

Clinical Genetic and Clinical Genomic Data Standards for Healthcare IT

Presented to the Commonwealth of Virginia Health IT Standards
Advisory Committee (HITSAC)

On June 20, 2013

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Co-Chair Clinical Genomics Workgroup,
Health Level Seven International (HL7)

Disclaimers

- Co-chair HL7 Clinical Genomics Workgroup
- HL7 Clinical Genomics Liaison, College of American Pathologists' Cancer Biomarker Reporting Committee
- Member of the Federally-mediated Clinical Grade-VCF/GVF (i.e. genomic data file format) Workgroup
- BioMedical Informaticist at Partners Healthcare and Dana-Farber Cancer Institute
- MBA – Candidate at Babson College
- Member of Babson's Butler Venture Accelerator
 - Working with Dr. Kevin Hughes to commercialize Hughes RiskApps software for family history and identification and management of high-risk patients within the area of personalized medicine

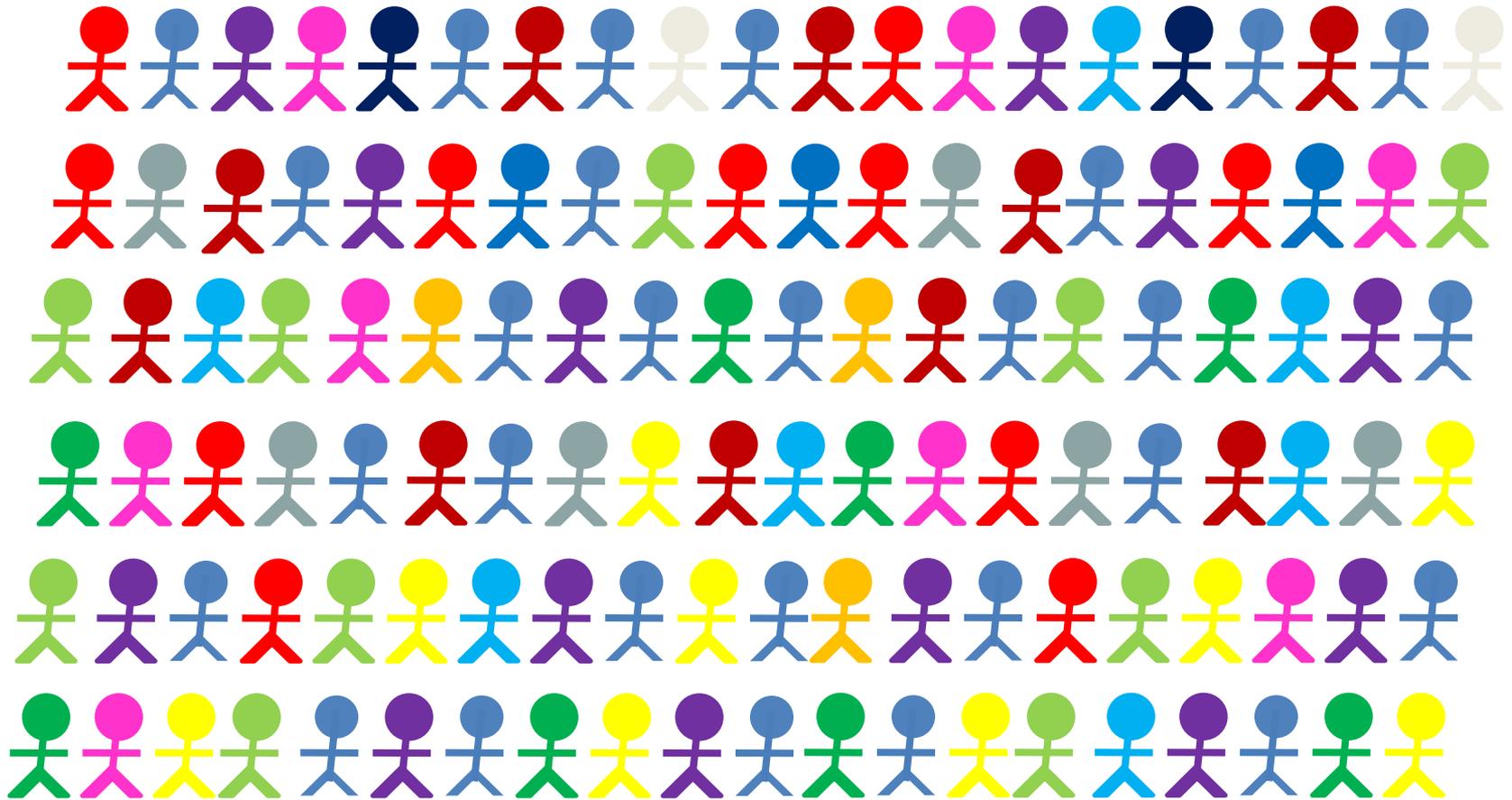
Clinical Genetic Standards

HIT Standards for Current Clinical
Genetic Testing

Developing a common understanding through use cases

CLINICAL GENETIC USE CASES

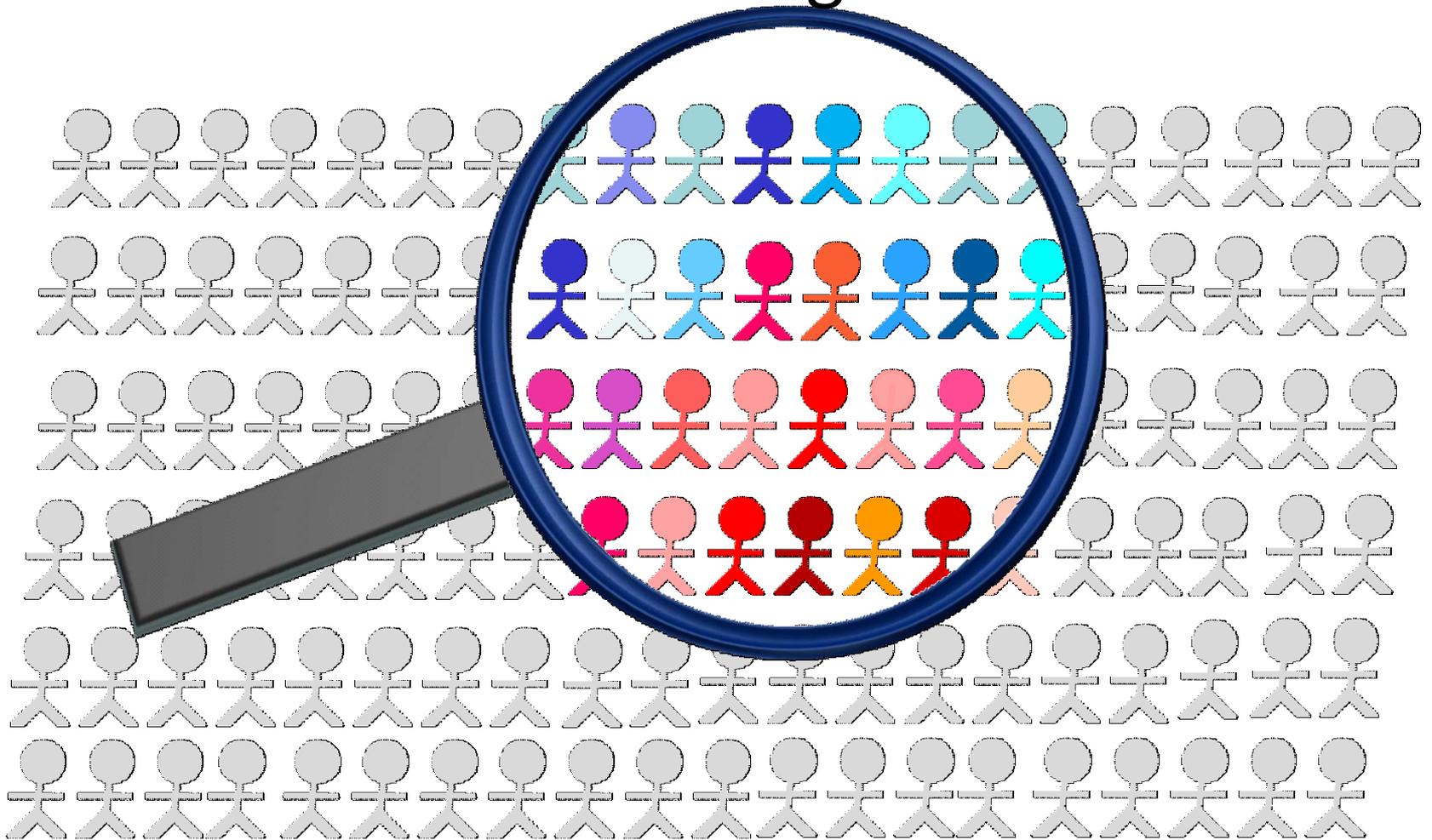
Proactive Health Plan: Predictive Risk and Breast Cancer



Proactive Population Management and Knowledge Update

- Dr. Jones receives notification that the clinical interpretation of Ms. Smith's breast cancer genetic risk test has changed from 'unknown clinical significance' to 'positive-high risk'.
- Dr. Jones writes a letter to Ms. Smith that informs her of the new interpretation, requests an appointment, and offers support to communicate the potential risk to other family members
- Ms. Smith is automatically registered in the Breast Cancer Risk, Population Management Registry.

Pharmacogenomics, Toxicogenomics and Pharmacovigilance



Pharmacogenomics – Drug Efficacy

- Mr. Jones is diagnosed with a form of non-small cell lung cancer. Molecular testing identifies a mutation in the EGFR gene. EGFR mutations have been associated with responsiveness to Tarceva treatment.
- Mr. Jones isn't responding to Tarceva and after time is placed on another treatment.
- Retrospective outcomes analysis reveals when mutation A is present patients are unresponsive to Tarceva. That is, mutation A is a resistance mutation.
- A drug – genetic contraindication alert is created and future patients are placed on alternative therapy.
- Secondary use of clinical genetic data for research enables development of a new drug not blocked by mutation A.

Toxicogenomics

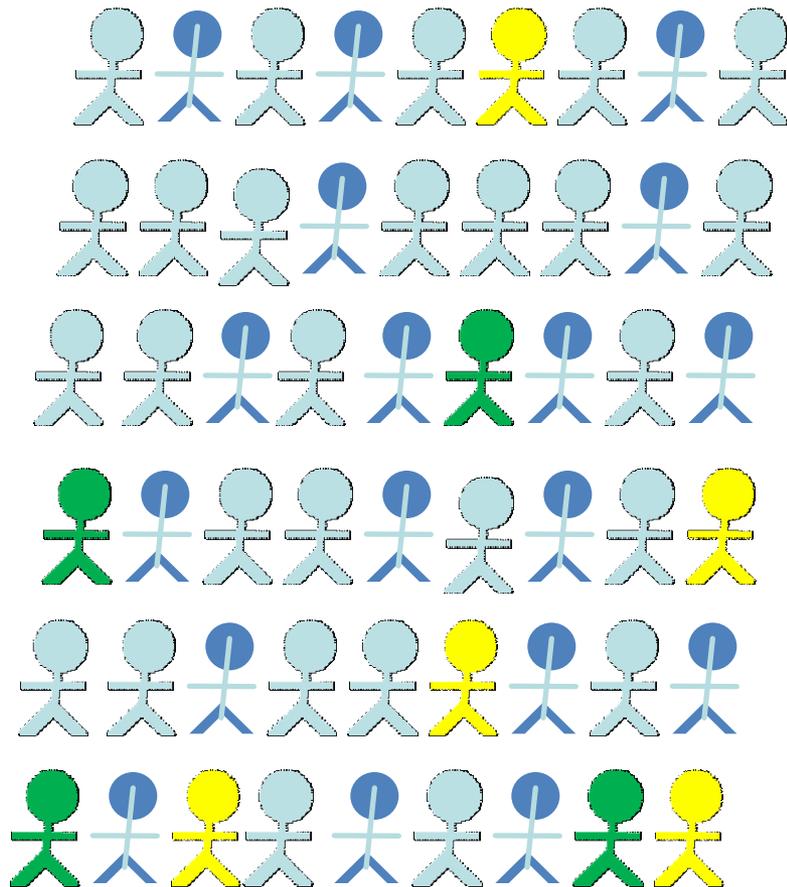
- Mrs. Carter lost her hearing as a child. Her children's pediatrician recommends she get a genetic test to rule out a mitochondrial mutation associated with hearing loss when treated with an aminoglycoside antibiotic .
- Mrs. Carter is found to carry the mutation and genetic testing reveals that 2 of her 3 children also carry the mutation.
- The children's pediatrician updates their medical records with the drug allergy.

