Welcome, introduction and opening remarks (Dan Masys and Teri Manolio)
Co-chairs Dan Masys and Teri Manolio thanked participants for, despite the weather, joining the workshop either in-person or remotely. Teri and Dan summarized the purpose of this workshop: to review the current goals and accomplishments of the eMERGE Network and to suggest future directions for NHGRI to consider as the possibility of an eMERGE Phase III approaches.

NHGRI Genomic Medicine portfolio (Eric Green)
The NHGRI has developed a purposely narrow definition of “genomic medicine” that is highly focused on the clinical utility of genomics. Eric outlined NHGRI’s current programs related to the clinical applications of genomics in the areas of: Cancer Genomics, Pharmacogenomics, Genomic Medicine ‘Test Drive’ Programs, Newborn Genomic Analysis, Clinical Genomics Information Systems and Ultra-Rare Genetic Disease Diagnosis. Many of NHGRI’s projects involve partnerships with other NIH institutes, such as The Cancer Genome Atlas (TCGA), and the Clinical Genome Resource (ClinGen). Eric invited attendees to subscribe to his monthly “Director’s Note” which catalogues NHGRI’s current projects and future plans.

eMERGE Program Overview (Rex Chisholm – the eMERGE Steering Committee Chair)
In eMERGE Phase I (2007-2011), the Network demonstrated the utility of linking electronic medical records (EMRs) to biorepositories for genomics research, allowing eMERGE to identify novel associations through genome-wide association studies (GWAS) as well as explore the ethical, legal, and social issues surrounding this kind of research. eMERGE I genotyped 17,046 biobank samples. Phenotyping using EMRs expanded from 5 primary site-specific phenotypes to 13 network-wide phenotypes. The Network has developed a model consent language for the scientific community to collect and store biospecimens and data for future research. Within the network, an eMERGE-wide data sharing agreement has been established to regulate sharing of genotyping and phenotyping data across the network. The Network together discovered associations between 19 phenotypes and 38 genes. Using PheWAS techniques to analyze 866 phenotypes in 13,617 European Americans, overlapping associations between hypothyroidism and thyroid cancer were observed. FOXE1 was shown to be a potential candidate gene for papillary thyroid carcinoma and may have associations with other thyroid diseases.

In eMERGE Phase II (2011-2015), two additional adult sites and three pediatric institutions joined the Network, and the scope broadened from GWAS using electronic phenotypes to include pilot clinical implementation studies. eMERGE II has expanded the electronic phenotyping library to continue discovery of genomic variants via GWAS and has initiated integration of actionable variants into EMRs for use in clinical care. Currently, the network has 328,895 participants with EMRs and ~76,000 samples genotyped. Imputation of the genotyped data using the 1000 Genome reference created a merged dataset including ~52,000 participants. Roughly 9,000 participants are undergoing targeted sequencing of pharmacogenetics genes in the eMERGE-PGx project. Accomplishments of eMERGE II in six key focus areas include:
1) Phenotyping: 44 phenotypes are either complete or in development.
2) Discovery: eMERGE has published multiple GWAS of different clinical phenotypes and phenome-wide association studies (PheWAS) including one on all NHGRI GWAS Catalog SNPs. A new Loss of Function (Null) Variants project is using bioinformatics approaches to identify rare, null variants and examine their EMR phenotypes. eMERGE-PGx is detecting novel variants and assessing their impact on clinical care.
3) Implementation: The site-specific genomic medicine pilots and PGx project are proof-of-concept studies.
4) Methods/tools: eMERGE has developed the PheKB, a publically available phenotype data repository; the eMERGE Record Counter for research planning purposes and feasibility assessment; downloadable Natural Language Processing (NLP) tools such as cTakes and MedEx; the genotyping QC pipeline; the ‘omics ancillary repository for EMR clinical decision support (CDS); the eMERGE Infobutton to point physicians to appropriate CDS resources; CDS systems; and the PGx variant and phenotype data repository (SPHINX).
5) **ELSI**: eMERGE was recently funded to survey attitudes in ~16,000 patients toward a proposed modification to the Common Rule on broad consent for genomics research. This will be important for policy.

