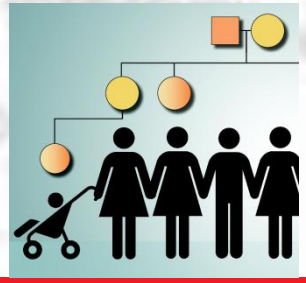


Developing evidence: the value of family health history

Lori A. Orlando, MD MHS

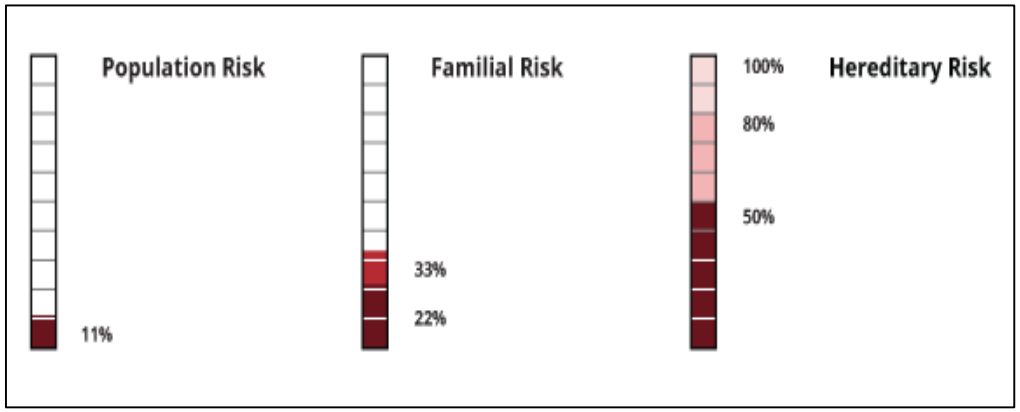
Family Health History

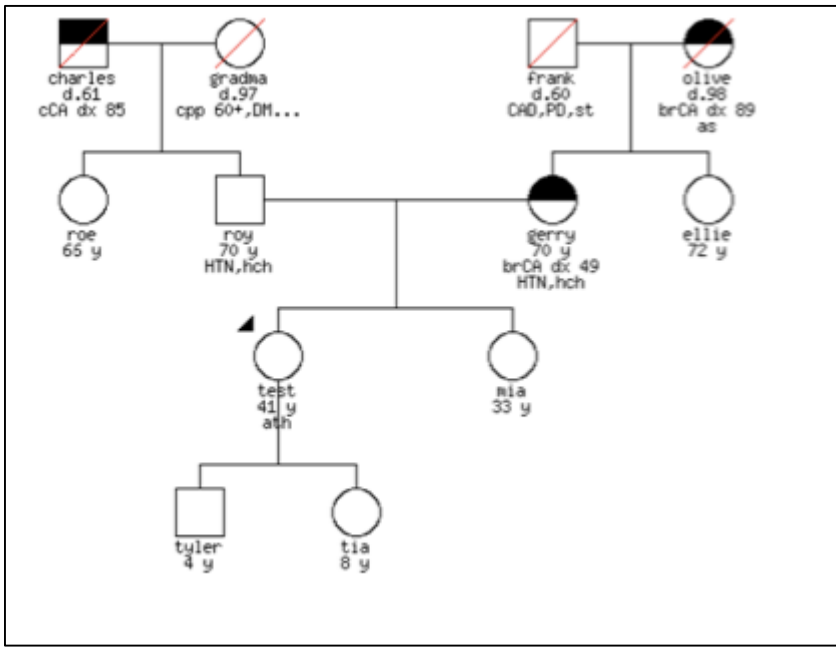
- Nominally “the first genetic test” (Francis Collins)
- Reflects both:
  - Shared environments
  - Shared genetics
- Imparts information only about risk
- Can (sometimes) be both more informative and more confusing than genetic/genomic results

Shared Genes

FHH Data contributes to assessing genetic risk in 2 ways

- **<u>Infer</u> genetic risk**





- **<u>Contextualize</u> genetic results**
- **Assess <u>co-inheritance</u>**

APPLIED GENOMICS & PRECISION MEDICINE

DukeMedicine

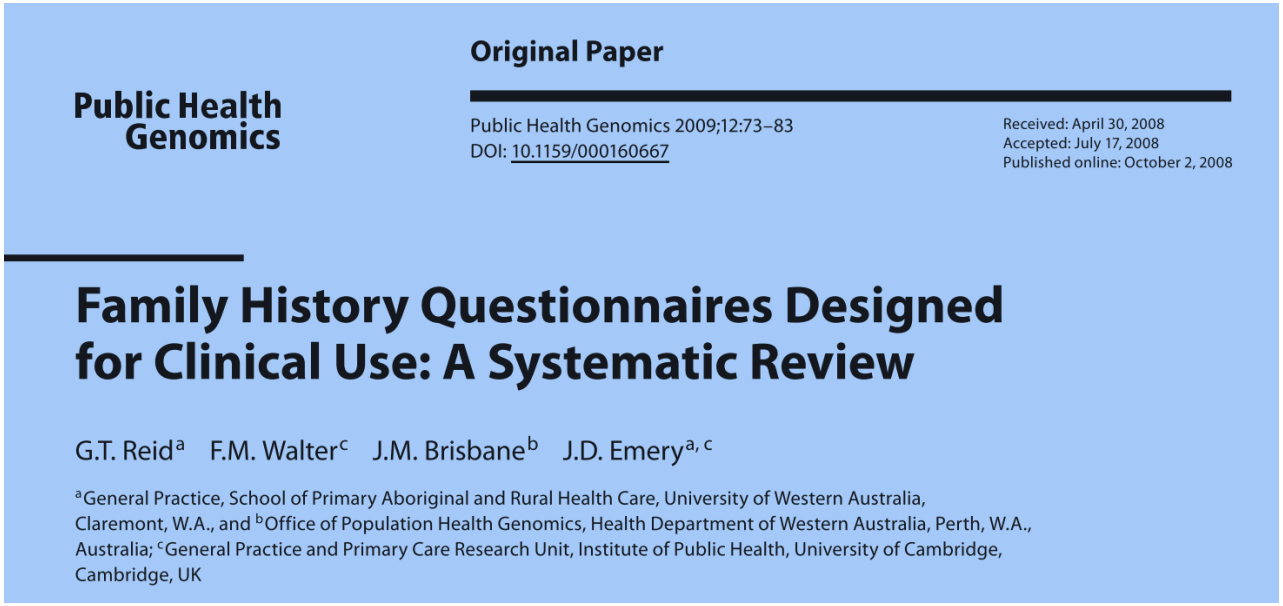
Evidence Summary

- Analytic validity
- Clinical validity
- Clinical Utility

ANALYTIC VALIDITY

Systematic Review FHH Data

- 12 studies of community populations
- Good agreement between patient-entered data and genetic counselor derived data



