NHGRI Genomic Medicine II

Challenges and obstacles to realizing genomic medicine addressable by NHGRI

Sequencing Working Group

Participants:

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Conference call dates:

4/19/12, 4/2/12, 3/6/12, 2/21/12, 2/7/12, 1/27/12

Summary:

Six conference calls were conducted for the sequencing subgroup. Recurrent themes were (a.) the need for standards, (b.) the need to not be repetitive with other groups having similar meetings (ACMG, NIST, CDC, etc.), and (c.) the need for central data repositories.

- **Section 1: Wet lab best practices.**
  - I. Key issue: Laboratories are in need of guidelines for operating platforms.
    a. Technologies are developing so quickly that it is difficult to define appropriate technical guidelines.
    b. Quality control metrics and measurable are not consistently defined.
  - II. Key issue: Need for communication between groups developing standards
    a. NIST, CDC, ACMG are all developing in parallel.
    b. For example, some groups are developing spike-in's and other quality control metrics.
  - III. Key issue: Laboratories are in need of standard samples for validating platforms

- **Section 2: Analytical best practices.**
  I. Key issue: Need of a defined set of standards and tools for analyzing genomic data
     a. Standards are needed to assess quality (duplicate rates, minimum coverage, quality metrics)
     b. Standards are needed for measuring false positives and false negatives (sensitivity/specificity)
     c. Standards should be platform independent.
  II. Key issue: Need for software, standards, and tools that feed into diagnostic market.
     a. Data analysis tools are developing so quickly that it is difficult to define appropriate parameters for analysis.
     b. Software and databases that lock, rather than dynamically change to support the fact that software and processes must be validated.

- **Section 3: Standards for reporting genomic data.**
  I. Key issue: Laboratories are in need of a defined set of standards for reporting genomic data.
     a. Expectations for covering the relevant regions based upon the indication for testing (disease gene/locus list, whole exome, whole genome).
     b. Standards for reporting secondary findings
     c. Quality thresholds for variants that are returned to patients and when confirmation (with the same technology or an orthogonal technology) is required.
  II. Key Issue: Reporting of clinical data is in need of standardization
     a. Most clinical data is non-structured.
     b. Clinical terminologies are not standardized.

- **Section 4: Central repository for clinical comparisons.**

I. Key issue: Determining the clinical relevance of genetic variation will require large cohorts of well phenotyped individuals, and centralized databases are needed.

   a. ClinVar is one example, but reporting standards are not always clear.
   b. BIC is another example, noting that Myriad stop reporting
   c. Different types of submissions: Observed variants such as in a phenotype to be diagnosed or healthy population.
   d. Large databases are needed to aid interpretation

II. Key Issue: Interpreting actionable variants

   a. What is an actionable variant, how do we deal with it.
   b. Managing Variants of Unknown Consequence
   c. Guidance for lab directors

- **Section 5:** Regulatory oversight and consenting.
  I. Key issue: Laboratories are in need of guidelines for how to operate in the genomic space including how to consent individuals for genomic studies and for offering clinical genomic testing.
     a. Regulatory bodies are not well versed in genomic technologies and analytical approaches and therefore will have challenges in creating appropriate guidelines and regulations.
     b. Technologies are moving quickly, requiring flexible and rapidly evolving approaches that are difficult to support in a regulatory environment.
     c. The availability of trained personnel as well as financial resources to consent patients for the return of complex genomic results and interpret those results for patients is a formidable challenge.