Welcome to the PHC Webinar Series on "Hot Topics in Pathology"

This lecture on **"Clinical Use of Whole Genome and Whole Exome Sequencing Today"** presented by David Bick, MD and Paula E. North, MD, PhD 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!

David Bick, MD

- Professor of Pediatrics and Obstetrics & Gynecology at Medical College of Wisconsin
- Section Chief of the Division of Genetics in the Department of Pediatrics at Medical College of Wisconsin
- Medical Director, Genetics at Children's Hospital of Wisconsin
- Director of the Advanced Genomics Laboratory in the Department of Pediatrics at the Medical College of Wisconsin

Paula E. North, MD, PhD FCAP

- Professor of Pathology, Traditional Pathway, Medical College of Wisconsin (MCW)
- Chief of Pediatric Pathology, Department of Pathology, MCW
- Medical Director of Pathology and Laboratory Medicine, Children's Hospital of Wisconsin
- Associate Director of the Children's Research Institute (CRI)
- Director of three research-supportive CRI Core facilities (Histology, Imaging, and Pediatric BioBank/Tissue Analytical Core)

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Clinical Use of Whole Genome and Whole Exome Sequencing Today

David Bick, MD and Paula North, MD, PhD

December 14, 2011

Topics

- David Bick
  - First clinical case at Children's Hospital of Wisconsin/Medical College of Wisconsin (CHW/MCW)
  - WGS program initiated in 2010 at CHW/MCW
  - Key counseling issues

- Paula North
  - WGS vs WES
  - Quality management strategies
  - Technical challenges in a CAP/CLIA environment
    - Instrumentation
    - Software
    - Reporting

Disclosures

The following relationship(s) exist related to this presentation:

- Children's Hospital of Wisconsin (CHW) and Medical College of Wisconsin (MCW) provide whole genome sequencing (WGS) for clinical use, and the patient is billed for these technical and professional diagnostic services.
- WGS is not an FDA approved test; the FDA has determined that such approval is not necessary.
- Testing (sequencing and analysis) is performed in a CLIA/CAP approved laboratory.

- Audience participation:
  - Information collected today by polling the audience may be used be used in future presentations & publications.
  - All information collected is anonymous.
  - You are not required to participate in the polling process.

[1]Footnote: Century Gothic, 9 pt, sentence case

Whole Genome Sequencing (WGS) & Whole Exome Sequencing (WES) is in clinical practice

Genome sequencing heralds new era in medical diagnostics

The University of Oxford and Illumina, a leading manufacturer of sequencing systems have announced a project that will push the boundaries of genome research into more generalised medical practice as the genomes of 500 people with a range of diseases – including cancer, immunological disorders, and rare inherited diseases – are to be sequenced in full detail. The results could have potential for offering diagnosis and treatment outcomes for individual patients in the future.

"It is a really exciting opportunity to explore the po generation sequencing into the clinic," said Professor Peter Donnelly, Director of the Wellcor Genetics at the University of Oxford. "Overall, we different conditions – we want to cast the net as learn the areas in which sequencing can make

Baylor College of Medicine offers Whole exome sequencing:

BCM-MEDICAL GENETICS LABORATORIES
WHOLE GENOME LABORATORY
PHONE: 800-411-GENE | FAX: 713-798-2787 | www.bcmgeneticlabs.org

WHOLE EXOME SEQUENCING REQUISITION (TEST CODE: 1500)

PATIENT INFORMATION

NAME: _____ _____ _____
LAST NAME FIRST NAME MI

DATE OF COLLECTIO

HOSPITAL#:

DATE OF BIRTH: ___ / ___ / ___
MM DD YY

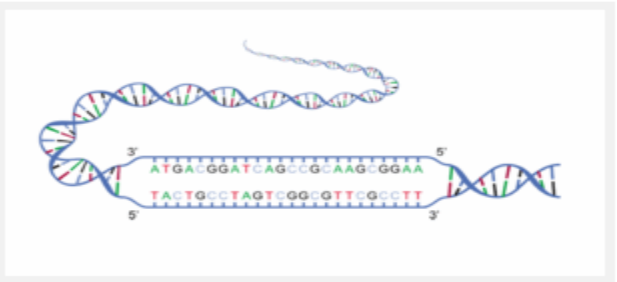
GENDER (Please select one): ☐ FEMALE ☐ MALE ☐ UNKNOWN

SAMPLE TYPE (Pleas

The Future Is Now: 23andMe Now Offers All Your Genes For $999

5 comments, 3 called-out + Comment now

Call it a dramatic sign of how far the field of genetics has come: Google-backed startup 23andMe is now offering consumers the ability to get their genes sequenced for $999.



WGS/WES is now in clinical practice

CENTER FOR PERSONALIZED GENETIC MEDICINE

HARVARD MEDICAL SCHOOL

Partners HealthCare System, which is affiliated with Harvard Medical School and includes Massachusetts General Hospital and Brigham and Women's Hospital, has enrolled its first family in the sequencing program and plans to follow the pilot effort by introducing the technology to its hospitals early in 2012.

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CLINICAL DIAGNOSTIC EXOME™

Ambry Genetics First to Offer Exome Sequencing Service for Clinical Diagnostics

ALISO VIEJO, California - September 29, 2011 - Ambry Genetics today announces that it is the first laborator
provide CLIA-approved exome services for applications in clinical diagnostics. After comprehensive review b
Ambry's staff of geneticists and medical directors, these results will allow clinicians to diagnose affected

Polling Question #1

Would you want to have your genome sequenced?

- yes
- no

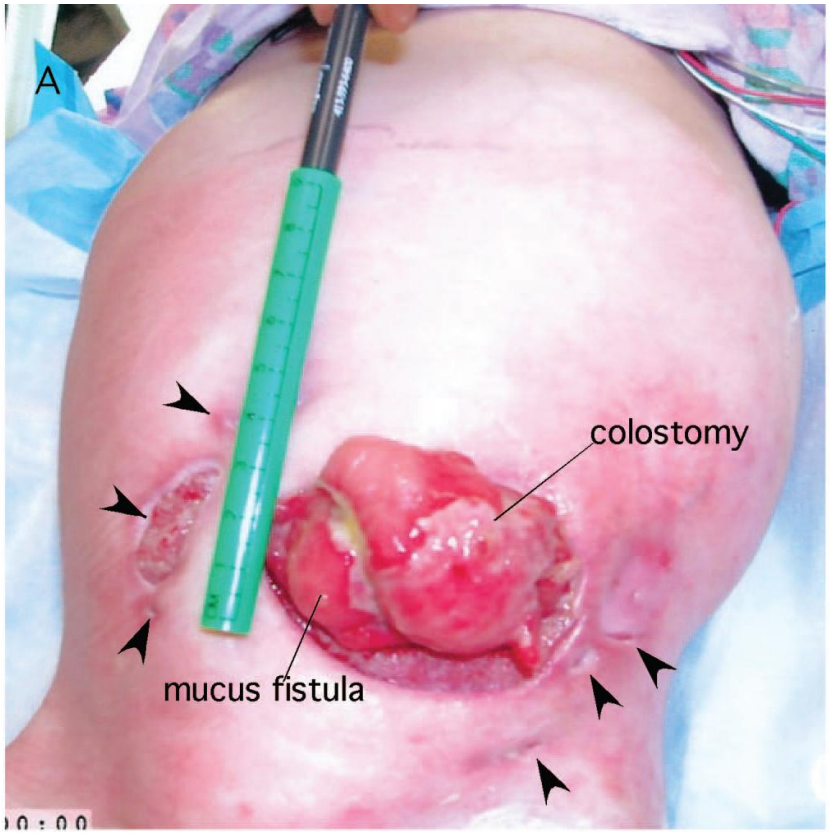
Polling Question #2

Education?

