

IT Infrastructure Required to Scale Personalized Medicine

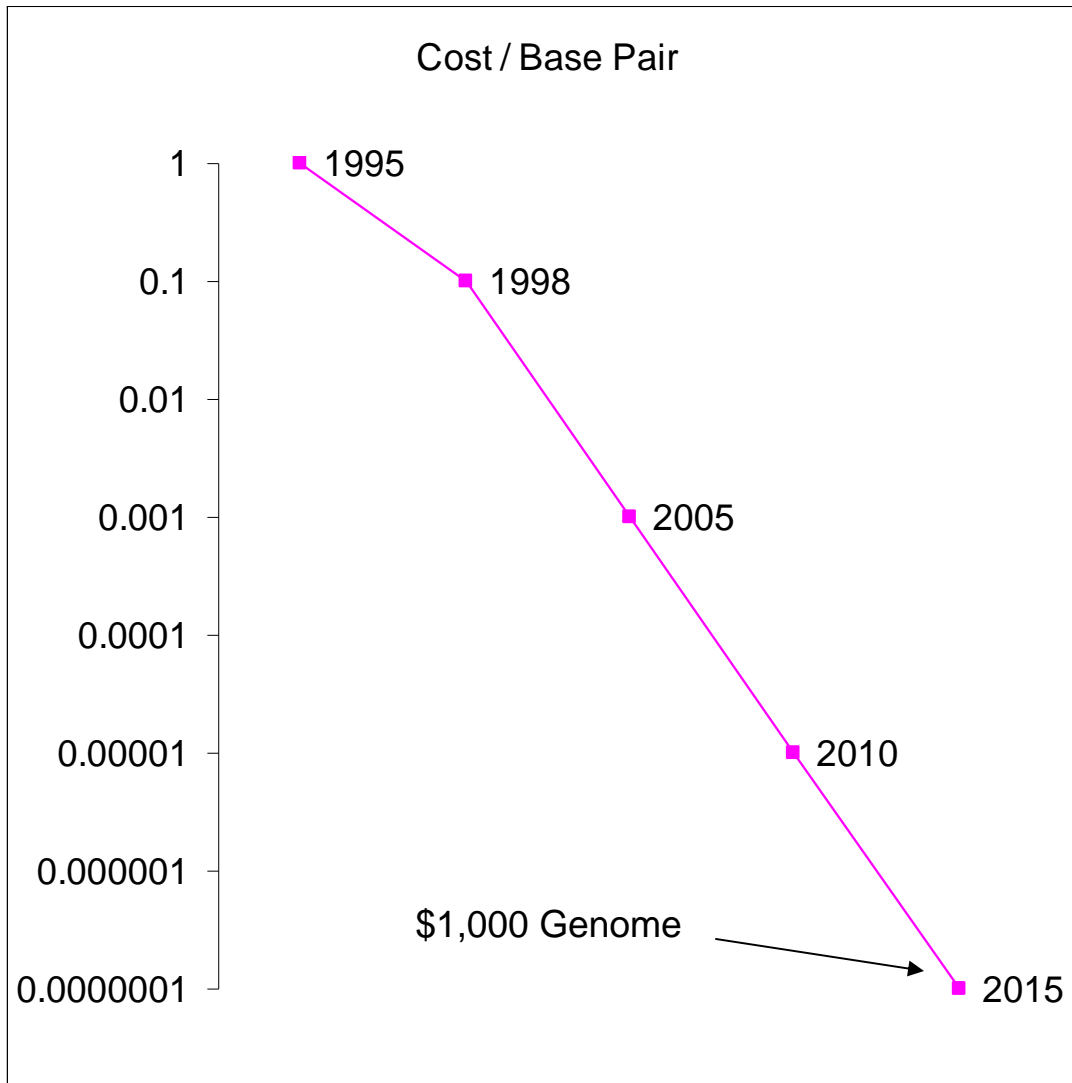
Sandy Aronson

Executive Director of Information Technology
Harvard Medical School – Partners HealthCare
Center for Genetics and Genomics

Our Goal

To build information infrastructure that improves patient care by enabling clinicians to effectively leverage increasing amounts of genetic and genomic data

Cost of DNA Sequencing



Data adopted from:

