Optimizing for Effective Use of Genomic Data in Patient Care

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PARTNERS HEALTHCARE | CENTER FOR PERSONALIZED GENETIC MEDICINE

HARVARD MEDICAL SCHOOL

Critical Needs for Optimized Genetic Medicine

1. Structured genetic data
2. Accurate and readily accessible data interpretation resources
3. Support for the value of high quality clinically relevant reports
4. Systems to support reanalysis and/or independent interpretations of genetic data

Structured genetic data

We have worked with the HL7 standards group to define a system for reporting genetic variation and test content.

Heterozygous, c.101C>T, p.Met34Thr, GJB2, Pathogenic

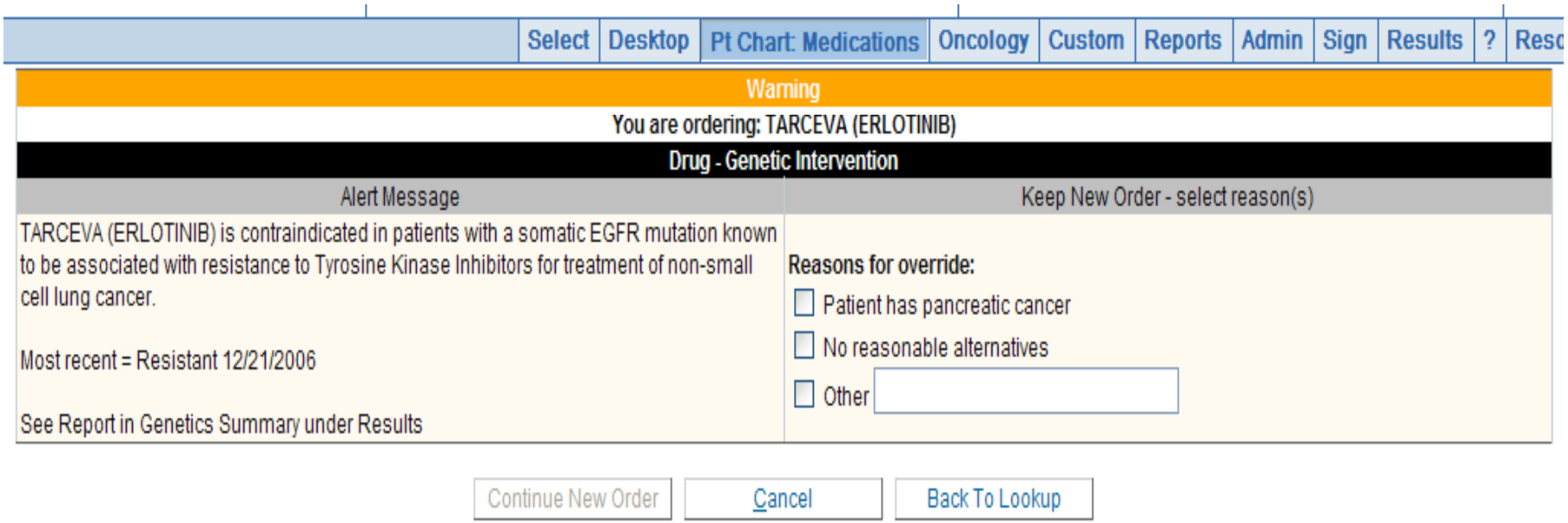
At Partners Healthcare, genetic data goes into an EHR (CDR) and research repository (RPDR) as structured data

