Just in time approaches to education

Benjamin Raby, MD, MPH

Associate Professor of Medicine
The Channing Division of Network Medicine
Director, Pulmonary Genetics Center
Division of Pulmonary and Critical Care Medicine
Brigham and Women's Hospital
Genetics Section Editor, UpToDate, Inc.

Conflict of Interest Declaration

- **UpToDate:** Annual royalties as Genetics Section Editor

- **GeneInsight:** No financial relationships, but conducting research activities in conjunction with development team.

Three vantage points

UpToDate Genetics Section Editor

Medical Genetics Subspecialist (Pulmonary)

Post-graduate Course Director

The scope of the problem

What genetic test should I order?

What is a haplotype?

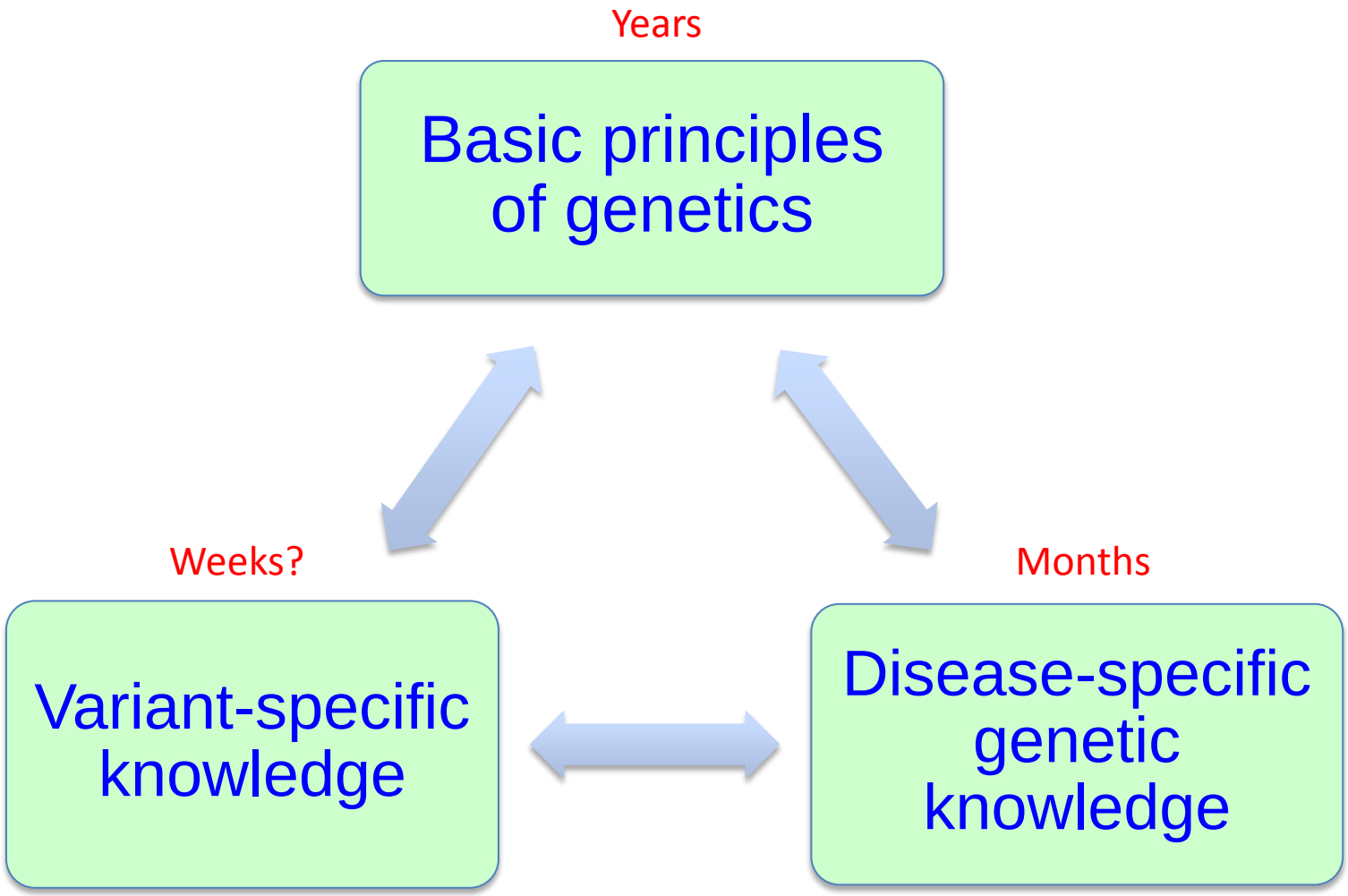
What is the significance of this mutation?

