

Clinical Assessment through Family Health History

*Identifying people at high risk for cancer,
cardiac disease and other chronic illness*

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Massachusetts General Hospital

Surgeon

The Newton-Wellesley Hospital Breast Center

People with hereditary syndromes

- *More likely to develop disease*
- *More likely to have morbidity*
- *More likely to die of that disease*

Management strategies can prevent or decrease morbidity and death IF...

We know who is at risk

Our Goal

Find every mutation carrier for every hereditary syndrome known to man before disease occurs

Adult hereditary syndromes: 188

Mendeliandisorder
Abdominal aortic aneurysm
Abdominal obesity-metabolic syndrome
Aceruloplasminemia
Adult polycystic kidney disease
Alstrom syndrome
Amyloidosis V
Amyloidosis VI
Amyloidosis VII
Antithrombin III deficiency
Apolipoprotein(a)
Apolipoprotein A-I
Arteriovenous malformation of the brain
Arthrogyposis and ectodermal dysplasia
Atherosclerosis susceptibility
Atrial cardiomyopathy with heart block
Autoimmune polyendocrinopathy syndrome, type I

AD Emery-Dreifuss muscular dystrophy
AD hemochromatosis
Autosomal dominant nemaline myopathy
AD pseudoxanthoma elasticum
AR dilated cardiomyopathy
AR hypercholesterolemia
AR nemaline myopathy 2
AR Noonan syndrome
Bardet-Biedl syndrome
Barth syndrome
Becker type muscular dystrophy
Berardinelli-Seip congenital lipodystrophy

Bicuspid aortic valve
Bloom syndrome
Brugada syndrome
CADASIL
Cardiac conduction defect
Cardiomyopathy-hypogonadismcollagenoma syndrome
Cataract and cardiomyopathy
Cerebral cavernous malformations
Cerebrotendinous xanthomas
Cerebrovascular disease with thin skin, alopecia and disk disease
Cortisol 11-beta-ketoreductase deficiency
Costello syndrome
Dilated cardiomyopathy
Dilated cardiomyopathy with wooly hair and keratoderma
Duchenne type muscular dystrophy
Dysfibrinogenemia
Ehlers-Danlos syndrome, type IV
Ehlers-Danlos syndrome, type VI
Ehlers-Danlos syndrome, type unspecified
Emery-Dreifuss muscular dystrophy
Endocardial fibroelastosis
Fabry disease
Familial antiphospholipid syndrome

Familial arrhythmogenic right ventricular dysplasia
Familial combined hyperlipidemia
Familial defective apo B
Familial defective release of tissue plasminogen activator
Familial hyperaldosteronism, type 1
Familial hypercholesterolemia
Familial hypertrophic cardiomyopathy
Familial hypertrophic cardiomyopathy with Wolff-Parkinson-White syndrome
Familial idiopathic prepubertal edema
Familial lipoprotein lipase deficiency
Familial mitral valve prolapse
Familial partial lipodystrophy
Familial pseudohyperkalemia due to red cell leak
Familial restrictive cardiomyopathy
Familial thoracic aortic aneurysm
Familial ventricular tachycardia
Fibromuscular dysplasia of arteries

Friedreich ataxia
Generalized juvenile polyposis with pulmonary AVM*
Hemochromatosis (classical and type 3)
Heparin cofactor II deficiency
Hereditary hemorrhagic telangiectasia, type 1
Hereditary hemorrhagic telangiectasia, type 2
Hereditary neurocutaneous angioma
Hereditary pancreatitis
Hermansky-Pudlak syndrome
Histidine-rich glycoprotein
Homocystinuria
Homocystinemia/homocystinuria due to N(5,10)-methylenetetrahydrofolate reductase deficiency
Hyperkalemic periodic paralysis
Hyperlipoproteinemia, type III
Hyperostosis frontalis interna
Insulin receptor defect
Insulin-resistant diabetes mellitus with acanthosis nigricans and hypertension
Intracranial berry aneurysm
Juvenile hemochromatosis
Kearns-Sayre syndrome
Leber optic atrophy
LEOPARD syndrome

Limb-girdle muscular dystrophy, type 1B
Long QT1 (Romano Ward syndrome)
Long QT2
Long QT3
Long QT4
Long QT5 (Lange-Nielsen syndrome)
Long QT6
Long QT7 (Andersen cardiodysrhythmic periodic paralysis)
Mal de Meleda
Malignant hyperthermia susceptibility 1
Marfan syndrome
Maternally transmitted diabetes-deafness syndrome
Maturity onset diabetes of the young

