eMEREGE Steering Committee Meeting
October 17, 2011

1. Program Office Report – Rongling Li
    a. 2nd eMERGE SC meeting, 1st ESP meeting
    b. New NHGRI deputy director – Dr. Mark Guyer (PhD) acting director extramural research
    c. Special advisors to NHGRI director
        i. Karen Rothenberg JD, MPA – 1 year sabattacal from ___
            1. Lead effort to critically analyze NHGRI
        ii. Marc Williams MD, special advisor for genetic medicine
    d. FY 2012 NIH and NHGRI proposed 2.4% increase/1.7% increase BUT Senate appropriations cut NIH budget -0.5% to NIH $30.5B and NHGRI -1% to $505.7M, HoR + 3.3% NIH, $31.7B
    e. Phase II start Aug 15, continue to recruit Pediatric sites. Sci merit rev Nov 28, earliest funding site May 2012.
    f. Goals for this meeting:
        i. Reinforce eMERGE phase II structure & strategic directions
        ii. Initiate interactions/collaborations w/Network & EMR vendors
        iii. Discuss workgroup goals, milestones, achievement approaches
        iv. Identify commonalities across sites/workgroups for collaborations
        v. Update ESP on site-specific aims/progress last 2 mo
        vi. Draft goals, milestones, timelimes, internal structure w/in workgroups
        vii. Build relationships w/PGRN & EMR vendors
        viii. Establish collaborations between sites/workgroups
        ix. Discuss & potentially approve first list of actionable variants for clinical trial/pilot studies
2. Phase II Network Overview Shared Goals – Rex Chisholm
    a. Introductions
    b. PGRN has been thinking about PGx side of clinical actionability/variants. Leverage what PGRN has already thought about, not reinvent the wheel, but build strong partnership.
    c. EMR workshop – recognize that sites use different vendors. eMERGE I – working together than working separately. Start to engage in dialog w/how data transferable, meaningful use, SHARP consortium,
    d. Open discussion about clinical implementation – discuss commonalities/differences across network – how best to leverage them
    e. Workgroup 2 hr face to face –
    f. Phenotyping – goal of 40 by end of eMERGE II
        i. By end of meeting – well prioritized list of phenotypes
    g. Genomics Genotype-Phenotype associations
        i. Use Phenotypes and GWAS to identify new variants (autoimmune hypothyroidism)
        ii. What does it take to integrate new site's data? (Genomics WG)
    h. Clinical Use:
        i. Defining actionability/clinical utility/validity/implementing (*and measuring*)
        ii. Integration into EMR/Clinical Decision Support (Visualization tools)
    i. Physician/Patient Attitudes
        i. Will physicians take advantage of ill defined variants – at what stage will they use them?
        ii. What do patients want?
        iii. Education is clear component – think of specific educational programs
    j. Consent/Regulatory
        i. Return of results
        ii. Range of regulatory and consent of different sites (commonality/difference)
    k. Privacy & security & CLIA
        i. CAP (?) or CLIA standard should be used?
    l. GT will be overwhelmed by *sequencing* in the upcoming years – dealing with integrating tsunami of data and obligation of eMERGE II to think about how to integrate (whole genome)

m. NHGRI sponsoring resources for centralized database to house clinical actionable variants (Dec 1st and 2nd)
n. Wisconson Q: Weakness w/phenotyping - effort to do sophisticated discrete phenotyping of broad diseases (heart failure/CAD)
    i. Algorithms use complex algorithms (lab values, ICD9 codes, meds etc) for inclusions and exclusions. Achieving 98% + PPV shows how complex and narrowly defined phenotypes are.
o. Workgroups
    i. Phenotyping
        1. Goals for WG session:
            a. Finalize charter
            b. Prioritize phenotypes – primary and secondary phenotypes set schedules
                i. eMERGE I – which phenotypes do we want to genotype
            c. Validation approaches
            d. High throughput phenotyping strategies
    ii. Genomics
        1. Goals for WG session:
            a. Build on phase 1
            b. Finalize charter
            c. Inventory of data by site
            d. Design of study for PGx
            e. De novo genotyping – discuss assay choices
            f. QC pipeline (Headed by Marylyn Ritchie) – data cleaning, imputation (David's expertise), analysis and methods
            g. First freeze of eMERGE II genomics data set (based in inventory to make network-wide resource, imputation will drive timeline)
            h. CNV data integration – outstanding for eMERGE I data set, planning to start calling CNV numbers
    iii. EMR integration
        1. Goals for WG session:
            a. Finalize charter
            b. Get decision support pushed through vendor systems not designed for this
            c. How far each group is with this
            d. Logic sharing for decision support?
                i. Took about a year for everyone to get better defined idea of what each site offers in eMERGE I
    iv. CERC
        1. Goals for WG:
            a. Find areas of collaborations
                i. Physician education, regulation, ___, consent (revisit – Return of Results for biobanks set up for research
                ii. Broaden WG to external members
                iii. Bioethics subcommittee
                iv. Multiple subgroups?
                v. Outreach education to specific providers? Family physicians, genetic counselors, NP, PA etc to educate family for sharing information
                vi. Regular assessment of how each of these are working to establish best practices
                vii. Clinical decision support led by ONCR (?) Brad Malin
    v. AV
        1. Goals for WG session
            a. Define criteria for actionability
                i. Mendelian, genetic risk scores, PGx
                ii. Exome sequencing

iii. Catalogue variants
b. Catalog variants
c. Incorporate specific ancestry support – eMERGE II has more diverse groups, recent GWAS on non-European descent, will be helpful
d. Randomized clinical trial – may not be possible for each variant, how to reach clinical validity

vi. Pharmacogenomic sequencing WG
vii. Participate in as many workgroups as can stand. Must produce charters, set of goals, turn into work plan with timelines and deliverables. Finalizing workgroup charters.

3. PGRN Workgroup
   a. Dan Roden – pharmacogentics: patients have variable response to drugs
      i. Clinical discriminators (gender, age)
      ii. Associations w/candidate gene polymorphs (ADME)
      iii. Single variant w/large effects to large pathways with smaller effects (PRGN paper 2006)
      iv. Phase I and Phase II – CYP2D6 ¼ of drugs metabolized by this, 7% have inactive variants
         1. Must be homozygous for 2 loss of function, or increased number of copies, need to know if cis or trans,
      v. When is this important for drug tx? Worry about drugs where narrow margin between drug efficacy and toxicity.
         1. Pro-drug to active metabolity (variability in drug)
         2. Parent drug to inactive metabolite
         3. Single pathway for elimination
      vi. Mayo clinic:
         1. 38 sub treated w/venlafaxine
            a. Is data set large enough to believe?
            b. Would you genotype pts before tx?
            c. ___
         2. NIGMS invest in PGRN
            a. 2000-2005 (12 sites)
               i. VIP (very important pharmacogenes)
               ii. PharmGKB website – deposit data, pathways
            b. 2005-2010 (11 sites)
               i. Outreach
                  1. International Warfarin pharmacogenomics consortium – aggregate data across world – ID common variants contributing to variable warfarin dose: CYP2C9 (Metab) and VKORC1 (drug target) – about 50% of variability
                  2. Wide variability in VKORC across ethnicities (promotor)
                  3. Rare sequence variants associated with high warfarin dose requirements (except Israel and Manhattan)
               ii. PGRN CGM – GWAS genotyping
                  1. 19 studies, 21,308 samples
               iii. Tamoxifen, transporter, clinical pharmacogenetics implementation, SSRI consortiums (worldwide, PharmGKB)
               iv. 2010-2015
                  1. 14 sites, organized by oncology, neuropsych, implementation, cardio, lung, consortia
                  2. Debbie Nickerson – exome sequencing Northwestern?
                     a. 2000 exomes (1500 caucasian, 500 aa)
                     b. Discovered that 3-5% pop have mutations in drug metab genes that not captured by tests b/c not common or described yet
               v. Case for preemptive genotyping

1. How many 'medical home' patients (out of 53,196) get drugs that can be recognized by PGx: 65% received one med w/in 5 years

c. PGRN-eMERGE synergies
    i. PGRN brings content expertise to algorithm development & implementation
    ii. eMERGE potential platform for implementation or discovery in PGx
        1. Must engage content experts to refine algorithms (PGRN experts in PGx)
d. Rex: How do we effectively collaborate with PGRN to make added value
    i. PGRN is always looking for more/larger patient sets – eMERGE can assist in bringing these patient/data sets
        1. PGpop (at VU) – patients with PGx phenotypes across multiple EMR, Marshfield, HMO networks, Biobank Japan
        2. PGRN develop platform to explore limited number very important pharmacogenes
            a. Set of 80 genes
            b. Who would use platform?
                i. Set of patients with drug response differences (whole exomes might be better)
                ii. Preemtive vision – VU uses ADME platform w/ 184 variants, but would like to move to larger platform
e. Rex: Level 1 of clinical genes should be on AV list
    i. IK: Which ones can be imputed, which ones on Illumina chips
    ii. DR: Platform agnostic, which are actionable? what is actionable based on clinical data?
    iii. Cinci: Fine mapping? Make set of actionable genes, then worry about the variants.
    iv. DR: Issue is that each investigator is obsessed w/their gene of interest. Thought has to be who are the other consumers of the chip?
    v. Cinci: If you start now, the detail of genes will be complete by end of 2 years
    vi. MR: Illumina, OMNI/ADME – evaluate imputation possibility based on GWAS data – probably not possible, but can try
    vii. EB: Pharmacy is changing all the time. How does PGRN factor in to moving target into pharmacies changes?
    viii. DR: PGRN is focused on drug response side. Insists on seeing dose, response, dose response. Switching drugs because of pharmacy/payer beneficiaries and don't know who really takes meds.
    ix. Map of international collaboration: not representative of explosion of populationship? Build relationships to include these people?
    x. DR: IWPC best example – East Asia, South Asia, (Africa) represented
    xi. Rochelle: Map shows where investigators are not subjects, investigators want diverse populations.
        1. 500-100 African subjects in PGRN 1

