *Wall Street Journal, New York Times, Time Magazine, Nature and Science*. Dr. Hakonarson has an extensive track record in human genetics. He has served previously in several senior posts in the biopharmaceutical industry, including as the director of Inflammatory and Pharmacogenomics Research and the vice president of Clinical Sciences and Development and CSO. Dr. Hakonarson has also been the principal and co-principal investigator on several NIH-sponsored grants, and he has published numerous high-impact papers on genomic discoveries and their translations in some of the most prestigious scientific medical journals, including *Nature*, *Nature Genetics*, *The New England Journal of Medicine and Cell*. *Time* Magazine listed Dr. Hakonarson's autism gene discovery reported in *Nature*, 2009, among the top 10 medical breakthroughs of that year. With over twelve years of experience in pioneering genomics research and genome-wide mapping and association studies, Dr. Hakonarson has intimate knowledge of the complexities of large-scale genomics projects and has put together the necessary infrastructure and workflow processes to unravel these complexities.

Personal Statement

My research interest focuses on human genetics, specifically the discovery and use of genetic variants and derived biomarkers in clinical medicine. My primary objective is to identify genetic variants that underlie complex medical disorders in children. In addition to working on complex pediatric disorders, including some of the most common and devastating medical problems that affect children worldwide, I also take into account that genetic variability's that predispose to a disease, while present at birth, may not be fully expressed until later in life and the disease itself may not manifest until much later. As such, my primary objective is to capture meaningful genetic variants in order to intervene and prevent disease as early as possible and to provide more focused treatment. With more than twelve years of experience in pioneering genomic research and genome-wide mapping and association studies, I have acquired intimate knowledge of the complexities of large-scale genomics projects and applied them to develop the necessary infrastructure and workflow processes to unravel these complexities in my role as the founder and director of CAG at CHOP. The center I direct is a high-throughput, highly automated genotyping and sequencing facility established to identify genetic variants that underlie differential response to drug therapies and susceptibility to complex medical disorders such as Type 1 Diabetes. I have also established a strong translational team to move these discoveries into clinical use.

Genetic Underpinning of Type – 1 Diabetes Summary

Hakon Hakonarson, MD, PhD

Diabetes impacts approximately 200 million adults worldwide, with micro-vascular and cardiovascular disease being the primary complications. 10% of cases are type 1 diabetes (T1D) sufferers, with the highest prevalence seen in populations of European ancestry. There is also evidence that the annual incidence has been on the increase[1,2].

T1D normally presents in childhood and occurs through the autoimmune destruction of pancreatic beta cells, preventing the production of insulin. It is well recognized that there is a strong genetic component to T1D so with the recent development of high throughput single nucleotide polymorphism (SNP) genotyping array technologies in last five years, investigators have been given the opportunity to search for risk conferring loci in genome wide association studies (GWAS) of T1D. Together with the already established genes that have been known for many years, at least sixteen loci (Table 1) have now been elucidated to contribute to the pathogenesis of T1D[3-11]. The next steps are to functionally follow up these genetic signals and to leverage this information to improve diagnosis, prevention and cure of these diseases.

T1D is a clear example of a complex trait that results from the interplay between environmental and genetic factors. There are many lines of evidence that there is a strong genetic component to T1D. The epidemiological data for geographic prevalence differences is one clear indicator, with populations of European ancestry having the highest presentation rate. T1D has high concordance among monozygotic twins and runs strongly in families, with the sibling risk being 15 times greater than the general population; this is in clear contrast to the 'less genetic' type 2 diabetes (T2D), where the sibling risk ratio is a relatively modest 3.5[12].

Large-scale genomic analyses, including GWAS meta-analysis of over 12,000 cases and 17,000 controls will be presented. Re-sequencing studies for most interesting T1D loci as well as whole genome sequencing data will be presented. Finally, functional characterization of the CLEC16A, a lead target in the pathogenesis of T1D, will be presented.

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Notes

Epigenomics

Karen Mohlke, PhD

Associate Professor,
Department of Genetics
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

Biography

Karen L. Mohlke, Ph.D., Associate Professor of Genetics at the University of North Carolina at Chapel Hill School of Medicine, was awarded the Ph.D. degree at the University of Michigan. Prior to joining UNC in 2004, she conducted studies to pinpoint type 2 diabetes susceptibility genes in the laboratory Francis Collins, M.D., Ph.D., at the National Human Genome Research Institute. She was one of the 2006 Pew Scholars in the Biomedical Sciences.

At UNC, Dr. Mohlke's lab searches for the genetic variants that influence common human traits with complex inheritance patterns, with the goal of determining the biological function of the identified variants. She was one of the scientists in the consortium, aptly named GIANT for Genetic Investigation of ANthropometric Traits, which authored the 2010 *Nature* paper, "Hundreds of variants clustered in genomic loci and biological pathways affect human height."

Notes

Epigenomics
Karen Mohlke, PhD

Gene regulation and genome function are influenced by the physical organization of DNA in cells. DNA is wound around histone proteins and packaged into complexes known as chromatin. The extent to which DNA is wrapped around histones, and thus the availability of genes to be activated, depends on chemical marks, such as methylation and acetylation, that modify the histones. If the histone marks lead to DNA that is wrapped tightly, a gene may be turned off, and if the marks lead to DNA that is wrapped more loosely, a gene may be turned on. Gene regulation is also influenced by methylation marks that influence the DNA backbone. Epigenomics is the genome-wide study of these chemical marks, which differ by cell type, can be inherited, and can influence health and disease (1).

Advances in high-throughput sequencing have enabled identification of epigenomic marks. Experimental approaches to identify open chromatin include DNase I hypersensitivity (2; 3) and formaldehyde-assisted identification of regulatory elements (FAIRE)(4). Histone marks can be identified by chromatin immunoprecipitation (ChIP)(5), and sites of DNA methylation can be identified at nucleotide resolution (6; 7).

Maps of epigenomic features can be used to localize noncoding regulatory elements such as promoters, enhancers, silencers, and insulators. These regulatory regions contain DNA variants that may affect transcription and influence disease. Although genome-wide association studies have identified dozens of loci associated with type 1 and type 2 diabetes and related traits, the underlying functional variants at these loci largely remain unknown.

Recently, we and others have characterized the epigenome of human pancreatic islets (8-11). We profiled chromatin by FAIRE coupled with high-throughput sequencing and identified ~80,000 open chromatin sites encompassing 1.0% of genomic sequence (8). We mapped sequence variants to open chromatin sites and found that rs7903146, a *TCF7L2* intronic variant strongly associated with type 2 diabetes, is located in islet open chromatin. Heterozygotes for rs7903146 exhibit differences between variant nucleotides in islet FAIRE signal, and the variant alters enhancer activity. These data suggest that genetic variation at the *TCF7L2* diabetes susceptibility locus acts in *cis* with local chromatin and regulatory changes. These and other studies demonstrate that epigenomic maps can guide identification of regulatory variants important for disease susceptibility.

These approaches can be applied to more tissue types and additional traits and diseases. The NIH Roadmap Epigenomics Consortium is producing maps for many different types of human cells (www.roadmapepigenomics.org)(12). This consortium is performing genome-wide analysis of more than 30 histone modifications, DNA methylation, open chromatin, and gene expression (www.epigenomebrowser.org). International groups are also performing large-scale epigenomics studies (ihec-epigenomes.org)(13). Understanding the patterns of epigenetic regulation of all cell types, during normal development and in response to the environment, will provide biological insights and better knowledge of disease mechanisms, which may lead to improved disease diagnosis, treatment and prevention.

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Notes

Immune Gene Variation in Type I DM

Stephen S. Rich, PhD
Director, Center for Public Health Genomics
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University of Virginia School of Medicine
Charlottesville, Virginia

Biography

Stephen S. Rich, PhD, is Director of the Center for Public Health Genomics at the University of Virginia School of Medicine. Dr. Rich received his B.S. in Mathematics from North Carolina State University, his M.S. in Population Genetics and Ph.D. in Quantitative Genetics at Purdue University. Following a postdoctoral fellowship in computer simulation, he joined the faculty of the University of Minnesota in 1980 in the Department of Laboratory Medicine and Pathology, advancing to the rank of tenured Professor. At the University of Minnesota, Dr. Rich developed his career-interest in the genetic basis of type 1 diabetes and diabetic complications, served as Associate Editor of Diabetes, and helped found the Institute of Human Genetics. In 1994, Dr. Rich moved to Wake Forest University School of Medicine and established a Center for Genetic Epidemiology and founded the Type 1 Diabetes Genetics Consortium (T1DGC), an international study that recruited 2800 affected sib pair families with T1D, performed numerous genetic studies, and made resources available to the scientific community. In 2007, Dr. Rich moved to the University of Virginia, where he is the Harrison Professor and Vice-Chair of Public Health Sciences and founding Director of the Cener for Public Health Genomics. The Center reflects the importance of the component parts – "genomics" and "public health". By its nature, the faculty of the Center has a focus on understanding the genetic basis of complex human disease and translating that information into means to increase the benefit for the public health. Examples of the research performed by faculty in the Center include understanding the genetic basis of (1) type 1 diabetes (2) ischemic stroke (3) second primary breast cancer from radiation treatment of a first primary breast tumor (4) diabetic kidney disease (5) bone metabolism and fracture risk (6) under-nutrition (7) vaccine failure and (8) chronic/recurrent otitis media. The combination of modern genomic technologies, from high throughput SNP genotyping to DNA sequencing, with statistical genetic, population genetic and bioinformatic tools, provides the University with a unique perspective on the application of genomics to translational health.

