Implementing Genomic Medicine Programs: The Laboratory Perspective

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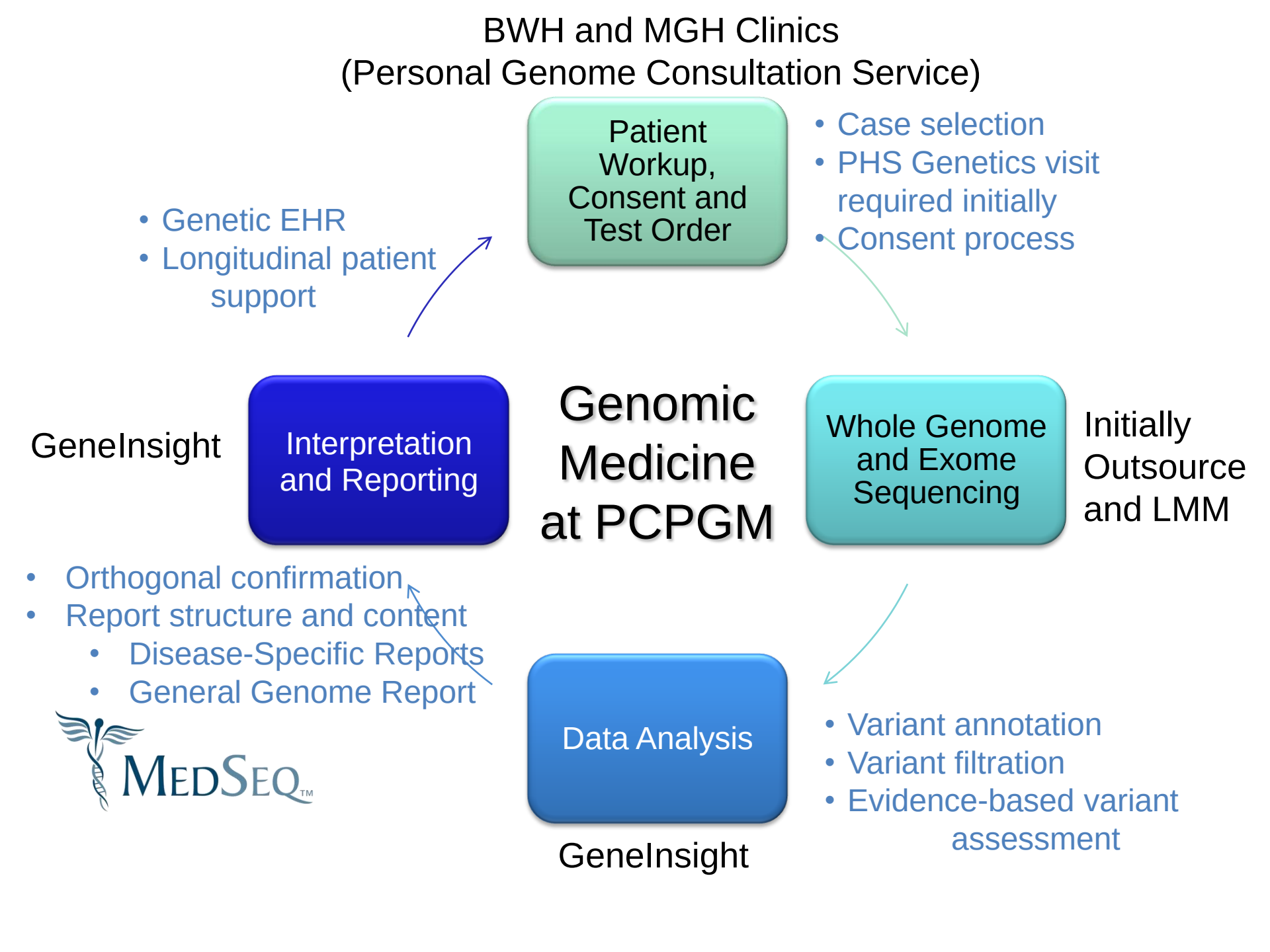
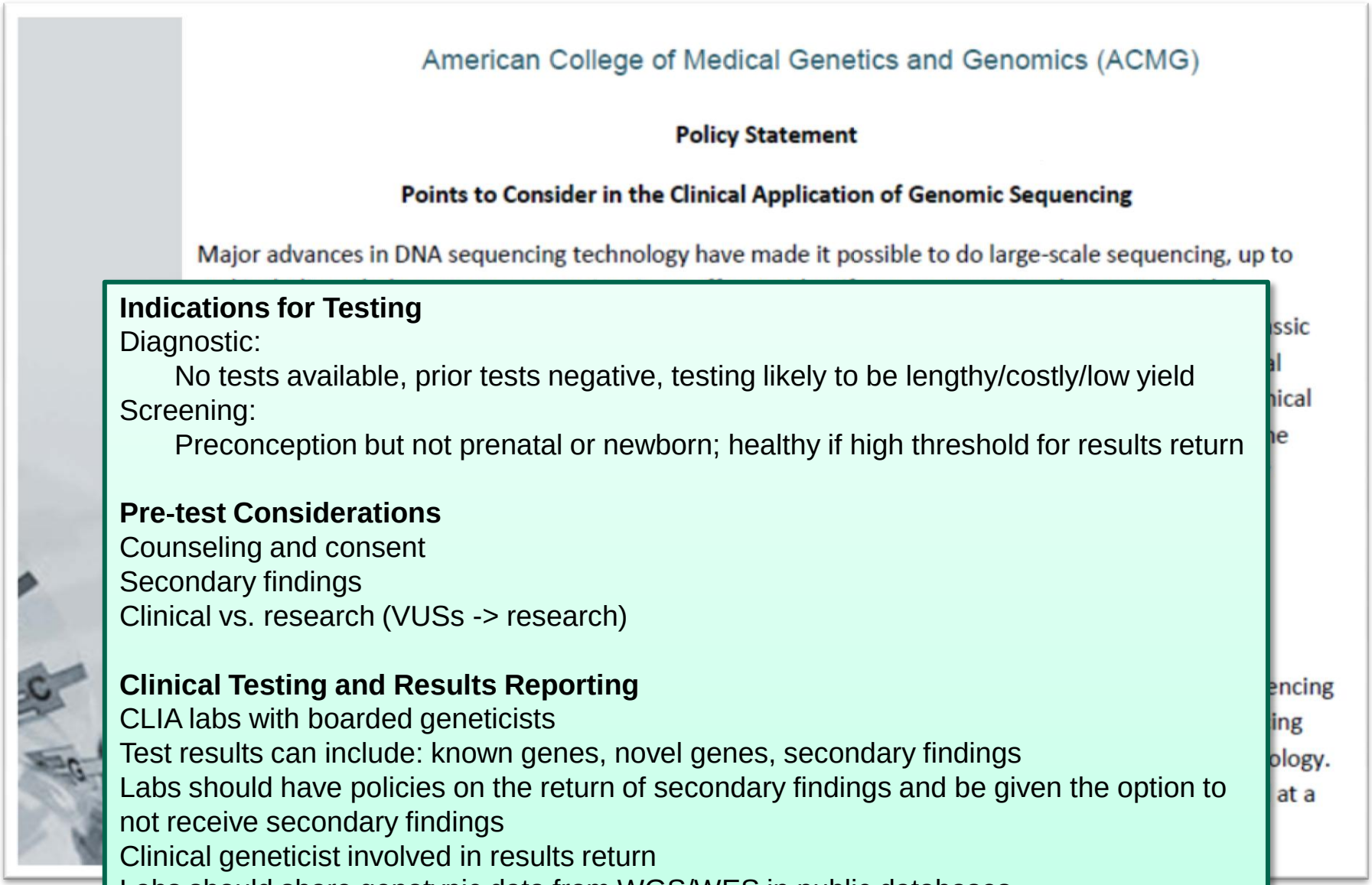
PARTNERS® HEALTHCARE | CENTER FOR PERSONALIZED GENETIC MEDICINE