Genetic variants must be universally understood by IT systems

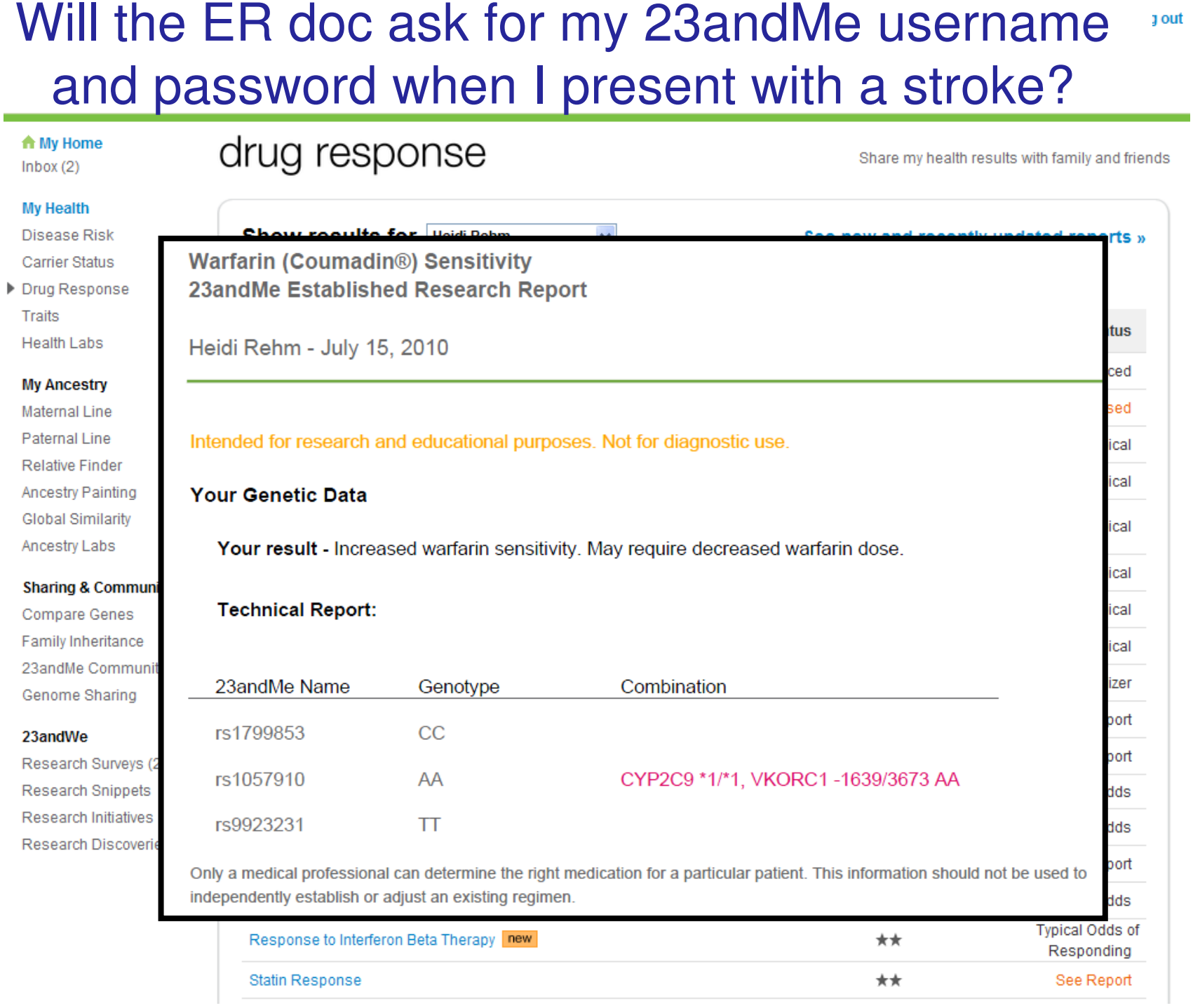
pdf text reports are not sufficient

Benefits of structured data

Enables use of clinical decision support tools that can leverage genetic data even as algorithms and use cases change over time



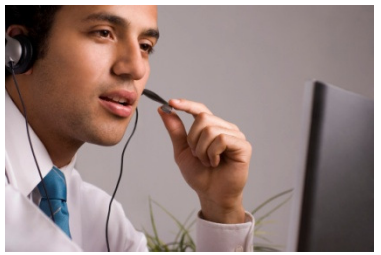
Will the ER doc ask for my 23andMe username and password when I present with a stroke?



Whole Genome Sequences Should be Stored in the EHR

Patient's Whole Genome Sequenced

Millions of Variants for Each Patient Stored in their EHR



EHR WGS Record Accessed as Clinical Symptoms Arise or Adverse Event Warnings are Leveraged

Proactive Alerts Generated as New Clinically Actionable Knowledge is Learned

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Variant Classification – We need a common set of terms and rules for classification

Variant classification rules for highly penetrant Mendelian disorders.	
PATHOGENIC	Segregation (LOD>3) **AND** frequency (Cases>>controls) data **OR** segregation (LOD 1.5-3 (5-9 meioses) and absent from large control set.
	De novo missense variant in proband with de novo disease (paternity confirmed).
	LOF variant (+/-1,2 splice, frameshift, nonsense, stop codon or initiation codon) provided that LOF is known mechanism for the gene and truncation is not at very C-terminus (premature stop 5' of the last 50 bases of penultimate exon).
	Strong functional data (mouse model, etc).
LIKELY PATHOGENIC	Moderate segregation data (LOD >1.5 (3-4 meioses).
	Case frequency statistically greater than control frequency
	Recessive disease: Missense variant found on second allele (trans data required) in combination with a pathogenic variant and with some other supporting data (absence in controls, strong computational data, etc).
UNKNOWN SIGNIFICANCE	Missense variant with limited case/control data
	Novel splice site variant outside +/-1,2 (-3, -5-->-10, +3-->+6, first and last 3 bases of exon).
	Conflicting info
	Novel/rare (<0.1% of any population) silent variant in gene where pathogenic splice variants are common.
	Variant for dominant disease detected in a control individual or in >1 disease with different cellular mechanism (e.g. HCM/DCM)
LIKELY BENIGN	Silent variant in genes without evidence of splicing variants causing disease or in genes where cases <500.
	Intronic variant outside splice consensus
	Recessive diseases: Variant seen frequently in probands and never or rarely with a second allele affected.
BENIGN	High frequency variants (≥1% silent, ≥3% missense) with sufficient case (e.g. >5 patients) and control data.