6) **Dissemination**: Through January 2014, eMERGE has published 109 total network projects and 295 total projects. eMERGE publications have been cited over 2,116 times. eMERGE is in a good position to identify risk variants and to systemize approaches to implementation.

**PANEL 1: Discovery vs. Implementation – Balancing**

**eMERGE Presentation (Dan Roden)**

Discovery science in eMERGE involves developing new algorithms/methods to utilize existing data across the Network and finding new approaches to discovering new associations. eMERGE implementation science will identify what should be implemented, what evidence matters, how to implement, and which communities to engage as participants and stakeholders. The large and diverse participant base in eMERGE provides a unique opportunity to develop evidence for the value of personalized medicine. To balance discovery and implementation, eMERGE will select areas of study that it is exceptionally well-positioned to address and will connect with external investigators who are also engaged in these areas. In the future, eMERGE should continue to perform PheWAS, conduct longitudinal studies, identify disease subtypes, and consider ancestry issues and other complex factors. This will allow eMERGE to develop methods to validate genetic variants, to determine how best to deploy research findings, and to measure outcomes and impact. Dan Roden affirmed that, as we implement, we learn; as we learn, we generate larger datasets. This is a way that discovery and implementation can feed off of each other.

**Reaction Presentation (Mary Relling)**

Mary gave two examples to demonstrate the complexity in using EMRs to identify drug-related adverse events. She pointed out that cumulated EMR data in eMERGE are a fantastic resource in parallel with tools query it for detailed information on schedule, timing or other factors that may confound the treatment/adverse effects. If enough evidence exists for the actionability of a variant, such as the 13 CPIC genes affecting response to ~60 drugs, then this should be implemented. If there is not sufficient evidence, then more clinical implementation research such as randomized clinical trials or observational studies of non-random differences across health care systems may be needed to inform findings. eMERGE is strongly positioned to conduct such research, using rigorous study designs and considering multiple possible confounding factors.

**Panel Discussion and Summary (Howard McLeod)**

eMERGE still needs to generate more discovery evidence and to create needed infrastructure before shifting entirely or exclusively to implementation science. The tension between “pure” discovery and pure implementation research is a strength of eMERGE, which may find an optimal balance in conducting research on implementation. The panel discussed the following issues:

- **‘Discovering’ should be in the right context.** It would be happening in the context of routine clinical practice rather than the artificial situations typical of clinical trials.
- **Implementation should be supported by high quality science.** It should work toward a relevant endpoint and involve people from multiple relevant disciplines (clinicians, IT, payers, etc).
- **Implementation projects drive the “learning” of learning health care systems, which merge quality improvement and practice.**
- **Evidence derives largely from research projects; discovery of genomic associations is still needed.**
- **eMERGE is well positioned to:**
  - Develop best methods for conducting pragmatic clinical trials to assess clinical implementation.
  - Establish learning health care systems and engage experts in clinical care and workflow.
  - Assess the clinical value of genomics to guide clinical care before implementation.
  - Address penetrance (particularly of Mendelian variants), heritability, and pathogenicity.
  - Study rare variants that could inform improved treatment of underrepresented minority patients.
  - Collaborate with similar genomics research efforts such as UK Biobank, Kaiser, and VA.
PANEL 2: EMR and Clinical Phenotyping – Challenges and New Opportunities

**eMERGE Presentation (Josh Denny)**

Electronic phenotyping has performed well in the network. PheKB.org is now extending phenotype knowledge beyond eMERGE. eMERGE will consider methods for evaluating algorithms received from outside institutions and sharing algorithms in a more structured way (not as Word documents or PDFs). The eMERGE Record Counter houses data from ~50,000 genotyped patients and quickly queries simple metrics such as genotype and phenotype frequencies. SPHINX also stores medication data and covers eMERGE PGx data. In the future, eMERGE should consider developing more detailed phenotypes and faster processes, improving accuracy and reproducibility of data and best methods in using EMRs for research. Structured data dictionaries used across the Network would be useful.