Original Paper

Public Health Genomics

Public Health Genomics 2009;12:73–83
DOI: 10.1159/000160667

Received: April 30, 2008
Accepted: July 17, 2008
Published online: October 2, 2008

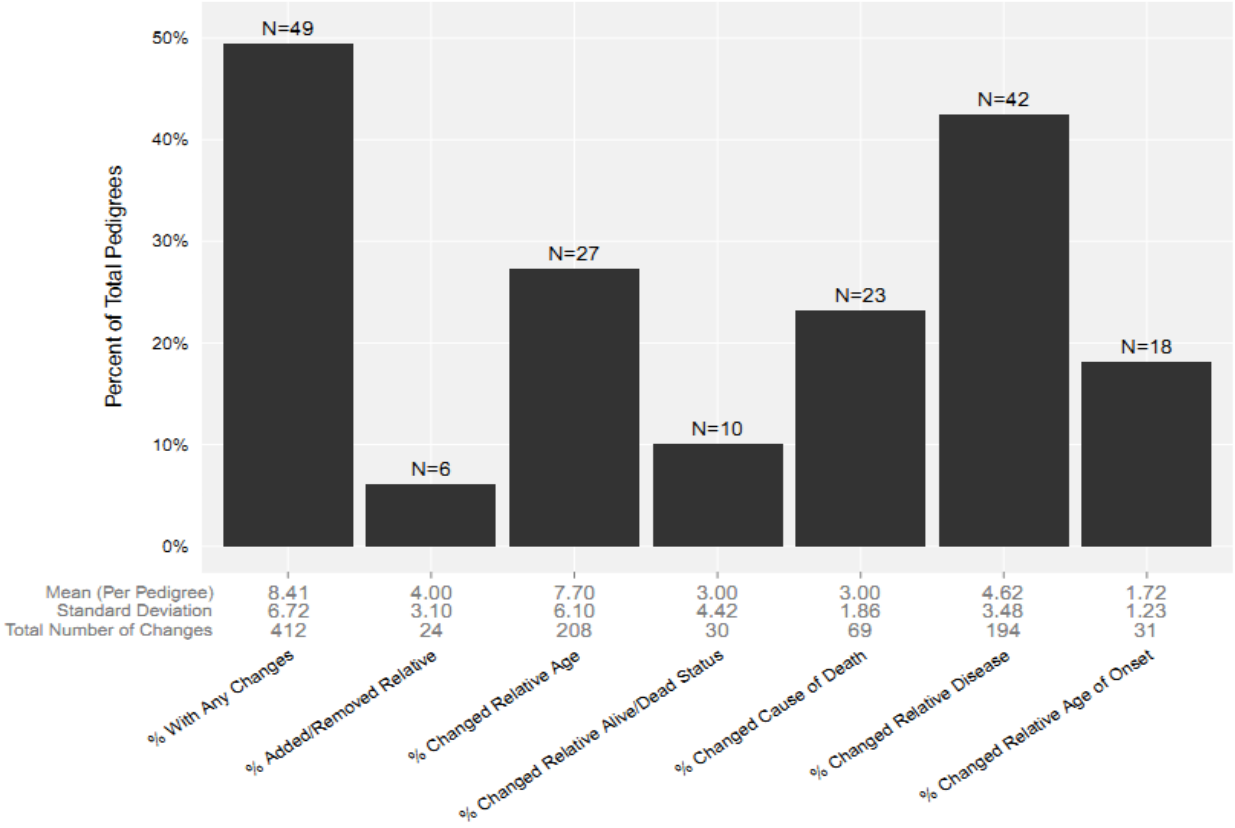
Family History Questionnaires Designed for Clinical Use: A Systematic Review

G.T. Reid[a] F.M. Walter[c] J.M. Brisbane[b] J.D. Emery[a, c]

[a]General Practice, School of Primary Aboriginal and Rural Health Care, University of Western Australia, Claremont, W.A., and [b]Office of Population Health Genomics, Health Department of Western Australia, Perth, W.A., Australia; [c]General Practice and Primary Care Research Unit, Institute of Public Health, University of Cambridge, Cambridge, UK

Our Data

- Genetic counselor review of 3 generation pedigrees entered by primary care patients for 3 months- data correlation very high
- Education critical!



16% with changed recommendation

- 6% from high risk to population risk
- 10% from population risk to high risk

DukeMedicine

CLINICAL VALIDITY

Shared Genes: Infer Genetic Risk

- Alone
  - *e.g. NCCN guidelines for HBOC testing*
- In combination with other information
  - *e.g. Dutch Lipid guidelines for familial hypercholesterolemia*
  - *BRCApro*
  - *MMRpro*

Shared Genes: I

- Alone
  - *e.g. NCCN guidelines for H*
- In combination with oth
  - *e.g. Dutch Lipid guidelines*
  - *BRCApro*
  - *MMRpro*

Hereditary Breast & Ovarian Cancer Program

Genetic Red Flags Checklist

HBOC: Is Your Patient at High Risk?

Genetic red flags are features of the personal or family medical history that suggest a higher than average genetic contribution to cancer. These are unusual presentations of cancer that are more likely when a genetic variant is present from birth. Use this checklist with the Risk Stratification tool.

+ or -	Red Flag	Explanation	Description
	Early age of onset	The average age for breast cancer diagnosis is > 50 yrs. Pre-menopausal breast cancer suggests an underlying susceptibility.	
	Bilateral disease/ multiple primaries	Although a tumor may metastasize, it is rare to have more than one primary cancer. Bilateral breast cancer, or breast and ovarian cancer in the same person suggest a predisposition.	
	Male breast cancer	Breast cancer is rare in males, and when it occurs, suggests a hereditary susceptibility.	
	Ovarian cancer	Ovarian cancer is rare except with a hereditary predisposition. A history of ovarian cancer is alone indication for further evaluation for HBOC.	
	Multiple affected relatives	Two or more close relatives* with the same or related cancers+ suggests a hereditary predisposition, especially when in consecutive generations.	
	Disease despite preventive measures	Some interventions like oophorectomy lower the risk for breast and ovarian cancer. If cancer occurs anyway, pre-existing susceptibility is more likely.	
	Ashkenazi Jewish ancestry	1 in 40 individuals of Ashkenazi ancestry carries a mutation in either the *BRCA1* or *BRCA2* gene.	
	Other notable history	Unusual physical features, birth defects, intellectual disability or other notable family history may indicate a different genetic syndrome. Discuss these with a genetics professional.	