Mutation Research 573 (2005) 13-40

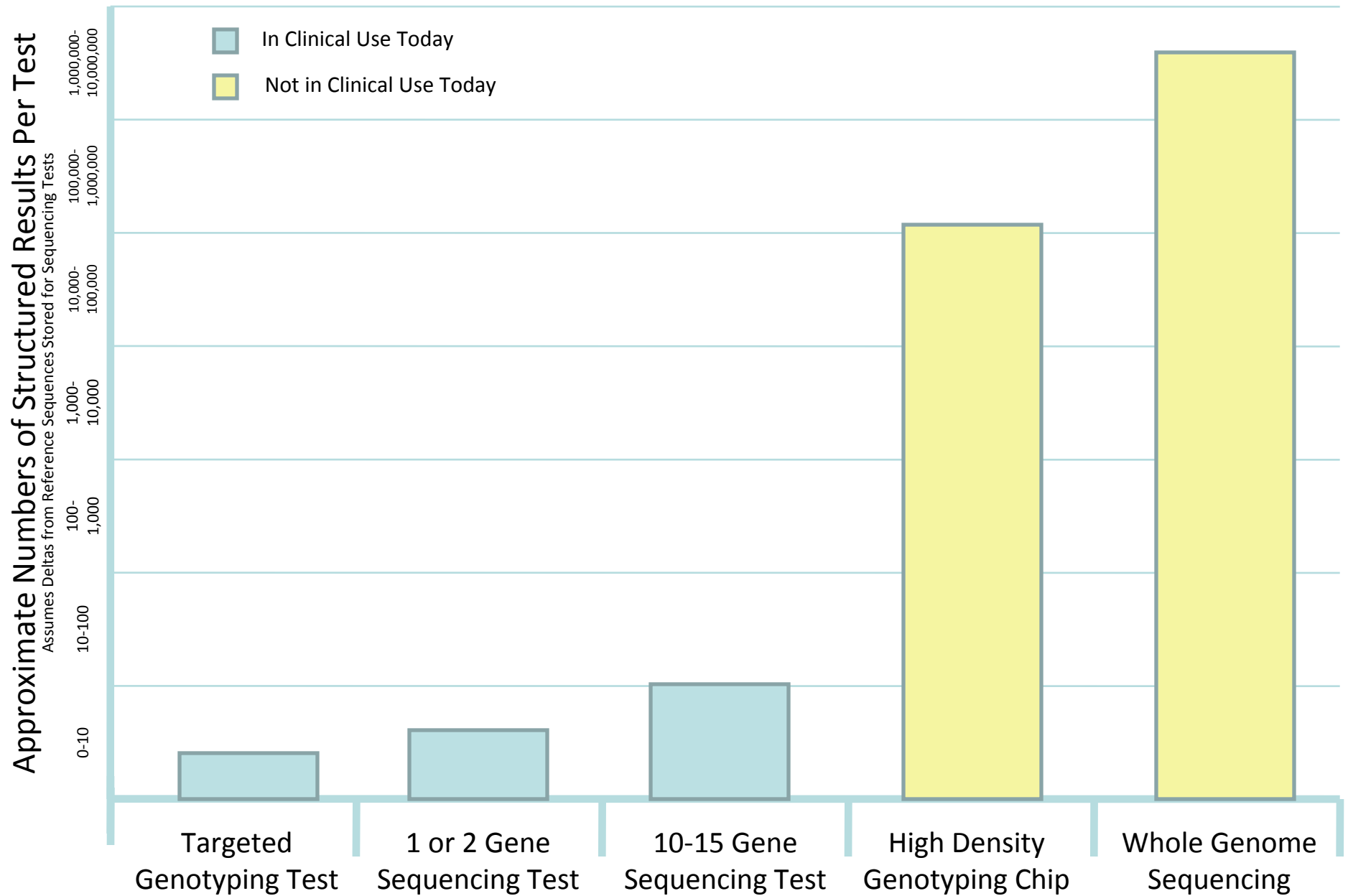
Community address: www

Review

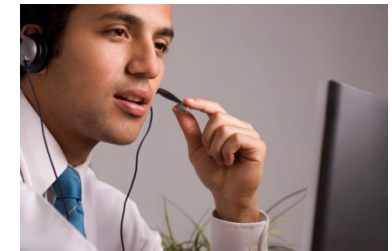
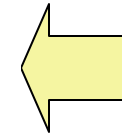
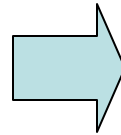
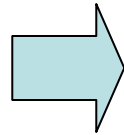
Advances in sequencing technology

Eugene Y. Chan *

Evolution of Genomic Technologies



Broad Spectrum Genotyping Model (Not Current Clinical Practice)



Broad Spectrum
Test Ordered
for General Use

Large Portions
(or all of)
Patient's DNA
Sequenced /
Genotyped

Hundreds of
Thousands to
Millions of
Variations for
Each Patient
Stored in
a Repository

Repository Routinely
Accessed to
Understand
Implications of
Patient's Genome

Will be Challenging
to Properly Support
in the Clinic

4 – 5 Million

Estimated Number of Differences Between
Each Person's DNA and a Universal
Reference Sequence

(Levy S, Sutton G, Ng PC, Feuk L, Halpern AL, et al. (2007) The diploid genome sequence of an individual human. *PLoS Biol* 5(10): e254. doi:10.1371/journal.pbio.0050254)