1. Pathologist
2. Non-pathologist attending MD
3. Medical student, resident or fellow
4. Ph.D.
5. Laboratory staff

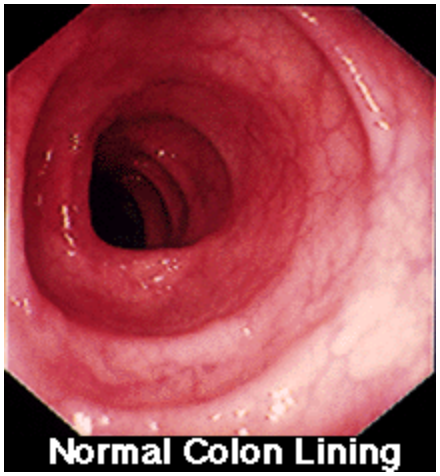
Nic's story

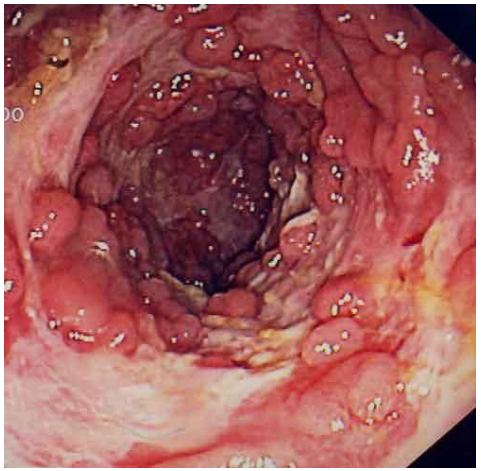
- Presented at 15 months: poor weight gain and a perianal abscess
- Progressed: Inflamation entire colon & developed fistulae to the skin
- Severe Crohn's
- Bowel rest, immunosuppression and other rx - failed
- In 3 yr: 142 anesthesia for various surgeries and treatments



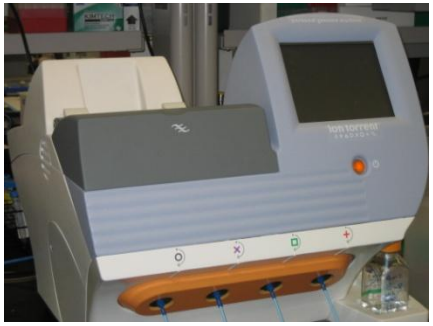
Difficult to treat a condition if you do not know the cause

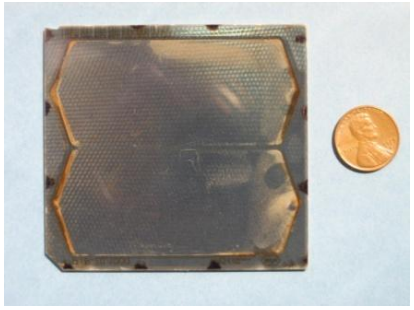
- The cause of Crohn's disease is unknown
  - chronic inflammatory reaction of the intestinal mucosa directed against microbiota of the gut in genetically susceptible individuals
  - Identified over 50 susceptibility genes
  - Immune system 'over-reacts' to gut flora
  - Medications suppress the immune system
- Nic's severity required a different approach
  - Sequence the genome
  - Hope to find a treatable genetic disorder

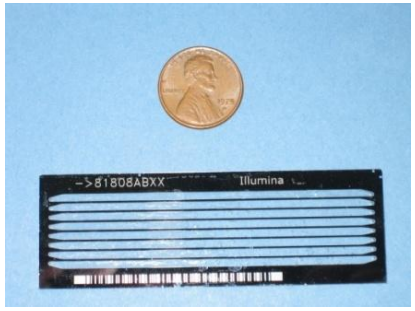


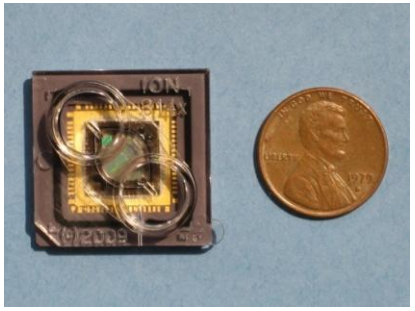


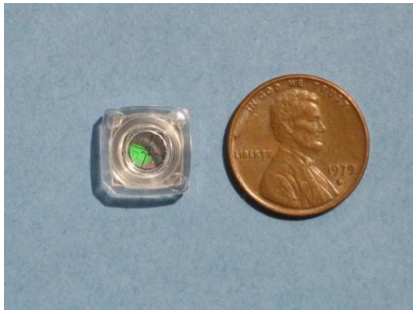
Next – generation (NexGen) sequencing also called massively parallel sequencing











Roche – 454 sequencer	Illumina – Hi-Seq	Life Technology – Ion Torrent	Pacific BioSciences - RS
500 Mb for $15K	9000 Mb for $15K	19 Mb for $99	32 Mb for $50
2nd generation	2nd generation	3rd generation	3rd generation

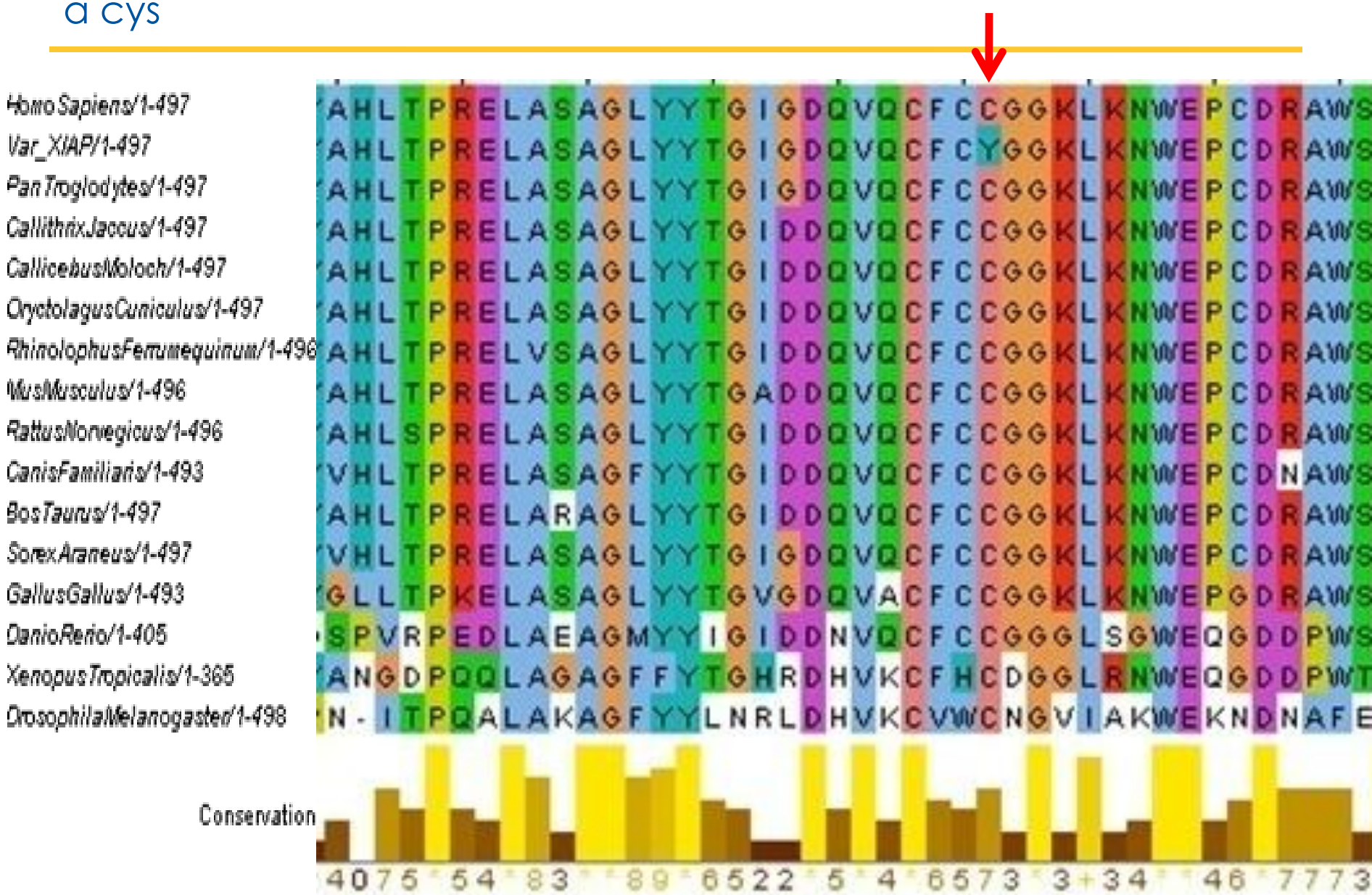
Analyzed Nic's Exome

- 16,124 variants (SNP, small dup, small del)
  - Map to reference genome
- 7,157 non-synonymous (changed an amino acid)
  - Filter thru variant database – dbSNP
- 878 novel variants (not in dbSNP)
  - Unaffected parents – filter for recessive & X-linked
  - Filter thru programs that predict whether change damages protein function
- 136 genes
  - Filter AA change based on evolutionary conservation program

More analysis

- 35 genes
  - Filter for genes that are not frequently inactive in the general population
- 5 genes
  - Filter for genes know to cause disease that are biologically relevance to patient
- 1 gene: XIAP - an X-linked disease
  - Developed an informatics package to do this – analysis took months!

