Genomic Data and Health Information Technology: The New Frontier

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Centers for Disease Control and Prevention

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Virginia Health Information Technology Standards Advisory Committee

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WHO WE ARE

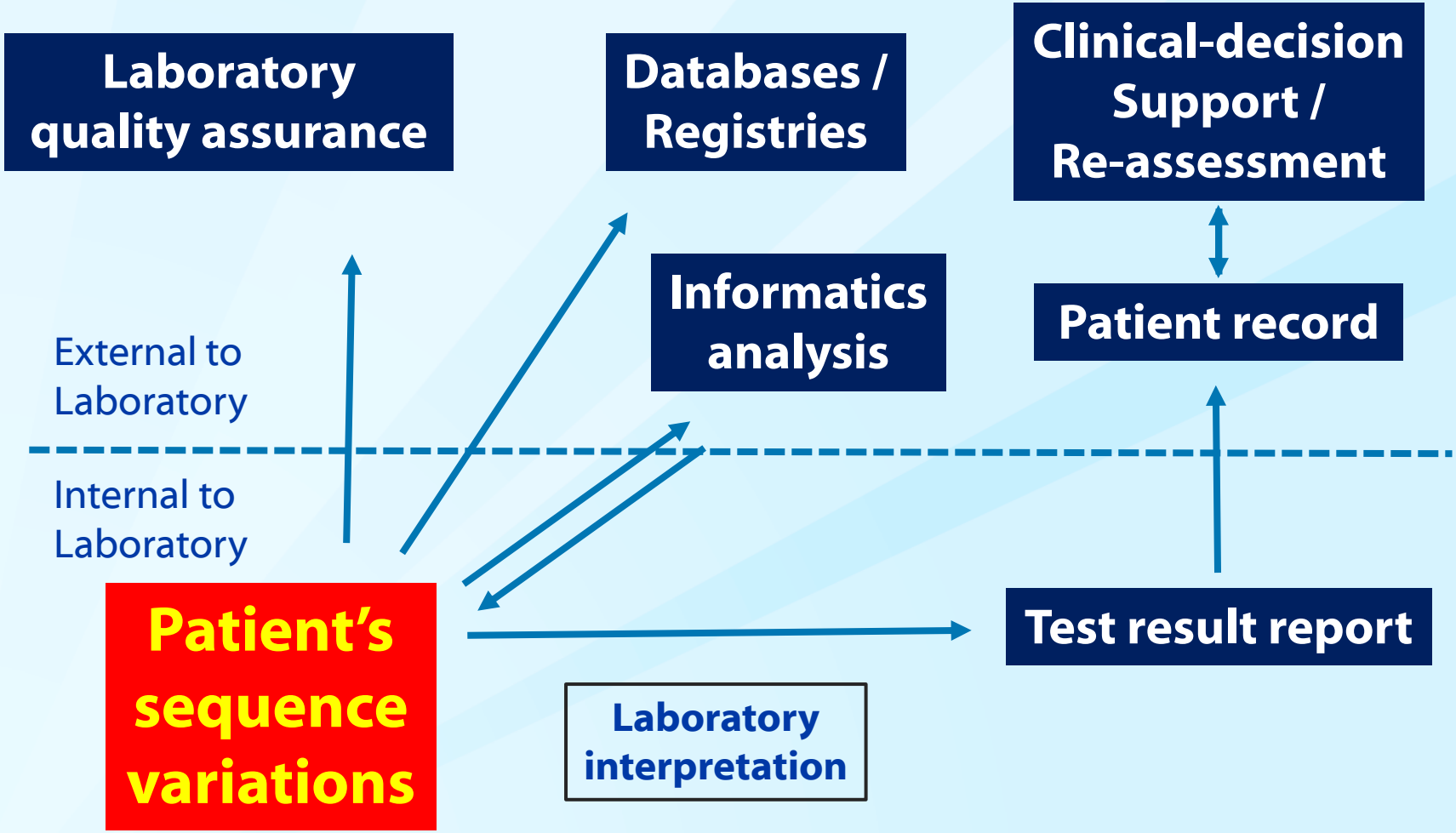
Division of Laboratory Programs, Standards, and Services (DLPSS)

Improve the quality of laboratory testing and related practices in the U.S. and globally through the development and evaluation of innovative training, technical standards, practice guidelines and reference materials.

Some activities

- Clinical Laboratory Improvement Advisory Committee
- Genetics Team
  - Next-Generation Sequencing
  - Reference materials
  - Test ordering / result reporting – test utilization
- Laboratory Health Informatics Team
- Clinical Laboratory Integration into Healthcare Collaborative
- Laboratory Medicine Best Practices

What Capability Do We Want to Develop?