**Reaction Presentation (Dan Masys)**

eMERGE can expand the EMR phenotype workforce by inviting CTSA awardees with EMR-derived research data warehouses to join PheKB to use and produce new phenotype specifications. eMERGE should consider what would be needed to scale up to include more collaborating institutions. eMERGE should also investigate whether complex phenotypes can be re-purposed and broken down into modular component sub-units. If so, then eMERGE institutions (and other interested research organizations) could build up high-quality cohort selection logic built on these sub-components, concatenated in combinations in a manner similar to modular software, for broader dissemination. Before implementation of a prototype consortium-wide closed-loop CDS pilot project, all of the needed components and effects measures must be in place, but eMERGE must determine when such a project would be ready to implement. CDS intervention types could include: educational prompts, data gathering prompts, guidance that improves certainty of diagnoses, guidance for best-evidence-based therapy selection, and information relevant to prevention and/or prognosis. “Closed loop” CDS means that systems are built not only to deliver guidance, but also capture and track whether intended users followed the guidance, as well as the relevant subsequent process and outcome measures. The ability to determine whether CDS was accepted or rejected, and to correlate that with outcomes, will be the essence of a systems approach to a ‘genomically enabled learning healthcare system.’

**Panel Discussion and Summary (Chris Chute)**

EMRs are evolving and developing increased capabilities. Standards and extensible methods will help improve accuracy and reproducibility. Phenomic approaches and longitudinal phenotypes are among the best ways to leverage the unique nature of the EMR. Current challenges of using EMR data for genomic medicine are:

- Some medical centers think of clinical data as simply a by-product of the clinical process, missing its unique value for clinical research.
- Labs are not yet prepared to provide coded data.
- Local politics of competing institutions may interfere with data sharing.
- EMR vendors are a couple of years behind as they are not incentivized to provide family history data or genomic data.

eMERGE has a unique opportunity to:

- Apply phenomic approaches to assess longitudinal, rare, pharmacogenomics, subtype phenotypes.
- Determine if Meaningful Use standards help clinical data normalization and poolability.
- Develop new methods to make phenotyping fast, accurate, and reproducible.
- Identify undiagnosed phenotypes in genotyped patients.
- Create “Modular” phenotypes to facilitate transportability.
- Assemble clinical leaders of major academic medical centers to interact with vendors to emphasize the value of utilizing EMR data as a clinical resource.
- Convene a forum to discuss economic benefits for vendors/medical centers/other stakeholders.
PANEL 3: EMR and Genomic Discovery - Beyond GWAS, Pharmacogenomics

**eMERGE Presentation (Marylyn Ritchie)**
In eMERGE-I, the Genomics WG focused on genotyping and sequencing, maintaining quality control of large-scale genomic data, and GWAS. In eMERGE-II, the WG focused on imputation, conducting more GWAS, gene-gene and gene-environment interactions, null variants, PheWAS and EWAS, and the PGx project. eMERGE should continue comprehensive analyses with existing data and perform more data generation via sequencing, high-throughput genotyping, and other techniques (e.g. tissues). To learn more about causality in a future phase, the Genomics WG is looking to explore longitudinal GWAS; pathway analysis using functional data such as ENCODE and GTEx; and integration of existing epidemiological data, GIS data, and other available data.

**Reaction Presentation (Debbie Nickerson)**
Sequencing would allow eMERGE to explore the spectrum of actionable variants and uncover Mendelian as well as common disease associations. Different approaches can be used, such as selected targets, exome, or whole genome sequencing. Careful selection of phenotypes for sequencing is key for discovery. Sequencing the tails of a phenotype distribution might be the best approach. eMERGE should examine non-coding and functional variants (ENCODE data) particularly relevant to ongoing eMERGE science.

**Panel Discussion and Summary (Steve Leeder)**
Discovery research should remain a high priority for eMERGE, which should:
- Prioritize phenotypes to focus on those uniquely facilitated by eMERGE methods.
- Determine the most appropriate approaches to study rare but collectively common variants.
- Generate dense data through sequencing (next generation, exome, targeted genes) and/or a genotyping platform that includes LoF variants.
- Apply alternative analytic study designs for discovery: extreme discordant phenotypes, tails of distributions, etc.
- Expand data collection processes: additional sources of RNA/DNA, environment data (such as PhenX toolkit), family history, co-morbidities (mining EMR data), etc.
- Develop analytic tools to incorporate other sources of data (e.g., ENCODE, GTEx) and environment data into analysis to explore potential pathogenic or causal variants.

