Personalized Cardiovascular Medicine: Harnessing the Power of Genetics

2019 Indiana-ACC Annual Meeting

19 October 2019

Katie Spoonamore, MS, CGC, LGC

@JKSpoonamore

Indiana University Health

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

or maybe…

Personalized Cardiovascular Medicine: Harnessing the Power of Genetics

2019 Indiana-ACC Annual Meeting

19 October 2019

Ben Helm, MS, CGC, LGC

@Bmhelm

Indiana University Health

INDIANA UNIVERSITY
SCHOOL OF MEDICINE

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?
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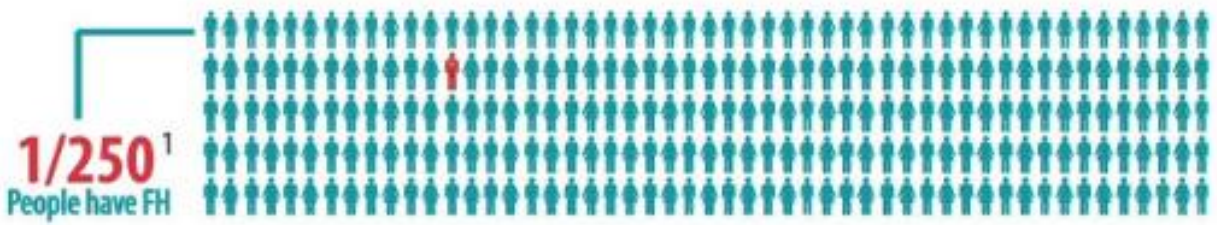
F + H = FH

Family history
of early cardiac events

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

Familial Hypercholesterolemia

SO MANY

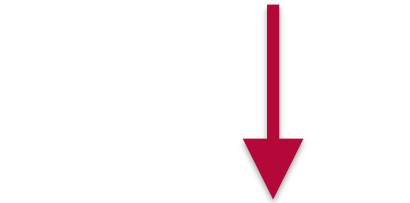


SO UNDER-DIAGNOSED

90%[3]
UNDIAGNOSED

THEN:

High cholesterol?

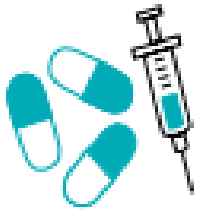


Give statins

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

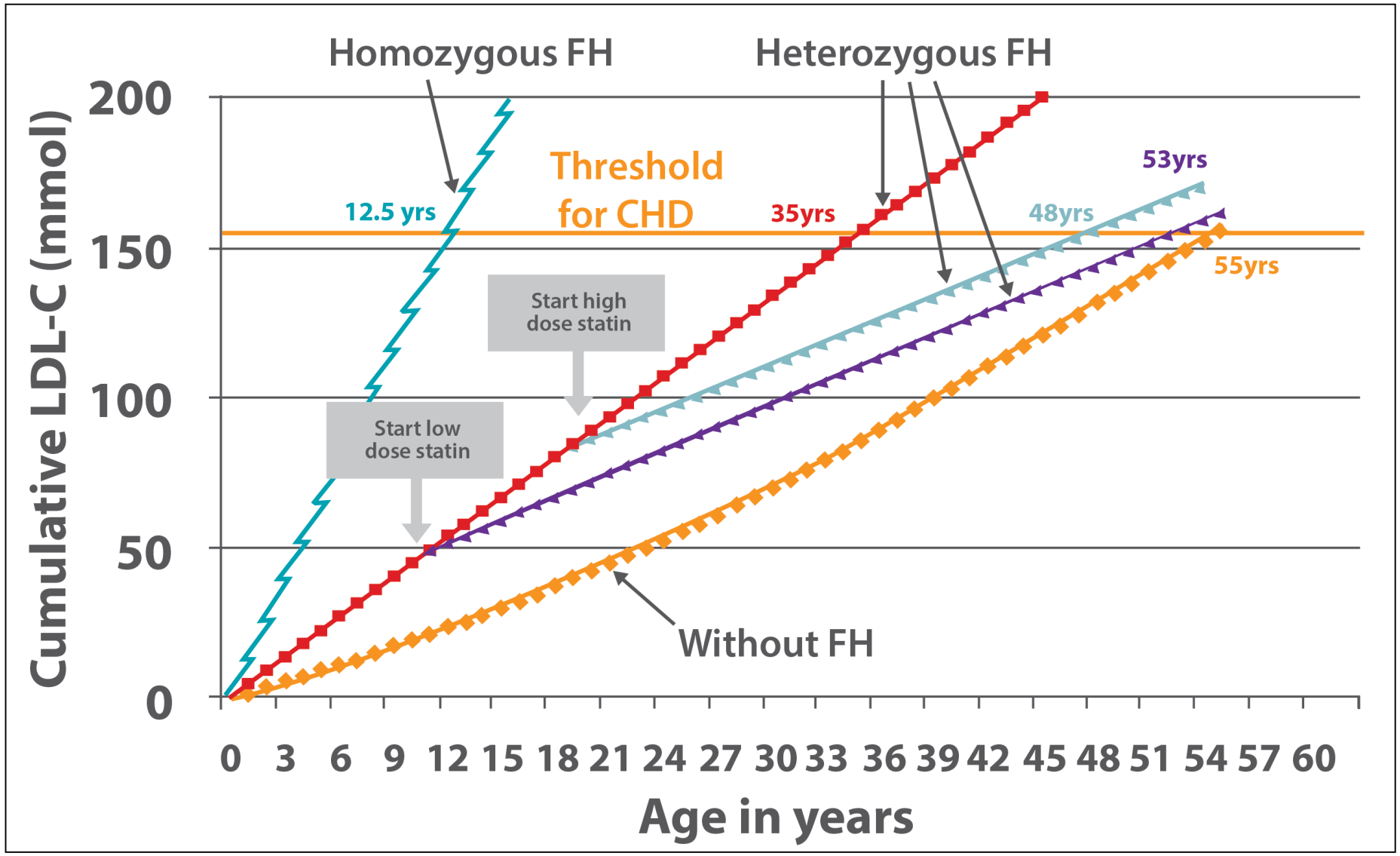
SO TREATABLE

Medications: statins, cholesterol absorption inhibitors, PCSK9 inhibitors and bile acid sequestrants

Apheresis: therapy to remove LDL cholesterol from the blood

Lifestyle Changes: heart healthy diet and regular exercise may help

Opportunity for Prevention



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

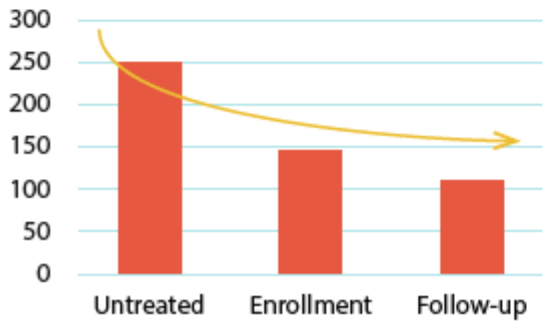
High rate of cardiovascular disease at enrollment

