Questions from the UM Learning Health Systems Collaboratory Seminar Series
Dr. Marc Williams

November 29, 2018

The following is a list of questions that were submitted by audience members but not read/answered during the Collaboratory Event. Dr. Marc Williams has graciously provided answers to these questions, which can be found below:

1. What sort of limits are there on the return of data to patients? **The only data actively returned are positive findings.** Can they get raw data from the exome? **We have decided that if someone requested their raw data we would provide the information of some type of mobile media. We've not had any requests to date.**

2. [I'm] interested in hearing a little more detail on the consent process, particularly related to family member's consent to have results returned to all 1° family members. **There is no consent process for family members—only the participant is consented which includes the consent for return of results. At the time of initial consent, there is no discussion about potential impact on family members. At the time of the return of result, we discuss the implication for relatives, with the highest risk being for 1ˢᵗ degree relatives. We provide information that the participant can provide to their relatives, but it's up to them if they share the information with some or all of their relatives. This reflects a transition from the research space to the clinical space. The reliance on the proband to communicate with family members is the current clinical standard of care. We are looking to study other ways to communicate to relatives using a research design.**

3. [It] looks like genome is the primary arbiter of risk? Are you looking at <u>all</u> risk or only genetic? What about SDOH, behaviors, substances, immunizations…? **This project is only looking at risk related to high impact genetic variants in genes known to be associated with disease. All of the things listed are relevant and most are addressed in our delivery system as part of usual care and are not the subject of research. At present this is a research project focused on use of genomic information with the assumption (correct or not) that other issues are being addressed.**

4. How to track at-risk family members? **Requires manual processes that rely on reporting by the participant and are prone to failure. We are able to track the impact on relatives that contact us to arrange for cascade testing, but that's a small percentage of at risk relatives.** What are they told? **They are provided with an information sheet about the condition, the gene, and the specific variant found in the participant, if the participant shares the sheet with family members. If they contact us we know what they are told, but otherwise we have no clue.** What do family members do? **We attempt to track this as noted above.** How are they tracked over time? **Same** Entry in EHR linked (family and probond?) **At present EHRs do not link relative medical records, so we have to create systems to track outside the EHR, but where possible drawing from the EHR.** What if they leave Geisinger or live in New York? **We provide information about local genetic providers and work with those providers to make sure they have the information. We can also arrange to do testing and return results using telemedicine.**

5. How do you balance the level of detail between comprehension and detailed disclosure? **Our patient engagement has provided insights into this balance which we incorporate in our materials. This is ongoing.** How do you stimulate level of engagement of patients? **Other than presenting them with the information about the result, its impact, and what they can do, we don't do anything else to stimulate interest. We're still studying how health behaviors are impacted to see if we will need to use different approaches to improve engagement.**

6. Who are controls? **Controls are participants enrolled in MyCode that do not have a variant found on the analysis.**

7. Are we missing important subpopulations because they are less likely to consent to receiving results? **We do analysis on patients that decline participation and we've not identified any subpopulations that seem less likely to consent. Again, Geisinger is overwhelmingly Caucasian Northern European. We've not done analysis on our participants from our New Jersey site as yet.**

8. What are the changes and challenges in the insurance models (access and cost) as we get more "precise" and can identify significantly higher utilizers (with higher cost)? **Important questions, but at present we're just developing the data to be able to begin to study the questions. We are convening meetings in 2019 with employers and payers to try and understand their perspective so that we can capture outcomes most relevant to them.**

9. Pharmaceutical company was mentioned as funder of study – how much is shared with them? **I'd refer you to the paper that describes the project. [PMID: 28008009 DOI: 10.1126/science.aaf6814] We do not share the individual patient level data on the clinical return of results, as that falls into clinical care which the company is not interested in.**

10. Where are the sequences being stored, and are they ever moved or shared as part of a public repository? **Sequences are stored in a secure cloud with controlled access by Geisinger and Regeneron investigators. There are subsets of the data that are deposited into publicly available databases if they are used as part of a funded project where data deposition is required by the funder (e.g., NIH).**

11. How much of the data is returned to patients? **See answer to #1**

12. Is the physician training video evidence based? **The videos are based on published professional guidelines where available. If not, we rely on expert consensus.**