9,582

OMIM Entries Either Added or Updated in 2007

(OMIM Website)

14.7 Minutes

The Medium Amount of Time a Clinician
Has to Spend with Each of Their Patients

(Middleton KR, Hing E. National Hospital Ambulatory Medical Care Survey: 2004 outpatient department summary. *Adv Data. Jun 23 2006(373):1-27.*)

Genomic Contributions to Clinical Decision Making

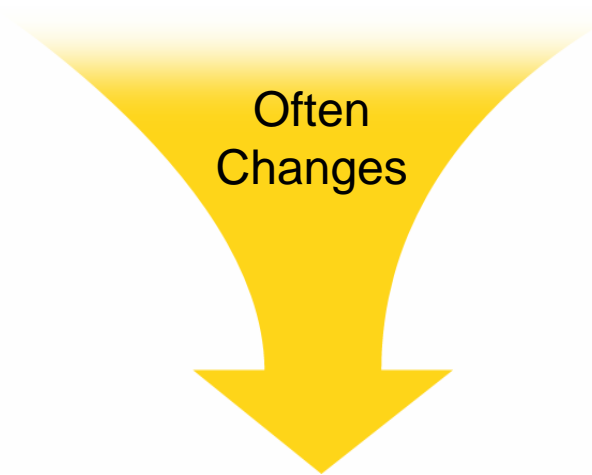
What Genetic Variations
Are Present in this Patient?