- 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



Individuals who had prior cardiovascular disease were more likely to meet targets because they were on 3-6 lipid-lowering therapies including PCSK9 inhibitors or were receiving lipoprotein apheresis

did NOT achieve LDL-C <100 mg/dL

did NOT achieve LDL-C <70 mg/dL

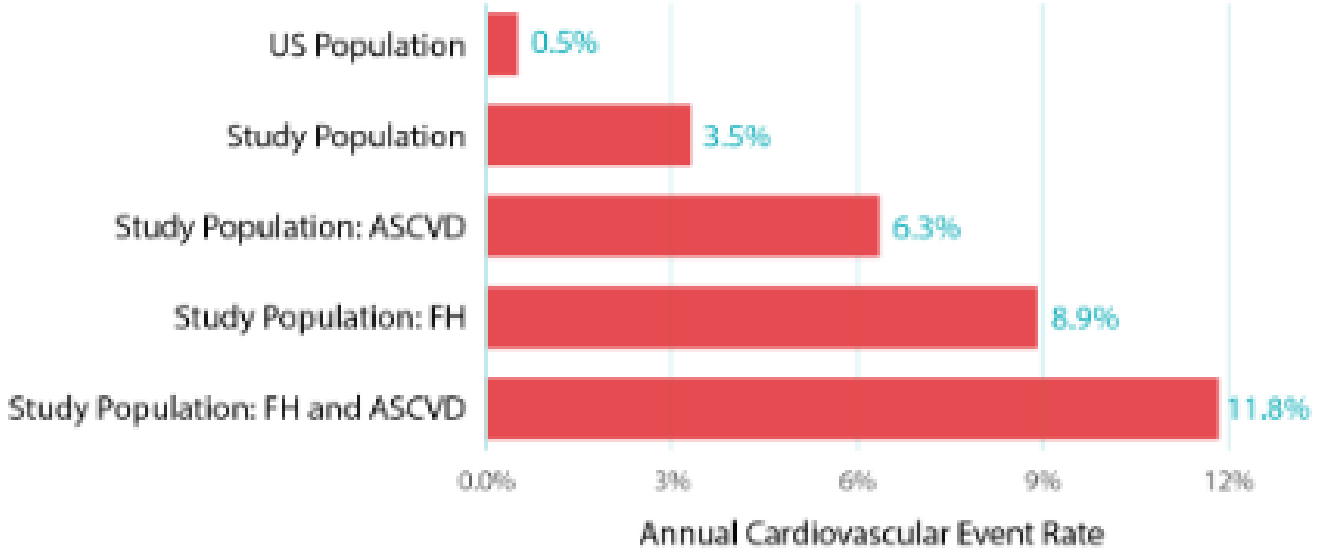
Duell, PB et al. Atherosclerosis, Oct. 2019, Vol. 289, 85-93

How are we doing with treatment?

Individuals with FH are at the highest risk

Real-world evidence highlights that individuals with FH prescribed PCSK9 inhibitors are at highest cardiovascular risk

(recalculated study data)



Myers, K. et al,
Circ Cardiovasc Qual Outcomes,
2019; 12:e005404

Genetic Testing

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 72, NO. 6, 2018

PUBLISHED BY ELSEVIER

THE PRESENT AND FUTURE

JACC SCIENTIFIC EXPERT PANEL

Clinical Genetic Testing for Familial Hypercholesterolemia

JACC Scientific Expert Panel

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Convened 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

DUTCH LIPID CLINIC NETWORK DIAGNOSTIC CRITERIA FOR FAMILIAL HYPERCHOLESTEROLEMIA[1-3]

Criteria	Point
Family History	
First-degree relative with known premature* coronary and vascular disease OR First-degree relative with known LDL-C level above the 95th percentile.	1
First-degree relative with tendinous xanthomata and/or arcus cornealis OR Children aged less than 18 years with LDL-C level above the 95th percentile.	2
Clinical History	
Patient with premature* coronary artery disease.	2
Patient with premature* cerebral or peripheral vascular disease.	1
Physical Examination	
Tendinous xanthomata	6
Arcus cornealis prior to age 45 years.	4
Cholesterol levels mg/dl (mmol/liter)	
LDL-C >= 330 mg/dL (≥ 8.5)	8
LDL-C 250 – 329 mg/dL (6.5 – 8.4)	5
LDL-C 190 – 249 mg/dL (5.0 – 6.4)	3
LDL-C 155 – 189 mg/dL (4.0 – 4.9)	1
DNA Analysis	
Functional mutation in the LDLR, apo B or PCSK9 gene	8
Diagnosis (diagnosis is based on the total number of points obtained)	
Defnite familial hypercholesterolemia	>8
Probable familial hypercholesterolemia	6 – 8
Possible familial hypercholesterolemia	3 – 5
Unlikely familial hypercholesterolemia	<3

