STATUS OF RECOMMENDATIONS FROM JUNE 5-6 2006
MULTI-IC SYMPOSIUM ON APPLICATION OF GENOMIC TECHNOLOGIES TO POPULATION-BASED STUDIES
(As of 5/17/07)

	Near-Term Administrative Action Items:	**Leadership**	**Status**
1.	Key elements of consent for genome-wide association studies (GWAS) should be collected, updated frequently, and made available to ICs and possibly to the outside community. A repository of model consent forms could be developed.	Symposium Panel 3, in collaboration with Nabel GWAS Data Sharing Committee	Sample consents from current NIDDK, NIGMS, NIMH, and NINDS repositories, and draft consent elements for NHGRI Medical Sequencing program, have been made available for review at http://www.genome.gov/Pages/Extranets/PopulationGenomicsTraining/consent.cfm
2.	Examples or collections of successful consortium agreements and genotyping quality control standards would be helpful.	Nabel Committee, with NIH/OD	Sample data use and consortium agreements and policies from current NCI, NHLBI, NIDDK, NIGMS, and NIMH programs have been made available for review at http://www.genome.gov/Pages/Extranets/PopulationGenomicsTraining/agreements.cfm
3.	Existing efforts should be coordinated, and new efforts initiated as needed, to develop common data elements for key phenotypes and environmental exposures for use in GWAS.	GEI can serve as a pilot, with GAIN, NCBI, caBIG, NHLBI	NCBI initiating coordinated efforts at defining database terms for GWAS studies in dbGaP at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gap , as described by Jim Ostell at 12/14/06 Town Hall Meeting at http://www.reffectcomments.org/GWAS/NIHTownHall/
4.	Agreed-upon standards for quality of genotyping and sequencing data should be disseminated.	NHGRI	
5.	Rigorous algorithms should be developed to define approaches to follow-up GWA signals with	GEI	GEI-supported “Think Tank” led by NIDA and NHGRI held in January 2007, summary and

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	sequencing: in which samples, over what interval, and what fraction of the interval (exons, promoters, conserved sequences, etc).		recommendations available on the GEI website at http://genesandenvironment.nih.gov/genetics/meetings/index.asp
6.	Standards for defining validity and replication of GWA findings should be developed.	NHGRI and NCI	Working group led by NCI and NHGRI held in November 2007, summary presentation available at http://www.capconcorp.com/gain2006/ppt/Manolio%7EHunter%20GAIN%20Replicwg%20Presentation%7E9A.pdf and summary manuscript submitted to *Nature*

	Intermediate Priority Goals:	Leadership	Status
7.	Efforts should be made to identify and prioritize high-impact exposures, such as those that are readily modifiable or that have substantial relevance to many diseases and traits. The long-term goal of these efforts should be to develop standardized tools for definition, collection, and analysis.	NIEHS, with GEI	RFA HG-07-006, "High-Priority Phenotype and Exposure Measures for Cross-Study Analysis in Genome-Wide Association Studies (http://grants.nih.gov/grants/guide/rfa-files/RFA-HG-07-006.html) released in March 2007 for funding in FY07
8.	GWA applications should be evaluated in review for plans to promote data accessibility. Review of GWAS may need to be multi-tiered, to ensure adequate evaluation of phenotype and study design (standardization, bias) as well as genomic issues such as genotyping technology and genetic effect.	Nabel Committee, with CSR, NHGRI, NIDCD	Consideration of completeness and quality of summary phenotype/exposure data included in initial peer review of GEI Study Investigators RFA (RFA HG-06-033 at http://grants.nih.gov/grants/guide/rfa-files/RFA-HG-06-033.html), approach developed by GEI Genetics Subcommittee in collaboration with NCBI, described in RFA and at

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			http://www.ncbi.nlm.nih.gov/WGA/programs/GEI/
9.	Accessible sources of data structures and formats for GWAS should be provided, to reduce reinventing the wheel and improve ability to compare and pool studies in the future.	NCBI, with GAIN, NHLBI, NEI	Standardized analyses of association findings and allele/genotype frequencies provided for NCI's Cancer Genetic Markers of Susceptibility Prostate Cancer scan at https://caintegrator.nci.nih.gov/cgems/browseSetup.do ; for NEI's Age-Related Eye Disease study at http://www.ncbi.nlm.nih.gov/SNP/GaP.cgi?rm=genomeTraitView&test_id=43&method_id=3 ; and for NINDS's Parkinsonism Study at https://queue.coriell.org/Q/snp_index.asp
10.	The benefits and risks of electronically tracking the research use of GWA data should be explored; consideration should be given to asking that GWA study name be used in abstracts of publications.	Nabel Committee, with NCBI	