Pharmacovigilance

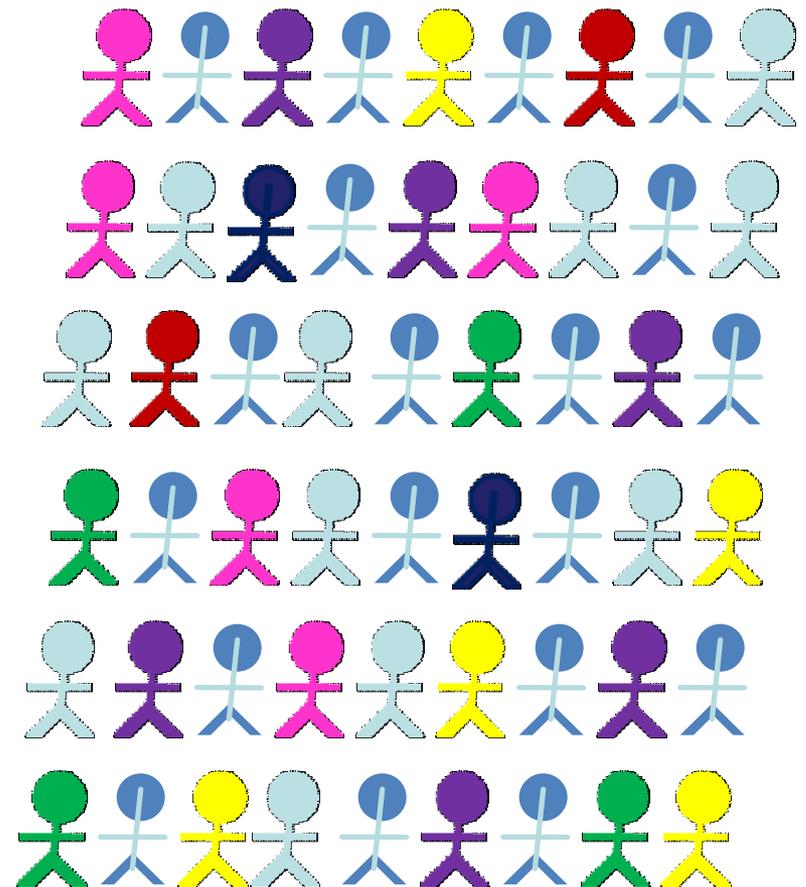
- Through a pharmacovigilance application, drug X is discovered to be associated with unexplained hearing loss, when given to children with mutation Y.

Newborn Screening and Risk Identification of Early On-set Disease

Current

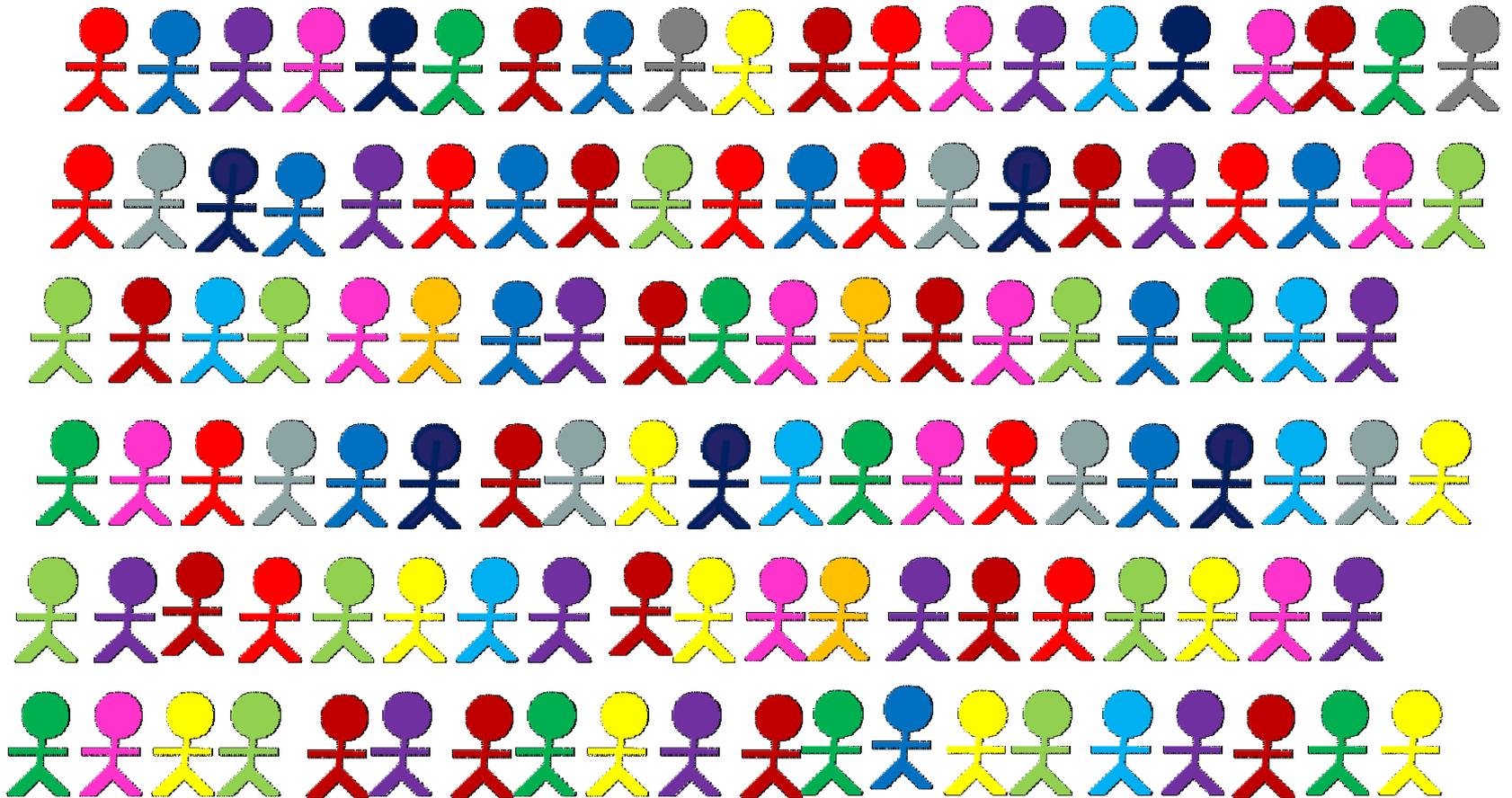


Near Future



Newborn Screening Patient Genomic Profile

Long-term Objective



Health Care ROI

- Movement to Proactive Health Management
 - Personalized, Preventive, and Precise
 - Focus on specific risks in specific patients
 - Increase surveillance of high-risk individuals
 - Able to use high-risk medications for targeted individuals
 - Reduce adverse events in high-risk individuals
- Improved Clinical Decision Support
 - Timely application of new genomic knowledge in delivery of healthcare
- Reduced Health Care Costs
 - Reduced adverse events
 - Decrease potential liability

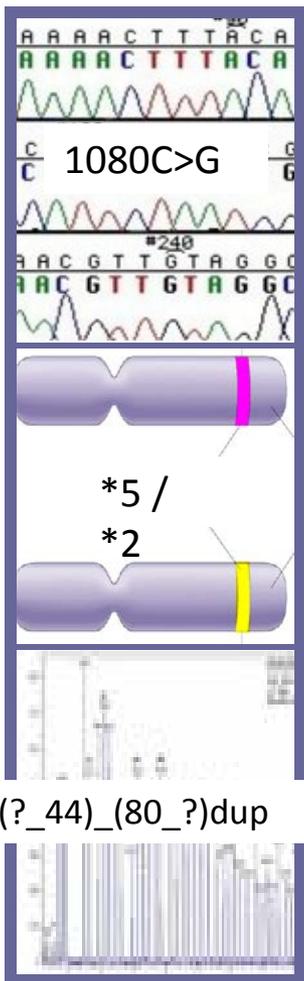
Requirements for Genetic/Genomic Data in Clinical Care

- Accessible in the EHR as Structured Data
- Integrated into Clinical Workflows
- Available to Clinical Decision Support
- Integrated into Data Warehouses
 - patient panel management, outcomes analysis, quality assurance, public health reporting and discovery research
- Maintained, Up-to-Date Interpretations



Clinical Genetic Healthcare IT Standards

Electronic Health Record Environment Requires Standardized Minimal Core Datasets



Sequencing, Genotyping, Chromosomal Analysis...

Patient & Security Context

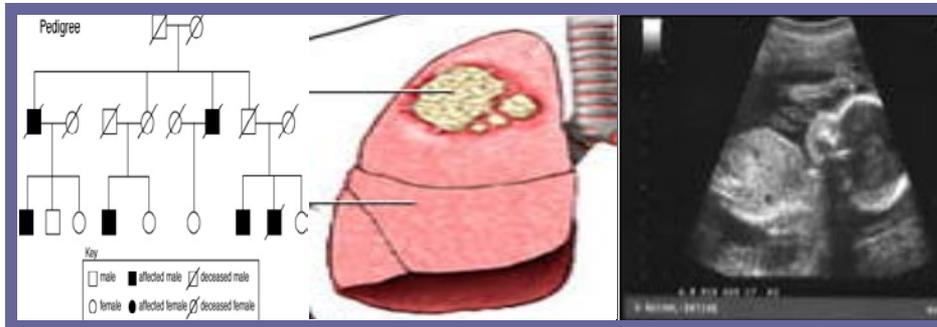
0000004 (MGH) Claus, Santa C, Jr. - Genetics Summary - Microsoft Internet Explorer

Address: http://ppd.partners.org:87/webresults/asppages/genetics.asp

Select | Lab Views | Summary Views: Genetics | LMR Summary | Links | Home | Resource

MGH BWH ALL

Date	Site	Primary Specimen	Indication	Test
06/27/2006	MGH	Lung - Fixed Tissue	Pharmacogenomic	EGFR_b
06/27/2006	MGH	Blood, Peripheral	Family History	HCM-pn1B, UCH-pn1A, HCM-pn1A
06/27/2006	MGH	Blood, Peripheral	Family History	565G>A (V189I), Exon 5, MYBPC3 C106-a, C130-a, DNMT-pn1A, COCH-a, PDUF4-a, MYO7A-a, PDS-a
06/27/2006	MGH	Blood, Peripheral	Pharmacogenomic	No mutations detected. EGFR-b, EGFR-a
06/26/2006	MGH	Fixed Tissue/Block (Lung) for EGFR	Pharmacogenomic	2156G>C (G719A), Exon 18, EGFR EGFR-a
				2235_2243del (E746_R748del), Exon 19, EGFR



Germline, Somatic, & Prenatal Variants



Diagnostic, Carrier Screening & Pharmacogenomics...

What might Personalized Genomic Medicine look like?

The image shows a screenshot of a medical software interface with several callout boxes highlighting key features:

- Reminders for Screening:** A callout box points to the 'Reminders' section at the top left, which includes a notification: '- Patient has H/O Angina on problem list and aspirin is not on the medication list. Recomm...
- Diagnostics and 'At Risk' for Disease:** A callout box points to the 'Social History' and 'Problems' sections. The 'Problems' list includes: Above knee amputation, Pr pelvic inflammatory disease - Major, Pr elevated cholesterol - Minor, Diabetes mellitus type 2, Gastroesophageal reflux disease, R/o fatty liver disease, Chronic obstructive pulmonary disease, H/o cold intolerance - Minor, Esophageal varices of diseases, Sick, and Cardiac transplant.
- Genetic BioMarkers for Drug Allergies or Sensitivities:** A callout box points to the 'Genetics Summary' section in the right-hand pane, which lists various genetic markers and their reactions.
- Pharmacogenomic Implications for Medications and Prescriptions:** A callout box points to the 'Medications' list on the left, which includes drugs like Abacavir, Amitriptyline, and others.
- Patient Genetic Profile:** A callout box points to the 'Genetics Summary' section in the right-hand pane.
- Genetic Implications for Procedures:** A callout box points to the 'Procedures' section at the bottom left.
- Genetics Incorporated into Care Plans:** A callout box points to the 'Advance Directives' and 'BMT Flowsheet' sections at the bottom.