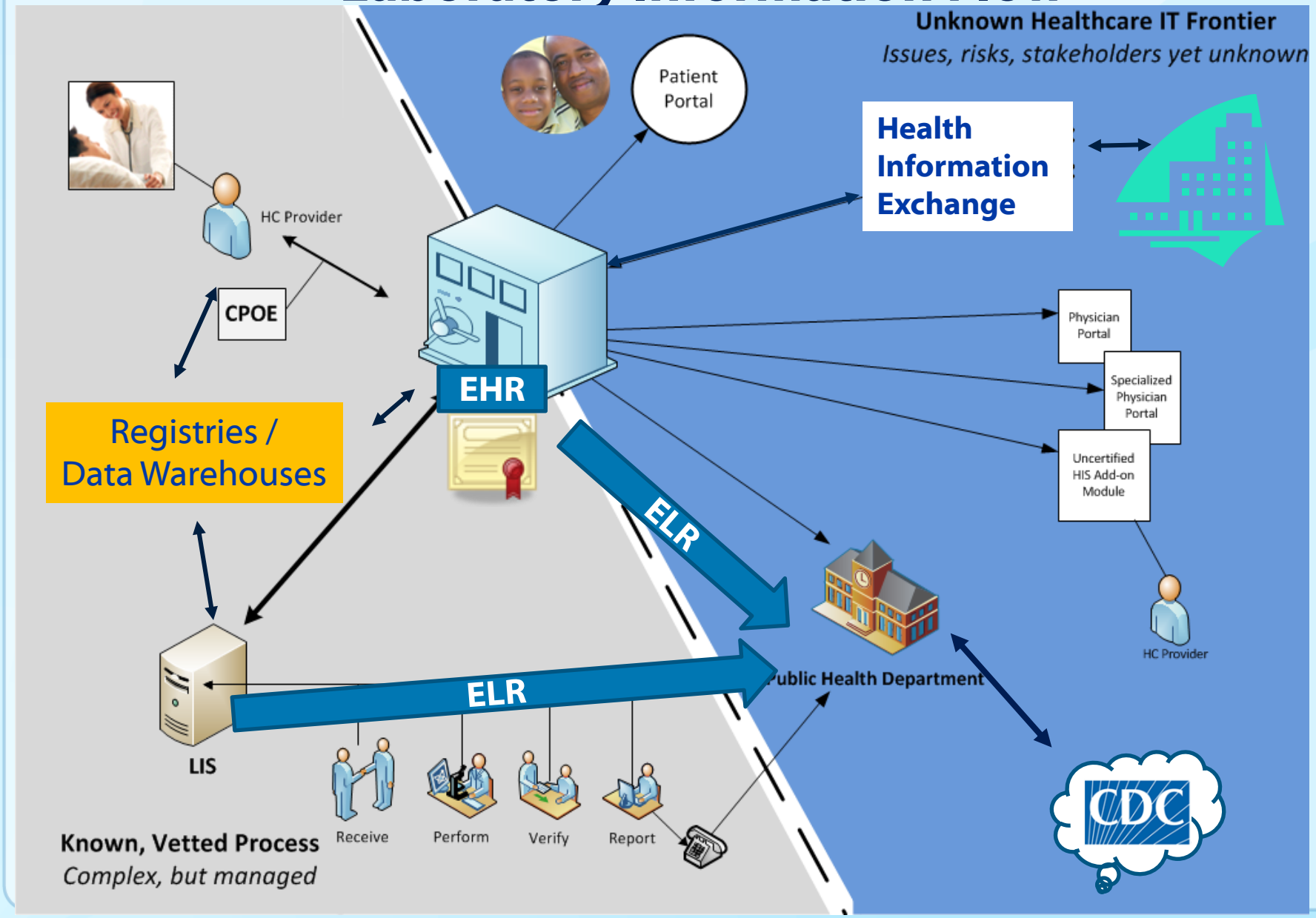


CDC DLPSS Health Information Team

The DLSS LabHIT Team was formed to facilitate the safe and effective integration of laboratory information in the EHR and health information technology for the benefit of patients and healthcare providers.

Engagement	Forum to Engage and Coordinate Laboratory Efforts	Laboratories Participate Early in EHR/HIT Planning	Regulations and Guidelines Incorporate Lab Input
Interoperability	Support Harmonization (SNOMED & LOINC	Harmonized Interfaces	Meaningful Comparisons of Lab Information
Usability & Contextuality	Explore Innovative Information Display	Results Interpreted Correctly	Adverse Outcomes Reduced

Laboratory Information Flow



The Influence of Clinical Genomics

- Diagnose rare diseases
- Directing cancer therapy selection
- Other clinical applications in development

Making a definitive diagnosis: Successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease

Elizabeth A. Worthey, PhD[1,2], Alan N. Mayer, MD, PhD[2,3], Grant D. Syverson, MD[2],
Daniel Helbling, B
Trivikram Dasu, PhD
Ulrich Broeck
James T. Casper, MD
John M. Rou

Worthey E.A. *et al.* *Genet Med.* 2011;13(3):255-62.

Identification of a Novel *TP53* Cancer Susceptibility Mutation Through Whole-Genome Sequencing of a Patient With Therapy-Related AML

***JAMA.* 2011; 305(15):1568-1576.**

HUMAN GENOMICS

Carrier Testing for Severe Childhood Recessive Diseases by Next-Generation Sequencing

Callum J. Bell,[1]* Darrell L. Dinwiddie,[1,2]* Neil A. Miller,[1,2] Shannon L. Hateley,[1]

***Sci Transl Med.* 2011: 3 (65) 65ra4**

Rapid Whole-Genome Sequencing for Genetic Disease Diagnosis in Neonatal Intensive Care Units

Carol Jean Saunders,[1,2,3,4,5]* Neil Andrew Miller,[1,2,4]* Sarah Elizabeth Soden,[1,2,4]*
Darrell Lee Dinwiddie,[1,2,3,4,5]* Aaron Noll,[1] Noor Abu Alnadi,[4] Nevene Andraws,[3]
Melanie LeAnn Patterson,[1,3] Lisa Ann Krivohlavek,[1,3] Joel Fellis,[6] Sean Humphray,[6] Peter Saffrey,[6]
Zoya Kingsbury,[6] Jacqueline Claire Weir,[6] Jason Betley,[6] Russell James Grocock,[6]
Elliott Harrison Margulies,[6] Emily Gwendolyn Farrow,[1] Michael Artman,[2,4] Nicole Pauline Safina,[1,4]
Joshua Erin Petrikin,[2,3] Kevin Peter Hall,[6] Stephen Francis Kingsmore[1,2,3,4,5]†

***Sci Transl Med.* 2012: 4, 154ra135**

Genomics in Clinical and Public Health Microbiology

APPLICATIONS OF NEXT-GENERATION SEQUENCING

Transforming clinical microbiology with bacterial genome sequencing

Xavier Didelot[1], Rory Bowden[1,2,3], Daniel J. Wilson[2,4], Tim E. A. Peto[3,4] and Derrick W. Crook[4,3]

Didelot X. et al., *Nature Reviews Genetics*, 2012

OPEN ACCESS Freely available online PLOS PATHOGENS

Opinion

Routine Use of Microbial Whole Genome Sequencing in Diagnostic and Public Health Microbiology