Rarely
Changes



What is the Significance of
the Variants Identified

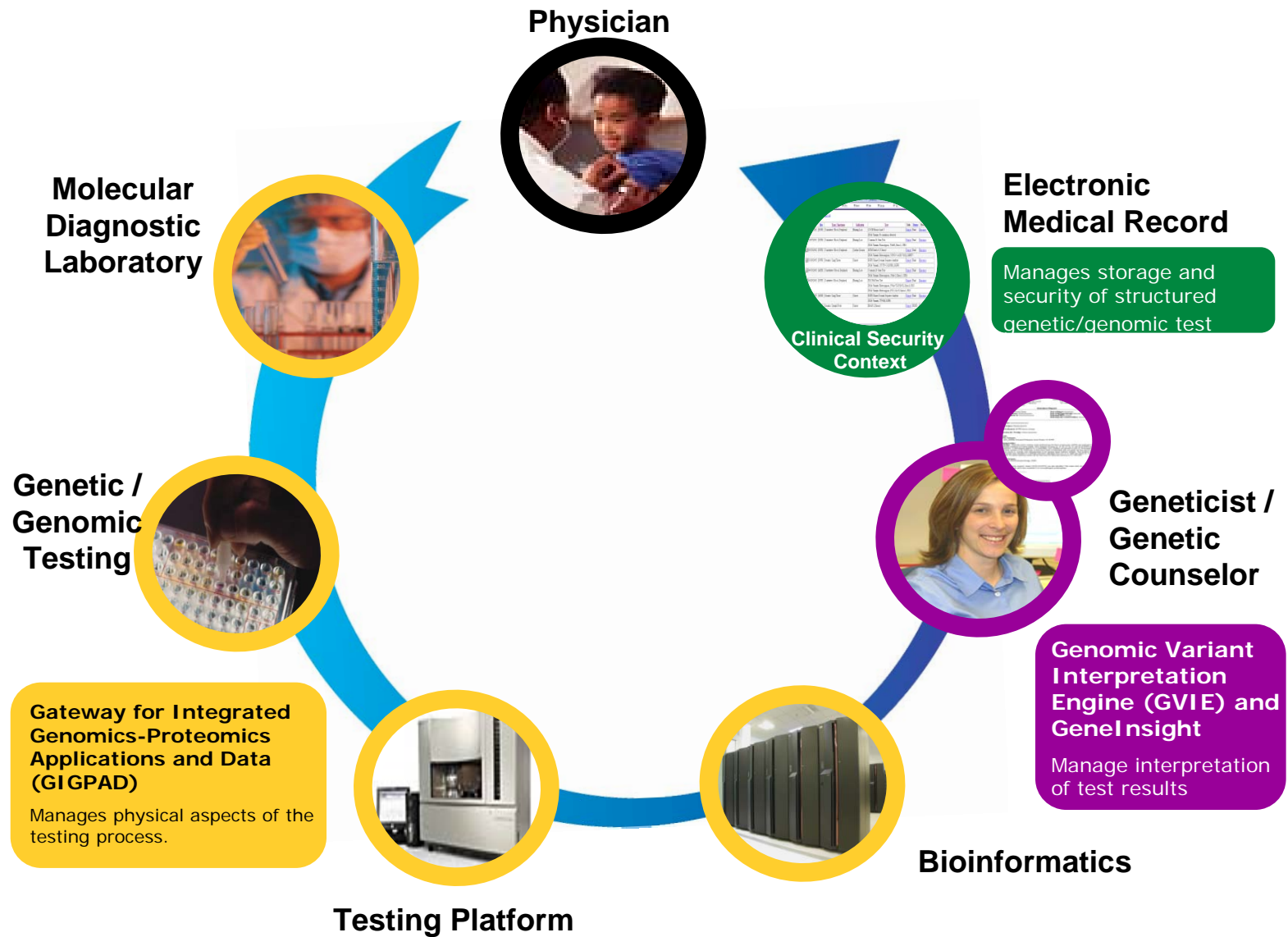
Often
Changes



Genetically Informed Decision Making Process



Supporting the Current Clinical Model



GeneInsight - DNA Variant Knowledgebase

Variant Status Flags: (R) needs review, (V) not valid, (D) don't validate, (N) has notes

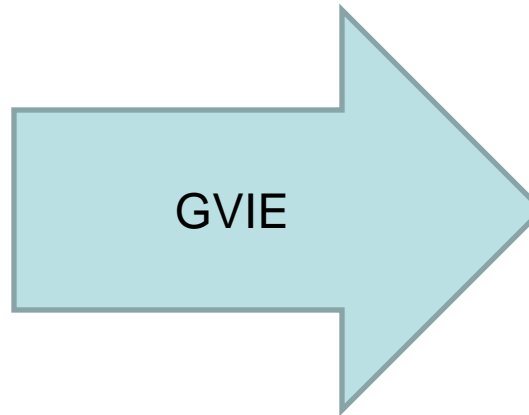
34 variants found, displaying all variants
Export options: CSV | Excel | XML | PDF

Gene	Allele	DNA	AA	**	Region	Category	Dis
TGFBR2		170-2A>G					
TGFBR2		571G>A	V191I				
TGFBR2		773T>G	V258G	R	Intron 1	Pathogenic	MFS, LDS, TAAD
TGFBR2		923T>C	L308P	R	Exon 4	Pathogenic	MFS, LDS, TAAD
TGFBR2		1006T>A	Y336N	R	Exon 4	Pathogenic	MFS, LDS, TAAD
TGFBR2		1063G>C	A355P	R	Exon 4	Pathogenic	MFS, LDS, TAAD
TGFBR2		1067G>C	R356P	R	Exon 4	Pathogenic	MFS, LDS, TAAD
TGFBR2		1069G>T	G357W	R	Exon 4	Pathogenic	MFS, LDS, TAAD
TGFBR2		1106G>T	G369V	R	Exon 4	Pathogenic	MFS, LDS, TAAD
TGFBR2		1151A>G	N384S	R	Exon 4	Pathogenic	MFS, LDS, TAAD
TGFBR2		1181G>A	C394Y	R	Exon 4	Pathogenic	MFS, LDS, TAAD
TGFBR2		1188T>G	C396W	R	Exon 4	Pathogenic	MFS, LDS, TAAD
TGFBR2		1195G>A	V387L	R	Exon 4	Pathogenic	MFS, LDS, TAAD
TGFBR2		1273A>G	M425V	R	Exon 4	Pathogenic	MFS, LDS, TAAD
TGFBR2		1322C>T	S441F	R	Exon 4	Pathogenic	MFS, LDS, TAAD
TGFBR2		1336G>A	D446E	R	Exon 4	Pathogenic	MFS, LDS, TAAD
TGFBR2		1346C>T	S449F	R	Exon 4	Pathogenic	MFS, LDS, TAAD
TGFBR2		1378C>T	R460C	R	Exon 4	Pathogenic	MFS, LDS, TAAD
TGFBR2		1379G>A	R460H	R	Exon 5	Pathogenic	MFS, LDS, TAAD

GVIE

Variants Identified In Patients

Gene	Allele	DNA	AA	**	Region	Category	Dis
TGFBR2	170-2A>G			R	Intron 1	Pathogenic	MFS, LDS, TAAD
TGFBR2	571G>A		V191I	R	Exon 4	Pathogenic	MFS, LDS, TAAD
TGFBR2	773T>G		V258G	R	Exon 4	Pathogenic	MFS, LDS, TAAD
TGFBR2	923T>C		L308P	R	Exon 4	Pathogenic	MFS, LDS, TAAD
TGFBR2	1006T>A		Y336N	R	Exon 4	Pathogenic	MFS, LDS, TAAD
TGFBR2	1063G>C		A355P	R	Exon 4	Pathogenic	MFS, LDS, TAAD
TGFBR2	1067G>C		R356P	R	Exon 4	Pathogenic	MFS, LDS, TAAD
TGFBR2	1069G>T		G357W	R	Exon 4	Pathogenic	MFS, LDS, TAAD



Laboratory for Molecular Medicine
 Center for Genetics and Genomics
 65 Landsdowne Street, Cambridge MA 02139
 Phone: (617) 768-1330 • Fax: (617) 768-1331