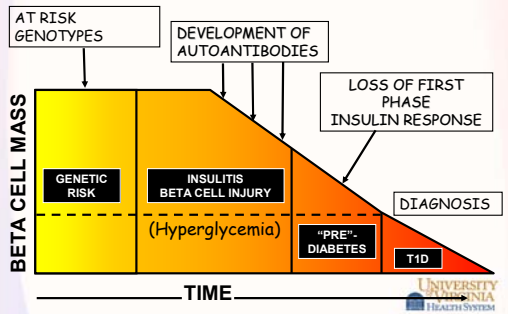
Notes

Immune Gene Variation in Type 1 Diabetes (T1D)

Stephen S. Rich, PhD

March 4, 2010

Stages in Development of T1D



Type 1 Diabetes Genetics Consortium

- Generate large sample collections of DNA and serum/plasma in families
- Interrogate the most significant genetic risk region in the genome – T1DGC MHC Fine Mapping Project
- Examine results from published reports of candidate genes – T1DGC Candidate Gene Project
- Search for novel genetic targets by scanning the human genome – T1DGC Genome-Wide Association Scan (GWAS) meta-analysis
- Make collections and data available to all *bona fide* researchers (http://www.t1dgc.org)

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GWAS meta-analysis
16 Novel Replicated T1D Regions

SNP	Chromosome	Gene	1-df *p*-values		
			Meta-analysis	Replication	Combined
rs3024505	1	*IL10*	2.2×10^{-6}	1.5×10^{-8}	1.9×10^{-9}
rs10517086	4		2.8×10^{-7}	2.1×10^{-4}	4.6×10^{-10}
rs9388489	6	*C6orf173*	5.1×10^{-8}	1.4×10^{-5}	4.2×10^{-13}
rs4948088	7	*COBL*	2.7×10^{-6}	1.9×10^{-3}	4.4×10^{-8}
rs7020673	9	*GLIS3*	1.9×10^{-6}	1.3×10^{-4}	5.4×10^{-10}
rs10509540	10	*C10orf59*	6.9×10^{-8}	4.9×10^{-24}	1.3×10^{-28}
rs4763879	12	*CD69*	2.8×10^{-7}	1.1×10^{-5}	1.9×10^{-11}
rs1465788	14	*C14orf181*	1.4×10^{-6}	1.5×10^{-6}	1.8×10^{-11}
rs4900384	14		1.1×10^{-6}	4.2×10^{-6}	3.7×10^{-11}
rs4788084	16	*IL27*	5.2×10^{-8}	8.4×10^{-7}	2.6×10^{-13}
rs7202877	16	*CTRB2*	5.7×10^{-11}	1.2×10^{-4}	3.1×10^{-15}
rs2290400	17	*GSDML*	1.3×10^{-7}	8.2×10^{-7}	5.5×10^{-13}
rs425105	19	*PRKD2*	1.5×10^{-7}	2.6×10^{-5}	2.7×10^{-11}
rs2281808	20	*SIRPG*	5.0×10^{-7}	4.8×10^{-6}	1.2×10^{-11}
rs5753037	22	*LOC729980*	1.8×10^{-14}	5.8×10^{-4}	2.6×10^{-16}
rs2664170	X	*GAB3*	3.0×10^{-6}	5.8×10^{-4}	7.8×10^{-9}

Barrett, Clayton, Concannon *et al.*, Nat Genet 2009; 41:703-707

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Six Nominally-Replicated T1D Regions

SNP C	hromosome	Gene	1-df *p*-values		
			Meta-analysis	Replication	Combined
rs2269241 1		*PGM1*	5.9×10^{-6}	6.9×10^{-3} 4.	2×10^{-7}
rs1534422 2			6.7×10^{-6} 0.	025	2.1×10^{-6}
rs7804356 7		*SKAP2*	3.3×10^{-8}	5.1×10^{-3} 5.	3×10^{-9}
rs12444268	16	*UMOD*	2.0×10^{-6}	4.5×10^{-3} 1.	7×10^{-7}
rs72211097	17	*SMARCE1*	9.9×10^{-10}	8.3×10^{-3} 1.	3×10^{-9}
rs16956936	17	*DNAH2*	3.2×10^{-6}	9.7×10^{-3} 5.	3×10^{-7}

Barrett, Clayton, Concannon *et al.*, Nat Genet 2009; 41:703-707

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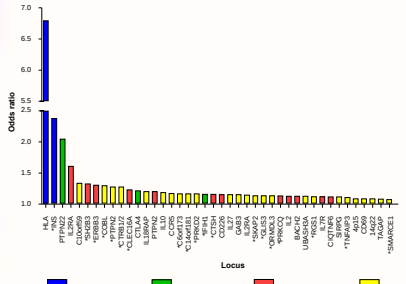

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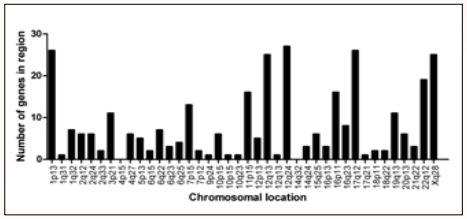
Known Gene Content in T1D Loci



* Numbers of genes contained within T1DGC GWAS regions defined by decay of linkage disequilibrium

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How to Follow a GWA?

Dense SNP genotyping within regions
- SNPs defined from 1000 Genomes
- reduced sets from the LD patterns in a region

Search for structural variants

Targeted DNA sequence analysis
- defining the target region
- sequence capture & sequence & analysis

Targeting coding regions (exons) in regions

Functional studies

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Dense SNP Typing - ImmunoChip

Custom high-density (200K) SNP chip
- Genome-wide significant SNPs from 9 autoimmune diseases (T1D, MS, RA, IBD, SLE, celiac, …)
- Efficiency -- ~50% of regions common to 2 or more diseases
- MHC SNPs (5K)

Large Sample Size
- 2800+ T1DGC ASP families (AP, EUR, NA, UK Networks)
- 15,000+T1D cases, including UKGrid, Denmark, EDIC/DCCT, GoKinD
- 15,000+ Controls, including B58BC, UKBS, NYCP, NIMH

Additional T1D/autoimmune samples
- SEARCH, nPOD, BDC, Sweden, ACDDR, TEDDY
- BDA Warren 1, Finland, African-American, Mexican-American
- Benaroya Research Institute (Fine mapping with function, DP3)

T1D Targeted Sequencing

Goals
- identify SNP variants
- - identify structural variants

Sample DNA pooling

Capture using Nimblegen solid support

Sequencing using Roche 454 technology

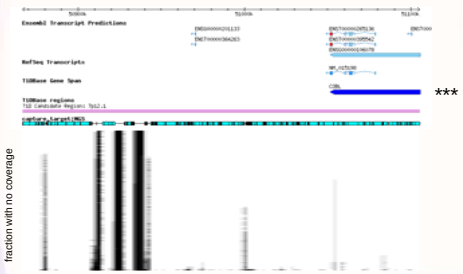
Targeted regions (genes of interest (at that time))
- 7p12.1 (*COBL*)
- 10q23.31 (C10orf59 = *RNLS*)
- 16q23.1 (7 genes)
- 19q13.32 (5 genes)

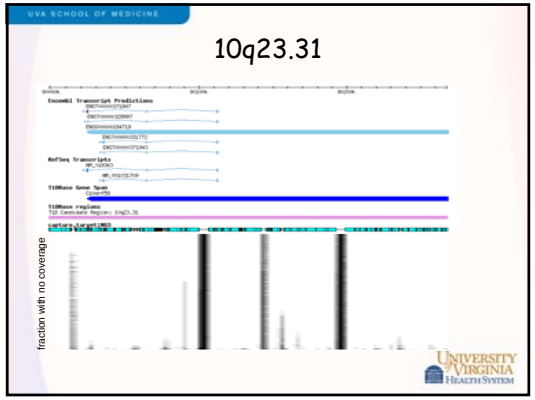
T1DGC Sequencing Study

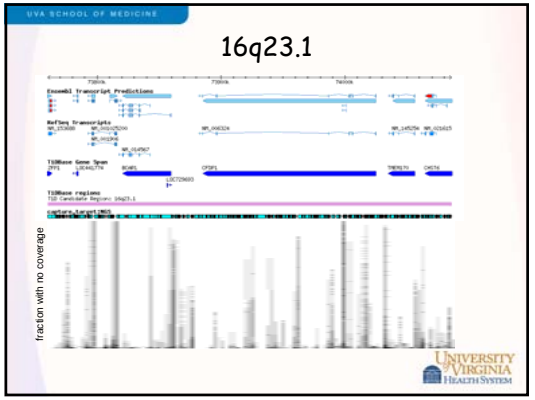
50 Case Pools 50 Control Pools

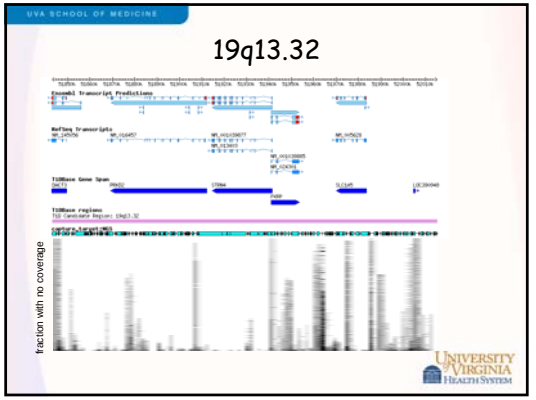
Each sample in a pool
has 500K/1M SNP genotyping
-Imputation
-Quality control
-Built-in barcodes

7p12.1




UVA SCHOOL OF MEDICINE
10q23.31
fraction with no coverage
UNIVERSITY OF VIRGINIA HEALTH SYSTEM


UVA SCHOOL OF MEDICINE
16q23.1
fraction with no coverage
UNIVERSITY OF VIRGINIA HEALTH SYSTEM


UVA SCHOOL OF MEDICINE
19q13.32
fraction with no coverage
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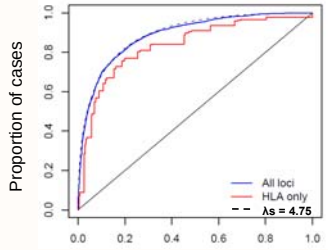
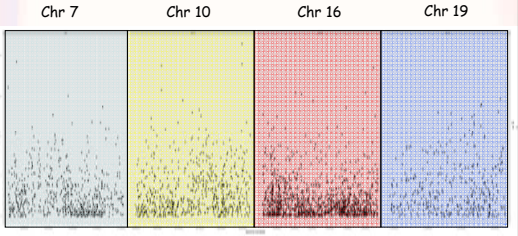
Progress in T1D targets

- From 454 runs, 9.3 Gbs in 35.9M reads, with average read length of 250-300 bp
- Used syzygy (Broad pooled SNP caller) and three other algorithms for SNP discovery
- Modeled allele counts in each pool as linear function of pool composition, apparent MAF, and disease association factor (evidence of association)
- rare SNPs: cluster based on location, function, use same model (with multivariate observations)
- first-pass analysis evaluating new (rare) SNPs for association with T1D *vs* GWA-associated SNPs

Prediction for T1D using only SNPs



Is there hope?



