National Human Genome Research Institute

National Institutes of Health

U.S. Department of Health and Human Services

Applying Genomic Data in Clinical Care: NHGRI's Genomic Medicine Activities

U.S. Department of Health and Human Services

National Institutes of Health

National Human Genome Research Institute

Teri Manolio, M.D., Ph.D.
Genomic Medicine V

May 28, 2013

Genomic Medicine: On the Threshold?

- Identify risk
- Prevent disease
- Improve diagnostics
- Improve treatments
- Increase access

PERS

doi:10.1038/nature09764

Chart omic medicine from e

Eric D. Green[1], M

There has been much progress in genomics in the ten years since a draft sequence of the human genome was published. Opportunities for understanding health and disease are now unprecedented, as advances in genomics are harnessed to obtain robust foundational knowledge about the structure and function of the human genome and about the genetic contributions to human health and disease. Here we articulate a 2011 vision for the future of genomics research and describe the path towards an era of genomic medicine.

Since the end of the Human Genome Project (HGP) in 2003 and the publication of a reference human genome sequence[1,2], genomics has become a mainstay of biomedical research. The scientific community's foresight in launching this ambitious project[3] is evident in the broad range of scientific advances that the HGP has enabled, as shown in Fig. 1 (see rollfold). Optimism about the potential contributions of genomics for improving human health has been fuelled by new insights about cancer[4–7], quickly. Although genomics has already begun to improve diagnostics and treatments in a few circumstances, profound improvements in the effectiveness of healthcare cannot realistically be expected for many years (Fig. 2). Achieving such progress will depend not only on research, but also on new policies, practices and other developments. We have illustrated the kinds of achievements that can be anticipated with a few examples (Box 2) where a confluence of need and opportunities should

Green ED, Guyer MS. *Nature* 2011; 470:204-13.

NHGRI Genomic Medicine Definition August 2012

Genomic Medicine: *An emerging medical discipline that involves using genomic information about an individual as part of their clinical care (e.g., for diagnostic or therapeutic decision-making) and the other implications of that clinical use.*

- Purposefully narrow
- By 'genomic,' NHGRI means direct information about DNA or RNA; downstream products outside immediate view
- NHGRI recognizes dominant portion of its current portfolio appropriately supports the foundational research that will ultimately produce the discipline of genomic medicine
- Fourth and fifth NHGRI strategic plan domains capture research activities under umbrella of genomic medicine
- Metaphorically viewed as key 'destination' for attaining mission of improving health through genomics research

Genomic Medicine Working Group of National Advisory Council on Human Genome Research

- Plan Genomic Medicine meetings, 2-3 per yr
- Provide guidance to NHGRI in other areas of genomic medicine implementation, such as:
  - Outlining infrastructural needs for adoption of genomic medicine
  - Identifying related efforts for future collaborations
  - Reviewing progress overall in genomic medicine implementation

NACHGR Genomic Medicine Working Group Members

Rex Chisholm	Northwestern
Geoff Ginsburg	Duke
Howard Jacob	Med Coll Wisconsin
Pearl O'Rourke	Partners
Mary Relling	St. Jude
Dan Roden	Vanderbilt
Marc Williams	Geisinger
Eric Green	Brad Ozenberger
Teri Manolio	Laura Rodriguez

Examples of Early Genomic Medicine Implementation Projects (June 2011)

- Tumor-based genotype-driven treatment
- Risk/susceptibility testing in relatives of mutation-bearing cancer patients (Lynch syndrome, *BRCA1/2*, etc.)
- Family history collection for assessment of individual risk
- Whole exome/genome sequencing for unknown disease diagnosis
- Complex disease risk advice (MI, T2DM)

Genet Med 2012; 15:258-67.

Genomic Medicine Colloquium Report
June 2011, Chicago, IL

REVIEW | Genetics inMedicine

Open

- Describe ongoing projects and challenges
- Identify common infrastructure and research needs
- Outline implementation framework for investigating and introducing similar programs elsewhere

Teri A… MD[3], M… [8], Mur… nD[12], Dav… D[15], Michae… armD[19], Alan … , PhD[1]

and Geoffrey S. Ginsburg, MD, PhD[23]

Although the potential for genomics to contribute to clinical care has long been anticipated, the pace of defining the risks and benefits of incorporating genomic findings into medical practice has been

relevant; lack of reimbursement for genomically driven interventions; and burden to patients and clinicians of assaying, reporting, intervening, and following up genomic findings. Key infrastructure needs

Genet Med 2012; 15:258-67.