b. Alan Schuldiner – U Maryland – Clopidogrel PGx
    i. Clopidogrel – most common anti-platelet therapy (with aspirin)
    ii. Site of action unknown when approved by FDA. Binds to ADP receptors on platelets preventing platelet aggregation and thrombosis
    iii. Great variability in response 4-33% could be considered non-responders
    iv. PAPI study – very homogenous population to limit confounders: 668 healthy Amish, tx clopid 1 wk, platelet aggregation great variability. On average population responded, but huge inter-

individual variability in response. All 668 Amish related to each other, get estimates of heritability, over 70% genetic component. GWAS – CYP2C19*2 gene (true metab gene, no platelet aggregation effect). 2-3 fold increased risk. 1/3 of population carries *2 allele, counts for 12 (large genetic contribution) % variation. CYP2C19 activates prodrug clopidogrel. 1.5 hrs ago, FDA black box warning, important variant can be measured, *2 variants should have alternative therapy

v. Clopidogrel coming off patent
vi. Prasugrel does not require CYP2C19 for activation, but is expensive and has higher bleeding rates (*2 variants one to two variants)
vii. No clinicians want to do genetic testing for clopidogrel therapy even after hearing about studies.
viii. 0.5% cardiologists are doing genetic testing today
ix. Barriers – lack of prospective randomized clinical trial, optimal clinical algorithm, logistics of genetic testing, heath care provider education, reimbursement (becoming less problem, some payers will cover), ethical/legal concerns, patients understand and want genetic testing
x. PAPI-2 study: prospective randomized trial of genotype directed antiplatelet therapy in CYP2C19 intermediate metabolizers. Pharmacoeconomic studies. Additional discovery study. Important step forward, but will take 3-4 yrs. Move agenda forward before prospective randomized trial is complete
xi. Clinical Pharmacogenetics Implementation Consortium (CPIC) – ID drug gene pairs where data is strong and clinical implementation is ready, published guidelines for genetic testing (clopidogrel) understandable for clinicians.
    1. Published tables (Aug CPT?) – break down algorithm for genotypes/phenotypes – suggestions for therapy to be provided
    2. PGRN Translational Pharamcogenetics Project (TPP) – work through science of implementation
        a. Several PGRN sites – implement PGx tests in health care systems - learn a lot from different systems from each systems. Will come up with best practices.
        b. 6 PGRN sites for implementation. 3 pilotes: TPMT/thiopurines; CYP2C19/clopidogrel; CYP2C9, CYP4F2, VKORC1/warfarin (All CLIA labs)
        c. Develop decision support for commonly used EMR
        d. Education for health care providers
        e. Collect implementation metrics
        f. Disseminate results
    3. Verigene CYP2C19 test (approx. 3 hrs turnaround time)
xii. What about other indications of clopidogrel (lower risk CAD, stroke, PAD)?
    1. Indication specific target pops?
xiii. What about other genetic variants?
xiv. VIPgx Resequencing Project
    1. Target most important PGx genes for cost effective resequencing
        a. Discovery, Implementation (CLIA labs)
    2. 83 genes (Coding plus 2kb flanking up/downstream), 546,330 bp
xv. Clopidogrel inactivated by carboxyesterace 1 – exome sequencing (nonsynom mut) CES1 G143E greater risk for bleeding (hyper responders) – rare functional allele needs larger population (eMERGE network may be able to fill requirement)
xvi. Questions:
    1. Russ Wilke: Defining heritability for drug response. Should eMERGE use heritability?
        a. AS: Shouldn't worry too much about heritability. Drug response traits are modestly heritable. PAPI was short term drug exposure, controlled – outcomes in outbred populations wider. If not as heritable may not be actionable.
    2. Rex: TPP project – add additional sites down the road. AV group, think about role for eMERGE actionable variants in that group. (clinical utility). CAD/PAD projects are ongoing and CES1 populations could be provided from eMERGE population.

3. RW: If find other tissue esterases important, we can re-interrogate our systems for other drugs metabolized by these esterases (statins inactivated by CES1). (CES2 inactivates prasugrel). Rex: provide drugs metabolized by tissue esterases.
4. Joseph Cannery: Internist perspective – don't know how to order tests? Will CDS be within each EMR or shared across?
    a. AS: Through Stanford/St. Jude developed common code that can be put in EPIC, CERNER and homegrown EMRs

c. Richard Weinshilboum – Mayo PGRN
    i. PGx clinical implementation:
        1. PGRN, CCC (cancer center), eMERGE, CIM (individual med), CSHCD (health care division) interactions critically important
    ii. Clinical Pharmacology & Therapeutics – editorial (Oct 2011)
    iii. Issues for PGx
        1. Evidence of clinical utility
        2. Objective clinical guidance (CPT paper)
        3. Genotyping CLIA approved lab – CAP is what really counts
        4. Must get genotype data in EMR
        5. Pharmacy Services must be involved (pharmacy and therapeutics dept have this data)
        6. CDS tools
        7. Involvement of clinical staff who would use the test
    iv. Mayo PGRN TPP – randomized prospective clinical trial required by cardiologists even though FDA blackbox warning
        1. Lab set up to give 3-4 hr turnaround time for point of care assay: CYP2C19*2, *3, *17.
        2. Engages cardiologist physician group – enthusiasm from physicians
    v. Breast Cancer
        1. Genome: germline and tumor somatic genome (must have samples from both to have meaningful data)
        2. Need to make this into two pictures to make easier to understand
            a. Variant in liver (germline) and variant in breast cancer (EGFR) have different response to drug
        3. NCI Cooperative groups, RIKEN center for genomic med – genotyping, Breast Cancer SPORE, Mayo PGRN
        4. GWAS studies - ~12,000 pts?
        5. "Human variation panel" 300 cell lines Liewei Wang
            a. Take 100 EA, 100AA, 100 HCA (Han Chinese American)
            b. 1.3million SNPs/cell line
            c. 1.4 million exon probed
            d. Make hybrid cells from each patient (xenograft)
        6. BEAUTY – genome seq guided adaptive breast cancer trial (many different talent)
            a. Target therapy – shift from cytotoxic agents toward molecular targets
            b. Neoadjuvant – treat before surgery; Adjuvant – treat after surgery
            c. Phase 1:
                i. Seq germline & tumor genomes
                ii. ID novel mut (Drug targets)
                iii. Determine fxn-mechanistic significance mutation using xenograft created from tumor and cell lines
            d. Phase 2:
                i. Use genomic info from Phase 1 to individualize breast cancer therapy
            e. Tumor Exome seq (until whole genome cheaper), then tumor RNA seq and methylation
            f. Germline DNA exome seq, germline SNP assay
            g. Xenograft
            h. Goals

i. Select responsive patients etc…

7. Population based PGx
    a. Preemptive population based PGx
        i. CIM Biobank (21,675 subjects)
        ii. VIP Capture and sequence in CLIA environ
        iii. Deposit selected gene seq in EMR
        iv. (Using DMET 250 genes, putting 2 genes (TPMT and CYP2D6, will include CYP2C19) – keep behind curtain. P&T committee decides what is out.)
        v. Systematically eval clinical resource utilization outcomes
    b. We are always behind the wave – need to seq (what do you do with BRACA1/2 genes?) ok, with drug metab genes, get pharmacy in the door, get foot in door to use seq
    c. Pilot study 50% not genotyped (45% psychiatry patients genotyped) fail tx (?)
8. Questions:
    a. DR: Tension between point of care decision support and broad preemptive genotyping. (VU data delivered days later, sometimes interferes w/care). Point of care data is the way to get docs on board.
        i. RW: Psych patients genotyped for CYP2C19 (citalopram), if show up in cath lab will pharmacy know about genotype and what to do if clopidogrel is ordered? At this point no.
    b. AS: Transient care provided to patients, how does preemptive genotyping fit with this?
        i. RW: Part of learning curve (Geisinger/Mayo receive all clinical care there). Take first step toward learning how to overcoming these problems.
    c. BK: Sociological barriers to therapy. Barriers to PGx adoption (10 yrs ago). What are sociological barriers?
        i. RW: Financing delivery, econ drug companies (takes away blockbuster drugs), reimbursement,
    d. IK: If we run large program, how much will data apply to minorities? How were genes selected?
        i. RW:
        ii. Rochelle: Process for nominating genes: broad community would be interest plus genes of personal interest, narrowed down, backward compatible with DMET and ADME platforms, would solve genotyping issues (HLA, CYP psuedogenes, CNV). Validate, and optimize prior to production.
        iii. AS: based on pharmacology and biology rather than genetics
        iv. DR: Every gene nominated by at least 2 separate groups with compelling reason to be on there.
9. Apply algorithms across eMERGE (plus Biobank Japan etc) to make large data sets, focus on implementation

vi. NHGRI – new plan (Green) addressing clinical med disease and healthcare. WG NHGRI staff, consult across NIH for implementation ready ideas. Lots of discovery projects. PGx was ready, resonated w/advisors other institutes. PGRN and NIGMS (Rochelle) CPIC project was exciting but wanted broader appeal. Take large scale seq platform, w/EMR, transport to other institutes. Will make high priority, but funding issues will play large role.