MELAS
Moyamoya
Multiple epiphyseal dysplasia with early-onset diabetes mellitus
Myotonic dystrophy
Naxos disease
Nephropathic cystinosis
Neurofibromatosis, type 1
Niemann-Pick disease (types C and E)
Nodal rhythm
Noonan syndrome
Obesity and endocrinopathy due to impaired processing of prohormones
Obstructive sleep apnea
Pancreatic beta cell agenesis with neonatal diabetes mellitus
Parkinsonism with alveolar hypoventilation and mental depression
Paroxysmal familial ventricular fibrillation
PHACE association
Pineal hyperplasia, insulin-resistant diabetes mellitus, and somatic abnormalities
Plasminogen activator inhibitor 1
Plasminogen defects
Polycystic ovary syndrome 1
Progeria
Progressive familial heart block, 1 and 2
Protein C deficiency
Protein S deficiency
Pseudoxanthoma elasticum
Schmidt syndrome
Sitosterolemia
Sneddon syndrome
Spontaneous coronary dissection

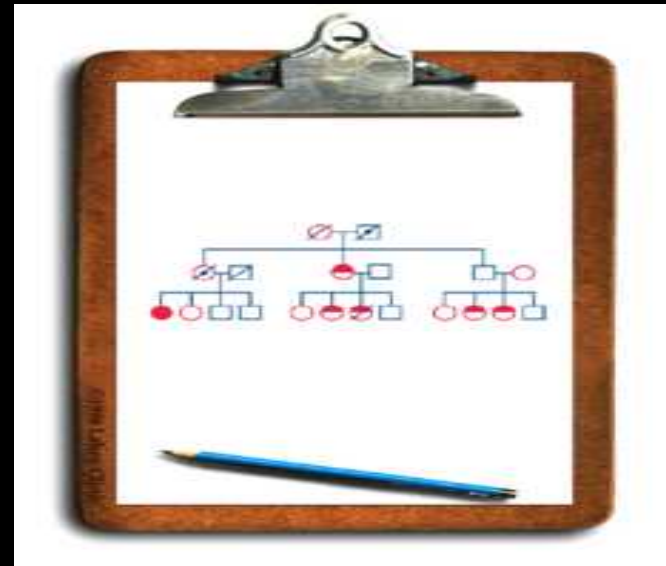
Stress-induced polymorphic ventricular tachycardia
Tangier disease
Tardive tibial muscular dystrophy
Thiamine-responsive megaloblastic anemia syndrome
Three M syndrome
Thrombophilia due to deficiency of activated protein C
Thrombophilia due to thrombomodulin defect
Tissue factor pathway inhibitor
Transient neonatal diabetes
Transthyretin

Tuberous sclerosis
Type I hyperlipoproteinemia due to apolipoprotein C-II deficiency
Type IV hyperlipidemia
Von Hippel-Lindau syndrome
Welander distal myopathy (SMAIII)
Werner syndrome
Williams syndrome
Wilson disease
Wolff-Parkinson-White
Wolfram syndrome
XL dilated cardiomyopathy
XL immunodysregulation, polyendocrinopathy, and enteropathy
XL sideroblastic anemia