	Other Recommendations:	**Status**
11.	The database of uncommon SNPs should be expanded. **(ongoing, NCBI and NHGRI)**	
12.	A template consent form that is widely, though not necessarily universally, acceptable may be useful if made available to IC staff.	Under consideration by the trans-NIH committee on genome-wide association studies (http://grants.nih.gov/grants/gwas/) but sample consents from current NIDDK, NIGMS, and NINDS repositories, and draft consent elements for NHGRI Medical Sequencing program, available at

	Other Recommendations:	**Status**
		http://www.genome.gov/Pages/Extranets/PopulationGenomicsTraining/consent.cfm
13.	The value of performing genome wide SNP genotyping on existing cell lines and making these data widely available should be explored.	
14.	A set of frequently asked questions for genetics and genetic epidemiology may be useful.	
15.	Investigators should be encouraged to deposit GWA data from well-characterized control samples in the NCBI database, though biases in participant selection and validity, and poor comparability of phenotypic measures, may limit the utility of such controls for comparison to cases drawn from other sources.	
16.	Trans-NIH policies, or guidelines if policies are unnecessary or premature, are needed for consent, data release, intellectual property, and publication. **(ongoing, Nabel Committee)**	Under development by the trans-NIH committee on genome-wide association studies (http://grants.nih.gov/grants/gwas/)
17.	Increased dialogue and engagement between IRBs and NIH is needed regarding the acceptability of broad consent, the inability to identify individual genetic variants to be studied, the need for data sharing, etc.; approaches could include FAQs, presentations at meetings such as PRIM&R, newsletters, publication in journal "IRB."	RFA HG-07-005, "Genome-Wide Studies in Biorepositories with Electronic Medical Record Data (http://grants.nih.gov/grants/guide/rfa-files/RFA-HG-07-005.html) released in March 2007 for funding in FY07, will address many IRB and consent issues
18.	A central IRB should be considered for GWA studies. An important charge will be to address potential conflicts in previously signed consent forms for pre-existing studies with evolving societal and scientific concerns, and to determine when exemptions or waivers could be granted or re-consenting of individual	RFA HG-07-005, "Genome-Wide Studies in Biorepositories with Electronic Medical Record Data (http://grants.nih.gov/grants/guide/rfa-files/RFA-HG-07-005.html) released in March 2007 for funding in FY07, will address many IRB and consent issues

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	participants may be needed.	
19.	Consideration should be given to future development of guidelines for distribution of biospecimens, including DNA, blood/serum, or tissue, from GWAS.	
20.	Issues to consider in prioritizing GWAS may include: a. The scientific and public health rationale for the study design b, Evidence of heritability of the condition or trait c. Reasons to suspect finding a common allele that confers a significant risk d. Quality and extent of available phenotypic and exposure data e. Epidemiologic features of this trait that make it a promising candidate for study (e.g., environmental and behavioral risk factors, special clinical relevance, special population, public health impact)	Many of these issues were incorporated into criteria for prioritizing applications for GWAS in GEI RFA HG-06-033, Study Investigators at http://grants.nih.gov/grants/guide/rfa-files/RFA-HG-06-033.html
21.	Descriptions of currently funded case-control and cohort studies believed by NIH staff or investigators to be suitable for addition of genomic technologies, or already pursuing genomic research, could be added to databases such as the ClinicalTrials.gov website.	Discussion with leadership of ClinicalTrials.gov revealed large number of observational studies already registered and plans for additional studies to be added; recommendations regarding additional fields provided per recommendation 22 below.
22.	The feasibility of enhancing the search functions of ClinicalTrials.gov for GWA studies should be explored.	Recommendations for modifying ClinicalTrials.gov fields relevant to observational studies prepared by multi-IC working group and submitted to NLM
23.	ClinicalTrials.gov should consider developing a parallel site for observational studies, as relevance and user-friendliness of the current site for non-intervention studies are limited.	Discussion with leadership of ClinicalTrials.gov revealed its suitability for observational studies with minor modifications, provided per recommendation 22 above.
24.	ICs should encourage addition of ancillary phenotypic and exposure	

	Other Recommendations:	**Status**
	measures to their existing studies if these would serve the needs of other ICs without interfering with the parent study.	
25.	Publications derived from existing study datasets should acknowledge the contribution of parent study investigators and credit the grants that supported the data collection.	
26.	Public concerns about research use of GWA genotype-phenotype data and whether the consent process accomplishes what it is intended to should be investigated. **(ongoing in part, NHGRI ELSI program)**	RFA HG-06-008, "Public Consultation to Inform the Design of Possible Large-Scale Studies of Genes and Environment in Common Disease" awarded in Sep 2006 (U01-HG004206-01, Kathy Hudson, PI)
27.	Consideration should be given to asking investigators to provide a template and documentation of the phenotypic and environmental data to be submitted to the GWA database at the time of application for NIH funding.	Template developed and used for GEI Study Investigator RFA HG-06-033, available at http://www.ncbi.nlm.nih.gov/WGA/programs/GEI/submission/instructions.html
28.	Consideration should be given to providing incentives for analysis of datasets incorporating genetic, exposure, and outcome data in large population studies, and for encouraging collaboration with population study investigator, to promote informed and productive use of these complex data sets. Support for collaborative efforts such as awarding small analysis grants, assisting outside investigators in applying for access, and inviting them to participate in cohort study functions have been very effective in bringing new investigators and disciplines into population-based studies.	
29.	A single standardized database for genotypes and phenotypes should be created and maintained by NIH through coordination of NCBI, caBIG, and similar efforts. **(ongoing)**	dbGaP initiated by NCBI at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gap , as described by Jim Ostell at 12/14/06 Town Hall Meeting at http://www.reffectcomments.org/GWAS/NIHT