4. EMR Integration
    a. Erwin – intro EMR
    b. Justin – intro into EMR-genomic data
        i. EMR genomic data is large (may not be largest)
        ii. Raw data is not human interpretable
        iii. Collect more data than use

iv. Collecting data before significance is understood – what that data means is changing over time
v. Sites have different EMRs – need to work in multiple environments
vi. Group Health
    1. Epic
        a. Carbamazepine, abacavir test cases
vii. Mayo
    1. GE Cenricity
        a. Randomized clinical trials
        b. Statins (TPP or PPP sites)
viii. Marshfield
    1. Internal (CattailsMD)
        a. Re-design will incorporate genomic information – start w/cataract
ix. Northwestern
    1. Epic, Cerner, eClinicalWorks
        a. Use cases not defined – waiting for AV, examine all pieces of clinical processes affected by integrating genomic info
x. Vanderbilt
    1. Raw results stored in intermediate database, then when ready moved into EMR
    2. Developing prospective models (TPP site) – warfarin, simvastatin, tamoxifen
xi. Geisinger
    1. Multiallelic risk models
    2. Similar to NW (outside Epic, but seamlessly integrated)
xii. Mt. Sinai
    1. Poly genetic (CAD)
    2. Integrate w/in Epic or outside like NW & Geisinger
xiii. Going from single value lab test, genetic panels, multi-genic
xiv. Raw data into data storage bad idea
    1. Use Radiograph info model – store raw data outside EDW and push into EMR when ready
    2. Filter by call rate etc, then filter by actionable variant, then add to EMR
xv. Questions for vendors:
    1. What data goes into EMR, what data is stored in ancillary systems?
    2. What CDSS is internal vs external to EMR?
    3. What should we focus on instead of re-inventing the wheel

c. Jessica Bartell (MD, MS, CPE) Clinical Informatics @ EPIC
i. Background in building things into EMR
ii. Integrated patient-centric EMR
iii. Mid-size to large medical groups, hospitals integrated health care organizations
iv. Interest and activity to integrate data into EMR for research
v. Focus: Clinical indicators (drug, disease related) – how to get into EMR and clinical care once defined
vi. Sources of data: genebank databases, EMR
vii. "Learning Health Care System" – coined by 2007 Lynn Ethridge
    1. Incorporating evidence based medicine into clinical care and back
    2. Patient care to research:
        a. Getting good info at point of care
        b. Optimize data collection from EMR for genomics studies (family history, linking family info)
        c. Help identify subsets of patients for research enrollment/analysis
        d. Linking with other datasets
    3. Research to patient care:

a. Workflow integration is key piece of making this work (nothing worse than bad workflow for patients/physicians) – need to integrate patient data at point of care
    i. Next gen patient centered care
    ii. Information to right person at right time
    iii. Translation of complex non-intuitive info *physicians need simple information at point of care to be useful
    iv. Competing priorities (time, chronic illness, social issues, information from internet wanting to discuss about illness)
    v. Taking sociology into account (environmental exposure)
b. Versioning based on evolving evidence – put together why decisions were made
c. Population management

4. Challenges
    a. Privacy and consent – largest issues we face, social/political issues, collection/use of data, disclosure of personal genetic information, federal/state law, patient preferences (even w/in families)
    b. Standardization
        i. Terminology for genetic indicators (chip, SNP, in/del)
        ii. Terminology for test results, annotations, interpretations (more established – easier for CDS, easier for point of care use)
        iii. Standards for genomic data interfaces
    c. Translation for patient care
        i. Education (physician, patient – risk education)
        ii. Tools (pictures to describe patient risk)
        iii. Priorities (truly informed consent, too much information about not verified data not good, need to use data with valid results)
    d. Opportunities
        i. Accelerate research & use of genetic information
        ii. Promise personalized med
            1. Screening, tailoring therapies, informing and empowering patients
        iii. This is critical piece of patient centered personalized medicine in use

viii. Mark Dente, MD – GE Cerner
1. Molecular medicine – intersection of 3 domains
    a. Medicine, genomics, information technology
    b. South Korea is interested in investing in
    c. GE interested in companion diagnostics
        i. Love concept of external clinical decision support (Arc)
        ii. CDC collab – external rules to drive knowledge management around food borne illness (Alliance Health Services (Chicago) – leverage external knowledge) – how to deal with short term alert, w/out alert fatigue
    d. Opportunities
        i. Contraindication alerts based on genomics, optimal dosing, alerts w/new variant
        ii. Privacy issues, interoperability, standards for information uploads
        iii. Patient engagement (security, privacy), patients bring in information from internet
    e. Challenges
        i. Data files
            1. Huge amount of data
            2. Invested heavily in developing (Mayo, Intermountain helping develop)
            3. Decision support – look at data more visually

4. External decision support take out of the EMR
5. Algorithms, predictive modeling to deal with large data sets

f. MQIC Membership: 22 million (HIPPA compliant)
   i. Can re-identify to get them in to clincial trial
   ii. Smoking history categorized in MANY different ways (terminology)
   iii. eMERGE can help industry be working on terminology – drive forward standards

g. Framework – Analytics platform
   i. Get data, create insight, visualize data, primary/secondary user of data, patient privacy, make valuable
   ii. Cycle time in development is long
      1. Prioritize what is wanted* (family history etc) guidance for vendors is wanted/necessary
      2. Security/Privacy is important
      3. External genomics component
      4. Knowledge bases
      5. Genomic analysis engine
      6. Integrate w/GE centricity

d. Mark Hoffman, PhD – VP Research Soln @ CERNER
   i. Work has gone info genetic information that will inform genomic information
   ii. Discreet storage of genetic information needed (systems in lab can support)
   iii. Pathology workflow not identical for genetics/genomics
   iv. Demand for cyto(cyber)genetics – karyotyping information
   v. High density information (array/sequencing) creates challenges
   vi. Lab is tasked with generating report
   vii. Can EMR data be updated to account for new sci knowledge
   viii. Based on CAP/CLIA certification (what is clinically legally valid result) – genomics may change that
   ix. Clinical Genetics workflow – leans on family history, CG patient encounter is longer than typical physician visit
   x. Meaningful use is critical – supporting things through meaningful use pipeline is best way to motivate EMR vendors
   xi. CDS support - Targeted toward non-geneticists
   xii. Engage EMR vendors can help extracting data from clinical system.
   xiii. Began working in clinical genomics in 2000
      1. Began w/HIV prescribing decisions – earliest that mol gen informed prescribing
      2. Manage two studies for CDC
      3. Prescribing decisions based on genetic information
      4. How do you express genetic findings? Individual SNPs vs allelic data?
      5. Support International Serious Adverse Event Consortium - data entry information
      6. Working with many diagnostics systems to integrate
   xiv. Clinical Bioinformatics Ontology (CBO)
      1. Everyone can download and use, curated, semantically integrated, enable acceptable use of mol genetic diagnostic information
   xv. EMR goald:
      1. Accelerate all aspects of workflow
         a. Laboratory
         b. Family history – get before patient gets into doc
         c. Clinician
         d. Administrative
      2. Decision support for non-experts
         a. Alert fatigue – monitor response to rules to figure out what will make physicians pay attention

3. Enhance research to reduce uncertainty
    a. eMERGE should focus on clinical outcomes improvement rather than ID new SNPs
4. Raw genomic info can be put into EMR, but interpretaive infor is important
5. CDS sits in/outside – cloud computing – having rules stored outside EMR is going to be more prevalent
6. Seeking ways for EMR vendors to follow common pathways is good for all
7. Creating demand for vendors to change EMR through changing clinical care/treatment

e. Discussion:
    i. External knowledge management – expert domains
    ii. Want guidance where to prioritize development (family history, genetic)
    iii. EL: Can't just graft this onto the way medicine is done today. Can't do primary care in 15 minute visit. Secure portals! Can't think of as just a ways to put information into system, need to think about new ways to change the way medicine is done is important
        1. J: patient centered medical home, bring right info to patient/physician, set new framework for healthcare to support incorporation of genomics, meaningful use is pushing healthcare in the way of new practice
        2. MD: Bundle payment (why did captiation not work, b/c based on billing data not descriptive enough) – fundamental change in the way that care is being validated. Patient as consumer (high deductible plans) – how patients will interact, though portals? How to track chronic patients remotely?
        3. MH: Concept of medical home is important – want children to benefit from genetic testing – seek widest benefits from genomic testing. Meaningful use setsscene for everything, documentation of individual lab results
        4. MD: If patient wants to share genetic data broadly w/family, does 'uncle jim need to be consented because he can be identified? We need to address upfront rather than by regulation
    iv. Sanjay Udoshi (Geisinger): How can we build common ground through different EMR systems?
        1. MD: Engage ONC to come up with stage 2/3 genomic criteria data, codify family history, smoking history, <u>harmonization of data standards.</u>
        2. J: eMERGE tells vendors what is needed will help to get standardized response (terminology). Pushing policy makers, currently responding to legislation
        3. MH: utilizing standards (continuity of care document) – focus on what can be in CCD and will help standardization. Understanding scope someithinglike CCD format will help interoperability
        4. MD: will help point out voids in CCD document- framework
    v. Chris Chute: Workflow – EMR decision support is fragmented esp in PGx usecases (pharmacy committees, dedicated databases, DDI, separate from EMR). How do you see integration of synergistic systems to work with EMR
        1. J: Understanding how genomic and clinical data work together.
        2. MD: Content development and expression of content. Have roadmaps to consume external content. External rules engine that expresses content (model). Content, content maintenance, write once publish many. Using CCD level document (not granular). Need domain expertise to develop content.
        3. MH: Setting goals to achieve (interoperability, CDS) is the most likely path to successfully interoperability. Standards how express data is important.
    vi. Joseph Cannery: Meaningful use is creating contradictory forces – how will it be worked out in genomics. Guarantee privacy, HIPPA, but share more and more information. Make privacy issues in genomics hotter.
        1. MD: What do we need to do to ensure that patient gets what they need to manage disease in medical home. Need ppl at NIH, ONC to say meaningful use requires data sharing protection. Genetic anit-discrimination law gave a lot of cover to do what needs to be done. Data Privacy is important.