Approaches

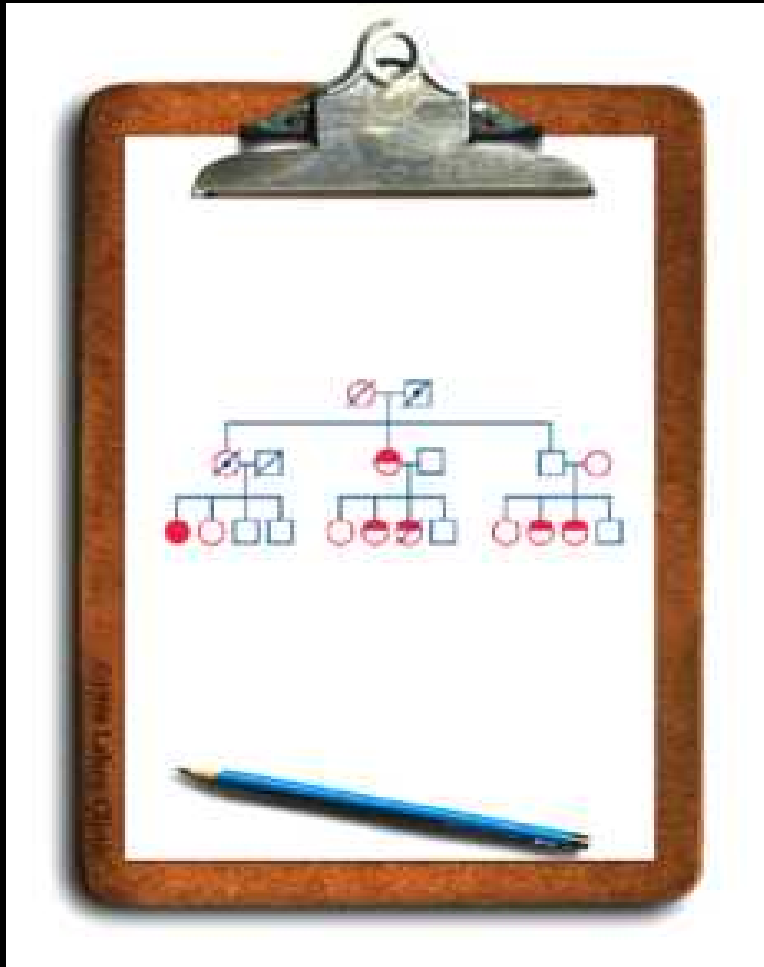


Test the population



Look for family history patterns and test those at risk

Family history



Multiple relatives affected

Young age at diagnosis

Multiple primary cancers

Unusual Cancer

Male breast cancer

Guidelines and Models

$$P(M|H) = \frac{P(H|M)P(M)}{P(H)}$$

$$LR = \frac{P(H|M)}{P(H|N)}$$

$$P(M|H) = \frac{LR}{LR + P(N)/P(M)}$$

$$LR = \frac{b_M(30)}{b_N(30)} = \frac{0.0088}{0.00016} = 55$$

$$LR = \frac{1 - B_M(\text{age})}{1 - B_N(\text{age})}$$

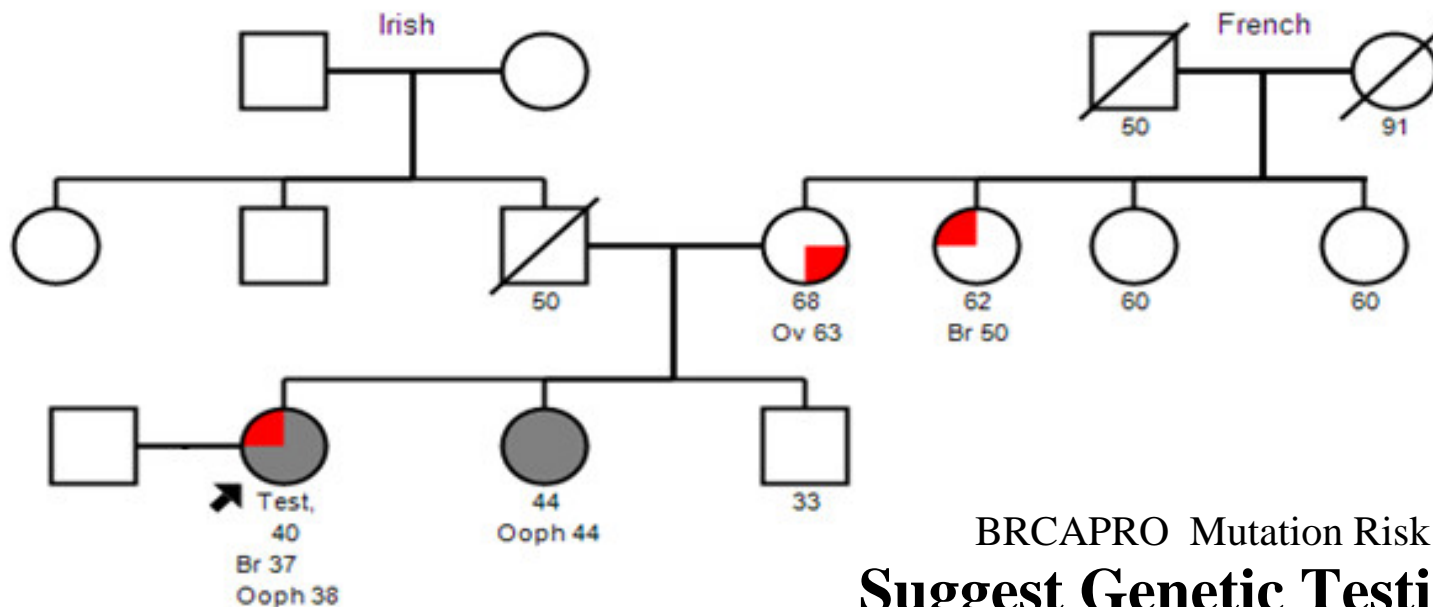
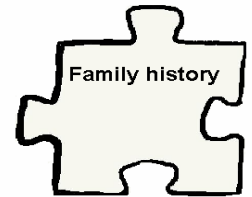
1. Member of a family with a known *BRCA1/BRCA2* mutation
2. Personal history of breast cancer plus one or more of the following:
 - a) Diagnosed 40 years, with or without family history
 - b) Diagnosed 50 years, or bilateral, with at least one close blood relative with breast cancer diagnosed 50 years or at least one close blood relative with ovarian cancer
 - c) Diagnosed at any age, with at least two close blood relatives with ovarian cancer at any age
 - d) Diagnosed at any age with breast cancer with at least two close* blood relatives with breast cancer, especially if at least one is diagnosed before age 50 years or has bilateral disease
 - e) Close male blood relative has breast cancer
 - f) Personal history of ovarian cancer
 - g) Is of ethnic descent associated with deleterious mutations (e.g., Ashkenazi Jewish)
3. Personal history of ovarian cancer plus one or more of the following:
 - a) At least one close* blood relative with ovarian cancer
 - b) At least one close* female blood relative with breast cancer at age 50 years or bilateral breast cancer
 - c) At least two close* blood relatives with breast cancer
 - d) At least one close* male blood relative with breast cancer
 - e) Is of Ashkenazi Jewish descent
4. Personal history of male breast cancer plus one or more of the following:
 - a) At least one close male blood relative with breast cancer
 - b) At least one close female blood relative with breast or ovarian cancer
 - c) Ashkenazi Jewish descent
5. Family history only: close family member (on the same side of the family) meeting any of the above criteria

Carry 188 sets of guidelines in your pocket?