Many terms in use:
Mutation
Variant
Polymorphism
SNP

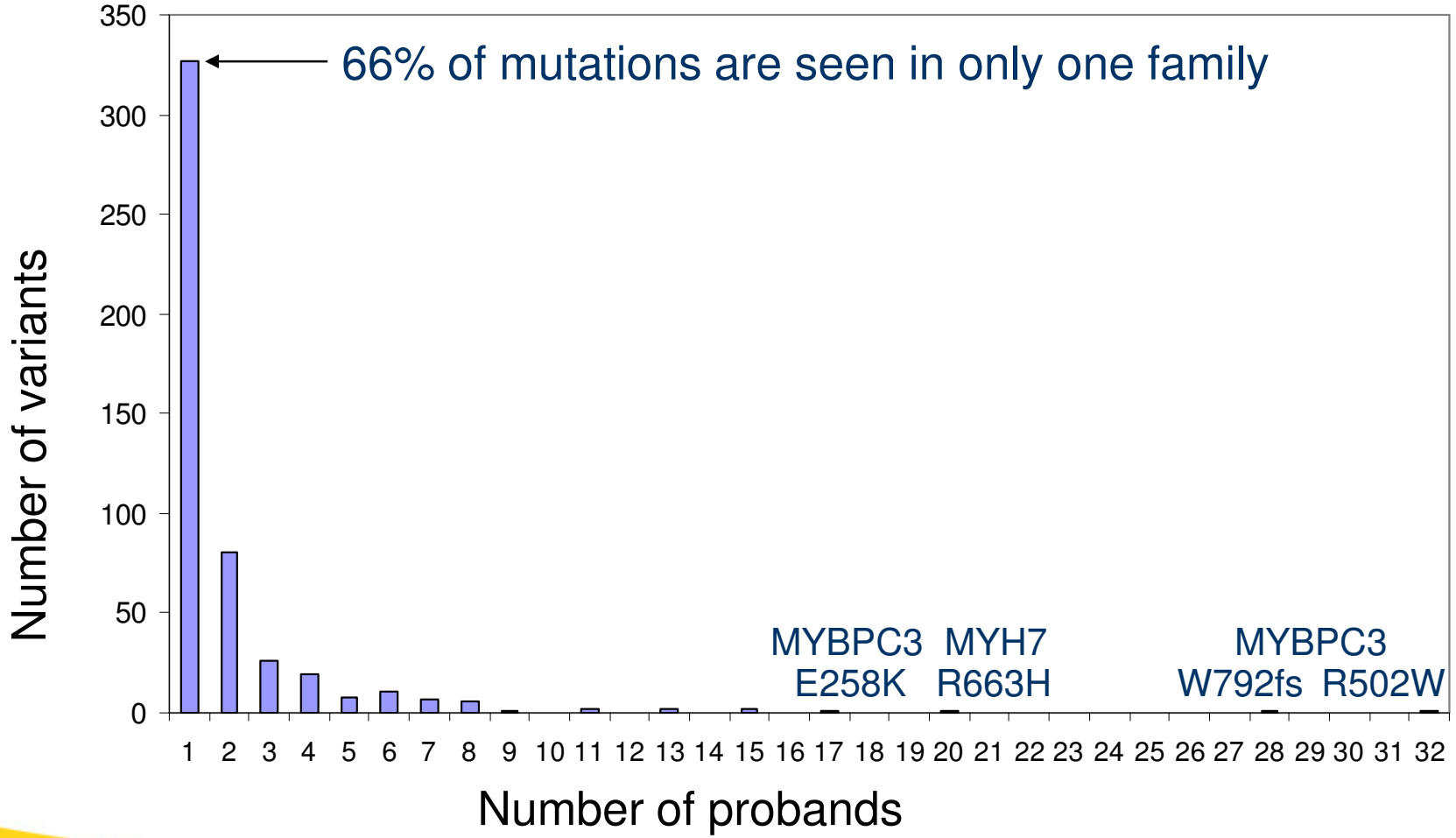
Pathogenic
Deleterious
Disease-associated

Possibly
Probably
Likely

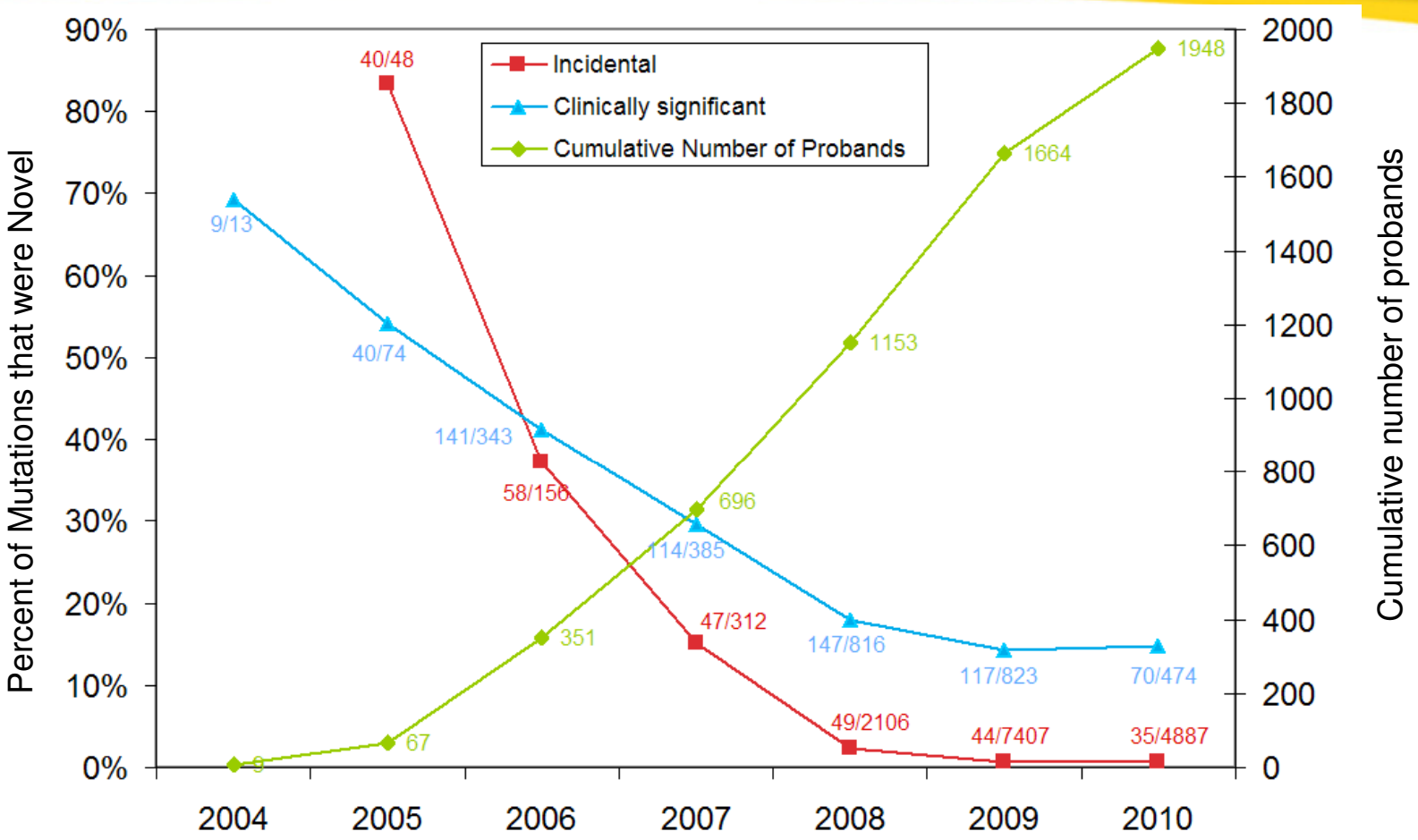
VUS (variant of unknown significance)