Unit Number(s) _____
 Lab Address(es) _____
 Patient Name _____
 Birth Date _____
 Age Sex _____

MOLECULAR DIAGNOSTICS REPORT

Specimen Type: Lung - Fixed Tissue Report Date: 12/07/2006
 Related Accessions: _____ Received Date: 12/07/2006
 Referring Physician: XXXXXXXXXXXX Referring Facility: MGH
 Cigar: T: _____ Referring Pw: MEN
 Lab Control Number: _____

GENETICIST = XXXXXXXX
TEST PERFORMED = EGFR+
TEST DESCRIPTION = EGFR Partial Gene Sequencing (Exons 18-21)
INDICATION FOR TEST = Adenocarcinoma

RESULTS

DNA VARIANTS:
 2163C>T (T790M), Exon 20, EGFR, Resistant
 2252T>G (L858R), Exon 19, EGFR, Responsive

INTERPRETATION:
Conclusion: The T790M mutation in combination with the L858R mutation has previously been described in an individual with acquired resistance to EGFR-TKIs (Pao et al., 2009).

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 inhibitors (erlotinib and gefitinib) therapy in approximately 90% of patients with advanced lung non-small cell carcinoma.

METHODS:
 DNA was isolated from the cleaved 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, retesting 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 Analytical Laboratory for Molecular Medicine (LMM, 45 Landsdowne Street, Cambridge, MA 02139) (Lab#210105307). It has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The LMM has determined that such clearance or approval is not necessary.

REFERENCES:
 Komayashi S, Boggon GJ, Dayanan T, Janne PA, Koehler O, Meyerson M, Johnson BE, Eck MJ, Tereci D, Hainsworth B. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. N Engl J Med. 2009;361:2585-2594.

EHR

(0000004 MGH) Claus,Santa C, Jr.- Genetics Summary - Microsoft Internet Explorer provided by Partners HealthCare System

Sites: MGH BWH ALL

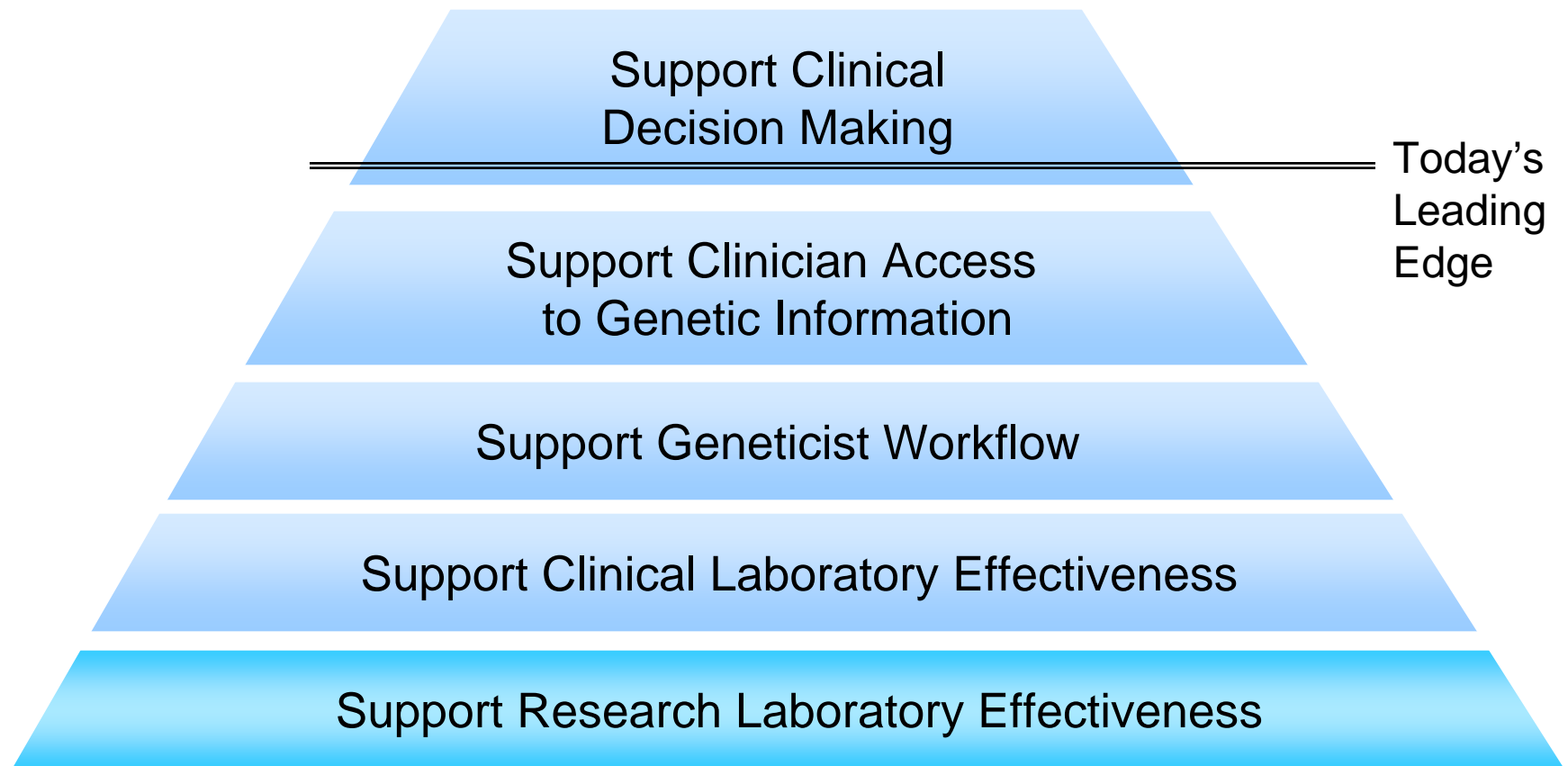
-	Date	Site	Primary Specimen	Indication	Test	Status
+	06/27/2006	MGH	Lung - Fixed Tissue	Pharmacogenomic	EGFR-b	Amend/Addenda
+	06/27/2006	MGH	Blood, Peripheral	Family History	HCM-pn1B ; UCH-pn1A ; HCM-pn1A	Final
-	06/27/2006	MGH	Blood, Peripheral	Family History	CX26-a ; CX30-a ; DFNMT-pn1A ; COCH-a ; POU3F4-a ; MYO7A-a ; PDS-a	Final
					No mutations detected.	
+	06/27/2006	MGH	Blood, Peripheral	Pharmacogenomic	EGFR-b ; EGFR-a	Final
-	06/26/2006	MGH	Fixed Tissue/Block (Lung) for EGFR	Pharmacogenomic	EGFR-a	Final
					2235_2243del (E746_R748del), Exon 19, EGFR	