Clinical Decision Support (CDS)

- Apply Algorithms/Guidelines to patient data
 - Identify best course of action
- Results displayed as intuitive Visualizations



BRCAPRO Mutation Risk 25%

Suggest Genetic Testing

Facilitates best action as part of workflow

CDS

Currently: Dependant on paper plus memory

BERMUDA FAMILY HISTORY QUESTIONNAIRE

Name: Jane Doe BirthDate: 1/9/55 Ethnicity: Caucasian Phone: 781 555 6665

RELATIVE	NAME (First,maiden,surname)	CANCER TYPE	AGE DIAGNOSED	COMMENTS
Self				
Sister	<u>Jane Smith</u>	<u>Breast</u>	<u>35</u>	
Sister				
Brother				
Brother				
Daughter				
Daughter				
Son				
Son				
Mother	<u>Mary Doe</u>	<u>Ovary</u>	<u>45</u>	<u>died 50</u>
Grandmother (mother's side)				
Grandfather (mother's side)				
Aunt (mother's side)	<u>Mary Smith</u>	<u>Colon</u>	<u>40</u>	<u>strayed</u>
Aunt (mother's side)				
Uncle (mother's side)				
Uncle (mother's side)				
Cousin (mother's side)				
Cousin (mother's side)				
Father	<u>Bob Doe</u>	<u>Prostate</u>	<u>60</u>	
Grandmother (father's side)				
Grandfather (father's side)				
Aunt (father's side)				
Aunt (father's side)				
Uncle (father's side)				
Uncle (father's side)				
Cousin (father's side)				
Cousin (father's side)				
(Example: Mother	Jane Brown Smith	Breast	39	deceased)

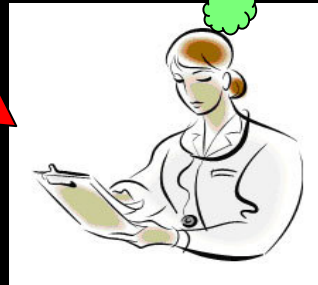
Bermuda Cancer Genetics Risk Assessment Program
Bermuda's First Cancer Genetics Clinic

C/O Partners International Program 101 Merrimac Street Boston, MA 02114 USA (617) 724-4987

Currently: Paper + memory



Patient
completes
paper form



Reviews data
using memory
of guidelines



Orders Genetic
Testing

EHR: Paper + extra work + memory



Patient completes paper form



Staff enters data into the EHR



Reviews data using memory of guidelines



Orders Genetic Testing

Today's EHR: Data is hard to find and synthesize into one coherent picture

01/02/1968 (41 yrs.) F

Select Desktop Pt Chart Summary Oncology Custom Reports Admin Sign Results ? Resource Popup

Reminders
- Patient is overdue for mammogram (rec'd q 1 year). PHx indicates average risk for breast cancer.

Problems
Enter new problem... Add New
Dysplastic nevus
Malignant tumor of breast
PH ovarian cancer

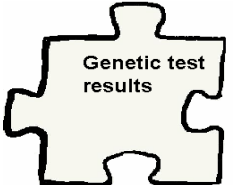
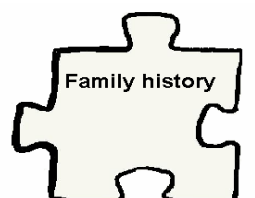
Medications
Enter new medication... Add New
Calcium 500 + D (CALCIUM CARBONATE 1250 MG (500MG ELEM CA)/ VIT D 200
Estrone (ESTRADIOL 2MG (RING)) 2 MG (7.5MCG/2-H VAG RING) PV x1

Procedures
Enter new procedure... Add New

Notes
Add New
12/27/2005 Office Note
12/13/2005 Social Work
12/13/2005 Office Note
12/13/2005 Office Note
11/29/2005 Social Work
11/29/2005 Office Note
11/15/2005 Consent Form:Scanned
11/15/2005 Consent Form:Scanned
11/15/2005 Social Work
11/15/2005 Office Note
11/08/2005 Patient Note
11/07/2005 Consent Form:Scanned
11/07/2005 Office Note
11/01/2005 Genetics - Results
11/01/2005 Patient Note
11/01/2005 Office Note
10/24/2005 Patient Note
10/20/2005 Patient Note
09/30/2005 Lab Report:Scanned
09/30/2005 Patient Note
09/30/2005 Physical Exam
09/28/2005 Genetics-Pedigree

Item Name	07/22/2005	11/10/2009	11/24/2008	07/15/2008	06/15/2008
BLOOD PRESSURE	136/81	136/81	136/81	122/72	122/72
TEMPERATURE	99.1 F	97.6 F	97.6 F	97.6 F	97.6 F
PULSE	70	67	62	62	62
RESPIRATORY RATE	16	16	16	18	18
O2 SAT					
HEIGHT	66.25 in	66.25 in	66.25 in	66.25 in	66.25 in
WEIGHT	137 lb	142 lb	137 lb	137 lb	137 lb
BMI	22.0	22.0	22.0	22.0	22.0
PAIN LEVEL	0	0	0	0	0

Infusion Flowsheet
BMT Flowsheet
Visits
Allergies
Add New
Allergen Reaction
USA
Sticky Notes
Add New
Customize



CDS

Today's EHR

01/02/1968 (41 yrs.) F

Reminders
- Patient is overdue for mammogram (rec: q 1 year). FHx indicates average risk for breast cancer.