NHGRI's Genomic Medicine Research Program

Program	Goal	Σ $M	Years
eMERGE II	Use biorepositories with EMRs and GWA data to incorporate genomics into clinical research and care	30.4	FY11-14
eMERGE-PGx	Apply PGRN's validated VIP array for discovery and clinical care in ~9,000 patients	6.7	FY12-14
CSER	Explore infrastructure, methods, and issues for integrating genomic sequence into clinical care	66.5	FY12-16
RoR	Investigate whether/when/how to return individual research results to ppts in genomic research studies	5.7	FY11-13
CRVR	Develop and disseminate consensus information on variants relevant for clinical care	14.0	FY13-16
GMPDP	Develop and disseminate methods for incorporating patients' genomic findings into their clinical care	24.8	FY13-16
Newborn Sequencing	Explore possible uses of genomic sequence information in the newborn period	10.0	FY13-16
UDN*	Diagnose both rare and new diseases by expanding NIH's Undiagnosed Diseases Program	67.9	FY13-17

Seven-year total = $225M; average ~ $32M/year; *Funded by Common Fund, managed by NHGRI

eMERGE Site-Specific Genomic Medicine Implementation Pilots

Site	Goal
CCHMC	*CYP2D6* variants and post-operative opioids
CHOP	β-adrenergic agonists and *βAR* variants in asthma
Geisinger	*IL28B* variants and chronic hepatitis C treatment; WGS for undiagnosed diseases
Marshfield	*CFH* and risk of age-related macular degeneration
Mayo	RCT of 42 SNP-genomic risk score for CHD vs Framingham score alone for attitudes, behaviors
Mount Sinai	RCT of *APOL1* genotype vs clinical risk factors for hypertensive nephropathy prevention, management
Northwestern	Effect of return of *HFE* and *FVL* risk variants on physician and patient attitudes, behaviors
Vanderbilt	Expanded PGx testing

Enhanced Partnership with Pharmacogenomics Research Network

NIGMS Home > Research Funding > Featured Funding Programs

NIH Pharmacogenomics Research Network

PGRN

The **NIH Pharmacogenomics Research Network (PGRN)** is a network of scientists focused on understanding how a person's genes affect his or her response to medicines. Funded since 2000, the PGRN has a Vision and Mission.

PharmGKB

The **Pharmacogenomics Knowledge Base** (PharmGKB) is an integrated knowledge base for pharmacogenomics linking phenotypes and genotypes.

The following institutes contribute support to the Pharmacogenomics Research Network:
NIGMS, NHLBI, NCI, NIDA, NICHD, NHGRI, NIMH, NIAMS, ORWH

http://www.nigms.nih.gov/Research/FeaturedPrograms/PGRN

CPIC Gene-Drug Guidelines

Clin Pharmacol Ther 2011-2013

Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Met Dos

MV Rel
M Carr

Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P45 and Ger

SA Sco
DM Ro

Clinical Pharmacogenetics Implementation Consortium Guidelines for *CYP2C9* and *VKORC1*

JA John
MTM L

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Codeine Ther (*CYP*

KR Crew
and TC S

Clinical Pharmacogenetics Implementation Consortium Guidelines for *HLA-B* Genotype and Aba

MA Mart

The Clinical Pharmacogenomics Implementation Consortium: CPIC Guideline for *SLCO1B1* and

RA Wilk
DM Rod

Clinical Pharmacogenetics Implementation Consortium Guidelines for Human Leukocyte Anti

MS Hers
and MT

Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Tricyclic Antidepressants

JK Hicks[1], JJ Swen[2], CF Thorn[3], K Sangkuhl[3], ED Kharasch[4], VL Ellingrod[5,6], TC Skaar[7], DJ Müller[8], A Gaedigk[9] and JC Stingl[10]

Collaborative NHGRI Pharmacogenomics Project with PGRN in eMERGE Network

- PGRN's Very Important PGx (VIP) Gene Sequencing: array developed to identify rare sequence variants in 84 PGx genes
- eMERGE-PGx will apply validated VIP array for discovery and clinical care in ~9,000 patients
  - Can be exported to other CLIA-certified labs
  - Permit genotyping of common and rare variants and discovery of new ones
  - Use PGRN's Clinical PGx Implementation guidelines and institutional approvals for influencing clinical care