Summary

Transition from GWA scan to gene discovery
- Dense SNP mapping (ImmunoChip)
- Targeted sequencing (region & exon)
- Structural variants (not tagged by SNPs)

Transition from common to rare variants

Shift from SNP-centric to gene-centric

Functional studies of T1D-associated genes

Availability of data and samples (NIDDK Central Repository (www.niddkrepository.org))

Acknowledgements

University of Virginia
Stephen Rich
Pat Concannon
Joe Mychaleckyj
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Aaron Quinlan
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Jo Howson
Jason Cooper
David Clayton
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Wellcome Trust/Sanger Center
Matt Hurles, Jeff Barrett

T1DBase is a collaboration:

Supported by DK062418, DK085695, JDRF

1. Morahan G, Mehta M, James I, Chen WM, Akolkar B, Erlich HA, Hilner JE, Julier C, Nerup J, Nierras C, Pociot F, Todd JA, Rich SS; Type 1 Diabetes Genetics Consortium. Tests for genetic interactions in type 1 diabetes. Diabetes 2011 Mar; 60 (in press)
2. Manichaikul A, Mychaleckyj JC, Rich SS, Daly K, Sale M, Chen WM. Robust relationship inference in genome-wide association studies. Bioinformatics 2010 Nov 15;26(22):2867-73. PMID: 20926424
3. Concannon P, Rich SS, Nepom GT. Genetics of type 1A diabetes. N Engl J Med. 2009 Apr 16;360(16):1646-54. Review. No abstract available. PMID: 19369670
4. Concannon P, Chen WM, Julier C, Morahan G, Akolkar B, Erlich HA, Hilner JE, Nerup J, Nierras C, Pociot F, Todd JA, Rich SS; Genome-wide scan for linkage to type 1 diabetes in 2,496 multiplex families from the Type 1 Diabetes Genetics Consortium.and the Type 1 Diabetes Genetics Consortium. Diabetes. 2009 Apr;58(4):1018-22. PMC2661598
5. Barrett JC, Clayton DG, Concannon P, Akolkar B, Cooper JD, Erlich HA, Julier C, Morahan G, Nerup J, Nierras C, Plagnol V, Pociot F, Schuilenburg H, Smyth DJ, Stevens H, Todd JA, Walker NM, Rich SS; The Type 1 Diabetes Genetics Consortium. Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. Nat Genet. 2009 May 10. [Epub ahead of print] PMID: 19430480
6. Chen WM, Manichaikul A, Rich SS. A generalized family-based association test for dichotomous traits. Am J Hum Genet 2009 Sep; 85(3):364-76. PMID: 19732865
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8. Concannon P, Onengut-Gumuscu S, Todd JA, Smyth DJ, Pociot F, Bergholdt R, Akolkar B, Erlich HA, Hilner JE, Julier C, Morahan G, Nerup J, Nierras CR, Chen WM, Rich SS; Type 1 Diabetes Genetics Consortium. A human type 1 diabetes susceptibility locus maps to chromosome 21q22.3. Diabetes 2008 Oct; 57(10);2858-61. PMID: 18647951
9. Pociot F, Akolkar B, Concannon P, Erlich HA, Julier C, Morahan G, Nierras CR, Todd JA, Rich SS, Nerup J. Genetics of type 1 diabetes: What's next? Diabetes 2010 Jul;59(7): 1561-71. PMID: 20587799

Notes

From Genomics to Personalized Metabolic Medicine

Philippe Froguel, MD, PhD
Professor of Genomic Medicine,
Chair of the Department of Genomics of Common Diseases
School of Public Health Hammersmith Hospital
Imperial College
London, United Kingdom

Biography
Philippe Froguel passed his Medical Degree in 1986 in Paris and obtained a PhD in 1991 from Paris 7 University. He is currently Professor and Head of the Department of Genomics of Common Disease at the Hammersmith Hospital, Imperial College London, UK. He is also director of a CNRS research group at Pasteur Institute, Lille, France.

His scientific career is entirely focused on the genetics of common diseases in humans, especially diabetes and obesity. He is author of >400 Pubmed indexed publications. He has developed candidate gene, positional cloning and positional candidate gene approaches In monogenic and polygenic T2D and obesity. He published in February 2007 (Sladek et al, Nature) the first Genome Wide Association Study In a common disease (T2D) using ·high density microarrays (most referred paper in diabetes research), and in 2008 the first GWAS analysis related to quantitative traits related to glucose control. His work led to several breakthroughs (MODY genes glucokinase, and HNF-1α; neonatal diabetes gene ABCCBfSUR1; obesity genes leptin receptor, MC4R, FTO; glycemia/T2D genes KIR 6.2, SLC30A8/ZnT8, HHEX, G6PC2, MTNR1B; "diabesity" genes adlponectin, ENPP1/PC-1).

In 2010, he published the first evidence that finding in extreme obesity phenotypes rare Copy Number Variations can help to understand better the genetics of common obesity, contributing to elucidate the "hidden heritability" of metabolic diseases (Walters et al, nature).

Notes

Genomic Medicine in the Prevention of Cardiovascular Disease

Muredach P. Reilly, MB, MS
Associate Professor of Medicine and Pharmacology
Cardiovascular Institute
University of Pennsylvania
Philadelphia, Pennsylvania

Biography

Muredach P. Reilly , MB is an Associate Professo r of Me dicine at the University Of Pennsy lvania School Of Medicine. He attended medical school and at U niversity Col lege in Dubl in and com pleted his residency an d Cardiovascular Fellowship in Ireland. He ca me to the Un iversity of Pennsy lvania (Penn) in 1994 where he completed his Medicine Residency , Cardiovascular Clin ical and Resear ch Fellowships, as well as his Masters i n Science and Clinical Epidem iology. He was appointed Assistant Professor of Medicine and in 2002 and was promoted to Associat e Professor in 2010. Dr. Reilly is also Director of the Translational Core Laboratory, Clinical and Transitional Rese arch Center at P enn. At Penn, he has rec eived num erous teach ing and young investigator awards. In 2 010 he was elected to the Am erican Societ y for Clinical Investigation and awarded the Special Recognition Award of th e American Heart Association C ouncil of Arteriosclerosis, Thrombosis and Vascular Biology.

Dr Reilly's research interests include mechanisms of atherosclerosis in metabolic syndrome, diabetes and obesity, the role on innate i mmunity i n prom oting atherosclero tic risk in metabolic sy ndrome, and the genom ics of hum an atherosclerosis and cardiovascular risk.

His research program has been fully funded by the NIH since 2002 and he has published numerous arti cles in leading journals including the Lancet, Nature Genetics, Circulation and Journal of the American College of Cardiology.

Notes

Genomics of Coronary Artery Disease

Muredach P. Reilly MB MS
Associate Professor of Medicine and Pharmacology
Cardiovascular Institute
University of Pennsylvania

DISCLOSURE INFORMATION:
Research grants from Glaxo Smith Kline, Merck & Co, NIH.

UNLABELED/UNAPPROVED USE:
None

Overview

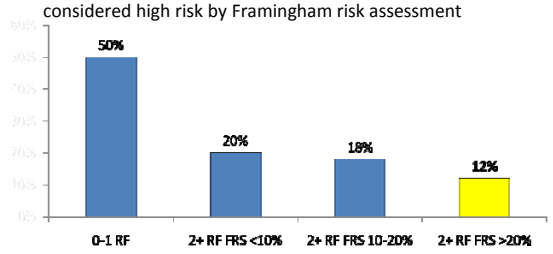
- CAD phenotypes
- Lipids – informative example
- CHD – CAD/MI
  - Penn GWAS of CAD phenotypes
  - CARDIoGRAM & beyond
- Sequencing projects - DNA
- Risk prediction and future

Coronary Heart Disease (CHD)

- CHD is the single largest killer of men and women in the US
- Each year 1.5 million people have a myocardial infarction
- At least 250,000 apparently healthy persons die of their first MI each year
- Traditional risk factors explain only ~60% of MI and CHD death.

Using Risk Factors Alone Underestimates Risk

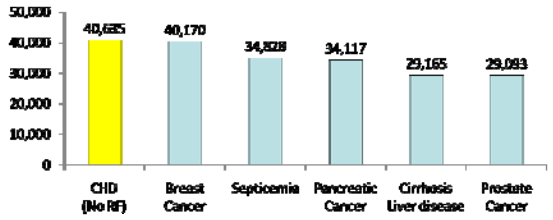
Among 222 younger patients (mean age 50, 75% men) presenting with myocardial infarction, only **1 in 8** were considered high risk by Framingham risk assessment



Akosah. JACC 2003;41:1475.