HARVARD MEDICAL SCHOOL


BWH and MGH Clinics
(Personal Genome Consultation Service)
Patient Workup, Consent and Test Order
• Case selection
• PHS Genetics visit required initially
• Consent process
• Genetic EHR
• Longitudinal patient support
Genomic Medicine at PCPGM
Whole Genome and Exome Sequencing
Initially Outsource and LMM
Interpretation and Reporting
GeneInsight
• Orthogonal confirmation
• Report structure and content
• Disease-Specific Reports
• General Genome Report
MEDSEQ™
Data Analysis
GeneInsight
• Variant annotation
• Variant filtration
• Evidence-based variant assessment

Challenges for the Clinical Implementation of WES/WGS

- Sequencing technologies are changing rapidly
- Computational requirements are unprecedented
- Result confirmation with orthogonal methods: Sanger, independent NGS platform, genotyping, MLPA, FISH, CMA
- WES/WGS vs. Disease Panels: WES/WGS have reduced analytic performance
- Return secondary findings
- Updating results over time
- Human variation is enormous and rare; phenotype and genotype data sharing will be critical



Indications for Testing
Diagnostic:
No tests available, prior tests negative, testing likely to be lengthy/costly/low yield
Screening:
Preconception but not prenatal or newborn; healthy if high threshold for results return

Pre-test Considerations
Counseling and consent
Secondary findings
Clinical vs. research (VUSs -> research)

Clinical Testing and Results Reporting
CLIA labs with boarded geneticists
Test results can include: known genes, novel genes, secondary findings
Labs should have policies on the return of secondary findings and be given the option to not receive secondary findings
Clinical geneticist involved in results return
Labs should share genotypic data from WGS/WES in public databases

ACMG Workgroups
Secondary Findings (Co-Chairs: Robert Green and Les Biesecker)
NGS/WES/WGS Laboratory Standards (Co-Chairs: Heidi Rehm and Pinar Bayrak-Toydemir)

One size does not fit all for WES/WGS Analysis

Sporadic disorders: Sequence parents/child trio and examine de novo variants (1-2 per exome, ~175/genome)

Nachman MW, Crowell SL (2000) Estimate of the mutation rate per nucleotide in humans. Genetics 156(1): 297–304.

Recessive disorders: Examine genes with biallelic mutations (prioritize those with truncating variants)

Power increased with multiple sibs

Consanguineous families: Search for homozygous rare variants

Dominant disorders: Examine multiple distantly affected family members and select for shared variants

Can perform linkage to identify candidate genomic regions to analyze

Cancer: Compare somatic and germline results

Identify variants sporadically occurring in tumor

Approaches to improve WES and WGS Data

Supplement WGS with WES

- Improves coverage of exonic sequences for which data analysis is primarily targeted

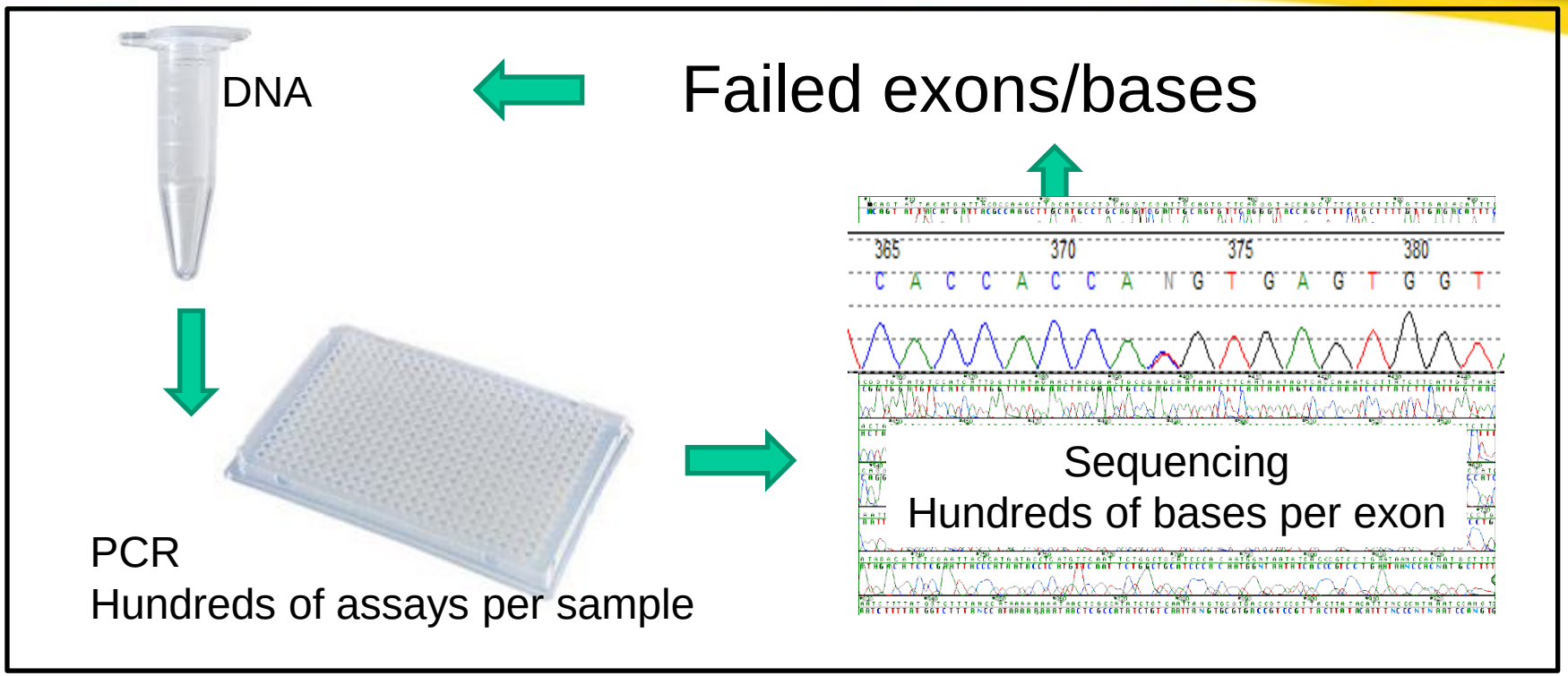
Supplement WES with Clinical Exome

- Improves analysis of genes with known association to disease

Analyze genome/exome with multiple technologies

- Some errors are platform-specific

Supplemental and Confirmatory Testing by Sanger

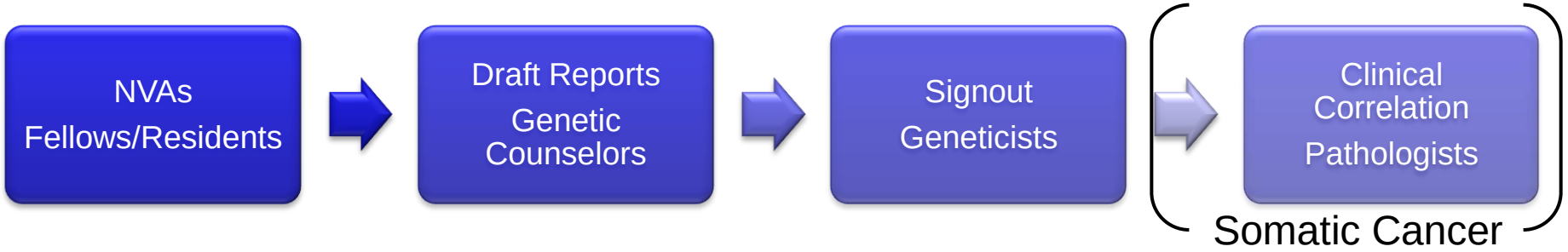


- For targeted tests, missing data is added by Sanger
- Even for WES/WGS there may be critical content that must be covered
- Adding custom design of confirmatory assays from WES/WGS is a significant added challenge

Average Time to Assess a Variant

~300 NVAs/month

NVA Type	Average
NVA with no dbSNP/ESP data or publications	21.5 min
NVA with dbSNP/ESP data only	24.6 min
NVA with publications	119.6 min