The interface also displays a list of providers, a 'Pharmacies' section, and a 'Family History Problem' table at the bottom right.

Family History Problem	Relative
Stomach cancer	Mother
Breast Cancer	Mother

At the bottom of the screen, there is a status bar with the text '1532 - 601(10,191,30,0,0,370)' and 'Local intranet'.

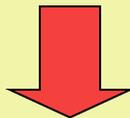
Genetic Test Result & Interpretation

(Presented to the clinician in narrative form)

Coded Genetic Test
Coded Overall Result
(e.g. Positive/Negative; Responsive/Resistant)

Coded Disease or Drug

Structured Mutations/Variants



Test X was Positive
for **mutations** associated
with **Disease Y**

or

Resistance to treatment
with cancer **Drug Z**

 HARVARD MEDICAL SCHOOL  PARTNERS

**Laboratory for Molecular Medicine
Center for Genetics and Genomics**
65 Landsdowne Street, Cambridge MA 02139
Phone: (617) 768-3500 - Fax: (617) 768-3513

Unit Number(s)
Lab Accession
Patient Name
Birth Date
Age Sex

MOLECULAR DIAGNOSTICS REPORT

Specimen Type: Lung - Fixed Tissue Report Date: 12/07/2006
Related Accession(s):
Referring Physician: XXXXXXXXXXXXXXXX Received Date: 12/7/2006
Copies To: Referring Facility: MGH
Lab Control Number:

GENETICIST = XXXXXXXXXXXX

TEST PERFORMED = EGFR-a

TEST DESCRIPTION = EGFR Partial Gene Sequencing (Exons 18-21)

INDICATION FOR TEST = Adenocarcinoma

RESULTS

DNA VARIANTS:
236C>T (T790M), Exon 20, EGFR, Resistant
2573T>G (L858R), Exon 21, EGFR, Responsive

INTERPRETATION:
Resistant. The T790M mutation in combination with the XXXXX mutation has previously been described in an individual with acquired resistance to EGFR-TKIs (Fao, et al., 2008).

TEST INFORMATION

BACKGROUND:
Somatic mutations in the kinase domain of the epidermal growth factor receptor (EGFR) have been shown to predict response of tumors to tyrosine kinase inhibitor (gefitinib and erlotinib) therapy in approximately 80% of patients with advanced lung non-small cell carcinoma.

METHODOLOGY:
DNA was isolated from the dissected tissue and the nucleotide sequence encoding the four exons of the kinase domain (exons 18-21) of EGFR was analyzed by PCR and capillary gel electrophoresis. When necessary, testing is also performed on the blood specimen to determine if an identified variant is specific to the tumor or present constitutively. This test was developed and its performance characteristics determined by the Harvard Medical School/Partners Healthcare Laboratory for Molecular Medicine (LMM, 65 Landsdowne Street, Cambridge, MA 02139; CLIA#22D1005307). It has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary.

REFERENCES:
Kobayashi S, Boggon TJ, Dayaram T, Janne PA, Kocher O, Meyerson M, Johnson BE, Eck MJ, Tenen DG, Halzou B. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2009 Feb 24;360(8):702-47

Patient Genetic Profile in Partners' Longitudinal Medical Record (LMR)

0000004 (MGH) Claus, Santa C, Jr. - Genetics Summary - Microsoft Internet Explorer
(Launched August 2006)

Address <http://ppd.partners.org:87/webresults/asppages/genetics.asp>

Select Lab Views Summary Views: Genetics LMR Summary Links Home Resource

MGH BWH ALL

Date	Site	Primary Specimen	Indication	Test	Status
06/27/2006	MGH	Lung - Fixed Tissue	Pharmacogenomic	EGFR-b	Amend/Addenda
06/27/2006	MGH	Blood, Peripheral	Family History	HCM-pnlB ; UCH-pnlA ; HCM-pnlA	Final
06/27/2006	MGH	Blood, Peripheral	Family History	565G>A (V189I), Exon 5, MYBPC3 CX26-g ; CX30-g ; DFNMT-pnlA ; COCH-g ; POU3F4-g ; MYO7A-g ; PDS-g	Final
06/27/2006	MGH	Blood, Peripheral	Pharmacogenomic	No mutations detected. EGFR-b ; EGFR-a	Final
06/26/2006	MGH	Fixed Tissue/Block (Lung) for EGFR	Pharmacogenomic	2156G>C (G719A), Exon 18, EGFR EGFR-a 2235_2243del (E746_R748del), Exon 19, EGFR	Final

2906 - 1

This slide is intended to illustrate general IT functionality.

Content displayed is not intended for clinical use.

Screen configurations may not reflect the current version of the application

Genetic Clinical Decision Support

(Leveraging structured genetic test results, launched in LMR, March 2007)

Warning	
You are ordering: TARCEVA (ERLOTINIB)	
Drug - Genetic Intervention	
Alert Message	Keep New Order - select reason(s)
TARCEVA (ERLOTINIB) is contraindicated in patients with a somatic EGFR mutation known to be associated with resistance to Tyrosine Kinase Inhibitors for treatment of non-small cell lung cancer. Most recent = Resistant 12/21/2006 See Report in Genetics Summary under Results	Reasons for override: <input type="checkbox"/> Patient has pancreatic cancer <input type="checkbox"/> No reasonable alternatives <input type="checkbox"/> Other <input type="text"/>

This slide is intended to illustrate general IT functionality.
Content displayed is not intended for clinical use.
Screen configurations may not reflect the current version of the application

Extending HIT for clinical genetics

CLINICAL GENETIC DATA STANDARDS

HHS – ONC Use Cases

Personalized Healthcare

U.S. Department of Health and Human Services
Office of the National Coordinator for Health Information Technology



Personalized Healthcare Draft Detailed Use Case

January 18, 2008

Newborn Screening

U.S. Department of Health and Human Services
Office of the National Coordinator for Health Information Technology



Resource Guide for Newborn Screening
Draft Detailed Use Case

September 19, 2008

Implementation Guide for Structuring Clinical Genetic Test Results in the EHR

- DNA Variants within a Gene
- Gene Alleles
- Interpretations associated with
 - Drug Efficacy
 - Drug Metabolism
 - Carrier Testing
 - Disease (Risk /Diagnosis)
- Test Definition
- References to Public Knowledge (e.g. PubMed, PharmGKB and OMIM)

V2IG_CG_LOINCENVAR_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 LOINCENVAR R2-2013

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

5/5/2013

Sponsored by:
Clinical Genomics Work Group

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HHS-ONC & HL7 Family History Work

Minimal Core Dataset

Journal of the American Medical Informatics Association Volume 15 Number 6 November / December 2008

723

Position Paper ■

New Standards and Enhanced Utility for Family Health History Information in the Electronic Health Record: An Update from the American Health Information Community's Family Health History Multi-Stakeholder Workgroup

W. GREGORY FEYER, MD, PhD, MARY BETH BICLEY, DRPH, MSN, ANP, KRISTIN M. BENNER, PhD, THE FAMILY HEALTH HISTORY MULTI-STAKEHOLDER WORKGROUP OF THE AMERICAN HEALTH INFORMATION COMMUNITY

Abstract Family health history is a complex, multifaceted tool for assessing disease risk that can offer insights into the interplay between inherited and social factors relevant to patients care. Family health history tools in electronic health records can enable the user to collect, represent, and interpret structured data that properly supports clinical decisions. If these data can be made interoperable, important health information can be shared with minimal duplication of effort among entities involved in the continuum of patient care. This paper reviews the efforts by the American Health Information Community's Family Health History Multi-Stakeholder Workgroup to create a core data set for family health history information and to determine requirements to promote incorporation of such information in electronic health records. The Workgroup is a component of the U.S. Department of Health and Human Services' Personalized Health Care Initiative.

■ J Am Med Inform Assoc. 2008;15:723-728. DOI 10.1197/jamia.M2793.

Family Health History and Health Information Technology: An Opportunity for Synergy

As our scientific understanding of the molecular and genetic/ genomic basis for health and disease improves, the importance of family health history as a predictive tool continues to increase. Although currently underutilized in health care, family health history information can play a central role in enhancing the uptake and effectiveness of preventive services for a variety of disorders that affect public health.^{1,2} Family health history can clarify a patient's potential disease risk and treatment options and inform differential diagnosis in symptomatic patients. Additionally, guidelines for screen-

ing and management of common disorders, including diabetes, cancer, and cardiovascular disease, incorporate family health history information.³⁻⁶ However, obtaining a family health history is time-consuming, and many primary care providers are insufficiently trained to appropriately interpret the information they obtain.⁷ Numerous studies show that health care providers often obtain minimal to no family health history in the context of health care visits.⁸ With the transition from paper-based systems to electronic personal health record (PHR) and electronic health record (EHR) systems, this situation may worsen as many of these systems are underdeveloped with regard to family health history capabilities.

A potential solution to optimize the use of family health history in clinical medicine is to develop health information technology (HIT) systems that facilitate patient entry of family health history information and provide automated clinical decision support for health care providers. Several web-based tools have been developed to facilitate patient collection of family health history information, most notably My Family Health Portrait (MHPHP), freely available at www.familyhistory.hhs.gov, created by a collaboration between the Centers for Disease Control and Prevention (CDC), the Office of the Surgeon General, and the National Human Genome Research Institute of the National Institutes of Health, and the CDC's Family HealthLink™. The format, which has been tested extensively in a variety of user populations, helps patients to collect and organize their family health history but does not include interpretive capabilities. The latter, currently available as a research tool (<http://www.cdc.gov/genomics/about/family.htm>), helps patients collect family health history information and incor-

Affiliations of the authors: Genomic Healthcare Branch, National Human Genome Research Institute, National Institutes of Health, Department of Health and Human Services (WGF), Bethesda, MD; Office of the U.S. Surgeon General, Department of Health and Human Services (MBB), Washington, DC; American Association for the Advancement of Science, Personalized Health Care Initiative, Department of Health and Human Services (KMB), Washington, DC. The authors thank Gregory J. Downing, DO, PhD, Charles A. Goldbrowne, Jr., PhD, and Lauren Kim for their assistance in the preparation of this manuscript.

For members of the AHIC Family Health History Multi-Stakeholder Workgroup please see Appendix 1 "Family Health History Multi-Stakeholder Workgroup," available as an online data supplement at www.jamia.org.

Correspondence: W. Gregory Feyer, MD, PhD, Chief, Genomic Healthcare Branch, National Human Genome Research Institute, Building 31, Room 4B09, 31 Center Drive, Bethesda, MD 20892; e-mail: wfeyer@nhgri.nih.gov.

Received for review: 03/12/08; accepted for publication: 07/25/08

Implementation Guide



HL7 Clinical Genomics Work Group

The Family History Standard –

Implementation Guide

(US Realm)

December 2012

Pedigree R1 Co-Editors:

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US Realm IG Co-Editors:

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³Deane-Farber Cancer Institute and Partners Healthcare.

⁴Lantana Consulting Group.

⁵Life Technologies.

⁶Intermountain Healthcare.

⁷Avon Comprehensive Breast Evaluation Center, Massachusetts General Hospital.

Current HIT Clinical Genomics Data Standards

Ensure transfer of data between systems ...

Health Level Seven – HL7

Ensure standard description of tests, results, and interpretations ...

LOINC, Logical Observation Identifiers Names and Codes
HGVS Nomenclature, Human Genome Variation Society
HGNC, Human Gene Nomenclature Committee
RefSeq, Reference Sequences NCBI
dbSNP. Single Nucleotide Polymorphism
ISCN, International Society for Cytogenetics Nomenclature

Ensure standard context for interpretations (i.e. associations) ...

SNOMED & RxNORM

Other References

LRG, OMIM, COSMIC, PubMed...