Using Risk Factors Alone Underestimates Risk

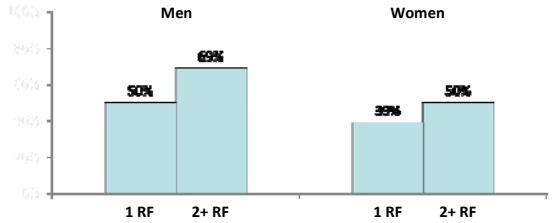
- 10% of patients with fatal CHD have no traditional risk factors[1,2]
- With CHD accounting for 406,351 deaths in the US annually,[3] the number of patients dying from CHD without any traditional risk factors exceeds that of other public health priorities[4]



[1]Khot. JAMA 2003;290:898. [2]Greenland. JAMA 2003;290:891. [3]CDC Mortality Statistics 2007. http://www.cdc.gov/nchs/fastats/lcod.htm. AHA Heart Disease and Stroke Statistics 2010 reported CHD at 425,425 in 2006. [4]American Cancer Society 2009. CDC Mortality Statistics 2007.

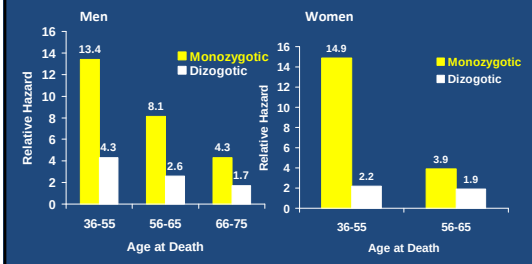
Treating Everyone Overestimates Risk

Lifetime risk of cardiovascular disease is indeed high in patients with major risk factors; however it is far from 100%, even in the presence of 2+ major risk factors and assuming survival to 95 y



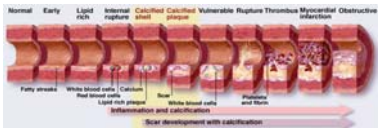
Lloyd-Jones. Circulation 2006;113:791. Framingham Heart Study. n=3564 M, 4362 W, 111777 person-years.
*Major risk factor: TC>240, SBP>160, DBP>100, current smoker, or diabetic.

Risk of CHD Death in Twins: Atherosclerosis is highly influenced by genetics



Marenberg M, NEJM 1994

Genomics of CAD: Promise and Challenge

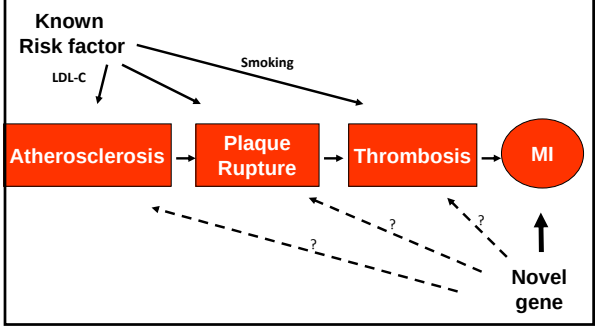


- Novel mechanistic-pathophysiologic insights
- Novel risk pathways and risk factors
- Novel therapies
- Identify high risk individuals – customized risk assessment

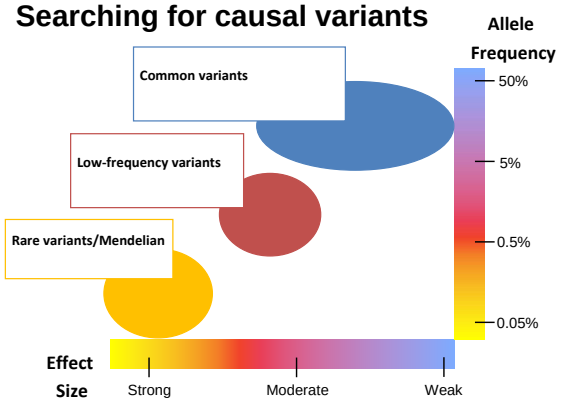
Genetics of Coronary Atherosclerosis

- Traditional cardiovascular risk factors that are influenced by genetic variation
- Other genes that contribute to coronary atherosclerosis and CHD

Pathophysiologic Pathways to Clinical CHD Events



Searching for causal variants



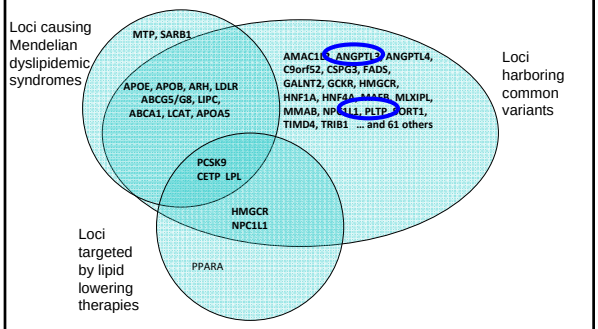
GWAS in > 100,000 individuals: 95 lipid loci

LDL-C			HDL-C			Triglycerides	
ABCG5/8	HFE	SORT1	ABCA1	HNF4A	PDE3A	ACSS2	GALNT2
ABO	HMGCR	ST3GAL4	ABCA8	IRS1	PGS1	AFF1	GCKR
ANGPTL3	HNF1A	TIMD4	ADM	KLF14	PLTP	ANGPTL3	IRS1
APOA	HPR	TOP1	ANGPTL4	LACTB	PPP1R3B	ANKRD55	JMJD1C
APOB	IDOL	TRIB1	APOA	LCAT	SBNO1	APOA	LIPC
APOE	IRF2BP2		APOB	LILRA/B	SCARB1	APOB	LPL
BRAP	LDLR		APOE	LIPC	SLC39A8	APOE	LRP1
BTNL2	LDLRAP1		ARL15	LIPG	STARD3	BTNL2	MLXIPL
CBLN3	LPA		C6orf106	LPA	TRIB1	CAPN3	MSL2L1
CETP	MAFB		CETP	LPL	TRPS1	CETP	NAT2
CILP2	MOSC1		CITED2	LRP1	TTC39B	CILP2	PINX1
CYP7A1	NPC1L1		CMIP	LRP4	UBASH3B	COBLL1	PLA2G6
DNAH11	OSBPL7		COBLL1	MACF1	UBE2L3	CTF1	PLTP
FADS	PCSK9		DOCK6	MC4R	ZNF648	CYP26A1	TIMD4
FRK	PLEC1		FADS	MLXIPL	ZNF664	FADS	TRIB1
GPAM	PPP1R3B		GALNT2	MMAB		FRMD5	TYW1B
							ZNF664

Total Cholesterol					
ERGIC3	EVI5	FUT2	RAB3GAP1	RAF1	SPTY2D1

Teslovich, et al Nature 2010

Mendelian syndrome genes and existing molecular targets harbor common SNPs



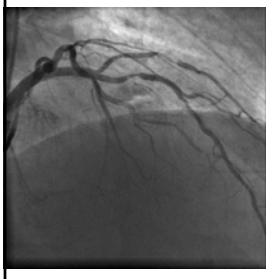
Teslovich, *Nature* 2010

GWAS: New Loci for CAD and MI (as of mid 2010)

Locus	SNP	RAF	OR	p-value	Genes
9p21	rs1333049	52%	1.20 (1.16-1.25)	$2.8 \cdot 10^{-21}$	*CDKN2A, CDKN2B, ANRIL*
1p13.3	rs599839	77%	1.13 (1.08-1.19)	$1.1 \cdot 10^{-14*}$	***PSCR1, CELSR2, SORT1***
1q41	rs3008621	72%	1.10 (1.04-1.17)	$5.4 \cdot 10^{-8*}$	*MIA3*
10q11	rs501120	84%	1.11 (1.05-1.18)	$9.5 \cdot 10^{-8*}$	***CXCL12***
6p24	rs12526453	65%	1.13 (1.08-1.17)	$1 \cdot 10^{-9}$	*PHACTR1*
2q33	rs6725887	14%	1.17 (1.11-1.23)	$1 \cdot 10^{-8}$	*WDR12*
21q22	rs9982601	13%	1.19 (1.14-1.27)	$6 \cdot 10^{-11}$	*SLC5A3, MRPS6, KCNE2*
6q26-27	haplotype	18%	1.20 (1.13-1.28)	$1.2 \cdot 10^{-9}$	***SLC22A3, LPAL2, LPA***
3q22.3	rs9818870	15%	1.15 (1.11-1.19)	$7.4 \cdot 10^{-13}$	*MRAS*
19p13.2	rs2228671	11%	0.82 (0.76-0.89)	$2.1 \cdot 10^{-7}$	***LDLR***
12q24	rs3184504	38%	1.13 (1.08-1.18)	$8.6 \cdot 10^{-8}$	*SH2B3 locus*
12q24.3	rs2259816	36%	1.08 (1.05-1.11)	$4.8 \cdot 10^{-7}$	*HNF1A, C12orf43*

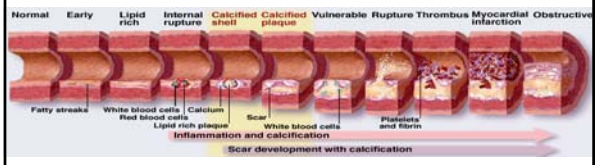
McPherson, *Science* 2007
Helgadottir, *Science* 2007
WTCCC *Nature* 2007
Samani, *NEJM* 2007
MI-GEN, *Nat Genet* 2009
Erdmann, *Nat Genet* 2009
Gudbjartsson, *Nat Genet* 2009
Trégouët, *Nat Genet* 2009
Soranzo, *Nat Genet* 2009

PennCath Genetics



- Cath-lab recruitment
- 1998-2003
- N=3,815
- CAD sub-phenotype and biomarker studies

CAD Sub-phenotypes

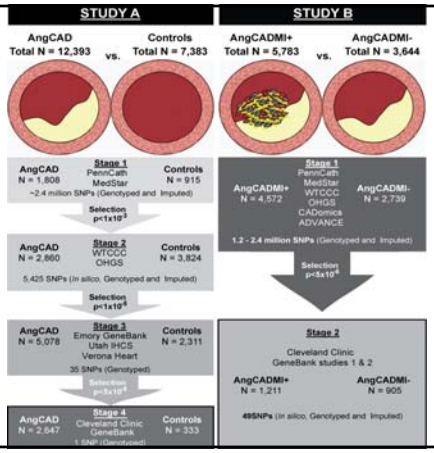


Known Risk factors

Genetic Risk factors?