Phylogenetically conserved AA in XIAP – Nic had a tyr instead of a cys



XIAP (inhibitor of apoptosis protein 3) mutations cause X-linked lymphoproliferative (XLP) syndrome

- Fatal or near-fatal EBV infection - lymphadenopathy, hepatosplenomegaly, fulminant hepatitis, hepatic necrosis, and profound bone marrow failure
- Hypogammaglobulinemia
- Lymphomas (cancer of lymphocyte) or other lymphoproliferative disease
- 70% of individuals with XLP die by the age of 10 years
- Only possible cure is a bone marrow transplant
- **Nic's symptoms did not match so XLP was not considered!!**

Nic had a bone marrow transplant – all of his findings resolved

MCW/CHW Whole Genome Sequencing program started summer 2010

- Goal: Clinical utilization of WGS for diagnostic purposes in a pediatric population
- Purpose: Define molecular etiology of complex, rare, likely monogenic diseases for medical decision-making
  - Employ whole genome sequencing
- Key to success: Senior leadership of CHW & MCW involved at the beginning

MCW/CHW WGS Program

- Case Nomination
- Review Committee – MDs, ethicists, scientists
  - Assure that all reasonable testing already done, testing will advance clinical care and is medically necessary
  - 41 reviewed, 14 in process
- Genetic counseling

Counseling regarding results

- Primary Result (1°)
  - Likely pathogenic change(s) felt to be responsible for the patient's phenotype

- Secondary Result (2°) or "incidental finding"
  - Result likely *unrelated* to the patient's phenotype
  - BUT felt to cause a different disease/greatly increase risk for a different disease

Incidental findings:
Sequencing finds a genetic condition that was unexpected

- 'Medically actionable':
  - refers to a variant in a gene where knowledge of the particular variant will affect medical decision making such as initiation of a treatment
- 'Not medically actionable':
  - refers to variants that increase the individual's risk for a disease where no treatment is proven to significantly change medical decision making.

Examples – childhood onset

Medically actionable

- Biotinidase deficiency
  - unable to recycle the vitamin biotin
  - Seizure, hypotonia, ataxia, developmental delay
  - Biotin rx prevents all problems
  - Childhood onset – treatable

Medically not actionable

- Tay-Sachs disease
  - Hexosaminidase A deficiency
  - Unable to degrade glycosphingolipid GM2 ganglioside in the brain
  - progressive neurodegeneration
  - starting at 6 mo of age
  - Death before age four years
  - Childhood onset – not treatable

Examples – adult onset

Medically actionable

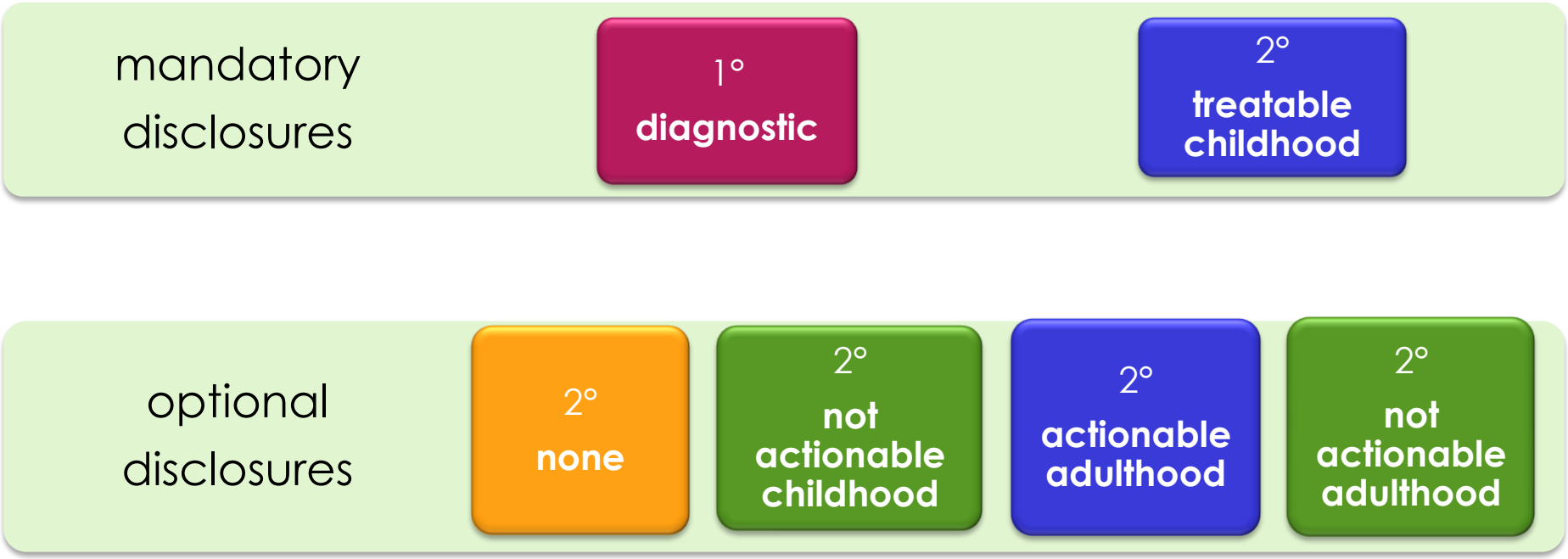
- BRCA1 – autosomal dominant breast and ovarian cancer
  - Common before 50 yo
  - 57% breast by 70 yo
  - 40% ovarian by 70 yo
  - Can has mastectomy & oophorectomy
    - Reduces risk 90%
  - Adult onset – treatable

Medically not actionable

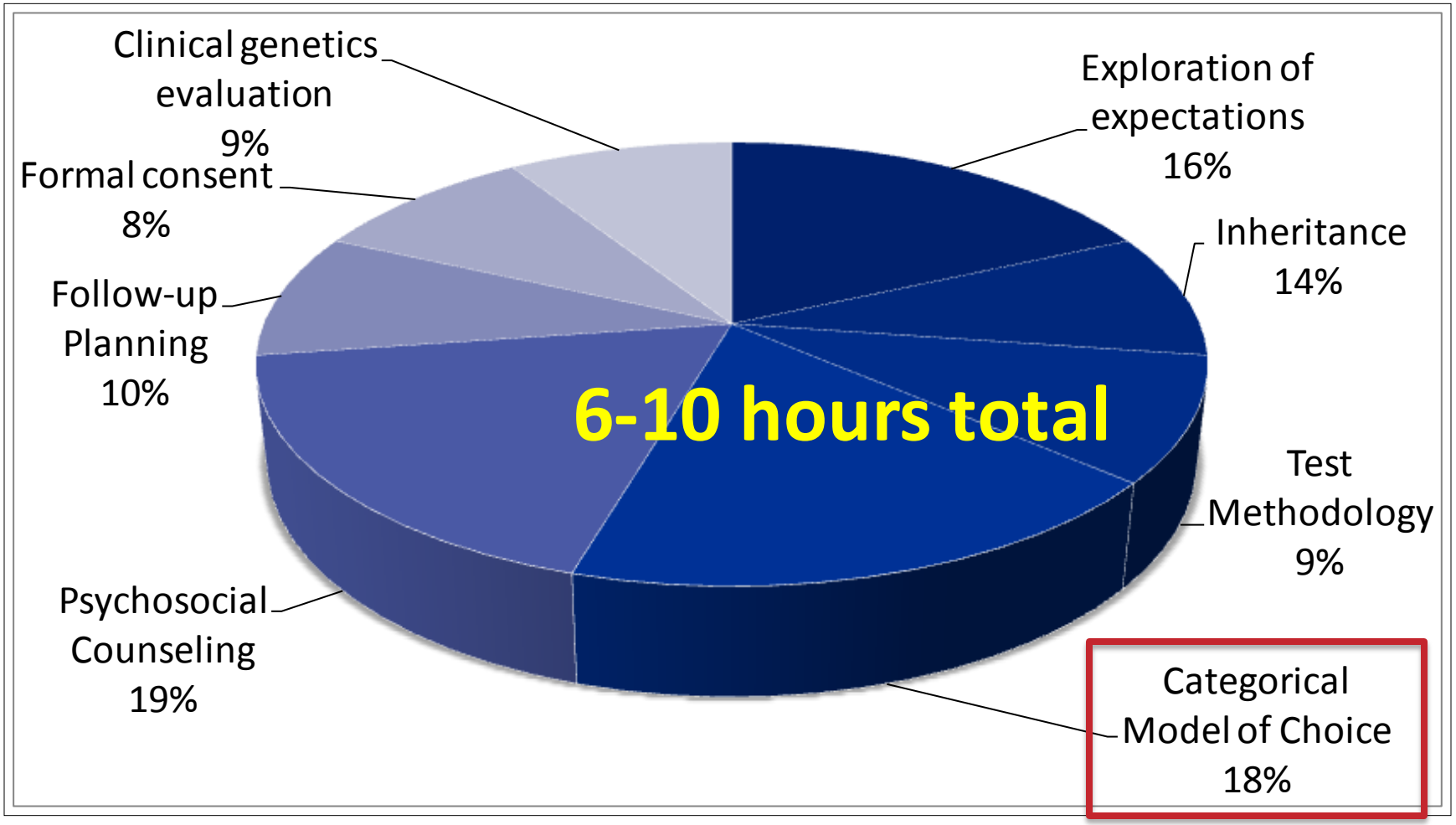
- Familial Alzheimer – autosomal dominant
  - PSEN1, PSEN2, APP
  - Onset in 40's & 50's
  - Severe memory failure eventually incapacitating
  - Confusion, poor judgment, language disturbance, agitation, withdrawal, hallucinations
  - Adult onset – not treatable

Sequencing a child can give information about the parents !