LOINC Panels Serve as a Template for DNA Variant Details

LOINC Code	Name	Example value	source
51958-7	Transcript Reference Sequence Identifier	NM_005228.3	NCBI RefSeq
48018-6	Gene identifier	EGFR	HGNC Nomenclature
48004-6	DNA Sequence Variation	c.2573T>G	HGVS Nomenclature
48003-8	DNA Sequence Variation identifier	rs121434568	NCBI dbSNP
48002-0	Genomic source class	Somatic, Likely Somatic, Unknown Origin, Likely Germline, Germline	LOINC Answer List
51961-1	Drug efficacy sequence variation interpretation	Resistant, Responsive, Presumed Resistant, Presumed Responsive, Unknown Significance, Benign, Presumed Benign, Presumed Non-Responsive	LOINC Answer List

HL7 v2.5.1 Laboratory Reporting of Genetic Results

Header

3-7^Medication assessed^LN||337525^Erlotinib^RxNorm|||||F|20080702100909|||||Laboratory for Molecular
2D1005307^^^CLIA&2.16.840.1.113883.4.7&ISO|1000 Laboratory Lane^Ste. 123^Cambridge^MA^99999^USA^B
2-0^Genomic source class^LN||LA6684-0^Somatic^LN|||||F|20080702100909|||||Laboratory for Molecular
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Medicine^L^22D1005307^^^CLIA&2.16.840.1.113883.4.7&ISO|1000 Laboratory Lane^Ste. 123^Cambridge^MA^99999^USA^B
OBX|4|FT|51969-4^Genetic analysis summary report^LN||\...<Report Text>

Findings (repeat panel as needed)

Genetic analysis discrete result panel^LN||20080702000000|||||20080703000000|||||
55208-3^DNA analysis discrete sequence variation panel^LN||20080702000000|||||20080703000000|||||
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OBX|3|CWE|51958-7^Transcript reference sequence identifier^LN||NM_005228.3^2.16.840.1.113883.6.280|||||F|20080702100909|||||Lab
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OBX|4|CWE|48003-8^DNA sequence variation Identifier^LN||rs121434568^99HPCGG-LMM-MARKER|||||F|20080702100909|||||Laboratory for Mo
Medicine^L^22D1005307^^^CLIA&2.16.840.1.113883.4.7&ISO|1000 Laboratory Lane^Ste. 123^Cambridge^MA^99999^USA^B
OBX|5|CWE|48004-6^DNA sequence variation^LN||c.2573T>G
^2.16.840.1.113883.6.282|||||F|20080702100909|||||Laboratory for Molecular Medicine^L^22D1005307^^^CLIA&2.16.840.1.113883.4.7&ISO|1000 Laboratory Lane^Ste. 123^Cambridge^MA^99999^USA^B
Exon 19|||||F|20080702100909|||||Laboratory for Molecular Medicine^L^22D1005307^^^CLIA&2.16.840.1.113883.4.7&ISO|1000 Laboratory Lane^Ste. 123^Cambridge^MA^99999^USA^B
OBX|10|CWE|48002-0^Genomic source class^LN||LA6684-0^Somatic^LN|||||F|20080702100909|||||Laboratory for Molecular
Medicine^L^22D1005307^^^CLIA&2.16.840.1.113883.4.7&ISO|1000 Laboratory Lane^Ste. 123^Cambridge^MA^99999^USA^B
OBX|11|ST|47998-0^DNA sequence variation display name^LN||
c.2573T>G (p.Leu858Arg), Exon 21, EGFR, Responsive|||||F|20080702100909|||||Laboratory for Molecular Medicine^L^22D1005307^^^CLIA&2.16.840.1.113883.4.7&ISO|1000 Laboratory Lane^Ste. 123^Cambridge^MA^99999^USA^B
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HL7 v3 CDA-based Laboratory Reporting of Genetic Results

Header

- Ordering and performing organizations and clinicians
- Patient identifying information
- Test(s) performed
- Indication for testing
- Specimen information
- Interpretation context and overall result → Genetic Disease Assessed = Dilated Cardiomyopathy & Genetic Disease Analysis Overall Interpretation = Positive

Findings (repeat panel as needed)