Problems
Dysplastic nevus
Malignant tumor of breast
FH ovarian cancer

Click open 4 screens

Date	Family History Problem	Risk	Relative
08/12/2009	Ovarian cancer		Mother

01/02/1968 (41 yrs.) F

Reminders
- Patient is overdue for mammogram (rec: q 1 year). FHx indicates average risk for breast cancer.

Problems
Dysplastic nevus
Malignant tumor of breast
FH ovarian cancer

Notes
12/27/2005 Office Note
12/13/2005 Social Work
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11/15/2005 Social Work
11/15/2005 Office Note
11/08/2005 Patient Note
11/07/2005 Consent Form/Scanned
11/07/2005 Office Note
11/01/2005 Genetics - Results
11/01/2005 Patient Note
11/01/2005 Office Note
10/24/2005 Patient Note
10/20/2005 Patient Note
09/30/2005 Lab Report/Scanned
09/30/2005 Patient Note
09/30/2005 Physical Exam
09/28/2005 Genetics - Pathology

Dear [Name],

This letter is to summarize your visit on November 1, 2005. The purpose of the meeting was to discuss your BRCA1 and BRCA2 test results for alterations in the BRCA1 and BRCA2 genes at our first meeting on September 23, 2005. At that time you elected to proceed with testing for alterations in the BRCA1 and BRCA2 genes. The analysis was performed at a commercial laboratory called Myriad, making it a high accuracy test. Your test results are as follows: you have an alteration in the BRCA1 gene, which was sent for analysis.

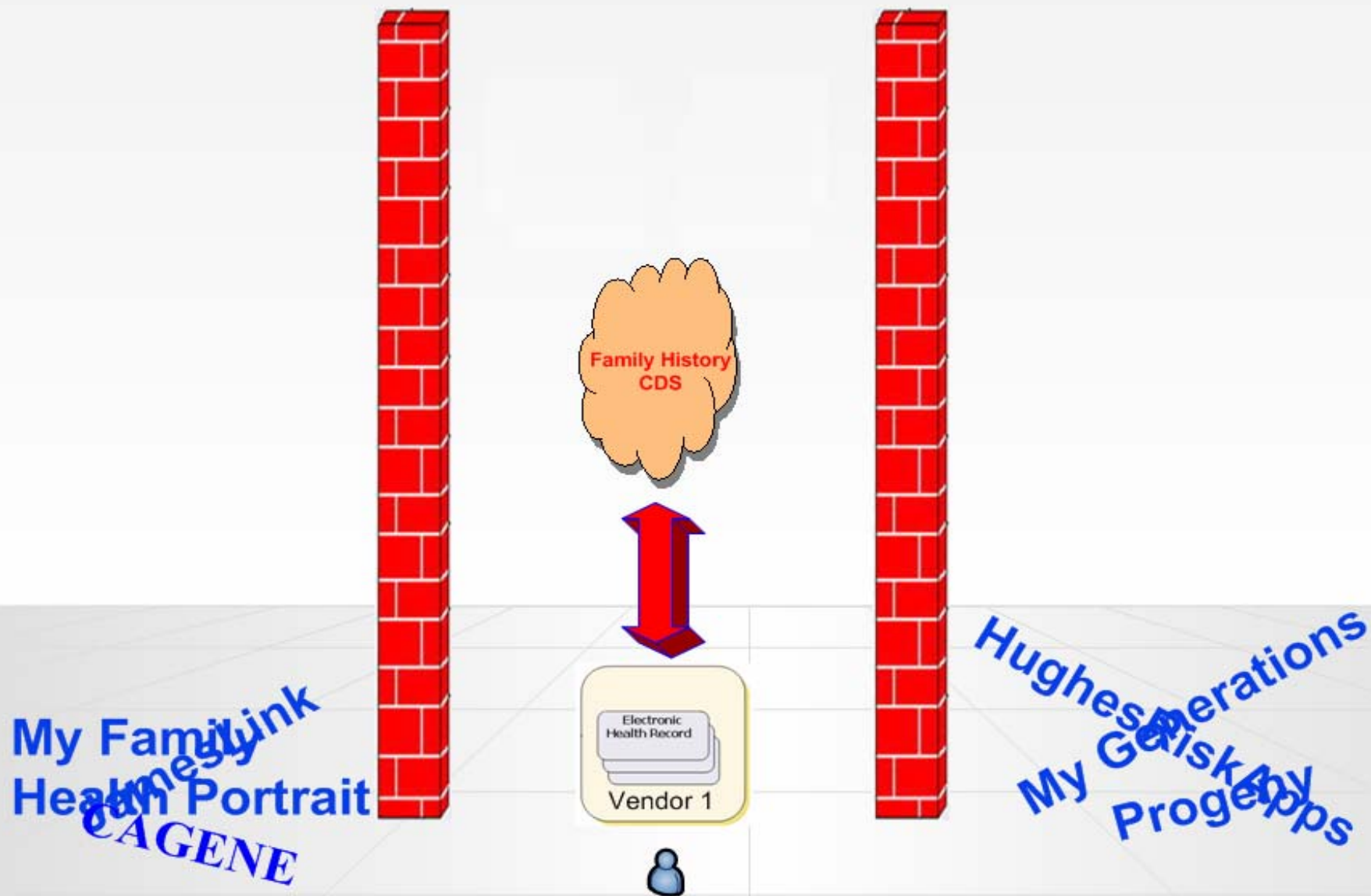
The results of this test revealed that you have an alteration in the BRCA1 gene. The name of this alteration is 2137del4 and it is the most common, at least in part, why you developed cancer. The analysis was performed at a commercial laboratory called Myriad, making it a high accuracy test. Your test results are as follows: you have an alteration in the BRCA1 gene, which was sent for analysis.

