Welcome to CAP’s “Hot Topics in Pathology” Webinar Series sponsored by the Personalized Health Care Committee

This webinar on “Transforming the Diagnostic Evaluation of Inherited Disorders with Next Generation Sequencing” is presented by Karl V. Voelkerding, MD, FCAP.

Your host is Jill Kaufman, PhD. For comments about this webinar or suggestions for upcoming webinars, please contact Jill Kaufman at jkaufma@cap.org

THE WEBINAR WILL BEGIN MOMENTARILY. ENJOY!
Karl V. Voelkerding, MD, FCAP

- Professor of Pathology at the University of Utah
- Medical Director for Genomics and Bioinformatics at the ARUP Laboratories
- Former President of the Association for Molecular Pathology
- Member of the CAP’s Personalized Health Care Committee
- Chair of the CAP’s Next-Generation Sequencing Work Group that recently developed the first laboratory accreditation requirements for clinical next-generation sequencing.
Transforming the Diagnostic Evaluation of Inherited Disorders with Next Generation Sequencing

Karl V. Voelkerding, MD, FCAP

April 23, 2013
Disclaimer

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Disclosure

- Dr. Voelkerding has no relevant financial relationships with commercial interests to disclose
Genome sequencing in microfabricated high-density picolitre reactors

Marcel Margulies1*, Michael Egholm1*, William E. Altman1, Said Attiya1, Joel S. Bader1, Lisa A. Bemben1, Jan Berka1, Michael S. Braverman1, Yi-Ju Chen1, Zhoutao Chen1, Scott B. Dewell1, Lei Du1, Joseph M. Fierro1, Xavier V. Gomes1, Brian C. Godwin1, Wen He1, Scott Helgesen1, Chun He Ho1, Gerard P. Irzyk1, Szilveszter C. Jando1, Maria L. I. Alenquer1, Thomas P. Jarvie1, Kshama B. Jirage1, Jong-Bum Kim1, James R. Knight1, Janna R. Lanza1, John H. Leamon1, Steven M. Lefkowitz1, Ming Lei1, Jing Li1, Kenton L. Lohman1, Hong Lu1, Vinod B. Makhijani1, Keith E. McDade1, Michael P. McKenna1, Eugene W. Myers2, Elizabeth Nickerson1, John R. Nobile1, Ramona Plant1, Bernard P. Puc1, Michael T. Ronan1, George T. Roth1, Gary J. Sarkis1, Jan Fredrik Simons1, John W. Simpson1, Maithreyan Srinivasan1, Karrie R. Tartaro1, Alexander Tomasz2, Kari A. Vogt1, Greg A. Volkmer1, Shally H. Wang1, Yong Wang1, Michael P. Weiner4, Pengguang Yu1, Richard F. Begley1 & Jonathan M. Rothberg1

454 Life Sciences

Nature 437 (7057) 376-380
Paradigm Shift

Sanger Sequencing
Qualitative

Next Generation Sequencing
Qualitative and Quantitative
High Throughput
New Landscape of Genetic Testing

- Single-Gene Diagnostics
- Multi-Gene Diagnostics
- Exome
- Whole Genome

Increasing Complexity
Multiple Genes Responsible

Locus Heterogeneity

Clinical Phenotype

Multiple Mutations Possible

Allelic Heterogeneity

Technically Difficult to Test For by Sanger Sequencing
Multi-Gene Panel Diagnostics

Cardiomyopathies
- Hypertrophic
- Dilated
- Arrythmias
  - 10-35+ Genes Each

Mitochondrial Disorders
- Mitochondrial Genome
- Nuclear Genes > 100 Genes

Primary Immune Deficiencies
- 40+ Genes

Next Generation Sequencing Technology Makes Multi-Gene Panel Diagnostics Feasible
Hypertrophic Cardiomyopathy – Model for Multi-Gene Diagnostics