PennCath and MedStar GWAS Samples

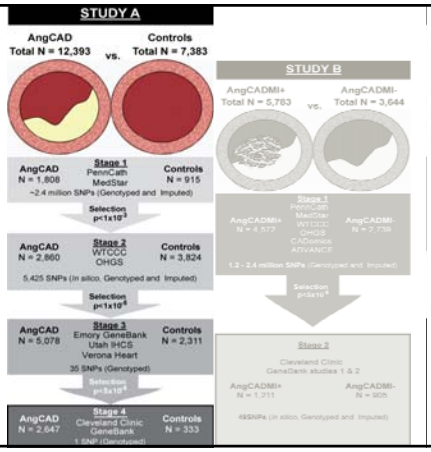
	PennCath		MedStar	
	AngCAD	Control	AngCAD	Control
Number of subjects	933	468	875	447
Study Criteria				
Case-Control Definition	AngCAD: aged <66y, one or more vessels ≥ 50% stenosis, ~50% MI. Controls: men aged >40y and women aged >45y (Angiography normal or <10% stenosis in all vessels).		AngCAD: individuals aged <61y, one or more vessels ≥ 50% stenosis, ~50% MI. Controls: individuals aged >45y (Angiography normal or <10% stenosis in all vessels).	
*Mean Age (y)	52.7±7.6*	61.7±9.6*	48.9±6.4*	59.7±8.9*
Female, N (%)	221 (24)	243 (52)	289 (33)	244
MI, N (%)	**469 (50)**	**0**	**421 (48)**	**0**
CABG, N (%)	209 (22)	0	169 (19)	0
PCI, N (%)	293 (31)	0	506 (58)	0
Cardiovascular risk factors				
Diabetes, N (%)	228 (24)	52 (11)	273 (31)	85 (19)
Hypercholesterolemia, N(%)	748 (80)	292 (62)	698 (80)	261 (58)
HTN, N (%)	572 (61)	230 (49)	668 (76)	271 (61)
Smoking, N (%)	427 (46)	163 35)	465 (53)	223 (50)
BMI (kg/m^2)	29.8±5.6	28.9±6.4	31.7±6.8	31.3±7.9
Coronary Angiography				
1 Vessel Disease, (%)	259 (28)	0	340 (39)	0
2 Vessel Disease, (%)	266 (29)	0	200 (23)	0
3 Vessel Disease, (%)	353 (38)	0	287 (33)	0



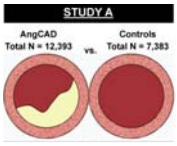
Established CAD/MI Loci are not Related to MI in Patients with Established AngCAD

SNP	Chr	Location	Position (NCBI36)	Effect allele*	Effect allele frequency†	Gene(s)	(A) AngCAD vs. Control OR (95% CI)	*P*	Effective sample size§	(B) AngCADMI+ vs. AngCADMI- OR (95% CI)	*P*	Effective sample size§
rs646776	1	1p13	109620053	T	0.79	CELSR2, PSRC1, SORT1	1.33 (1.22, 1.44)	7.88×10^{-11}	7790	1.02 (0.94,1.11)	0.69	6916
rs17465637	1	1q41	220890152	C	0.72	MIA3	1.09 (1.01, 1.18)	0.02708	7790	1.03 (0.95, 1.11)	0.55	6360
rs11206510	1	1p32	55268627	T	0.82	PCSK9	1.03 (0.94, 1.13)	0.4857	7790	1.02 (0.94, 1.11)	0.65	8436
rs6725887	2	2q33	203454130	C	0.13	WDR12	1.28 (1.15, 1.45)	1.74×10^{-5}	6454	0.99 (0.91, 1.08)	0.87	8436
rs9818870	3	3q22	139604812	T	0.16	MRAS	1.15 (1.03, 1.27)	0.009773	6656	0.96 (0.89, 1.04)	0.25	8436
rs12526453	6	6q24	13035530	C	0.66	PHACTR1	1.17 (1.09, 1.26)	1.45×10^{-5}	7790	1.05 (0.98, 1.12)	0.20	8196
rs4977574	9	9p21	22088574	G	0.53	ANRIL, CDKN2A, CDKN2B	1.3 (1.22, 1.39)	4.78×10^{-14}	7790	1.00 (0.94, 1.06)	0.96	8436
rs1746048	10	10q11	44095830	C	0.86	CXCL12	1.08 (0.97, 1.18)	0.1681	7790	1.04 (0.95, 1.14)	0.42	8436
rs11066301	12	12q24.3	111355755	G	0.46	ATXN2, SH2B3, PTPN11	‡	‡	‡	1.03 (0.96, 1.10)	0.42	6676
rs1122608	19	19p13	11024601	G	0.75	LDLR	1.18 (1.09, 1.28)	0.0001568	6454	0.98 (0.91, 1.05)	0.62	8436
rs9982601	21	21q22	34520998	T	0.13	SLC5A3, MRPS6, KCNE2	1.18 (1.07, 1.30)	0.001106	7790	1.07 (0.97, 1.18)	0.15	6676

McPherson, *Science* 2007
Helgadottir, *Science* 2007
WTCCC, *Nature* 2007
Samani, *NEJM* 2007
MI-GEN, *Nat Genet* 2009
Erdmann, *Nat Genet* 2009
Gudbjartsson, *Nat Genet* 2009
Tregouet, *Nat Genet* 2009
Soranzo, *Nat Genet* 2009

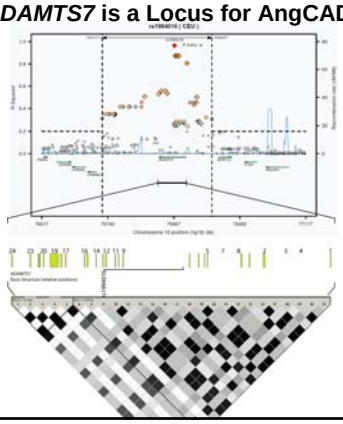


Study A: AngCAD vs. Controls: ADAMTS7 is a Locus for AngCAD

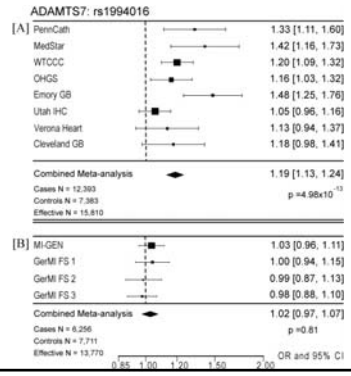


SNP	Chr	Position (NCBI-36)	Risk allele	Risk allele freq.	Gene	Stage 1 OR (95% CI) *P*	Stage 2 OR (95% CI) *P*	Stage 3 OR (95% CI) *P*	Stage1&2&3 OR (95% CI) *P*	Stage 4 OR (95% CI) *P*	All Stages Combined OR (95% CI) *P*
rs1994016	15	76867289	C	0.60	*ADAMTS7*	1.37 (1.20, 1.57) 3.94×10^{-6}	1.19 (1.10, 1.28) 7.01×10^{-6}	1.14 (1.06, 1.23) 0.000497	1.19 (1.13, 1.25) 2.41×10^{-12}	1.18 (0.98, 1.41) 0.0767	1.19 (1.13, 1.24) 4.98×10^{-13}
					Case N	1,808	2,860	5,078	9,746	2,647	12,393
					Control N	915	3,824	2,311	7,050	333	7,383
					Effective sample N	2,380	5,910	6,350	14,640	1,170	15,810

ADAMTS7 is a Locus for AngCAD



ADAMTS7 is a Locus for Angiographic CAD… but not for MI *per se*

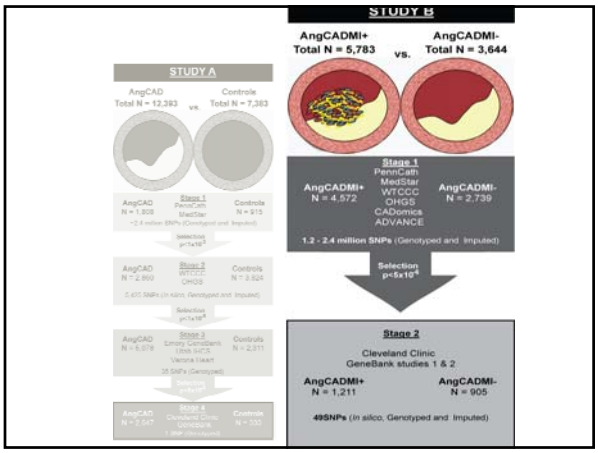


AngCADMI+ vs. AngCADMI-: OR 1.04, *P*=0.02, N=9,425

ADAMTS7

- *ADAMTS* genes (20) have similar structure; preproregion, a reprolysin-type catalytic domain, a disintegrin like domain, a thrombospondin type-1 (TS) module, a cysteine-rich domain, a spacer domain, a COOH-terminal TS module
- *ADAMTS7* degrades cartilage oligomeric matrix protein (COMP) and has been implicated in inflammatory arthritis and bone growth
- Over-expression of *ADAMTS7* accelerates vascular smooth muscle cell (VSMC) migration *in vitro* and exacerbates neointimal thickening following carotid artery injury *in vivo,* likely through degradation of COMP (Wang et al).
- Suggest *ADAMTS7* may regulate plaque size but not plaque stability and may be a novel therapeutic target for progression of atherosclerosis but appears less likely to be one for prevention of MI in high-risk patients.