What is a genotype?

Is genetic testing indicated?

Should I recommend screening for relatives?

JIT education must address three types of interconnected genetic information

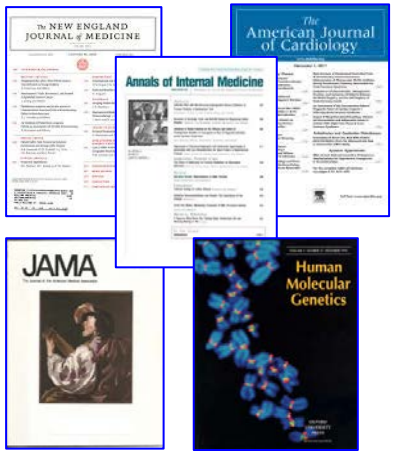


The most widely used just-in-time clinical reference

- Continuously reviewed medical literature (~460 journals)
- > 10,000 topics in 21 specialties
- Three-tiered peer review process
- Demonstrable improvements in quality of patient care
- Used by > 850,000 clinicians from 29,000 institutions & practices in 164 countries
    - Subscriptions with 90% of U.S. academic medical centers
- > 254 million queries in 2013
    - 484 topic reviews per minute

UpToDate: Continuous just-in-time clinical reference

Monthly review



Section Editors

Authors

Peer-reviewers Editors

UpToDate Users

UpToDate: Genetic Content

Basic Principles

Glossary of genetic terms
Basic principles of genetic disease
Overview of Mendelian inheritance
Overview of genetic variation
Cancer and genetics
Genetic association studies
Principles of complex genetic traits

Genetic counseling and testing

Tools for genetics and genomics:
- Polymerase chain reaction
- Gene expression profiling
- Cytogenetics
- Next-generation DNA sequencing

Reporting of incidental genetic findings

Disease-specific content

Sickle Cell Anemia
Beckwith-Wiedemann syndrome
Microcephaly: A clinical genetics approach

Genetics of Alzheimer disease
Genetics of Asthma
Familial dilated cardiomyopathy
Genetic testing for breast & ovarian cancer
Molecular genetics of colorectal cancer
Chromosomal microarray in obstetrics

Embedded content:
- Epidemiology of diabetes
- Pathogenesis of pulmonary fibrosis

UpToDate: Genetic Content

Basic Principles: Overview of Genetic Variation

RARE CHROMOSOMAL ABERRATIONS

Chromosomal abnormalities that are visible using light microscopy can be classified into those due to aberrant chromosome number and those due to abnormal chromosome structure. These variants can result in well-characterized syndromes, although many structural abnormalities are rare or unique. Chromosome aberrations typically result from either chromosome recombination errors during meiosis (for germline mutations) or aberrant chromosomal segregation during meiosis or mitosis. Large-scale variants can be evaluated using a variety of cytogenetic approaches, including karyotyping, fluorescence in-situ hybridization (FISH), and array comparative genome hybridization (array CGH) applications. (See 'Aneuploidy' below and 'Structural chromosome abnormalities' below and "Tools for genetics and genomics: Cytogenetics and molecular genetics".)