Claudio U. Köser[1,2*], Matthew J. Ellington[2], Edward J. P. Cartwright[1,2], Stephen H. Gillespie[3], Nicholas M. Brown[2], Mark Farrington[2], Matthew T. G. Holden[4], Gordon Dougan[4], Stephen D. Bentley[4], Julian Parkhill[4], Sharon J. Peacock[1,2,4,5]

Koser C.U. et al., *PLOS* Vol 8, Issue 8, 2012

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Whole-Genome Sequencing and Social-Network Analysis of a Tuberculosis Outbreak

Jennifer L. Gardy, Ph.D., James C. Johnston, M.D., Shannan J. Ho Sui, Ph.D., Victoria J. Cook, M.D., Lena Shah, M.Sc., Elizabeth Brodkin, M.D., Shirley Rempel, R.N., Richard Moore, Ph.D., Yongjun Zhao, D.V.M., Robert Holt, Ph.D., Richard Varhol, M.Sc., Inanc Birol, Ph.D., Marcus Lem, M.D., Meenu K. Sharma, Ph.D., Kevin Elwood, M.D., Steven J.M. Jones, Ph.D., Fiona S.L. Brinkman, Ph.D., Robert C. Brunham, M.D., and Patrick Tang, M.D., Ph.D.

Gardy J.L. *et al. N Engl J Med* 2011; 364:730-739

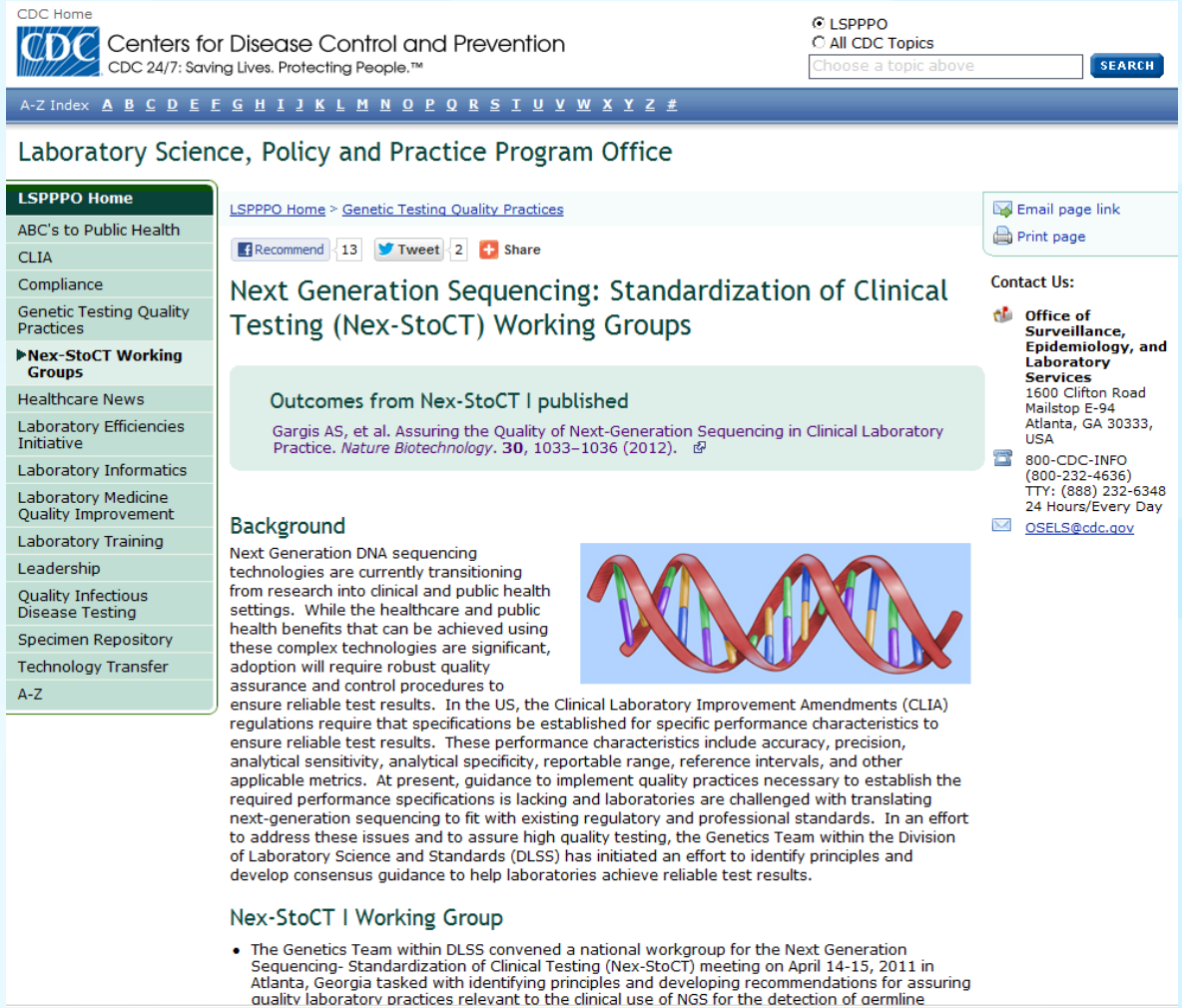
- Species identification
- Culture-independent microbiology
- Drug susceptibility testing and detecting virulence determinants

A framework for human microbiome research

The Human Microbiome Project Consortium*

HMPC. *Nature* 2012; 486:215–221

Next-Generation Sequencing – Standardization of Clinical Testing (Nex-StoCT)



CDC Home

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives. Protecting People.™

LSPPPO
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Laboratory Science, Policy and Practice Program Office

LSPPPO Home
- ABC's to Public Health
- CLIA
- Compliance
- Genetic Testing Quality Practices
- **Nex-StoCT Working Groups**
- Healthcare News
- Laboratory Efficiencies Initiative
- Laboratory Informatics
- Laboratory Medicine Quality Improvement
- Laboratory Training
- Leadership
- Quality Infectious Disease Testing
- Specimen Repository
- Technology Transfer
- A-Z

LSPPPO Home > Genetic Testing Quality Practices

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Next Generation Sequencing: Standardization of Clinical Testing (Nex-StoCT) Working Groups

Outcomes from Nex-StoCT I published

Gargis AS, et al. Assuring the Quality of Next-Generation Sequencing in Clinical Laboratory Practice. *Nature Biotechnology*. **30**, 1033–1036 (2012).