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

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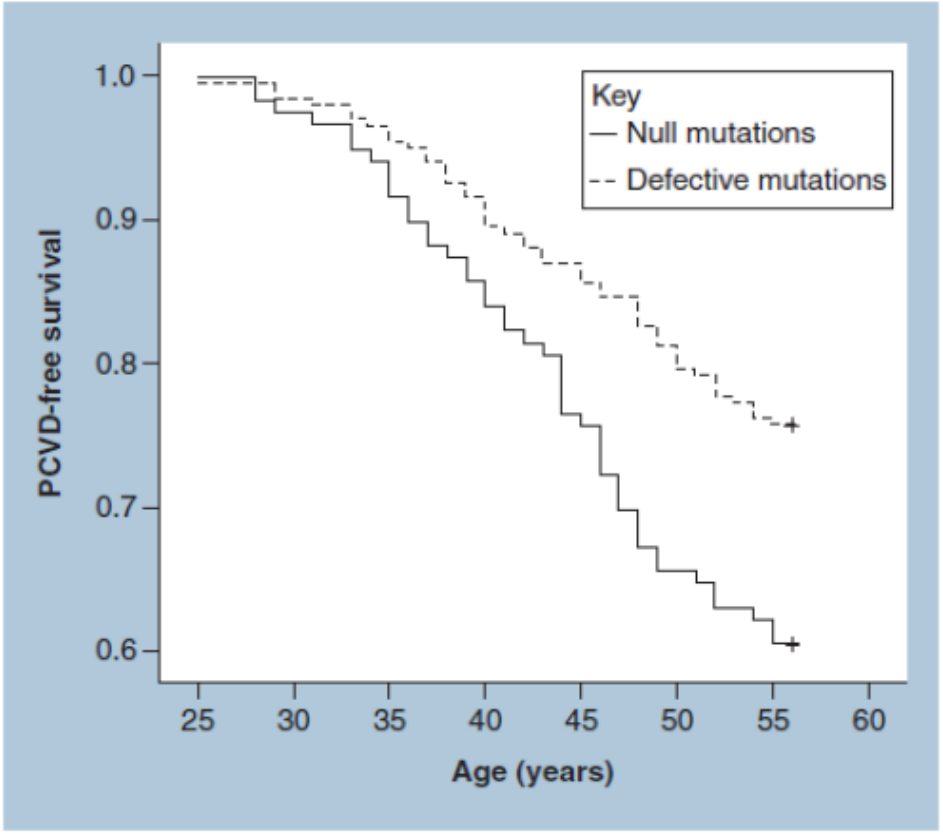
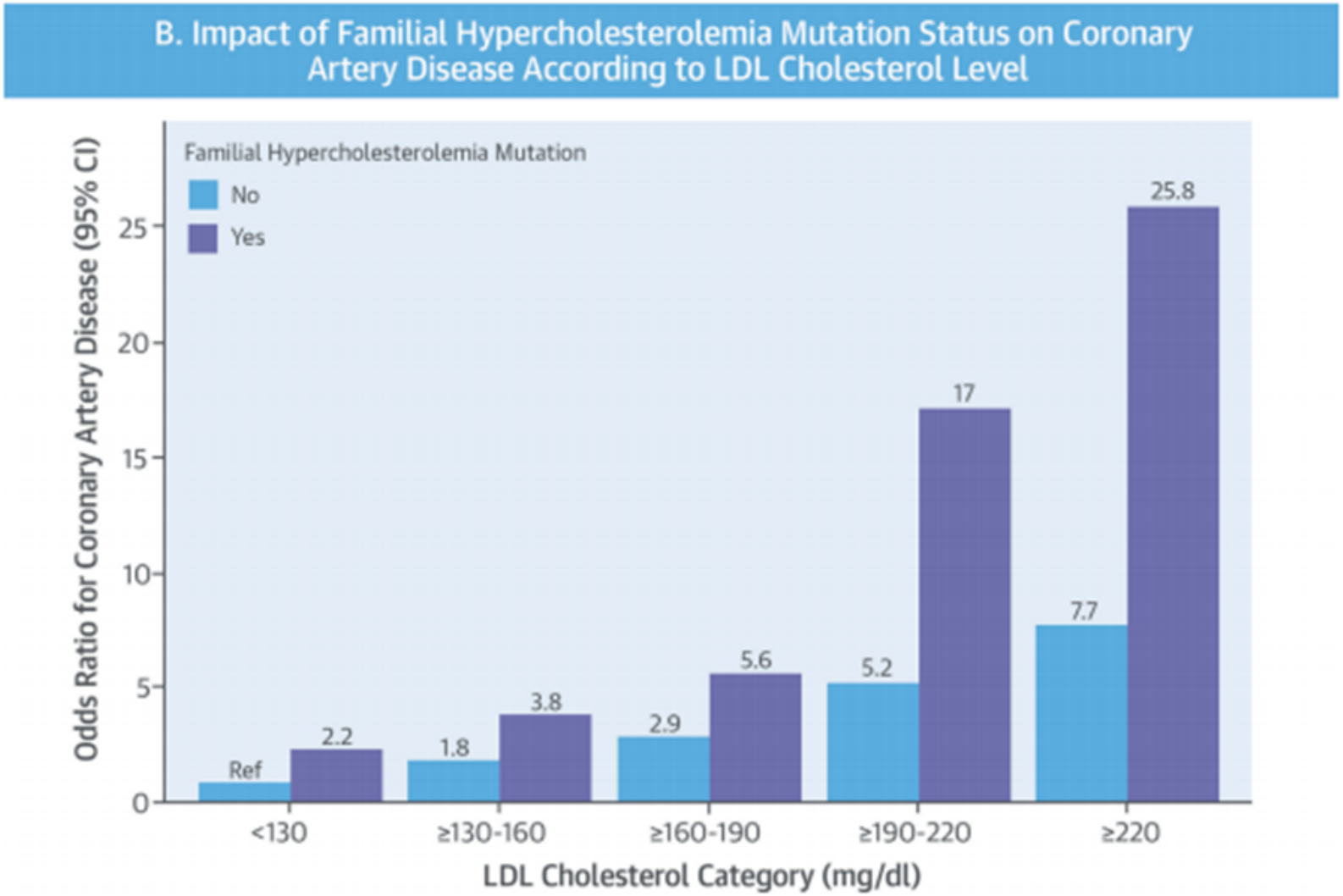