UpToDate: Genetic Content

Disease-specific content: Genetics of hypertrophic cardiomyopathy

MUTATIONS IN SARCOMERIC PROTEIN GENES

- Types of mutations
- Genes
- Pathogenic mutations and variants of uncertain significance
- Frequency of identified mutations

PATHOGENESIS

SARCOMERIC GENE MUTATIONS CAUSING HCM

- Cardiac myosin binding protein-C gene
- Cardiac beta-myosin heavy chain gene
- Troponin T gene
- Troponin I gene
- Alpha tropomyosin gene
- Myosin regulatory or essential light chain gene
- Other genes

NONSARCOMERIC CAUSES OF LV HYPERTROPHY

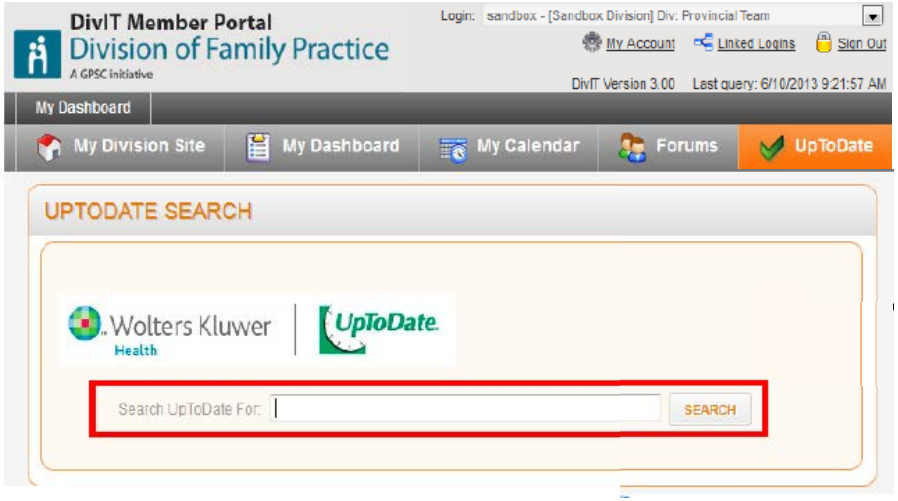
- Alpha-galactosidase A and Fabry disease
- RAS MAPK pathways genes and Noonan syndrome
- PRKAG2 and LAMP2 genes
- Renin-angiotensin system polymorphisms

CLINICAL APPLICATIONS OF GENETIC TESTING

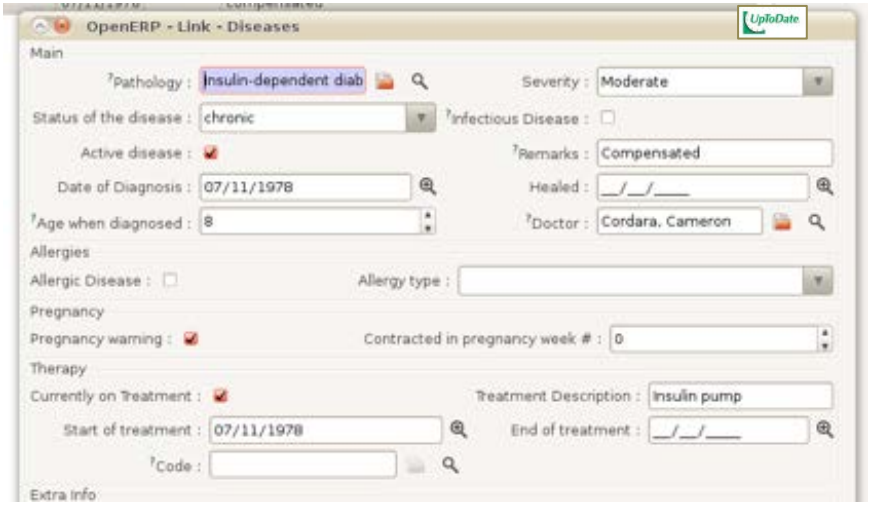
- Screening of family members for HCM
- Genotype-phenotype relationships
- Predicting prognosis with mutations