PANEL 4: Genomic Testing – Actionability, Validation, and Standards of Lab Reports

**eMERGE Presentation (Laura Rasmussen-Torvik)**
Genotyping in eMERGE-II has largely been performed in connection with clinical genomics pilot projects and the network pharmacogenomics (PGx) project. PGx is using the PGRNSeq platform of 84 pharmacogenetic genes. For the most part, PGRNSeq sequencing produces research results, though some research results have clinical validation. Actionable variants will be re-genotyped in a CLIA-approved environment if not done so initially. The EMR Integration (EMRI) workgroup is working to integrate CLIA genotypes as computed results. Reports to clinicians will include clinical interpretations with the findings. The eMERGE PGx Project has catalyzed PGx Implementation projects across the Network and in some cases stimulated additional resource allocation from the participating medical centers. The eMERGE PGx has also served as a test bed for the practical challenges associated with an implementation process.

**Reaction Presentation (Heidi Rehm)**
eMERGE should consider expanding its genotyping focus to gene-phenotype pairs instead of genotype-phenotype pairs allowing for collaboration with groups like ClinGen. ClinGen focuses on gene-based clinical actionability and supports evidence-based curation by community experts. The ACMG guidelines for NGS clinical laboratory standards state that validation must cover all types of rare variants investigators might encounter and address homologous regions. For common variants, validation should be variant-specific. Orthogonal confirmation may not be needed if sufficient validation has been performed, quality metrics are high, and workflow has low risk for sample swaps. In terms of variant calling, joint calling in batches and targeted “genotype” calling on raw NGS data can improve data accuracy. Heidi recommended...
that variants going to EMRs should be restricted to those with analytical and clinical validity. When variant classification changes, then the variant’s original and new classification should be sent to the clinician.

**Panel Discussion and Summary (Dick Weinshilboum)**

It was suggested that eMERGE:

- Follow the guidelines for NGS clinical laboratory standards recently published by the ACMG.
- Address issues on portability and standards for sharing files when patients move from one institution to another.
- Potentially put together a paper on the various approaches to minimizing CLIA obstacles, such as sequencing non-CLIA biorepository samples and only calling back and re-collecting CLIA-certifiable samples from participants to whom they saw the need to return results.
- Conduct economic analyses assessing the impact of RoR.
- Establish broad biobank consent to easily return CLIA research results to EMRs for clinical use.
- Study the impact of re-contact and re-annotation of actionability—what are the best methods, who is responsible for it, etc.

**PANEL 5: Informed Consent, Education and Governance – ELSI**

**eMERGE Presentation (Maureen Smith)**

A cross-network model language consent document has been created, and a pediatric model consent language is in process for pediatrics. eMERGE has also developed a framework for addressing return of results within the network and has engaged stakeholders to inform a variety of issues, including data sharing and related privacy issues and the value of genomic research. eMERGE has developed educational methods for physicians and patients, assessed application of data sharing guidelines within the network, and compared institutional oversight across sites. eMERGE is conducting a survey across the 10 eMERGE institutions related to the notice of proposed rulemaking, focusing on acceptance of broad consent and views on data sharing. Future eMERGE initiatives may focus on integrating bioethics aims into scientific studies, assessing the impact of genomic medicine, continuing to engage with stakeholders, and educating IRBs and clinical practitioners.

**Reaction Presentation (Wendy Chung)**

ELSI studies are complicated by the variable approaches to measuring impact of consent/education in the context of different local communities. A major challenge is the variability of IRB knowledge and expertise on genomic issues, leading to unnecessary variability in policies and decisions about similar research issues. The collective expertise and resources of eMERGE provide unique opportunities to study local differences across IRBs including differences in knowledge and expertise; to develop educational materials for IRBs to help standardize their decisions; to develop RoR policies for special populations, such as minors, deceased participants, and those with diminished capacity; to disseminate and promote uptake of best practices and effective “products” for education at time of medical decision-making through the EMR; and to coordinate RoR from central data source as secondary users don’t have same investment or access.

