



Realizing the Value of Genomic Decision Support in Healthcare Systems: *Opportunities, Challenges, and Strategies for Success*

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Physician Knowledge Gaps (Informational Needs)

What genetic syndrome should I suspect in this patient?

What genetic test should I order?

How do I interpret the genetic findings?

What are the next steps in management?

When should I refer the patient?

Who else in the family should get testing?

Where can I find management guidelines?



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Clinical Decision Support
(CDS) tools for clinicians
lacking genomic expertise

I. Select FH management guidelines and convert text into computer-interpretable modules

AHA/ASA Guideline

2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

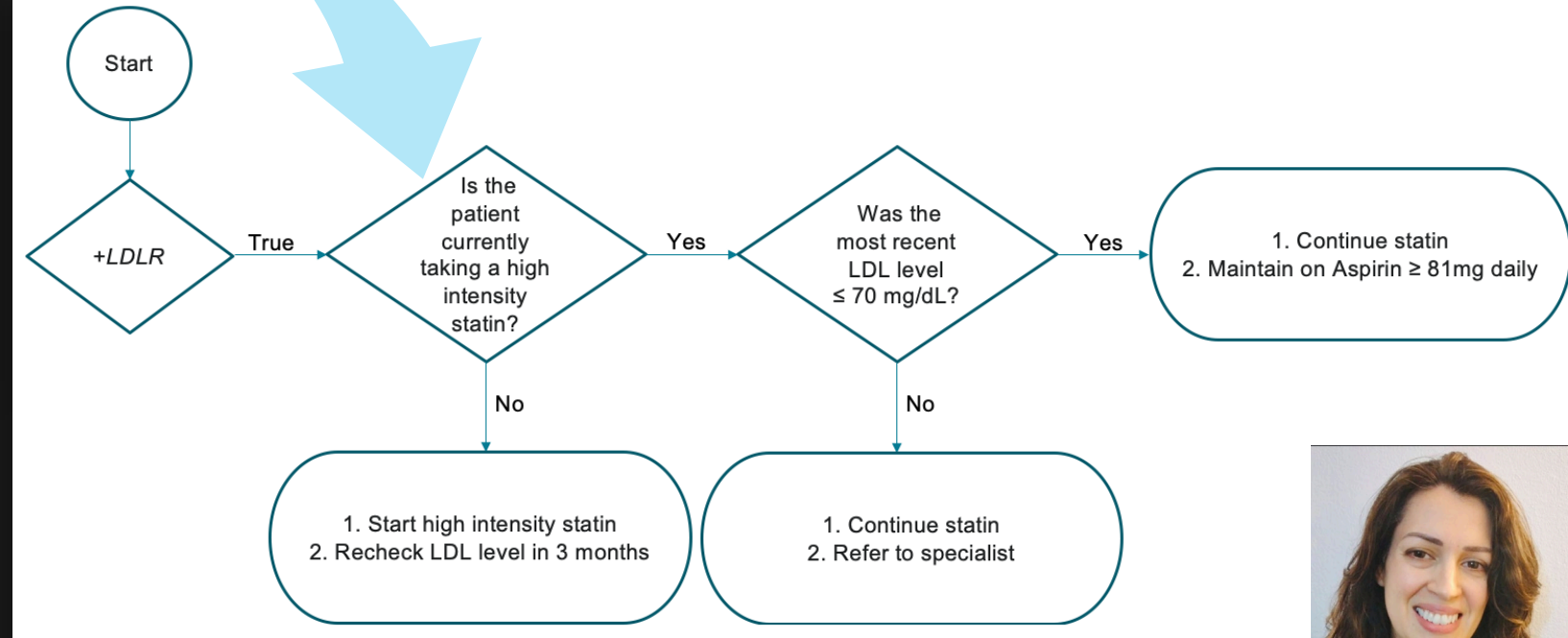
Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

Endorsed by the Society for Academic Emergency Medicine and Neurocritical Care Society

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

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Decision Tree Modeling



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Develop a Genome-informed CDS tool for Familial Hypercholesterolemia (FH)

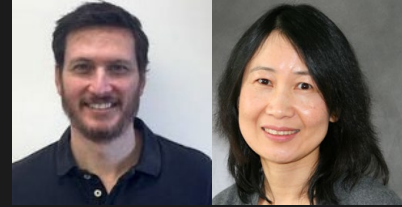
II. Conducted a scenario-based evaluations of decision tree's logic among target users and assessed ease of use and usefulness in clinical practice