Categorical Model of Choice



Counseling Time



Polling Question #3

Your child is having their genome sequenced. Would you want to be told of an incidental finding that is childhood onset & treatable (e.g., Biotinidase def.)?

1. yes
2. no

Polling Question #4

Your child is having their genome sequenced. Would you want to be told of an incidental finding that is childhood onset & not treatable (e.g., Tay-Sachs disease)?

1. yes
2. no

Polling Question #5

Your child is having their genome sequenced. Would you want to be told of an incidental finding that is adult onset & treatable (e.g., BRCA1 – early onset breast cancer)?

1. yes
2. no

Polling Question #6

Your child is having their genome sequenced. Would you want to be told of an incidental finding that is adult onset & not treatable (e.g., Familial Alzheimer – autosomal dominant)?

1. yes
2. no

Who should decide?

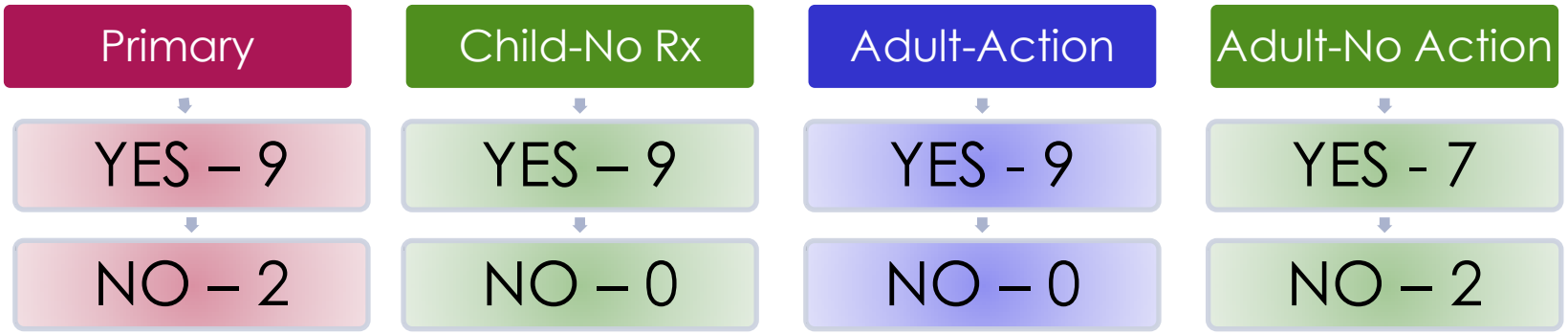
- A parent decides to find out about adult onset diseases in their child
- Now the child has lost the right to decide NOT to know
  - Perhaps a parent will not leave an inheritance to the child who will develop Alzheimer disease
  - Perhaps the child would not want to know that they will get Alzheimer disease

Polling Question #7

Your child is having their genome sequenced. Should you be excluded from knowing an incidental finding that is adult onset & not treatable (e.g., Familial Alzheimer – autosomal dominant)?

1. yes
2. no

Decision-Making
Parental Decisions



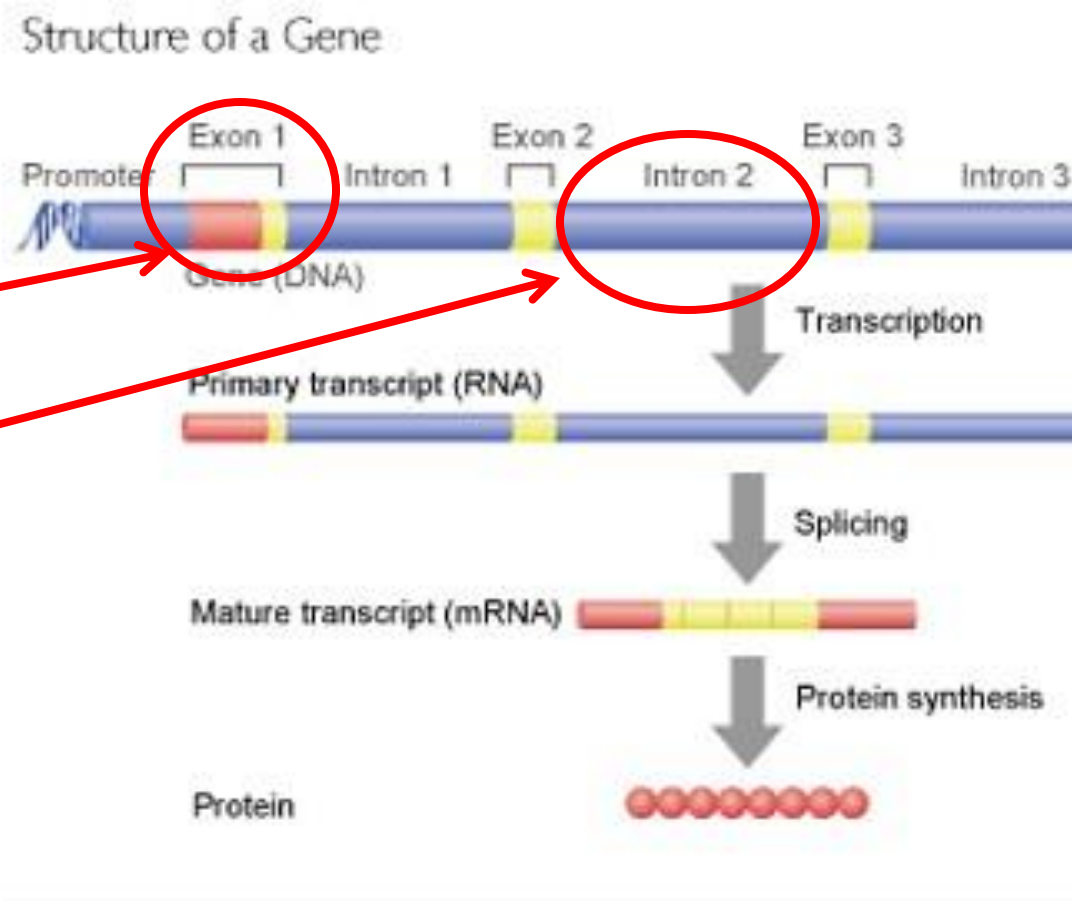
Families have follow up each year because their decision may change and variant may change categories

Laboratory Considerations in WGS/WES

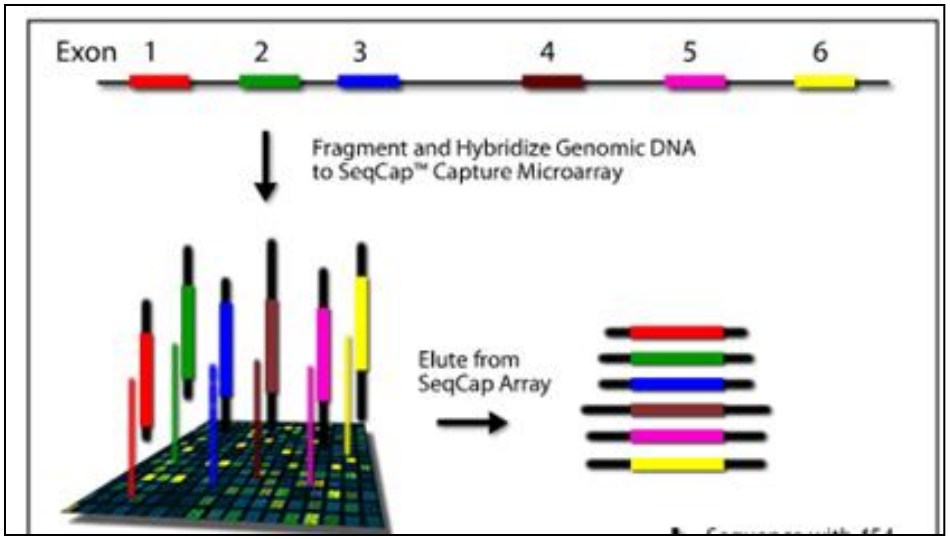
- WES vs WGS
- Considerations in a CAP/CLIA environment
  - Instrumentation
  - Software
  - Reporting
  - Quality Management

Exome sequencing – sequence of the coding region

- Human Genome: 20K to 25K genes
- Genes
  - Genes composed of exons that code for AA of a protein
  - Introns are spacer regions that are spliced out
  - Can interpret a change in AA sequence such as an Arg to a stop codon