	Other Recommendations:	**Status**
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30.	Limited subsets of phenotypic and exposure data that are amenable to common definition and standardized collection in GWAS should be identified in near future	RFA HG-07-006, "High-Priority Phenotype and Exposure Measures for Cross-Study Analysis in Genome-Wide Association Studies (http://grants.nih.gov/grants/guide/rfa-files/RFA-HG-07-006.html) released in March 2007for funding in FY07
31.	Efficient methods for transmitting and handling terabytes of data are needed.	
32.	Databases should be tailored for intended users, anticipating who users are likely to be.	
33.	Web-based interfaces and tools are needed for rapidly visualizing associations in GWAS.	Software for display and analysis of GWAS data under development in ENDGAME program led by NHLBI (website under development)
34.	Automated data analysis tools should be developed to identify heterozygotes in DNA sequence traces more efficiently.	
35.	"Federation" of datasets should be considered for housing very large capacity, infrequently used data outside of central databases.	
36.	Comprehensive GWA panels are needed for different populations. **(ongoing in part, extension of HapMap)**	
37.	A "cosmopolitan" GWA panel (that will work in numerous or all populations) should be developed, either through shared resources or public availability of custom sets appropriate for admixed or under-represented populations.	
38.	Flexible and cost-effective technologies are needed for studies involving varying numbers of SNPs per subject, ranging from genome-wide (~10^6 SNPs) through replication studies (~10^4 – 10^3 SNPs) through candidate SNP characterization	

	Other Recommendations:	**Status**
	(~ 10^1 SNPs). **(ongoing, NHGRI)**	
39.	Better methods should be developed for scoring structural variations. **(ongoing, NHGRI)**	
40.	Continued improvements are needed in sequencing technology, moving toward the $1,000 genome. **(ongoing, NHGRI)**	RFA HG-06-015, "Near-Term Technology Development for Genome Sequencing" and RFA HG-06-020, "Revolutionary Genome Sequencing Technologies – The $1000 Genome" released in Sep 2006 by NHGRI
41.	Effective methods should be developed for targeted resequencing of regions of 100kb – 1 Mb that show evidence of association to produce extended haplotypes.	
42.	Better methods for phenotyping (rigorous, standardized, inexpensive, non-invasive, limited burden, appropriate for controls) are needed, particularly for phenotypes relevant to a wide variety of diseases and disability.	RFA HG-07-006, "High-Priority Phenotype and Exposure Measures for Cross-Study Analysis in Genome-Wide Association Studies (http://grants.nih.gov/grants/guide/rfa-files/RFA-HG-07-006.html) released in March 2007 for funding in FY07
43.	Better methods for measuring environmental exposures should be developed. **(ongoing, GEI Exposure Biology component)**	Five GEI RFAs released in Fall 2006: RFA-CA-07-032, "Improved Measures of Diet and Physical Activity for the Genes and Environment Initiative"; RFA-DA-07-005, "Field-Deployable Tools for Quantifying Exposures to Psychosocial Stress and to Addictive Substances for Studies of Health and Disease"; RFA-ES-06-011, "Environmental Sensors for Personal Exposure Assessment"; RFA-ES-06-012, "Biological Response Indicators of Environmental Stress Centers"; RFA-ES-06-013, "Biological Response Indicators of Environmental Stress"
44.	Improved education of non-epidemiologists regarding the biases inherent in clinical case series and convenience controls is needed.	Education session entitled, "Study design issues in population-based genetics and genomics research" developed by NHGRI for Oct 2007 American Society of Human Genetics meetings
45.	Methods for weighting SNPs in GWAS according to prior likelihood of association should be explored.	

	Other Recommendations:	**Status**
46.	Better methods for optimizing efficient use of limited DNA in a series of initial GWAS and replication samples are needed.	
47.	Better methods for assessing gene-gene and gene-environment interactions should be developed. **(ongoing in part, NHLBI, NIGMS)**	GEI-supported RFA HL-07-010, "Methods of Analysis of Gene-Environment Interactions in Complex Diseases: The Genes and Environment Initiative" released in Fall 2006 by NHLBI