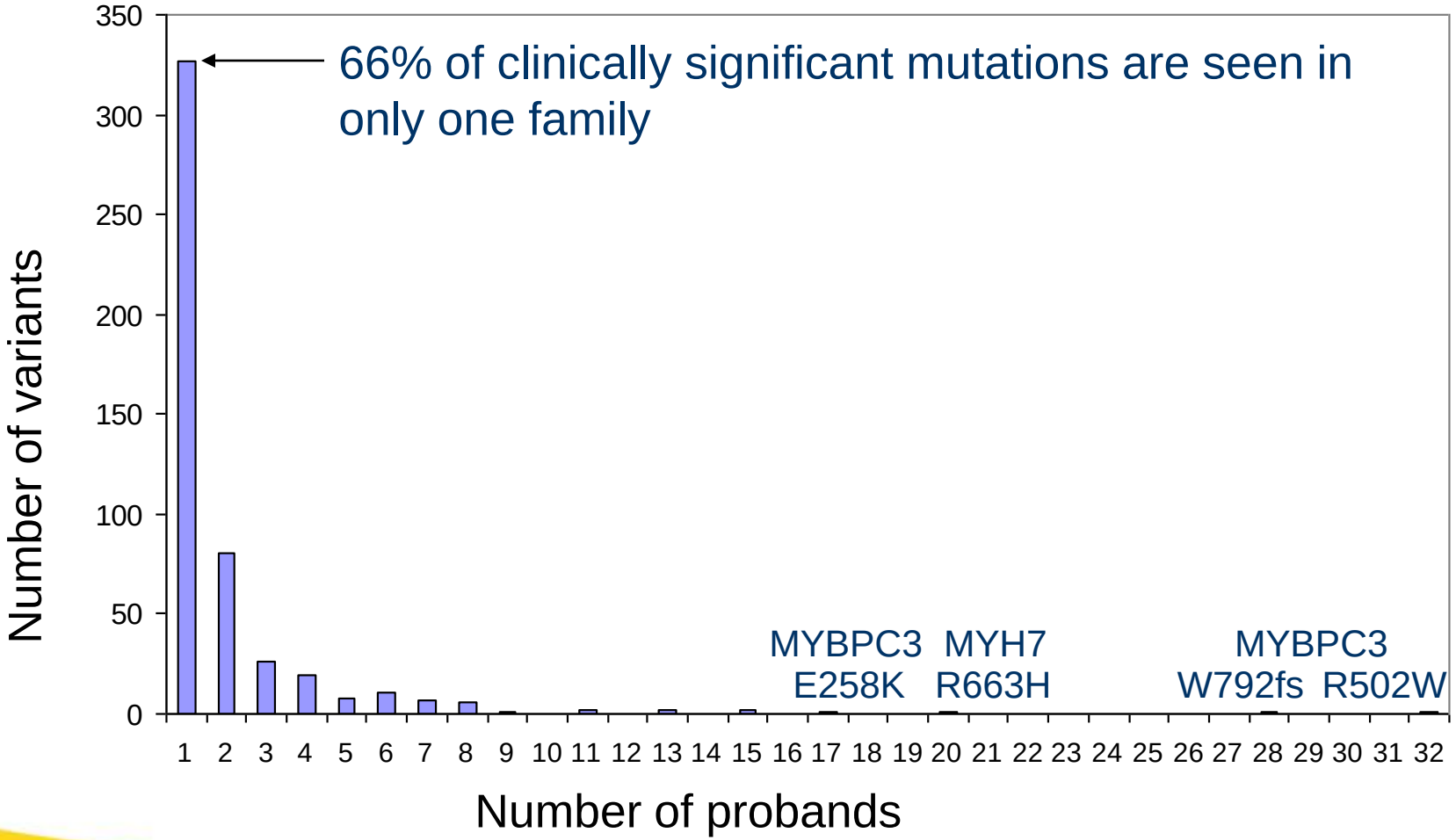


NVA includes:

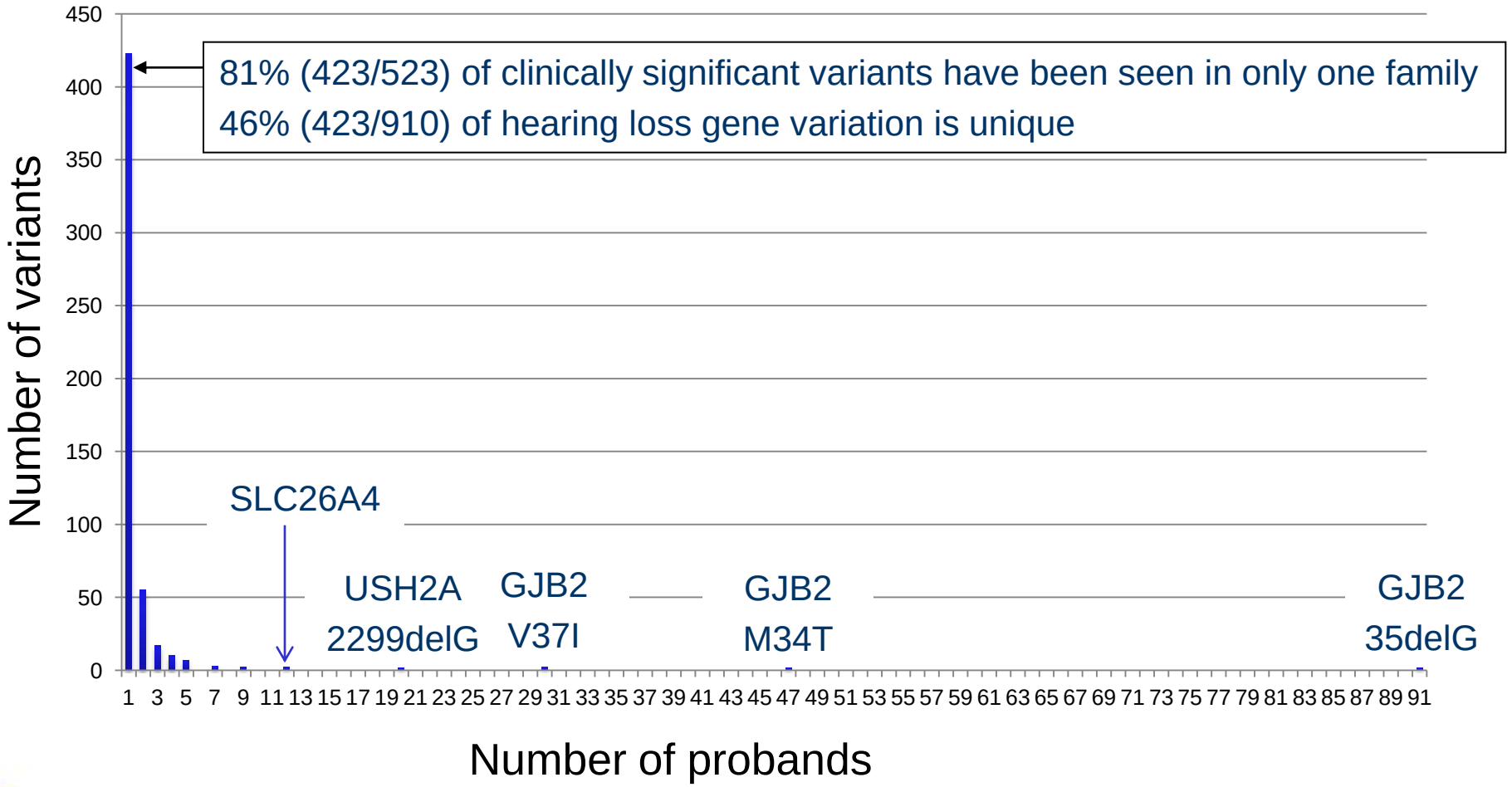
- Searches (Google, PubMed, Variant Databases)
- Assessment of data from literature and databases
- *In silico* assessments (PolyPhen, alignments, splicing, etc)
- Segregation studies with family members
- Evidence-based classification