**Panel Discussion and Summary (Reed Pyeritz)**

Bringing together ELSI people at a cross-NHGRI consortia meeting would ensure that there is no overlap in efforts and would produce strategies for shared challenges. eMERGE should:

- Collaborate with related NIH and Patient Centered Outcomes Research Institute (PCORI) projects.
- Work with the Inter-Society Coordinating Committee (ISCC) to create provider education materials.
- Identify issues on which it is best positioned to inform policy; i.e., re-contacting participants upon new discoveries.
- Conduct formal assessment of the legal issues surrounding implementation, as payers and administrators will respond best to hard data. eMERGE should engage payers as key stakeholders.
- Test participant response to pediatric consent language.
- Demonstrate how institutions work together to effectively address issues identified by IRBs as done previously with data sharing, and educate IRBs on key issues in genomic medicine implementation.
• Study patient perspectives by developing patient portals and developing/deploying consent forms.
• Develop methods and policies for updating information as it changes over a participant’s lifespan.
• Develop a model across the network for conducting economic/value-based research, including data on how genetic information is persistent and reusable over a period of time.
• Explore legal barriers including CLIA, HIPAA, re-contacting participants, RoR, consent for incorporation into EMRs, and mapping responsibilities within the EMR environment. The legal issues of ANPRM can also be considered.
• Evaluate the impact of different formats for informed consent in genomic research.
• Consider networking IRBs across eMERGE through widespread IRB agreements. Over the course of the next 12 months, this will be implemented across CTSAs through the IRBshare program.

**PANEL 6: Return of Genomic Results – Current Applications and Challenges**

**eMERGE Presentation (Iftikhar Kullo)**
eMERGE is generating evidence of clinical validity and actionability and developing appropriate methods for returning findings. On the discovery side, there are many research questions related to RoR such as incidental findings, the mechanism and timing of RoR, consent, patient preferences, CLIA confirmation, documentation in EMRs, family members, and pediatric settings. Potential projects include whole exome studies of 1,000 participants per site to test phenotypes, penetrance, pleiotropy, and pediatric considerations; targeted sequencing for the 56 ACMG genes to determine pathogenicity, penetrance, informing kin, etc.; clinically indicated panels, i.e. cardiomyopathies, pediatric syndromes; and high-density genotyping of common and rare variants. eMERGE has identified its stakeholders and is collaborating with several other RoR-related research groups. Not conducting research in CLIA-certified labs complicates RoR as investigators will many times need to go back to IRBs for approval.

**Reaction Presentation (Larry Meyer)**
Most VA research subjects would be interested and would want all individual results returned. Concerns were raised about RoR discussions being too paternalistic. eMERGE should consider that often preferences change at the time of the test. Releasing this information could potentially increase genetic literacy. Evaluating risk score data for macular degeneration and other eMERGE phenotypes would be a good start and then eMERGE can follow up with subjects on preference over time and literacy. eMERGE should determine what clinical tests require specific consent as there is a range of sensitivity of clinical tests, from TPMT to Huntington’s disease. eMERGE needs to determine where to draw the line for genetic tests requiring consent and counseling. eMERGE should assess community preferences for consent for genetic testing in practice. eMERGE can also examine issues in engaging EMR CDS.

