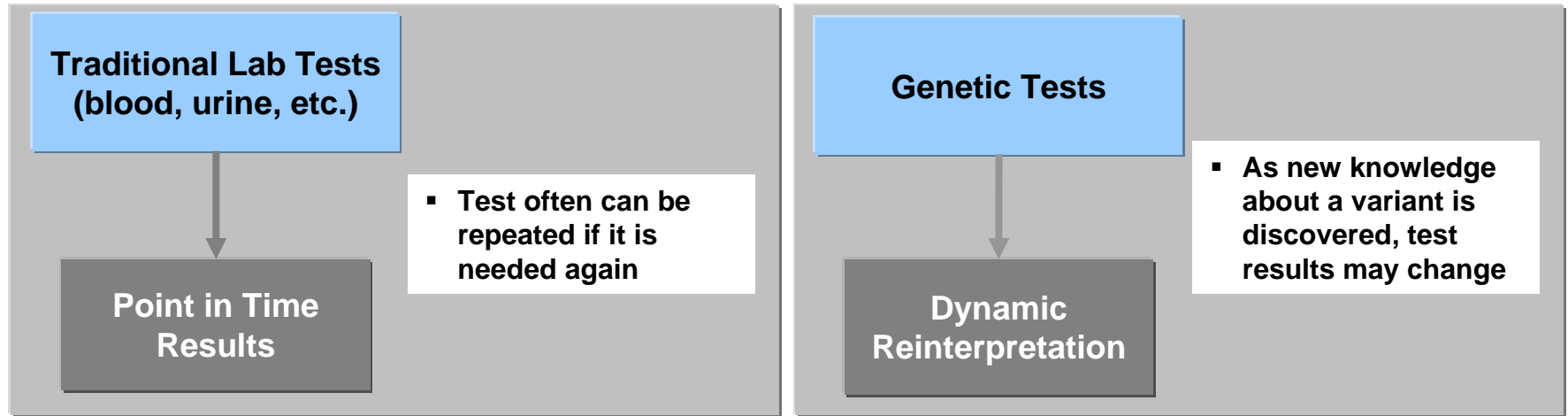




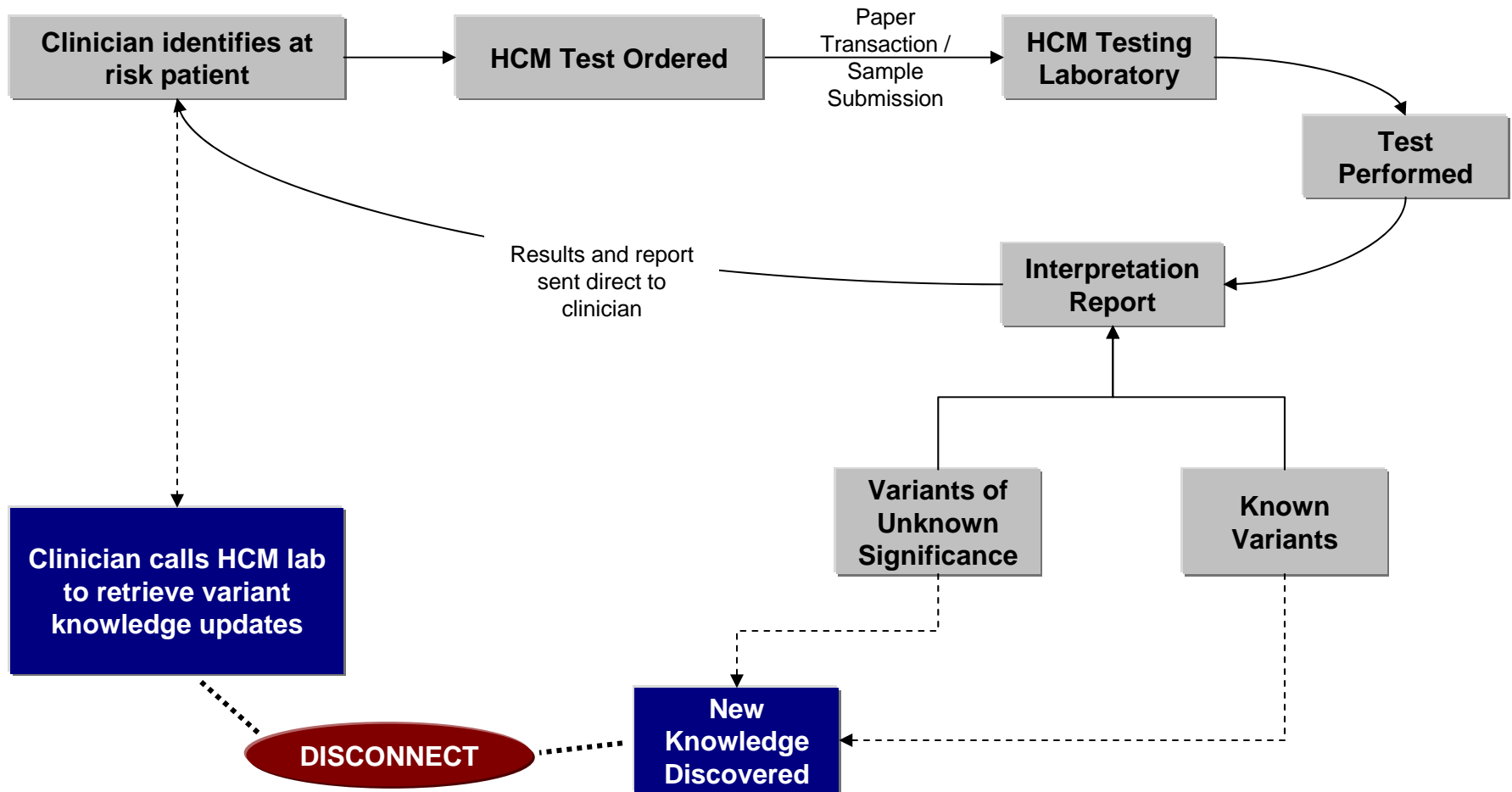
Touch-points for incorporating Genetic Data and Knowledge Into Clinical Processes