Rationale for Genetic Testing cont…

- 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



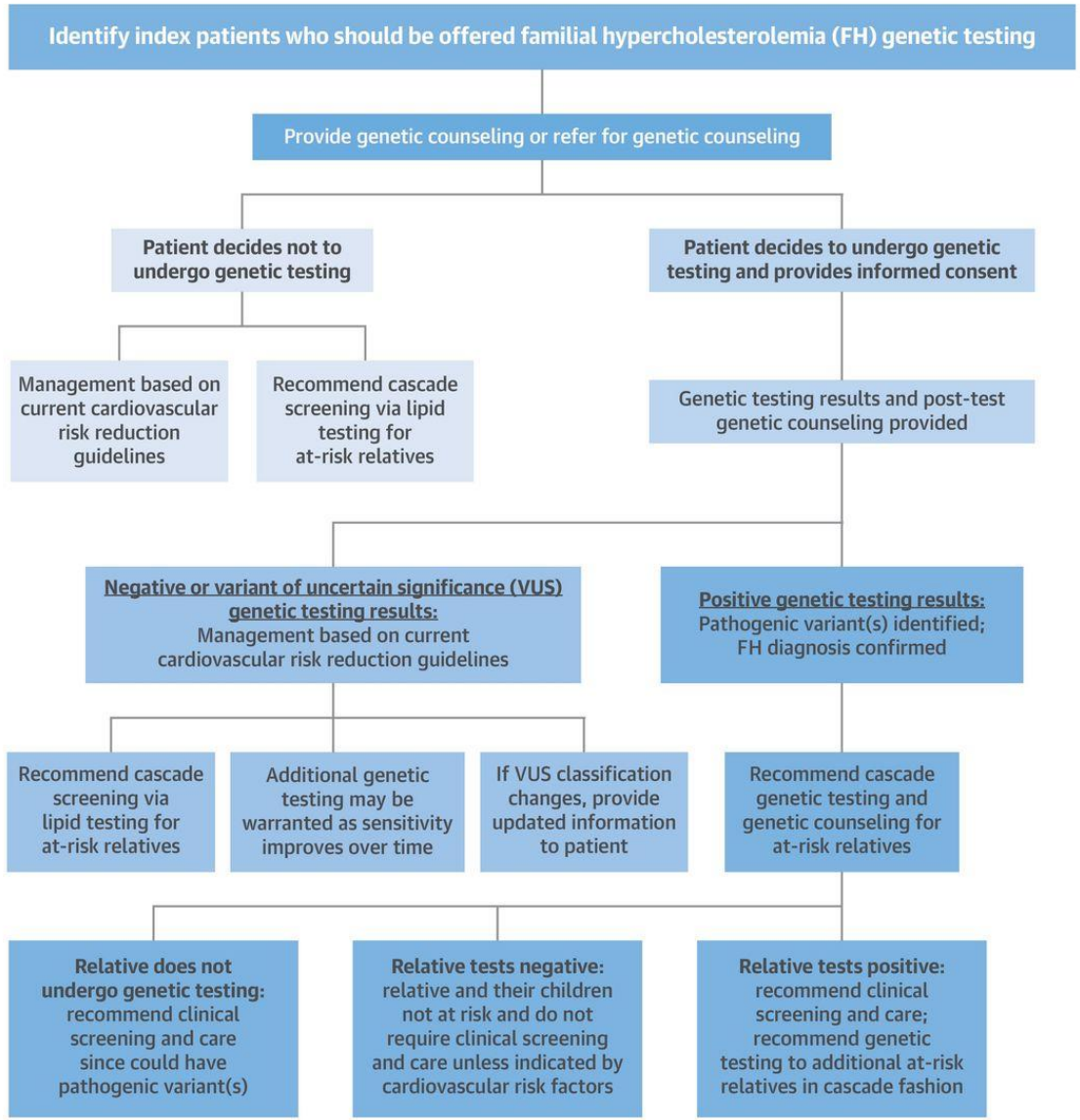
Alonso et al. Expert Rev Cardiovasc Ther 11(3), 327-342 (2013).