*Close relatives include parents, children, siblings, grandparents, aunts/uncles and first cousins.

+HBOC-related cancers include breast, ovarian, prostate, melanoma and pancreatic.

APPLIED GENOMICS & PRECISION MEDICINE

Shared Genes: Infer Genetic Risk

- Alone
  - *e.g. NCCN guidelines for HBOC testing*
- In combination with other information
  - *e.g. Dutch Lipid guidelines for familial hypercholesterolemia*
  - *BRCApro*
  - *MMRpro*

Shared Genes: I

- Alone
  - *e.g. NCCN guidelines for H*
- In combination with oth
  - *e.g. Dutch Lipid guidelines*
  - *BRCApro*
  - *MMRpro*

Appendix 1: Dutch Lipid Clinic Network Criteria for making a diagnosis of Familial Hypercholesteroloemia (FH) in adults

		Score
Family history		
First-degree relative with known premature coronary and/or vascular disease (men <55 years, women <60 years) or First-degree relative with known LDL-cholesterol above the 95th percentile for age and sex		1
First-degree relative with tendinous xanthomata and/or arcus cornealis or Children aged less than 18 years with LDL-cholesterol above the 95th percentile for age and sex		2
Clinical history		
Patient with premature coronary artery disease (ages as above)		2
Patient with premature cerebral or peripheral vascular disease (as above)		1
Physical examination		
Tendinous xanthomata		6
Arcus cornealis prior to age 45 years		4
LDL-cholesterol (mmol/L)		
	LDL-C ≥8.5	8
	LDL-C 6.5–8.4	5
	LDL-C 5.0–6.4	3
	LDL-C 4.0–4.9	1
DNA analysis: functional mutation in the LDLR, APOB or PCSK9 gene		8
STRATIFICATION		Total score
Definite FH		≥8
Probable FH		6–7
Possible FH		3–5
Unlikely FH		<3

APPLIED GENOMICS & PRECISION MEDICINE

Shared Genes: Infer Genetic Risk

- Alone
  - *e.g. NCCN guidelines for HBOC testing*
- In combination with other information
  - *e.g. Dutch Lipid guidelines for familial hypercholesterolemia*
  - *BRCApro*
  - *MMRpro*

Important Considerations

- Guidelines developed based on evidence
  - What is family health history measuring?
  - What evidence links family history to the outcomes?
  - How was the evidence assessed?

Guideline Differences

TABLE V. Comparison of Genetic Counseling (GC) Referral Recommendations Between MeTree, and the NCCN's Colon and Breast Cancer Guidelines, and the Michigan Department of Community Health's Cancer Family History Guide (CFHG)

	MeTree GC referral		
	No, N (%)	Yes, N (%)	Total
CFHG GC referral			
No	768 (64.9%)	94 (7.9%)	862 (72.8%)
Yes	86 (7.3%)	236 (19.9%)	322 (27.2%)
Total	854 (72.1%)	330 (27.9%)	1,184 (100%)
NCCN breast cancer GC referral			
No	891 (75.3%)	12 (1.0%)	903 (76.2%)
Yes	114 (9.6%)	167 (14.1%)	281 (23.7%)
Total	1,005 (84.9%)	179 (15.1%)	1,184 (100%)
NCCN colon cancer GC referral			
No	1,070 (90.4%)	103 (8.7%)	1,173 (99.1%)
Yes	0 (0%)	11 (0.9%)	11 (0.9%)
Total	1,070 (90.4%)	114 (9.6%)	1,184 (100%)

- Breast/ovarian cancer differences:
  - NCCN refers for any relative with ovarian cancer or breast cancer < age 45
- Colon cancer differences:
  - MeTree includes Bethesda criteria for any relative, NCCN only if the proband, FDR or SDR had colon cancer

What about common complex diseases?

FHH is better predictor the current genomic tests

- Coronary Artery Disease
  - Framingham risk score does not include FHH
  - Europeans multiple Framingham x 2.5 for FDR with premature CAD
  - Canadians multiple Framingham x 2 for FDR with premature CAD
- Diabetes risk
  - 3.2% without FDR to 14.3% (absolute risk) with FDR*
  - SNP OR varies ~2-3

*Annis AM, Caulder MS, Cook ML, Duqette D. Prev. Chronic Dis. 2005 2(2)

CLINICAL UTILITY

Quality of FHH Data

	Baseline FHH N=390 for all and 227 for deceased	MeTree N=1184 for all and 1179 for deceased
Quality Criterion		
• 3 generations	0 (0%)	1184 (100%)
• Relatives' lineage	111 (28.4%)	1184 (100%)
• Relatives' gender	356 (91.2%)	1184 (100%)
• Pertinent negatives	173 (44.3%)	1184 (100%)
• Age of disease onset	71 (18.2%)	854 (72.1%)
• Cause of death	213 (98.1%)	695 (58.9%)
• Age of death	172 (75.7%)	1156 (98.0%)

- 58.9% talked with their relatives
- Mean # of relatives talked to: 2.89 (SD 1.58)

Quality of FHH Data

	Baseline FHH N=390 for all and 227 for deceased	MeTree N=1184 for all and 1179 for deceased
Quality Criterion		
• 3 generations	0 (0%)	1184 (100%)
• Relatives' lineage	111 (28.4%)	1184 (100%)
• Relatives' gender	356 (91.2%)	1184 (100%)
• Pertinent negatives	173 (44.3%)	1184 (100%)
• Age of disease onset	71 (18.2%)	854 (72.1%)
• Cause of death	213 (98.1%)	695 (58.9%)
• Age of death	172 (75.7%)	1156 (98.0%)

- 58.9% talked with their relatives
- Mean # of relatives talked to: 2.89 (SD 1.58)

Quality of FHH Data

	Baseline FHH N=390 for all and 227 for deceased	MeTree N=1184 for all and 1179 for deceased
Quality Criterion		
• 3 generations	0 (0%)	1184 (100%)
• Relatives' lineage	111 (28.4%)	1184 (100%)
• Relatives' gender	356 (91.2%)	1184 (100%)
• Pertinent negatives	173 (44.3%)	1184 (100%)
• Age of disease onset	71 (18.2%)	854 (72.1%)
• Cause of death	213 (98.1%)	695 (58.9%)
• Age of death	172 (75.7%)	1156 (98.0%)

- 58.9% talked with their relatives
- Mean # of relatives talked to: 2.89 (SD 1.58)