Drugs Proposed for Implementation in eMERGE-PGx, by Site

Site	abacavir	carbamazepine	clopidogrel	codeine	interferon	montelukast	morphine	omeprazole	ranitidine	simvastatin	thiopurines	warfarin
CHOP		X				X	X	X	X		X	
CCHMC				X								
Geisinger			X							X		X
GHC/UW		X										
Marshfield			X							X		X
Mayo	X	X	(X)		X					(X)	X	(X)
Mount Sinai			X							X		X
NU			X							(X)		X
Vanderbilt			X							X	X	X

(X) = planned

Drugs Proposed for Implementation in eMERGE-PGx, by Site

Site	abacavir	carbamazepine	clopidogrel	codeine	interferon	montelukast	morphine	omeprazole	ranitidine	simvastatin	thiopurines	warfarin
CHOP	X	X	X	X	X	X	X	X	X	X	X	X
CCHMC	X	X	X	X	X	X	X	X	X	X	X	X
Geisinger	X	X	X	X	X	X	X	X	X	X	X	X
GHC/UW	X	X	X	X	X	X	X	X	X	X	X	X
Marshfield	X	X	X	X	X	X	X	X	X	X	X	X
Mayo	X	X	(X)	X	X	X	X	X	X	(X)	X	(X)
Mount Sinai	X	X	X	X	X	X	X	X	X	X	X	X
NU	X	X	X	X	X	X	X	X	X	(X)	X	X
Vanderbilt	X	X	X	X	X	X	X	X	X	X	X	X

(X) = planned

NHGRI's Genomic Medicine Research Program

Program	Goal	Σ $M	Years
eMERGE II	Use biorepositories with EMRs and GWA data to incorporate genomics into clinical research and care	30.4	FY11-14
eMERGE-PGx	Apply PGRN's validated VIP array for discovery and clinical care in ~9,000 patients	6.7	FY12-14
CSER	Explore infrastructure, methods, and issues for integrating genomic sequence into clinical care	66.5	FY12-16
RoR	Investigate whether/when/how to return individual research results to ppts in genomic research studies	5.7	FY11-13
CRVR	Develop and disseminate consensus information on variants relevant for clinical care	14.0	FY13-16
GMPDP	Develop and disseminate methods for incorporating patients' genomic findings into their clinical care	24.8	FY13-16
Newborn Sequencing	Explore possible uses of genomic sequence information in the newborn period	10.0	FY13-16
UDN*	Diagnose both rare and new diseases by expanding NIH's Undiagnosed Diseases Program	67.9	FY13-17

Seven-year total = $225M; average ~ $32M/year; *Funded by Common Fund, managed by NHGRI

Published 2006 Wiley-Liss, Inc. American Journal of Medical Genetics Part A 140A:1033–1040 (2006)

Special Reports

Circ Cardiovasc Genet 2010; 3:574-80.

Ethical and Practical Guidelines for Reporting Genetic Research Results to Study Participants

Updated Guidelines From a National Heart, Lung, and Blood Institute

"…an independent, national central advisory committee should be established to review evidence for genetic risk factors to offer guidance to investigators, research institutions, and IRBs regarding when a genetic result is well enough understood and has sufficiently serious clinical implications to justify an obligation to return genetic research results to study participants."

Abstract—In January 2009, the National Heart, Lung, and Blood Institute convened a 28-member multidisciplinary Working Group to update the recommendations of a 2004 National Heart, Lung, and Blood Institute Working Group focused on Guidelines to the Return of Genetic Research Results. Changes in the genetic and societal landscape over

Clinically Relevant Variants Resource (CRVR): Purpose and Goals

Purpose: Identify and disseminate consensus information on genetic variants relevant to clinical care

- Identify genetic variants with likely implications for clinical care and incorporate these variants and evidence into a resource for practice guidelines
- Establish a process for transferring this information to appropriate clinical organizations for development of these guidelines
- Build upon existing programs, unify, reduce duplicative efforts across research/clinical organizations

What We Mean by "Actionable"

- Evidence not sufficient for unequivocal CU
- Sufficient to determine how already available information could be used in clinical context
- Intermediate stage between CV and CU ("If you had it, would you use it?")
- May allow consideration of ethics, law, and policy in RoR to move to appropriate expertise
- Allows more flexibility for clinicians, institutions to tailor use of variant information to patient, clinical setting, and local standards of practice

Clinical Sequencing Exploratory Research: RFAs HG-12-008 and 12-009

Purpose: Investigate challenges to applying genomic sequence data to the care of patients.