EMR-based Point-Of-Care Interfaces

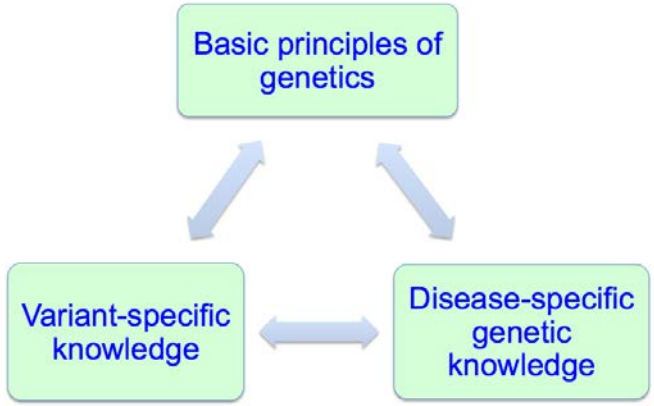
Direct query of UpToDate



Result specific queries

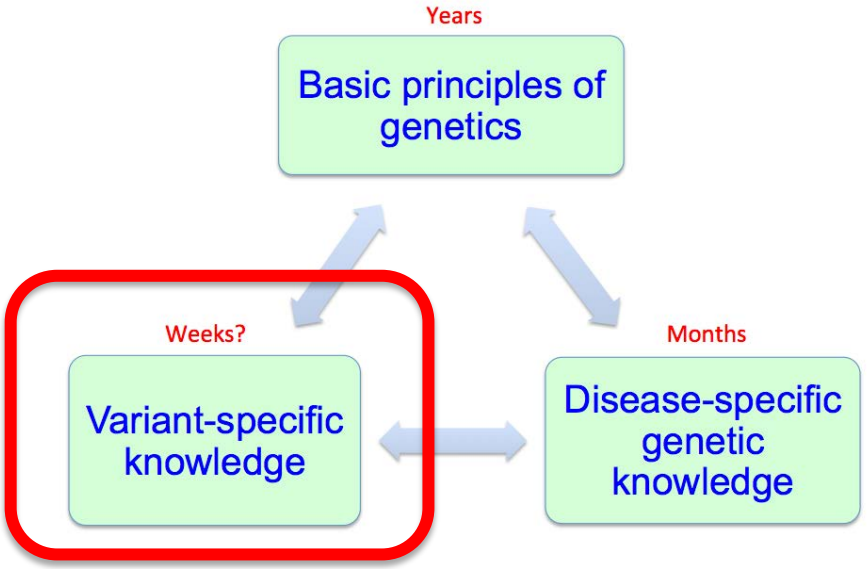


In development:
Integrated calculators
Decision-management solutions



Variant-Specific Knowledge Requires Additional Support & Modalities

- Most rapidly evolving data type
- MDs need most help deciphering
- Many variants are private
- New knowledge regarding previously reported "benign" or "VUS"



CME through genetic test reports

Unsupported report

PiZ genotype: ZZ (N = MM)

Pi phenotype: Z (N = M)

Pi serum level: 4 uM (N > 20)

Supported report

The ZZ genotype is pathogenic for alpha-1 antitrypsin deficiency, resulting in the hepatic accumulation of PiZ protein and reduced levels of circulating Pi protein.

Patients with ZZ genotype are at increased risk for the development of cirrhosis and hepatocellular carcinoma.

Serum Pi levels <10uM are associated with accelerated lung function decline, particularly among smokers.

Spirometry is advised. The use of replacement therapy with pooled plasma-derived PiM is supported for patients with reduced Pi levels with an FEV1 of less than 80% predicted …

Detailed supported test results

TEST PERFORMED - Cystic Lung Disease Panel; SeqConfirm

TEST DESCRIPTION - Cystic Lung Disease Panel (8 genes) Sequence Confirmation Test