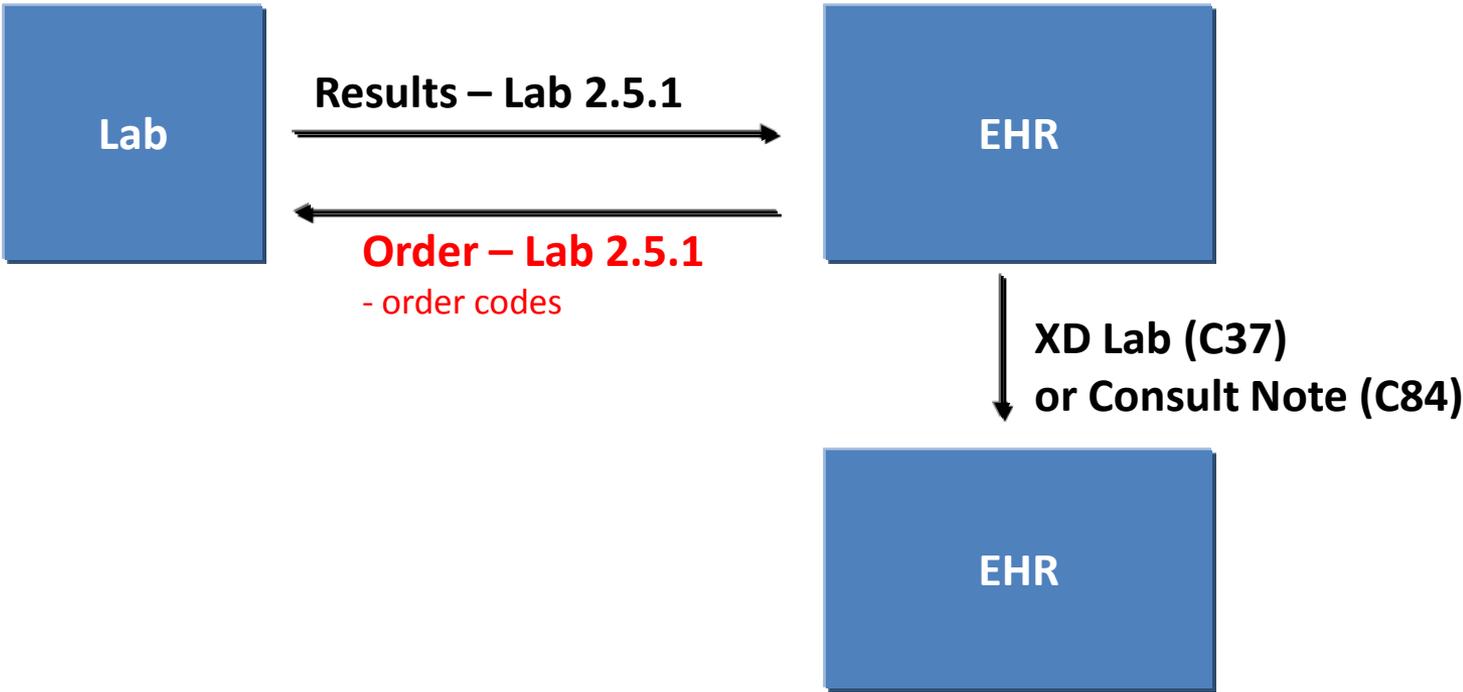
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<value xsi:type="CD" code="LA6690-7" codeSystemName="LOINC" displayName="Substitution"/></observation></entryRelationship>
<entryRelationship typeCode="SUBJ"><observation classCode="LOC" moodCode="EVN">
<code code="53037-8" codeSystemName="LOINC" displayName="Genetic disease sequence variation interpretation"/>
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.....<observation classCode="PHN" moodCode="DEF">
<code code="53037-8" codeSystemName="LOINC" displayName="Genetic disease sequence variation interpretation"/>
<value xsi:type="CD" code="LA6669-1" codeSystemName="LOINC" displayName="Pathogenic"/></observation>

```

Clinical Genomic Messaging Standards from HITSP & HL7



Assets

Gaps

HL7 Implementation Guides for Clinical Genetic Workflow

- Laboratory Reporting for Gene Variants associated with Disease Diagnosis, Disease Risk, Drug Metabolism and Drug Efficacy and Tumor Genotyping
- Laboratory Reporting for Cytogenetics (anticipated July 2013)
- Genetic Test Report (*CDA format for above testing types*)
- Family History/Pedigree
 - Support for genetics – risk assessment and recording of genetic test results
- CDA-based Genetic Test Report

Clinical Genomic Standards

HIT Standards for Emerging
Clinical Genomic Testing
&

Advanced Functionality and Workflows

Unifying clinical genomic stakeholders through common domain analysis model

CLINICAL SEQUENCING DOMAIN ANALYSIS MODEL

HL7 Clinical Sequencing Domain Analysis Model

V3DAM_CG_CLINSEQ_R1_01_2013JAN



1. Define specimen identification needs
2. Define use cases/scenarios
3. Define standard data representations, terminology, minimal core data sets and useful extensions
4. Identify standards for above
5. Obtain necessary OID's and LOINC codes
6. Pilot and iterate incorporating lessons learned

HL7 Version 3 Domain Analysis Model:
Clinical Sequencing, Release 1
January 2013

HL7 Comment Only Ballot

Sponsored by:
Clinical Genomics Work Group

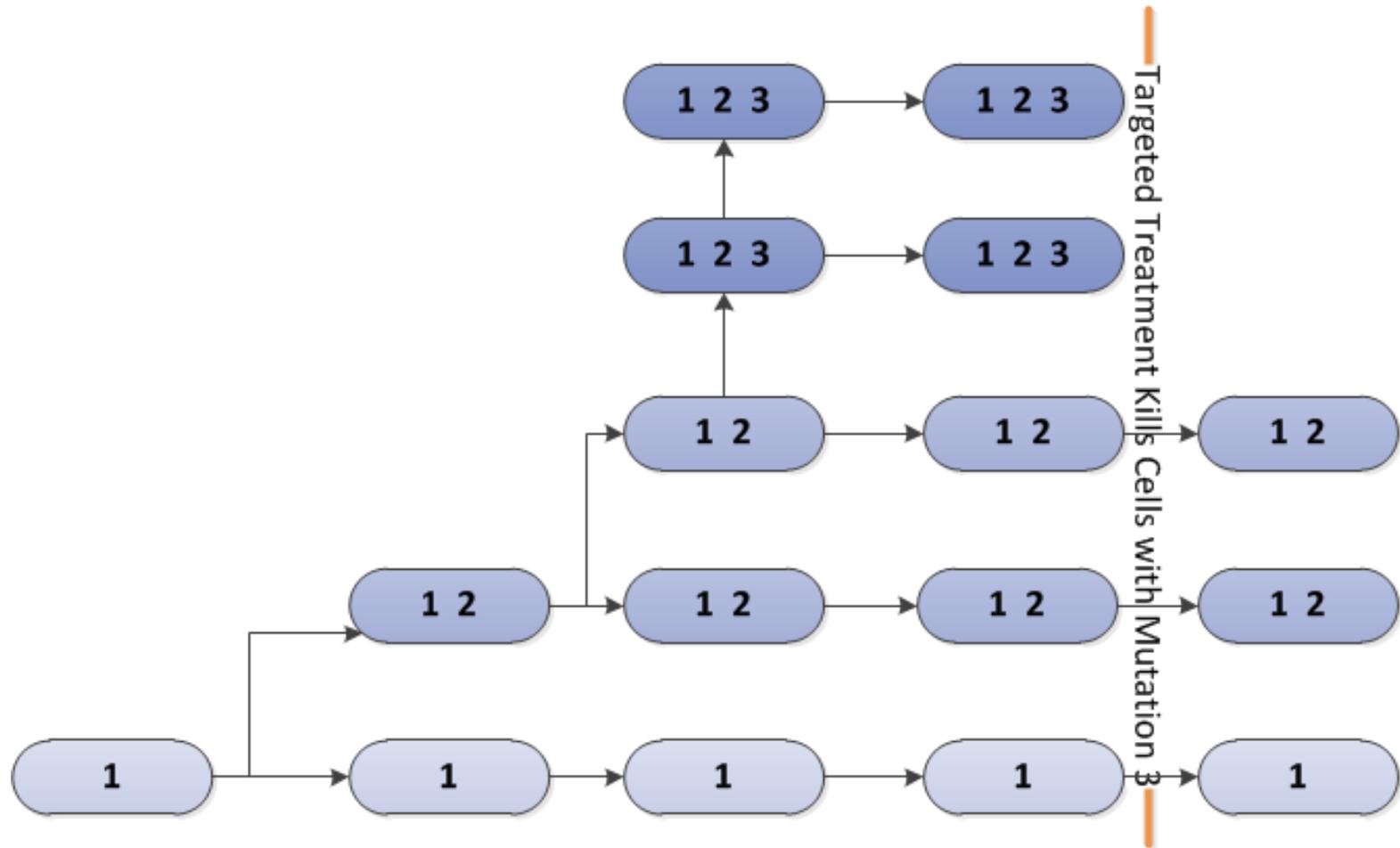
Principal Contributors:
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Questions or comments regarding this document should be directed to Mollie Ullman-Cullere at mullmancullere@partners.org.

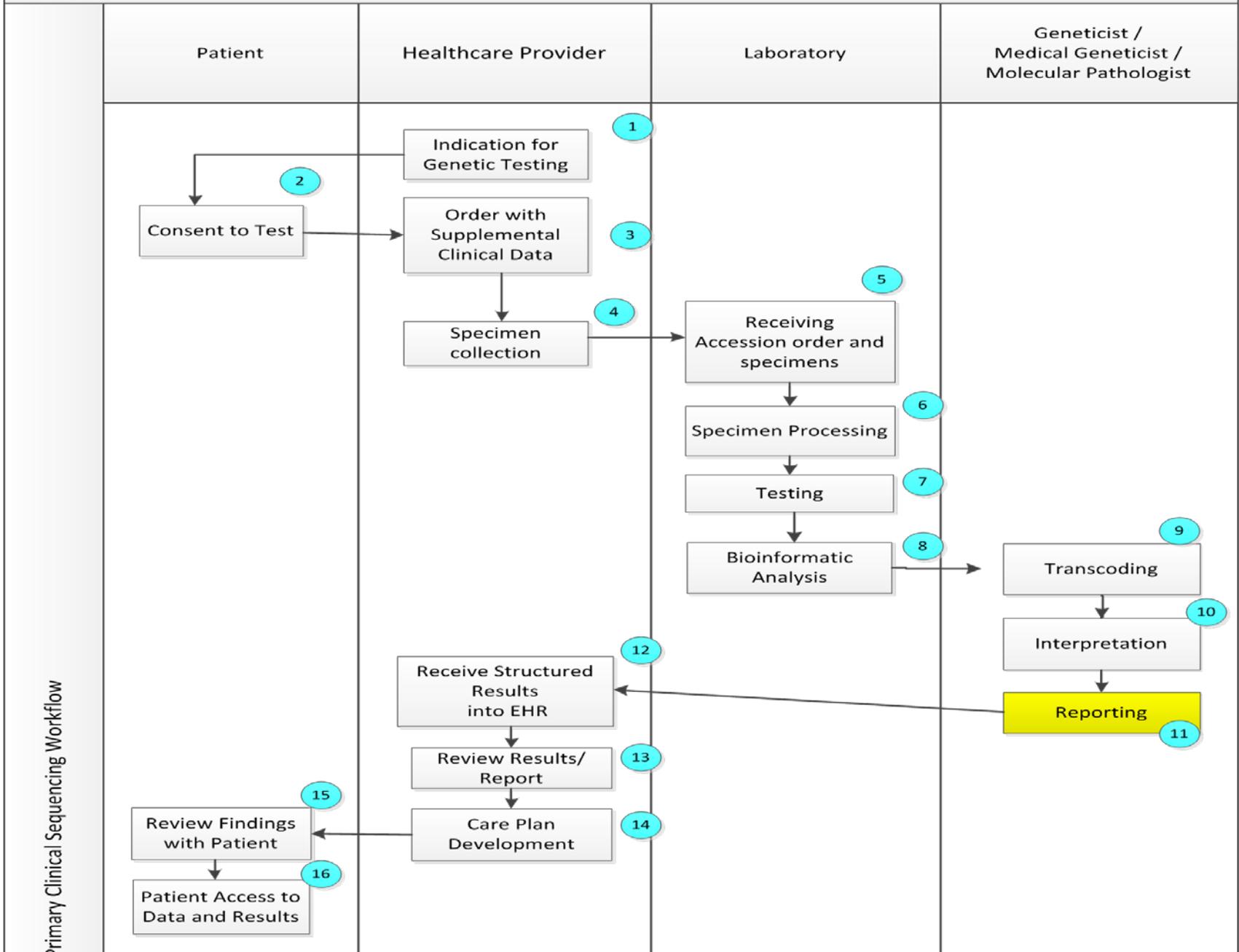
Specimen Identification

- Germline testing for biomarkers/mutations (usually inherited)
- Tumor testing for somatic (tumor specific biomarkers/mutations)
- Pediatric testing for biomarkers/mutations causal to rare early childhood conditions
- Prenatal testing which may be reported on the maternal medical record
- Infectious disease testing

Time Presents Additional Challenges for Somatic and Infectious Disease Testing

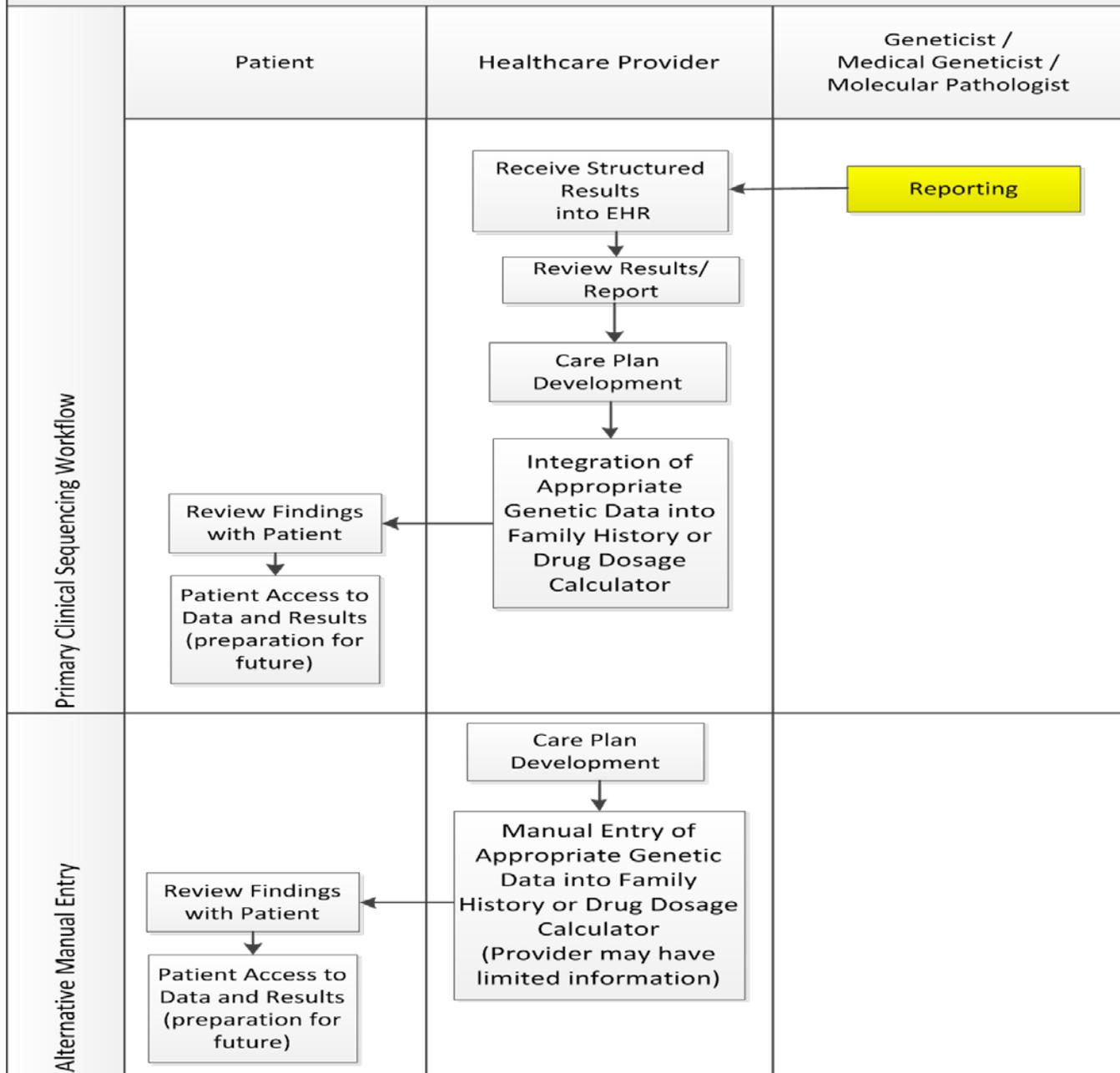


Clinical Sequencing Workflow – Germline Testing

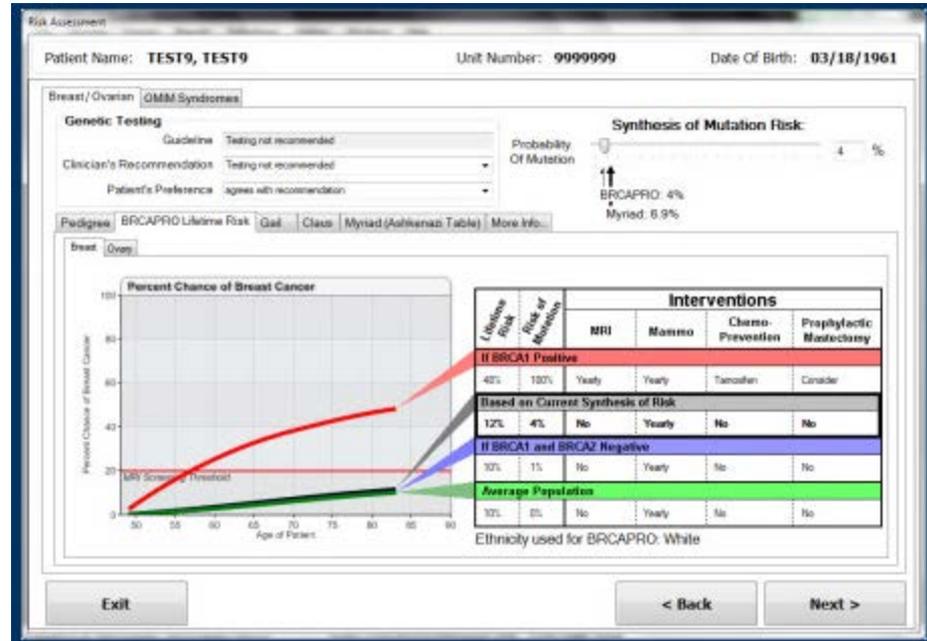
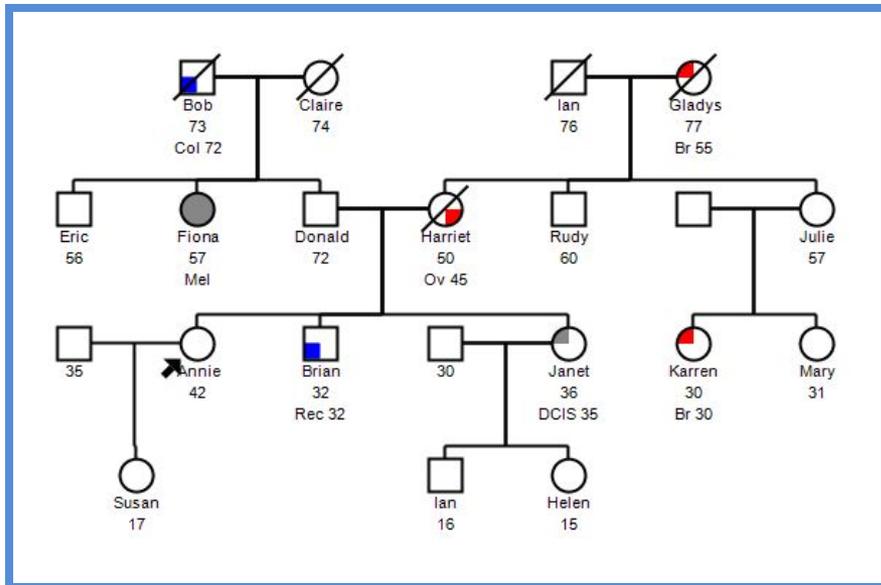


Primary Clinical Sequencing Workflow

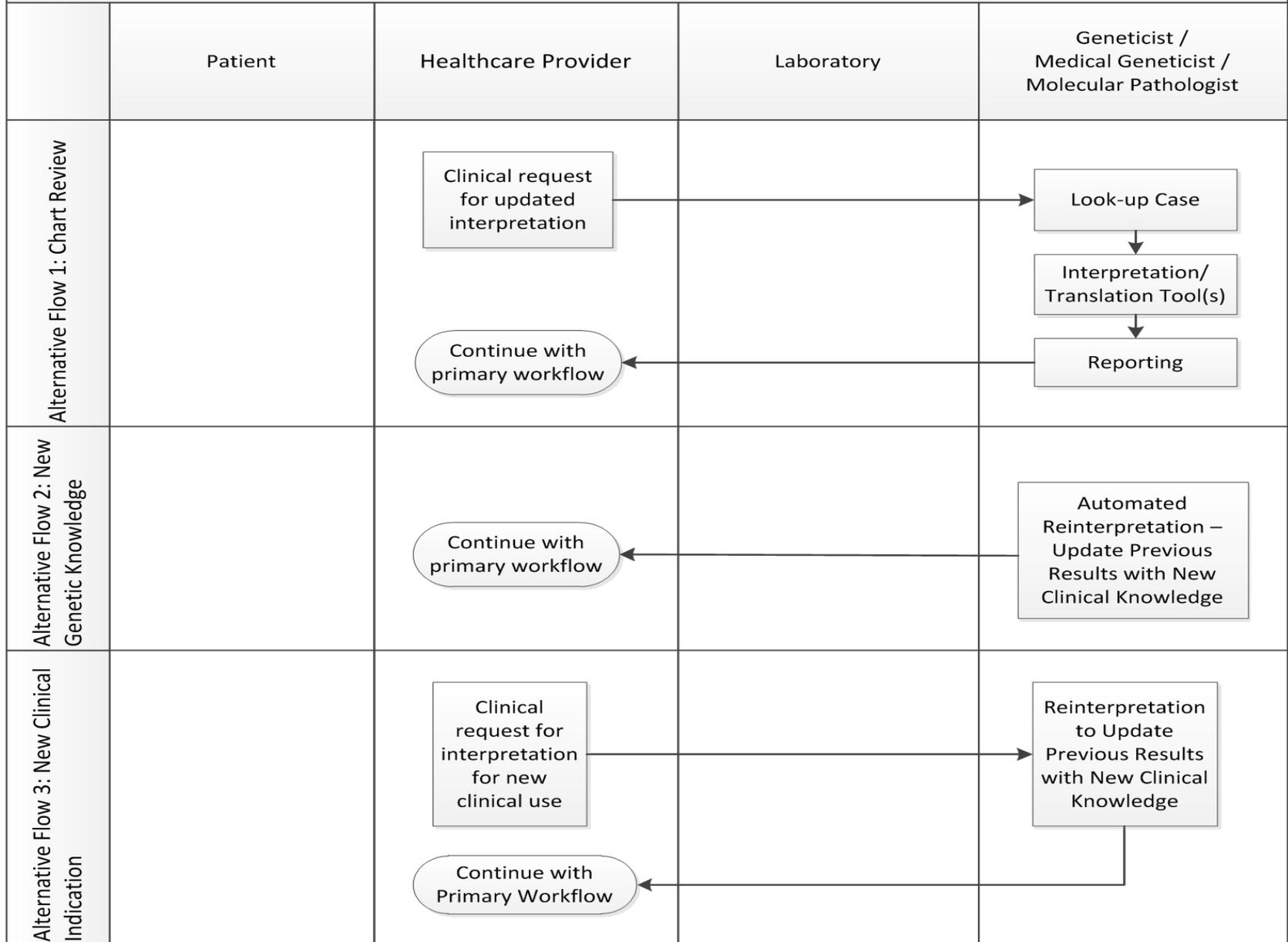
Decision Making Tools: Family History or Drug Dosage Calculator



Family History based Risk Calculation & Treatment Plans