How Genetic Tests are Different



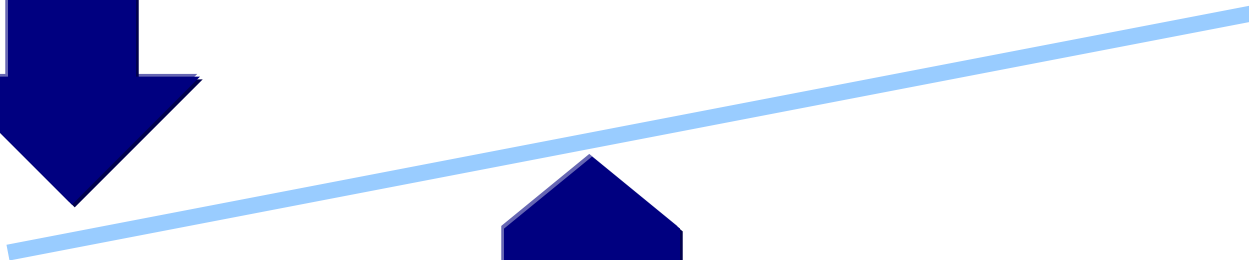
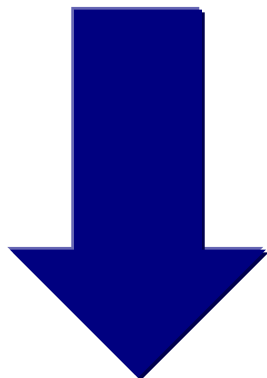
- Output is highly structured
- Volume of output is at times large – and the volume of output per test is growing