Prevalence = ~ 1 in 500 – 1,000

Teenage to Adult Onset
Autosomal Dominant
Arrhythmias/Angina
Sudden Death

Normal  Hypertrophic

HCM – Genetic Disorder of Cardiac Sarcomere

Myofibril

Sarcomere

Kamisago et al. NEJM 343(23):1688
## Hypertrophic Cardiomyopathy Genes

<table>
<thead>
<tr>
<th>Protein</th>
<th>Gene</th>
<th>Mutations</th>
<th>Gene Size bp</th>
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<tbody>
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<tr>
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Total Gene Size: 906,737 bp
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NGS: Next-Generation Sequencing
Hypertrophic Cardiomyopathy – Model for Multi-Gene Diagnostics

Value of Genetic Testing

- Confirm Genetic Etiology
- Specific Mutation Identification
- Family Risk Counseling/Testing

Medical Management

Beta and Calcium Channel Blockers
Antiarrythmics – Cardioversion – Implantable Defibrillators
Transplantation
Multi-Gene Panel Diagnostics

More Comprehensive Compared to Single Gene Sanger Sequencing

Gene Content = Based on Current Knowledge

Facilitated by New Platforms
Lower Capital Costs
Faster Sequencing Process

Illumina MiSeq
Ion Torrent PGM
Multi-Gene Diagnostics Require Gene Enrichment

Genomic DNA

Amplification Based
- PCR or LR-PCR
- RainDance ePCR
- Fluidigm
- Ion Torrent and Illumina
- Agilent Haloplex

Array Capture Based
- In Solution Target Probes
  - Agilent
  - Nimblegen
  - Illumina

Enriched Genes

NGS
Multi-Gene Diagnostics Require Gene Enrichment

Genomic DNA

Amplification Based
- PCR or LR-PCR
- RainDance ePCR
- Fluidigm
- Ion Torrent and Illumina
- Agilent Haloplex

Array Capture Based
- In Solution Target Probes
  - Agilent
  - Nimblegen
  - Illumina

Enrichment Method - Difficult Choice - Substantial Cost Investment
Considerations in Designing Multi-Gene Panels

Suitability of Enrichment Method for Laboratory

- Is the Technical Workflow (Manual) Adoptable in Your Setting?
  - Is it Possible to Automate the Workflow?

- Is the Enrichment Method Compatible with Your Sequencing Platform?
  - How Many Samples can be Barcoded and Pooled for Sequencing?

- What Data Analysis Pipeline will be Required?
  - Vendor Supplied or In House Custom Developed
Perform *In Silico* Designs with Enrichment Methods

- Free Designs Using Vendor Software
  - Valuable to Compare Design Results between Method Options

- What Percentage of Gene Targets will be Enriched?
  - Are there *In Silico* Predicted Problem Areas?
Considerations in Designing Multi-Gene Panels

Expect *In Silico* versus Empiric Results Differences

- Characterize Problem Areas
  - Inadequate Sequence Coverage of Some Target Regions
  - Regions where Data Analysis indicates Homologous Sequence Interference
Case Example Multi-Gene Panel Design

Project Goal

- Multi-Gene Panel for Primary Immune Deficiencies
- Sequencing Platform – Illumina MiSeq
- In Silico Designs Performed and Agilent Haloplex Chosen
- In House Custom Data Analysis
Haloplex Enrichment Theory and Practice

1. Digest and Denature Genomic DNA

2. Hybridize Biotin Target Probe Library to Form “Tri-Molecular” Circular Complexes

3. Capture and Ligate to Form Closed Target Circles
4. PCR Amplify Targets and Incorporate Sequencing Adapters and Indexes
### Coverage (%)

- **Exome**
- **Halo 150**
- **Halo 250**

#### Predicted Target Coverage %
- IFNGR1: 100
- IFNGR2: 100
- STAT1: 100
- IL12B: 100
- IL12RB1: 100
- IKBKG: 37
- TYK2: 100
- CYBB: 99.9
- IRF8: 100
- ISG15: 100

**Pseudogene Prevents Full Coverage Design**
Addressing “Gaps” in Multi-Gene Panels

Genomic DNA → Enrichment → Target Genes → NGS Library Prep → Next Generation Sequencing → Bioinformatics → Interpretation

Genomic DNA → PCR → “Target Gene Gaps” → Big Dye Terminators → Sanger Sequencing → Bioinformatics → Interpretation
Multi-Gene Panel Diagnostics - Summary