User	Unmet Information Needs
1	"I think you should also list the different high intensity statins"
2	"I'd like to see a link to the full guidelines in the tool"
3	"This doesn't work when the LDL is already less than 70. The user isn't then prompted to start a high intensity statin"
4	"Is genetic testing diagnostic for this condition?...The diagnostic criteria need to be shown here because I don't know what it is... and the flowchart makes no mention that this is diagnostic for FH"
5	"The first branch point does not give enough information" "I'm unclear as to when I should refer to a specialist" "I didn't know what the LDL goal is supposed to be unless they're already on a high intensity statin"
6	"I'd just to have to know more information about their cardiovascular risk before being able to feel comfortable managing the patient on my own"



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III. Made iterative changes and then implemented the prototype into the EHR as a proof of concept



inYP Fasel, David Logout Search

Patient List Registry Patient Data Explore My Profile SANDIEGO, CARMEN A • Jan 3, 1933 • 86y • M ← →

Profile Data Review Summaries Immunizations Care Team

Summaries

- Lab - Main
- Lab - Other
- Lab - Microbiology
- Problem History
- Visit History
- Procedure History
- Bug-Drug History
- Problem List
- Allergy List
- Dashboards
- Ambulatory Medicine
- Ambulatory Pediatrics
- Transplant Kidney
- Transplant Heart
- Transplant Liver
- Oncology Pediatrics
- OB/Gynecology
- Perioperative
- Transfusion - West
- Transfusion - East (beta)
- Kidney Disease
- Genetics
- Visualization
- Vitals / I&O / Meds
- 24h Vitals
- 24h I&O
- Common Lab Results

Genetic Variant Alerts

Disease Risk	Gene	Pathogenic Variant	Interpretation	Genetic Report	Clinical Decision Support
Familial hypercholesterolemia	LDLR	chr19 g.11224296G>A	Likely Pathogenic	eMERGE Report	FH Decision Tree

Organize by data relevant to: Familial hypercholesterolemia

Vital Signs

Item	Value	Date
BMI	41.6	11-12-18
Weight(kg)	123.33	11-12-18
Height	172	11-12-18
SBP	121	11-12-18
DBP	66	11-12-18
Heart Rate	77	11-12-18

Medical History

Cardiovascular related

- Chronic kidney disease, stage 2 (mid) [N18.2] 2018-01-01
- Type 2 diabetes mellitus with unspecified diabetic retinopathy with macular edema [E11.311] 2018-01-01
- Atherosclerotic heart disease of native coronary artery [I25.10]

All medical history

- Family history of asthma
- Personal history of noncancer treatment, presenting ha

Medications

Lipid Lowering Medication

- Atorvastatin 40mg PO qd
- Alirocumab (Praluent ®)

All Medications

- Hydroxypropyl M-Cel 0.2
- Aspirin 81mg PO qd

Clinical Alerts

- 87 yo non-AA F
- Risk Profile: Smoking: Never Smoked
- 10-yr ASCVD Risk 27%

Laboratory Studies

Item	Latest Value	Date
Chol Total	300	03-23-13
LDL Cholesterol	250	03-23-13
HDL Cholesterol	50	03-23-13
Triglycerides	300	03-23-13
Hemoglobin A1c	5.0	03-23-13
Glucose	100	04-13-18
Creatinine	0.7	04-05-18

Cardiovascular studies

Electrocardiogram and diagnostic report

- 12-lead electrocardiogram 2018-01-01
- 12-lead electrocardiogram 2018-05-09
- Diagnostic report 2018-05-09

Echocardiography

- Adult Echocardiographic Report 2018-01-01



eMERGE-Seq Panel Sequencing Report

ADDENDUM

07/26/2018
This report was corrected to update the description of the Sanger confirmation status.

PATHOGENIC AND/OR LIKELY PATHOGENIC VARIANTS DETECTED

A heterozygous c.1444G>A (p.Asp482Asn) likely pathogenic variant in the LDLR (NM_000527.4) gene was detected in this individual, which was confirmed by Sanger sequencing. Defects in LDLR are the cause of familial hypercholesterolemia (FH) [MIM 143890], a common autosomal semi-dominant disease that affects about 1 in 300 to 1 in 500 individuals. The receptor defect impairs the catabolism of LDL, and the resultant elevation in plasma LDL-cholesterol promotes deposition of cholesterol in the skin (xanthelasma), tendons (xanthomas), and coronary arteries (atherosclerosis). Heterozygous individuals are at high risk for coronary heart disease: untreated men clinically presenting with familial hypercholesterolemia have a 50% risk of a fatal or nonfatal coronary event by age 50 years; untreated women have a 30% risk by age 60 years [PMID 21600525, 21712404, 15177124]. Homozygous individuals experience severe CAD by their mid-20s and the rate of either death or coronary bypass surgery by the teenage years is high. The c.1444G>A (p.Asp482Asn) variant in the LDLR gene has been reported in patients with hypercholesterolemia [PMID 8535447, 23375686, 20236128, 16159606, 21326404; legacy name 461]. This variant was observed in five heterozygous individuals in the ExAC population database (<http://exac.broadinstitute.org/variant/19-11224296-G-A>). Aspartate at position 482 of the LDLR protein is conserved in mammals and while not clinically validated, computer-based algorithms (SIFT and PolyPhen-2) predict this p.Asp482Asn change to be deleterious. This c.1444G>A (p.Asp482Asn) variant is thus classified as likely pathogenic.