2. J: Balance between good sharing and good privacy is delicate.
3. MH: Info sharing – public health surveillance

vii. Rex: Comment on where EMR vendors are in terms of implementing genomic info in EMR to use for clinical care? How would you advise eMERGE to proceed? (Precompetitive space – where all implement stuff that will be widely used) Should we build prototypes? Let EMR vendors go first?
1. MD: Also look at as precompetitive space. Not concerned because all have ways to differentiate themselves. Rising tide raises all ships. Ad hoc today. EDW can accept genomic warehouse, or data warehouse specifically for genomics? Strong prototypes would be great. join clinical decision support consortium – may join, next funding cycle soon.
2. J: Something that needs to be shaped by many organizations, need to cooperate with all vendors, need as much consensus as possible, use cases, robust prototypes. Specific as possible about what is needed during development and project to where want to be.
3. MH: Standards are the best place for collaborations. Optional standards used variably, but required standards and funded standards are interesting.

viii. DR: Notion that eMERGE is implementation is not quite true… we are more discovery. Discovery should remain front and center in the way the system is designed.

ix. BK: Comparative effectiveness research. Clinical trials are gold standard, can we think about different secondary use of EMR to be gold standard or compare to gold standard? What do we accept as nature of evidence and how EMR gets set up in terms of how get set up for genetic databases.
1. J: Comparative effectiveness is part of HIT policy. Would like to discuss about how related to genetic research, not largely discussed in most forums. Mostly discussed for traditional medicine. Uncharted territory.
2. MH: Informatics experiments can be performed with rules. Popup alerts, alert fatigue, passively embed information (not used vs not alert fatigue).
3. MD: Secondary use of EMR data is spot on. Whole division that does research about this. Prospective/retrospective research, pharmacovigilance research. Go to FDA jointly to use EMR to provide safety monitoring. Provide real time nightly update of early phase II drug trial design.

f. EB: No one is prepared to go it alone, want direction, standards, prototypes

5. Clinical Integration
a. DR: Dan Masys tasked fall 2009 get program together in 1 year for genomic-drug prescribing. Lesson 1: top down doesn't always work, but this was an absolute requirement b/c need institutional leadership buy in, hire faculty, admin/analyst support get attention to get done. Implementation plan – engage 6-7 communities, ethics, patient attitudes, pharmacy, genomics, practitioner, patient community. Focus on clopidogrel/CYP2C19 as first step. Engage intervential cardiologists. Clinician champion (senior members who was very interested in getting it done). FDA label, genotyping platform engage clinical pathologists (Illumina ADME) ensure that QC for specific SNPs were called appropriately, institutional approval. Have entire set of clopidogrel data reviewed by Pharmacy & Therapuetics committee. Has big say in how drugs used in institution. Genomics, assay validation, informatics (Large part) – how does system respond to electronic prescription – have it look at genomics – (started w/ *2*2 homoz) – give advice to physicians to prescribed prasugrel. Evidence got better for *1/*2 variants – had to circle back change CDS. Think about next gene-drug pair: simvastatin SLCO1B1 variants – FDA eliminate high dose use in all patients, now we will engage at lower. Warfarin – deliver proper dose with the first dose. CYP2D6 Tamox or atamoxitine. How often do physicians pay attention and follow advice. Initial project based on FDA label change. IRB said this is standard of care, don't need consent. Line for genetic information being used to treat in Consent to Treat form. Metric – when faced with a patient who is available for PREDICT. 2 out of 3 cardiologists offered opportunity to test patients genetics. Ongoing looks at evidence. Requirement to put genotyping into CLIA environment (deliver reliable results). Better get genetic variant data right the first time. How to go from research to Quality Improvement: FDA black box warning was impetus.
b. JD: Went though many iterations to get cardiologist buy in. Went from 30% to about 90% now.

c. DR: At beginning thought it was too complicated, but now view as big experiment and not. Deliver results 3 days after test, may be too long for some drugs. Clopidogrel was a good one to start with. Look at outcomes in detail, supervised IRB activity. Use GT platforms, how data goes back into EMR. 1 instance *2 appears in the patients record. 1st page is drug allergies etc, very limited, later will be difficult. Patient portal (MHAV) 140,000 registered users, most contact is b/c Rx is out. Genotype and regular data is displayed.
d. RW: Lessons go beyond clopidogrel. Trait highly heritable, tight therapeutic index, clinically severe ADE, clinically severe results of failure.
e. DR: 3,500 patients in so far + data.
f. CMcCarty: physician ed other than alerts?
    i. DR: 4 face to face sessions w/interventional cardiologists. Many other grand rounds, departmental meetings. Don't have online tool for them to go to. Talk about it frequently. Medcial grand rounds timed just before rolled out new one across med center.
g. EB: High profile pubs coming out that challenges this approach. Have you been challenged based on high profile papers challenging validity of CYP2C19?
    i. DR: Big debate in CV community. Do you belive that you should GT all patients before all clopidogrel Rx? But you look at biology, meta-analyses… there is an effect. Would you use info available if it was there? (softer data) Patients would like it ifyou belive data. Yes, have been challenged. Anti-platelet therapy (ticagalor). Interventioinalists, use ticagalor in hospital, then they can take cheap drug clopidogrel at home (by then GT will be available). Devil is in the details even for 1 drug. What is the dose, alternate Tx strategy, etc.
h. RW: Mayo is currently genotyping in mood disorder psychiatry clinics. Echoed Dan's comments about engaging multiple stakeholders, local culture will be different. Having a champion is important. Beginning is important b/c that alters culture. Reveals idiosyncratic issues for each site, for what barriers are. Had PT that could be measured with outcomes. Psych just started doing it, fewer SE, higher compliance. Cardiologists require RCT, before starting.
i. RG:
    i. What to integrate:
        1. Mendelian diseases: HFE – still controversial, some recessive traits (actionability may be low) undiagnosed. 14/3500 at Mayo have variant but only 5 had diagnosis.
            a. BM: over 100 ICD9 codes that correspond to mendelian diseases – don't want to make into genetic exceptionalism.
            b. EB: PGx was ready for primetime.
            c. TM: Common Disease Variants – Not enough common disease variants to do something with now, need more research.
            d. EB: Large percent of patients who could be reclassified and treated differently
        2. PGx,
        3. patterns of variant based risk scores (moves beyond disease risk variant to reach stat sig)
        4. Ancillary project – annotating variants will be helpful may be more meaningful
    ii. When to integrate:
        1. Sites that have made it happen, need to dive in before 100% certainty
        2. As needed vs proactively? Instantaneous data vs delayed data?
    iii. Versioning data
        1. Data will change over time – need to update CDS
    iv. How to integrate:
        1. External data sources linking in (popular with Vendors)
        2. What does Decision Support look like? 1 is easy, more is complicated, pattern of variants vs 1 allele?
            a. RW: stoplight colors with each antipsychotic
        3. Policy/Legal issues
    v. Transition from research to clinical care – what does it look like? (We just went ahead and did it) – debate about if this is the right answer – get past jumping in, balance that w/risk

vi. Role for “traditional” quality improvement process. VU – this is standard of care improvement. Other institutions may not see it that way. Mayo – room to improve existing best practices. QI should pick up errors.
vii. How to measure success?
    1. VU – evidence for improving care
    2. Mayo – decreased hospitalization, increased compliance
viii. How does consent need to change? Is it covered under current consent to treat form?
    1. Reword as: What constitutes a need for consent to treat forms to change?
    2. JS: Pure treatment side, feedback loop from care to research. Consent from
    3. John (cinci) – GT becomes more and more sophisticated, clin lab provides more detailed return of results, extension of genetic tests. Demonstration of utility – try to return results as part of ‘beneficience’.
ix. What do we do to achieve physician acceptance?
x. What do patients want?
xi. Patient education materials
    1. Mayo patient education – sophisticated brochure at time to tx, prior to electronic alert, was done of clinical interaction. Document went to individual.
    2. Dave Merazik runs 5 day course to educate physicians
xii. How do we measure efficacy?
xiii. How to transfer genetic information if patients move around?
xiv. Consider economics.
    1. DR: Balser wants this data to go to payers to convince them to pay for it (10,000 patients will be needed to convince).
    2. JD: Set up a system, provider referral where they can get electronic/paper letters refer back to the physician.
xv. Who owns information?
    1. Payer (someone who will make personal $$$ gain)
    2. Strong support for data sharing if will go for better good.