Typical HCM Workflow



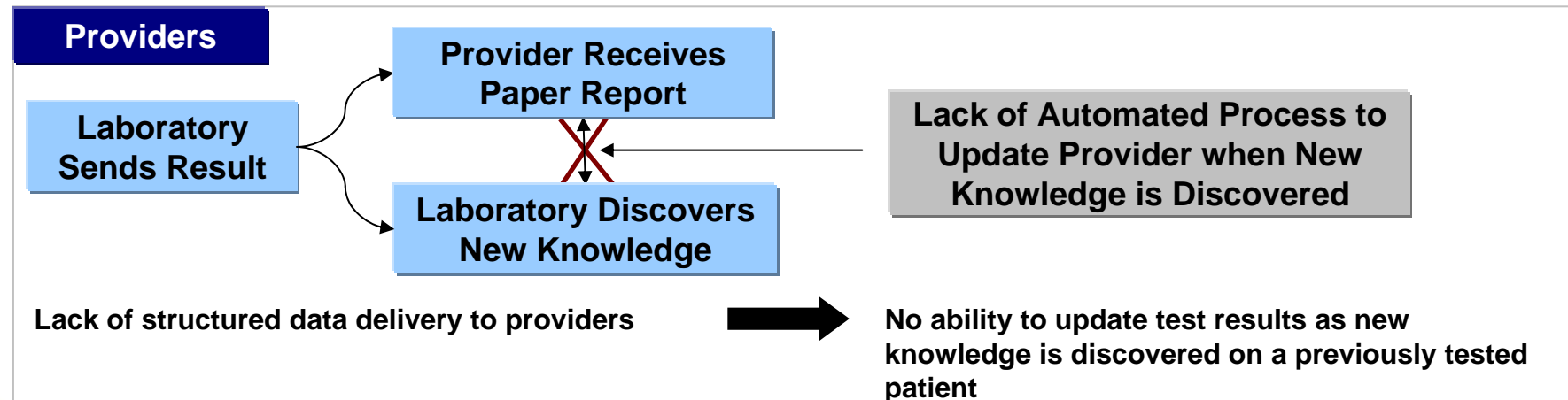
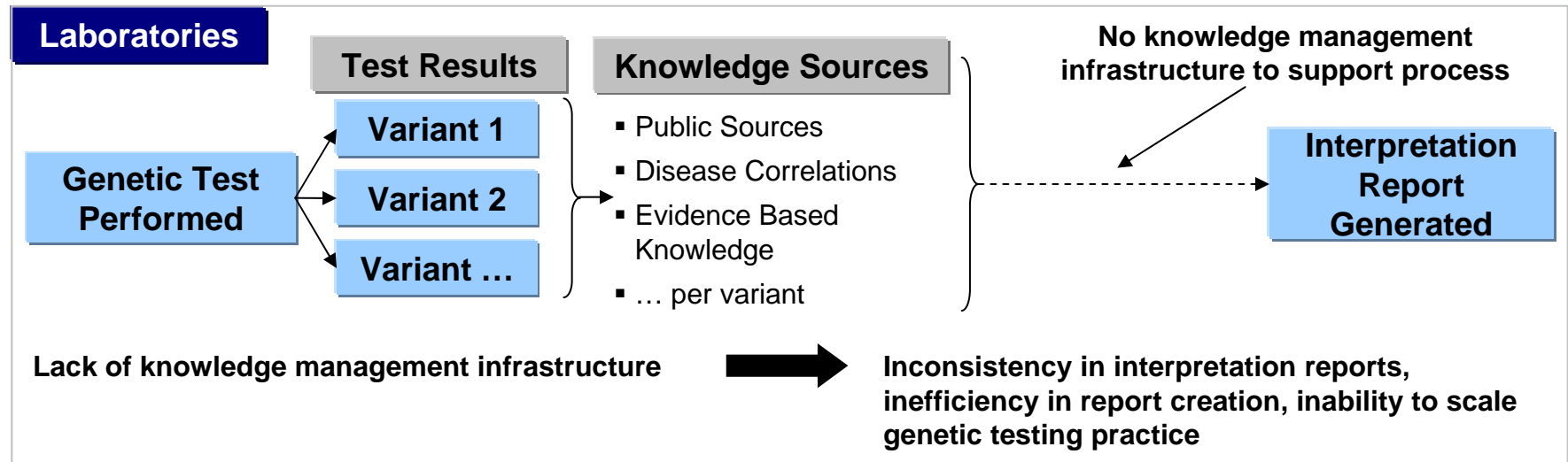
Clinical Implications of Falling Sequencing Cost

Cost of Sequencing



- Test availability
- Test volume
- DNA assayed / test
- # variants identified / patient
- # of diseases assessed / test
- # variants with unknown or evolving clinical significance

Knowledge Management Challenges





Provider Infrastructure

The Most Important Touch Point is the Clinician Display

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

Variant Knowledge Update

Current Category*

Pathogenic

Reported Category

~~Unknown Significance~~

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

Updated Variant Information

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



Laboratory Infrastructure

Knowledge Base

GENEINSIGHTSM SUITE DEMO Welcome, Sandy Aronson
Support | Log Out

[Users](#) [GeneInsight](#) [My Account](#) [CMS](#)

[Tests](#) [Diseases/Drugs](#) [Genes](#) [Variants](#) [References](#) [Report Generation](#) [Report Search](#)

Disease/Drug Details

Name: HCM (DISEASE)
Area: Cardiomyopathy
Code(s): MIM 192600 (Hypertrophic Cardiomyopathy)
Abbreviation: HCM **Default Genomic Source:** Germline
Inheritance: Dominant
Number of Families: 3
Description: Familial hypertrophic cardiomyopathy (HCM) is inherited as an autosomal dominant disease that is caused by dominant-negative-acting sarcomere protein gene mutations.