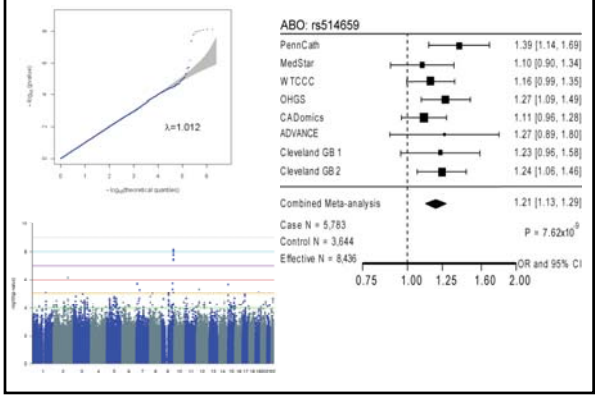
Wang L. *Circ Res*. 2009 Mar 13;104(5):688-98.



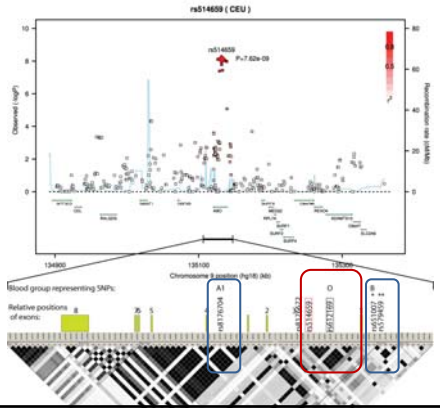
Study B: AngCADMI+ vs. AngCADMI-

	PennCath		MedStar		WTCCC		OHGS		CADomics		ADVANCE		Cleveland GB #1		Cleveland GB #2	
	MI+	MI-	MI+	MI-	MI+	MI-	MI+	MI-	MI+	MI-	MI+	MI-	MI+	MI-	MI+	MI-
No. of subjects	470	463	421	454	1377	533	950	590	1214	592	140	107	272	337	939	568
Country	USA		USA		UK		Canada		Germany		USA		USA		USA	
Definitions	All: Age <66y; at least one coronary artery with ≥ 50% stenosis.		All: Age <61y; at least one coronary artery with ≥ 50% stenosis.		All: Age <66y; coronary disease, & family history of CAD.		All: Age ≤55y (M) or ≤ 65y (F); at least one coronary artery with ≥ 50% Diabetics excluded		All: Age > 20y; stenosis ≥ 50% in at least one coronary artery.		All: Age ≤45y (M) ≤55y (F); CAD ≥50% stenosis in at least one artery, or revascularization.		All: CAD ≥50% stenosis in at least one artery or history of revascularization at enrollment.			
Mean Age	**53±7**	**55±9**	**46±6**	**50±5**	**48±7**	**51±7**	**47±7**	**50±7**	**59±10**	**63±8**	**45±6**	**47±5**	**68±9**	**68±9**	**59±10**	**57±9**
Female (%)	25	25	24	32	20	22	21	29	21	23	55	57	28	30	21	30
MI (%)	100	0	100	0	100	0	100	0	100	0	100	0	100	0	100	0
CABG %	22	23	24	15	42	74	33	30	NA		NA		31	17	54	33
PCI %	41	21	55	61	22	36	48	34	NA		NA		49	30	57	41
Cardiovascular risk factors																
Diabetes mellitus (%)	26	23	30	31	12	12	0	0	19	23	19	23	62	48	0	0
Hypercholl(%)	79	80	88	84	78	78	44	49	60	56	23	38	91	89	94	91
HTN (%)	58	64	77	76	41	46	46	48	70	76	29	41	81	78	73	69
Smoking (%)	**44**	**47**	**58**	**48**	**78 71**		**74**	**68**	**70**	**58**	**59**	**61**	**70**	**69 79**		**66**
BMI (kg/m²)	30±5	29±6	31±6	32±7	27±4	27±4	28±5	28±4	28±4	27±3	30±6	31±7	30±5	30±5	29±5	29±5
Coronary Angiography																
1 V Dis %	**24**	**31**	**31**	**46**	**NA**	**NA**	**36**	**36**	**24**	**29**	**NA**	**NA**	**24**	**37**	**22**	**32**
2 V Dis %	**28**	**28**	**36**	**30**	**NA**	**NA**	**23**	**28**	**30**	**32**	**NA**	**NA**	**32**	**28**	**22**	**26**
3 V Dis %	**39**	**36**	**27**	**19**	**NA**	**NA**	**32**	**30**	**46**	**39**	**NA**	**NA**	**37**	**27**	**39**	**29**

Study B: AngCADMI+ vs. AngCADMI-



ABO is a Locus for MI in Patients with AngCAD



Glycotransferase-deficient *ABO* Variation Protects Against MI in Patients with AngCAD but is not Associated with AngCAD *per se*

		AngCADMI+vs. AngCADMI-* OR (95%CI)	*P*	AngCADMI+vs. Control* OR (95%CI)	*P*	AngCADMI-vs. Control* OR (95%CI)	*P*
(A) rs514659	C allele	1.39 (1.14, 1.69)	0.0009	1.33 (1.06, 1.66)	0.014	1.00 (0.81, 1.25)	0.97
(B) ABO Blood group†	A vs. O	1.49 (1.11, 2.00)	0.0072	1.37 (1.02, 1.84)	0.035	0.92 (0.69, 1.23)	0.57
	B vs. O	2.15 (1.37, 3.40)	0.00055	1.78 (1.15, 2.78)	0.0081	0.83 (0.51, 1.34)	0.42
	AB vs. O	1.65 (0.85, 3.25)	0.12	1.35 (0.71, 2.60)	0.36	0.82 (0.41, 1.62)	0.63
	A/B/AB vs. O	1.62 (1.23, 2.13)	0.00038	1.44 (1.10, 1.90)	0.0070	0.89 (0.68, 1.17)	0.43

(C) PennCath non-O blood groups (n=801): no association of rs514659 with AngCADMI+ OR 0.90 (0.59 to 1.38); *P = 0.63*

GWAS identify Pleiotrophic Effects of the ABO Locus on Cardiovascular Traits

- Historical associations with ABO blood groups
- Recent GWAS Associations
  - Venous Thrombosis
  - Von Willebrand Factor
  - Factor VIII
  - Sol-ICAM-1
  - E-selectin
  - P-selectin
  - TNF alpha
  - Pancreatic Cancer
  - LDL-Cholesterol
  - Sitosterol
  - RBC
  - MCHC
  - Hemoglobin
  - Alkaline Phosphatase
  - Angiotensin Conv Enzyme

Trégouet, *Blood* 2009 | Paré, *PLoS Genet* 2008
Smith, *Circulation* 2010 | Paterson, *ATVB* 2009
Chasman, *PLoS Genet* 2009 | Barbalic, *Hum Mol Genet* 2010
Qi, *Hum Mol Genet* 2009 | Chung, *Pharmacogenomics J* 2010

ABO: Novel Insights into an "Old Story"

- Terminal glycotransferase – encoding blood group antigens
- Longstanding association with lipids, CHD and thrombosis
- GWAS reveals diverse pleiotrophic effects – including plasma levels of multiple endothelial secreted proteins
- Protection from MI and thrombosis may be related to ABO modulation of VWF and Factor VIII
- Association with CHD likely via multiple glycomic pathways
- Glycomic pathways as targets for modulation of CVD

Summary: Penn-GWAS

- Most established loci associated with AngCAD but not MI *per se*
- *ADAMTS7* is a locus for atherosclerosis but not directly for MI
- *ABO* is a locus uniquely for MI but not atherosclerosis
- CHD genes likely have different pathways to CHD - in the presence of atherosclerosis unique genetic factors may precipitate MI
- Mechanistic and therapeutic implications

Reilly MP et al. *Lancet* 2011;377:383

CARDIoGRAM

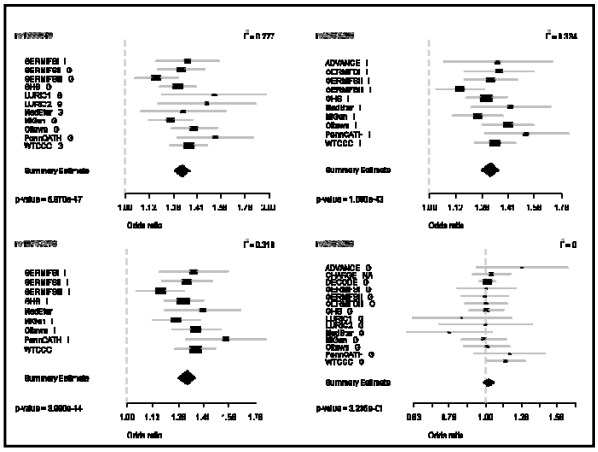
Coronary ARtery DIsease Genome-wide Replication And Meta-Analysis

ADVANCE, CADomics, CHARGE, deCODE, GerMIFS I, II, and III (KORA), LURIC/AtheroRemo, MedStar, MIGEN, Ottawa, PennCath, WTCCC

Over 22,000 cases and 60,000 controls with imputed GWAS data in excess of 2 million SNPs

CARDIoGRAM

Study	N	% MI	% female	Mean (SD) Age
ADVANCE	278 / 312	50.4	57.9 / 59.0	45.8(6.2) / 45.3(5.7)
CADomics	2078 / 2952	58.3	21.9 / 50.5	60.8(10.1) / 55.3(10.8)
CHARGE	2287 / 22024	48.0	33.4 / 59.9	60 (7.9) / 63.1 (8.0)
deCode	6640 / 27611	54.7	36.3 / 61.9	74.8(11.8) / 53.7(21.5)
GERMIFS I	884 / 1604	100.0	49.4 / 50.8	50.2(7.8) / 62.6(10.0)*
GERMIFS II	1222 / 1287	100.0	33.1 / 48.3	51.4(7.5) / 51.2(11.9)*
GERMIFS III (KORA)	1359 / 1604	100.0	31.7 / 51.4	57.6(8.8) / 55.1(8.3)*
LURIC/ AtheroRemo	652 / 213	71.9	20.3 / 46.0	61.0(11.8) / 58.3(12.1)
LURIC 2	486 / 296	79.0	23.4 / 48.6	63.7(9.4) / 56.4(12.7)
MedStar	875 / 447‡	48.1	33.0 / 54.6	48.9(6.4) / 59.7(8.9)
MIGen	1274 / 1407	100.0	37.2 / 39.9	42.4(6.6) / 43.0(7.8)*
OHGS	1542 / 1455	61.6	24.1 / 48.0	48.7(7.3) / 75.0(5.0)
PennCath	933 / 468‡	50.3	23.7 / 51.9	52.7(7.6) / 61.7(9.6)
WTCCC§	1926 / 2938	71.5	20.7 / 50.0	49.8 (7.7) / §

