NSGC Pre-Conference Symposium

Diagnostic Exome Sequencing as the Standard of Care

Session Description:

Since its inception as a clinical test in 2011, Diagnostic Exome Sequencing (DES) has rapidly gained acceptance by the medical community. This technology has transformed the field of medical genetics by its ability to pinpoint rare genetic lesions in an unbiased and efficient way, allowing thousands of patients who previously underwent a battery of invasive, expensive, time-consuming, and often uninformative tests to finally receive a correct diagnosis.

Through this symposium, appropriate for those experienced with or new to DES, we aim to provide an unbiased, in-depth look at the state of DES today, delving into how it is rapidly becoming the standard of care in clinical genetics. The symposium includes a wealth of experts in the area of DES. It will begin with an introduction by David Goldstein, PhD of Columbia University, who will discuss the state of rare disease diagnostics in clinical genetics today, including how microarray and DES have become technological partners in diagnosis. Next we will provide an updated technological overview of DES including analysis, interpretation, and the importance of accurate phenotyping. Some common clinical management questions will be explored, such as, “Should I order a panel or an exome?” and “When is it appropriate to order an exome for a cancer phenotype?” A panel representing four laboratories performing DES will share their interpretation processes, detection rates, and unique and interesting findings. We will next explore specific data analyzing the cost-effectiveness of DES and propose systems in which it could be more cost-effective, followed by a discussion of how early and accurate genetic diagnosis is crucial to guide optimal care for patients and their families. Finally, we will provide an in-depth review of secondary findings including positive yields, ethical issues such as consent and return of results, current attitudes, and recommendations. To conclude, Leslie Biesecker, MD of the NIH will speak to refining aspects of secondary variant screening as we transition to predictive medicine.

Additional Information:

This Pre-Conference Symposium proposal is being submitted by genetic counselors from two laboratories offering DES (Ambry Genetics and GeneDx). Given the concerns about conflict of interest, the organizers and speakers will be transparent about potential conflicts of interest, and will strive to avoid any commercial biases in the presentation materials. Material specific to any commercial laboratory will only be presented during the comparative panel described below.

Learning Objectives:

- Gain perspective on the current state of DES from technological, research, clinical, and genetic counseling perspectives
- Recall data regarding the clinical use of DES, such as detection rates, and how these data contribute to clinical genetics diagnosis and management of patients
- Appreciate that the high diagnostic rate of DES, implications for patient care after a diagnosis, and clear costs savings are making DES well-suited to become the standard of care in diagnostic medicine
- Identify current attitudes, policies, and recommendations surrounding secondary findings

OUTLINE
Diagnostic Exome Sequencing as the Standard of Care

1. **Diagnosing Genetic Diseases Today: (20 min)**
   David Goldstein, PhD (Columbia University) (Shashi paper)

2. **Exome 101: Technological Basics, Analysis, and Interpretation (20 min)**
   Technology, coverage, bioinformatics, importance of filtering parameters (inheritance vs. phenotype), medical review, importance of accurate phenotyping
   Kelly Farwell Hagman, MS, CGC

3. **Navigating the Testing Options: Gene Panels or Exome? (20 min)**
   Holly LaDuca, MS, CGC

4. **Exome Sequencing for Cancer Phenotypes: (20 min)**
   Elizabeth Chao, MD (UCI)

5. **Exome Sequencing Results (80 min)**
   Neal Z. Niu, PhD (Baylor)
   Joshua Deignan, PhD (UCLA)
   Cheryl Scacheri, MS, CGC (GeneDx)
   Sha Tang, PhD (Ambry)

6. **Cost-Effectiveness of Exome Sequencing (20 min)**
   Emily Farrow, PhD, CGC (Soden paper**)**

7. **The Clinical and Management Impact of Diagnostic Exome Sequencing (60 min)**
   David Goldstein, PhD (Columbia University) (10 min)
   Julia Wynn, MS, CGC (Columbia University) (25 min)
   Julie Cohen, MS, CGC (Kennedy Krieger Institute) (25 min)

8. **All about Secondary Findings (60 min)**
   - Secondary findings analysis: Positive yield, coverage, limitations, challenges (10 min)
     Layla Shahmirzadi, MS, CGC
   - Evolution of secondary findings results: Attitudes, Recommendations, Policies (20 min)
     Kelly Ormond, MS, CGC, LGC
   - Refining aspects of secondary variant screening: The transition to predictive medicine (30 min)
     Leslie Biesecker, MD (NHGRI- NIH)