Background

Next Generation DNA sequencing technologies are currently transitioning from research into clinical and public health settings. While the healthcare and public health benefits that can be achieved using these complex technologies are significant, adoption will require robust quality assurance and control procedures to ensure reliable test results. In the US, the Clinical Laboratory Improvement Amendments (CLIA) regulations require that specifications be established for specific performance characteristics to ensure reliable test results. These performance characteristics include accuracy, precision, analytical sensitivity, analytical specificity, reportable range, reference intervals, and other applicable metrics. At present, guidance to implement quality practices necessary to establish the required performance specifications is lacking and laboratories are challenged with translating next-generation sequencing to fit with existing regulatory and professional standards. In an effort to address these issues and to assure high quality testing, the Genetics Team within the Division of Laboratory Science and Standards (DLSS) has initiated an effort to identify principles and develop consensus guidance to help laboratories achieve reliable test results.

Nex-StoCT I Working Group

- The Genetics Team within DLSS convened a national workgroup for the Next Generation Sequencing- Standardization of Clinical Testing (Nex-StoCT) meeting on April 14-15, 2011 in Atlanta, Georgia tasked with identifying principles and developing recommendations for assuring quality laboratory practices relevant to the clinical use of NGS for the detection of germline

Contact Us:

Office of Surveillance, Epidemiology, and Laboratory Services
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Mailstop E-94
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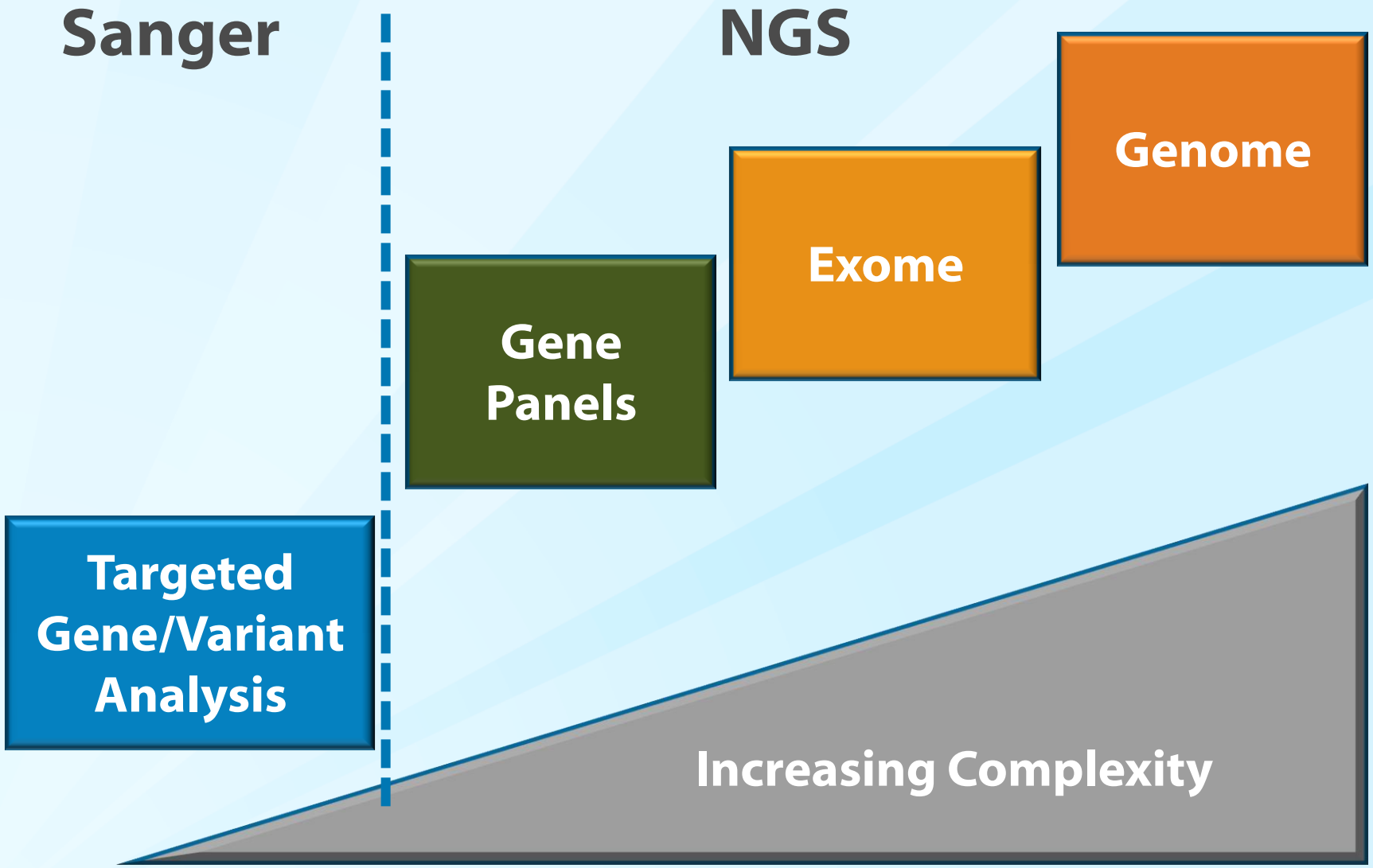
24 Hours/Every Day