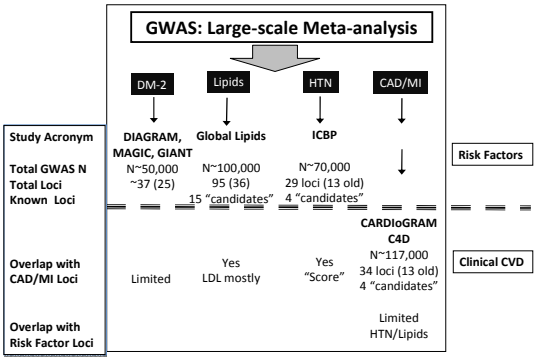


CARDIoGRAM: Association of previously published loci for CAD and MI

Band	SNP	Gene(s) in region	n	Risk allele frequency (risk allele)	CARDIoGRAM	
					OR (95% CI)	P
1p13.3	rs599839*	*SORT1*	83,873	0.78 (A)	1.11 (1.08; 1.15)	$2.89 \cdot 10^{-10}$
1p32.3	rs11206510***	*PCSK9*	102,352	0.82 (T)	1.08 (1.05; 1.11)	$9.10 \cdot 10^{-08}$
1q41	rs17465637****	*MIA3*	25,197	0.74 (C)	1.14 (1.09; 1.20)	$1.36 \cdot 10^{-08}$
2q33.1	rs6725887*	*WDR12*	77,954	0.15 (C)	1.14 (1.09; 1.19)	$1.12 \cdot 10^{-09}$
3q22.3	rs2306374*	*MRAS*	77,843	0.18 (C)	1.12 (1.07; 1.16)	$3.34 \cdot 10^{-08}$
6p24.1	rs12526453*	*PHACTR1*	83,050	0.67 (C)	1.10 (1.06; 1.13)	$1.15 \cdot 10^{-09}$
6q25.3	rs3798220**	*LPA*	32,584	0.02 (C)	1.54 (1.36; 1.74)	$9.62 \cdot 10^{-12}$
9p21.3	rs4977574*	*CDKN2A/B, ANRIL*	84,256	0.46 (G)	1.29 (1.23; 1.36)	$1.35 \cdot 10^{-22}$
10q11.21	rs1746048***	*CXCL12*	136,416	0.87 (C)	1.09 (1.07; 1.13)	$2.12 \cdot 10^{-10}$
12q24.12	rs3184504*	*SH2B3*	67,746	0.44 (T)	1.07 (1.04;1.10)	$6.35 \cdot 10^{-06}$
19p13.2	rs1122608*	*LDLR*	49,693	0.77 (G)	1.14 (1.09; 1.18)	$9.73 \cdot 10^{-10}$
21q22.11	rs9982601*	*MRPS6*	46,230	0.15 (T)	1.18 (1.12; 1.24)	$4.22 \cdot 10^{-10}$

Trilogy of Large-scale Meta-analysis of CAD

Consortium	Discovery	Replication	Platform	No, of new loci
CARDIoGRAM	86,995	49,343	GWA	13
C4D	30,485	39,583	GWA	5
IBC 50K	50,588	57,594	50K	4



CAD/MI: CARDIoGRAM, C4D, IBC 50K (submitted)
HTN: ICBP (submitted)
DM-2: Zeggini et al. Nat Gen 2008; 40:638. Voight et al Nat Gen 2010; 42:579
Lipids: Global Lipids; Teslovich et al. Nature 2010; 466:707-13.

What do we know?

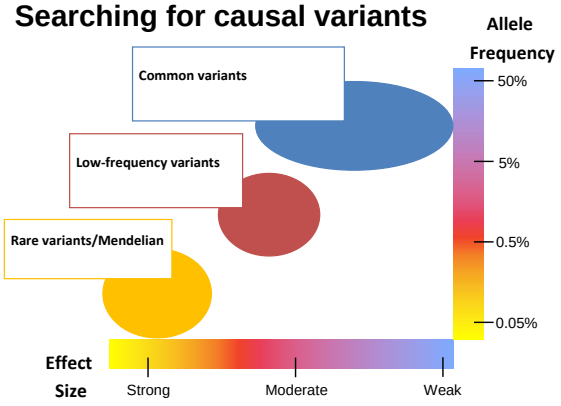
- Most loci novel - hypothesis?
  - Culprit gene uncertain
  - Mechanisms unknown
  - Directionality unknown
- Two thirds have no relationship with known risk factors
  - (One third may relate to lipids, HTN…)
- Some lipid and HTN loci relate to CAD
- **New models of atherosclerosis and CAD!**

Where is the Heritability?

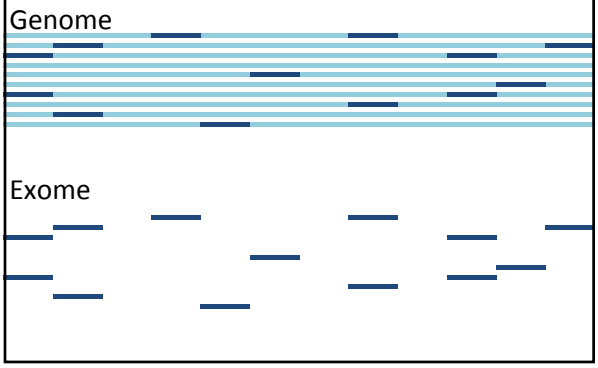
- CAD less "genetic" than previously thought
- Even larger GWAS studies required – e.g., lipids and height
- Structural variation CNVs
- Low frequency and rare variants – sequencing discoveries
- Gene-gene and gene-env interactions

- Regardless plenty to do!

Searching for causal variants



Exome sequencing is unbiased and efficient

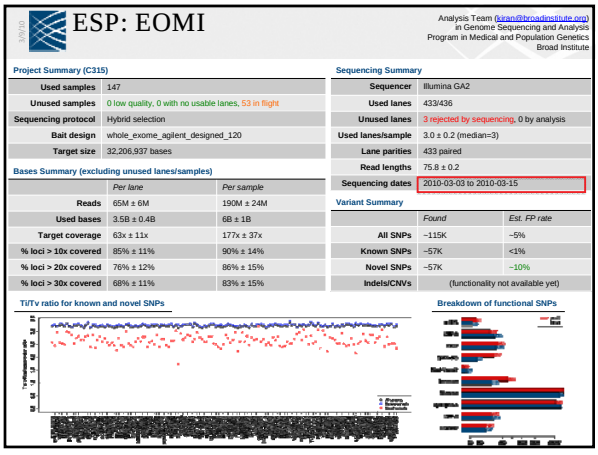


ExomeSeqProject (ESP) EOMI Team

Heart GO		Seattle GO	WHISP	Broad GO	
Chris O'Donnell (co-convener)	Bruce Psaty	Debbie Nickerson	Chris Carlson	Sekar Kathiresan (co-convener)	John Spertus
Eric Boerwinkle	Alex Reiner		Becky Jackson	Goncalo Abecasis	Nathaniel Stitziel
Greg Burke	Herman Taylor		Gerardo Heiss	Sharon Cresci	Shamil Sunyaev
Adrienne Cupples	Russ Tracy		Charles Kooperberg	Ron Do	Hooman Allayee
Aaron Folsom			Alex Reiner	Deb Farlow	David Altshuler
David Herrington			Jacques Rossouw	Stacey Gabriel	David Siscovick
Leslie Lange				Stanley Hazen	Steve Schwartz
Ethan Lange				Daniel Rader	
Jim Wilson				Muredach Reilly	

Study design informed by three observations
(1300 cases and 1700 controls)

- The younger the age at MI, the greater the heritability M<50, F <60
- Selecting extremes of a trait distribution likely to improve power
- Genetic discovery may be enhanced by studying multiple ethnicities (i.e., low-frequency PCSK9 nonsense mutations only present in blacks)



ESP: EOMI

Analysis Team (kiran@broadinstitute.org)
in Genome Sequencing and Analysis
Program in Medical and Population Genetics
Broad Institute

Project Summary (C315)

Used samples	147
Unused samples	0 low quality, 0 with no usable lanes, 53 in flight
Sequencing protocol	Hybrid selection
Bait design	whole_exome_agilent_designed_120
Target size	32,206,937 bases

Bases Summary (excluding unused lanes/samples)

	Per lane	Per sample
Reads	65M ± 6M	190M ± 24M
Used bases	3.5B ± 0.4B	6B ± 1B
Target coverage	63x ± 11x	177x ± 37x
% loci > 10x covered	85% ± 11%	90% ± 14%
% loci > 20x covered	76% ± 12%	86% ± 15%
% loci > 30x covered	68% ± 11%	83% ± 15%

Sequencing Summary

Sequencer	Illumina GA2
Used lanes	433/436
Unused lanes	3 rejected by sequencing, 0 by analysis
Used lanes/sample	3.0 ± 0.2 (median=3)
Lane parities	433 paired
Read lengths	75.8 ± 0.2
Sequencing dates	2010-03-03 to 2010-03-15

Variant Summary

	Found	Est. FP rate
All SNPs	~115K	~5%
Known SNPs	~57K	<1%
Novel SNPs	~57K	~10%
Indels/CNVs	(functionality not available yet)	

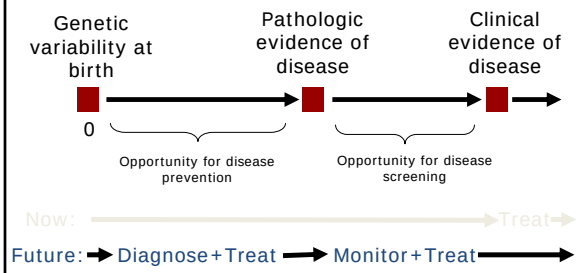
Ti/Tv ratio for known and novel SNPs

Breakdown of functional SNPs

Using Genetics to Assess Risk of Coronary Artery Disease

Could a panel of single nucleotide polymorphisms associated with coronary artery disease be used clinically to assess risk and guide intensity of preventive therapy?

