Personalized Cardiovascular Medicine: Harnessing the Power of Genetics

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@Bmhelm
either way...

Disclosures:

- None
Roadmap:

- What’s most common? What’s most under-recognized?
- You do genetic testing for that?
- Isn’t genetic testing still really expensive?
- Can’t people just test for things at home on their own now? DIY Genome Analysis
Roadmap:

▪ What’s most common? What’s most under-recognized?
▪ You do genetic testing for that?
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▪ Can’t people just test for things at home on their own now? DIY Genome Analysis
Familial Hypercholesterolemia

Family history of early cardiac events

High LDL cholesterol: above 190 mg/dL in adults and 160 mg/dL in children

SO MANY

1/250 People have FH

SO UNDER-DIAGNOSED

90% UNDIAGNOSED
THEN:

High cholesterol?

Give statins

NOW:

PERSONALIZED MEDICINE!

- Most accurate, correct clinical diagnosis
- Personalized risk stratification
- Specific genotype offers additional information
- More treatment options
- Preventative medicine opportunities galore!

...and still give statins
SO YOUNG

Untreated women have a **30% risk** of having a **heart attack** by age 60.²

Untreated men have a **50% risk** of having a **heart attack** by age 50.²

SO PREDICTABLE

SO TREATABLE

**Medications:**
- statins
- cholesterol absorption inhibitors
- PCSK9 inhibitors
- bile acid sequestrants

**Apheresis:**
- therapy to remove LDL cholesterol from the blood

**Lifestyle Changes:**
- heart healthy diet
- regular exercise
Opportunity for Prevention

Graph showing the cumulative LDL-C (mmol) over age in years for Homozygous FH, Heterozygous FH, and Without FH. The threshold for CHD is indicated at different ages, with start of high dose statin and start of low dose statin marked.

Nordestgaard BG et al. Eur Heart J 2013; 34:3478-3490a
How are we doing with treatment?

Goal achievement and cardiovascular outcomes among adults with familial hypercholesterolemia: CASCADE FH® Registry

1900 patients with Familial Hypercholesterolemia
Median age 56 years
Mean age at FH diagnosis 50±18 years
61% female; Untreated LDL-C 249 mg/dL

High rate of cardiovascular disease at enrollment
1196 without diagnosed cardiovascular disease
704 with diagnosed cardiovascular disease

Majority of FH individuals did NOT meet guideline-based LDL cholesterol targets despite 2/3 of patients taking two or more lipid-lowering medications

Adults under specialty FH care were able to further lower LDL-C, but not far enough

Mean LDL-C Results Over Time

52% did NOT achieve LDL-C <100 mg/dL
78% did NOT achieve LDL-C <70 mg/dL

How are we doing with treatment?

Real-world evidence highlights that individuals with FH prescribed PCSK9 inhibitors are at highest cardiovascular risk (recalculated study data).

Clinical Genetic Testing for Familial Hypercholesterolemia

JACC Scientific Expert Panel

Amy C. Sturm, MS, a, b Joshua W. Knowles, MD, PhD, b,c,d,e Samuel S. Gidding, MD, a,d,e Zahid S. Ahmad, MD, a,e Catherine D. Ahmed, MBA, f Christie M. Ballantyne, MD, f Seth J. Baum, MD, f,g Mafalda Bourbon, PhD, h,i Alain Carrié, MD, PhD, j Marina Cuchel, MD, PhD, k Sarah D. de Ferranti, MD, MPH, l Joep C. Defesche, PhD, m Tomas Freiberger, MD, PhD, n,o Ray E. Hershberger, MD, o G. Kees Hovingh, MD, PhD, p Lala Karayan, MPH, q Johannes Jacob Pieter Kastelein, MD, PhD, s Iris Kindt, MD, MPH, t Stacey R. Lane, JD, MBE, u Sarah E. Leigh, MSc, PhD, v MacRae F. Linton, MD, w Pedro Mata, MD, PhD, x William A. Neal, MD, y,z Børge G. Nordestgaard, MD, DMSc, z,w Raul D. Santos, MD, PhD, a,b Mariko Harada-Shiba, MD, PhD, x Eric J. Sijbrands, MD, PhD, a,b Nathan O. Stitzel, MD, PhD, a,b Shizuya Yamashita, MD, PhD, a,b,c,c,d,e,f,g Katherine A. Wilemon, BS, h,i David H. Ledbetter, PhD, h,i Daniel J. Rader, MD, h,i Convoyed by the Familial Hypercholesterolemia Foundation
Rationale for Genetic Testing

- <10% of patients with FH are diagnosed
- Genetic testing will facilitate diagnosis
- Ultimately reducing/preventing ASCVD
- Genetic testing is underutilized (3.9% of CASCADE Registry)
- Atherogenic risk has genetic determinants
  - FH mutations + additional pathogenic + protective variants
- Pathogenic variant type independently predicts response to therapy and attainment of LDL goals
Rationale for Genetic Testing

- Physical exam findings are not sensitive
  - 8% had xanthomas in US study
- LDL cutpoints miss patients with FH
  - >50,000 patient with whole exome sequencing
  - Only 24% with a FH variant had probable/definite FH by Dutch Lipid Clinic criteria
  - Only 55% had a max LDL >= 190
- Cascade LDL screening is not reliable
  - Significant phenotypic overlap
- Genetic testing leads to 3x increase in patients taking medications
  - Even with LDL <130, CAD risk if higher in individuals with FH
Rationale for Genetic Testing cont...