Quality of FHH Data

	Baseline FHH N=390 for all and 227 for deceased	MeTree N=1184 for all and 1179 for deceased
Quality Criterion		
• 3 generations	0 (0%)	1184 (100%)
• Relatives' lineage	111 (28.4%)	1184 (100%)
• Relatives' gender	356 (91.2%)	1184 (100%)
• Pertinent negatives	173 (44.3%)	1184 (100%)
• Age of disease onset	71 (18.2%)	854 (72.1%)
• Cause of death	213 (98.1%)	695 (58.9%)
• Age of death	172 (75.7%)	1156 (98.0%)

- 58.9% talked with their relatives
- Mean # of relatives talked to: 2.89 (SD 1.58)

- **Pre-MeTree < 4% of FHHs were hih-quality (single relative)**
- **Post-MeTree 99% of FHHs were high-quality (single relative)**

FHH-based Risks in General Population

TABLE IV. Frequency of Hereditary Syndrome Risk and Familial-Risk Recommendations for Each Clinical Decision Support Condition

Disease	Recommendation	Frequency among all participants (N ¼ 1,184), N (%)	Frequency among eligible participants[a], N (%)
Hereditary syndrome risk	Genetic counseling[b]	308 (26.0%)	308/1,184 (26.0%)
Breast cancer	Breast MRI	10 (0.8%)	10/694 (1.4%)
	Chemoprophylaxis	58 (4.9%)	58/694 (8.3%)
Colon cancer	Start colon screening early	114 (9.6%)	114/1,178 (9.7%)
	More frequent colonoscopies	107 (9.0%)	107/1,178 (9.1%)
Ovarian cancer	Referral to gynecology	14 (1.2%)	14/694 (2.0%)
Thrombosis	Genetic testing[b]	42 (3.5%)	42/1,184 (3.5%)
	Genetic counseling[b]	29 (2.4%)	29/1,184 (2.4%)

[a]The number of participants eligible for a recommendation in that disease category. Those with the disease are removed and for breast cancer and ovarian cancer, men are removed.

[b]These recommendations make up the "hereditary syndrome risk" group, the others up the "familial-risk" group.

Orlando, LA, et al. AGMJ 2014; 166:24-33

	Patients at Increased-Risk who Meet Criteria for Risk Management Strategy			Patients Not at Increased-Risk who Do Not Meet Criteria for Risk Management Strategy		
Risk Management Strategy	Total N	Before MeTree N (%)	After MeTree N (%)	Total N	Before MeTree N (%)	After Metree N (%)
Hereditary Cancer: Genetic Counseling	124	0 (0%)	18 (14.5 %)	364	0 (0%)	1 (0.2%)
Breast Cancer: MRI	4	1 (25%)	3 (75%)	280	5 (1.8%)	1 (0.4%)
Breast Cancer Chemoprevention	26	0 (0%)	0 (0%)	258	0 (0%)	0 (0%)
Ovarian Cancer: Gynecology	2	0 (0%)	1 (50%)	282	12 (4.2%)	9 (3.2%)
Thrombosis: Genetic Testing	11	1 (9.1%)	2 (18.1%)	477	0 (0%)	0 (0%)
Thrombosis: Genetic Counseling	7	0 (0%)	4 (57.1%)	481	0 (0%)	0 (0%)
Total	174	2 (1.1%)	28 (16.1%)	2,142	17 (0.8%)	11 (0.5%)

Decreasing Mismatch in Risk Level and Risk Services

- Pre-MeTree 2/19 (10%) undergoing increased risk management were at increased risk
- Post-MeTree 28/39 (72%) were at increased risk.

New Frontiers: contextualize genetics

- PALB2*
  - *No FHH breast cancer risk 33% by age 70*
  - *2 or more FDRs with breast cancer risk 58% by age 70*
- BRCA
  - *Lifetime breast cancer risk 45-65%*
  - *No FHH breast cancer?*
    - ***Counsyl tested 2500 women in San Diego for free***
    - ***4.2% tested positive, half did not meet NCCN criteria***
- Variants of Undetermined Significance

* N Engl J Med 2014; 371:497-506

FHH – New Horizons

- FHH more informative than we think?
  - Social network analysis
  - Relationships between relatives
  - Estimate heritability
  - Disease clustering
- Differentiating Environmental from Heritable Risk
  - Environmental conditional risk
  - Estimate environmental relative risk

FHH – New

- FHH more infor
  - Social network
  - Relationships b
  - Estimate herita
  - Disease cluste
- Differentiating E
  - Environmental
  - Estimate envir

Genetic network and sub-networks of diseases

Fig 2. Network of diseases in 1st degree relatives

Diseases are nodes, conditional relative risks are the edges connecting the diseases (Bonferroni adjust p-value < 0.05). Each color denotes a connected cluster, thicker lines represent smaller p-values, and arrows point from the proband's disease to the 1st degree relative's disease.

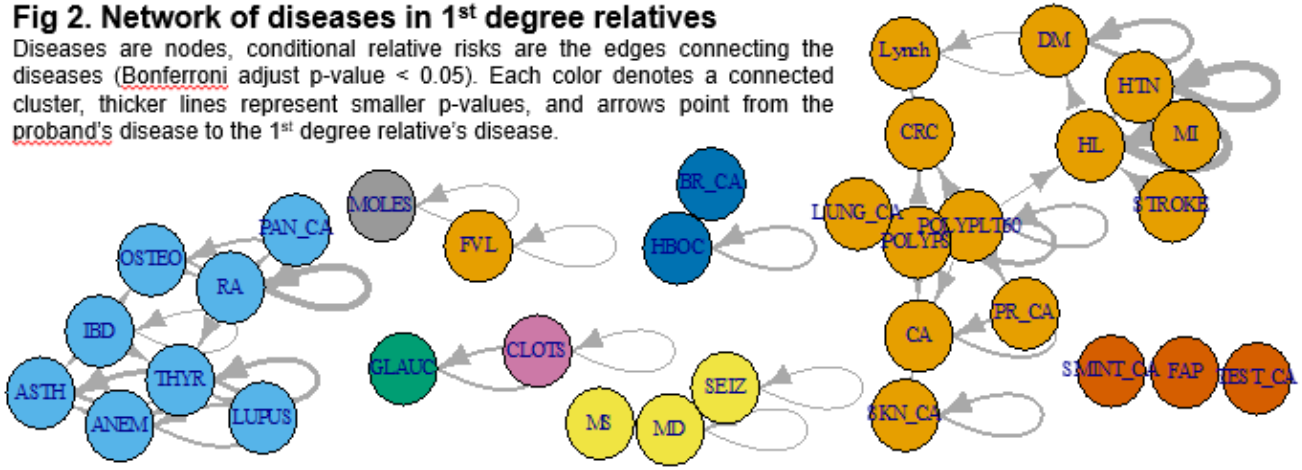


Fig 3. Consistency across relationship types

Overlap of disease pairs with Bonferroni adjusted p-values < 0.05 in all three relative types: self*, 1st, and 2nd degree relatives.
*Instances of disease A == disease B are omitted.