Rationale for Genetic Testing cont...



Khera, A.V. et al. J Am Coll Cardiol. 2016;67(22):2578-89.

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



Sturm, A.C. et al. J Am Coll Cardiol. 2018;72(6):662-80.

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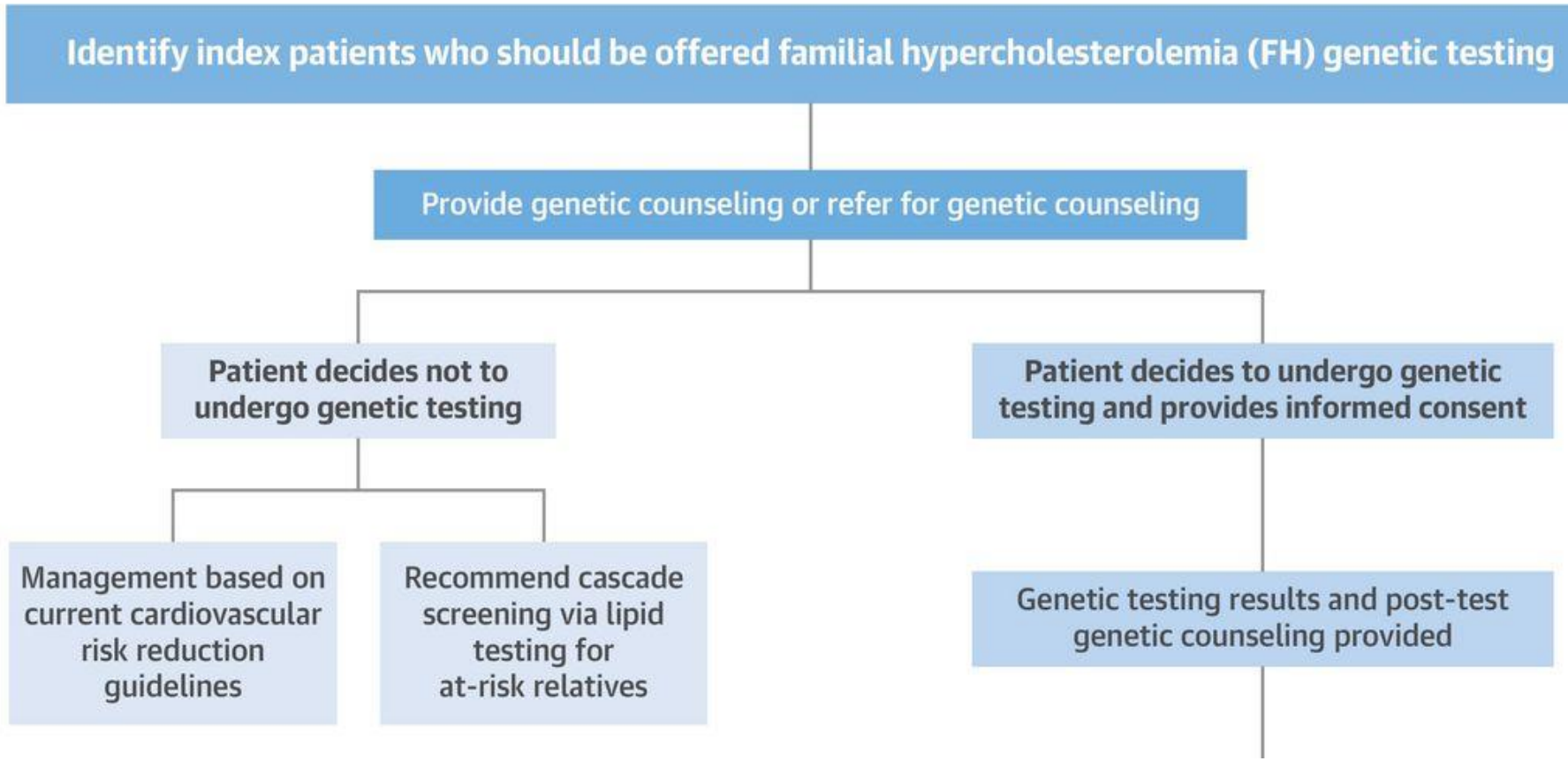
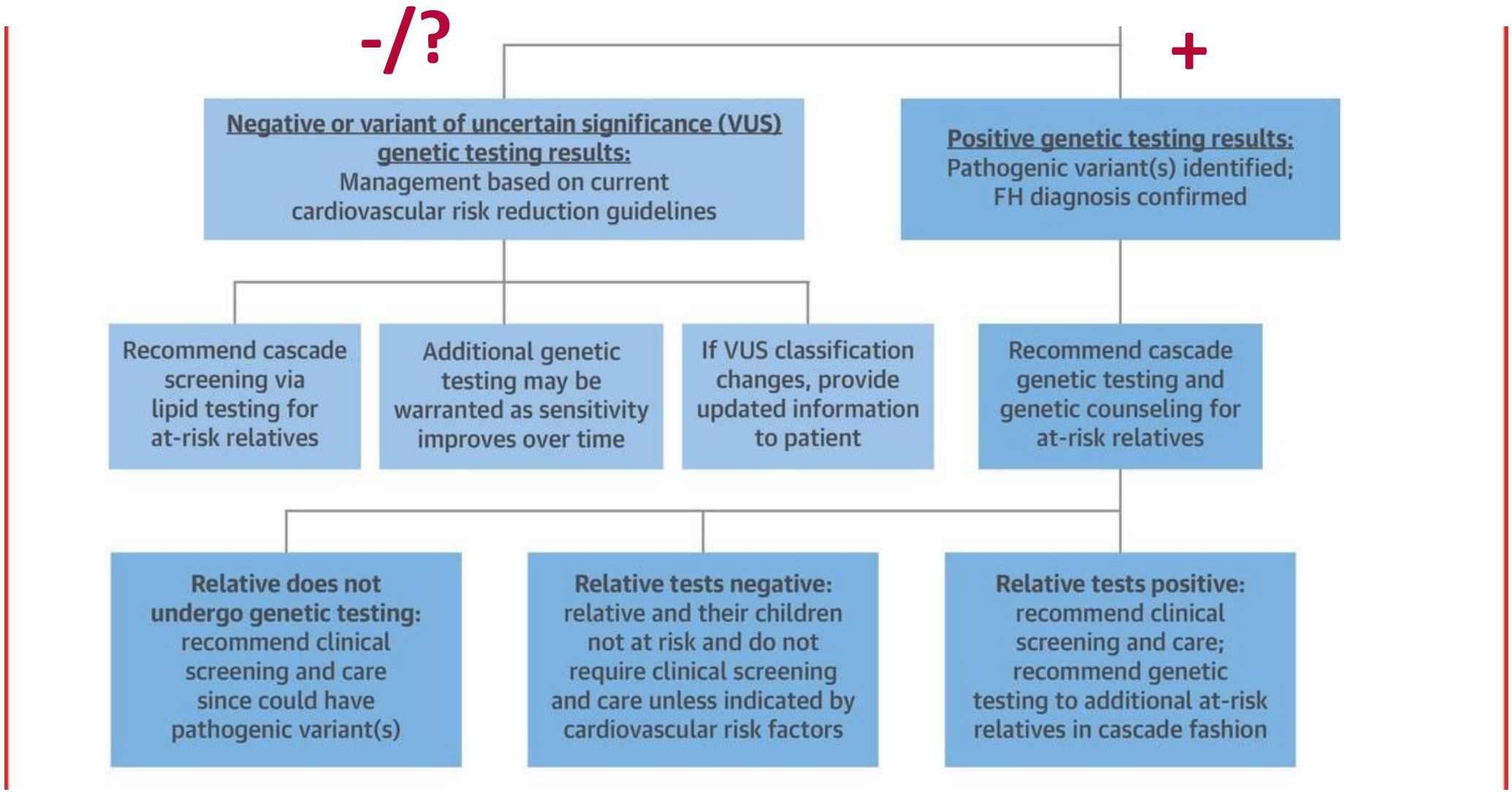