[Edit Details](#)

Associated Tests [Interpretations](#) [Recommendations](#) [Comments](#) [References](#) [Genes](#) [Variants](#)

31 tests found, displaying 1 to 25. [First/Prev] **1** 2 [Next/Last]

Test Code	KV Test Code	Test Name	Versions	Status	Actions
ImACTC-a_L	ImACTC-km_L	ACTC Gene Sequencing	version 1 (08/16/2007 -)	Active	View Panels Update/Correct Delete Retire
ImACTN2-a_L	ImACTN2-km_L	ACTN2 Full Sequencing	Version 1 (02/17/2009 -)	Active	View Panels Update/Correct Delete Retire

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

Templates

GENEINSIGHTSM SUITE DEMO

- Users
- GeneInsight
- My Account
- CMS
- Tests
- Diseases/Drugs
- Genes
- Variants
- References
- Report Generation
- Report Search

Edit Template Block

Block Type: INTERPRETATION

Sequence Number: (Next Seq #)

* Description: 2 Variants w/o variant text

Notes:

Template

Insert Dynamic Variable | Add Rules for Selected Text | Prepend Blank Line | Append Blank Line | Re-Synchronize Editor

DNA sequencing of the coding regions and splice sites of `$(TestGeneList)` identified the variants listed above. No clinically significant DNA variants were detected in the other genes analyzed.

`$(IncludeTemplate_33961187_Variant-Text)`

The presence of two pathogenic variants may lead to earlier onset and/or increased severity of disease. It would be important to determine whether these variants are present in cis (on the same copy of the gene) or in trans (on different copies) to understand the impact to the gene and accurately predict the risk to future offspring. This can be accomplished by testing this individual's biological parents. Please note that the laboratory can attempt testing on tissue specimens from deceased family members. It should be noted that the expression of `$(PatientDiseaseNames)` is the product not only of a gene variant, but also of other modifier genes and environmental factors. The significance of a variant should always be interpreted in the context of the individual's clinical manifestations.

In summary, it is very likely that the one or both of these variants are causative of `$(PatientDiseaseNames)` in this individual. The presence of two pathogenic variants may result in an earlier age of onset or more severe disease than one would expect if only one variant was present. However, the presence of only one of these variants is also likely to be sufficient to cause disease.

In summary, it is possible that the `$(MatchVariant_1_AminoAcidChange)` variant is primarily responsible for

[-] Red Text	
(Show Remove Add Blank Line Before or After -- Def Variant Set -- -- Fo	
<input type="checkbox"/>	Variant Category **
And	<input type="checkbox"/> Variant Category **
And	<input type="checkbox"/> ---- Select a Variable ----
[-] Blue Text within Red Text	
(Show Remove Add Blank Line Before or After -- Def Variant Set -- -- Fo	
<input type="checkbox"/>	Variant Category Type **
And	<input type="checkbox"/> Variant Gene **
And	<input type="checkbox"/> ---- Select a Variable ----

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

Variant Specific Categorization

GeneInsight (SM) Suite Demo

Full Details | Frequency | Notes | References | **Interpretation** | Interp. History

Proposed Interpretation

Revision Comments:

Interpretations:

Diseases/Drugs	Category	Variant Interpretation
HCM (Remove) -- Select to Add Disease/Drug --	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

Add Interpretation

Approval: Approve Proposed Interpretation

Approval Comments:

Cancel Save

Current Interpretation

Status: Approved by Matthew Varugheese on 04/05/2010 01:22 PM.