HCM Gene Mutations – 3000 cases tested

>500 clinically significant mutations identified



Hearing Loss Gene Mutations – 2000 Cases Tested



Variant Data Problem

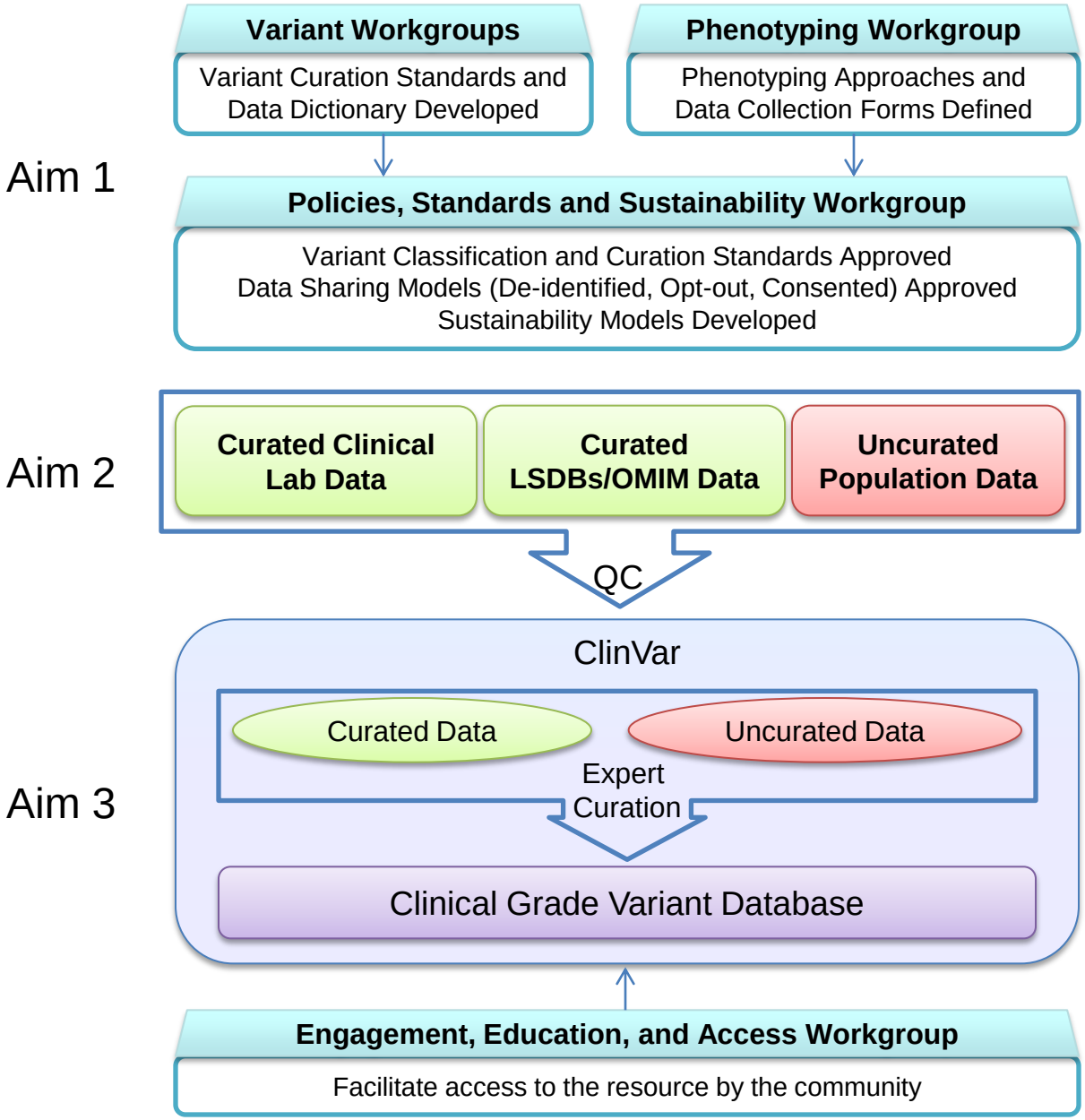
dbSNP contains lots of data but is mostly un-annotated

Most annotated publically available variant data comes from initial research studies with small control populations.

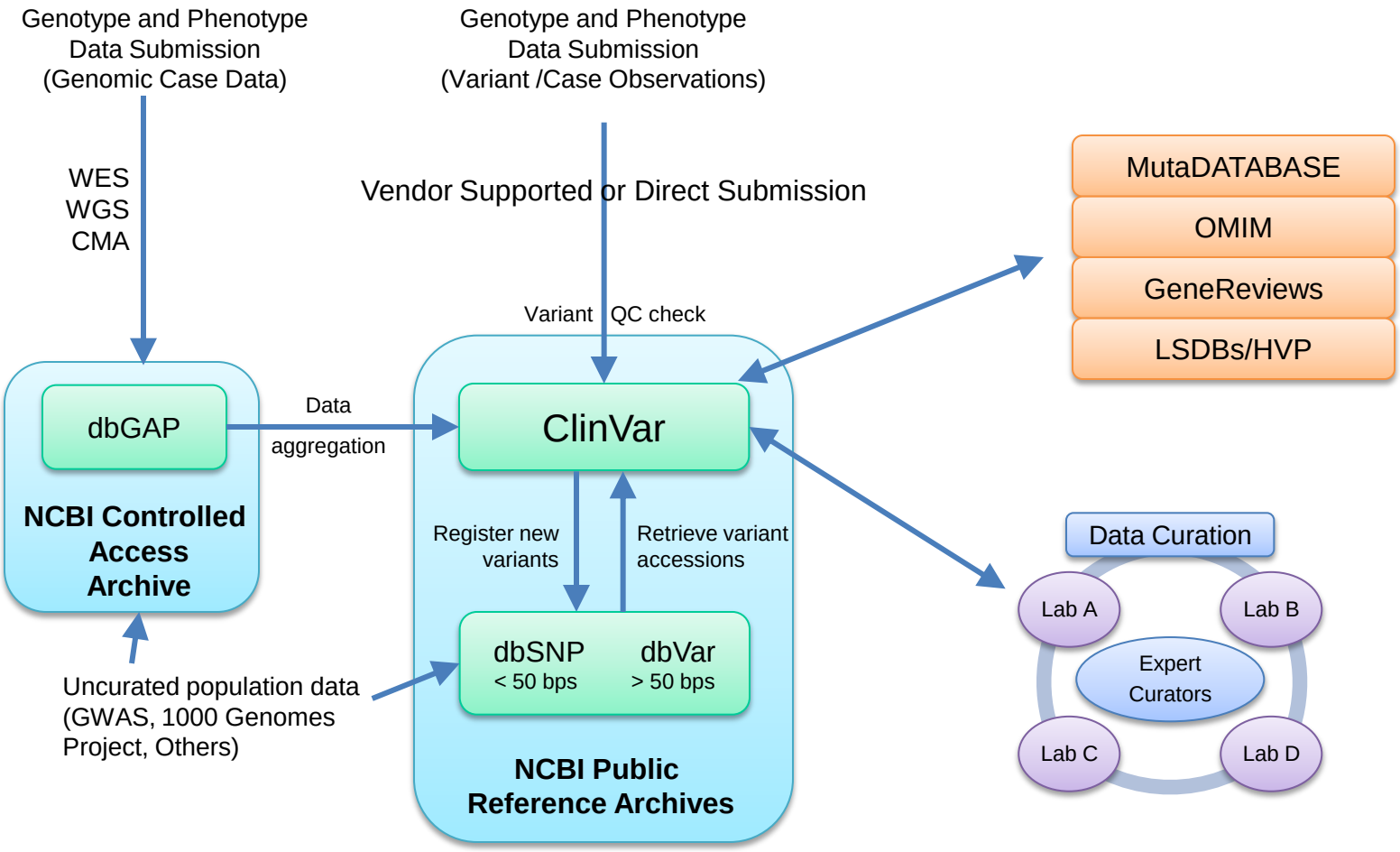
- 27% (122 of 460) of literature-cited disease mutations were judged to be common polymorphisms, sequencing errors or had a lack of evidence of pathogenicity. (Bell et al., 2011)

Subsequent data sits in the clinical labs and is not well published or available.