HCM Gene Mutations

>1400 mutations identified (published or seen by LMM)

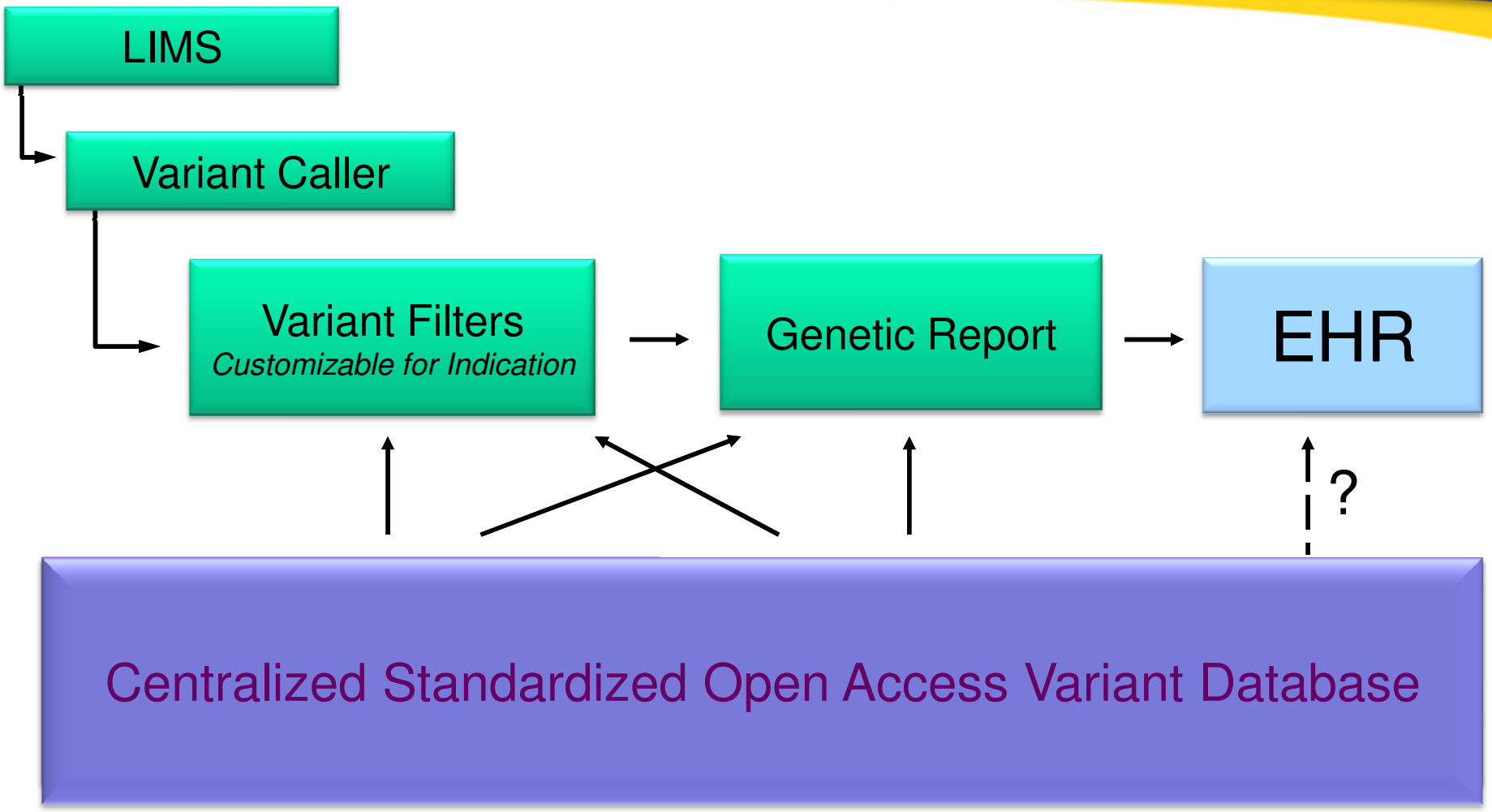


Rate of Newly Identified HCM Mutations



Myriad detects 10-20 new missense variants each week despite testing >150,000 people for BRCA1/2 (Slide from W. Grody with data from B. Ward)