Goals:

1. Generate clinically valid genomic sequence data relevant to individual patient's care
2. Interpret and translate these data for the physician and communicate to the patient
3. Examine the ethical and psychosocial implications of bringing broad genomic data into the clinic

Clinical Sequencing Exploratory Research: RFAs HG-12-008 and 12-009

Site	Disease	Highlights
Baylor*	Pediatric Cancer	Web-based platform with graphical display to facilitate physician disclosure of data to parents
Brigham	Healthy Pts, HCM	RCT of WGS information vs. current standard of care
CHOP	Pediatric Diseases	Tools for identifying and consenting patients, determine how patients should be counseled before testing, what results should be returned
Dana-Farber	Solid tumors	Incorporate genomic information into management plans
UNC	Cardiomyo-pathy, cancer	WES as diagnostic tool, including under-represented populations
UW*	CRC and Polyposis	RCT of usual care vs. addition of exome analysis

*Co-funded by NCI.

Genomic Medicine Pilot Demonstration Projects: RFAs HG-12-006 and HG-12-007

Purpose: Demonstrate feasibility of, and develop methods for, incorporating patients' genomic findings into their clinical care

Goals:

1. Expand existing GM efforts and develop new projects and methods, in diverse settings
2. Contribute to evidence base regarding outcomes of implementing GM
3. Define and disseminate processes of GM implementation, diffusion, and sustainability in diverse clinical settings

Genomic Sequencing and Newborn Screening Disorders: RFA HD-13-010

Purpose: Explore the possible use of genomic sequence information in the newborn period

Goals:

1. Acquire and analyze genomic datasets in the newborn period;
2. Advance understanding of specific disorders identifiable via newborn screening through promising new DNA-based analysis
3. Examine ethical, legal and social implications of possible implementation of genomic sequencing of newborns

Mak eality

Mammoth pointers

Larson, G. *The Complete Far Side*. 2003.