**Panel discussion and Summary (Lisa Parker)**
With its integrated infrastructure for conducting empirical ELSI research, eMERGE has a real opportunity to examine ELSI issues on an individual participant level as well as systems level such as economics, impact on healthcare cost, quality assurances, and privacy protection.
• Highly penetrant variants are more clinically demanded. eMERGE can learn more about the impact of penetrance on ELSI issues.
• eMERGE might consider developing a scoring scale for actionability driven by physician and researcher opinions. An evidence base must be developed to support actionability. It will also be important to see what providers and patients feel is actionable and to collect public opinion on the ACMG list.
• RoR studies should include diverse populations, both by race/ethnicity and age.
• eMERGE might examine impact of RoR to proband’s relatives.
• eMERGE should evaluate the impact of increasing access to EMRs and examine what information patients want in their records and how they would like this information to be displayed.
• eMERGE is well positioned to assess what happens long-term after RoR—lifestyle/behavior changes?
The eMERGE Infobutton project has two objectives: 1) to develop a new information resource based on eMERGE II and PGx scenarios and 2) to implement Infobuttons within EMRs at eMERGE sites. After content developers have filled out the eMERGE template and target end users have been fully engaged, eMERGE will evaluate its resource by surveying target end users before implementation. As is required for inclusion by Meaningful Use, the OpenInfobutton, in collaboration with the University of Utah, is being integrated into eMERGE EMRs. The EMR Integration group is working with the CSER Informatics group and agreed to produce a white paper on where genetic information should appear in EMRs. The group will need to study transportability, customizability, and the ability to extract real-time, patient-level data from transactional EMRs. eMERGE can study the ability to extract real-time patient level data for selected genomic medicine use cases and measure comparative effectiveness of approaches enhancing patient and provider education through EMRs, personal health records (PHRs) and patient portals. The group will need to determine who is best to handle the results presented by a patient portal.

eMERGE-PGx should work with EMR vendors as well as clinical leadership who have control over what is placed in EMRs. It will be important to study the accuracy and efficiency of use cases in terms of workflow. Other challenges include re-interpretation of genomic analyses and patient data and maintenance of CDS information. Versioning will be important so that rationale behind past clinical decisions and reports can be retrieved and understood. CDS alerts should include alternative treatments along with warnings. CDS and patient portals will become more routine in non-genomic medicine. However, some patients will not use the portals no matter what, and eMERGE will need to be able to produce alternative forms to present genetic information. Need for physician education and complexity of the information present challenges for automation. eMERGE should build regular review, reinterpretation and revision at multiple levels—genomic interpretation, patient data, and CDS.

There is a need for buy-in at various levels, especially by IT staff. Understanding clinician needs and stressors, including the potential for CDS alert fatigue, will be critical. Certain vendors are more amendable to modifying their systems than others. eMERGE will need to:

- Move from process-based outcomes to clinical outcomes.
- Have institutional leaders clearly specify to vendors what should be included in EMRs since scaling CDS is of general interest to develop standards for all of medicine, not just for personalized medicine.
- Generate data on efficiency, cost-effectiveness, and ease of implementation when pitching to chief medical informatics officers (CMIOs) and institutional IT groups, such as data from studies of Stevens-Johnson Syndrome (SJS)/toxic epidermal necrosis (TEN) or CYP2D6 and drug safety.
- Measure different medical specialties’ attitudes and perceptions when encountering the same EMR text. Bringing in more opinion leaders will act as a unified clinician front and help identify how eMERGE can improve workflow design.
- Leverage National Patient-Centered Clinical Research (PCORnet) efforts and recognize the value of providing results to the patient as the only person in their healthcare system who’s a constant.
- Determine the structure of how information will flow into EMRs when it is ready to implement.
- Compare EMR outcomes measurement to see how many people are actually using the CDS tools.
- Create more formal resources to assist others in implementation (could follow the PheKB model); share what CDS rules work, at least in a pseudo-code version, as well as share guidance about what sorts of genomic information should be where in the EMR.
**Panel 8: Genomic Medicine in Pediatric Patients – Obstacles and Future Directions**

**eMERGE Presentation (Hakon Hakonarson)**

eMERGE is covering several areas in pediatrics, including phenotyping, consent, genotype-phenotype association discovery, PGx, and clinical implementation. A major obstacle in pediatrics is incongruity between pediatric and adult phenotypes. To resolve this issue, eMERGE pediatric sites have developed a primary/validation strategy for phenotyping and have revised their list of candidate phenotypes to increase overlap with adult phenotypes (such as asthma and obesity). eMERGE is also developing pediatric model consent language. CNVs may be particularly important in pediatric conditions and represent a domain that can be leveraged across sites. eMERGE can use EMRs to provide proper control data and to increase confidence for the Database of Genomic Variants (DGV) findings. In the future, eMERGE should consider developing and implementing across all sites a cost-effective informative SNP array that would genotype eMERGE samples for low frequency variants with high potential for pathogenic impact.