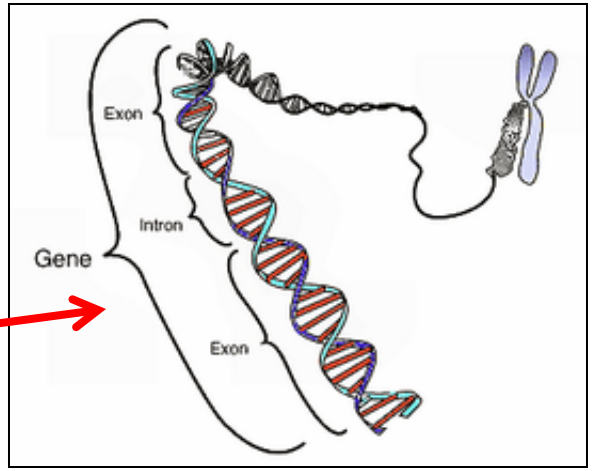


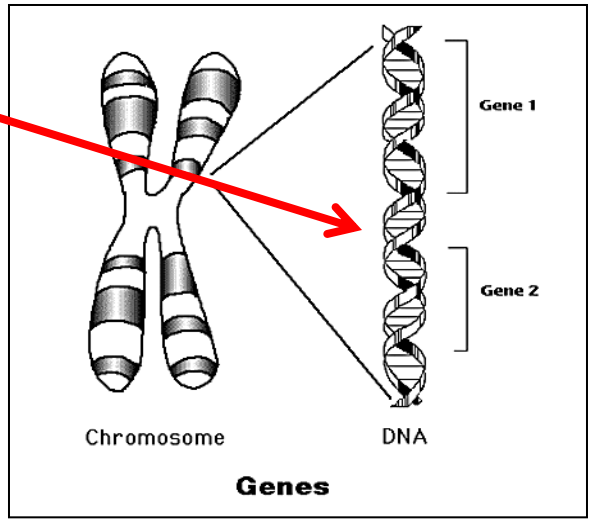
- Exons are shown as colored part of gene
- Capture array has complementary sequence of each exon bound to solid support
- Single strand DNA of exons hybridize
- Selected DNA sequenced
- 1% of the genome



Whole genome sequencing (WGS)

- Human genome = 3.1 billion base-pairs
- WGS – determining the sequence of an individuals genome
  - Includes sequence of the genes – exons & introns
  - Includes sequence of regions between genes





WES vs WGS

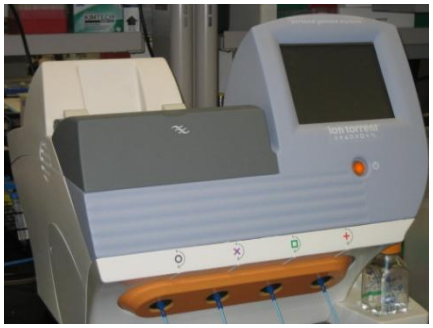
Advantages of WES

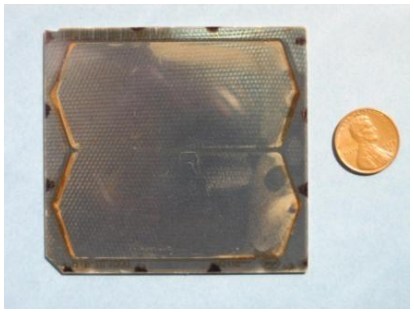
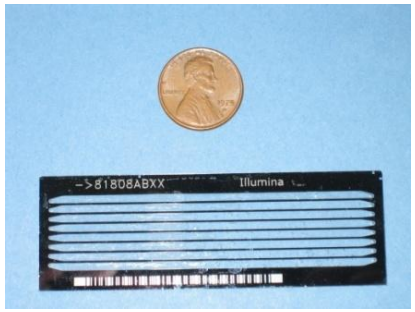
- Exome is 1% of genome
  - WES costs much less than WGS
- Exome includes only the coding region
  - Tools to interpret changes best developed for exons

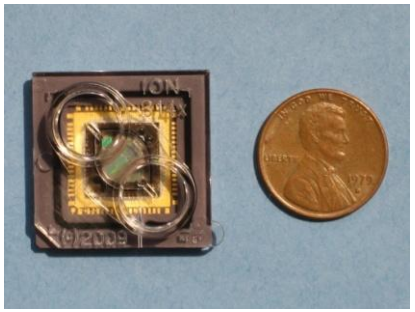
Advantages of WGS

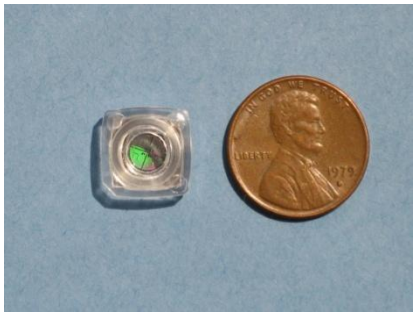
- WGS has better coverage
  - Exome capture array does not capture all exons
- Certain parts of introns and regions between genes can be used to make a diagnosis of disease

How does it work?
Next Generation (NexGen) technologies produce millions of short lengths of DNA sequence





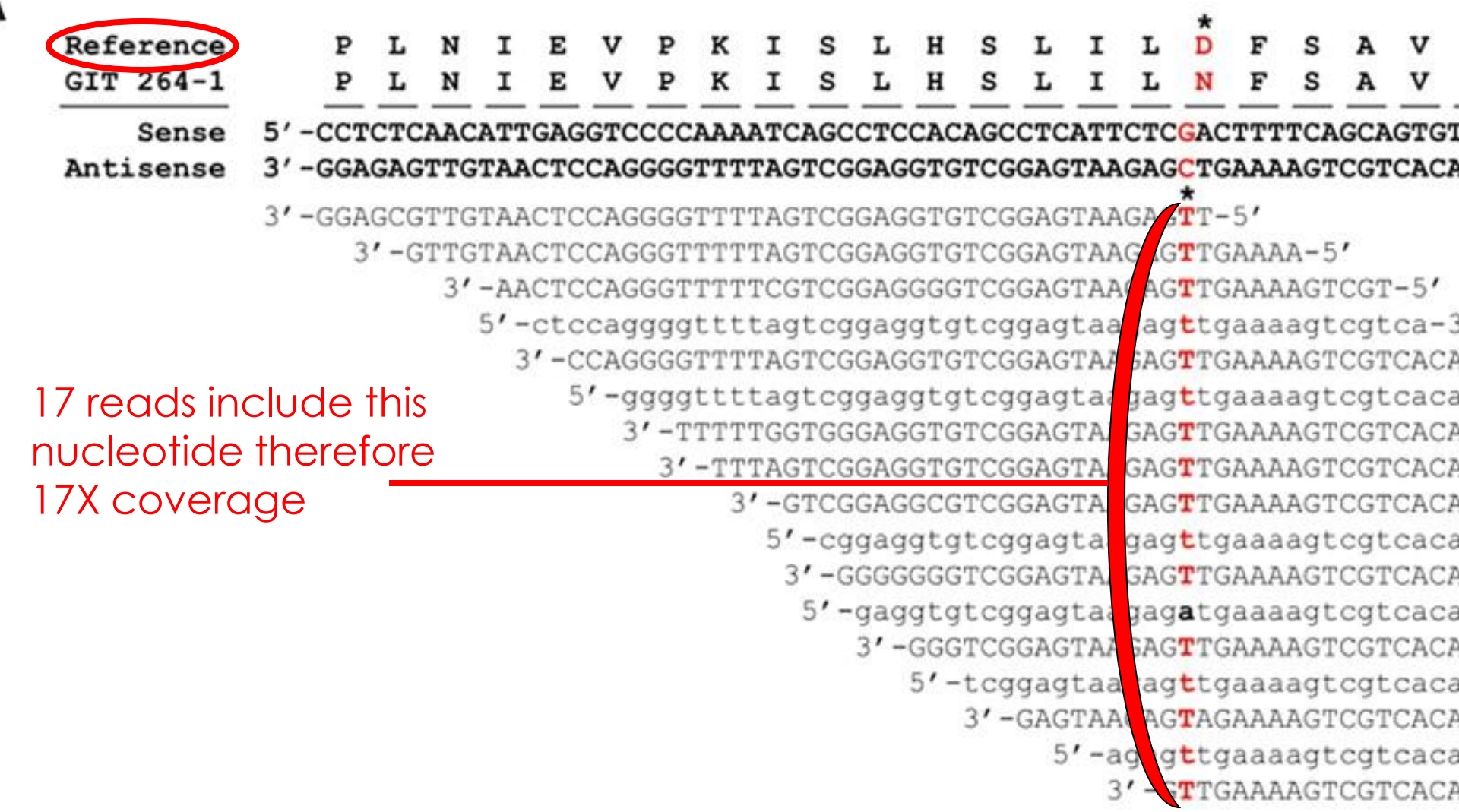
Roche – 454 sequencer	Illumina – Hi-Seq	Life Technology – Ion Torrent	Pacific BioSciences - RS
500 Mb for $15K	9000 Mb for $15K	19 Mb for $99	32 Mb for $50
2nd generation	2nd generation	3rd generation	3rd generation

A short length of sequence is called a read

- Example: Illumina Hi- Seq
- Each read is 100 bp
- 160M of these reads!
- Jigsaw Puzzle….
  - Need to connect sequences to each other