6. Intro of ESP
7. eMERGE II Goals
    a. Phenotyping
    b. Genomics Genotype-Phenotype
        i. ~50K genotype records
    c. Clinical
        i. Defining actionability/clinical utility/validity
        ii. Integration into EMR/Visulaization/ Clinical Decision Support
            1. Strong openness to continue dialog between Vendors & eMERGE
    d. Physician & Patient Attitudes/Education
        i. What do patients andphysicians need to understand to use genomic data appropriately?
    e. Consent/Regulatory
        i. Interface between research and clinical use
        ii. In uncharted territory
    f. Privacy/Security/CLIA/CAP
        i. Some have completed eMERGE I in CLIA/CAP environment
        ii. Now need to re-complete in CLIA/CAP
    g. Workgroups
        i. 2 hrs face to face time, 1-2 phone calls, charter (not legal document, set of goals to focus attention on what they want to accomplish – work plan, milestones, deliverables)
            1. Phenotyping (discuss next 26 phenotypes)
            2. Genomics (imputation – multiple platforms, QC, when to freeze eMERGE II data)
            3. EMR integration (how to put data into med records)
            4. CERC (multiple subgroups)
            5. Actionable Variants (which genetic variants will be used, what are criteria)
    h. ESP Recommendations
        i. Collaborations to use phenotype algorithms in generalizable way – priority for phase 2, EMR workgroup will be responsible for this (?) – guidelines for algorithms posted on website
        ii. C&CC – July data sharing conference – large group of policymakers & external members, working on white paper, invited CAB members from each site, helped network understand their role in network.
        iii. Cross network manuscripts – 16 network manuscripts currently in development, Hypothyroidism paper just published (great example of cross network activities), in discussion about sequence data
        iv. ESLI findings to inform institutional NIH and other policies, dbGAP deposition – C&CC hosted data sharing conference, office of civil rites, ANPRM rep, discussion. Brad Malin continues work on privacy in eMERGE II to inform policy, leading network effort related to risks of data sharing
        v. Develop transportable phenotypes – publich phenotyping libratory on the website, new eMERGE II members have used algorithms
        vi. External groups that want ot use eMERGE resources – UK biobank will be invited to future meeting
        vii. Informatics collaborate w/SHARP – Mayo leads SHARP and considerable overlap between SHARP & Mayo
        viii. Improve visibility w/in greater sci community – trying to get in front of audiences, Howard brought up positive view of Josh Denny's presentation at conferencelast week
        ix. Re-identifyability – Brad Malin
        x. Informatics cooperate implementing algorithms across network – eMERGE II primary site algorithm development, secondary site will validate, rest of sites implement
        xi. Feedback to EMR community – yesterday EMR vendors discussed, three vendors appreciate being able to sit down in 'safe' environ to discuss
        xii. Smoking, EtOH – dbGAP, published numberous about meaningful use and smoking

xiii. Algorithm development PPV – available, Josh PheWAS from VU
xiv. Validate phenotype algorithms across network – phase II bring in additional ethnic diversity
xv. Sequence data – C&CC prioritized completing ongoing projects, sharing sequence data, pharmacogenomics sequencing exploring how to get data into system
    1. Questions:
        a. HML: EMR session, please mention specifics of collaboration. Appreciate network taking recommendations to hear

8. Mt. Sinai - EB
    a. Large Academic med center serving upper Manhattan communities - > 1000 inpatient beds, large outpatient ~7000 visits/year. Top 20 NIH funding.
        i. Central Harlem – AA
        ii. East Harlem – Hispanic, AA
        iii. Upper East Side – Caucasian
    b. Health disparities in diverse upper manhattan communities, lifestyle management
        i. CH – obesity, no exercize
        ii. EH – obese, HBP, no exercize
        iii. UES
        iv. NYC
    c. IPM – focus for genomic efforts w/in community
        i. Core efforts EMR linkable repository of DNA, plasma and genomic data
        ii. Consented, permits recontact, reconsent and sharing data
        iii. ~ 19K patients (Sept 2007) consented
        iv. Research: metabolic, CV, renal disease T2D, CAD, CKD, Neuropsych, liver disorder, community & provider education
        v. ~600 donors/month (40% Hispanic, 30% AA, 30% Caucasian)
        vi. MSDW – enterprisewide resource for clinical information (Steve Ellis, Kash Patel, key architects)
        vii. EPIC (outpatient, inpatient, ED) data uploaded to Data Warehouse
    d. Biobank needs to be populated with as much genomic data as possible
        i. ~3K genotyping data (Cardiac-Renal PT)
        ii. Targeted validation (SNPS) ~8000
        iii. PGx SNPs – clopidogrel, warfarin, statin, metformin response
        iv. Early 2012 – CLIA environment data
        v. Exome variants
    e. Integration w/EMR – MtSinai Epic team, IPM team – approach of genomic information with EPIC
        i. External genomic data being pushed to EPIC, live 2nd quarter 2012
    f. SA
    g. PT Group
        i. Subcontract w/Columbia DBMI
        ii. Mt Sinai IMP
        iii. Phenotypes
            1. CKD in HTN, diabetes
        iv. Cross-population validation of potentially actionable variants, clinically valid SNPS for polygenic scores
            1. CKD, T2D
                a. Verified specific SNPs for specific pops, develop polygenic risk scores
        v. Investigators – genetic epidemiology analysis
        vi. ENGAGE – education
        vii. Implementation –
            1. D3 risk alleles, predictive modeling
        viii. Questions
            1. Geraldo: Is ENGAGE run from the site?
                a. Clinicians, genetic counselors, drawing on faculty from institution, funded from institute

b. HML: How is enrollment?
    i. Actively recruited, recruiters posted across campus, face to face consultation
    ii. Single standard consent
c. HML: How many people asked?
    i. Participation rate is 85-90%

9. Marshfield – Murray Brilliant
    a. Population cohort 20K, 40% of available population in Marshfield and surrounding communities
    b. >90% Caucasian - 1870-1890 large immigration – ancestry German (Catholics/Lutherans)
    c. Data going back ~ 30 yrs electronic format, virtually all med care by M, inpatient, outpatient & meds
    d. ESAB – ELSI board
    e. SA: ophthalmic, 5K/20k genotyped, 24 total exome seq, 1 total genome seq, 175 in pipeline for whole exome seq
    f. Community advisory group, Nov 10 advisory board meeting – sharing genetic data, ROR, focus groups w/physicians
        i. Consented for not sharing results, will be reconsented to return results
    g. Scientific milestones
        i. Developed algorithms for ophthalmic
        ii. Community engagement – 3-4 newsletters/year to keep them up to date w/progress w/samples
        iii. Plan to improve EMR for ophthal conditions (also derm)
            1. Like to draw, not amenable for extraction
            2. Working w/ophthal to design graphical user interface to capture critical data (relevant for research and clinical use)
    h. Methodology – pop
        i. Marshfield employees engaged
    i. Control: digital ink over tech,
        i. Survey: prefer radio buttons, handwriting recognition, slider bars, drop down menus, number lines
            1. How long take to fill out forms, prefer?
            2. Conclusions, continue to use ink over forms, drop down forms for data, get diabetic status in problem list, further development interface & implementation on track to be included with EMR updates
                a. Questions:
                b. LP: 5 clinicians in this phase, refusals in participation?
                    i. Pre-selected b/c they were asked to evaluate, haven't encountered pushback. Easier to work w/small dept of ophthal (buy in from chair). Doing this will help with their being able to eval. See as win-win.
                c. EB: Will need to go retrospective to caputure old data?
                    i. Developed electronic algorithms, manually review old forms
                d. HML: Big effort, what are plans to take across institutions?
                    i. Share experience w/development of these forms to caputure data
                    ii. CMC: Going back to review EMR PPV, INstitutinal develop EMR
                e. HML: Great time to engage groups across institution, ophthal may be easy to integrate compared to others.