Clinical Sequencing Workflow – Germline Testing - continued



Genetic Test Results and Up-to-date Knowledge

GenInsightSM Clinic Demo User Guide | Support [REDACTED] Log Out

Patient Search **Tests** Users

[REDACTED] (DEMOA-MRN) [REDACTED] Male

IMPORTANT USAGE & DATA LIMITATIONS

Accession #	Status	Test	Overall Interpretation	Indication	Primary Specimen	Genomic Source
[REDACTED] View Report	FINAL, [REDACTED]	HCM CardioChip (11 Genes Sequenced) Sequence Confirmation Test	<i>(Possibly Outdated)</i>	Clinical diagnosis of concentric HCM with Wolff-Parkinson-White syndrome	Blood, Peripheral, [REDACTED]	Germline

Variant	Reported	Families	Current Category*	Reported Category
Heterozygous c.1030C>T (p.His344Tyr), Exon 9, PRKAG2 (Germline)	11	9	Pathogenic	Unknown-Significance

* The current category field displays the variant significance only within the diseases/diagnoses that have been integrated on each report, primarily defined by the ordered test. Additional interpretations, if present, outside these diseases/diagnoses are not considered.

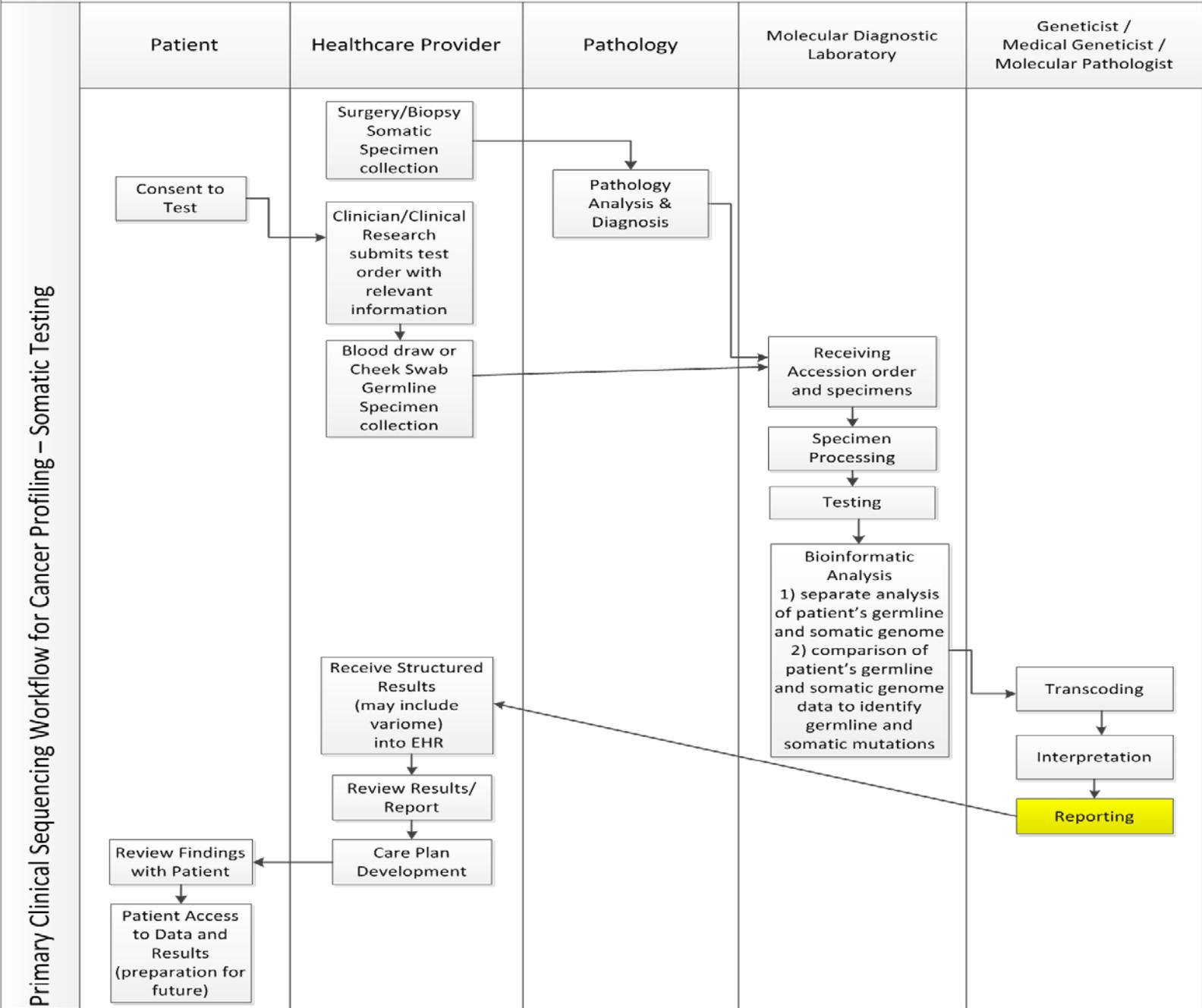
The GenInsight suite: a platform to support laboratory and provider use of DNA-based genetic testing

Human Mutation

Volume 32, Issue 5, pages 532-536, 22 MAR 2011 DOI: 10.1002/humu.21470

<http://onlinelibrary.wiley.com/doi/10.1002/humu.21470/full#fig4>

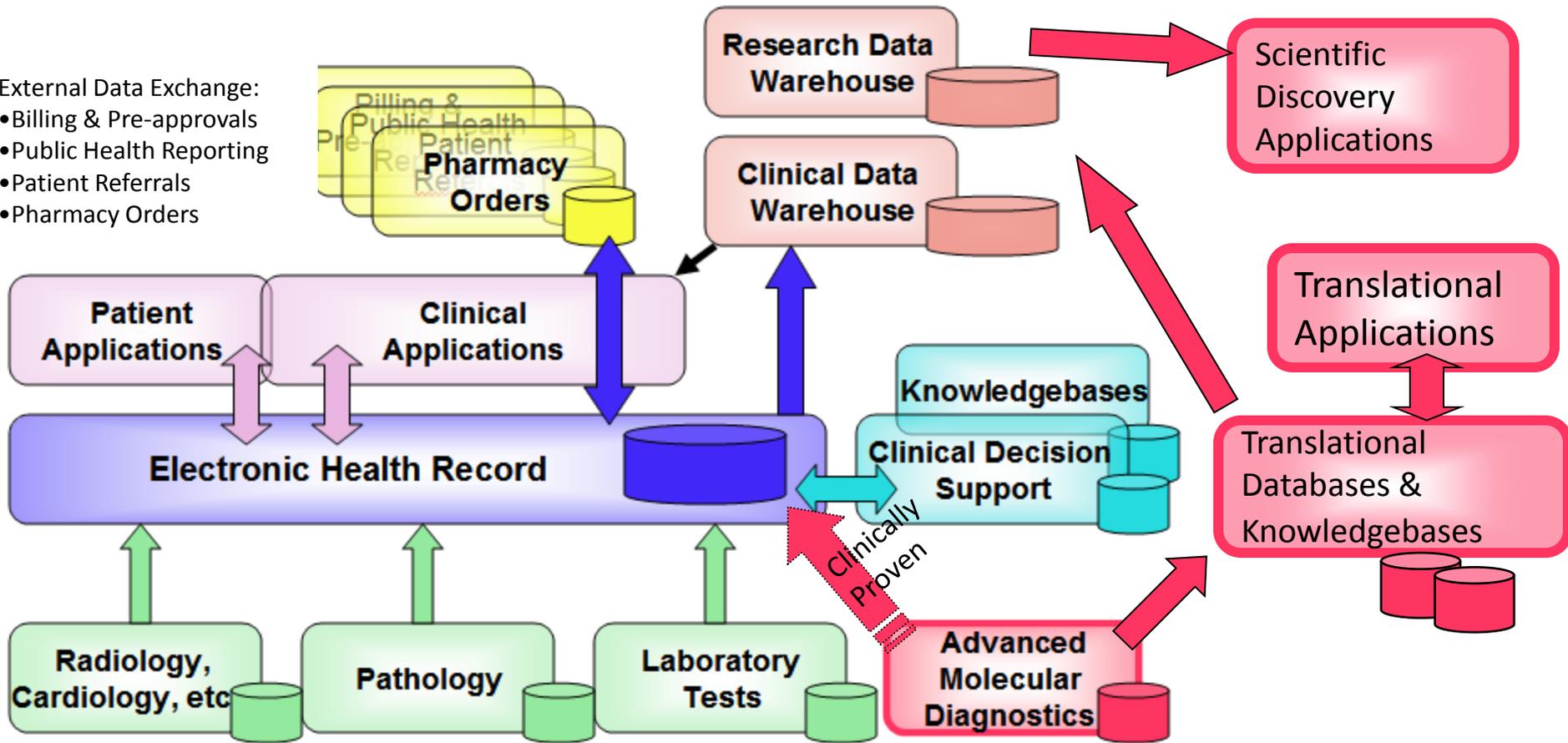
Clinical Sequencing Workflow for Cancer Profiling – Somatic Testing



Primary Clinical Sequencing Workflow for Cancer Profiling – Somatic Testing

Using Transitional Frameworks for Cancer Genomics

- External Data Exchange:
- Billing & Pre-approvals
 - Public Health Reporting
 - Patient Referrals
 - Pharmacy Orders



Additional Use Cases

- Public Health Reporting
 - Cancer Registry
- Donor Matching for Transplantations
 - National Marrow Donor Program
- Clinical and Research Data Warehouses
- FDA and Clinical Trials
 - Adverse Event Reporting and Clinical Trial Submissions
- Newborn Screening - extended clinical workflow
- Infectious Disease
- State Health Exchange Networks
- Other – missing use cases???

Workgroups to Watch

College of American Pathologists' (CAP) Cancer BioMarker Workgroup

- CAP, CDC & Cancer Registry initiative to obtain LOINC codes for clinical tumor biomarkers and code cancer templates
- Biomarkers provided to NCBI for inclusion in MedGen and annotated/linked to dbSNP, ClinVar, and Genetic Test Repository (GTR)

CDC, NIST, NCBI, FDA and community experts/stakeholders from the clinical laboratory, bioinformatic and healthcare IT standards community has been formed to develop a clinical grade

- Develop clinical grade VCF/GVF file formats for genomic data

HL7 Clinical Genomics Workgroup

- Representatives participating in above workgroups for harmonization and extension of HL7 standards

CAP Cancer BioMarker Reporting Workgroup

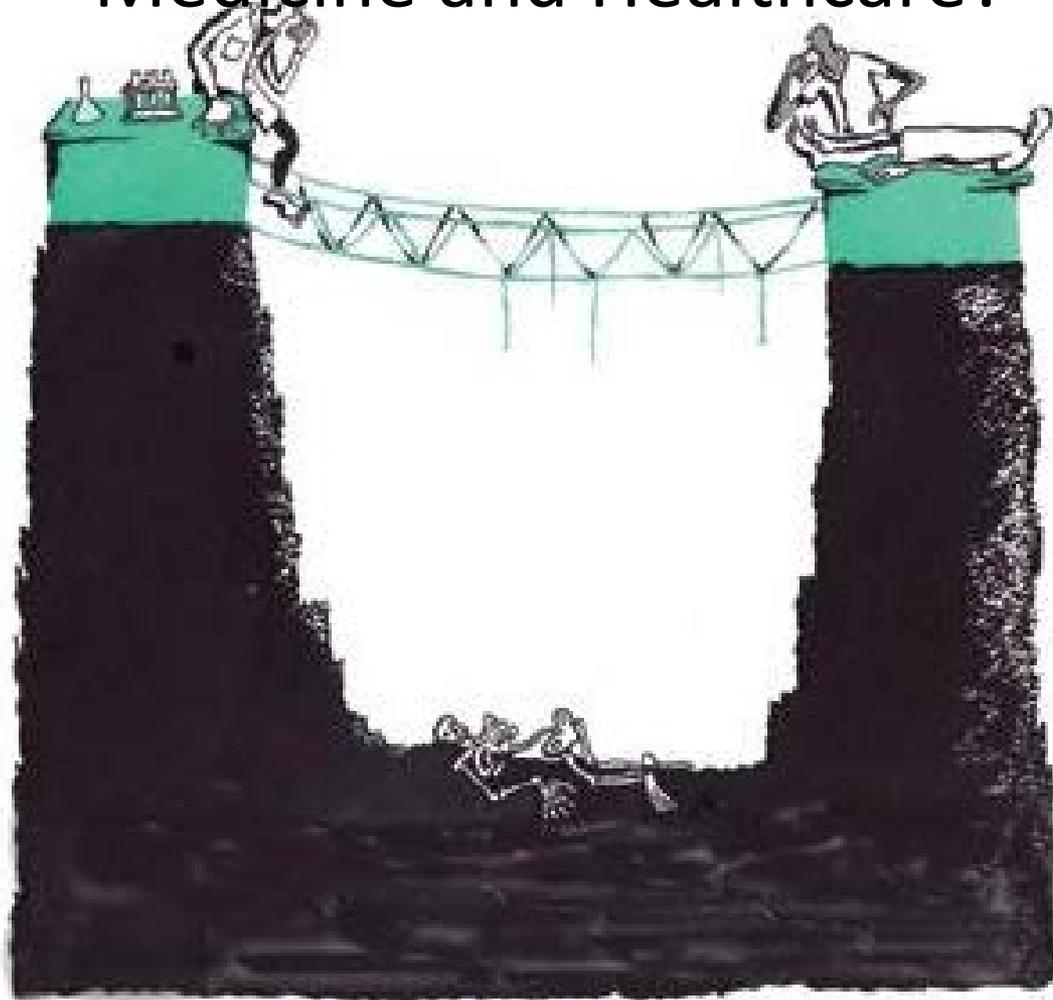
- How will bioinformaticists, molecular pathologist, oncologists, pharmacists, and cancer registrars understand specific biomarkers associated with pharmacogenomics, prognosis, and diagnosis, when a biomarker may be caused by thousands or millions of different DNA changes?