1	1	203	322	TGAAAAATTAATGAAATATATGCTATCCGCTCACAC
1	1	229	353	TTAAGATTTTAAATTATTTAGGGTGCATCAGCTTCC
1	1	110	436	TATAAGTTAATATTGTGTATAACCTTTTAGCCACAC
1	1	211	303	TTCTTAACAGGGTGAGTTCCCTGGTTATCCAATACC
1	1	99	329	TTTTATACTTCATGGTTTTTGTGGTGTCAAAAATCT
1	1	221	277	GAATGTATTCCAATATCAAAGAGCAAATTCCACCAC
1	1	225	370	TGATAAGTATAAGTGATTATTGTAATTATGTTTGAG
1	1	243	244	GTTGAACATTCCTTTTCATAGAGCAGTGTTGACACA
1	1	186	360	TATACCACTGTGCATGTTAATAAACGAGGTTGTTTG
1	1	167	333	TAGATAGCTAGGTTGGGAAGTGAAATGATCAGCTTT
1	1	213	333	TTAAAAAAAAAGAAAAAAAAAAGAAAACTAGGCTAC
1	1	244	338	TTCTTTTGTTCCCTAACCTGCCGGACTCCTTCCCAC
1	1	120	382	TAATTTTTATGTTTTTGTAGAGATGGGGTTTCTCCG
1	1	117	201	TCTTTAAAGATCTTTCCGGACACTTTTGGAAAAGAG
1	1	232	321	GATGCATTGCTATGCCTCCCAGTCCGCAACTTCACG
1	1	205	318	TACCCCTTGACTCTTCTTTTGTTACCATTTTTCCCC
1	1	102	449	TTTCAAATTATTATTTATTGCTCATTGTGTTTTTTG
1	1	209	276	TATTCAAAAACAATTTGTTTAAATTTAAAAATGAAC
1	1	197	309	TCATATGAAGCAAATTGTTTTGATCAACTCTCATAT
1	1	209	341	TATGCAAGGAAACAGTTCGCGATGCTCCCGTTTGCG
1	1	201	239	TTTCAATATATGCAGTCTGGTTCCAGAGTTTTTAAT
1	1	247	502	TCTCAATTTGCTATTGTAGTTATTGTTTTACTGTTG
1	1	119	420	GGTGAAGAAACAAAGGCCTGCAAAGTTCCTTCCTAC
1	1	323	445	TTAAGGTACTCAGCACTTTCTACGGCATTACGCGGG
1	1	244	254	GTTAAGTTTGGCCTCTTGCCTGGCATCACTTGCCTT
1	1	233	321	GGACAATTGCAATGCTCACAATTCGGAAACTTCCGC
1	1	95	416	TGGTTGGTACATTTCACATAAATGGAATCACATAAT
1	1	100	587	TAATGTTAAACTGTTAATAATGCTTGCTCCCAGGAA
1	1	119	481	GAACCCAGAAATCACACCTCAGTTTATCCTGGGCCT
1	1	239	312	GGAACCGTCTTCGACTGTGCCGCCTGACGCAAAGGC
1	1	101	312	TGGACAAAGAAGGTGTCTGGGCAATAGAAACAGTGT
1	1	145	341	TCTTCTTGTAAATTTGTTTTAAGTTTTTTATATATG
1	1	530	242	ACCCACACAACTGAACCCACATCACATGACAAGACT
1	1	224	220	TGTTTGTTGAACTCCCGTCATATTGGCTCCCTTGCT
1	1	364	491	TATCTCTTCGTAGCCCCTCTGTGTATGTTCTTCCTC
1	1	214	608	GTTGTGATTGCTCATTAAGACTCTGAACAATACTCA
1	1	196	533	TTCTACGTGTGGCCTTCAGTACTTTTCTTGGGCCTT
1	1	174	351	TCGACGCCGTTTCCCTTCGGGTCCACACGGTGTTTG
1	1	116	344	GAATTGAATCAATTCGGAGACTGTGCGATCGGCCGC
1	1	215	533	TAAGTGTCTATCACGGCCAAGACGCAGGCTGGGTGC
1	1	223	207	TTCTGTTTAAATGCTTGTTCGATGGCTTGTTAGAAG
1	1	121	377	GGCGGGGCGGGGGAGACGCCGGGCCCAGCCCGCCCC

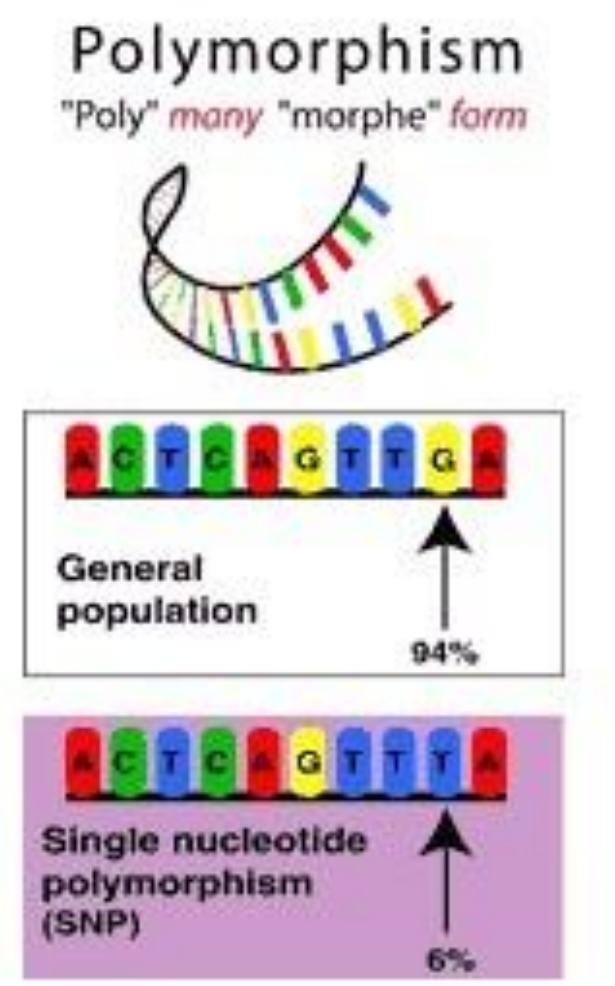
Aligning each 'read' against sequence of reference human genome



17 reads include this nucleotide therefore 17X coverage

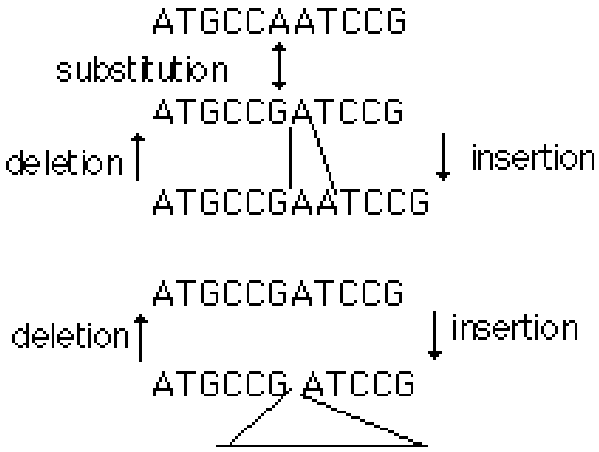
Major challenges to the use of genomic data

- There is no reference/normal human genome
  - More than 2 million SNPs are different between any two unrelated individuals
  - Software cannot map all reads
- NCBI (National Center for Biotechnology Information) maintains:
  - Reference assembly of the human genome that is derived from many individuals
  - Databases of variants



Other challenges

- The current reference human genome (called Hg19 or Build 37) has 250 gaps
- Much variation not in Hg19
  - WGS can end up with unmapped reads
  - Read with an insertion or deletion may not map to ref genome
- Ref genome & database of variants improving
- Current NexGen devices works well for single bp substitutions
- Others variation problematic



- Partial list of genomic variants and structures
  - Single base-pair substitutions
  - Insertions
  - Deletions
  - Adjacent insertion and deletion
  - GC rich regions
  - Trinucleotide repeats
  - Copy number variants
  - Homopolymer tracts
  - Translocations
  - Inversions
  - Short tandem repeats
  - Pseudogenes
  - Highly polymorphic regions (e.g. HLA locus)

Instrumentation considerations

- Roche 454, Life Technologies SOLiD, and Illumina most frequently used
  - Each with pros/cons
  - Machines generate reads & quality score for each nucleotide of each read
  - Reads mapped to human genome
  - Differences between the reference human genome and the patient recorded in a file: variant file
- Clinical laboratory: validation
  - Must validate the test for each type of variant that the system is designed to detect
  - Include DNA isolation, library preparation, sequencing run and data analysis
  - Validate using samples with known mutations
- Clinical laboratory: controls in each run and proficiency testing

Unresolved instrument issues

- Manufacturers frequently improve reagents and steps in the process
  - Changes require re-validation before clinical use.
  - This re-validation is expensive.
  - As an option, a lab can send the sample to a CAP/CLIA lab for sequencing then analyze the resulting variant file in-house.
- Currently there are no reference materials for validation, proficiency testing or quality control for each run
  - Labs currently choose samples from their own institution or Coriell Institute
- Clinical Laboratory: establishing precision
  - Repeatability - testing sample multiple times
  - Reproducibility – testing by multiple operators during different runs
  - The optimal number of runs and samples is not established.