10. Mayo – Iftikhar Kullo
    a. PPL
    b. Aims
        i. Translational genomics, new PTs, genetic risk scores (polygenetic) CAD and develop tools to convey risk, integrate into EMR (AV+ risk scores), CDS and links to knowledge repository, ELSI: RCT eval comprehension & response to genetic info
    c. Cohort: 3500 to 7K GWAS
        i. PAD cases, controls; ResHTN, VTE cases & controls, pancreatic cancer controls (660W, 510/650)
    d. Phase 2

i. EMR phenotypes (CR, HF, VTE, ADE)
    1. Cardiorespiratory fitness
        a. Algorithm developed 3120
    2. VTE – major issue, SCD b/c of PE
        a. Algorithm complete ~1400 cases
    3. HF
        a. Development (sue belinski)
    4. PGx – ADE & Drug Response
        a. LDL statins – 1023
        b. Statin myopathy –
        c. PAD – 335 new
        d. RBC indicies 3356 new
ii. Merge & QC genotypes
iii. Clinically AV & genetic risk score
iv. RCT

e. Gentic Risk
    i. Modify framinngham risk score
    ii. Quantify gentic risk score
    iii. Develop genetic pictograms to show genetic risk and framingham risk
f. Integrating genomics into EMR
    i. Started working on, informatics
    ii. Link "Ask Mayo expert" into MER
    iii. CDS –
g. RoR
    i. Communicate genomic risk – how effective
    ii. Ongoing work with CAB
h. RCT
    i. ID 150 patients in eMERGE I cohort at risk for CHD
    ii. Consent, draw blood in CLIA environ, 25 SNPs, randomize to genomic vs non genomic information, meet w/genetic counselor, assess comphrehension after meeting and at later dates
i. Working w/ Centern for individualized med at Mayo
    i. 5 translational programs, infrastructural programs leveraged to accomplish efforts
    ii. Biobank – 22K participants, 57% women, 43% Olmsted country (lots of data)
        1. Consent –main biobank
        2. Multiple outlying disease specific banks (Vascular diseases repository 3K)
j. Collab
    i. eMERGE, PGRN, SHARPn (Chris has ties to this), GE
k. Questions:
    i. LP: RCT patient response in year 3-4. Biomed ethics – primary person not on site
        1. Hoping to start in yr 2. Plan to recruit 2 additional staff in this area.
    ii. EB: 6K in eMERGE study – those have full genome, 22K have samples
    iii. Geraldo: ADE, CHD risk. Complex trait, how much variance do SNPs account for? Contrast this w/easly ID risk factors (Framingham). Is this conceptually sound paradigm? Is this mostly about awareness that genetic risk can account for 3% risk?
        1. Markers may reclassify individuals at intermediate risk
    iv. HML: Engage collab for future meeting

11. Geisinger – David Carey (not ledbetter)
    a. NE Penn – Geisinger Clinic 1/3 primary care, 2/3 specialists, own operate inpatient/outpatient, Geisinger Health Plan. Cover 1/3 Penn.
    b. Demog: older, poorer, sicker. BMI adult male outp 30, female 32, 11% over 40BMI, smoking higher than nat ave. rural. Stable demog, multi-generational families 96% white, 2% hispanic, 2% AA.
    c. EPIC EMR 1995
    d. 2006 MyCode (biobank) 1996: 36K patients consented

i. Research assistants in primary care clinics – inclusion adult, outpatient and understand consent form. As close to population samples as possible. Enroll through obesity, vasc surg, womens cliic
ii. Broad consent, put in EMR, then blood draw taken for research at next blood draw, tubes in CLIA, then banked
iii. Data taken in process of clin care. Can do most data in de-identified manner. CDIS is replica of EPIC data, but easier to explore.
iv. SA: discovery, implementation, socio-cultural issues
v. PT:
    1. Primary phenotypes
    2. Genotype data on OMNI Express. Data deposited in dbGaP. Talking w/Ifthikhar about PAD data sharing.
vi. Discovery to Clinical Care
    1. Clinical Implementation – ID patients, best practice alert, order genomic test, genomic test (yellow w/in epic, blue outside of epic)
vii. Question:
    1. LP: Ethics has unique,dramatic ethics policy issue. ID genetic info about not doing well w/bariatric surgery (last chance). Opportunity to discuss, if they want to go forward with intervention but genetics don't show it will be beneficial. Policy question, will you not let them have surgery?
        a. Docs interested in this. 30% patients 2 yrs later have re-gained weight. Being counceled for other therapy, or extra intensive counseling
    2. HML: What are opportunities to share across network
        a. Collab w/mayo around vascular disease. Primary response to bariatiric surgery as phenotype.
    3. Geraldo: PGx
        a. PAPI2 trial site. Use some of approaches developed at VU to do preemptively. Warfarin or Plavix. Pushback from cardiologists who don't support using this in clinical care. Find champion and begin.

12. VU – DR
    a. Implemented children ~ 1 yr ago, 11% AA, Unknown (admin issue) most Cauc, some AA same distribution as known
    b. eMERGE I:
        i. 3572 EA, 2421 AA
        ii. VESPA: 4304 samples
        iii. Total anticipated end 2011: 15,593
        iv. High density chips: metabochip, immunochip, maybe exonchip
    c. BioVU validation, PheWAS description, stat methods to compare across populations (J. Schildcrout)
    d. VGER: ECG, PR, clopidogrel
    e. In prep: PheWAS, fine mapping AA, QRS, hypothyroidism and TSH, ResHTN
    f. VESPA – GO grant
        i. Do known PGx signals replicate? YES
            1. Clopidogrel after coronary stent – CYP2C9*2 & ABCB1, don't find PAR1 signal.
            2. Steady state warfarin dose – CYP2C9/VKORC1
        ii. ID records w/variable drug response
        iii. N=9600 samples w/institute support
        iv. PTs: heart & kidney, vanco (150 peds), warfarin bleeding, amiodarone tox, metformin, ACEi cough, cox2 inhib & MI, early repol
    g. PREDICT –
        i. Select pts who are at risk for receiving a drug w/PG actionability
            1. GT for many PGx variants – ready for many other drugs
            2. Review by Pharmacy & Therapeutics committee – buy in is important!
        ii. J. Schildcrout – how many ppl in medical home of VU might be exposed to drugs with PGx
            1. 65% exposed to at least 1 drugs

2. 1 patients was exposed to 18/58 drugs
3. Estimated number of adverse events mitigated 348

iii. Clopidogrel – 3,257 (Sept 15, 2010 started)
1. 85 *2/*2
2. 620 hets *1/*2

iv. Next 6 weeks – warfarin w/hip/knee replacement
v. Statin high dose
vi. Aziothioprine/TPMT
vii. Point of care decision support – advice not directed command, input from cardiologists, pharamcists etc
viii. Deliver info to providers (EMR) and patients (portal)

h. PT: Disease – complication or disease-drug-outcome
i. GT-PT- refinement –
j. PREDICT – what info do patients want to see
k. Privacy – what happens when add patient projector (Phase I – how much info can you allow investigators see w/out re-ID?) Phase 2 : disease – drug – time how much re-ID potential
l. PT – manual review until PPV is > 95%, find in BioVU, deploy across other sites
i. Primary: Upper/lower GI
ii. Primary: Statins
iii. Secondary: ACEi cough, zoster
iv. VESPA related (PGx)

13. GH/UW – Eric Larson (GH) & Gail Jarvik (UW)
a. EL: Public interest research group
b. EMR lab 1988, pharmacy 1977, EpicCare 2003
c. Unique MyGroupHealth and ___
d. ADPR/ACT: One of largest brain autopsy samples (lots ofcontrols) >65
e. NWGIM: prospective biorepository 50-65 yr old, reflective of Seattle populations
f. GJ: older age + drug records, give a lot of info about medications (PGx)
g. Aims: Discovery, Implementation, Collab
i. Discovery: ~ 3500 GT subjects
1. PTs: BuGWAS – susceptibility to infections – extrapolate to learning about immune system
a. Zoster
b. C. diff – PPI use seems to increase suscept on top of genetic
c. Onychomycosis
2. DruGWAS – statin, antihypertensive, response to SSRI
3. LonGWAS – hematocrit and glycemia change over time
4. ChroWAS – relationship karyotypic abnormalities and bone marrow disorders, OR=4 for bone marrow txplant

ii. Implementation in EMR - EL
1. HLA genotyping for Allopurinol, abacavir, carbamazepine
2. Qualitative needs assessment – knowledge attitudes beliefs
3. Test functional prototypes – focus on HLA ADRs
4. Design & test decision care support – prescribing meds
a. Timeline, on target for getting started
5. Pubs: ELSI (Privacy, ROR, __), ALZ disease consortium

iii. Integration into care
1. Questions:
a. EB: Say more about clinical decision support. What is sample size? How many have relavent genetic data known?
i. EL: Sample size not known. SS in grant is based on # prescribed drug. Test ppl in CLIA lab for drug suscepti GTs, feed back to Rxer.
b. Geraldo: What drives choices of longitudinal PTs?

i. GJ: Wanted labs routinuely measured in healthy patients.

c. Would carry over to networks?
   i. GJ: Yes, WBC was found very frequently over time
d. JM: GWAS on outcomes C. Diff. Complicated PT for behave outcomes? Do you work w/specific people on those? Drug response? How do you determine ADE to SSRI? Based on clinician definition or metrics?
   i. GJ – Paul Crane is lead. How long are people maintained on drugs or switched as indicator of success/failure
   ii. EL – Greg Simon and others have used this type of response to improve compliance in depression care.
e. HML: Work with other HMOs around the country? Different from other systems?
   i. EL: Large bariatric surgery cohort in network, could collab w/Geisinger. What we've learned in eMERGE can be spread.
f. HML: HMO application network, get traction if HMOs like Geisinger, Essentia, Marshfield, GroupHealth continue to do this.
   i. EL: planning on collaborating w/them.