INDICATION FOR TEST - Personal history of spontaneous pneumothorax

RESULTS

DNA VARIANTS:
Heterozygous c.1285dupC (p.His429ProfsX26), Exon 11, Pathogenic

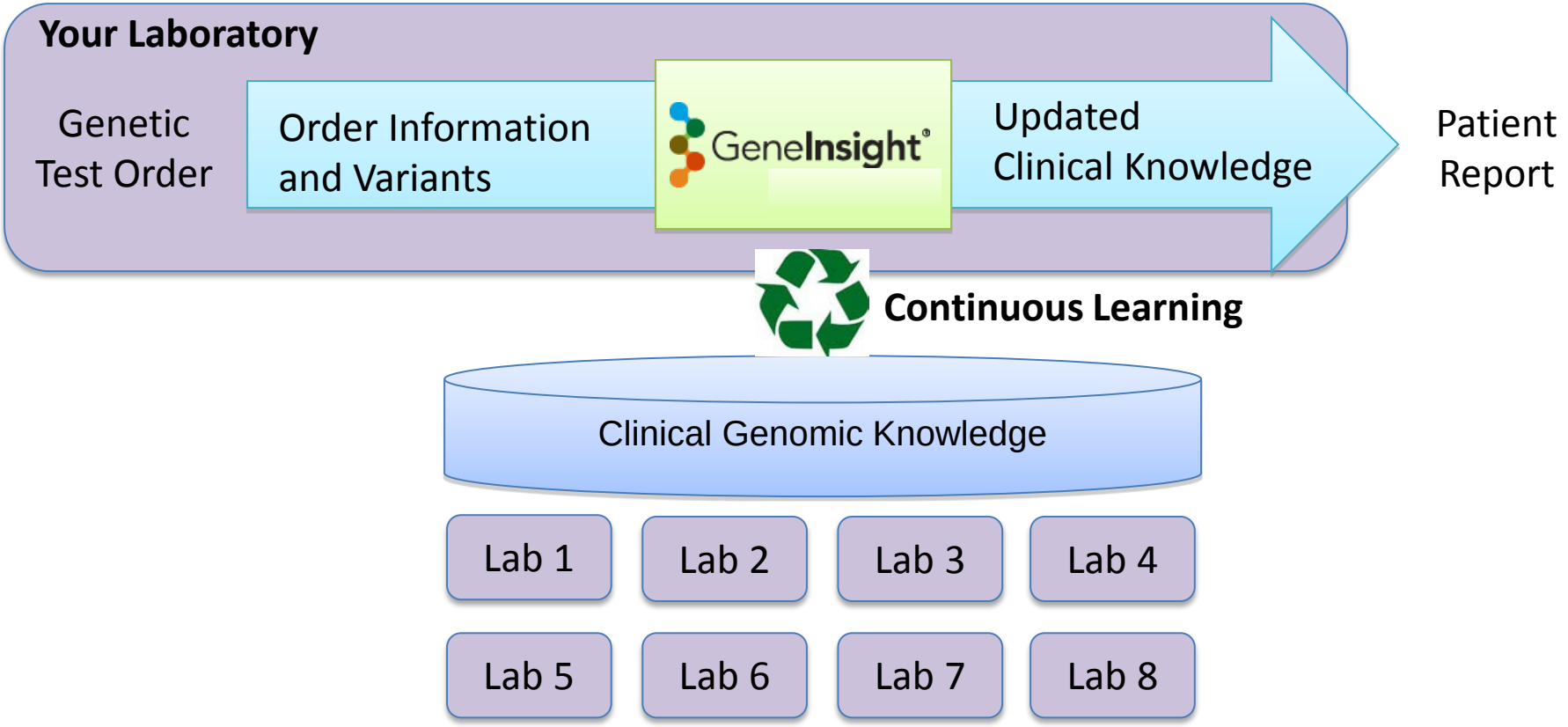
INTERPRETATION:
Positive. DNA sequencing of 8 genes associated with cystic lung disease syndromes identified the variants listed above.

SUMMARY: This individual carries one previously published pathogenic BHD variant (a frameshift variant in FLCN). This finding is consistent with this patient's clinical presentation and is pathogenic for Birt Hogg Dube Syndrome.

The **His429ProfsX26** variant in FLCN has been reported in >30 families with documented Birt Hogg Dube Syndrome and is located in the polycytosine tract in exon 11, which is a mutational hotspot in FLCN (Schmidt 2004, Toro 2008). In addition, this variant has not been identified in large and broad European American and African American chromosomes by the NHLBI Exome Sequencing Project. This frameshift variant is predicted to alter the protein's amino acid sequence beginning at position 429 and lead to a premature termination codon 27 amino acids downstream. This alteration is then predicted to lead to a truncated or absent protein. In summary, this variant meets our criteria to be classified as pathogenic (http://pcpgm.partners.org/LMM) based upon loss of heterozygosity of the FLCN gene, which is predicted to initiate tumor formation in Birt Hogg Dube Syndrome.