13. How comfortable do the physicians feel conveying genetic testing results to patients? **In general, not too comfortable, but getting better. The support materials and availability of the genomic screening and counseling program and disorder-specific consultants and clinics are very helpful in supporting the physicians.**

14. How often are patients being referred to genetic counseling? **Over 80% of participants choose to meet with our genetic screening and counseling program and the majority of encounters are with genetic counselors. PCPs refer some additional patients after they've met with them.**

15. Does the physician training video get updated to reflect current recommendations? **For the conditions that we are returning results, there hasn't been the need to revise, but they will be updated as needed. As we develop more functionality to provide decision support and point of care 'just-in-time' education in the EHR, I suspect we'll retire the videos.**

16. How should genetic information change screening guidelines – especially for those that are negative? Could that actually decrease cost and increase value? **This has been examined and, at present, a negative screen for variants does not lower risk sufficiently to reduce**

recommended population screening. At some point, particularly as polygenic risk scores are better understood, there may be a way to reduce screening interventions for those a low risk.

17. Can you expand on the notion of rules-based idea of PM? **I think the easiest example is a decision support rule for pharmacogenomics. Specific genomic information (variants in *CYP2C19 *2/*2*) can be translated into a phenotype (poor metabolizer) that can be used to fire a decision support rule when the physician goes to order clopidogrel that says choose an alternative medication. We can develop rules for the single gene Mendelian disorders that could look like: pathogenic variant in *BRCA1* present, female patient, surveillance recommendations A/B/C. I think that we're at early days here but can begin to see how approaches might be applied, but a lot of work to do.**

18. How can this kind of LHS effort be funded / sustained for lower income groups? **Sustainability is a major issue. At present in the US healthcare system sustainability is dependent on reimbursement which affects access which disproportionately impacts certain groups, including low income. If this model persists, then we'll have problems, and not just in precision health. The LHS model as applied at Geisinger is agnostic to payer, insurance, and income status. If you're seen at our system, you get the same care as organized using the LHS model. This is true for the research project which is open to anyone. However, we recognize that the current reimbursement system impedes access to our healthcare delivery system, and we aren't able to reach out to those that can't get in the door. I don't think precision health will solve this problem, but we have to work hard to be sure precision health isn't making the problem worse.**

19. How must / should policy change to protect people from bringing forth this genetic information? **I'm not sure what this question is referring to, although I think it's related to the risk for genetic discrimination. I don't think any additional policies are necessary as genetic information already has additional protections over and above other healthcare data through the Genetic Information Non-discrimination Act which protects against use by health insurers and employers. Of course this doesn't extend to life or long term disability insurance, but there are no protections for any other health information being used for those either.**

20. Out of 225,000 participants consented into the research study, how many exomes have been sequenced? **At present, just under 93,000. We expect another 40-50,000 to be completed in the next 6 months.**

21. What are the regulatory / legal / administrative hurdles for taking research sequencing to target CLIA genomic testing? **Our process follows current regulation in that we send a CLIA sample to a CLIA lab which runs the analysis (for a single variant) and issues a report. It's an additional step, but it doesn't raise barriers that aren't already there.**

22. Do you re-contact when new information is attainable? **Yes.**

23. The slide that showed this work can lead to higher costs – not necessarily improve value-based care – how can this be better controlled for efficient use of resources? **The first step is to collect the data to be able to understand the actual impact on cost and outcomes in order to determine the value. Only with the data can we begin to work on efficiencies. It's why we're doing this as a research project rather than just implementing as part of clinical practice.**

24. How frequently is your database updated with the new "pathogenic" associations that are being reported weekly? **We don't maintain a database of variants—we rely on publicly available databases like ClinVar. Each time we do an analysis of our sequences, we use the most up to**

date version of these databases. We intend to reanalyze sequences previously analyzed with each batch in order to make sure we are using the most recent knowledge. Also, how do you handle the false positives and inform patients? **If we have a pathogenic variant that we have returned that is reclassified as not pathogenic we contact the participant, provide the information and offer to see them to discuss the change in interpretation. We also communicate with the participant's physician.**

25. Are patients and primary care physicians involved in study design? **We aspire to have the relevant stakeholder and participants in the proposed research involved in the study design.**