It is very difficult for people to predict how they will react to learning about the presence of an altered BRCA1 gene in their family. Some people feel that it is important to inform their relatives of the BRCA1 alteration in the family. At times this may be challenging, and the best way to do this, I am also available to speak to any other family members if they would like more information before deciding. Please do not hesitate to contact me at any point in time in the future if you or your family members have questions or concerns. I am happy to help, should they have any questions.

BRCA1 Positive

Monolithic Approach

Vendor creates CDS from scratch



Gap analysis

Functionality Lacking in EHR for FH

Interoperability

Patient data entry

Simplified clinician data entry

Graphical

Table

Clinical Decision Support

Pedigree drawing

Risk algorithms

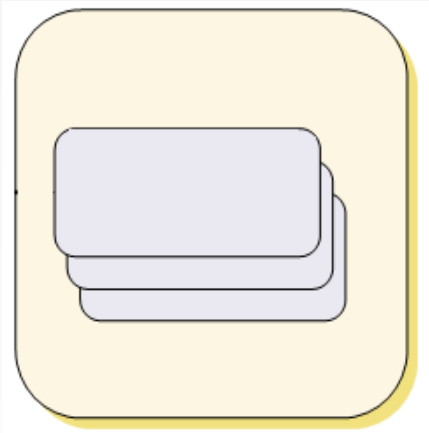
Guidelines

Letter/Note generation

**The American Health Information Community (AHIC)
Personalized Health Care Workgroup
Recommendations to Secretary 2007**

... Modular family history tool

**... collection of family health history within
the EHR...messaging of ... information to a
variety of richer ... tools that perform risk
analyses... results of ... calculations ...
returned to the EHR ... curation**



Niche/Modular Software

Innovative approaches to data entry

- Patient data entry

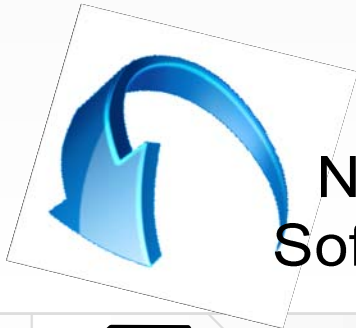
- Clinician data interface

Innovative approaches to CDS

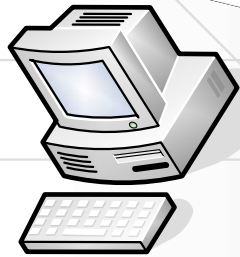
- Risk Algorithms, Guidelines

- Visualization appropriate to user

- Pedigree drawing



**Niche
Software**



EHR as a repository

Core data set

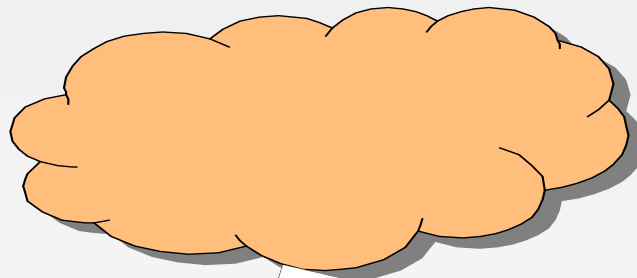
Interoperable



Testing and iteration possible

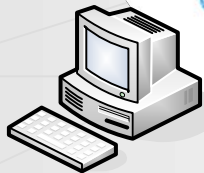
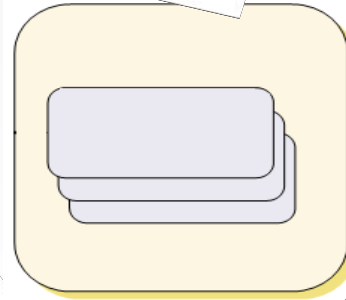