OSELS@cdc.gov

1. **Implementation in a Clinical setting**
2. **Design/optimization of an informatics pipeline**
3. **Data representation and messaging**

Website: www.cdc.gov/osels/lspppo/Genetic_Testing_Quality_Practices/Nex-StoCT.html

Evolution of Sequencing Capabilities



Next Generation Sequencing: The Clinical Workflow

1. Indication for testing
2. Counseling
3. Specimen Collection, Transport, Management, and preparation
4. Sequence analysis
   a) Library preparation
   b) Machine sequencing
   c) Alignment
   d) Identify sequence variants
   e) Variant annotation
   f) Identify relevant variants
   g) Confirmatory testing
   h) Clinically relevant variants and result report
5. Communicating results / Counseling
6. Integration into clinical decision making

Physical patient sample

Digital patient sample

Interpreting Sequence Results

Sequence variants (position/type)

↓

Variant Annotation

→

- Functional studies
- Predictions (PolyPhen, SIFT, etc)
- Prevalence
- Segregation
- Database representation (e.g., dbSNP, ClinVar, etc.)

↓

Variant Analysis/Classification (What is clinically relevant?)

- Benign
- Likely Benign
- Variation of Unknown Significance
- Likely Clinically Relevant
- Clinically Relevant

Describing a Variant

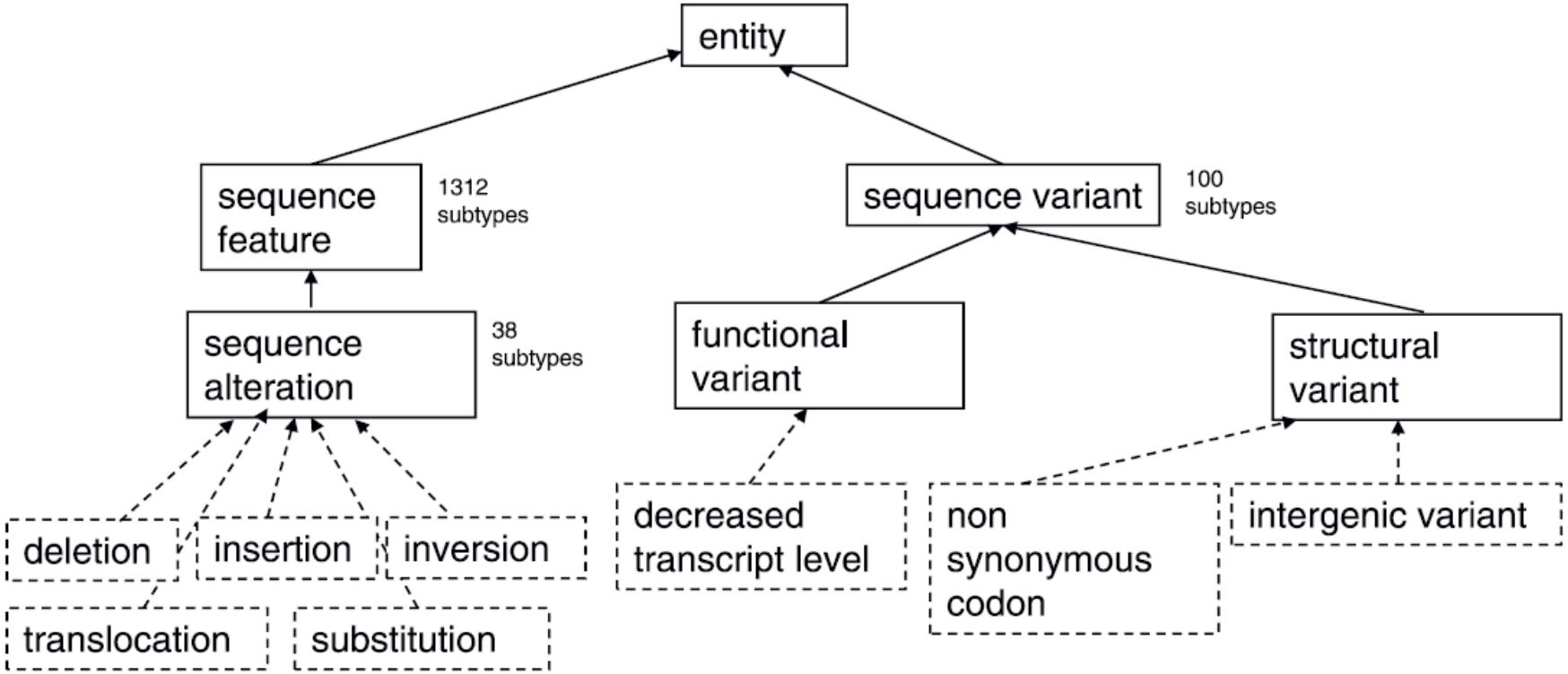


Figure 1 The top-level terms in the Sequence Ontology used in variant annotation. There are 1,792 terms in SO, most of which (1,312) are sequence features. There are 100 terms in the ontology that are kinds of sequence variant, of which the two top level terms are shown, and three sub-types, shown with dashed lines, that demonstrate the detail of these terms. The parts of SO that are used to annotate sequence variation files are sequence alteration to categorize the change (five subtypes shown with dashed lines), sequence feature to annotate the genomic features that the alteration intersects, and sequence variant to annotate the kind of sequence variant with regards to the reference sequence.