IT Support for Whole Genome/Exome Sequencing



MutaDATABASE and ClinVar Projects

MutaDATABASE – initiated by Patrick Willems
ClinVar – initiated by NCBI

Goal: Universal human gene variant database which is centralized, standardized and freely available.
Model: ISCA Consortium led by David Ledbetter

Policies and Standards Workgroup

- Defines polices around data submission, access, usage and ownership
- Develops incentives for data submission
- Works with standards bodies to ensure adherence to existing standards and development of new standards
- Monitor and interface with overlapping efforts to ensure consistency and minimization of duplicative efforts
- Develops standards and policies surrounding consent and submission of phenotypic data

Variant Data Workgroup

- Defines database structure and data elements for submitted variants and patient cases
- Defines terminologies and standards for variant classification
- Work with NCBI to implement

Curation Workgroup

- Define process for curating variants and what retrospective and external curations to accept
- Develops process for prospective curation by expert groups
- Execute pilot curation projects

Phenotyping Workgroup

- Implement phenotyping data collection process defined by standards and policies workgroup

US Clinical Labs Willing to Submit Data

Clinical labs agreeing to submit:

ARUP
Athena Diagnostics
Correlagen
Duarte
Emory
GeneDx
Genzyme
Greenwood
Harvard-Partners LMM
Baylor
LabCorp
Mayo
Quest
Univ Chicago

Clinical labs declining:

Myriad
Prevention Genetics

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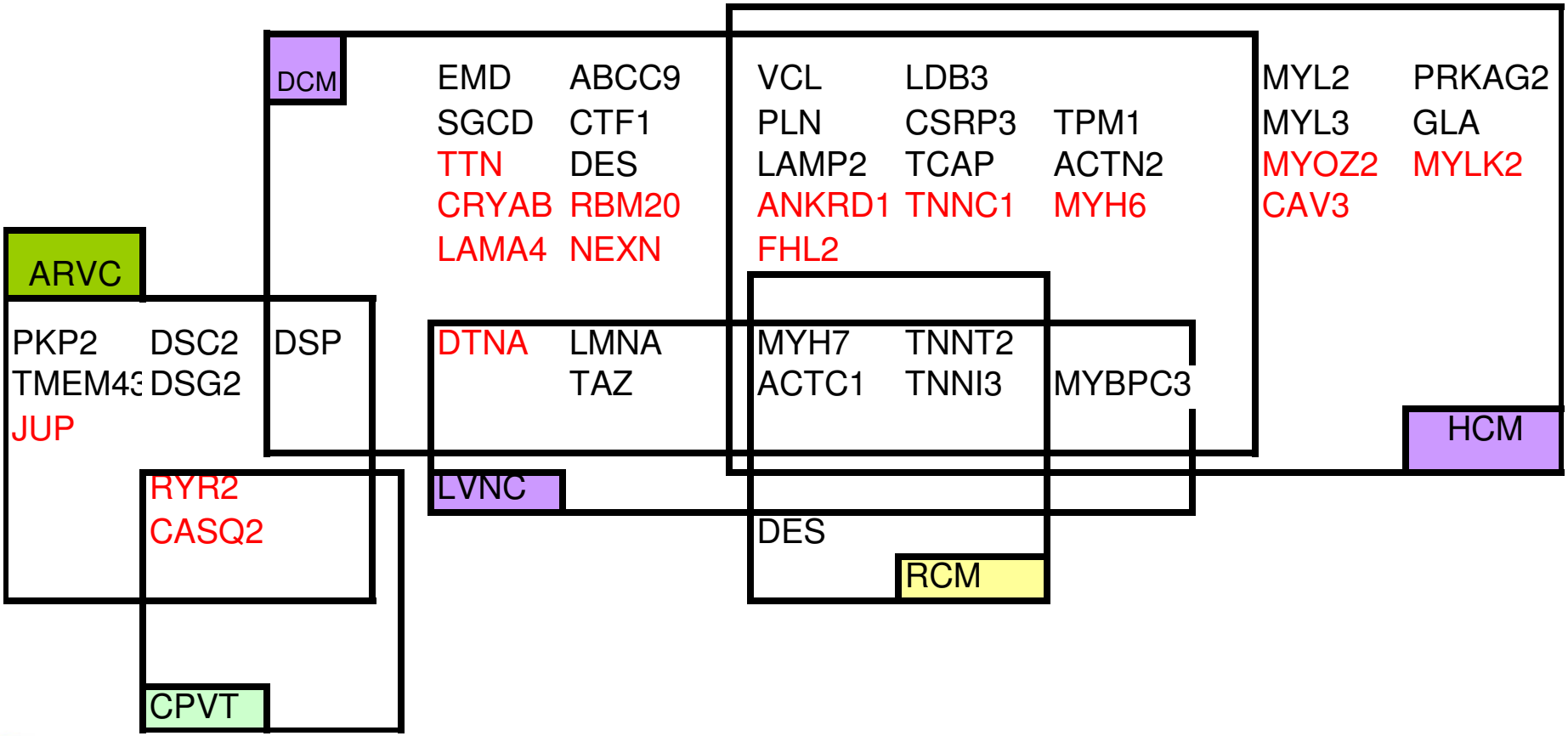
5. Real-time integration of genetic data in clinical care

