Question 1:

July 10, 2019 3:27 PM from Lily Lou to all panelists: Can you discuss the relative costs of the various tests compared to the expected yield of meaningful results in various clinical scenarios?

Answer 1:

Prices will vary depending on providers and expected yield of meaningful results will also vary depending on the type of patients. We are slowly but surely amassing the data and evidence. I hope the examples at the end of the webinar shows the clinical utility in at least a subset of patients. The goal is to continue sharing patient experiences and discussing clinical utility in a variety of patient population.

This article discusses costs of WES and WGS in general: K. Schwarze etal. Are whole-exome and whole-genome sequencing approaches cost-effective? A systematic review of the literature. Genetics in Medicine (2018) 20 (10): 1122-1130. https://doi.org/10.1038/gim.2017.247

The following article talks about the cost of microarray versus karyotyping:

Li, Y., Anderson, L.A., Ginns, E.I. et al. Cost Effectiveness of Karyotyping, Chromosomal Microarray Analysis, and Targeted Next-Generation Sequencing of Patients with Unexplained Global Developmental Delay or Intellectual Disability **Mol Diagn Ther(2018) 22: 129.** https://doi.org/10.1007/s40291-017-0309-5

Question 2a/b:

July 10, 2019 3:31 PM from Chen Wan to all panelists: what is your current practice for incidental findings?

July 10, 2019 3:52 PM from Kamlesh Athavale to all panelists: for the sequenced patients/families, what about incidental findings of adult disease impact (brca, apoE4, etc)?

Answer 2a/b:

How incidental findings are handled depend on the ordering institution. Most commercial genomic sequencing will report all findings whether it fits with the patient's presenting characteristics or not. The field of genomics is evolving and like Dr. Stephen Kingsmore stated during the webinar more discourse is needed with all stakeholders including bioethicists to determine the best practice.

At RCIGM we only report the findings we encounter while doing a phenotype driven analysis of the genome in the critically ill child. We do not look for all pathogenic variants of disease. Furthermore, we have developed the practice of allowing the family to opt in or out of incidental

findings (findings we just happen upon while doing a symptom driven evaluation of the affected child) for themselves and their children.

Question 3a/b:

July 10, 2019 3:32 PM from Kamlesh Athavale to all panelists: hi, do you want to comment on whether or not the variants of unknown significance and phenotypes go anywhere for later validation by another baby w/ similar phenotype and same variant showing up later?

July 10, 2019 3:33 PM from laurie steiner to all panelists: How do you handle variants of unknown signficance? How do you determine if these variants are related to the infant's phenotype?

Answer 3a/b:

There are a few researchers who currently pursue variants of unknown significance suspicious (VUSS) by either querying databases for patients with similar presentations and similar mutations to help clarify significance and others who are pursuing animal models to determine a plausible implication.

Question 4:

July 10, 2019 3:33 PM from Lily Lou to all panelists: It would be helpful to develop cost analyses like the cost of preventing one case of NEC--perhaps data on LOS savings with earlier diagnosis. Especially to distinguish between tests like WGS vs. WES.

Also, hospitals and payors are pushing for moving testing to the outpatient setting vs. the bundles hospital setting. Of course life/ death decision making requires in hospital testing, but it is worth thinking about what tests might be delayed without negatively impacting patient care.

Answer 4:

Agree. Please refer to the following article: Rapid whole-genome sequencing decreases infant morbidity and cost of hospitalization. NPJ Genom Med. 2018 Apr 4;3:10. doi: 10.1038/s41525-018-0049-4. eCollection 2018, for a discussion of the effect of genomic sequencing on hospital cost savings.

Question 5:

July 10, 2019 3:46 PM from Chen Wan to all panelists: The final examples compellingly demonstrated the potential for rWGS to lead to actual diagnosis and inform treatment; what barriers have you regularly encountered to making rWGS a first-line approach?

Answer 5:

rWGS is not approved as part of the hospital bundle.

Insurance companies' assessment that rWGS is still experimental and wanting more evidence.

Question 6:

July 10, 2019 3:48 PM from Kamlesh Athavale to all panelists: As you note, we have high buyin for getting to WGS quickly, but we get push back because the hospital gets reimbursed for all the care, including this test in a bundle, but it gets charged/ reimbursed on an individual test basis for outpatients. Any suggestions on how to argue to allow for the inpatient use to be separately charged, short of compiling your reports and keep making the economic case w/ the data you're providing?

Answer 6:

Unfortunately, the only method we have right now is by using this data.

Something that has helped to streamline the process at our hospital is the development of a letter of necessity that already references the different articles showing the utility of rWGS. Empty spaces are left for the requesting physician to quickly add the reason for requesting the test and the expected benefits to management in that particular case.

We currently have a case manager dedicated to processing of the medical of necessity paper work who directly communicates with insurance companies and so far, we are seeing some success with approvals outside of the hospital bundle.

Question 7:

July 10, 2019 3:49 PM from Kamlesh Athavale to all panelists: is there any potential use of comprehesive EHR and/or images of the patient to be assimilated to help 'quantify' phenotype details that the clinicians might not capture?

Answer 7:

Great question. In our recent article “Diagnosis of genetic diseases in seriously ill children by rapid whole-genome sequencing and automated phenotyping and interpretation. Sci Transl Med. 2019 Apr 24;11(489). pii: eaat6177. doi: 10.1126/scitranslmed.aat6177.“ we have shown how this process can be effectively automated with no loss of data integrity.

Question 8:

July 10, 2019 3:52 PM from Leah Burke to all panelists: This is Leah Burke, the geneticist where Roger Soll is located. I do use OMIM and the other databasses all the time. The problem is getting the coverage for the genetic testing.

Answer 8:

Agree. We are working hard to generate and publish the evidence and have also been diligent in responding to inquiries from insurance companies hoping to keep an open dialogue.

Question 9:

July 10, 2019 3:57 PM from melissa gassett to all panelists: what is your experience with the Face2Gene app in developing a DDx (in the absence of a clinical geneticist)?

Answer 9:

We do not have any personal experience with this app. There appears to be some limitations to the usefulness of this app as reviewed by Elie Dolgin in the January 7, 2019 issue of Nature, *doi: 10.1038/d41586-019-00027-x*

Furthermore, the fact that infants frequently present with incomplete characteristics of the disorder as described in literature may limit the application of apps like Face2Gene in this patient population.