Software considerations

- Each manufacturer uses different program for
  - Nucleotide quality score
  - Mapping reads to human genome
  - These are frequently updated & require revalidation
- Depth of coverage
  - An error can occur in a nucleotide in a read
  - Must have a number of reads with same result at a nucleotide
  - Entire genome not covered evenly by reads
  - Test accuracy depends on depth of coverage
- Sensitivity & Specificity
  - Need to assess variants across entire genome in each run
  - Labs currently compare SNP array data from patient with NexGEN results from patient

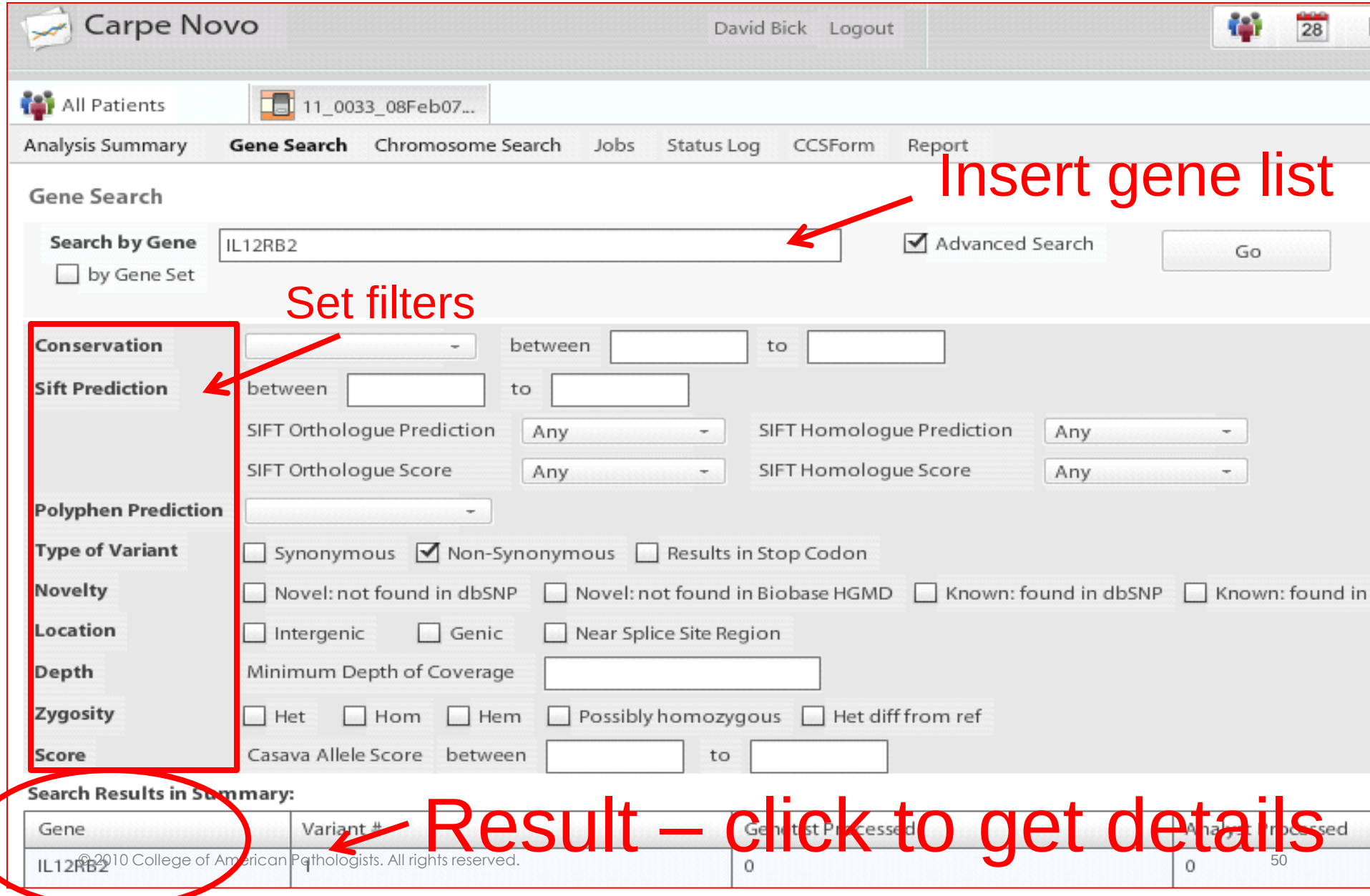
Unresolved software considerations

- Adequate depth of coverage for a given nucleotide has not been established
  - Recent study suggested 95% of genome is callable at 40X average coverage
- Reference materials composed of read files can be used for software validation, quality control and proficiency testing
  - Currently labs used variant tables from other laboratories

Evaluation of variants generated by instrument/software

- Each variant evaluated info in a variety of databases & prediction software:
  - Known mutations
    - Human Gene Mutation Database
    - Online Mendelian Inheritance in Man
  - Stop, readthough, missense
    - NCBI , Ensembl
    - SIFT, Polyphen2
  - Splice-site
    - GeneSplicer
  - Evolutionary conservation
    - PhastCons
  - Novel /rare variants
    - dbSNP, Exome Variant Server

Tools combined in Carpe-Novo interface



Reporting results

- Recommend confirmation with another method (Sanger sequencing, qpcr…)
- Patients/Families provide input to lab regarding reporting 'incidental findings'
- Start with a list of genes connected to patient's phenotype
  - Expand to entire genome if this fails
  - This can limit the 'incidental findings'
- Report genes that have insufficient coverage
  - 7X coverage of a nucleotide has >0.99 theoretical power to detect a heterozygous allele in a di-allelic system
  - This process can generate a 'reportable range' for a patient's genome
  - Allows physician to know what genes were not covered
- Reference range = types of variation NexGen finds
  - At present: only single nucleotide substitutions
- Errors in research literature for disease causing variants

Polling Question #7

Would you want to have your genome sequenced?

1. yes
2. no

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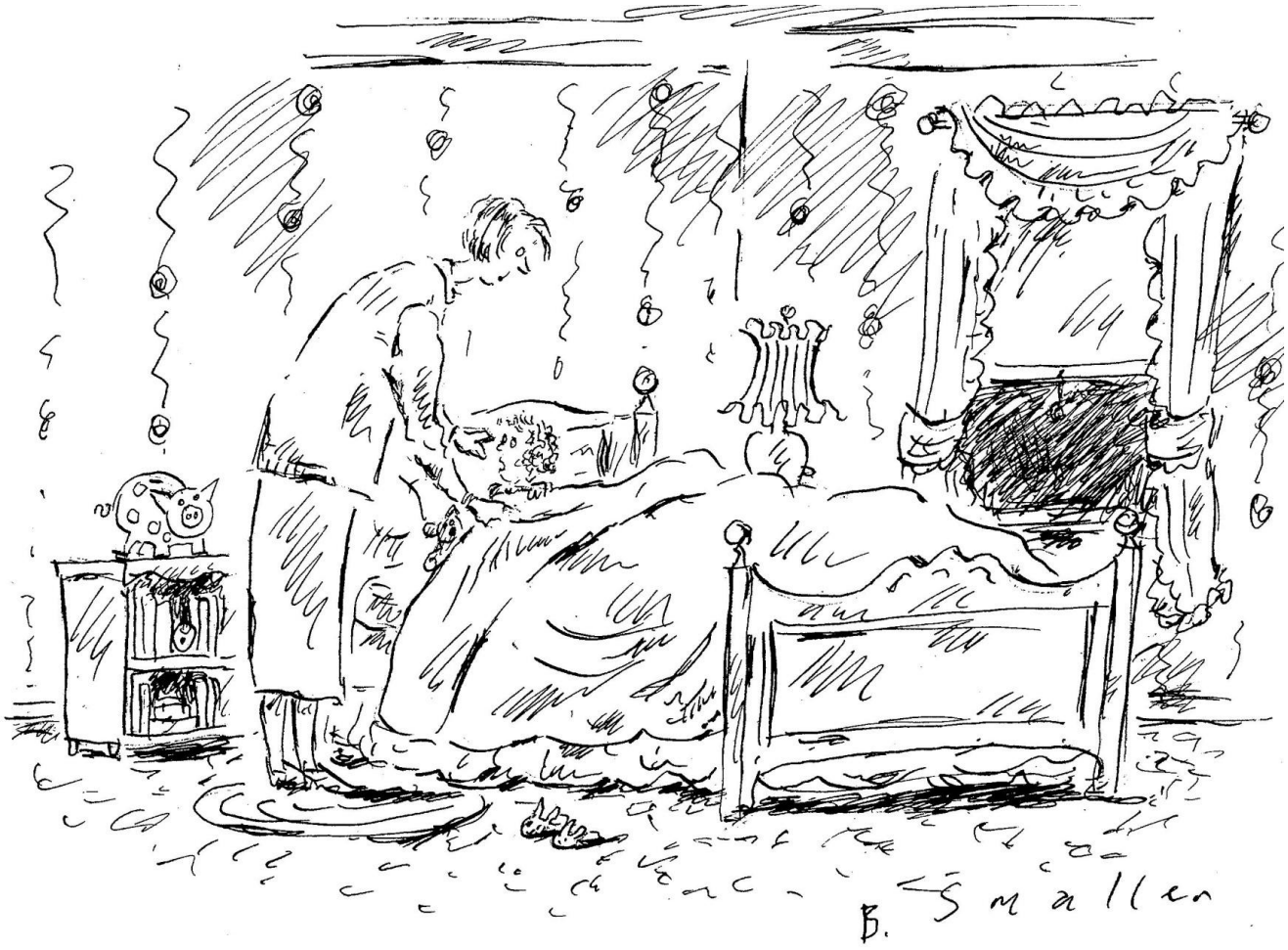
Thank you!.....