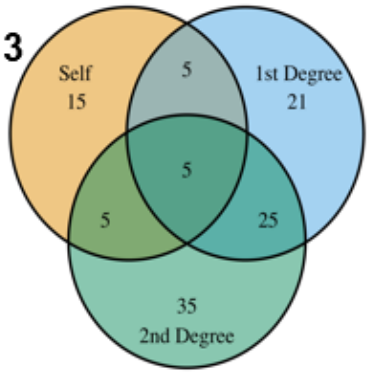
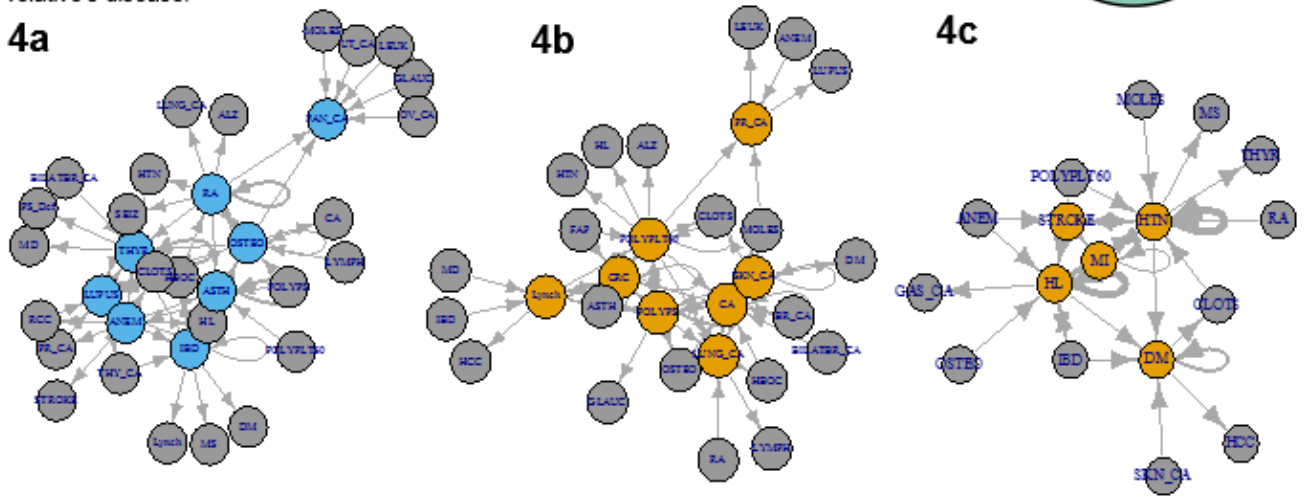


Fig 4a-c. Sub-networks of diseases in 1st degree relatives

Three sub-networks seeded using clusters identified in Figure 2, autoimmune (a), cancer (b), and metabolic syndromes (c). Included edges (disease pairs) contained a minimum of one disease from the clusters noted above with FDR adjusted q-value < 0.05. Thicker lines represent smaller p-values and arrows point from the proband's disease to the 1st degree relative's disease.



APPLIED GENOMICS & PRECISION MEDICINE

FHH – New Horizons

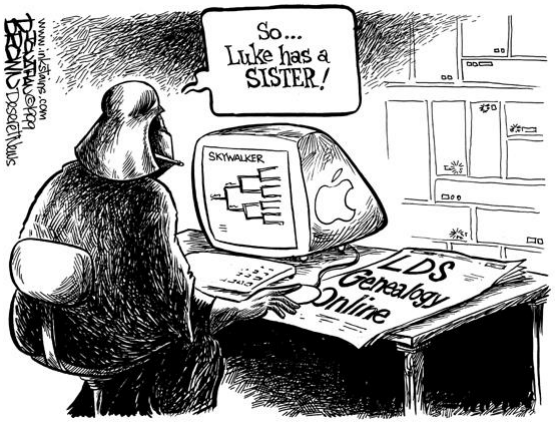
- FHH more informative than we think?
  - Social network analysis
  - Relationships between relatives
  - Estimate heritability
  - Disease clustering
- Differentiating Environmental from Heritable Risk
  - Environmental conditional risk
  - Estimate environmental relative risk

IMPLEMENTING IN CLINIC

Barriers by Stakeholder

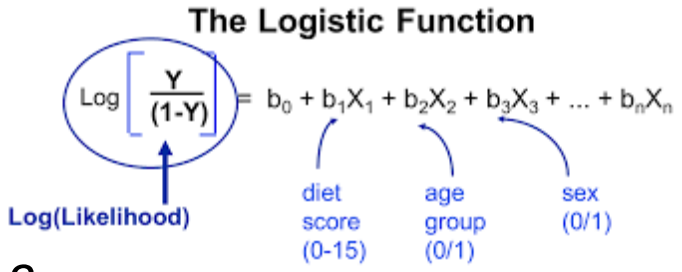
Patient

- *Education*
- *Accuracy*



Provider

- *Time*
- *Awareness*
- *Complexity*



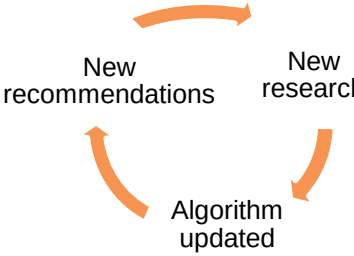
Health System

- *Inadequate systems for data collection & providing actionable information*
- *Tools that interact with the EMR*
- *Awareness of population impact*

Ideal Flow of FHH Information

Patient at Home

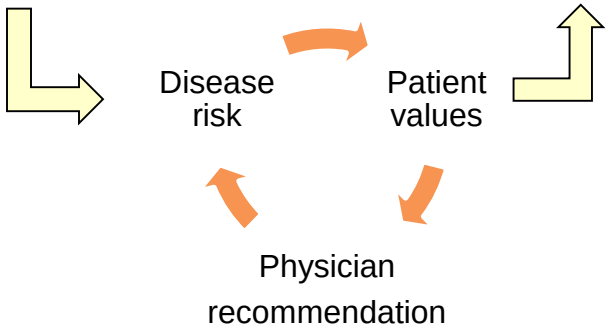
Data sent to medical record, processed and report generated