LMM Pan Cardiomyopathy Test

6 diseases, 46 genes, 1024 exons, 239,000 bases



Courtesy of Birgit Funke

Clinically relevant reporting of genetic data

Accurately interpret the impact of each variant on a gene or protein

Lab

Accurately interpret a set of variants relevant to a single phenotype (both alleles in recessive diseases, assessment of modifiers, complex genetics)

Accurately relay the relevance of the identified variants in the patient's presentation

?

Determine how to apply the genetic information to the care of the patient (and the patient's family members)

Physician

Model for genetic care package

Genetic consult service being planned through Partners Healthcare

First service focused on cardiomyopathy testing for cardiologists

Cardiologists with genetics expertise would combine patient phenotype and family history together with genetic report results and generate a patient/family care recommendation

We are considering using our GeneInsight software infrastructure, which uses rules based templating algorithms to generate custom genetic reports

Goal to assist the average cardiologist in how to interpret genetic data and integrate it into patient care

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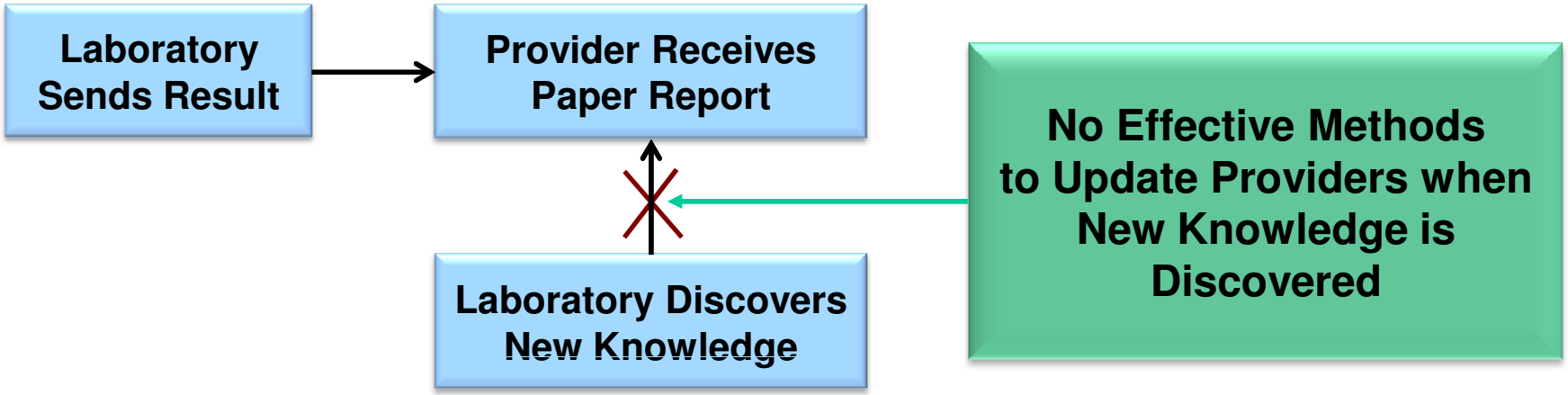
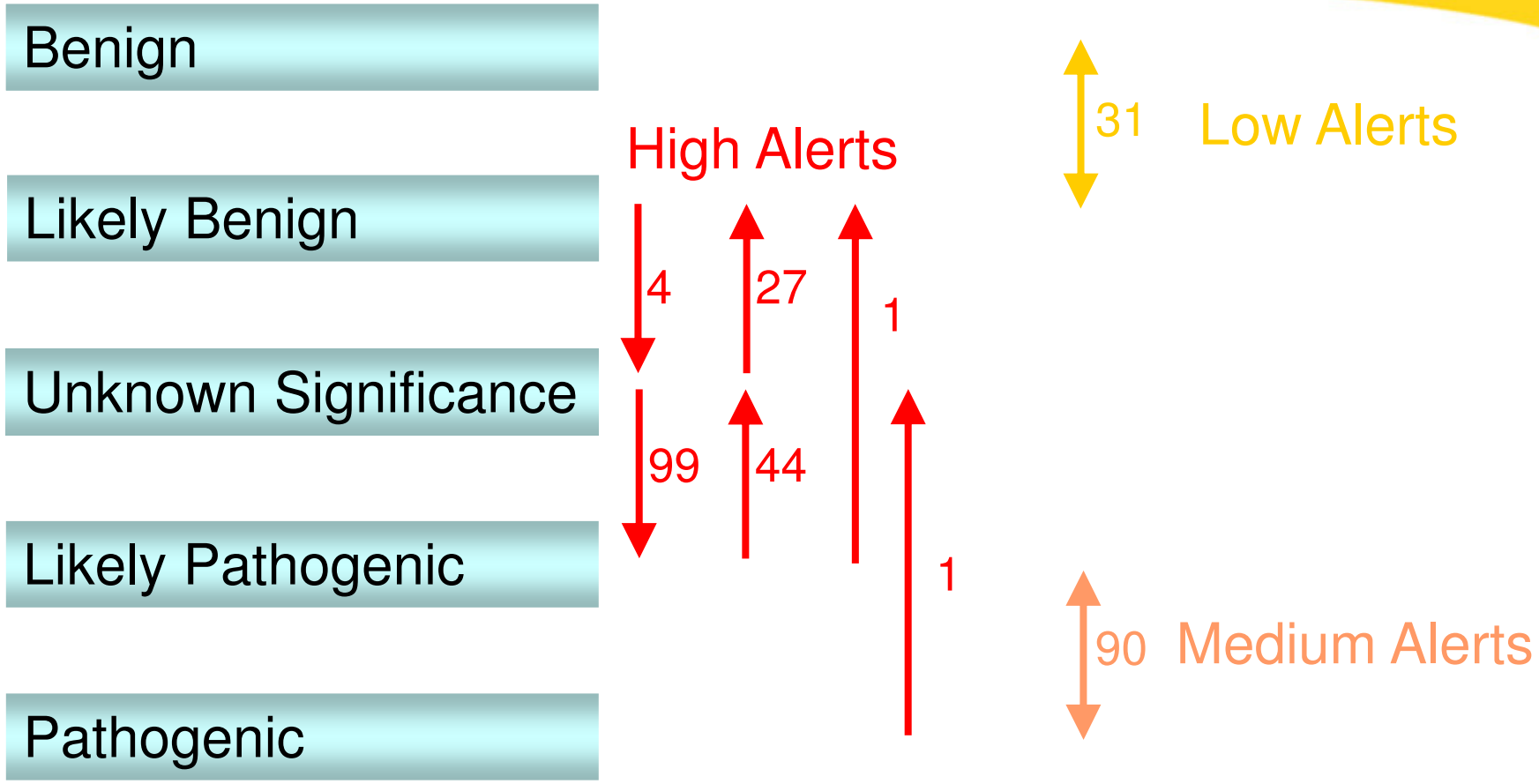
How do we update reported variant knowledge?