 - Mapping whole genome sequencing data to clinically actionable biomarkers
 - Maintaining knowledge – clinical implications and orderable tests
 - Collecting population data and outcomes
 - Contextualizing within the clinical disease – cancer checklists

Federally Mediated Clinical Grade-Genomic Data File Formats

- Compared to clinical genetic standards bioinformatic standards are a 'wild west'
 - Standardizing genomic standards for clinical use
 - Harmonizing tools development
 - Creating a common language for data interoperability

Implementation Roadmap,
Need for Innovation
&
A Call to Action

How do we not make this a picture of Genomic Medicine and Healthcare?



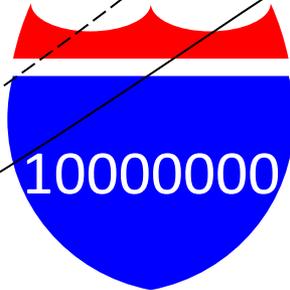
B. MELLOR

Not For Open Access *Butler, D. Translational Research: Crossing the Valley of Death. Nature 453, 840-842 (2008)*

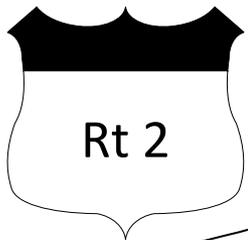
Copyright 2011 - All Rights Reserved

What do we need to bring genomics into clinical care in a cost-effective manner, with patient safety first?

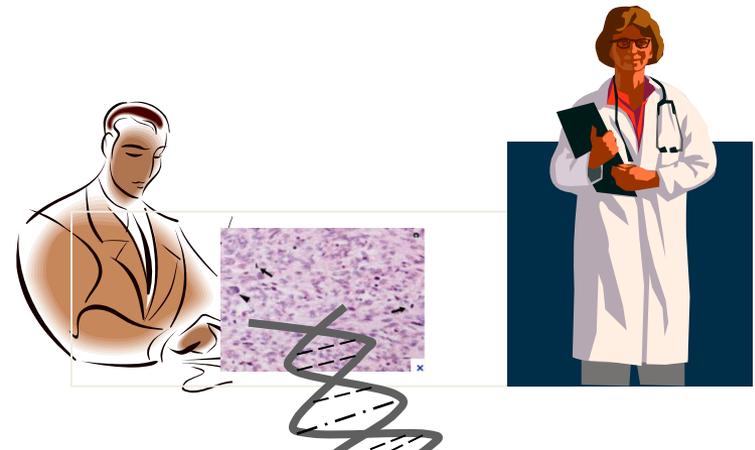
Exome-Genome Sequencing



Genetic Test



Targeted Sequencing



Traditional Lifecycle of Cancer Therapy



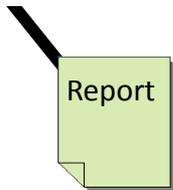
Surgery ★

Was the correct operation performed?

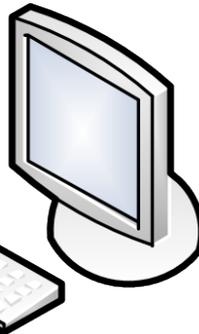


Pathology ★

Was the correct diagnosis reported?



Oncologists Read Reports & Writes Prescriptions in the Electronic Medical Record



★ Previous medical error

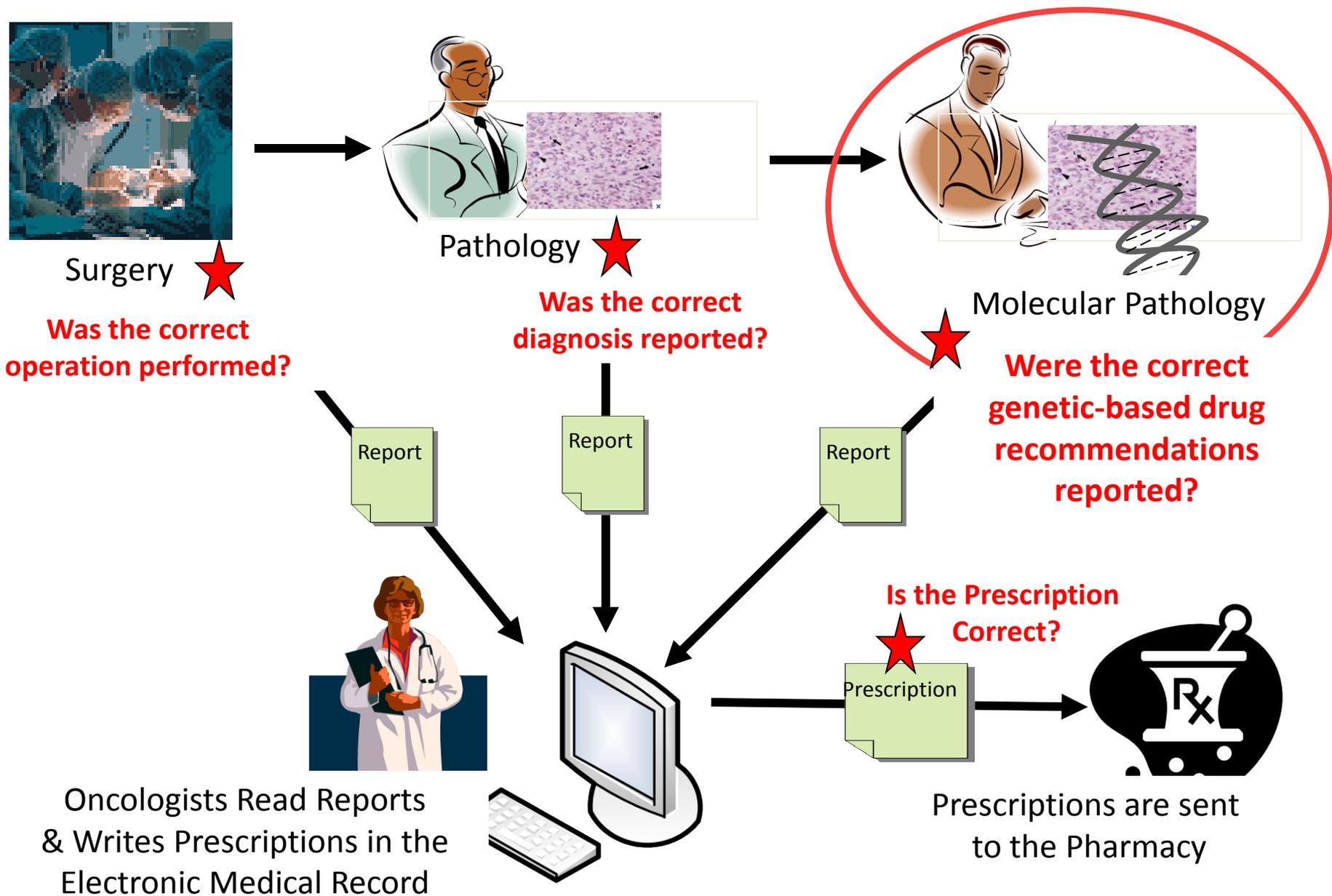
Is the Prescription Correct? ★



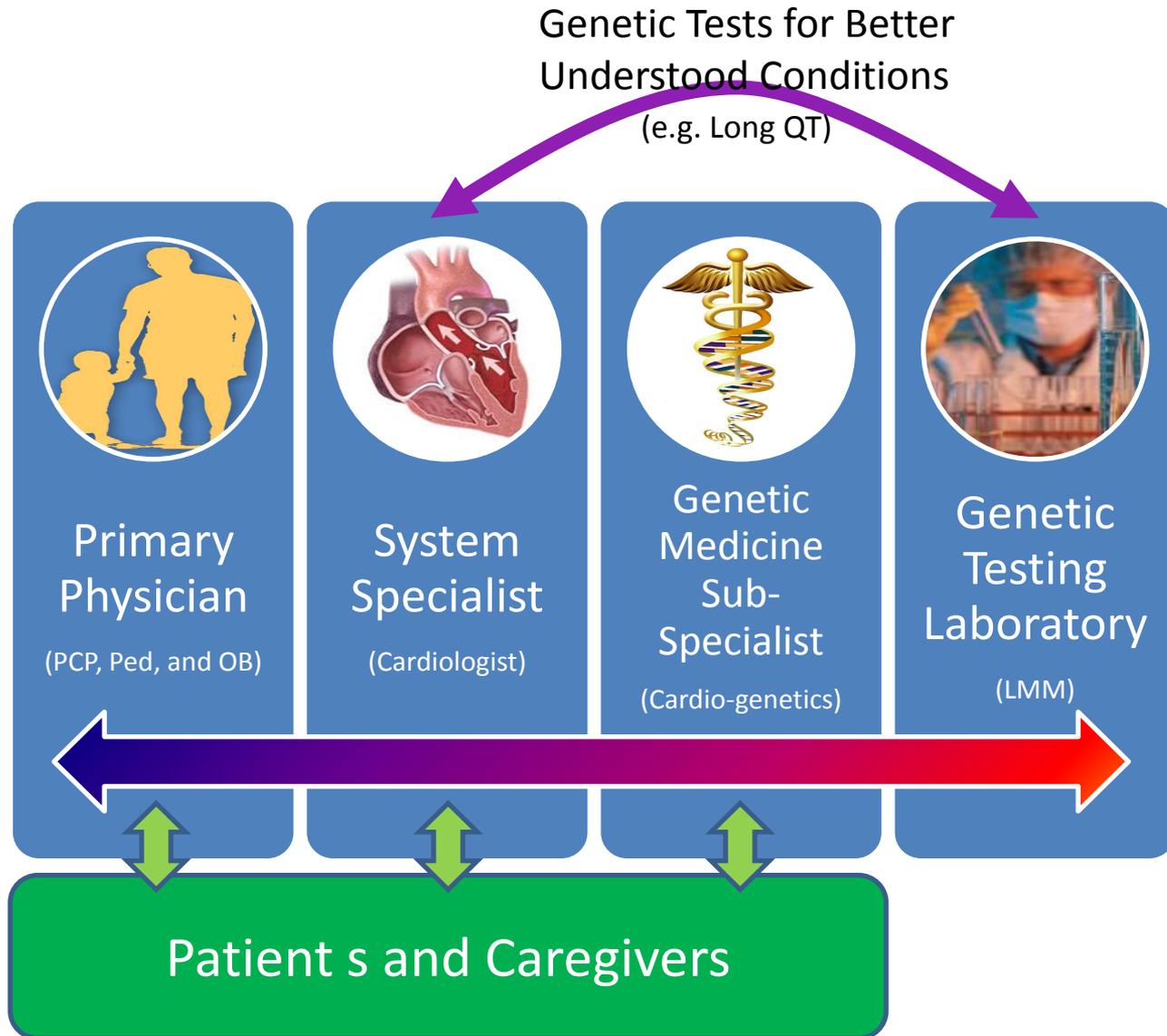
Prescriptions are sent to the Pharmacy



Lifecycle of Cancer Therapy Informed by Genetics



Healthcare IT Support for Personalized Medicine



State Genetic Privacy Laws - 2008



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Genetic Privacy Laws

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Updated January 2008

RESOURCES

Related Documents

Health

Special Topics - Genetics

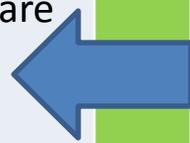


Members

State and Statute	Personal Access to Genetic Information Required	Consent Required to				Define as Personal Property		Specific Penalties for Genetic Privacy Violations
		Perform/ Require Genetic Test	Obtain/ Access Genetic Information	Retain Genetic Information	Disclose Genetic Information	Genetic Information	DNA Samples	
Alabama								
Alaska §18.13.010-100		x	x	x	x	x	x	x
Arizona §20-448.02		x			x			
Massachusetts §111.70G		x			x			x
Virginia §38.2-508.4					x			
Total	4	12	7	8	27	5	1	19

Current Landscape

Historic Industry Practice	Emerging Industry Practice		Healthcare IT Data Standard
Paper based, narrative reports	Electronic reports, moving from narrative to synoptic reporting (e.g. enables computer parsing)		Electronic reports transmitted with computer readable findings
No consistent reporting formats	Increasingly consistent report formats, incorporating healthcare IT data standards into written reports		Structured/coded findings, transmitted with report, use standard nomenclature and contain references to external knowledge