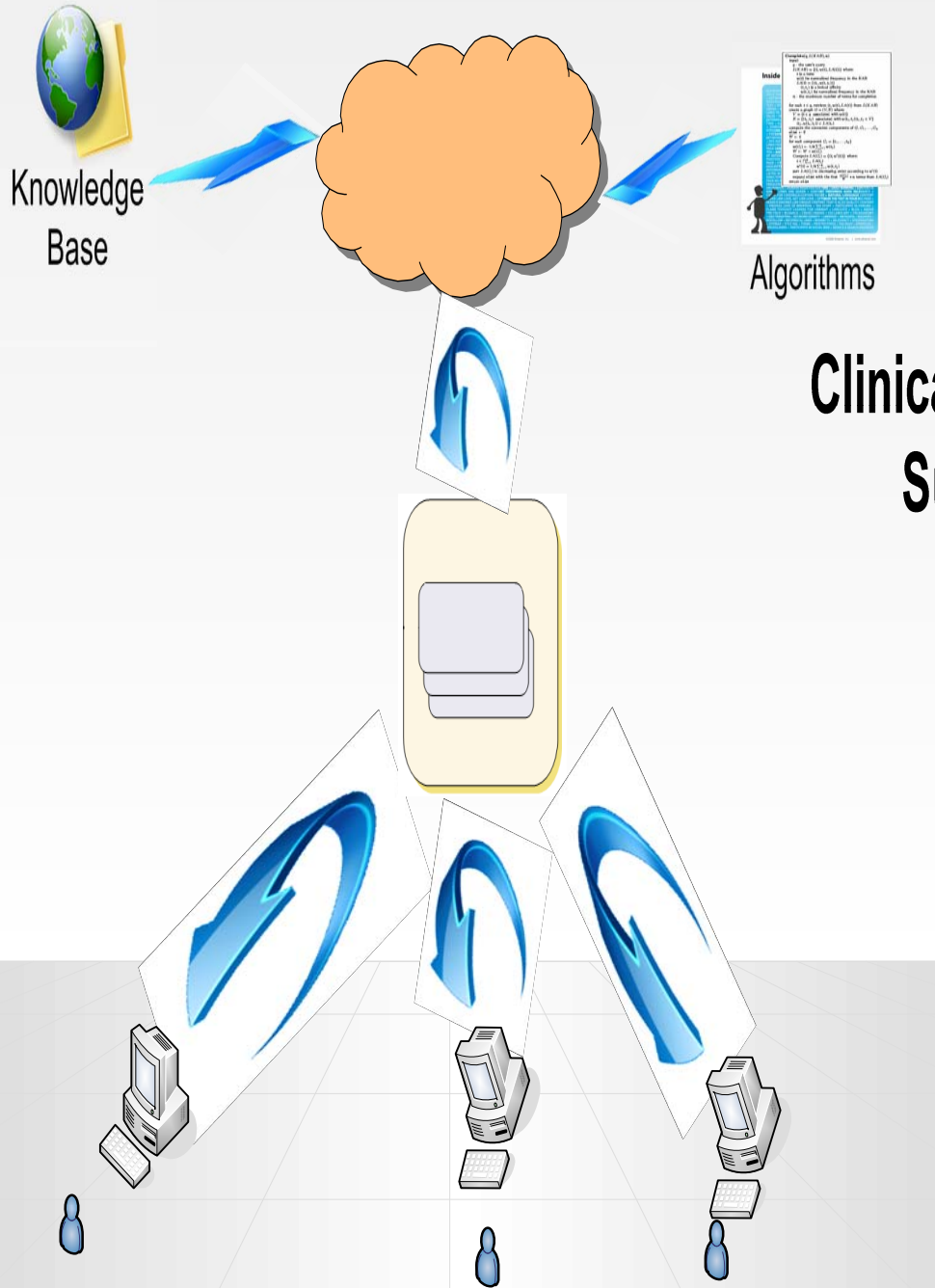
Knowledge Base



Algorithms

Clinical
S





- **EHRs as data repositories**
 - Adopt AHIC core data set
 - Adopt HL7 Pedigree Standard
 - Genetic Testing standards
- **External applications**
 - CDS as web services
 - Knowledge bases, guidelines
 - Maintained by specialty bodies
- **Niche software**
 - Rather than monoliths

Adopt AHIC core data set

MINIMUM DATA STRUCTURE FOR EACH RELATIVE

- **Defining Family relationships**
 - Name
 - Identifier
 - Mother ID
 - Father ID
 - Bloodline (**Maternal, Paternal, Unknown**)
 - Ethnicity
- **Clinical Information**
 - Diagnosis (**Can be many**)
 - Age of diagnosis
 - Current status (**Alive or dead**)
 - Current age or age of death
 - Gene tested
 - General result (**Deleterious, Unknown significance, Polymorphism, No mutation**)
 - Specific result (**Actual sequence**)