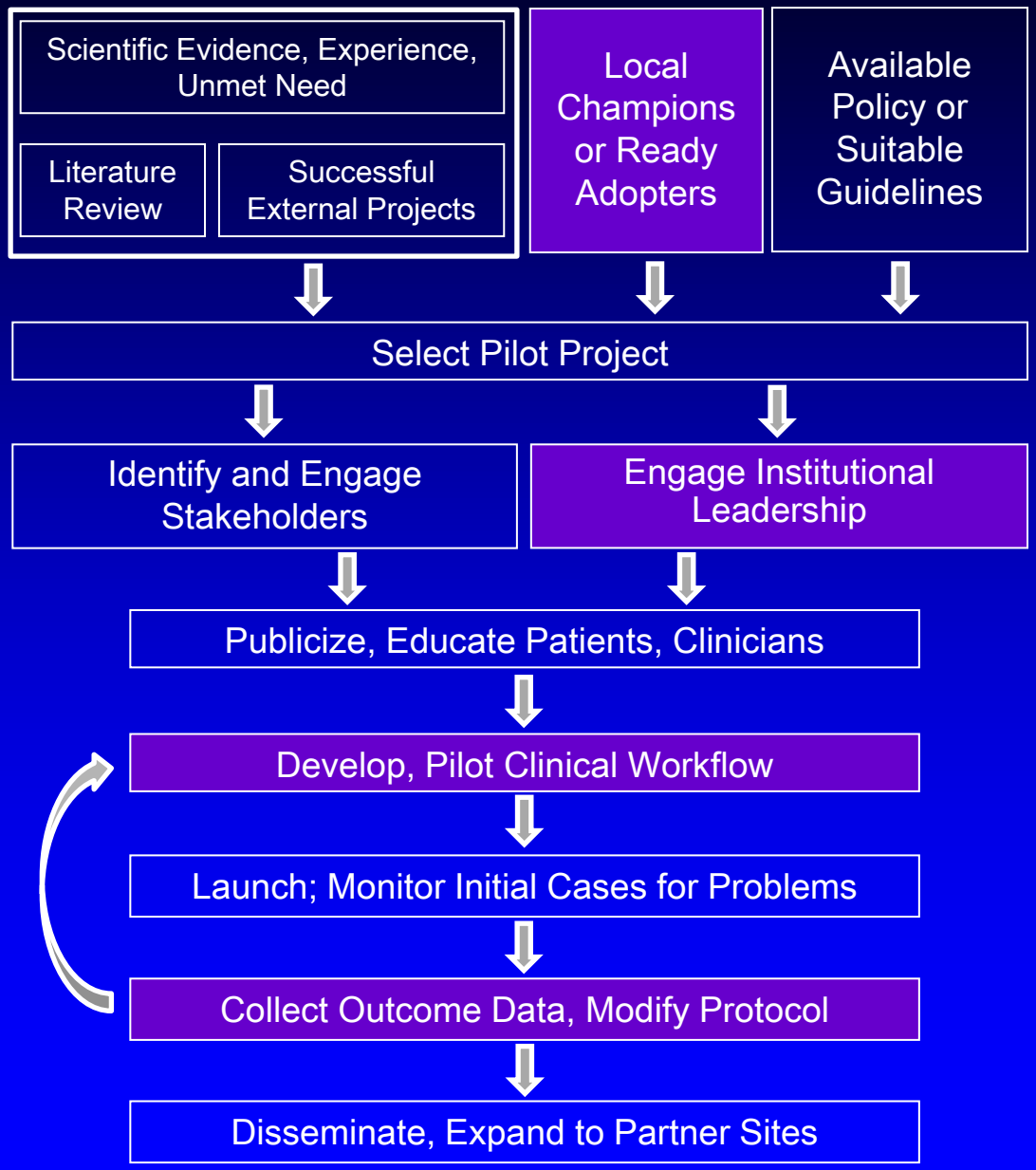
Selected NHGRI Genomic Medicine Activities

	eMERGE	CSER	Phen X	GM Mtgs	CRVR	GMDP	Newborn Seq	FHx
Variant/Assoc Discovery	++	+					++	
Transportable Phenotypes	++		++					
Evidence Generation	++	++				++	+	+
Variant Clinical Implications	++	++		+	++	+		
Consent, Concerns	++	++				+	++	+
Methods Dissem	++	+	+	++		++		
Variant Reporting and Use in Care	+	++				+	+	
Clinician/Pt Educ	++	+		+	+	+	+	
Decision Support	+	+				+	+	+
Policy Devel	+	+		+				

eMERGE, Electronic Medical Records and Genomics Network; CSER, Clinical Sequencing Exploratory Research; PhenX, Phenotype and Exposure Toolkit; CRVR, Clinically Relevant Variants Resource; GMDP, Genomic Medicine Demonstration Projects; FHx, Family History Implementation

Components of GM Implementation Strategies	UK	Canada	Italy	ESF	CAP	IOM	AMA
Service delivery infrastructure for requesting and receiving genomic results	X		X	X	X		
Provider- and patient friendly, model genomic interpretive test reports and patient consultations					X		
Bioinformatics infrastructure for relating clinical characteristics to variants	X	X	X	X	X	X	X
Data sharing in accessible research databases	X			X	X		X
Standardized phenotypic, patient, variant, and reference information	X			X	X	X	X
Assessment of health economics and cost-effectiveness	X	X	X		X	X	X
Evidence of clinical validity and utility	X	X	X	X	X	X	X
Consent model	X			X			X
Training/workforce development	X		X	X	X		
Ethical and legal framework to protect against potential abuses	X	X			X		X
Engaging public and building awareness	X	X	X	X			
Genomics-based risk stratification and communication		X	X				
Genomics-based drug development, selection, and repurposing		X	X			X	
Genetic test regulation or registration			X		X		X
Regulatory frameworks adapted to changes in disease taxonomy and new diagnostic categories				X			
Use of patented medical information and conflict of interest in medical innovation					X	X	X
Reimbursement for genomic testing, interpretations and consultations					X		X

Implementation Roadmap



Genet Med 2012; 15:258-67.