- Kaplan-Meier curves for early CAD-free survival in FH men with null and defective LDLR mutations

- Patients with null mutations had significantly higher CAD frequency

Rationale for Genetic Testing cont...

B. Impact of Familial Hypercholesterolemia Mutation Status on Coronary Artery Disease According to LDL Cholesterol Level

CENRAL ILLUSTRATION: The Genetic Testing Process in an Index Patient (Proband) and Family

Identify index patients who should be offered familial hypercholesterolemia (FH) genetic testing

Provide genetic counseling or refer for genetic counseling

Patient decides not to undergo genetic testing

Management based on current cardiovascular risk reduction guidelines

Recommend cascade screening via lipid testing for at-risk relatives

Patient decides to undergo genetic testing and provides informed consent

Genetic testing results and post-test genetic counseling provided

**Negative or variant of uncertain significance (VUS) genetic testing results:**
Management based on current cardiovascular risk reduction guidelines

Recommnend cascade screening via lipid testing for at-risk relatives

Additional genetic testing may be warranted as sensitivity improves over time

If VUS classification changes, provide updated information to patient

**Positive genetic testing results:**
Pathogenic variant(s) identified; FH diagnosis confirmed

Recommend cascade genetic testing and genetic counseling for at-risk relatives

Relative does not undergo genetic testing: recommend clinical screening and care since could have pathogenic variant(s)

Relative tests negative: relative and their children not at risk and do not require clinical screening and care unless indicated by cardiovascular risk factors

Relative tests positive: recommend clinical screening and care; recommend genetic testing to additional at-risk relatives in cascade fashion

**Central Illustration:** The Genetic Testing Process in an Index Patient (Proband) and Family

Identify index patients who should be offered familial hypercholesterolemia (FH) genetic testing

Provide genetic counseling or refer for genetic counseling

Patient decides not to undergo genetic testing

Management based on current cardiovascular risk reduction guidelines

Recommend cascade screening via lipid testing for at-risk relatives

Patient decides to undergo genetic testing and provides informed consent

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Negative or variant of uncertain significance (VUS) genetic testing results:
Management based on current cardiovascular risk reduction guidelines

- Recommend cascade screening via lipid testing for at-risk relatives
- Additional genetic testing may be warranted as sensitivity improves over time
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Relative does not undergo genetic testing; recommend clinical screening and care since could have pathogenic variant(s)

Relative tests negative: relative and their children not at risk and do not require clinical screening and care unless indicated by cardiovascular risk factors

Positive genetic testing results:
Pathogenic variant(s) identified; FH diagnosis confirmed

- Recommend cascade genetic testing and genetic counseling for at-risk relatives
- Recommend clinical screening and care; recommend genetic testing to additional at-risk relatives in cascade fashion
Let’s not forget about Lp(a)!

Scientific Statement

Use of Lipoprotein(a) in clinical practice: A biomarker whose time has come. A scientific statement from the National Lipid Association

Don P. Wilson, MD*, Terry A. Jacobson, MD, Peter H. Jones, MD, Marlys L. Koschinsky, PhD, Catherine J. McNeal, MD, PhD, Børge G. Nordestgaard, MD, DMSc, Carl E. Orringer, MD
Roadmap:

- What’s most common? What’s most under-recognized?
- You do genetic testing for that?
- Isn’t genetic testing still really expensive?
- Can’t people just test for things at home on their own now? DIY Genome Analysis
Cardiomyopathies
- HCM
- DCM
- ARVC/D
- ACM
- RCM

Arrhythmias
- LQTS
- BrS
- CPVT
- SQTS
- Afib
- PCCD

Unexplained SCA/SCD

Cardiac Amyloidosis

Lipidemias
- FH
- Lp(a)
- Hypertriglyceridemia

Aortopathies
- Marfan Syndrome
- Loeys-Dietz Syndrome
- Nonsyndromic familial TAAD

Congenital Heart Defects
- Highly heritable lesion (ex: LVOT)
- Looks familial
- Co-occurring non-cardiac findings
- Concern for syndromic cause

Pulmonary Arterial Hypertension
Complete penetrance

Variable penetrance

Variable expressivity

Variable penetrance and expressivity

Unaffected
Roadmap:

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Paying for genetic tests:

- Insurance coverage has improved
- Sponsored testing programs (e.g. partnerships with pharma companies and patient advocacy organizations)
- No additional charge, time-limited cascade family testing programs
- Self-pay prices as low as $200/$250
- ...even applies to post-mortem genetic testing!
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Everybody’s doing it...

Up, up, and away
Total number of people tested by consumer genetics companies, in millions.

12,275,000!
DIY Genetic Testing

- It’s inexpensive
- It’s easily accessible
- It “feels” like personalized medicine
- Variety of motivation:
  - Curiosity
  - Lack of family history health information
Beware third-party interpretation tools!