Reese et al. – A standard variation file format for human genome sequences
Genome Biology 2010 11:R88

Variant Call File Format

genomic position

Variant alleles

variant metadata

phasing

sample genotypes

```
#CHROM POS     ID        REF ALT    QUAL FILTER INFO                              FORMAT      NA00001        NA00002
20     14370   rs6054257 G   A      29   0      NS=3;DP=14;AF=0.5;DB;H2           GT:GQ:DP:HQ 0|0:48:1:51,51 1|0:48:8:51,51
20     17330   .         T   A      3    q10    NS=3;DP=11;AF=0.017               GT:GQ:DP:HQ 0|0:49:3:58,50 0|1:3:5:65,3
20     1110696 rs6040355 A   G,T    67   0      NS=2;DP=10;AF=0.333,0.667;AA=T;DB GT:GQ:DP:HQ 1|2:21:6:23,27 2|1:2:0:18,2
20     1230237 .         T   .      47   0      NS=3;DP=13;AA=T                   GT:GQ:DP:HQ 0|0:54:7:56,60 0|0:48:4:51,51
20     1234567 microsat1 G   D4,IGA 50   0      NS=3;DP=9;AA=G                    GT:GQ:DP    0/1:35:4       0/2:17:2
```

Designed to be used within the laboratory and not implemented for the sharing of data with others

Finding The One that is Disease Associated (Crohn disease-like illness – atypical)

Start here

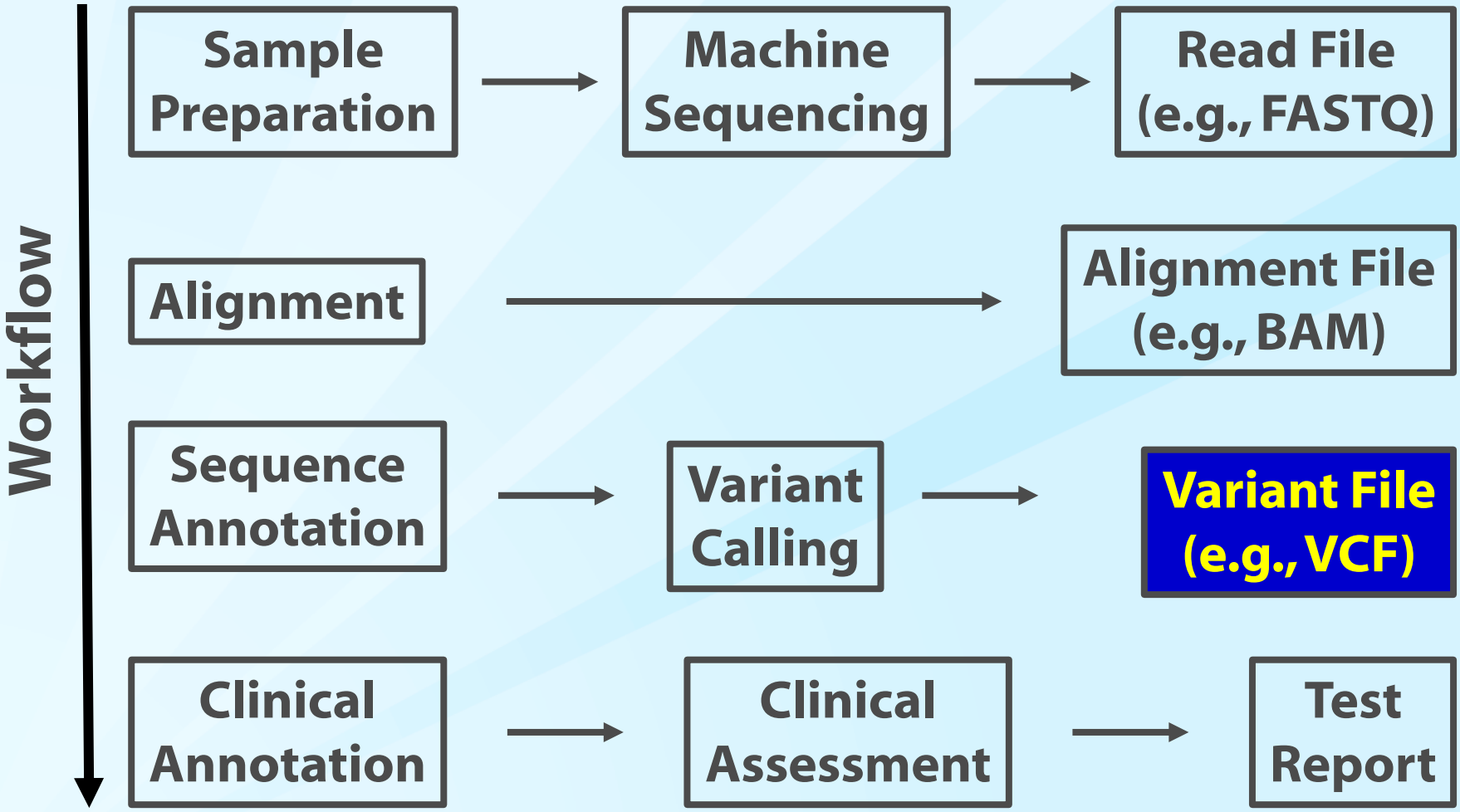
Category A	
High confidence variants	16,124/1,527
Genic variants (variants within genes; i.e., excluding intergenic variants)	16,012/1,504
Insertions	222/72
Deletions	240/136
Substitutions	15,550/1,296
Protein coding variants (variants within the protein coding exons of genes)	15,272/1,407
Insertions	147/65
Deletions	239/119
Substitutions	14,886/1,223
Nonsynonymous variants (variants resulting in an amino acid change)	7,158/879
Insertions	117/51
Deletions	232/112
Substitutions	6,799/706
Substitutions—introduction of a homozygous stop	13/2

Category B	
Variants in genes where two variants were predicted to be damaging	66
Altering highly conserved positions	18
Not known to frequently contain deleterious mutations	4
Novel and confirmed	0
Homozygous or hemizygous	70
Predicted to be damaging	17
Novel (against dbSNP 130)	8
Altering highly conserved positions	4
Not found in reference genome sequences	2
Not known to frequently contain deleterious mutations	1

End here (XIAP)

Genet Med 2011:13(3):255–262

The NGS Workflow and Associated Data Files



Clinical-Grade Variant Work Group

current focus

Established Clinical-Grade Variant Work Group

↓

Develop principles and recommendations

- File format / content considerations
  (e.g., use of genomic coordinates, variant representation, metadata)

