Tuesday October 8

Return of Results Session
Moderators: Wylie Burke & Erwin Bottinger

Iftikhar Kullo/Wylie Burke, Introduction

- Criteria for ROR, what results should be returned, how to do so
- Goal – joint conversation with focus on 'edge' cases
    - Arguments in favor and against returning
- eMERGE began as a discovery effort and in phase 2 focus is implementation
- Still using GWAS to find clinically useful SNPs but moving into clinical utility

Gail Jarvik, CSER

- What is returnable? What is actionable?
- Manuscript summarizing how initial 6 sites thinking about returning results
    - Discrepancies across CSER sites
    - Adult vs. pediatric study populations, split for generally pediatric onset conditions
    - 4 groups had an a priori list, 2 didn't
- UW ROR Committee
    - Familial Mediterranean Fever
        - Argument - if you have the disease it should be diagnosed vs. it may be helpful for diagnosis
        - No unanimous agreement, watch list pending penetrance information
    - Gaucher disease
        - General discussion, if do not have other symptoms no evidence that enzyme replacement would help
        - All not in favor of inclusion other than biochemical geneticist
    - Neurofibromatosis, type 1
        - Range of differences across CSER sites (lower vs. higher threshold +/- patient preference)
        - Most split within UW group
        - Implications for children of affected? Carrier status including transmission not immediately actionable
    - Unanimous criteria – setting the bar very high/conservative, focus on most important things to return
    - Questions
        - How to engage experts in the disease?
            - Broad community of expertise in UW community
        - When does patient preference come in?

Cindy Prows, eMERGE

- Initial reaction, not to return C282Y homozygotosity to children based on low penetrance and adult onset; however is preventable and cannot reverse effects
- Already had results for children and choosing whether to return, not deciding whether to test
- 13/17 are research samples – parents did consent for ROR
    - What is age of 13? If >18 have they been reconsented?
- Requires submission of problem reports to IRB and they decide on return
- Return to males only? Test children if mutation identified in the family?

Discussion

- Important not to necessarily consider this an either/or questions
    - First rule – prior probability, what info do we have about the individual to inform us about relevancy? Incorporate info from HER
    - However, can help with diagnosis and clinical decision making if individual is asymptomatic
    - May only want to return when info is relevant ex. Pgx results
- Value of screening? Concern with overdiagnosis
- No consensus conceptual framework at each site let alone across consortium – may lead to uncontrolled variation
    - However, variability within CSER is important to learn what works and what does not
- How much investigation is required to find things?
    - Some sites more specific with respect to what to look for or not. It is a choice to look.
- Was CLIA involved in decision about HFE return?
    - Not a factor, arguments presented to IRB
- Labs vs. clinician making 'bedside' decision – concern with decisions being made based on partial information
- To clarify – CSER table was regarding returning clinical results, may not if id'd by GWAS
- Difference in study designs, different background for return and may or may not ask preferences across sites
- Needs to be a partnership between clinicans and labs before something is entered into the medical record
- Research – different judgment because we are trying to see what happens vs. trying to predict what people would do

- Complex when no a prioir consent other than the consent to treat
    - Higher threshold to return, in a clinical lab do not give back what not asked for
- How do we think about threshold?
    - Evidence for pathogenicity regardless, evidence that gene causes phenotype and evidence for actionability
        - Actionability may depend more on context
    - Tough to collect an evidence base unless we err on the side of returning more
- Do we need to create consensus guidelines that take into account expertise in specific diseases?
    - Where expertise is available, worth engaging
    - Findings are from deliberate search vs. what happens in clinical practice
    - There is a need for consensus but keeping it within genetics community may not be ideal
- Continuum of actionability and what are the components?
    - Broader approach incorporated into 'ClinGen' to score genes systematically
- Context – severity of illness in patient may reflect their choices
- **What are the range of contextual factors that influence our decisions?**