HL7 Pedigree Standard

- **ANSI and HITSP approved**
- **In use by**
 - **HughesRiskApps**
 - **Progeny**
 - **CancerGene**
 - **Surgeon General**
 - **Dana Farber Risk Model Web Service**

Genetic Testing standards

- Partners and Intermountain are now exchanging genetic test results via a V2 standard

CDS as web service

- Dana Farber Web Service
 - Uses HL7 Pedigree Standard
- Developing a wrapper with HL7 CDS Committee

Potential Problem & Solution

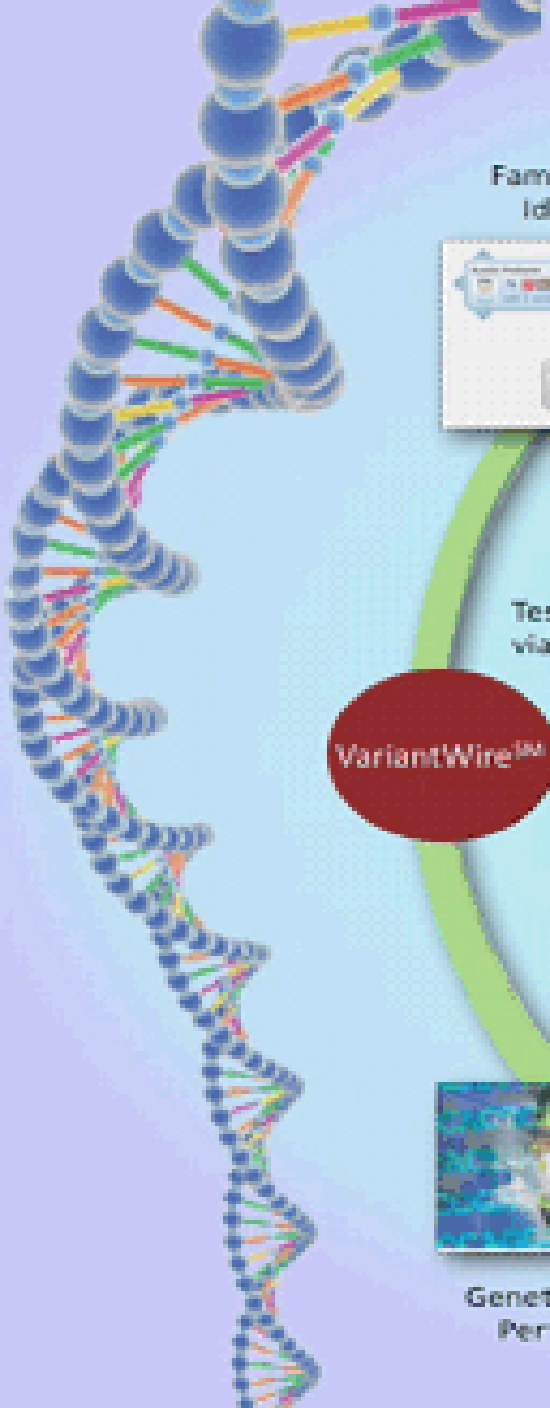
- Potential problem: one-off CDS services
 - Requires custom interfacing
 - Hinders adoption
- Potential solution: standard CDS service framework

HL7/OMG Decision Support Service (DSS) standard

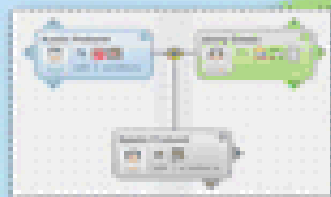
- **Common framework for CDS services**
 - HL7 DSTU, OMG beta-specification
- **OpenCDS: open-source reference implementation**
 - Project lead: Ken Kawamoto, MD, PhD, CDS WG co-chair (kawam001@mc.duke.edu)
 - Alpha release expected winter 2010
- **Personalized medicine applications**
 - WarfarinDosing.org
 - Bayes-Mendel risk service

Knowledge bases, guidelines

- **Working with March of Dimes, Genetic Alliance and NCHPEG to develop a prenatal genetics knowledge base**



Family Hx Risk Identified



Physician uses data to make clinical decisions



Intermountain EMR



Results transferred via VariantWire

VariantWireSM


**Intermountain[®]
Healthcare**
Clinical Genetics Institute
at LDS Hospital

Testing ordered via VariantWire

VariantWireSM

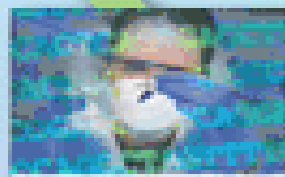
Sample Analysis



Results Generated



Genetic Testing Performed



Niche software to serve as a module for an EHR

- **Demo of software and web service**

The Future

- **EHRs as data repositories**
 - Adopt core data set
 - Adopt standards for interoperability with niche software
- **Patient data entry facilitated**
 - PHR, Web, Kiosk, Tablet systems
- **Genetic Testing Labs transmit structured data**
 - Adopt standards for interoperability
- **Niche software**
 - Test and refine FH collection, analysis and display
- **CDS as web services**
- **Knowledge bases, guidelines as web services**
 - machine readable, maintained by specialty bodies