-/?
+
Negative or variant of uncertain significance (VUS) genetic testing results:
Management based on current cardiovascular risk reduction guidelines
Positive genetic testing results:
Pathogenic variant(s) identified;
FH diagnosis confirmed
Recommend cascade screening via lipid testing for at-risk relatives
Additional genetic testing may be warranted as sensitivity improves over time
If VUS classification changes, provide updated information to patient
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

Let's not forget about Lp(a)!

Journal of Clinical Lipidology (2019) 13, 374–392

Journal of Clinical Lipidology

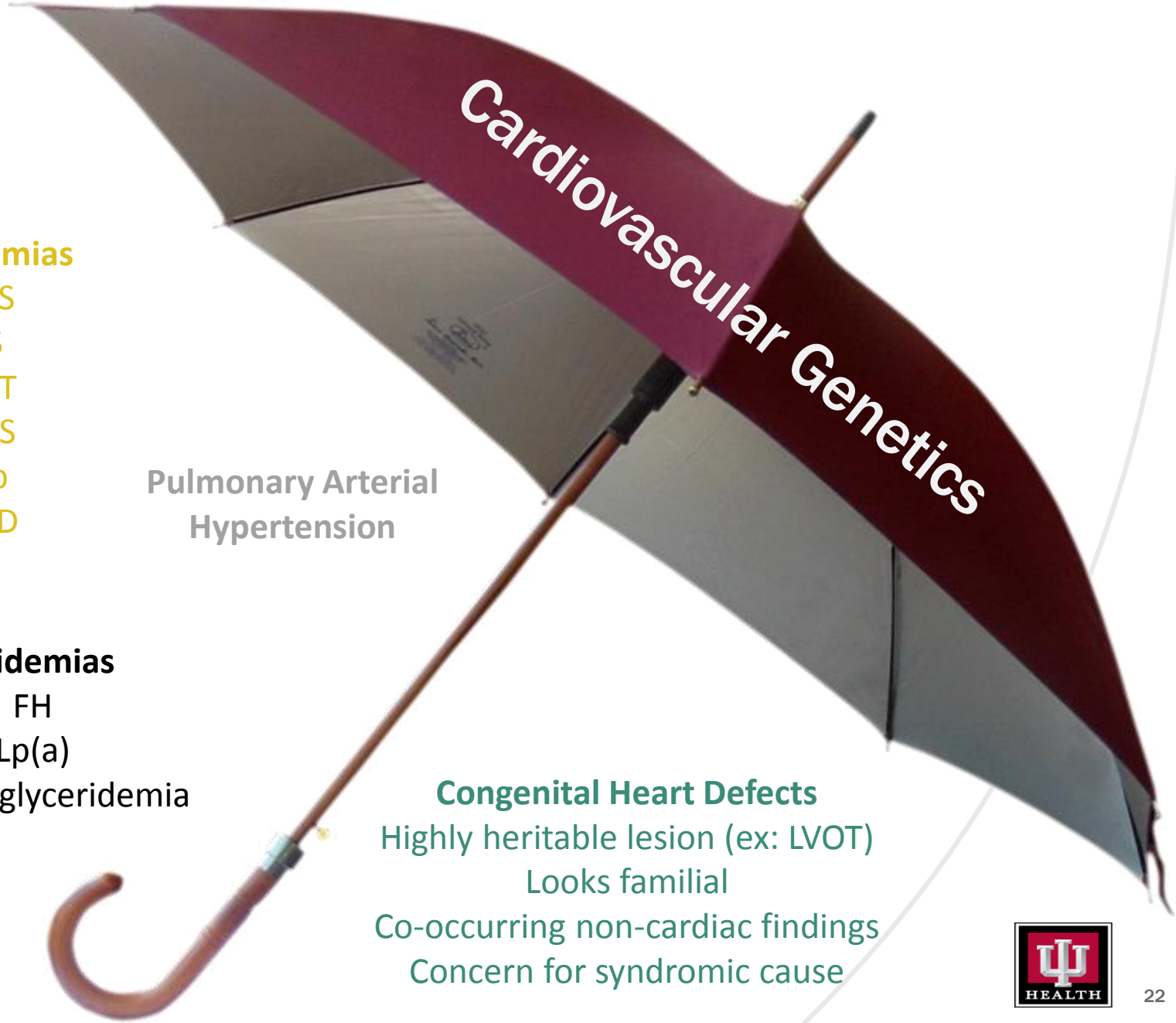
Scientific Statement

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

Pulmonary Arterial Hypertension

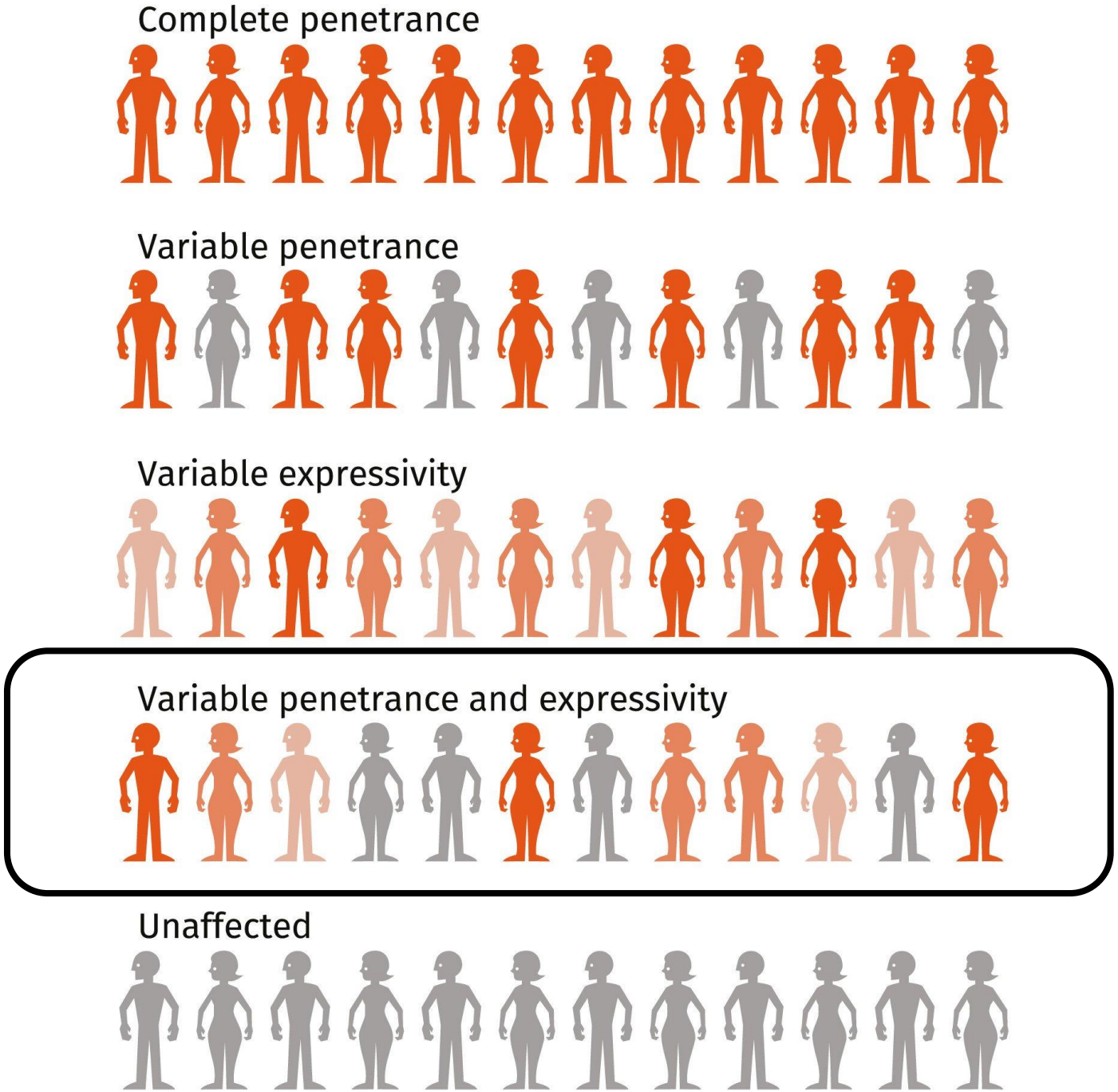
Unexplained SCA/SCD

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



https://www.garvan.org.au/research/kinghorn-centre-for-clinical-genomics

Roadmap:

- What's most common? What's most under-reco
- You do genetic testing for that?
- Isn't genetic testing still really expensive?
- Can't people just test for things at home on thei