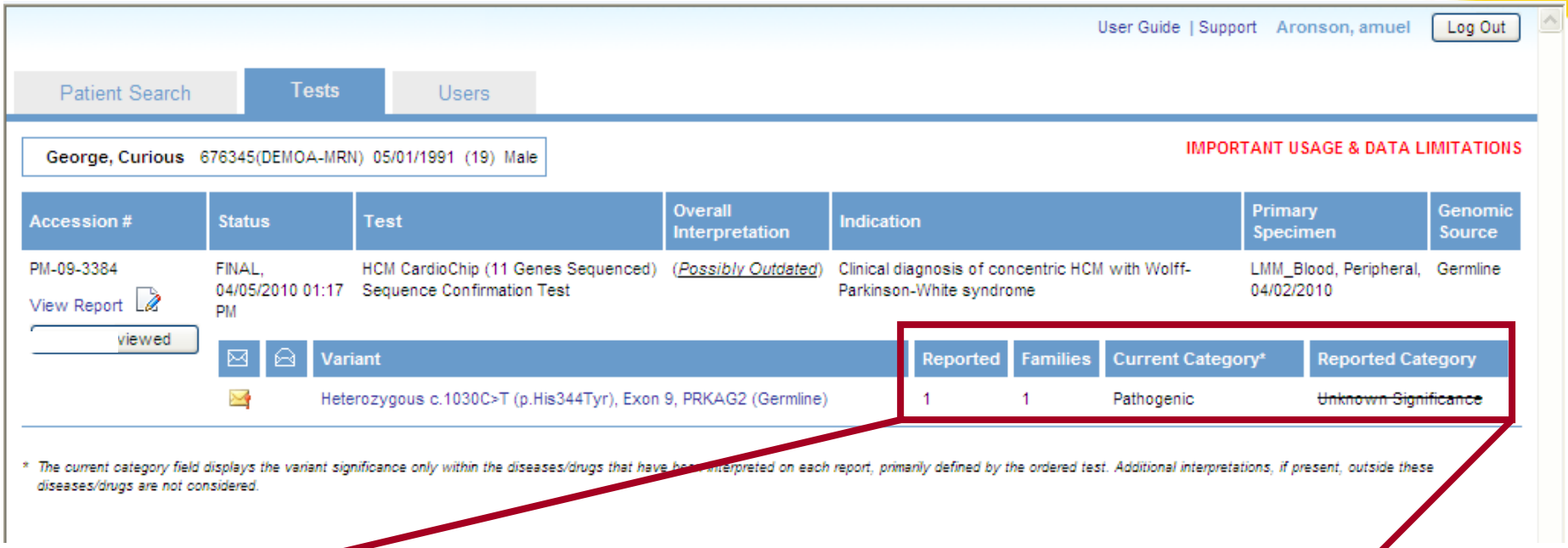
ACMG 2007 Guidelines: The testing laboratory…should make an effort to contact physicians of previously tested patients in the event that new information changes the initial clinical interpretation of their sequence variant.