Genomic Medicine Funding Opportunities

Part I Overview Information

Department of Health and Human Services

Part 1. Overview Information

Department of Health and Human Services

Part 1. Overview Information

Department of Health and Human Services

Part 1. Overview Information

Department of Health and Human Services

Part 1. Overview Information

Department of Health and Human Services

Part 1. Overview Information

Department of Health and Human Services

Part 1. Overview Information

Department of Health and Human Services

Part 1. Overview Information

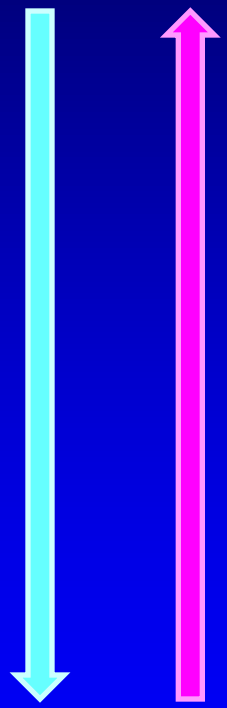
Participating Organization(s)	National Institutes of Health (NIH)
Components of Participating Organizations	This Funding Opportunity Announcement (FOA) is developed as a Common Fund initiative (http://commonfund.nih.gov/) through the NIH Office of the NIH Director, Office of Strategic Coordination (http://dpcpsi.nih.gov/osc/). The FOA will be administered by the National Human Genome Research Institute (NHGRI/NIH), (http://genome.gov) on behalf of the NIH.
Funding Opportunity Title	**Clinical Sites for an Undiagnosed Diseases Network (UDN) (U01)**
Activity Code	U01 Research Project – Cooperative Agreements
Announcement Type	New
Funding Opportunity Announcement (FOA) Number	**RFA-RM-13-004**

http://www.christusrex.org/www1/sistine/28b-Abias.jpg

eMERGE-PGRN Partnership

PGRN Pharmacogenomics Research Network

- State of art PGx array
- Ability to update
- Gene-drug guidelines
- CLIA standards and QC



- Privacy concerns
- Electronic phenotyping
- Large pt base
- Less PGx-focused labs

The *eMERGE* Network
electronic Medical Records & Genomics

“The more we find, the more we see, the more we come to learn.

The more that we explore, the more we shall return.”

Sir Tim Rice, *Aida*, 2000

Genomic Medicine IV, Jan 28-29, 2013

Accreditation Council for Graduate Medical Education

Accreditation Council for Continuing Medical Education

American Academy of Pediatrics

American College of Cardiology

American College of Medical Genetics and Genomics

American College of Physicians

American Congress of Obstetrics and Gynecology

American Heart Association

American Society of Clinical Oncology

Association of Professors of Human Medical Genetics

Proposed Specific Activities of ISCC

- Review and assess maturation of genomic sciences from lab to clinic and bedside
- Commission working groups to provide guidance on trans-professional society issues
- Review professional society guidance on request
- Identify and disseminate metrics for monitoring success of physician educational programs
- Provide venue for sharing effective genomic education materials and practices across professional societies
- Collaborate with groups leading education efforts for other health providers
- Assist ACGME and ACCME in programs to support physician education throughout their careers

NHGRI Genomic Medicine Meetings, 2013

- GM V, May 28-29, 2013, Bethesda MD
  - Engage federal agencies to discuss potential overall US strategies for gm implementation
  - Explore current activities, needs, obstacles
  - Identify common interests and opportunities, plans for collaboration and strategy development
- GM VI, Sept 2013, Washington area
  - Explore current activities, needs, obstacles
  - Identify common research gaps to ensure evidence only need be generated once
  - Develop plans international collaboration

Avoiding Meeting Hell

"Oh, man! The coffee's *cold!* They thought of *everything!*

Larson, G. *The Complete Far Side*. 2003.

Clinical Utility and "Actionability"

- CU: "…evidence of improved measurable clinical outcomes, and its usefulness and added value to pt management decision-making" (EGAPP 2009)
- Typically net, concrete benefit to patient
- Must meet very high evidentiary bar (even RCT?)
- Perspectives differ widely on importance and "clinical nature" of outcomes; varies by context
- Thresholds may need tailoring to cost, burden, and risk of proposed intervention
- Addressing such nuances requires careful, considerate, *local* deliberation
- Can be informed by expert consensus