Olha/Adobe Stock

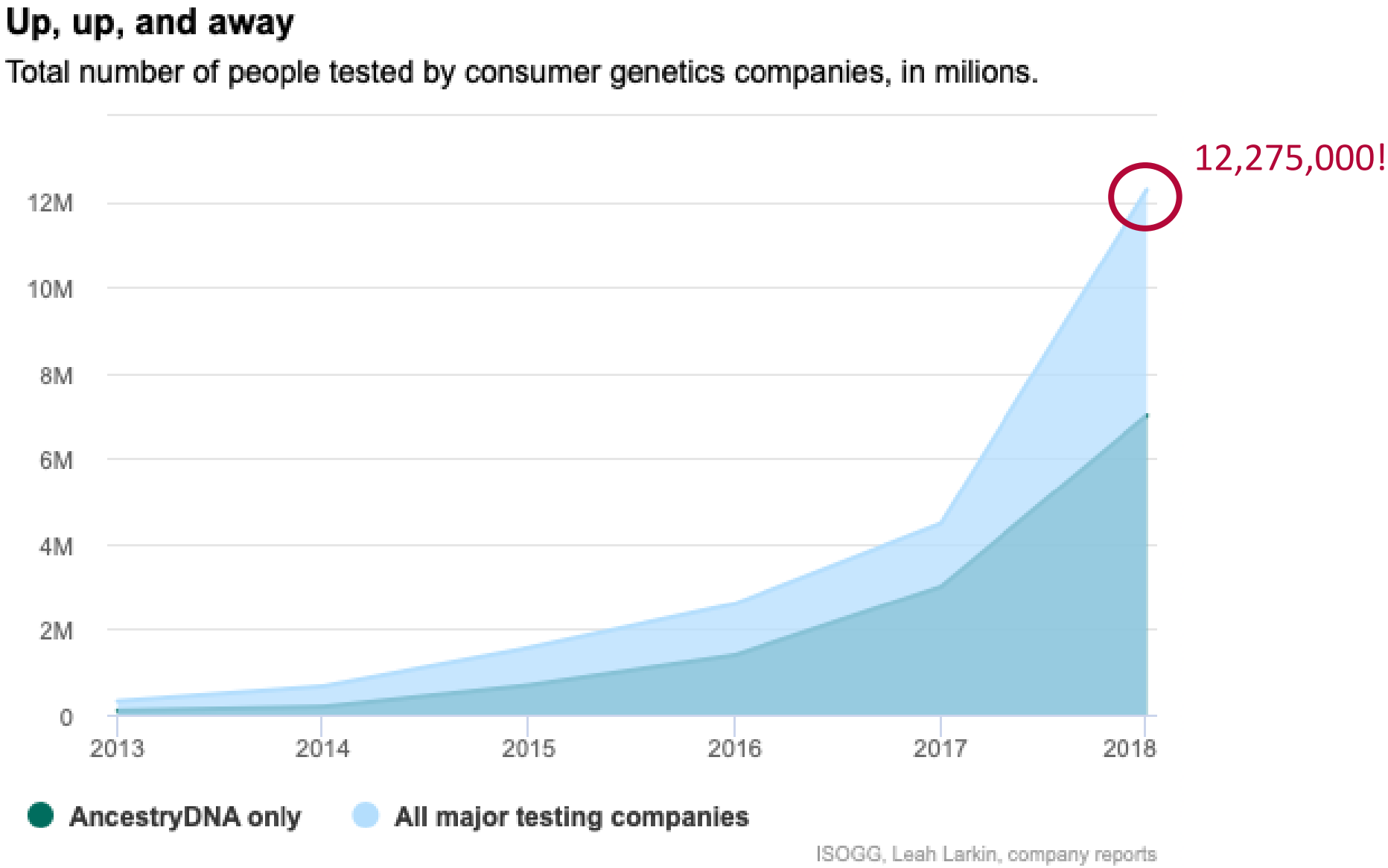
Paying for genetic tests:

- 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!

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

Everybody's doing it...

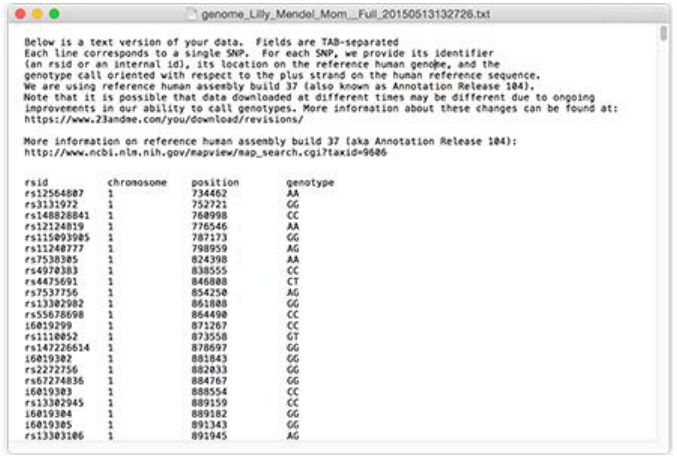


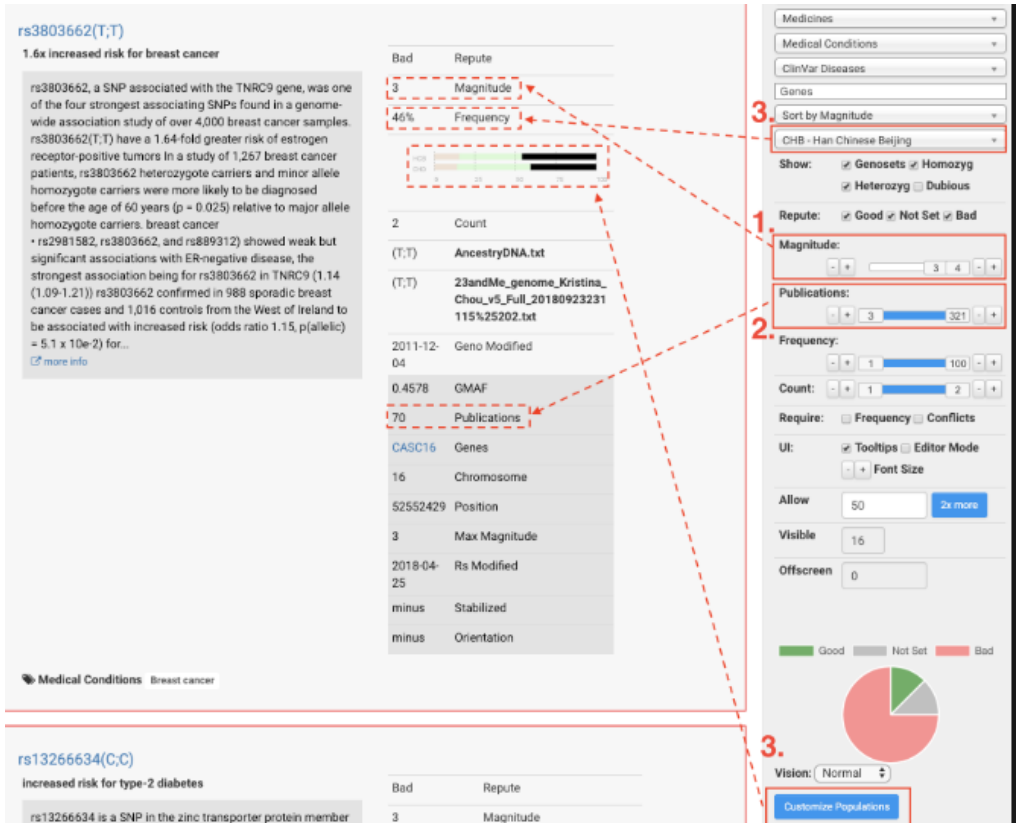
DIY Genetic Testing

- 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!