CDSS

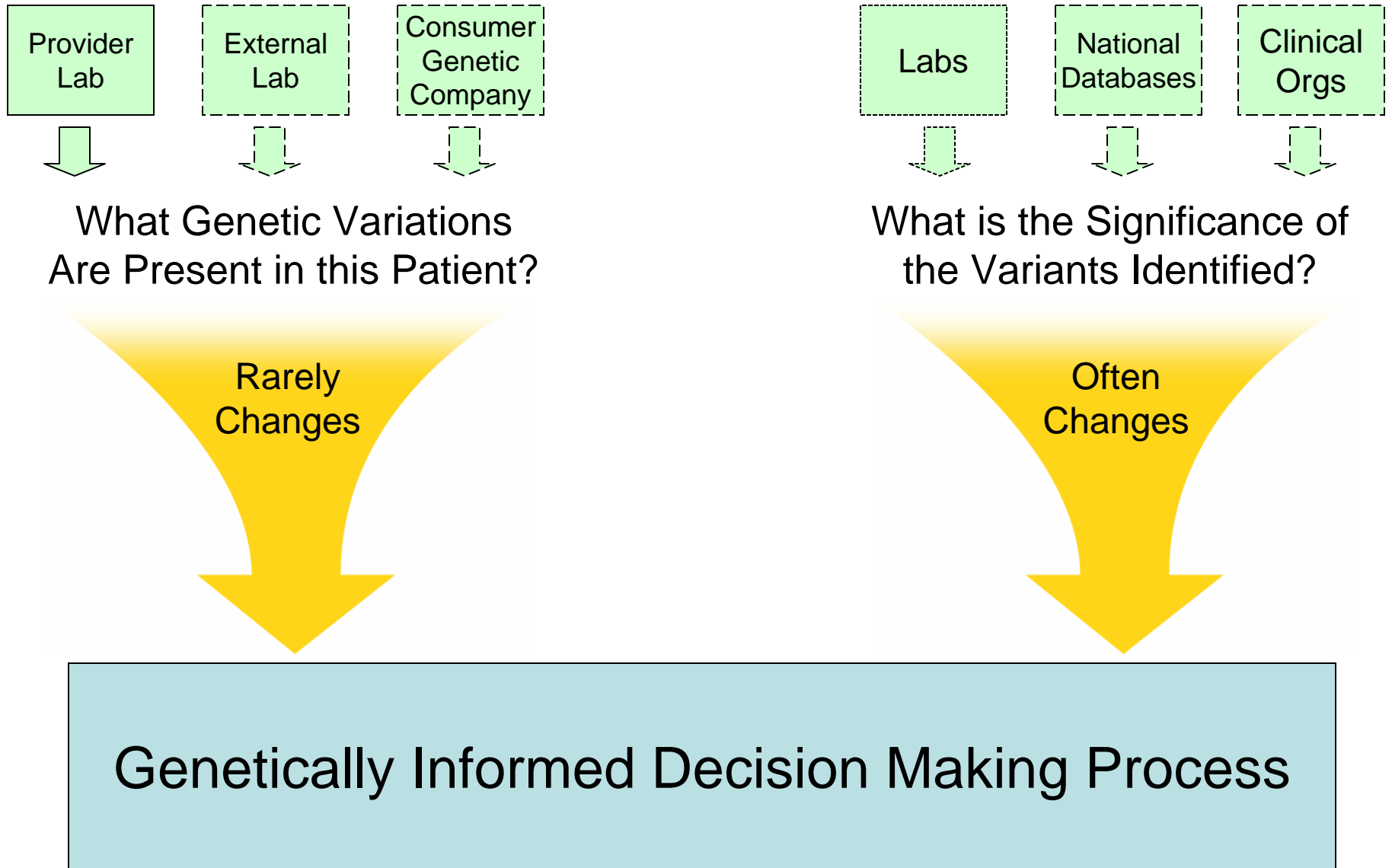
Select	Desktop	Pt Chart: Medications	Oncology	Custom	Reports	Admin	Sign	Results	?	Resc
Warning										
You are ordering: TARCEVA (ERLOTINIB)										
Drug - Genetic Intervention										
Alert Message					Keep New Order - select reason(s)					
TARCEVA (ERLOTINIB) is contraindicated in patients with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