Creation of a Universal Human Genomic Mutation Database

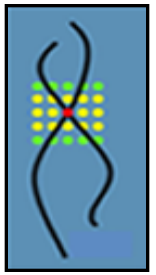


Overview of Data Flows and Systems



The ISCA Consortium

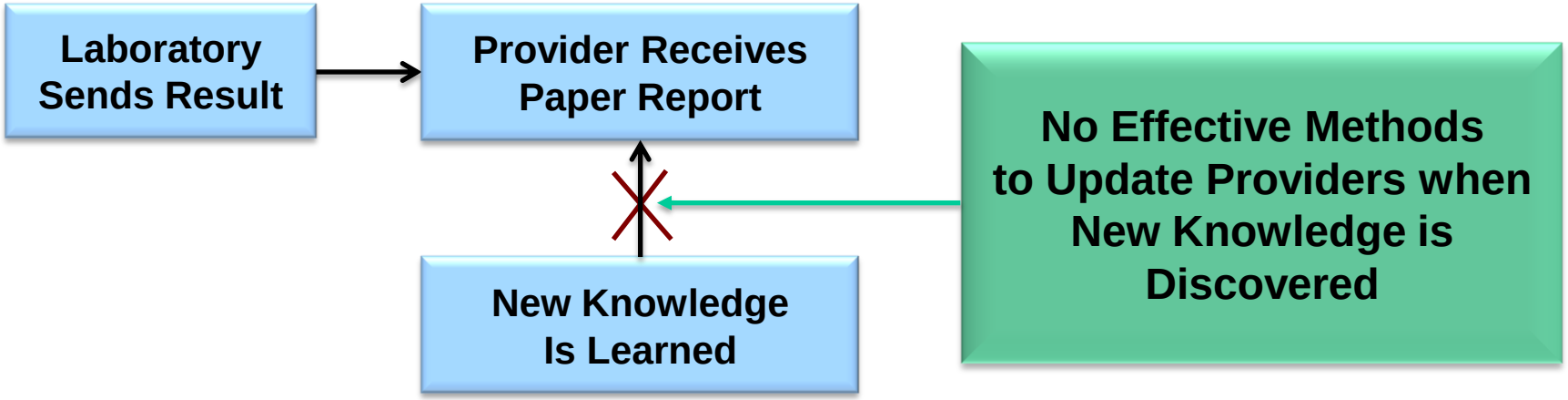
- Established in 2007
- Over 160 institutional members worldwide
- Over 1,200 registered individual members
- The ISCA Consortium database now includes CNV data on ~30,000 postnatal clinical cases



Laboratories Who Have Agreed to Share Data for U41 Grant

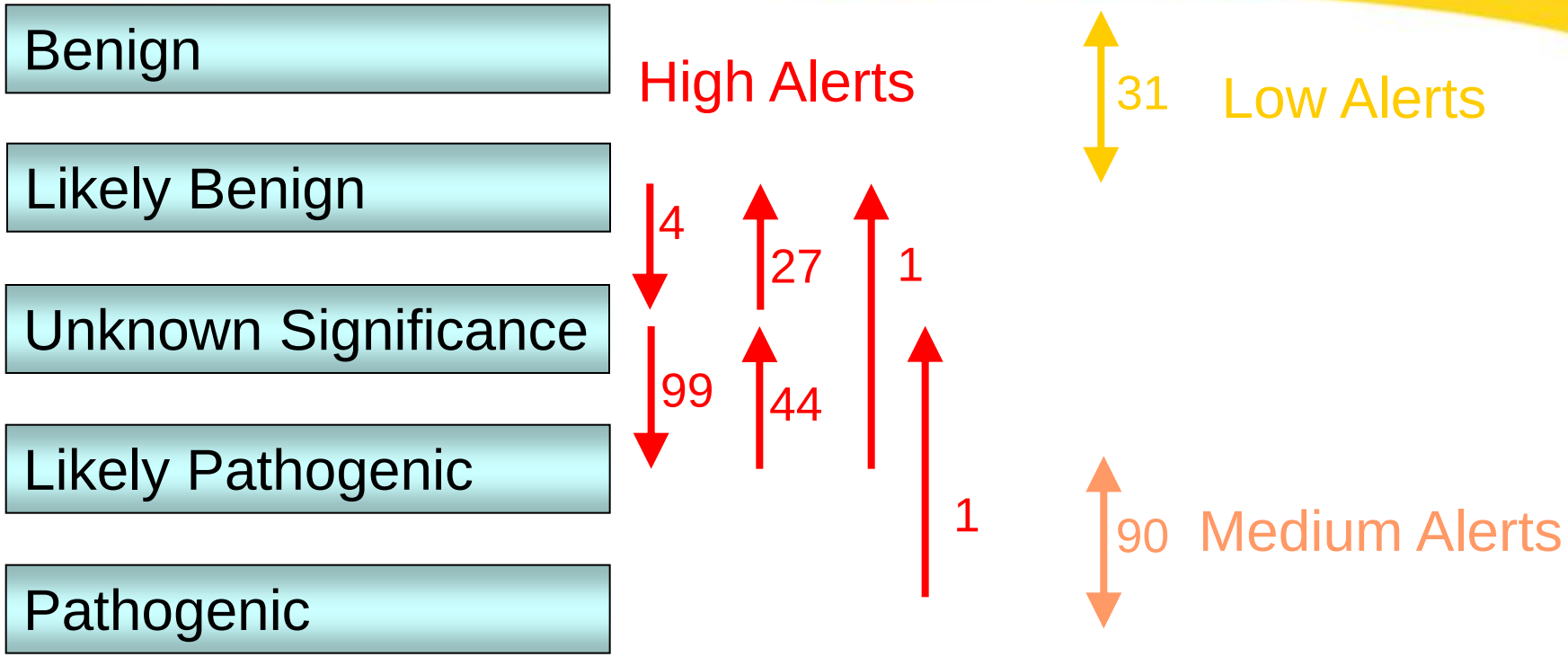
Laboratories	HCM	Noonan	HCrC	Metabolism	DevDelay	CMD	PTEN	ZEB2	Other	Cases
Ackerman Lab, Mayo	1000								(LongQT)	**1000**
Alfred I Dupont Hospital for Children		488			138					**626**
All Children's Hospital St. Petersburg					TBD					**TBD**
ARUP		121	TBD	500	670		179		3800	**5270**
Athena Diagnostics		TBD								**TBD**
Baylor Medical Genetic Laboratories		TBD			17000					**17000**
Boston University		TBD			TBD					**TBD**
Children's Hospital Boston		TBD								**TBD**
Children's Hospital of Philadelphia					623			8		**631**
Children's Mercy Hospital, Kansas City, MO					TBD			100	604	**704**
Cincinnati Children's Hospital				538						**538**
City of Hope Molecular Diagnostic Laboratory					TBD					**TBD**
CureCMD						475				**475**
Detriot Medical Center					TBD					**TBD**
Emory University		395	195		700	253	255	80	8283	**10161**
Fullerton Genetics Laboratory					TBD				TBD	**TBD**
GeneDx	2018	2300		727	400		4023		TBD	**9468**
Genomic Medicine Institute, Cleveland Clinic							TBD			**TBD**
Greenwood Genetics		695			220		275			**1190**
Henry Ford Hospital				27						**27**
InSiGHT			25000							**25000**
LabCorp/Correlagen	1000	TBD	TBD						5500	**6500**
Mayo Clinic			9000	1450	945					**11395**
Mt. Sinai School of Medicine		193								**193**
Nationwide Children's Hospital		475			TBD					**475**
Nemours Biomolecular Core, Jefferson Medical College		348								**348**
Oregon Health Sciences University					TBD					**TBD**
Partners Laboratory for Molecular Medicine	3900	2426	10						53117	**59453**
Quest Diagnostics			TBD	TBD	TBD					**TBD**
Transgenomics	1000									**1000**
University of Chicago					3215			46	5904	**9165**
University of Nebraska Medical Center		124			TBD					**124**
University of Oklahoma		107								**107**
University of Sydney					720					**720**
Women and Children's Hospital					100					**100**
Wayne State University School of Medicine					TBD					**TBD**
Cases Per Disease Area	**8918**	**7672**	**34205**	**3242**	**23911**	**728**	**4732**	**234**	**77208**	**160850**

How do we update reported variant knowledge?