EMR Integration Session

Peter Tarczy-Hornoch & Justin Starren

Justin Starren, Workflow & Genomic Decision Support

- Why is it hard to come up with vignettes good
    - Lots of variation in bringing in genomics
    - But, patterns emerge
    - Looking at patterns
- All Patterns follow the same 5 general steps
    - Trigger
        - Consumer based or population based?
        - Screening or diagnostic?
        - Therapeutic Guidance or
        - Unknown
    - Order
        - Consumer

        - Default
        - Decision Support System
        - Primary Care Provider
        - Clinician
    - Assay
        - Single gene up to exome
    - Format
        - Textual Report
        - Lab Result
        - Structure Text Result
        - Raw data
    - Interpretation
        - Consumer
        - Decision Support System
        - Primary Care Provider
        - Clinician
- Together, far too many possible combinations. We can look at specific examples that are ubiquitous in the field of genetics
    - 23 & Me; Consumer based genetics
    - Newborn Screen; Population based screening
    - BRCA & Clopidogrel: Trigger Screening based on family background.
    - Classic Genetic Consult: Diagnostic Clarification
    - Warfarin: Therapeutic Guidance
    - Unknown Disease: Whole Genome Sequencing w/ raw data
    - Future: Everyone gets a whole genome and depend on the EMR to sort through the magnitude of raw data.
- Conclusions
    - No such thing as a typical genomic workflow
    - Genomic Healthcare mirrors the complexity of healthcare. No one size fits all program, but rather multiple software tools that will overlap

Andrea Hartzler, Guiding Carbamazepine prescribing with HLA*B1502; Use case & reflections of clinicians

- From Group Health Cooperative at UW, who is looking at the feasiibiliyt of integrating genomic data into the EMR
- Use case, looking at carbamazepine & HLA*B1502
- Background
    - Carbamazepine
        - Anticonvulsant drug

        - Treats seizure control
    - HLA*B1502
- Current Practice, following the workflow of a neurologist prescribing Carbamazepine
    - Enters CBZ
    - Receives a generalized alert, so cancels order and obtains patient's consent to looking into genes
    - Orders genetic test
    - Wait 10 days, receives a positive results, prescribes a positive drug
- Future Practice; same case
    - Enters CBZ
    - Receives a personalized result, immediately gets a positive result, prescribes an alternative drug.
- Contextual Interviews with Clinicians
    - Methods
        - Hour long interview, discuss workflow with clinicians.
        - Discuss barriers and limitations.
        - Use illustrated case vignettes
    - Results
        - CBZ prescribing is rare
        - Barriers include indistinct alerts and a balance between urgency with wait time.
        - Personalized medicine can save time, money, and improve care
        - ELSI concerns, increased workload, need for referrals
        - Prototype design; need to make results visibile, scalable, and fit in the workflow appropriately upstream.
- Fitting Results Upstream in Workflow
    - Results should inform prescribe decision.
    - Passive guidance? Patient summary? Pre-populated orders? Support for drug selection differ for drug dosing?

Eliezer Van Allen, Web Portals & Challenges for EMR Integration

- CanSeq Project Background
    - Patients who have progressed cancer, sequence whole genome, and then look at care
    - Looking into web portal, which is viewed upstream of the clinician
    - Translate research-grade somatic and germline genomics for clinical use

- Goals
    - A need for an accessible and approachable interface
    - Built our own using R code
    - Integrate with external resources
    - Integrate with existing/emerging EMR systems
- Current Implementation
- Challenges
    - Existing EMR support for portals
        - Limited/no support for external website
        - Flatten web document into PDF?
    - Decision support integration
    - Need for context-specific apps?
    - Content generation & curation
    - Intellectual property issues?

Questions & Moderated Discussion

- Issues and obstacles regarding ownership of open-source software and commercial EMR was discussed
- Need to represent genomic data in a means to run rules off of; need to move from local issues to a generalizable method to increase adoption.