Becoming a “New First Tier” Approach
- Application to a Growing Number of Inherited Disorders

Implementation Challenges for Laboratories
- Choosing a Technical Approach
- Assay Optimization and Data Analysis
- Scaling Gene Numbers Increases Interpretive Review Time
New Landscape of Genetic Testing

- Whole Genome
- Exome
- Multi-Gene Diagnostics
- Single-Gene Diagnostics

Increasing Complexity
Human Exome

~ 1.5% of the genome

~ 20,500 genes

“Repository” of Mendelian Mutations

“Journey to the Center of the Earth”
Jules Verne 1864
History of Exome Sequencing

“Genetic Diagnosis by Whole Exome Capture and Massively Parallel DNA Sequencing”

Choi et al PNAS 2009 – Congenital Chloride Diarrhea Gene

>150 Gene Discoveries
Recessive-Dominant-De Novo
April 2013

OMIM Database - April 2013
7401 Disorders with Known or Suspected Mendelian Inheritance

3,752 Disorders with Molecular Basis Known
Potential for Further Molecular Diagnoses is Large
Platform Options for Exome Sequencing

Illumina HiSeq 2000 or 2500

Ion Torrent Proton
Exome Sequencing Laboratory Workflow

Genomic DNA

Library Preparation

Next Generation Sequencing Library

Hybridize to Exome Capture Probes

Exome Enriched Library

Next Generation Sequencing

Bioinformatics Analysis
Exome Sequencing Read Data

Primary Sequence Alignment
BWA/Novoalign

Refined Sequence Alignment
GATK

Variant Calling
SAMTools/GATK

Variant Annotation
Annovar

FastQ File Format

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Workflow for Causal/Candidate Gene Identification

Annotated Exome Variants ~ 20,000

Prioritization by Heuristic Filtering
- Filter Out Common Variants
  - dbSNP/1000 genomes
  - Variant Frequency
- Pathogenicity Prediction Filtering
  - SIFT/PolyPhen
  - GERP

Prioritization by Likelihood Prediction
- Pedigree Information
- Genetic Linkage
- Intersects
- Variant Impact
- Prioritization
- Missense
- Nonsense/Frameshift/Splice Site/Indels
- Cross Reference Databases
  - HGMD/OMIM/Locus Specific

VAAST Algorithm

Candidate Variants/Genes
Several to Dozens
Causal/Candidate Variants/Genes

? Previously Implicated in Phenotype Known or Novel Genetic Variant

? Biologically Compelling Candidate Gene and Variant

Sanger Confirmation in Patient/Family

Correlation Studies Establishing Causality

Interpretive Report

Clinical Laboratory Testing

Genetic Screening Similar Phenotype Pts Controls

Functional Studies In vitro/In vivo
Criteria for Choosing Patients for Exome Sequencing

- Genetic Etiology Strongly Suspected
- Standard Testing Negative or Impractical
- Diagnosis Likely to Impact Treatment and/or Management Decisions
- Diagnostic Yield is Greater in Family Studies
  - Families with Multiple Affected Members
NIH Undiagnosed Disease Program – 2011 Report
5 Molecular Diagnoses in 30 Patients/Families (17%)
Several Compelling Candidate Genes

Exome Sequencing – “Diagnostic Yield”

Difficult to Determine [Yet]

Currently: Largely Single Case Reports
Anecdotal Series ~20-30% Diagnosis
Exome Sequencing – “Diagnostic Yield”

Diagnostic Yield Expected to Increase - By How Much?