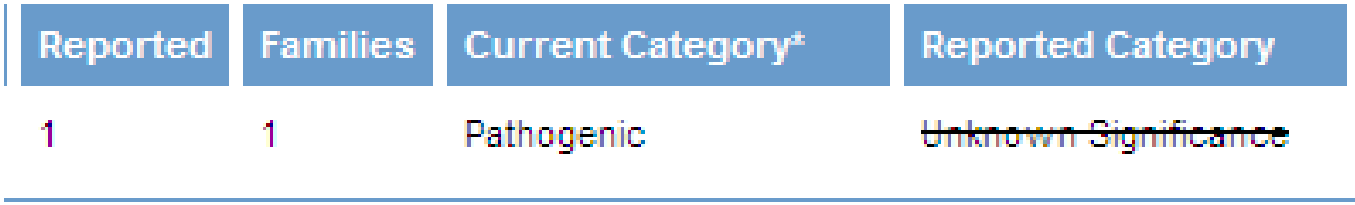
Variant Classification Changes – HCM Data



~300 category changes over 5 years impacting over 1000 patients

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, ROM, Danon disease, myopathy, Fabry disease, ARVD/C, Barth syndrome*

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

Challenges of report updating

The lab does not have reliable methods of determining who is currently caring for a patient and how to reach the patient or their physician when knowledge changes

The healthcare environment will need systems for enabling changing access to patient genetic data

Patients will need to update their current healthcare providers

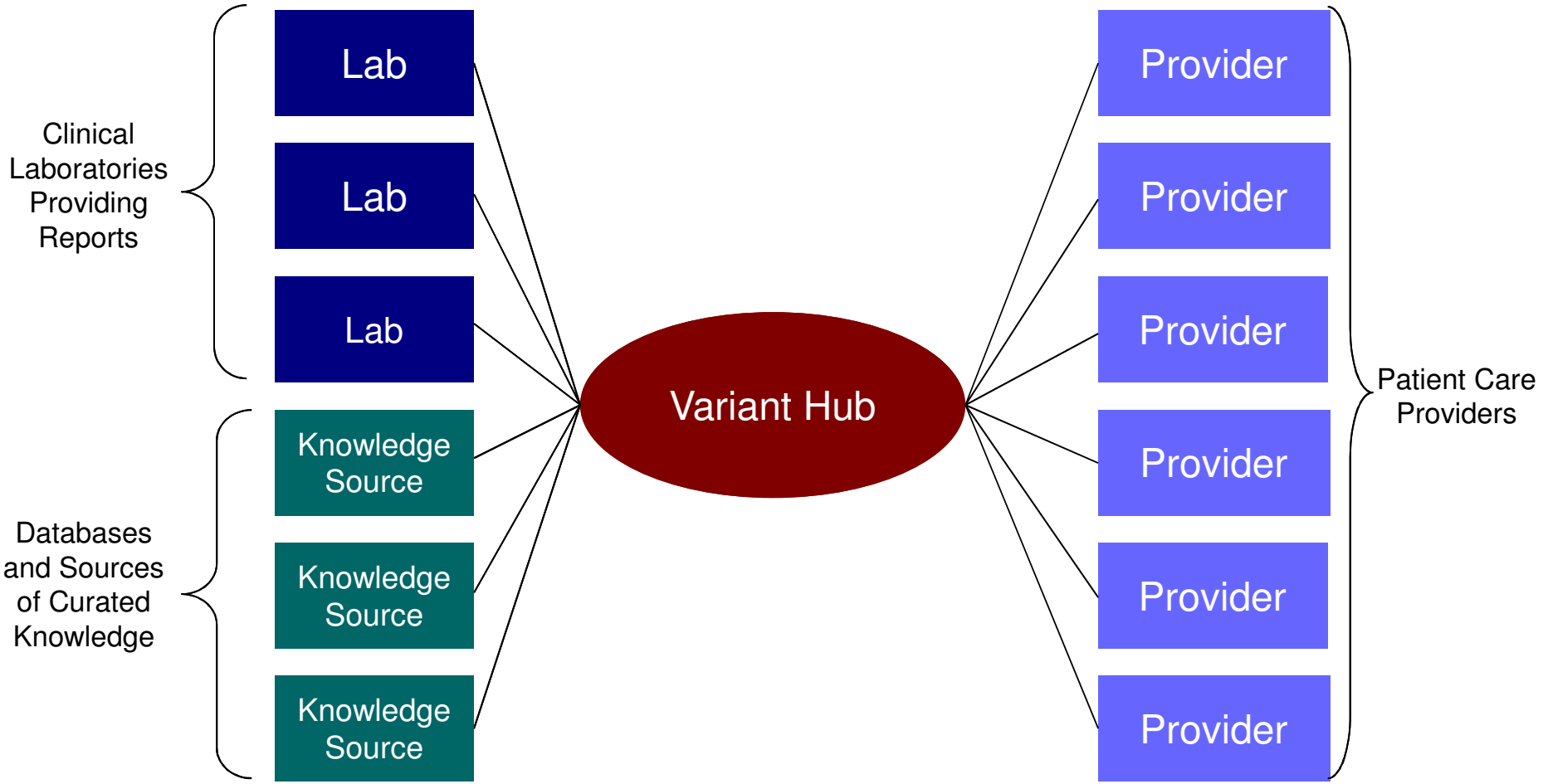
GeneInsight Clinic - Alternate use cases

Used for IRB approved research studies

Oncologists requesting use for clinical trial notification

The system can also enable multiple knowledge source feeds

The Network We Believe is Necessary



Our Developing GeneInsight Network