Appointment

Patient-Physician

Healthcare Plan



Help is Available! FHH Tools

- Global Alliance for Genomics and Health has a catalogue of existing tools and their capabilities

  https://genomicsandhealth.org/work-products-demonstration-projects/catalogue-global-activities-family-history-tools

- Many are companies associated with genetic testing labs and very few provide clinical decision support

Program	Decision Support Diseases	Completed By	Publicly Available	Who Receives Output	Available at Point of Care	Action Oriented Recomm.
MeTree©	colon, breast, and ovarian cancer; aortic aneurysm, heart disease, stroke, diabetes, hereditary cancer syndrome, hereditary cardiovascular syndrome, hereditary liver diseases	**Patient online or physician's office**	**In future**	**Patient and physician**	**Yes**	**Yes**
Schroy et al.	colon cancer	Physician	Unknown	Physician	Yes	No
GRACE	breast cancer	Patient in physician's office	Unknown	Patient, clinical nurse specialist, physician	Yes	No
Family Healthware	coronary heart disease, diabetes, stroke, colon, breast, and ovarian cancer	Patient online	No	Patient	No	No
Family HealthLink	coronary heart disease, cancer	Patient online	Yes	Patient	No	No
CRIS	colon cancer	Patient in physician's office	No	Patient and physician	Yes	No
MyGenerations	cancer	Patient online	Yes	Patient	No	No
Hughes Risk Apps	breast and ovarian cancer, colon cancer, hereditary cancer risk	Patient – clinician can revise online or physician's office	Yes	Patient and physician	Yes	No
Health Heritage.net	87 diseases: multiple cancers, diabetes, neuromuscular diseases, and cardiovascular diseases	Patient online	In future	Patient	No	No
Invitae	Cardiac disease, colon cancer, cmt, breast cancer, pancreatic cancer	Physician online	Yes	Patient and Physician	?	No
MyFamily	Cancer, cardiology, GI- proprietary algorithms	Patient	In future	Physician	Yes	Yes
Myriad	29 cancers	Patient	Yes	Patient	No	No
Power Lineage	cancer	Patient and Physician	Yes	Physician	No	No

MeTree

- Patient facing web-based software program
- Educates patients on what and how to collect FHH
- Gives patients time to collect FHH
- Easy to use graphical user interface
- Creates 3+ generation pedigree
- Generates risk scores and evidence-based risk stratified prevention recommendations for selected conditions
- Clinical decision support for patients and providers
- Evidence guidelines monitored with updating of rules

SMART-FHIR

What exactly is SMART-on-FHIR

SMART

- Substitutable medical apps, Reusable Technology
- Authentication through OAuth2
- HTML5 and Javascript permits views in an “app window”
- Microinteractions which allows wrapping of data into different “views”

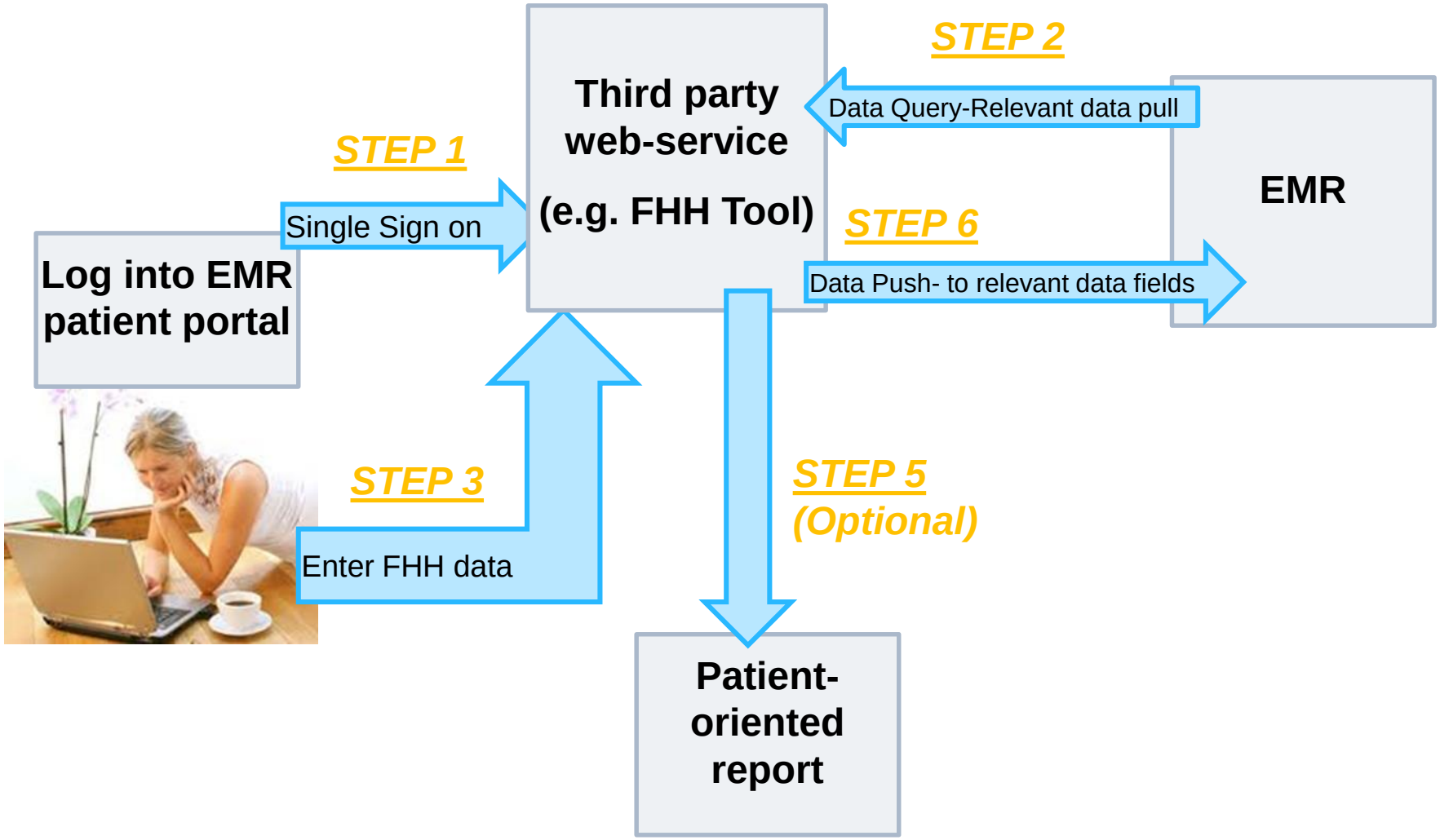
FHIR

- Fast health interoperability resource
- ReSTful API (resource oriented)
  - Bi-directional data transfer
- FHIR profiles
  - include a growing list of defined resources
  - Permits plug and play interoperability
  - Leverages standardized nomenclatures (snomed, rxnorm, loinc, CVX, etc..)
- Extensions for data not already defined