Driving Forces

- Increasingly Sophisticated Bioinformatics Will Improve Variant Detection
- Growth in Knowledge Base of Disease Causing Genes and Variants

Conversion to Whole Genome Sequencing
- Filling in the Gaps
Exome Sequencing – Case Vignette

“Diagnostic Odyssey”

8th Century BC
Exomes for “Diagnostic Odyssey”

First Year of Life: Seizures/Dystonia
Third Year of Life: MRI with Leukodystrophy
Exomes for “Diagnostic Odyssey”

Dystonia
Leukodystrophy

Heuristic Filtering + VAAST + Interpretive Review

Top Three Candidate Genes

1 Recessive
2 X-Linked
X-Chromosome PLP1 (Proteolipid Protein 1) Gene Mutation

c.617T>A, p.M206K – Novel Mutation*
PMD = Pelizaeus-Merzbacher Disorder
Dysmyelination/Leukodystrophy
PLP1 Mutations

SIFT Score 0.01
Exome Sequencing – Summary

Powerful New Approach to Inherited Disorders
- Now Available as a Diagnostic in Several Referral Laboratories

Implementation Challenges for Laboratories
- Technically Demanding and Capital Equipment Intensive
- Complex and Evolving Data Analysis Requirements
- Diagnostic Yield Needs Management of Expectations
New Landscape of Genetic Testing

Increasing Complexity

Single-Gene Diagnostics

Multi-Gene Diagnostics

Exome

Whole Genome
Questions ?

voelkek@aruplab.com
Save the Date for These Upcoming FREE Webinars

- **In Vivo Microscopy**
  Tuesday, June 11, 10:00—11:00 AM Central
  - Gary J. Tearney, MD, PhD, FCAP, and Maria M. Shevchuk, MD, FCAP

- **Pediatric Genomic Medicine**
  Wednesday, July 17, 1:00—2:00 PM Central
  - Stephen Kingsmore, MB, ChB, BAO, DSc, FRCPath

- **Colon Cancer and Molecular Tests**
  Tuesday, September 10, TBD
  - Joseph Willis, MD, FCAP

Register by going to [cap.org/webinars](http://cap.org/webinars)
## CAP Learning – Transforming the Diagnostic Evaluation of Inherited Disorders with Next Generation Sequencing

<table>
<thead>
<tr>
<th>Course</th>
<th>Learning Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Next Generation Sequencing for the Clinical Laboratory CE/CME/SAM – 0.0</td>
<td>Next generation sequencing (NGS) is undergoing a translation from the biomedical research community into the clinical laboratory. Applications being developed and implemented include multigene panel testing, exome and whole genome sequencing for inherited disorders, and oncology and pathogen diagnostics. Because NGS is a relatively young and rapidly evolving technology, implementation in the clinical laboratory is challenging both at the technical and bioinformatics data analysis levels. In addition, establishing NGS in a clinical laboratory requires a considerable investment in infrastructure in terms of capital expenditures and personnel. In this context, a key ongoing bottleneck for clinical laboratories beginning to utilize NGS is data analysis due to the unique bioinformatics aspects. However, the barriers to implementation are starting to be lowered as a consequence of a greater diversity of platform options, automation, and bioinformatics tools. This seminar will provide an overview of current options and approaches for NGS-based diagnostics. Further, developing and implementing NGS for diagnostic applications in inherited disorders will be covered in greater depth.</td>
</tr>
<tr>
<td>Clinical Next Generation Sequencing: Just Another Lab Test CE/CME/SAM – 0.0</td>
<td>This webinar will briefly review the common techniques that are in current use for NGS, highlight the most common NGS platforms, and use case studies to demonstrate limitations of many existing bioinformatics software packages that can impact clinical NGS. Implications for cost and reimbursement will be featured. The presentation will not focus on minutia of interest (or intelligible) to only experts in the NGS field; instead, a broader discussion will take place of the conceptual issues that must be considered when NGS is performed in routine clinical practice.</td>
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# CAP Learning – Transforming the Diagnostic Evaluation of Inherited Disorders with Next Generation Sequencing