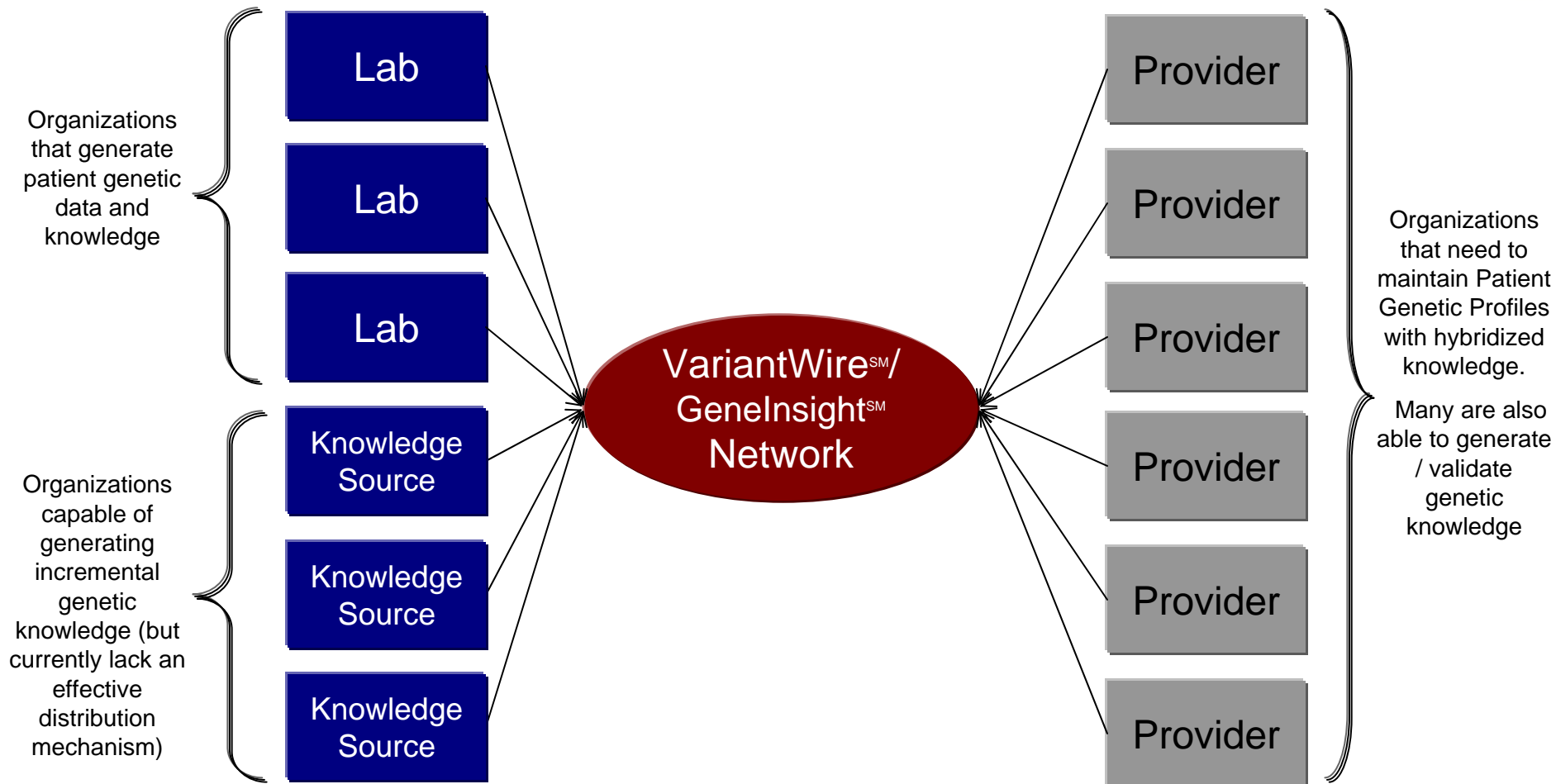
Interpretations:

Diseases/Drugs	Category	Variant Interpretation
		The His344Tyr variant has not been reported in the literature nor previously identified in our laboratory. Th