"You'd tell me if I was genetically modified?"

Next in the Series of Free PHC Webinars

- **Non-Small Cell Lung Cancer Biomarkers Guidelines,** Wednesday, January 25, 11:00-12 pm CT
  - Marc Ladanyi, MD, FCAP and Neal I. Lindeman, MD, FCAP
- Go to www.cap.org/institute For All Upcoming Webinars!
- Past Webinars Available Now Online at www.cap.org/institute
  - Who Wants to Eat Your PHC Lunch?
  - Validating Whole Slide Imaging Systems for Diagnostic Use in Pathology
  - The Why, What and How of Identifying Patients at Risk
  - How to Have Successful Patient Interactions
  - Next-Generation Sequencing for the Clinical Laboratory
  - Accountable Care Organizations
  - Whole Genome Analysis as a Universal Diagnostic
  - How to Build and Fund a Financially Viable Molecular Lab

CAP Learning – New Molecular Oncology CME Activities

- **Last of 6 new online courses, all offering .5 CME**
  - **BRAF Mutation Testing in Thyroid Cases**
    - Recognize the importance of BRAF mutation testing for preoperative diagnosis of thyroid cancer
    - Recognize importance of interpretation of molecular testing results have on patient management
    - Recognize how selection of patient with cytologically indeterminate thyroid nodules for molecular testing can enhance the accuracy of cytologic diagnosis
- **Developed by members of the CAP Molecular Oncology committee**
- **Pricing:** $25.00 member / $50.00 non-member

CAP Learning – Other Molecular Oncology CME Activities

Course	Learning Objectives
Molecular Pathology: An Introduction to DNA Technology and Diagnostic Applications (SAM eligible) CME/SAM – 2.0	-Identify potential application of molecular pathology -Describe the chemical structure and properties of DNA and RNA -Explain the different types of genetic variations -Identify diagnostic techniques in molecular pathology
Archives Applied: *KRAS* (SAM eligible) CME/SAM – 1.0	-Identify whether anti-EGFR therapy is an appropriate treatment method for a patient case -Describe advantages and limitations of specific *KRAS* mutation testing methods -Identify the appropriate elements to include in the report for a patient case -Describe the current role of *KRAS* mutation testing for management of patients with metastatic colorectal cancer
Archives Applied: Molecular Test Validation (SAM eligible) CME/SAM = 1.0	-Identify the appropriate: -test parameters for an analytic quantitative or qualitative test -clinical performance characteristics for test validation -performance characteristics for a quantitative or qualitative test -elements to include in test validation documentation -Identify pre-validation considerations for a proposed molecular pathology test
Archives Applied: Molecular Diagnostics of Soft Tissue Tumors (SAM eligible) CME/SAM = 1.0	-Recognize which genetic alterations seen in soft tissue tumors are amenable to molecular diagnostics using routine clinical genetic approaches -Describe characteristics of chromosomal translocations in soft tissue sarcomas Identify the advantages and limitations of conventional cytogenetic analysis for soft tissue tumors -Identify approaches for assessing inactivation of a tumor suppressor gene, for example the SMARCB (*INI1*) in soft tissue tumors -Identify the advantages and limitations of molecular cytogenetic analysis for soft tissue tumors

CAP Learning – Other Molecular Oncology CME Activities

Course	Learning Objectives
Molecular Testing for AML Cases CME – .5	-Recognize molecular oncology knowledge and skills required of pathologists that can mitigate problems and enhance patient care with respect to specimen handling -Realize the effects that appropriate specimen handling and communication throughout all stages of diagnosis have in enhancing patient care -Reflect on your own knowledge and skills in specimen handling and patient care, and identify what can help you and your practice be more effective in these areas of molecular oncology
BRAF Mutation Testing in Melanoma CME – .5	-Follow quality assurance policies and procedures to ensure adequate sample collection and proper handling techniques for molecular oncology tests -Use appropriate result reporting principles for incorporating molecular test results into surgical pathology reports
Molecular Testing for Lymphoma Cases CME - .5	-Recognize molecular oncology knowledge and skills required of pathologists that can mitigate problems and enhance patient care with respect to specimen handling -Realize the effects that appropriate specimen handling and communication throughout all stages of diagnosis have in enhancing patient care -Reflect on your own knowledge and skills in specimen handling and patient care, and identify what can help you and your practice be more effective in these areas of molecular oncology
Adenocarcinoma and EGFR and KRAS Mutation Testing CME - .5	-Recognize the indications for EGFR and KRAS molecular testing as they pertain to non-small cell lung cancer -Interpret molecular diagnostic test results and correlate them with the diagnosis pertaining to non-small cell lung cancer

CAP Learning – Other Molecular Oncology CME Activities

Course	Learning Objectives
Molecular Diagnosis of Ewing Sarcoma CME - .5	-Review sample requirements and handling for RT-PCR, FISH, and cytogenetic analysis as they pertain to evaluating mesenchymal neoplasms -Describe the advantages and limitations of genetic approaches commonly used in the classification of mesenchymal neoplasms to include conventional karyotyping, FISH, and RT-PCR
BPFT Testing Self Study CME /SAM – 2.5	-Explain the ASCO-CAP ER/PR Testing Guidelines and their implications for lab procedures, test results and patient care. -Explain the ASCO-CAP HER2 Testing Guidelines and their implications for lab procedures, test results and patient care. -Determine if the assay and tissue sample are appropriately matched per the ASCO/CAP Guidelines. -Explain the biology of fixation interactions with assay performance. -Explain the potential use of molecular analysis in patient care decisions. an mitigate problems and enhance patient care with respect to specimen handling
HER2 FISH Test Interpretation Accuracy CME/SAM – 1.5	-Accurately interpret HER2 FISH tests. -Correct for HER2 FISH interpretative errors. -Recognize the relationship between HER2 FISH test results and patient treatment.
BPFT Reporting CME/SAM – 1.5	-Apply the ASCO-CAP ER/PR and HER2 Guideline criteria to all reports in a standardized manner. -Create consistent, standardized and integrated reports. -Remediate inconsistent data and provide a resolution in an integrated report. -Create patient friendly reports. -Use formatting techniques to create clear and understandable reports.

CAP Learning – Other Molecular Oncology CME Activities

Course	Learning Objectives
ER IHC Test Interpretation Accuracy CME/SAM – 2.0	-Plan and perform a proper ER IHC test validation. -Accurately perform and interpret ER IHC tests, including the proper evaluation of appropriate controls and test tissues. -Evaluate and integrate ER staining patterns with clinical and morphologic findings. -Identify the relationship and impact of ER IHC test results on patient treatment.
HER2 IHC Test Interpretation Accuracy CME/SAM – 2.0	-Plan and perform a proper HER2 IHC test validation in accordance with ASCO-CAP guidelines for HER2 testing. -Accurately perform and interpret HER2 IHC tests, including the proper evaluation of appropriate controls and test tissues. -Evaluate and integrate HER2 staining patterns with clinical and morphologic findings to help improve concordance with HER2 FISH results. -Identify the relationship and impact of HER2 IHC test results on patient treatment.

Reminder: CAP Learning Portal Launches

NEW!

CAP Learning Portal

- The CAP Learning Portal landing page on the cap.org website replaces the current Education Programs page design. A user must log into cap.org in order to access further information.
- The CAP Learning Portal includes new tools to support the learning needs of pathologists such as:
  - Learning Options search/catalog
  - Competency Model for Pathologists
  - Personal Progress Check (member only tool)
  - My Learning Plan (member only tool)
  - Help Center
- 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 Molecular Oncology educational offerings:
  1. Log in to the cap.org website
  2. Click on Launch Portal
  3. Click on the Learning Options tab
  4. Type Molecular Oncology in the Search box

     A list of available learning options displays