ACMG 2007 Guidelines: The testing laboratory…should make an effort to contact physicians of previously tested patients in the event that new information changes the initial clinical interpretation of their sequence variant.

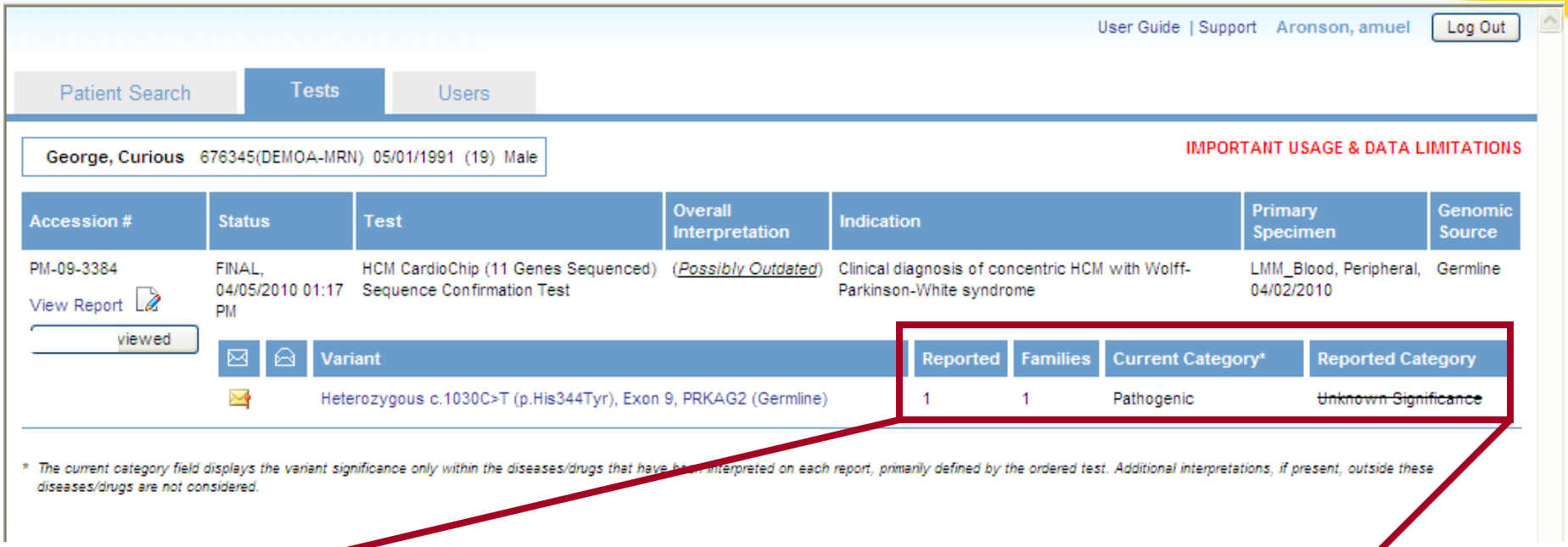
Variant Classification Changes – HCM Data

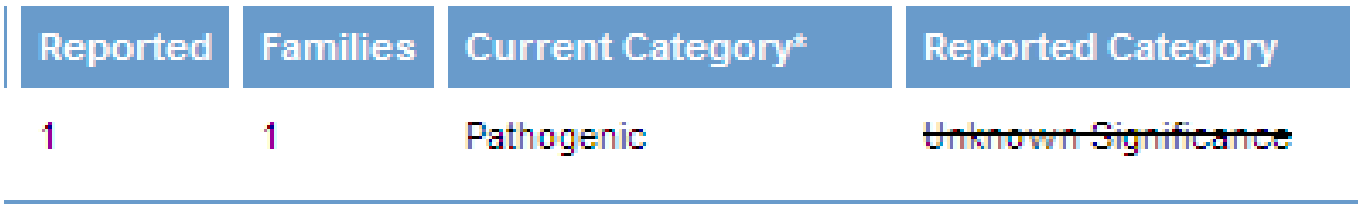


~300 category changes over 5 year (~4% of reports/yr)

Aronson SJ, Clark EH, Varugheese M, Baxter S, Babb LJ, Rehm HL. Communicating new knowledge on previously reported genetic variants**.** *Genetics in Medicine.* Pub. online Apr. 2012.

GeneInsight Clinic℠ Interface





Registered with FDA as a Class I Exempt Medical Device

Updated Variant Information

Individual Reported Variant Interpretation History (Variant 1 of 1)

IMPORTANT USAGE & DATA LIMITATIONS

Warning: This page only lists information on a single variant. This is outside of the patient report context and may be insufficient for re-interpretation of the patient report.

Heterozygous c.1030C>T (p.His344Tyr), Exon 9, PRKAG2 (Germline)

Report	(FINAL, 04/05/2010 01:17 PM), HCM CardioChip (11 Genes Sequenced), Sequence Confirmation Test
Patient	**George, Curious** 676345(DEMOA-MRN) 05/01/1991 (19) Male
Current Category*	Pathogenic (**Reported:** ~~Unknown Significance~~)
Counts	Reports (1), Families (1)

Alerts

Status	!	Date	Type	Message
Unreviewed	!	04/06/2010 10:27 AM	Non-incidental Level Change	The category for the PRKAG2 c.1030C>T (p.His344Tyr) association to HCM changed from Unknown Significance to Pathogenic.

Mark Reviewed

Current Knowledge** Approved 04/05/2010 01:22 PM by Matthew Varugheese

Diseases/Drugs	Category	Variant Interpretation
HCM	Pathogenic	The His344Tyr variant has not been reported in the literature nor previously identified in our laboratory. The His344 residue is well conserved from fruitfly to mammals, and the His344Tyr variant occurs within the CBS domain region where all pathogenic PRKAG2 variants have been identified to date. In addition, the presence of concentric HCM and Wolff-Parkinson-White syndrome in the first proband identified with this mutation, which are clinical features consistent with PRKAG2 mutations, as well as follow-up testing showing that the variant arose de novo, provide strong support for this variant being pathogenic.

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

** *The Current Knowledge only includes the following Diseases/Drugs Interpreted on Report: HCM, DCM, LVNC, RCM, Danon disease, myopathy, Fabry disease, ARVD/C, Barth syndrome*

Data in this slide should not be used for any clinical purpose.

RISGIM Study (Refining IT Support for Genetics in Medicine)