Community engagement / feedback (through website)

↓

Develop and evaluate use cases

Pilot in laboratory, clinical settings, HIEs

Share with oversight, standards, and accreditation organizations

Publications

Desired Features of a Clinical-Grade Variant File

1. Accurately represent (position , type, reference, quality)
   1. Variant calls
   2. Reference calls
   3. No-calls
2. Represent the full spectrum of variant calls, not just small variants (e.g. CNVs, SVs)
3. Define complete allele (haplotype)
   1. HLA
   2. Pharmacogenomics
4. Provide sufficient meta-data for variant file to be interpreted outside the laboratory

Metadata (Proposed)

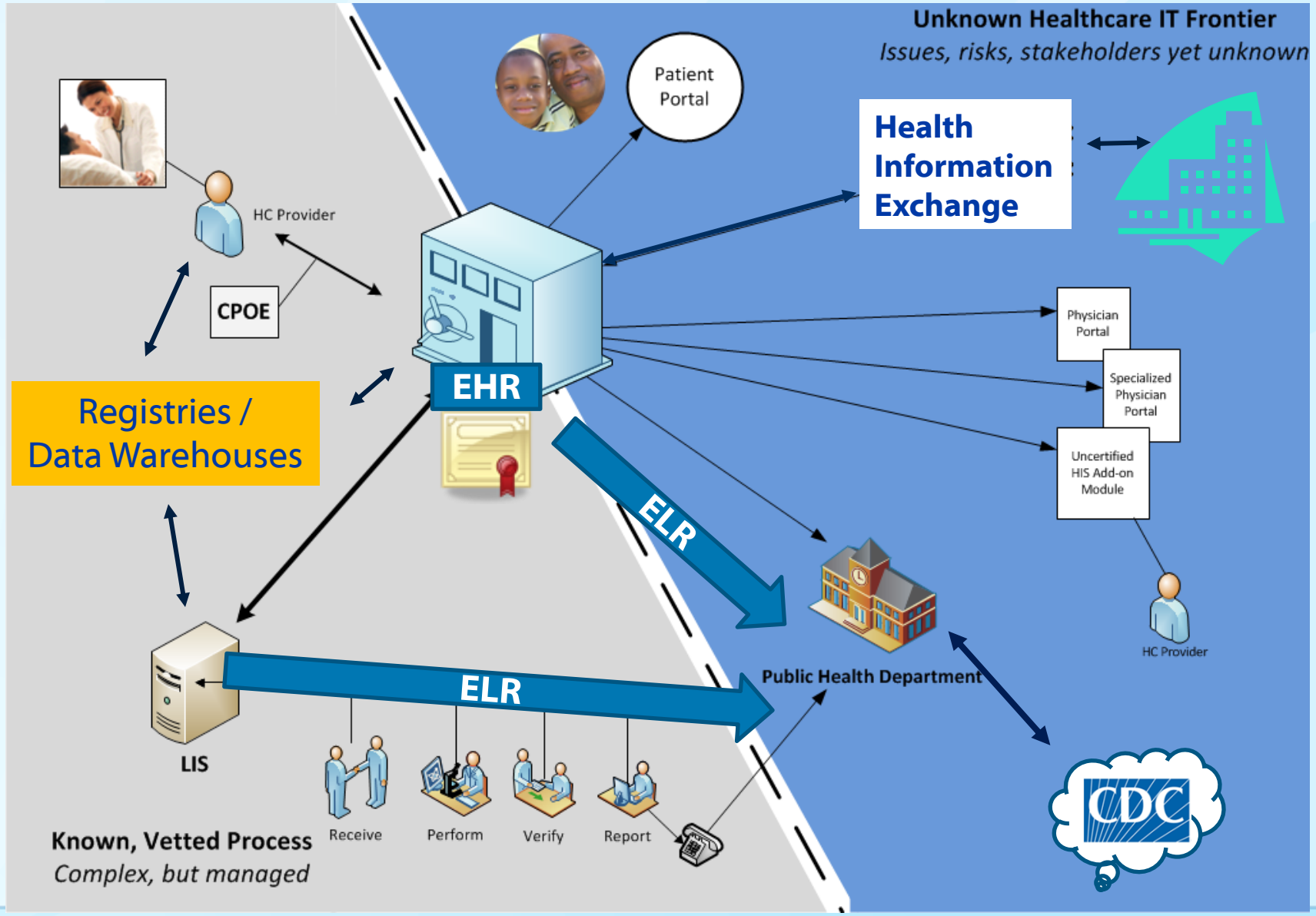
- General information (Protected Health Information issues?)
  - Patient identifier
  - Laboratory identifier
  - ICD 9/10 codes
  - Clinical presentation features
- Data relevant to NGS laboratory test procedures
  - Instrumentation / Software
  - Performance specifications
- Data relevant to describing the genome
  - Reference assembly / annotation sets
  - Regions covered at high confidence
- Data relevant to describing the variants
  - Standard descriptors (e.g., HGVS, dbSNP, COSMIC)

How do we develop, pilot, implement, and promote the adoption of a clinical-grade variant file?