Table 1: Details of Pathogenic and Likely Pathogenic Variants

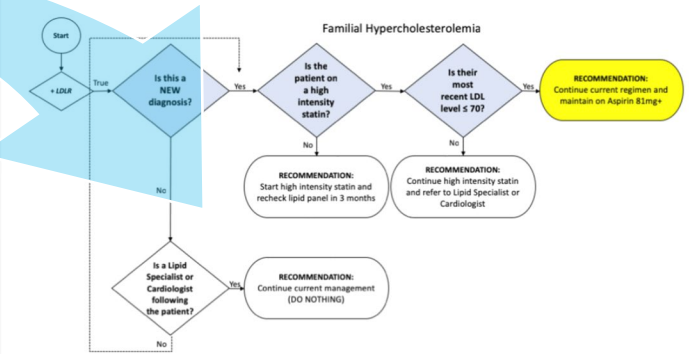
Disease	Inh.	Gene Position (NCBI 37)	Variant	Zyg.	Notes	Interpretation
Familial hypercholesterolemia [MIM 143890]	AD	LDLR	chr19 g.11224296G>A	c.1444G>A p.Asp482Asn	Heterozygous rs139624145; PMID 8535447, 21326404, 16159606; rs139624145 Confirmed by Sanger sequencing	Likely Pathogenic

Genetic Clinical Decision Support Tool

MRN-313131 | Sandiego, Carmen | DOB: 1964-12-11

Condition: Familial Hypercholesterolemia (FH), Gene: LDLR

This patient has a pathogenic variant in the gene LDLR which puts them at high risk for FH. Use this tool to guide treatment.



Recommendation

Continue current regimen and maintain on Aspirin 81mg+

Back Start Over

Challenges

Solutions & Tradeoffs

Competing Guidelines



Merge multiple guidelines

Ongoing barriers to integrating raw genomic data in EHRs



Upload PDF files of genetic test results

Heterogenous IT Infrastructures



Create an interactive web-based decision tree within a customized EHR dashboard

Do clinicians
use unsolicited
genomic data
integrated into
the EHR?



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Only 1% of all the
eMERGE-3 genetic test
results in the EHR were
viewed by clinicians, who
did not initiate genetic tests



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Characteristics	Clinician Users N=30
Attendings	14 (47%)
Fellows	4 (13%)
Residents	9 (30%)
Nurse practitioners	3 (10%)
Anesthesiology	4 (13%)
Surgery	3 (9%)
Radiology	2 (6%)
Neurology	1 (3%)
Pathology	1 (3%)
Medicine	19 (63%)
During “regular” workhours[†]	23 (77%)
During “on-call” hours [†]	6 (20%)
During “regular” and “on-call” hours	1 (3%)
Outpatient/Ambulatory	18 (60%)
Inpatient/Hospitalized	11 (37%)
Both outpatient and inpatient settings	1 (3%)
Around the time of a scheduled outpatient clinical encounter	11 (37%)
Care team member of a hospitalized participants	11 (37%)
Established outpatient provider	5 (17%)
Not ascertained/Unknown	3 (10%)

Key Barriers

1. Disconnect between genomic discovery (by scientists) and healthcare delivery (by clinicians)
2. Lack of coordination, workflow support, and policy for liability at hospitals
3. Lack of current knowledge to practice evidence-based genomic medicine among clinicians
4. Poor EHR user interface (hard to make things found), alert fatigue, information fragmentation,
5. No genomic knowledgebase (standards-based, computable, reasonable, provenance checking)
6. Seamless integration between genomic knowledge base and current PubMed literature
7. Integration of the knowledge to EHR for automated triggering of genomic practice guidelines

Enablers

1. Opportunities: Learning health system development within CTSA hubs
2. EHR-based informatics research results + implementation science
3. Decades of clinical informatics research on knowledge representation and reasoning
4. Text mining and evidence inference
5. FHIR and other EHR data exchange standards

Sociotechnical Strategies for Success

1. Invest in informatics research for genomic evidence computing and genomic knowledgebase construction to enable scalable, sharable and computable inferences of genomic knowledge and harmonization of practice guidelines
2. Harmonize the interests of multiple stakeholders (EHR vendors, Hospital IT, genomic scientist, clinicians, and institutional leadership) to facilitate team science and implementation science
3. Forge collaborations to develop a learning health system for genomics (what is new evidence, who is affected, what needs to be done, etc)
4. Clinician-centered design of workflow support, referral support, CDS, etc.

Thank you!