LOINC: Not used	LOINC: Test name is LOINC coded – no standard naming convention, frequent duplicates		<p>LOINC: Used to structure findings/metadata</p> <p>Doesn't change test naming conventions, as it was felt that this should be addressed in the future with NCBI's genetic test registry</p>



Opportunity Space

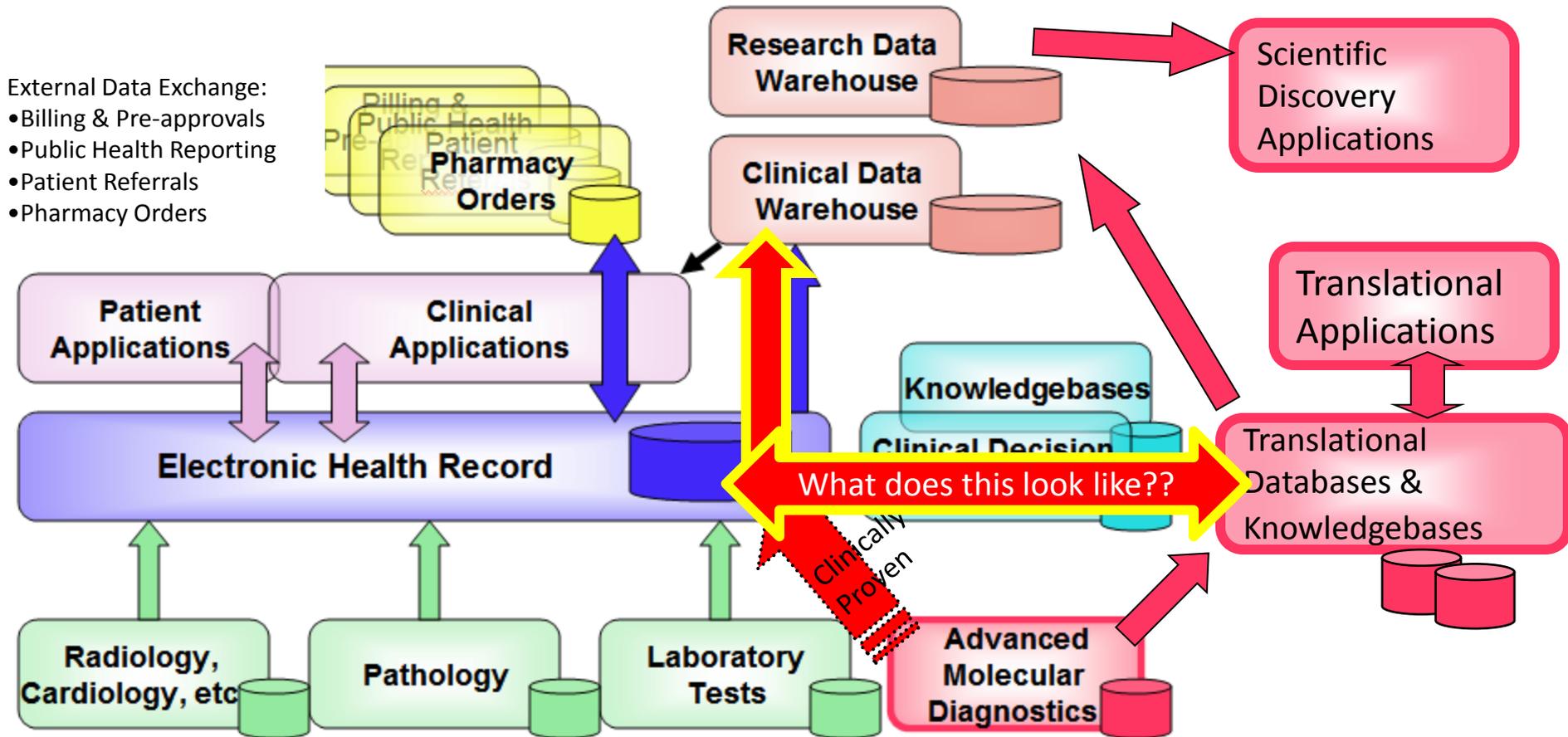
Current Implementation Roadmap Recommendations

(used by several pilot organizations)

1. Incorporate design in databases → reference sequences, HGVS nomenclature, etc...
 2. Implement design standard in laboratory reports and/or data files
 - E.g. Molecular diagnostic reports transmitted through a pathology reporting system or clinical grade-GVF or VCF file exchanged in a secure manner
 3. Validate utility of information model through active use in business
 4. Iterate on information model incorporating lessons learned
 5. Formally develop HL7 interfaces for fully codified/qualified data when business is ready
- Summary: You don't have to wait until the EHR is ready to receive the data.

Innovation Through Integration With Translational Frameworks

- Adheres to development best practices
- Uses Healthcare IT data standards and structured/codified data



What is needed to stimulate Healthcare IT innovation for personalized genomic medicine?

- Compelling value propositions
- Market
 - Customers: Community and Stakeholder engagement
 - Context : Meaningful Use, Electronic Medical Records (EMRs), State Genetic Privacy Laws and Next Generation Sequencing
 - Collaborators: EMR and Instrument Vendors, HHS/ONC, and Standards and Professional Organizations
 - Technical Feasibility: EMRs, Standards, Technology, and Software Innovators
 - Financial Feasibility: High cost of duplicative infrastructure investment and lost opportunity through lack of integrated repositories of structured data

Call to Action for HIT support of Personalize Medicine

- Compelling value propositions
 - Need well structured data repositories
- Customers : Community and Stakeholder engagement
 - ONC/HHS HIT activities disbanded & standards/use cases no longer available
 - Professional and Standards Organizations and Fed. Agencies slowly picking this up
- Context : Meaningful Use, EMRs, and Next Generation Sequencing
 - Need standards development/harmonization across stakeholder groups
 - Need review and updating of state genetic privacy laws in Post-GINA environment
- Collaborators : EMR and Instrument Vendors, HHS/ONC, and Standards and Professional Organizations
- Technical Feasibility → EMRs, Standards, Technology, and Software Innovators
 - Open vs. Closed EMR's – community needs to define requirements of an open EMR, demand them from vendors, and implement them
 - How do we promote and support software innovation and adoption?
- Financial Feasibility → High cost of duplicative infrastructure investment and lost opportunity through lack of integrated repositories of structured data
 - Invest in shared technology, data interoperability, data sharing, and software applications to create structured quality genetic data