[Continue New Order](#) [Cancel](#) [Back To Lookup](#)

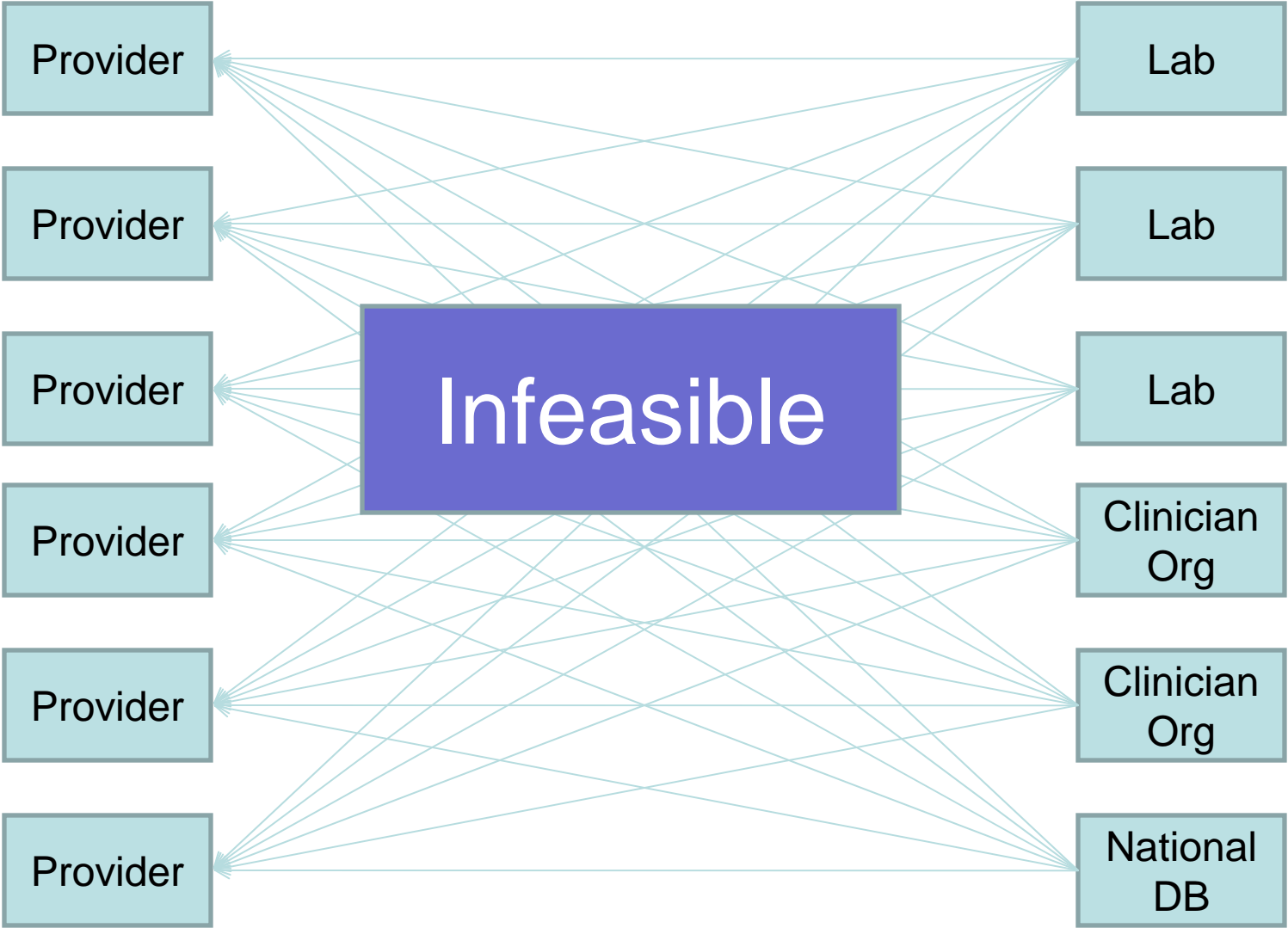
IT Support for the Clinical Practice of Genetic/Genomic Based Personalized Medicine