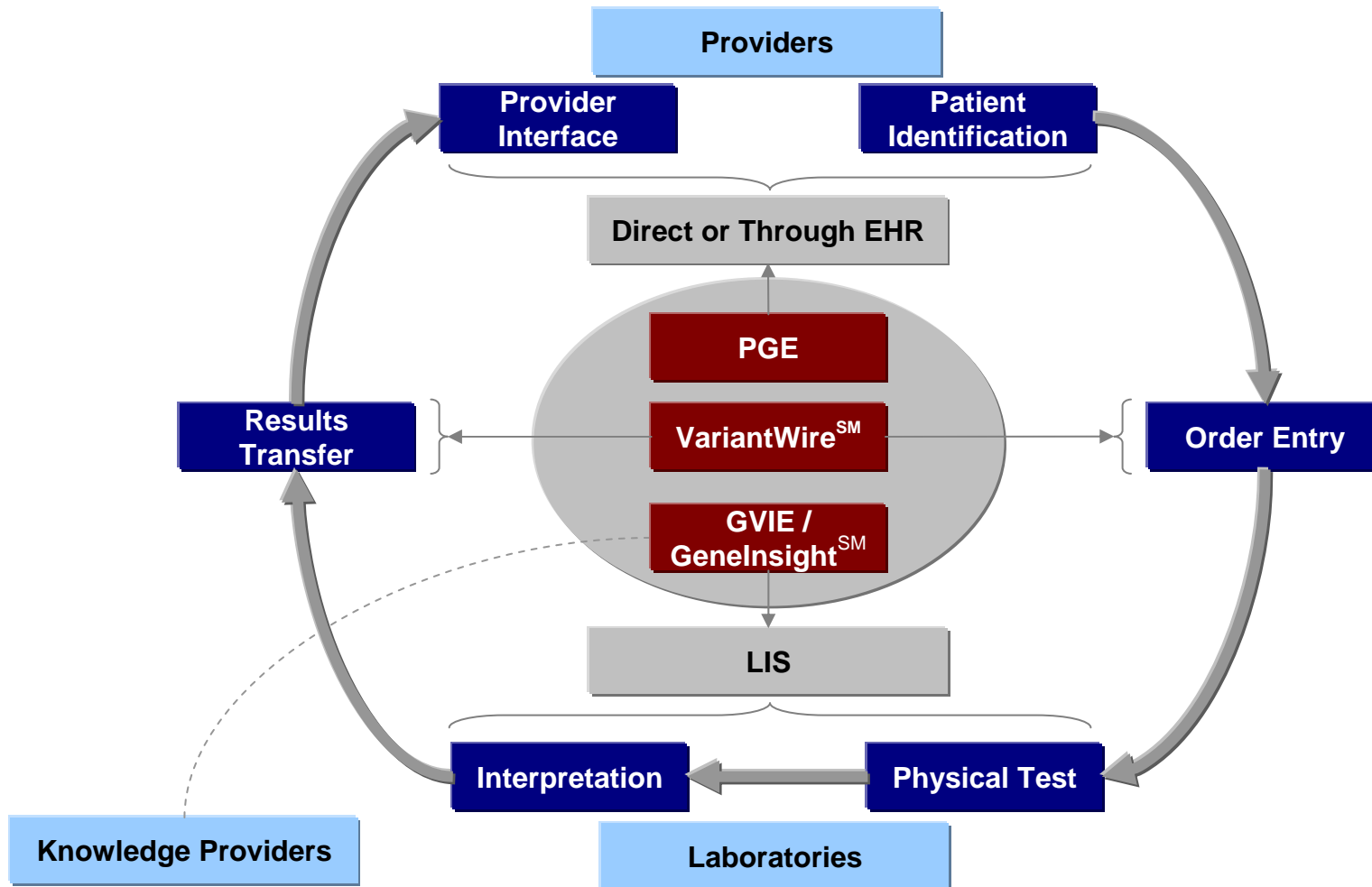
Pathogenic
Likely Pathogenic
Unknown Significance
Likely Benign
Benign
+ Pharmacogenomic Categories

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

Network Exchange Model



An Example Solution

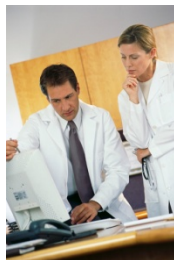


Note: VariantWire does not yet support order entry

Looking Towards the Future and Setting Goals

Institution A

Genomic Discovery Made
on Variant X



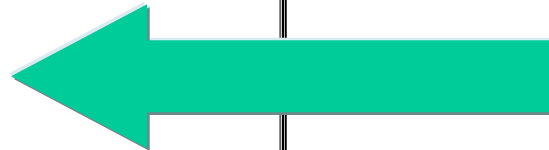
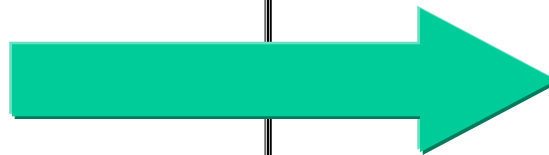
Doctor with Patient Harboring
Variant Y Receives Alert

World Wide

Doctor with Patient Harboring
Variant X Receives Alert



Genomic Discovery Made
on Variant Y



**We should not allow this boundary to
introduce a delay of more than a few minutes**

Contacts

Sandy Aronson

Executive Director of Information Technology, PCPGM
saronson@partners.org

Heidi L. Rehm, PhD, FACMG

Director, Laboratory for Molecular Medicine, PCPGM
Assistant Professor of Pathology, Harvard Medical School
hlrehm@partners.org