14. Northwestern – Maureen Smith
    a. NUgene – fully consented, gathered from internal med clinics, 90% agree to be recontacted for further research
    b. GWAS – 4951, data in dbGaP
       i. 1932 in eMERGE 1
    c. Aims:
       i. PT algorithms
          1. Led by Jeff hayes
          2. Expand PT library sharing and expansion (Abel Kho)
          3. Lower GI
             a. Diverticulosis
             b. Nonsyndromic polyps
          4. ADE
             a. Nephropathy
             b. ACEi cough (consulted w/VU)
       ii. Integrate into EMR
          1. Test clinical utility and personal value
          2. Combined physician and patient advisory boad to oversee
          3. Re-consent for re-genotyping – working w/CAB to revise consent form, IRB (CLIA, reconsent, genotype driven reconsent)
       iii. Proposed by Jonathan Berg – binning clinical variants (not fully penetrant)
          1. Examine how physicans and patients view this information.
          2. Focus on patient & physician outcome
          3. Physician education – to return results
             a. Genetic counselor will consent
             b. Primary physician will return results
          4. Pre-Post assessment w/patients
       iv. Integrate into EMR
          1. Implement external workflows
          2. Complete:
             a. Review framework of GIMQIC for decision support (internal med committee around decision support) – first time to use genetics
             b. Developed interface from external CDSS to Epic workflow
       v. Evaluate Key Translational Elements
          1. Regulatory, EMR decision support, Educate Physicians (work w/in system they have used) Underway – assessment of physician genetic knowledge

2. Ed patients through MyChart, physicians print out info for patient
3. Dissemination of lessons learned and best practices

vi. Questions:

1. Gerlado: Sequence of aims – timeline. Aim 4 are well on way, do happen simultaneously?
    a. All ongoing, EMR will take longer, advisory groups and consultation w/physicians. By end of year will consent patients and begin return results.
2. Is this in sequence w/rest of network?
    a. Seems to be similar to rest of network.
    b. PT is in parallel processing across network. Rate limiting: consent, EMR. External systems will integrate w/internal.

15. HML: Stength of sites is network. Each site looks great, but strength of site is collaboration of network.
16. PT Workgroup - JD
    a. Charter
        i. Already shared algorithms w/PGRN
        ii. Promote eMERGE to PRGN, SHARP, Beacon
    b. Network activities
        1. eleMAP – map variables to standar vocab, creat data dictionary to select appropriate (similar to amazon shopping cart), deposit dbGaP
        2. Hypothyroidism – reuse gentic data w/EMR – promote network activity, PheWAS, purpose driven OR = .74, PheWAS OR = .76
        3. PheWAS will be service to network and others
        4. PTs validated at 2 or more sites. PPV threshold – silver standard is good enough, don't need gold standard.
        5. Resistant HTN – Yellow what we though validation showed (some sites didn't have necessary data), compressed phenotype development in short time to meet genotype requirements. Need to have things like standards to represent PTs, how PTs implemented, develop computable forms that can be shared to elim errors.
        6. Hypothryoid 9 mo, ResHTN 6 mo to develop
        7. Best way was to share by flow charts Word docs – move towards best practices for sharing (KNIME, Drools)
        8. Privacy – model concerns, measure risks, mitigate risk w/out precluding research.
            a. BM current study - 1500 studies sharing info and risk look at projected changes for re-identifyabilty that have been proposed.
        9. Other goals: improved PT library, develop PheWAS to be service,
    c. eMERGE I phenotype prioritization
        i. 14 old phenotypes that may need to be implemented
        ii. Developing new PT, plus old PTs – some are mature, parts of large meta-analyses, some may be important co-variates for other studes
            1. High Priority:
                a. ResHTN – near sig GWAS – heiten value or look for replication sets
                b. PAD
                c. Diabetic Retinopathy
                d. T2D – important covariate
                e. Lipids – assist with current PTs
            2. Low Priority: rest
    d. eMERGE II phenotypes
        i. eMERGE1 – single site development then to network
        ii. eEMRGE2 – one site leads another co-develops, then deployed through network (secondary sites)
            1. Next couple months – circulate algorithms next 2 mo – knime and drools
            2. Integrate design of chart abstraction form
            3. Some sites attempt to do this through computable (knime & drools)

iii. Questions
1. Geraldo: What happens after these steps?
a. Creation and execution 2 mo. 1yr to 18 months to develop validate and execute across sites. Also trying to standardize, etc. Themes of work to make methods better and get PTs completed
2. MHL: How to help relationships with new centers?
a. Implementing old phenotypes difficult on new sites. Old sites work w/new sites to develop algorithm. Involved w/new sites before eMERGE 1 ended.

17. AV:
a. GWAS –
i. HapMap, high density SNP arrays
ii. Effect sizes were small, questions, what is clin actionability?
iii. Charge:
b. ACtionability
i. Validated tests (CLIA labs, valid assay) (IK)
ii. Significant alteration in hazard ration
iii. Would lead to changes in management, patient behavior, improve outcomes?
1. Surrogates
2. Long term
3. Magnitude of outcome change is relevant
iv. Chromosomal abnormalities, CNV, SNPs
v. Mendelian disesases (carrier states?) – not usually on chips (GJ)
1. Males w/HFE – carrier status
2. Carrier – prenatal planning
a. Not of immediate interest to AV group
vi. Complex disease (CHD, Macular Degen, AD, Breast and colon cancer) (IK)
1. Factor V Leiden (eMERGE 1 – not on 660)
2. Prothrombin gene (on 660)
3. ApoE (not captured)
4. Apo L (kidney disease AA) – protect from sleeping sickness
5. HLA association (potentially protect from infections)
a. Common variants w/modenst effects
i. Most!
ii. CHD, T2D, etc
b. Polygenic risk score
i. Ding et al in review
ii. Sig number reclassified – either higher or lower
1. Cross sectional analysis, not prospective
vii. PGx (GJ)
1. PD and PK
2. Build on work of PGRN
3. Handed an array design for sequencing, will examine what is actionable from that
4. Priorities
a. PGx
b. Genetic risk score: CV and renal risk
c. Collab w/other groups
c. eMERGE I
i. Sex chromosomal abnormalities
1. Klienfelter, Turner (some known, some unknown) – ID as potentially returnable results
a. Turner – loss of X chromosome may be acquired with age (more complicated than Klienfleter (germline only))
ii. Autosomal
1. Heme

iii. CNV
    1. SZ
    2. Autism
    3. Drug response, and ADR
        a. May not be actionable in adults, may be in kids

d. Questions:
    i. EB: have you made any specific decisions?
        1. Cardiac risk score
        2. Evaluate PGRN array
    ii. HML: Mary Relling (some non-PGRN members) 35 institutions – partner
    iii. J: whole exome/whole genome replacement? Patients access to the open records, do you have thoughs about how group will anticipate where people will have access to some/all data?
        1. Start w/most relevant to e2, multiple members involved w/exome/genome that plan to return incidental findings.
        2. Hope to set up structure so that implementing exome/genome info into records will be easier.
    iv. HML: Terri, how will this interact with other networks? Advocate on behlalf of eMERGE
        1. Exploring database of actionable variants. (AV program GJ part of develop board)
        2. ROR consortium – addressing how best to get this info to patient (GJ involved in one of these)

18. Clinical Implementation Discussion
    a. See above.
    b. 200 exome –some drug metab genes not well captured by chips (CYP2D6) capture, then next gen sequencing.
    c. ADME not all pass QC
    d. Implement PGN plat form 1000-2K subs per site
        i. Which subs, how to deliver data in CLIA, how to deliver advice to MDs (interpretation don't yet understand) science component, which ones are important
    e. Q:
        i. HML: Good opportunity (innovative), choosing high yield – difficult to choose high risk pop. Are there other people (companies) who will measure SNPs
            1. Good if funding is available to pull off
    f. Rex: Clinical implementation science
        i. Afirmative – good direction
        ii. A lot of things to do, each of these have a 'leap of faith' quality to it.
        iii. This was one of largest goals of eMERGE 2 (TM and RL)
        iv. Patient-physician education – database of education, timeline (Mayo/VU) nice ot catalogue that – prospectively implement at other sites. Phys education wasn't as necessary as thought, b/c they didn't want it. They accepted some level of black box.
    g. David Ledbetter (?) – GWAS for complex care vs medical genetics (when sufficient evidence to move to clin care. Already have process to move to clinc. Is pharmacogenomics clinical application a totally different area or expansion of genetics diagnostics? Are we using mol path, mol genetics diagnostics people, medical geneticists, genetic counselors at each sites to full potential?
    h. HML: istitutions view as QI
        i. DR: FDA warning was