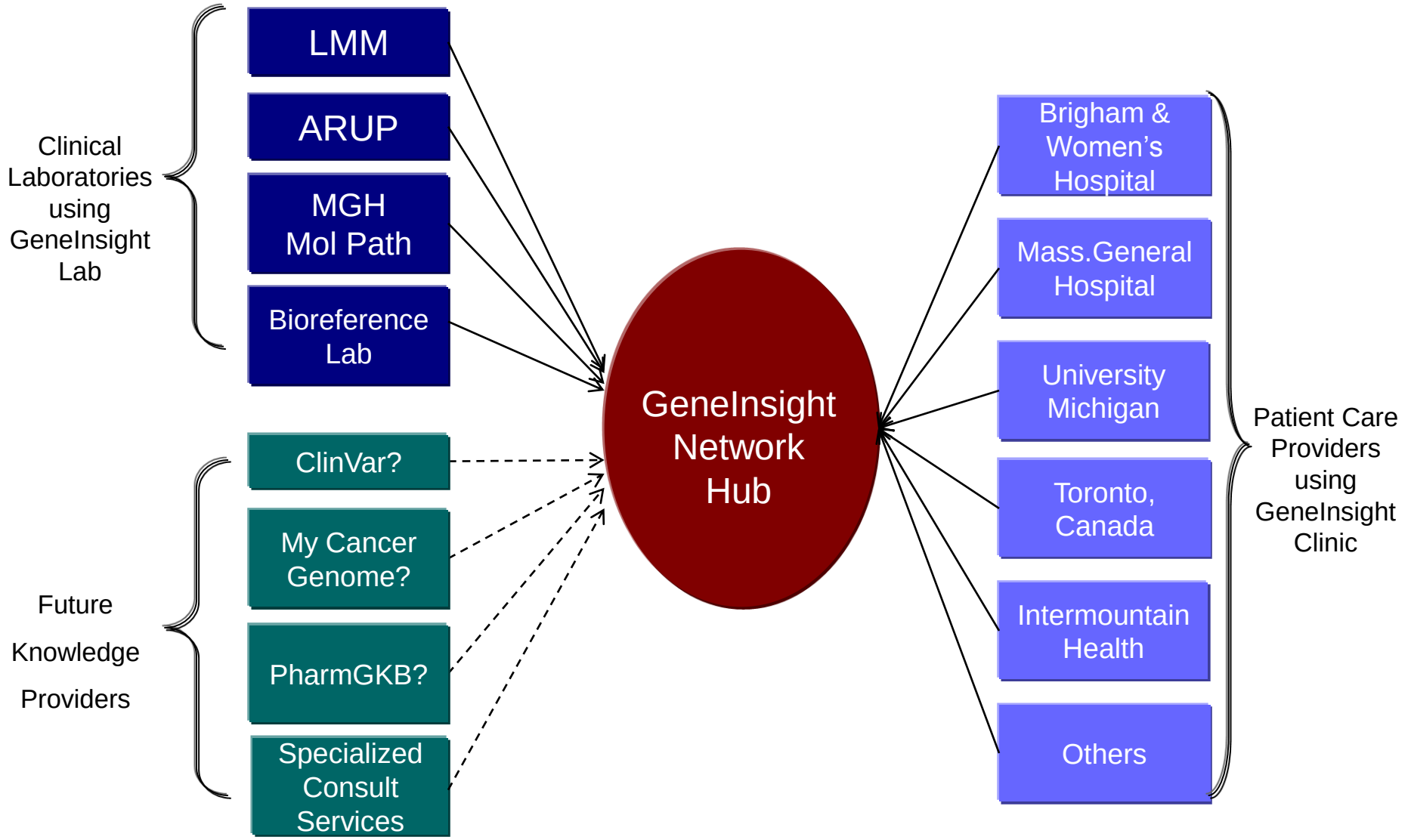
PI: David Bates NIH – NLM 1RC1LM010526-01

Software Usability Assessment	**Completion Rate (n=7)**	**Average Grade (n=7)**	**Error-Free Rate (n=7)**
Task 1 – GIC Report Alert – locate patient with new report CRITICAL TASK	100%	A-	100%
Task 2 – View Test Report and 'Mark Reviewed'	100%	A-	100%
Task 3 – GIC Variant Alert – locate patient(s) with variant update CRITICAL TASK	100%	A-	100%
Task 4 – Locate unreviewed alert and change in variant interpretation CRITICAL TASK	85.7%	A/A-	71.4%
Task 5 – Locate overall report interpretation	100%	A-	71.4%
Task 6 – Locate number of reports and families with variant tested at lab	14.3%	B+ *	14.3%
Task 7 – Locate evidence for variant update	100%	A	100%
Task 8 – Mark variant reviewed	57.1%	A *	57.1%
Task 9 – Locate all of a patient's variants. Locate reviewed variants info.	57.1%	B+	42.9%
Task 10 – Locate variant history for reviewed variant	85.7%	B+/B	57.1%
Task 11 – Conduct patient search by variant	85.7%	B	71.4%
Task 12 – Conduct a search for patients with unreviewed information	85.7%	B+/B	85.7%
Task 13 – Locate alert on an benign/likely benign variant LOW PRIORITY TASK	14.3%	A/A-	14.3%
Task 14 – Review GIC Alert Summary Email	100%	B	100%

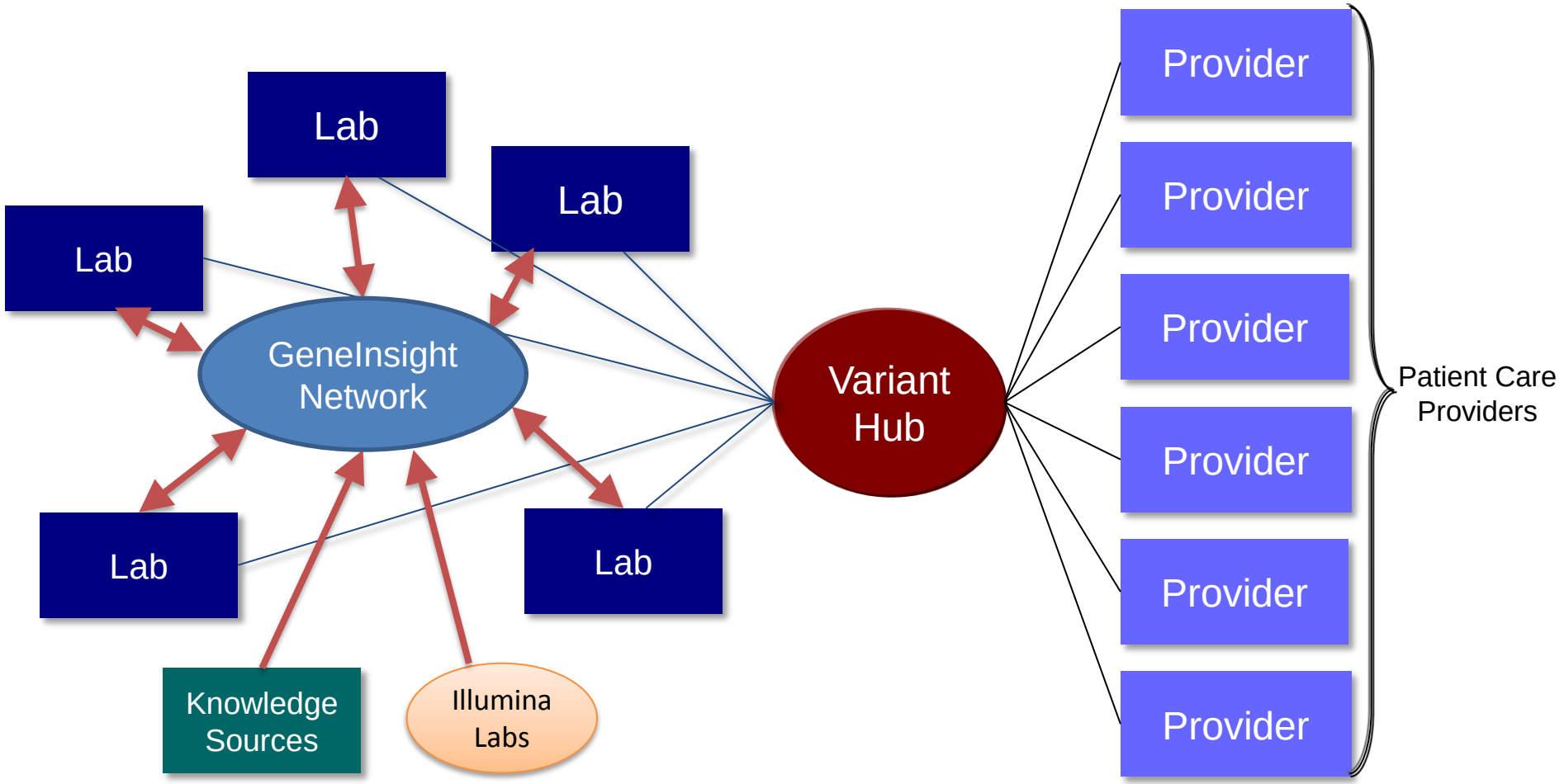
Adapting GeneInsight Clinic for Genomic Medicine

- As reports scale in content, alerting process will adapt to clinical decision support paradigms
- Up-to-date data is available when physician looks at a patient record
- Genetic data is accessed in real-time using CDS rules as needed (drug dosing, etc)
- We may use infrastructure for clinical trial notification

GeneInsight Laboratory Data Sharing Network



GeneInsight Laboratory Data Sharing Network



Shared Variant Knowledge and Interpretations

Variant Details: EGFR c.2369C>T (p.Thr790Met) <<

Gene: EGFR (NSCLC)
Transcript: NM_005228.3 [28 Exons, Coding 1..28]
Variant: c.2369C>T (p.Thr790Met)

Edit Variant

Full Details | Frequency | Notes | References | Interpretation | Interp. History | Assessments | Seq. Alignments | External Info.