Lifetime disease prevention and management based on genetic predisposition



deCODE MI measures 9p21 and 7 additional widely replicated variants that are independent of conventional risk factors

Chromosome	SNP
9p21.3	rs10757278
12q24.12	rs3184504
3q22.3	rs9818870
1q41	rs17465637
10q11.21	rs1746048
21q22.11	rs9982601
6p24.1	rs12526453
2q33.1	rs6725887

Addition of 9p21 variant to ARIC prospective cohort leads to significant increase in accuracy of MI prediction

-Expect reclassification rate to improve with 7 extra SNPs

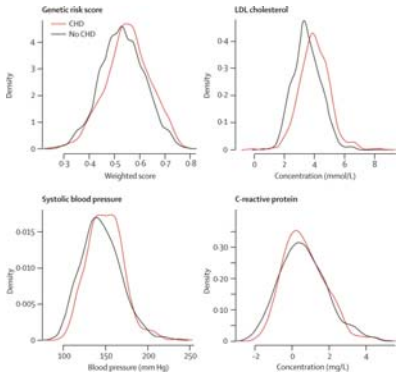
Ariel Brautbar; Christie Ballantyne; Kim Lawson; Vijay Nambi; Lloyd Chambless; Aaron Folsom; James Willerson; Eric Boerwinkle

12- 18% of patients in intermediate and intermediate-high categories are reclassified – change in LDL-chol target

10-year risk 0–5%	Low	3,428	3,237	191 (5.6)	0	0	191 (5.6)
Observed event rate†			*2.3*	*3.9*	*0*	*0*	*2.4*
10-year risk 5–10%	Intermediate	2,328	165 (7.1)	1,878	285 (12.2)	0	450 (19.3)
Observed event rate			*4.98*	*6.1*	*10.6*	*0*	*6.7*
10-year risk 10–20%	Intermediate-high	2,641	0	184 (7)	2,194	263 (10)	447 (17)
Observed event rate			*0*	*9.3*	*12.6*	*16.2*	*12.76*
10-year risk >20%	High	1,607	0	0	135 (8.4)	1,472	135 (8.4)
Observed event rate					*13.7*	*22.61*	*21.86*
	TOTAL	10,004	3,402	2,253	2,614	1,735	
Observed event rate		*1349*	*2.5*	*6.2*	*12.5*	*22*	*9.2*

* Percentage of individuals reclassified from ACRS based risk model after adding 9p21 allele to risk calculation. † Observed event rate have been extrapolated to 10-year rate (number of events per 100 people per 10 years of observation) from a follow up time of 14.6 years. **Conclusion:** The addition of the 9p21 allele to traditional risk factors, in the white population of the ARIC study, improved CHD risk prediction and reclassified a number of subjects, especially in the intermediate and intermediate-high risk categories. For the majority of the reclassified individuals, target LDL-C levels would be changed, thus altering therapy.

Multi-locus risk score for CHD



Ripatti S et al. *Lancet* 2010;376:1393

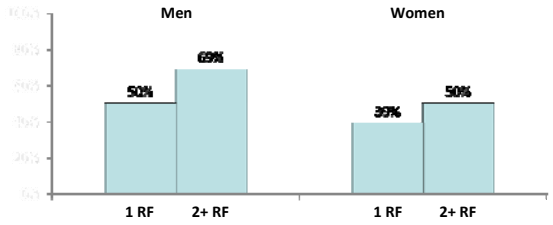
If his genetic risk panel suggests <u>high</u> inherited risk for CAD, one might:

- Be motivated to exercise more
- Be motivated to lose weight
- Have more intensive evaluation of blood pressure
- Have more intensive evaluation of impaired fasting glucose
- Start aspirin
- Start fish oil
- Start a statin

If his genetic risk panel suggests <u>low</u> inherited risk for CAD, one might…

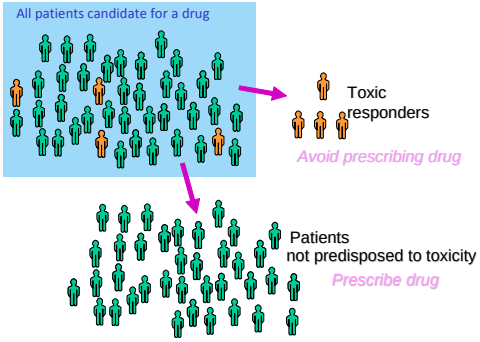
Treating Everyone Overestimates Risk

Lifetime risk of cardiovascular disease is indeed high in patients with major risk factors; however it is far from 100%, even in the presence of 2+ major risk factors and assuming survival to 95 y

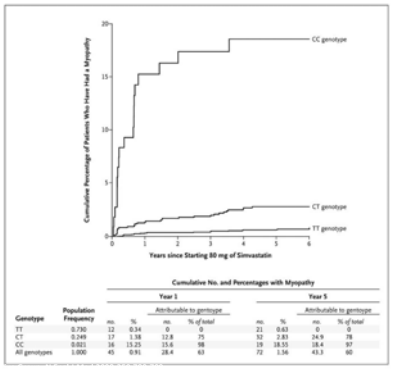


Lloyd-Jones. Circulation 2006;113:791. Framingham Heart Study. n=3564 M, 4362 W, 111777 person-years.
*Major risk factor: TC>240, SBP>160, DBP>100, current smoker, or diabetic.

Genetic testing for prediction of risk of adverse outcomes



Cumulative Risk of Myopathy Associated with Taking 80 mg of Simvastatin Daily, According to SLCO1B1



Cumulative No. and Percentages with Myopathy

Genotype	Population Frequency	Year 1				Year 5			
				Attributable to genotype				Attributable to genotype	
		no.	%	no.	% of total	no.	%	no.	% of total
TT	0.730	12	0.34	0	0	21	0.63	0	0
CT	0.249	17	1.38	12.8	75	52	2.83	24.9	78
CC	0.021	16	15.25	15.6	98	19	18.55	18.4	97
All genotypes	1.000	45	0.91	28.4	63	72	1.36	43.3	60

Personalized CVD Risk

- Further discovery – explain greater heritability
  - GWAS & sequencing
- Protective and risk alleles
- Refined phenotyping – atherosclerosis and MI
- Scoring added to traditional risk factor assessment and imaging Reveal directionality and mechanisms in model systems and human
- (Transcriptome, proteome, glycome)

Concluding Summary

- GWAS have identified multiple novel loci for CAD and risk factors
  - Now a major yield - despite negative press
- Large consortia efforts have evolved
  - Utility for future sequencing follow up
- Different loci may relate to distinct CAD clinical manifestations
  - Prognostic and therapeutic implications
- Metabochip
  - N >200,000; custom array 200,000 SNPs
  - Top GWAS SNPs and sequence SNPs for top CAD and risk factors
- Exome and whole genome sequencing for identification of causal variants and new loci
  - How to analyze – how to use
  - Functional and goldilocks alleles
- Functional studies in model systems and human – loss and gain of function of gene(s) at locus
- Use of humans as the experimental model
  - Use of IPS

Acknowledgements

- **U.Penn**
  - Muredach Reilly
  - Mingyao Li
  - Jing He
  - Stephanie L DerOhannessian
  - Liming Qu
  - Nehal Mehta
  - Atif Qasim
  - Ioannis Stylianou
  - Daniel J Rader
- MedStar – WHC
- WTCCC
- Ottawa Heart Genome Study
- Utah
- Verona
- Emory
- ADVANCE – Stanford
- CADomics
- Cleveland Clinic
- MI-Gen
- GerMIFS I, II, III
- GlaxoSmithKline

Acknowledgements

Broad Institute
- Sek Kathiresan
- Kiran Musunuru

MedStar/WHC
- Stephen Epstein

WTCCC
- Nilesh Samani

- NHLBI
- NIDDK
- NCRR
- GSK ADDi

- CVI
- ITMAT/CTSA
- IDOM/DERC
- PGFI

CARDIoGRAM EC
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Statistical Genetics
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- Zhen Chen
- Jing He
- Liming Qu

CHOP - CAG
- Hakon Hakonarson
- Long Zheng

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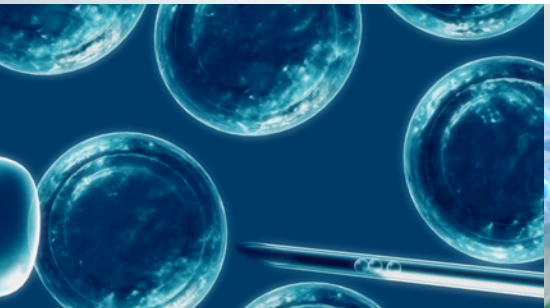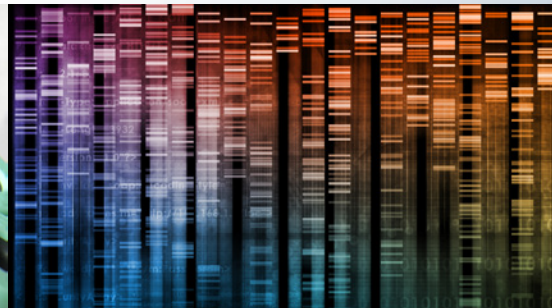
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