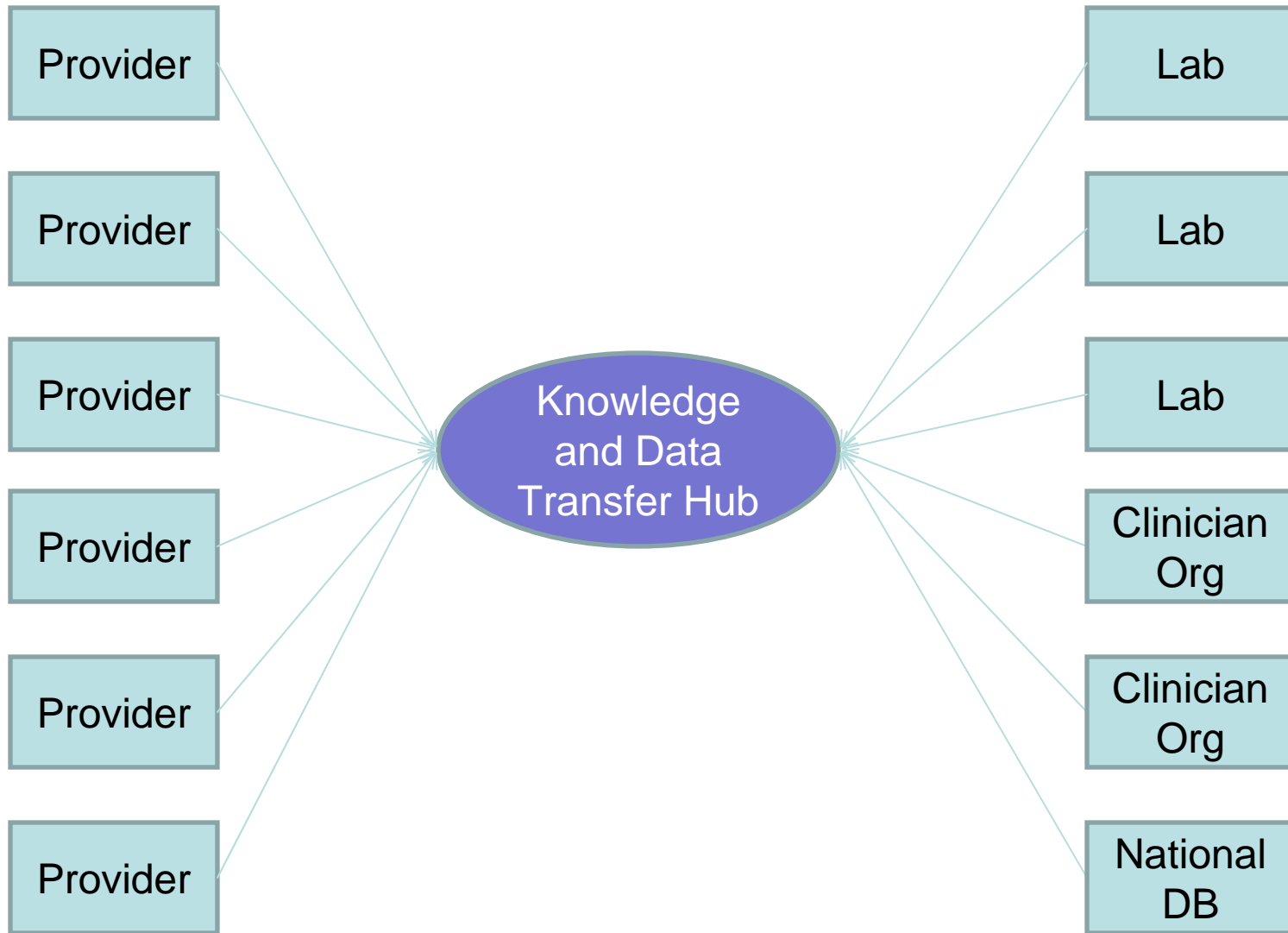
Information is Dispersed



The Many to Many Problem



The Hub Concept



GeneInsight Vision