Key Features of SMART on FHIR

- Takes advantage of standards-based modern technology expanding accessibility, scalability, and interoperability.
  - HL7 now considers FHIR to be the next generation .api
  - These tools are already in use by systems like facebook and google so widely familiar to programmers outside the healthcare space
- SMART and FHIR combine authentication and data transmission in a single plug and play app
- Open source with no license fees
  - Prior to 2013 HL7 charged licensing fees and even now in some cases fees apply
- Narrowly defined data for plug and play capacity
  - The Argonaut project supported by all major stakeholders developed narrowly defined data to avoid the use of "optionality" as much as possible
  - Extension permit optionality when needed and once built by early adopters submitted to help establish a new data standard
- Widely supported by major EMR vendors

Patient Flow



Provider Flow

STEP 1

Log into EMR

New Access Link to Web-Service creates an “applet” view in EMR window

Interactive Graphical Interface with web-service

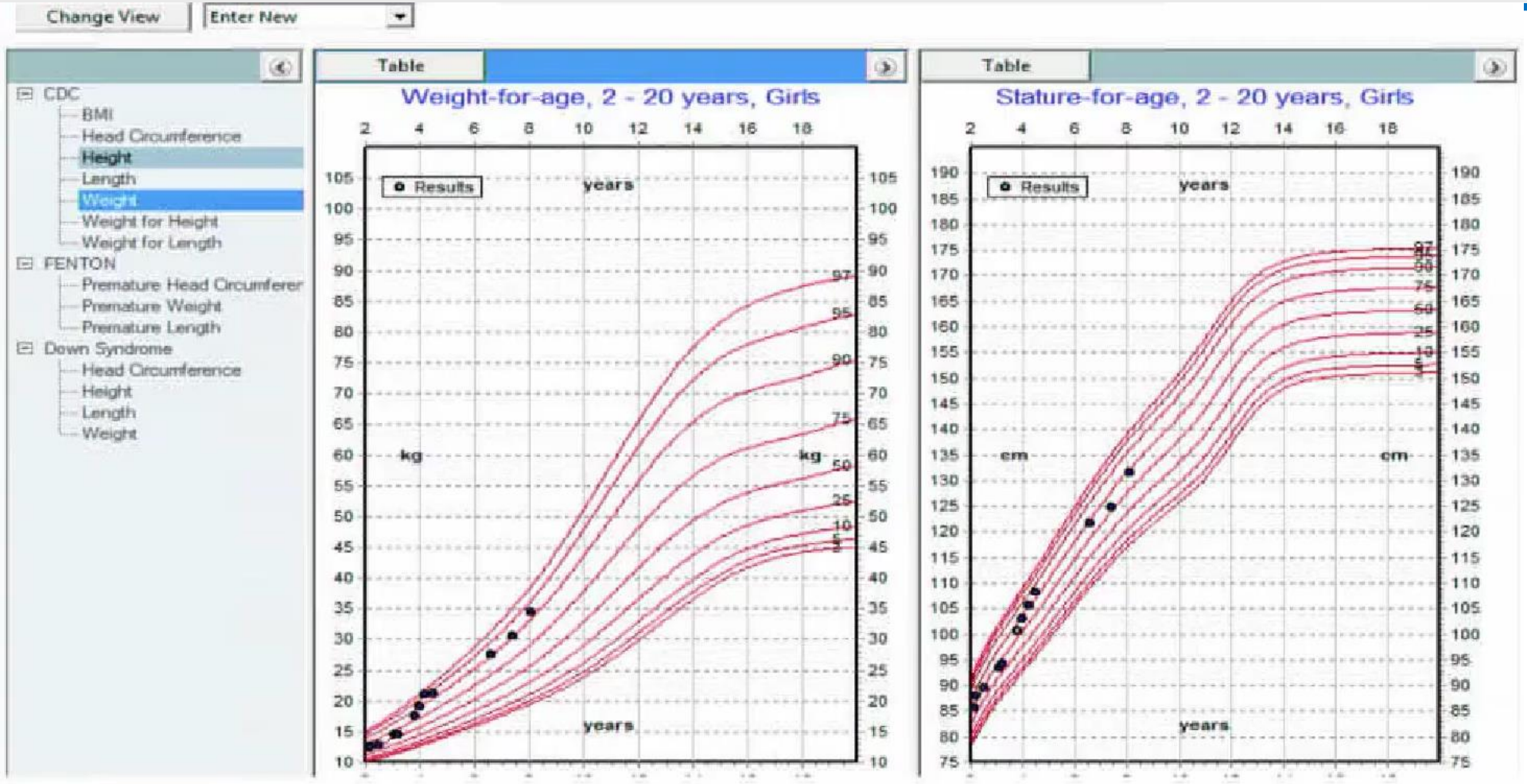
Supporting “multiple” views

EMR contains updated information

APPLIED GENOMICS & PRECISION MEDICINE

DukeMedicine

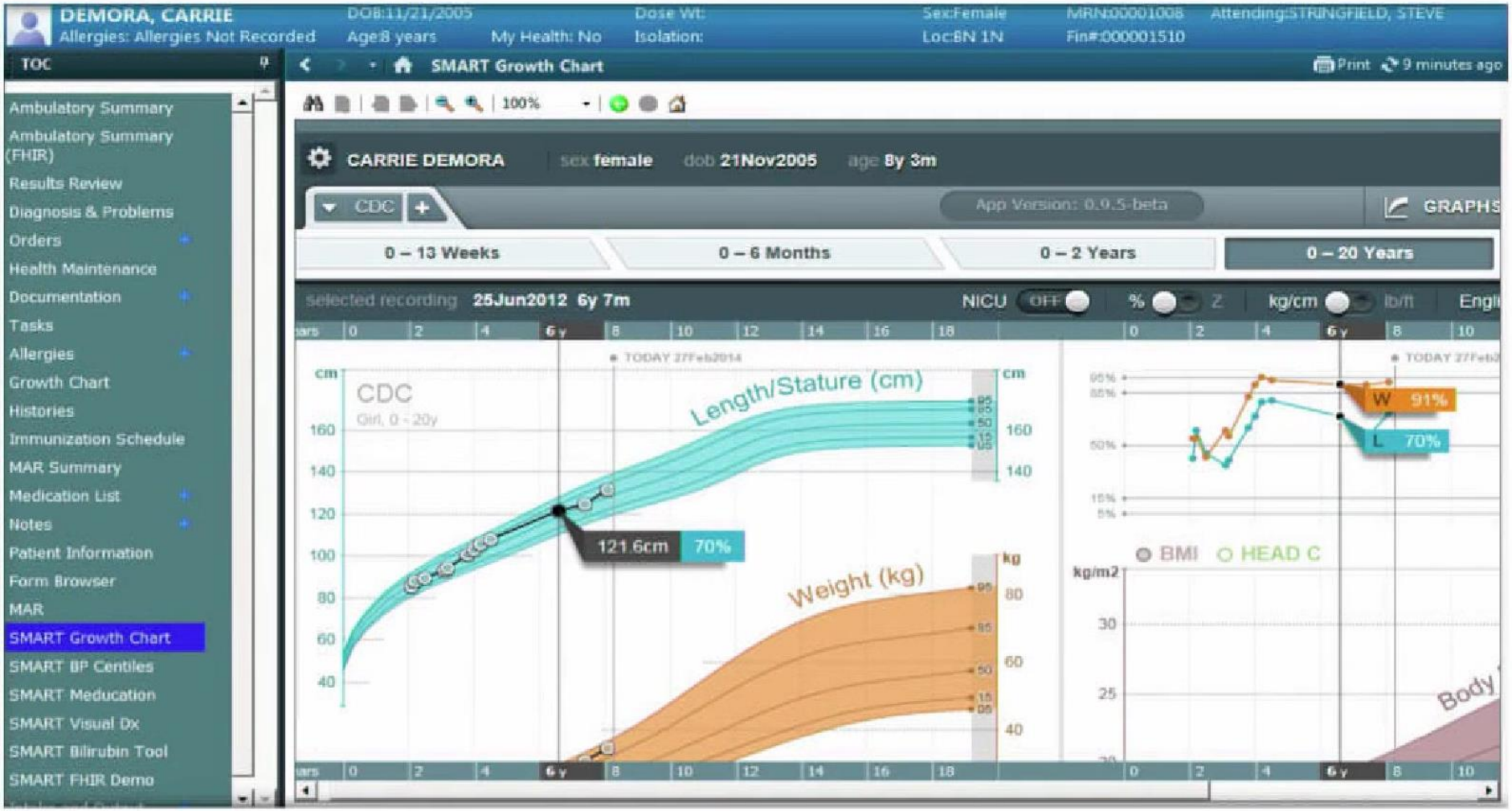
Example Provider View in Epic



APPLIED GENOMICS & PRECISION MEDICINE

DukeMedicine

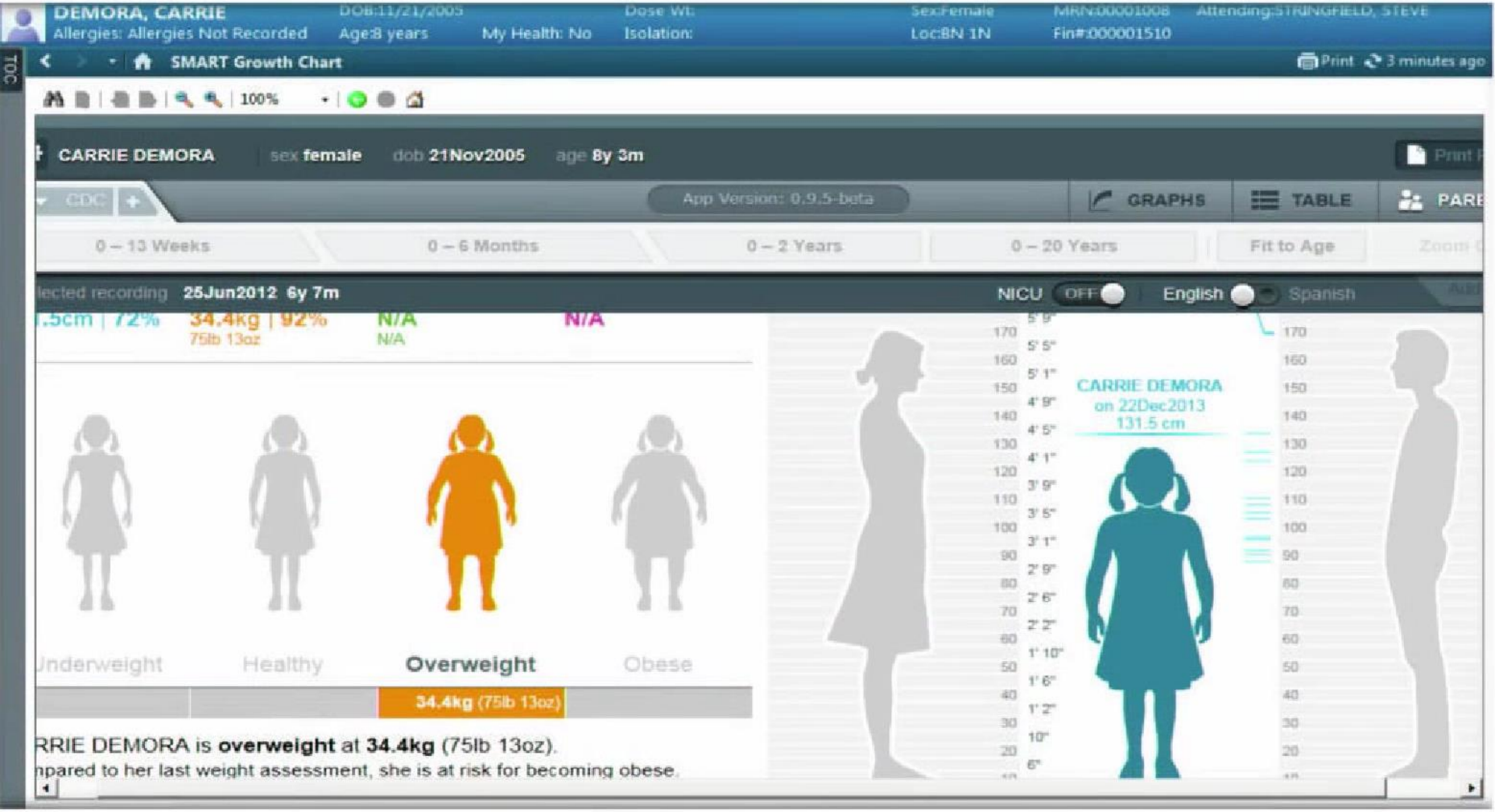
Data Visualization with FHIR



APPLIED GENOMICS & PRECISION MEDICINE

DukeMedicine

Multiple Views: Patient-oriented



APPLIED GENOMICS & PRECISION MEDICINE

DukeMedicine

Questions?