Ext. Source	Transcript	DNA	AA	Region	DNA Ty...	AA Type	Interp	# Rpts	# Fams	Source
LABX	NM_00522...	c.2369C>T	p.Thr790Met	Ex 20	Sub	Mis	Resist (NSCLC)	37	36	
LABZ	NM_00522...	2369C>T		Ex 20	Sub		Unclassified	1	1	

Full Details | Frequency | Notes | References | Interpretation | Interp. History | Assessments | Seq. Alignments | External Info.

LABX Information

 # Reports 37
 # Families 36

Category/Inher./Excl.
Resistant

Diseases/Drugs
Non-Small Cell Lung Cancer

Variant Interpretation

The T790M mutation in combination with other EGFR kinase domain mutations has previously been described in individuals with acquired resistance to EGFR-tyrosine kinase inhibitors (TKIs, Pao 2005). This mutation has been seen in tumors from patients who have been treated with TKIs and whose tumors also harbor a TKI susceptiblity mutation.

References

Source	Author(s)	Title	Year
PUBMED 15728811	Kobayashi S, Boggon TJ, Dayaram T, Janne PA, Koch...	EGFR mutation and resistance of non-small-cell lung cancer to gef...	2005

Close

Shared Case Histories

Report Search -- Add Parameter -- Variants Shown: Non-incidental | Probands Only ☐ | Include Non-clinical ☐ | Join Param. Rows Using 'OR' ☐

Source Instance	equals	Local and Remote			
Date: Sign Out	equals	08/30/2010	or 02/09/2012	or 01/31/2012	
Test Code	contains	SNaPshot	or lmEGFR-a_L	or lmOto-pnlA_L	

Go | Reset | Count | -- Saved Searches -- | Load | Save | Delete

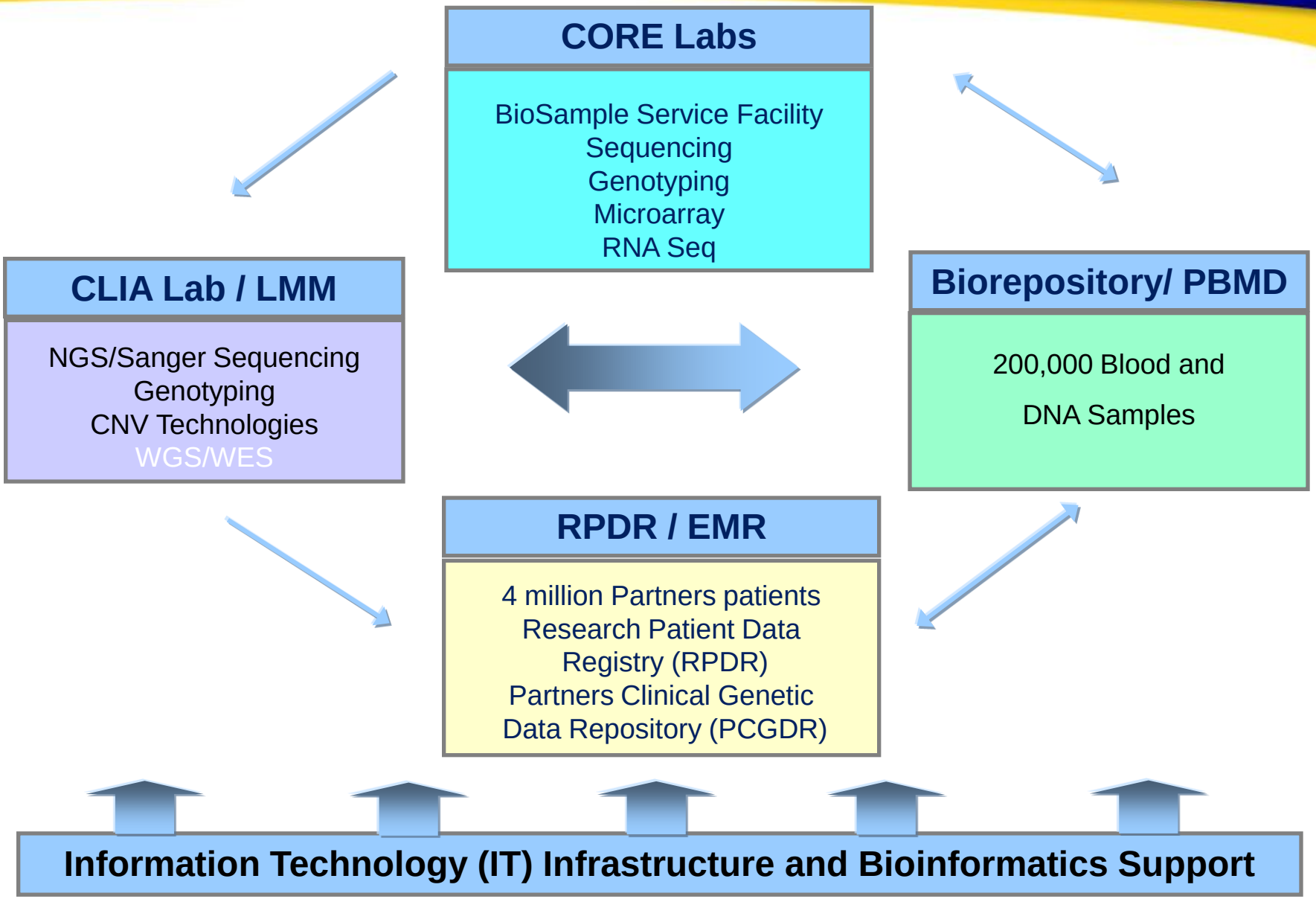
Matching Reports (List Variants for Currently Displayed Columns | Run Autodraft Analysis | Variant Column Help)
Note: reports that are not FINAL or not CLINICAL are highlighted in red.

Click header to sort. Control+click header to remove sort. Shift+click header to set last locked column.

Page 1 of 1 < Prev | Next > Copy Selected Rows | Download

Identifier	Family (*Proband)	Test(s)	Report Status	Last Sign Out Date	Result	Actions	KRAS c.35G>C (... *Path (...*	KRAS c.181C>T ... Path (...	EGFR c.2369C>T... Resist (...	EGFR c.2235_22... Resp (...	EGFR c.2573T>G... Resp (...	E c.
TV-12-J54321 Santa Claus Male	0*	lmOto-pnlA_L	Amendment...	01/31/2012 ...	Negative	Edit Rpt Edit Case						
PM-10-G02235 SANTA CLAUS Male, 61 yrs	FAM002	lmEGFR-a_L	Final	08/30/2010 ...	Positive	Edit Rpt Edit Case				No Allele St...	No Allele St...	
MGH:MGH-2012...		SNaPshot v3	Final	02/09/2012 ...			**No Allele ...	**No Allele ...				
MGH:MGH-2012... Male		SNaPshot v3	Amendment...	02/09/2012 ...	Resistant				**No Allele ...			No
MGH:MGH-2012...		SNaPshot v3	Final	02/09/2012 ...								

Central Components of PCPGM



Acknowledgements

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Christa Martin
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Patrick Willems
David Ledbetter
Andy Faucett
Erin Riggs
Erin Kaminsky
David Miller
Elaine Lyon
Soma Das
Matt Ferber
Mike Murray
Robert Green
Robert Nussbaum
NCBI ClinVar Team