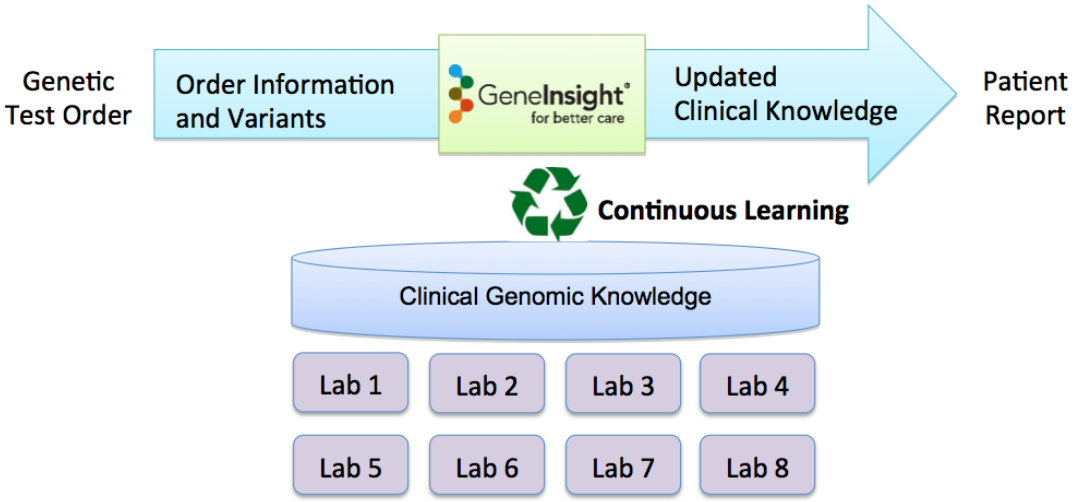
Birt Hogg Dube Syndrome is typically inherited in an autosomal dominant pattern. Each first-degree relative has a 50% (or 1 in 2) chance of inheriting a variant.

How do we keep up with new variation? Can knowledge be transmitted quickly?



Maintain continuous learning environment in the laboratory

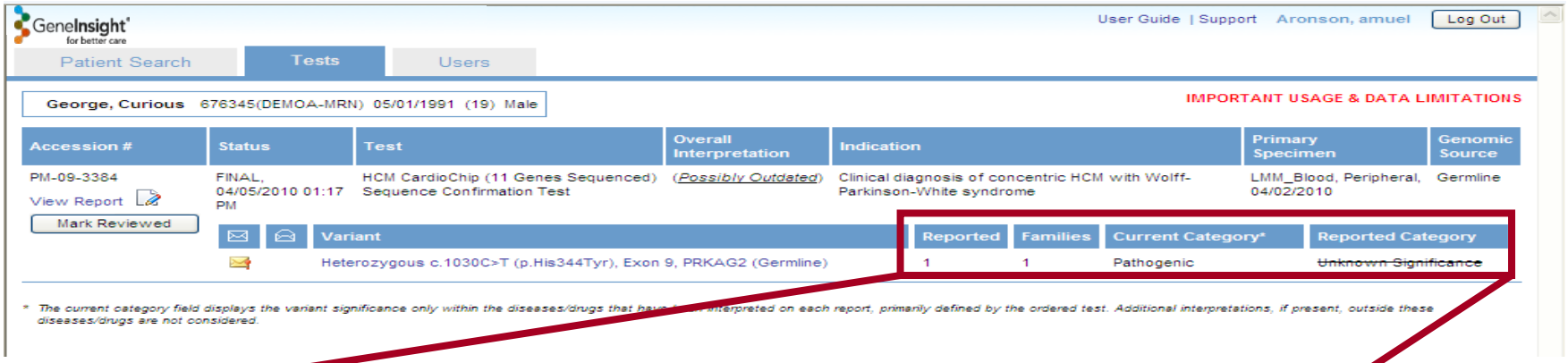
GeneInsight Clinic: continuous patient updates



Patient reports can become dynamic, updated as new information is generated and shared.

Improved communications between lab & physician

Continuous education



Conclusions

"Just in Time" genetic education resources are an important component in addressing the current deficiencies in clinical genetic knowledge