- Getting raw data is easy, potentially encouraged
Requires confirmation testing!

16% inappropriately called high risk

40% absent
There can be helpful nuggets in there...

44-year-old female presents to clinic for evaluation after reviewing her raw data from 23andMe testing; processing thru Promeathase revealed a SNP

- **KCNQ1 c.1637C>T Ser546Leu**
- Stated that she pursued DTC testing for ancestry information but didn’t want to leave any stones unturned
- No history of syncope, seizures but has a history of palpitations
- Clinical evaluation of the patient revealed a normal QTc of 428 msec
- Clinical genetic testing confirmed presence of the variant, and classified variant as truly pathogenic
- Exercise stress test was consistent with a diagnosis of LQTS
  - In recovery, her QTc prolonged to 500 msec
48y h/o seizures as child

52y h/o SCA + pacemaker/ICD

KCNQ1 (+)

Obligate Carrier

KCNQ1 (+)

d. 27y
SCD while dancing
h/o recurrent syncope

KCNQ1 (+)

44y palpitations

DTC SNP: KCNQ1 c.1637C>T p.Ser546Leu

10y

KCNQ1 (+)

8y

KCNQ1 (-)

KCNQ1 (+)

KCNQ1 (-)
Healthy 22-year-old male self-referred to an HCM clinic after his raw data from DTC testing; processing thru TPI tools revealed a SNP

*MYBPC3 p.Asp770Asn*

Significant anxiety about result: took medical leave from PhD program “to focus on [my] HCM and risk of sudden death”, was avid cyclist and quit, considered joining support group but didn’t feel ready to discuss the possibility of myectomy or transplant “yet”

Somewhat unsurprised by results because of reported h/o palpitations in childhood, and father’s reported LVH
Trouble...

- Clinical evaluation of the patient and review of the father’s records were all normal – *no evidence of HCM*
- Clinical genetic testing confirmed *absence* of the variant, and patient was released from screening for HCM
Trouble, Case #2...

- 22-year-old male died suddenly, “cardiac arrhythmia of unknown cause”
- DTC genetic testing completed
- “If you click the tools to see Raw Data, I found the below information that was the same for me and my deceased son.”
  - **TMEM43 rs63750743**-look at Clinical Significance-Pathogenic Allele-ARVC
  - **PKP2 rs193922674**-look at Clinical Significance-Pathogenic Allele-ARVC”
- 18-year-old sibling’s clinical screening
  - MRI read as “Concern for fibrosis within the free wall and apex of the RV with significant trabeculations along the anterolateral wall of the RV”
  - Immediately had primary prevention ICD placed
  - No genetic testing performed
d. 50y
(cancer)

DTC PKP2 c.2146-1G>C,
TMEM43 c.1073C>T

DTC PKP2 c.2146-1G>C,
TMEM43 c.1073C>T

d. 48y

(seizures)

54y

78y

DTC PKP2 c.2146-1G>C,
TMEM43 c.1073C>T

18y

“abnl cMRI”
+ ICD placed

2

d. 54y
(kidney dz)

d. 75y
(cancer)

78y

d. 60y
(cancer)

d. 77y
(kidney dz)

22y

(cardiac arrhythmia
Of unknown cause)
Trouble, Case #2...

- Referral to specialized center for inherited cardiovascular disease:
  - 18yo cardiac eval, including re-read of cMRI was **completely normal**
  - Mother’s cardiac eval was **completely normal**

- At mother’s insistence, based on DTC results – ARVC sequencing panel sent on 18yo siblings – negative

- At GC’s recommendation, found remaining sample from autopsy/toxicology – performed comprehensive post-mortem genetic testing with 120-gene panel – unfortunately negative
d. 60y (cancer)

d. 77y (kidney dz)

50y

DTC PKP2 c.2146-1G>C, TMEM43 c.1073C>T

DTC PKP2 c.2146-1G>C, TMEM43 c.1073C>T

18y

“abnl cMRI”
+ ICD placed

negative comprehensive genetic testing

54y (cancer)

78y

seizures

50y

279y d.77y (cancer)

272y (kidney dz)

279y d.75y (cancer)

281y

(cancer)

281y
d.60y (cancer)

d.77y (kidney dz)

294y (cardiac arrhythmia of unknown cause)

317y (cardiac arrhythmia of unknown cause)

317y

DTC PKP2 c.2146-1G>C, TMEM43 c.1073C>T

seizures

78y

2

normal cMRI, negative ARVC genetic testing
Trouble, Case #2...

- 18yo with unnecessary ICD (parents refuse to explant)
- 18yo with incorrect diagnosis
- Mother with immense guilt for 1 year that she carried the same pathogenic variant as her son
- Father NOT screened
- Overall, despite correcting the workup, family remains confused and disappointed in the genetic testing results
DIY Genetic Testing

- Don’t initiate for clinical purposes – if genetic testing is warranted, do it right
- Proceed with caution when presented DTC results in clinic
  - Confirm testing results in clinical lab
  - Don’t let your clinical evaluation skills be tricked!
Thank you!

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