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| 02-20-13 - Implementing Next Generation Sequencing (NGS) as a Clinical Tool in the Laboratory – Materials CE – 1.0 | - Learn about a revolutionary new technology that is being applied for diagnostic medicine.  
- Recognize the complexities of the next generation sequencing (NGS) workflow.  
- Identify CAP’s activities in the NGS area.  
- Identify the standards developed by the CAP for the laboratory analytical wet bench and bioinformatics workflow for NGS.                                                                                                                                                                                                                   |
| Molecular Diagnosis of Acute Myeloid Leukemia: Present and Future Challenges CE/CME/SAM – 0.0 | While personalized molecular approaches to solid tumors continue to evolve, genetic information has long been critical in the diagnosis and classification of acute myeloid leukemia (AML). This webinar will review the development of current diagnostic tools that further refine the distinct subtypes of AML, with a practical focus on questions likely to occur in the setting of a general pathology practice, including: How can molecular data be used to guide patient care? Which patients need molecular testing? Which genes should be evaluated and by what methods?  
In addition, the presenters will give an update to the 2008 WHO classification, including new information on established targets and novel gene mutations likely to impact clinical practice in the near future. Finally, we discuss the revolutionary changes coming to molecular diagnosis of AML in the dawning era of next-generation sequencing. |
The CAP Learning Portal includes content and tools designed to support the learning needs of pathologists. A user must login to cap.org in order to access the portal. In the portal, you will find:

- Learning Options search/catalog
- Competency Model for Pathologists
- Personal Progress Check
- My Learning Plan
- Help Center (Guides, Video, FAQs)

Benefits:
- Increase effectiveness to plan and manage learning
- Increase efficiency to target learning needs and identify premium learning solutions
- Increase satisfaction with learning solutions that meet specific learner needs
- Increase capability to maintain professional certifications
To learn more...

- For more details and to register for/access educational offerings:
  1. Log in to the cap.org website
  2. Click on the “Learning Portal” tab.
  3. Click on the “Browse Our Learning Catalog” tab
  4. Type your desired topic in the “Search” box or make a selection from the list provided.
     A list of available learning options displays
A New CAP Tool- Short Presentations On Emerging Concepts (SPECs)

- Pathology SPECs are:
  - Prewritten PowerPoint presentation on emerging topics where molecular testing plays a key role in patient management.
  - Designed for pathologists to customize and use for educating other physicians and health care leaders in their communities.
  - Focused on molecular tests that are actionable to patient care today.

- Now Available:
  - Emerging Concepts in the Workup of Colorectal Cancer
  - Emerging Concepts in Therapeutic Guidance for Metastatic Melanoma
  - Emerging Concepts in the Diagnosis and Workup of Thyroid Cancer
  - Emerging Concepts in Colorectal Cancer Hereditary Non-Polyposis Cancer (Lynch Syndrome)
  - Emerging Concepts in the Workup of Polycythemia and Thrombocythemia: JAK2

- To register, go to the [CAP Member tab](http://cap.org). You do not need to be a member to utilize this free tool.
A New CAP Tool - Pathology Resource Guides

The CAP has created the Pathology Resource Guides, a new tool to assist pathologists in understanding key emerging technologies. These Resource Guides are a new CAP member benefit available at no charge.

Molecular Diagnostic (single gene, small panel)
Genomic Analysis (large molecular panels, exome, genome)
Digital Pathology
In Vivo Microscopy

Register through the CAP member tab. You will receive periodic updates for two years.

Questions? Contact capguides@cap.org.
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  o Getting insights and feedback from peers
  o Accessing CAP resources
  o Keeping informed on professional issues

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Be there

CAP 2013 Policy Meeting
May 6–8, 2013
cap.org/advocacy

Engage Connect Influence
See, Test & Treat® brings cancer screenings to women in need!

- See, Test & Treat is a CAP Foundation-funded program that brings free, same-day cervical and breast cancer screening, diagnoses and follow-up care to women in medically underserved communities across the U.S.

- CAP member pathologists’ partner with gynecologists, radiologists and other medical professionals to lead See, Test & Treat programs in hospitals, clinics and other facilities.

- Women learn the importance of preventive care through annual exams, a Pap test, Mammogram and a healthy lifestyle.

See, Test & Treat Needs Your Financial Support. Visit foundation.cap.org and click on DONATE!
THANK YOU!

Thank you for attending our webinar “Transforming the Diagnostic Evaluation of Inherited Disorders with Next Generation Sequencing” by Karl V. Voelkerding, MD, FCAP.

For comments about this webinar or suggestions for upcoming webinars, please contact Jill Kaufman, PhD, Director of Personalized Health Care at jkaufma@cap.org

NOTE: There is no CME/CE credit available for today’s free webinar.