19. Genomics
    a. eMERGE 1:
        i. Inventory by site
        ii. Study design
        iii. Genotyping
        iv. QC, Analysis
            1. Monthly CC and weekly (QC)
    b. eMERGE 2:

i. Inventory:
    1. Sdf
    2. Sf
ii. Imputation will be largest focus

c. Inventory:
    i. 16,000 EA and 2755 AA from eMERGE 1
    ii. New Data and platforms – approx. 10k EA, 1K AA, 1200 hispanics
    iii. Still genotyping - Metabochip (geisinger, VU)
        1. Will affect when data are ready for
d. Basic QC performed by each site
    i. Draft QC parameters for sites to perform
        1. SNP/sample call rates
        2. HWE
        3. Sex chromosome
    ii. IBD relateds
    iii. HapMap (??)
e. Imputation – largestdrive
    i. Need survey of computational resources
    ii. What software, ref panel, dealing with existing vs new data
    iii. Data freeze for anlyssi and timeline
    iv. Ddb Gap deposition
        1. Issues to conside:
            a. Genotype data – variants but didn't assay directly, use ref panel to fill in blanks
            b. 5K samples in 50MB chunks – takes 4-6 weeks (David Crosslin)
        2. Software:
            a. IMPUTE, MACH, gravitating towards Beagle (some family structure, hits sweet spot with sample size)
        3. Ref panel:
            a. 1000 genomes panel (ONE ref panel) 14M variants from 1000 variants, emphasis on cosmopolitain panels bc of race mixture
        4. Imputation
            a. ACC – impute eMERGE 17K samples
                i. Access to processors – parallelize imputation
            b. New data sets – each sites do own imputation (take coordinating between ACC & Sites)
                i. Draft guidelines
                ii. Submit chrom 22 & X to ACC fro QC to follow same parameters
                iii. ACC can provide conputing resources (possibly) for individual sites
                iv. Timeline: Feb 2012 (if already set up) – dependent on study site resoursces and data availability (VU still genotyping – imputation will not happen by Feb 2012)
            c. Strategy:
                i. New data and ACC
                    1. Need raw data to MR to impute
                ii. Existing and new data and acc
                    1. New merged data avail: Oct 2012
                        a. Comsider meta analysis in meantime
        5. Analysis & Methods
            a. eMERGE 1: FOXE1 & hypothyroidism
            b. eMERGE 2: PGx
            c. CNV: use eMERGE 1 data set – call CNVs available (PennCNV)
            d. Characterization of Risk
                i. Estimate effect size

1. Winner's curse – discovery
2. Genetic risks score calc

ii. Genetic ancestry

iii. Modifiers

1. GxG, GxE
2. Sex
3. PGx

e. Interface with AV group

f. Analysis methods for X chromosome

g. Autosomal chrom abnormal (BAF & LogRRation)

h. Pleiotropic variants – PheWAS or other methods

i. Sequence data

6. Priorities
   a. Imputation – workable dataset for everyone
   b. Characterization of risk
   c. Discovery
   d. Other work:
      i. CNV, Pleiotropy etc
7. Questions:
   a. HML: At what level do you stop imputing?
      i. Discussed in f2f, do HapMap3, 1000 genomes? Filter variants (may not impute 14 million – singletons and doubletons are not imputable). Hopefully imputation software will evolve with 1000 genomes.
   b. CLIA level genotyping
      i. HML: format been discussed with group?
         1. Vigerous discussion about CLIA genotyped data. Some have CLIA approved some have none. Returning results – thinking more and more about it. PGx project will be done in CLIA environment.
      ii. HML: look beyond institution in room look to medical diagnostics labs to regenotype. They do a lot of stuff for free. May do CLIA level genotyping for PR reasons? Translating out to general – can't leave out b/c that's where most people get genotyping.
         1. Rex: Turn into research questions. How much added value to doing in CLIA vs research lab?
         2. HML: **(Very critical – b/c some ppl hide behind non-CLIA so don't return results or vice versa)

20. CERC – Maureen Smith, Andrew Faucett
    a. Large challenge to figure out goals to accomplish that made sense for network. (MS)
       i. Previous workgroup C&CC – some of things learned from this workgroup. BK – Return of results – broke out into theoretical workgroup andother workgroup focused on clinical – Malia Fullerton paper. Bringing in ELSI people outside eMERGE. Standardized consent language – led by someone outside eEMRGE (Laura Beskow – Duke) Amy McGuire ___. Continue to bring in pppl outside eMERGE.
    b. Charter
       i. Thinking about ROR – how to achieve that
       ii. Consent – reconsent
       iii. Education of genomic data – assess needs of patients and physicians
       iv. Create a resource on CLIA/CAP regulations – present at upcoming meeting?
       v. Liasons w/consortia working on ROR, integrating genetic health information into clinical care, liase w/CTSA, non-eMERGE ppl
       vi. Explore role and impact of personal utility (how patients will use data, change behavior) – ROR external workgroup

c. Additional Issues for network to consider: (AF)
    i. Legal issues w/ROR in clinical setting (research vs clinical results – capture which way)
    ii. Ancestry/ethnic issues in target screening and targeted therapy
    iii. Reimbursement issues assoc w/ genomic enabled medicine
        1. Initiate discussion w/payers and explore common agendas
            a. Geisinger – work with health plan to see what is important for them
    iv. Explore working on policy issues with vendors – may explore (funding provided)
d. Questions:
    i. LP: Policy and ethics issues that will come out of work? 18/50s manuscripts came out of C&CC. Lots of productivity, continue. Integration of EL issues into education and implementation.
    ii. HML: One reason C&CC was successful b/c every major player across country were involved. One reason they were accepted at high profile journals was because of well known senior authors. Keep senior investigators involved! (as well as junior ones who do most work)
        1. MS – want to keep major players involved, learned a lot
        2. BK – raised by Lisa early on – what you do when you have genomic predictors that indicate less than favorable response to therapy. Important topic to think about how to deal with this.
    iii. LP – dovetails nicely with issue of payers, clinicians, institutional policies esp if no better alternative tx.
    iv. HML – great opportunity to rewrite educational
        1. AF: Focus on Just In Time vs prospective eduction

21. EMR Workgroup – Justin Starren
a. Charter:
    i. Get at least one AV integrated and in action at each site
b. Phenome EMR integration – quality metrics of Meaningful Use Stage 2 guidelines (coming out in Jan)
c. Stretch goals –
d. Interaction w/number of groups: HL7, PGRN-TPP, Blackford Middleton, Rick Shiffman, Bob Greenes – more formal exchange of knowledge
e. Pubs
    i. Model for genomic-EMR integration at eMERGE sites – workflow exercise
    ii. Crossing the Omic Chasm – with outside partners
        1. Consensus, not going to be pouring raw genomic sequences into EMR – model will be similar to radiology – stored in tailored system – actionable parts move into system for CDS
    iii. "So you think you want genomic data in your EMR" – guide for sites considering this (Seems to be ELSI collaboration??)
f. Current state of the art and state of vision are far apart.
g. ID commonalitiles/differences
h. Need to know what first common variant will be from AV:
    i. High probability to change clinical impact – difficult to deal with now
    ii. Unambiguous classification into action groups
    iii. Penetrance
    iv. Coded data
    v. 3-4 AVs to choose from
i. Privacy model of genomic/family history for patient portals
    i. Does spouse, children, parents get to see data? Who can you share with? One bucket, multiple buckets
j. Scope
    i. Not tackling structured family history data (in forseeable future) – if lengthtens 6 min visit rule – won't do it.
k. Questions:
    i. EB: Needed help from other working groups. Lots of synergies between working groups. Many groups need to cross-talk. At the point of reporting to each other too late

ii. HML: Have one person from each committee on others. Target journals that community hospital EMR ppl read – early adoptors, gnomes (do nothing), trolls (active prohibition). Reach last two groups that rest of country can miss.
    1. Academic 'leading' institutions who want to lead but not getting bloody
    2. Rex: can have cross-WG phone calls. ACC can help with cross-talk. High frequency calls, and SC meetings facilitates cross talk
iii. Family history issue – interlinking information from others patients records gets dicey. Push vendors – how will people use genomic information in health records – security issue here.
iv. HML: External collaborations ongoing – where are they?
    1. Very early stage – proposed for AMIA spring congress w/reps from Vendors, HL7, PGRN and eMERGE groups

22. ESP Coments
    a. Geraldo:
        i. Very impressed with well conceived plans, bringing experience.
    b. Eta:
        i. Presentations were excellent, appreciate discussion of recommendatios
        ii. Consider other collabs: CTSA – informatics KFC
    c. LP:
        i. Didn't hear a lot about timelines, as work to develop them be sure to integrate timelines and activities across workgroups. Ex: if not defining Native American/ African American similarly across sites, becomes difficult to do later
        ii. Perceived differences between who was looking for and dealing w/high risk/penetrance/clinical impact variants. Differences between high risk, low risk.
        iii. C&CC group – impressed w/integration interdisciplinary w/in group. Integrate ELSI w/genomics. Highly productive, encouraged to continue.
    d. Jeff:
        i. Reinforcing kudos – impressed with maturation, publications well into fild, mainiaing balance between ELSI/theoretically and practical genomics
    e. HML:
        i. Few examples of real network. This work well together in positive ways! Reflects a way to make good output, sets example for other networks. Boring papers of "how we do it: need to get out as much as exciting sci papers.
        ii. Keep talking to EMR vendors – really soon! Both sides need to learn together.
        iii. Enjoyed the way new groups are integrating. Try to think of simple project to integrate new groups, consider publication of how to do this. Allow them to do old phenotype to being all to same place.
        iv. Several peds sites will join in future. Think about how to bring those groups in. May be real work, try to prepare for them. Some groups already have peds as part of biobanks.
        v. Number of senior ppl from phase 1, but some (not just in ELSI) that aren't here. Try to maintain as many senior people as possible. Need to make it clear so council and NHGRI other leadership. Do high impact research to get this point across.
    f. Rex:
        i. Comments helpful, usually right on target with what we knew we need to do.
        ii. Set strong priorities! Very strong agenda that excited about. Worry about bandwidth issues. May need to call on to for advice with suggested priorities. Make sure CERC is well supported and engaged as other WGs.
    g. HML:
        i. Going from 14-40 PTs, is a lot being asked of you. Not asking you to do less, b/c may figure out a way to do all. Sensitive to high charge.