**Reaction Presentation (Robert Nussbaum)**

It could be a strength that eMERGE has two paths of phenotyping—for adults and for children—as children are a currently underrepresented population in genomics. The re-consent process is a large issue in pediatrics. In addressing imputation of TPMT genotyping, eMERGE should determine what fraction of genotyped patients are actually exposed to 6TG therapy and provide data on outcomes and patient response. Sharing variant data with the International Collaboration for Clinical Genomics (ICCG) consortium would maximize information included in the public domain.

**Panel Discussion and Summary (Jeff Botkin)**

The pediatric component in eMERGE should:
- Consider expanding its network over time to increase the diversity of its participant base.
- Review whether there is a need to increase overlap between targeted adult and pediatric phenotypes.
- Consider its capacity to fill in gaps in understanding CNVs.
- Consider whether the time is ripe for a custom genotyping array with a broad spectrum of clinically relevant variants and CNVs, vs. a more broadly applied sequencing approach if costs are manageable.
- Consider analyzing more gene-environment interactions.
- Collaborate with the Newborn Sequencing project on topics such as the importance of genetic analysis of parents to clarify a child’s results.
- Identify if there are target conditions for genomic analysis that may have early clinical utility.
- Take opportunities to use the national birth defects registry to expand its population base.
- Find cross-cutting phenotypes as well as pediatric-oriented phenotypes, e.g. using opiates, fetal addiction syndromes, appendicitis, etc.
- Lead translation of genomics into pediatrics.
- Develop protocols for re-contacting parents of pediatric patients with recently discovered risks.
- Explore the risks of re-identification of de-identified information for use in re-consent and RoR.
- Explore clinical utility of intervening on potential adult onset disease risk in pediatric populations.
- Use new technology to detect methylation patterns that will change from child to adulthood, store this information, and apply it when research on methylation and epigenetics shows clinical relevance.

**Summary and Recommendations for Future Directions (Dan Masys and Teri Manolio)**

Workshop participants agreed that eMERGE is well-positioned for genomic research in several ways, including its focus on EMRs for phenotyping, phenome-wide studies, data re-use for genomic discovery, and integration of genomic findings and implementation in the EMR; its large size and diverse population; its inclusion of pediatric centers and potential for bringing genomic translation to pediatrics; its closely integrated infrastructure for empirical ELSI research on implementation; and its site-specific and network-wide efforts at implementing genomic findings in diverse clinical settings.

eMERGE can best contribute to the scientific community by continuing its emphasis on EMRs, developing new methods and tools for phenotyping, and leveraging the EMR for genomic discovery and clinical
implementation. eMERGE should continue to include both discovery and implementation, and is uniquely positioned to conduct research on implementation. Discovery in eMERGE should leverage the rich EMR phenotyping data and utilize state-of-the-art techniques for measuring genomic variation, including CNVs. Discovery studies in eMERGE should include additional sources of RNA/DNA, EMR-defined co-morbidities and environmental data to account for confounding factors, EMR-defined phenotypes of rare variant carriers; and functional data for identifying possible causative variants. Implementation research in eMERGE should include rare but collectively common disease-related variants that could inform improved treatment, explore differences in implementation among diverse subgroups, develop best approaches to variant re-annotation, and generate data on efficiency, cost-effectiveness, and ease of implementation. An ideal convergence of discovery and implementation research utilizing eMERGE’s unique strengths would involve sequencing highly clinically relevant genes, developing best methods for returning these results, and assessing their impact. The integrated ELSI infrastructure in eMERGE should continue to explore legal and economic implications of genomic medicine implementation, examine and minimize local differences across IRBs in genomics expertise and decision-making; and assess impact of RoR.

The workshop presentation slides and video recordings have been posted online at http://www.genome.gov/27555919.
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