26. Adverse outcomes: Anxiety, mood disorders, SI, unnecessary therapies / interventions – 50,000 patients tested, 122 BRCA (0.2%), only 8 diagnoses 3 Bre, 3 Pr – What did the other 114 BRCA-positive patients do? **We are currently reviewing these outcomes and expect to have a manuscript on this early next year. I can say that we've not seen any significant impact on psychological domains.**

27. Consent: What fraction of patients consent to participate in the study and its implications on health disparity – youth, children, seniors….? **I know our overall consent rate is above 85%. We've analyzed decliners and have not identified any significant predictors for decline. I don't know that we've done a separate analysis for the peds population (in this case its parents consenting their children for participation). When we ask decliners why they declined, most of the patients indicated that their medical issues and/or life situation were not conducive to participation at the time of invitation. A few indicated concerns about privacy or discrimination. Very few noted that the potential return of medically relevant results led to their decision.**

28. Other than the data coming from genetics, how is it different from applying public health paradigms into medicine? Generalizability **Fundamentally I don't think it's exceptional. We still need to determine the evidence to support its use as a population screening method, the evidence to support the interventions related to the disease, tracking outcomes, etc. The differences are the maturity of the evidence, which is early (again it's why this is a research project), and the current inability of EHR systems to represent the genomic information in a form other than a PDF.**

29. Does Geisinger data challenge current assumptions (e.g., USPSTF grade of "D") about utility of population-based BRCA screening? **Ours are among the first data that actually are relevant to this question. I wouldn't say that we are challenging the current determination (it's not an assumption) of USPSTF, but it provides data to address the utility of this approach. We'll need additional information from our study as well as others to have sufficient information to support a re-evaluation of the evidence by the USPSTF.**

30. Is prediction about optimal treatment based on rules alone or other approaches, such as predictive algorithms? **For the results we are returning, the guidelines are relatively simple and straightforward, so we can create simple 'rule sets' (really recommendations) to guide care. No predictive algorithms are needed at present.**

31. Is Geisinger also accumulating information on other Tier 1 or 2 conditions that could ultimately yield validated tests? **There are no other CDC Tier 1 conditions beyond Hereditary Breast and Ovarian Cancer, Lynch syndrome, and Familial Hypercholesterolemia. We are accumulating information on other conditions to see if there is sufficient evidence to consider them to be**

Tier 1. One that is promising is the C282Y homozygotes in HFE associated with hereditary hemochromatosis.

32. Does Geisinger track what it knows about <u>why</u> treatments are given? **This is difficult to track in an automated way, but we are using a variety of methods to determine if a treatment is attributable to the return of a result to a reasonable degree of certainty. The approach varies depending on the condition.**

33. Is scaling up feasible? Does our healthcare system have enough money to pay for the added costs? **This is the important question and we do not have sufficient information to answer the question at present. We hope our study will be contributing important information to begin to address this question. We have a large economic analysis underway to model the impact of this type of program from the US healthcare perspective that may help to answer those questions. A more important question is one of opportunity cost. If we pay for this what we'll we not be able to pay for? One of the reasons we are focused on genomics is that the US healthcare system is notorious for introducing new technology into clinical care on the basis of clinical plausibility and enthusiasm and a lack of evidence doesn't seem to impede this. We hope that by developing data early on, if this technology moves into care as seems inevitable, we hope it would be focused on those areas where there is reasonable value.**

34. What is needed for insurance to pick up these costs for surveillance? Level of evidence? Cost effectiveness? **We have no issues with insurance coverage for the surveillance, as the insurers already cover enhanced surveillance for individuals diagnosed with risk associated with HBOC, Lynch, etc. I would note that insurers generally do not use cost effectiveness as a criterion for coverage as most CE studies are done from a societal perspective rather than a payer perspective.**

35. What other barriers (beyond consent) exist that may keep people from being offered testing? **All the usual suspects that impair access to any health care modality. I'm not sure genetic information has unique barriers compared to other health information. The healthcare delivery system as currently designed to deliver recommended care about half of the time (the exception being anesthesiology where the profession has re-engineered care delivery to increase reliability to about 4 sigma). That's why the LHS is so important.**