Principles

- Must advance as a community
- Must build on the existing infrastructure (to constrain and adapt existing specifications to extent possible)
- Must integrate into existing oversight and evolving mechanisms of oversight / professional guidance
- Must integrate into evolving health IT structure
- Must be flexible to accommodate changing technologies and practices

Integration into the Evolving Health IT Framework



What Standards Exist

- File specifications (VCF, gVCF, GVF, etc. – dev. for research)
- Reference assembly / annotation sets
- HGNC (gene names and symbols)
- HGVS Nomenclature (for variant description)
- dbSNP – database of short nucleotide variations
- RefSeq – standard non-redundant sequence representations
- COSMIC – catalog of somatic mutations in cancer
- LOINC – coded laboratory and clinical observations
- ClinVar (in development) – sequence database linked to health implications
- ICD 9/10

Regulatory / Professional Standards and Guidance

- Centers for Disease Control and Prevention

  Next-Generation Sequencing: Guidance for the Translation from Research to Clinical Applications

- American College of Medical Genetics

  Standards for Next Generation Sequencing / Incidental findings

- College of American Pathologists

  Inspection Checklist

- HL7 Documents and Guides

- Clinical and Laboratory Standards Institute

  MM09 - Nucleic Acid Sequencing Methods in Diagnostic Laboratory Medicine

- Association for Molecular Pathology

  Guidance in progress (e.g., test validation)

HL7 Documents

HL7 VERSION 3
DOMAIN ANALYSIS MODEL:
CLINICAL SEQUENCING, RELEASE 1
DRAFT
(1ST BALLOT FOR COMMENT)

C

HL

Initial ver

Next Balloted V

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This document has been updated to re
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V3_IG_CANONPED_R1_INFORM_2013APR

HL7 Version 3 Implementation Guide: Family History/Pedigree Interoperability, Release 1 – US Realm

April, 2013

HL7 Informative Document

Sponsored by:
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V2IG_CG_LOINCGENVAR_R2_INFORM_2013MAR

HL7 Version 2 Implementation Guide: Clinical Genomics; Fully LOINC-Qualified Genetic Variation Model, Release 2

March 2013

HL7 Informative Document: HL7 V2IG CG LOINCGENVAR R2-2013

A Technical Report prepared by Health Level Seven International and registered with ANSI.

5/5/2013

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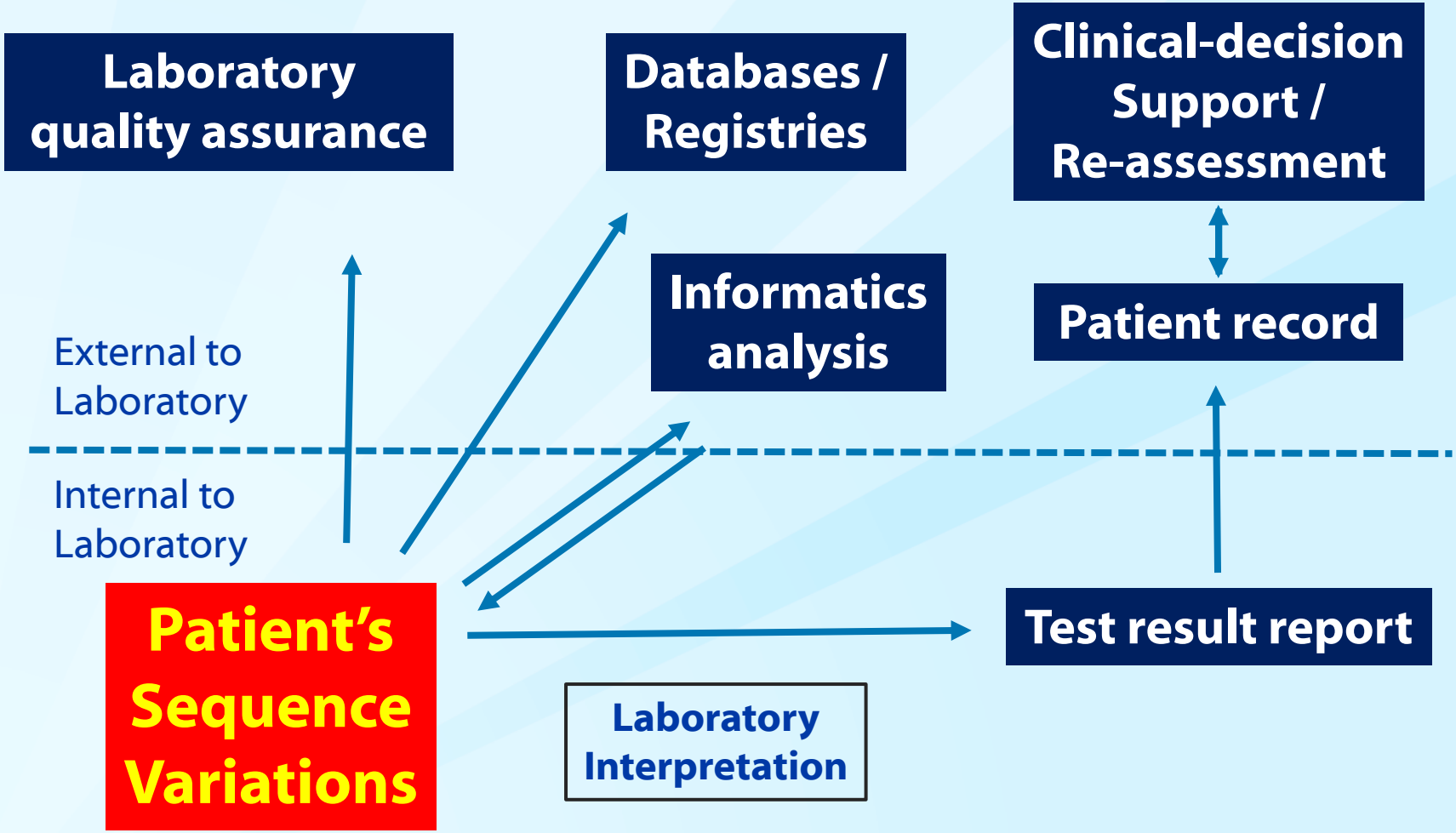
Products Sought

- Constrained rules for describing variants in the context of the patient and his/her genome
- Machine and human readable file format(s) (a balance)
- Able to be messaged for a variety of applications
- Use cases and pilot studies that provide evidence for utility

What Capability Do We Want to Develop?



Thank you!

- Questions about presentation?

- Questions for HITSAC

1. What aspects of the presentation are relevant to your vision for integrating genomics into Virginia's evolving healthcare IT infrastructure?

2. What suggestions can you offer to integrate into the scope of our work to serve your present and future needs?

For additional questions/discussion: Ira Lubin at ilubin@cdc.gov