ORIGINAL RESEARCH ARTICLE | Genetics inMedicine

Open

False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care

Stephany Tandy-Connor, MS, Jenna Guiltinan, MS, Kate Krempely, MS, Holly LaDuca, MS, Patrick Reineke, BS, Stephanie Gutierrez, BS, Phillip Gray, PhD and Brigette Tippin Davis, PhD, FACMG

40% absent

16% inappropriately called high risk

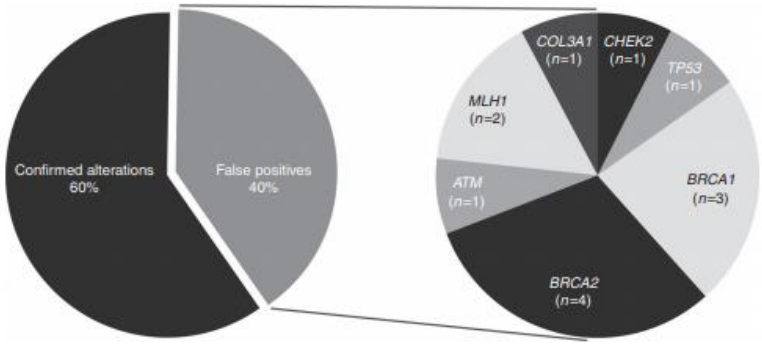


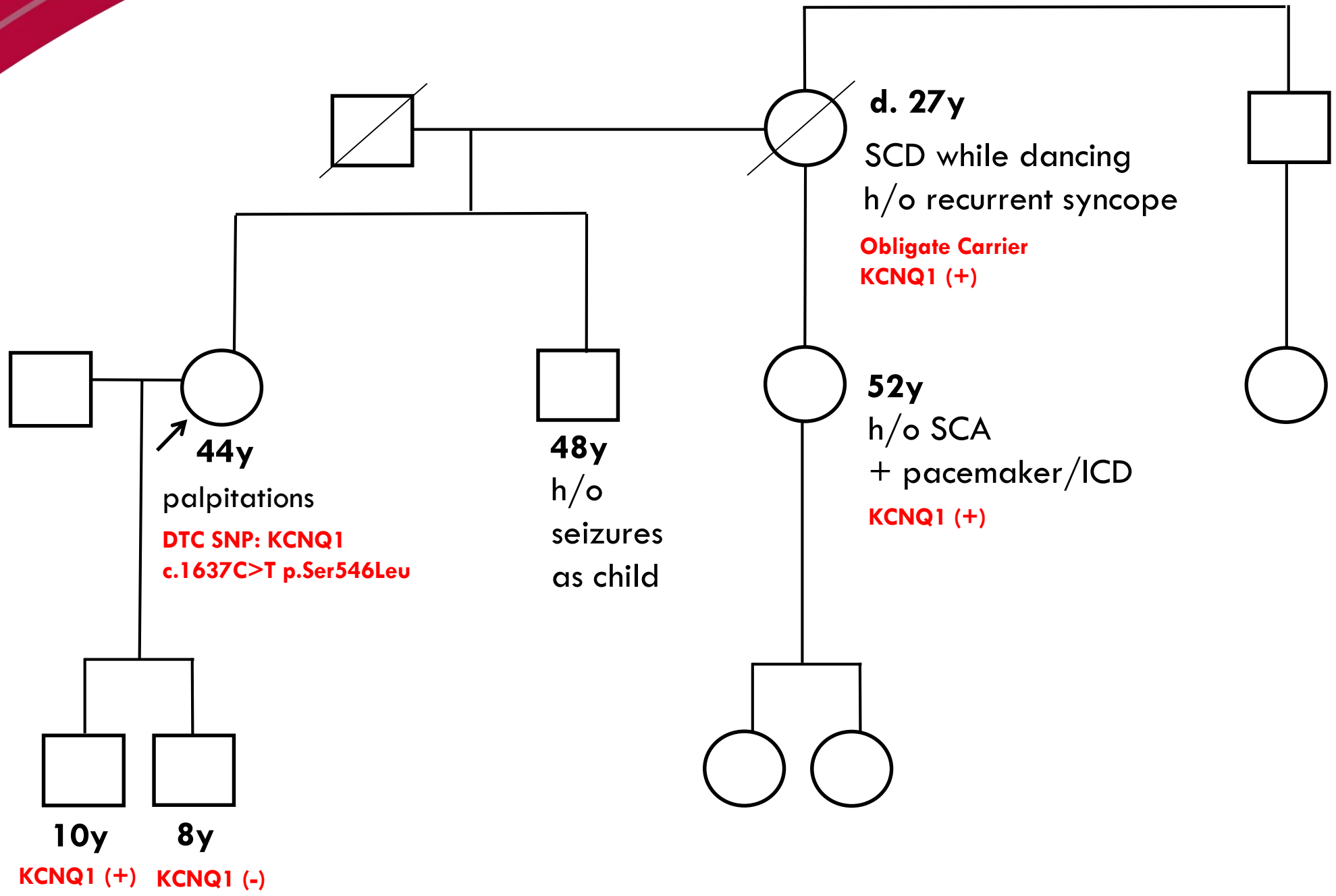
Figure 1 False-positive variants in clinically actionable genes. The pie chart on the left indicates of the variants analyzed, 60% were confirmed and 40% were false positives. The pie chart on the right shows which genes were involved with the false-positive cases and how often those false calls were detected in this study.

Gene	Variant	DTC/third party[a]	Ambry[b]	ClinVar[c]	ESP[d]	1000 Genomes[e]	dbSNP[f]
ATM	p.M1040V (c.3118A > G)	Increased risk	Benign	Benign	1.36%	0.95%	1.48%
BRCA1	p.Q356R (c.1067A > G)	Increased risk	Benign	Benign	4.59%	2.81%	3.97%
BRCA2	p.N372H (c.1114A > C)	Increased risk	Benign	Benign	23.32%	24.26%	24.44%
COL3A1	p.A698T (c.2092G > A)	Increased risk	Benign	Benign	21.39%	21.16%	19.16%
COL5A1	c.655-8689C > T	Increased risk	Deep intronic—benign	N/A	N/A	N/A	N/A
COL5A1	c.654+2749A > G	Increased risk	Deep intronic—benign	N/A	N/A	N/A	N/A
COL5A1	c.1827+399C > T	Increased risk	Deep intronic—VUS	N/A	N/A	N/A	N/A
COL5A1	c.1827+1142T > C	Increased risk	Deep intronic—benign	N/A	N/A	N/A	N/A

DTC, direct to consumer; N/A, not available; VUS, variant of unknown significance.
aVariant classification provided by the DTC company or a third-party interpretation service. bVariant classification provided by Ambry. cVariant classification provided in ClinVar (clinical laboratory submissions only). dExome Sequencing Project population frequency database. e1000 Genomes population frequency database. fdbSNP population frequency database.

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


d. 27y
SCD while dancing
h/o recurrent syncope
Obligate Carrier
KCNQ1 (+)
52y
h/o SCA
+ pacemaker/ICD
KCNQ1 (+)
44y
palpitations
DTC SNP: KCNQ1
c.1637C>T p.Ser546Leu
48y
h/o
seizures
as child
10y
KCNQ1 (+)
8y
KCNQ1 (-)

And it causes trouble…

COMMENT | Genetics inMedicine

Open

Direct-to-consumer raw genetic data and third-party interpretation services: more burden than bargain?

Tia Moscarello, MS[1], Brittney Murray, MS[2], Chloe M. Reuter, MS[1] and Erin Demo, MS[3]

Genetics in Medicine (2018) https://doi.org/10.1038/s41436-018-0097-2

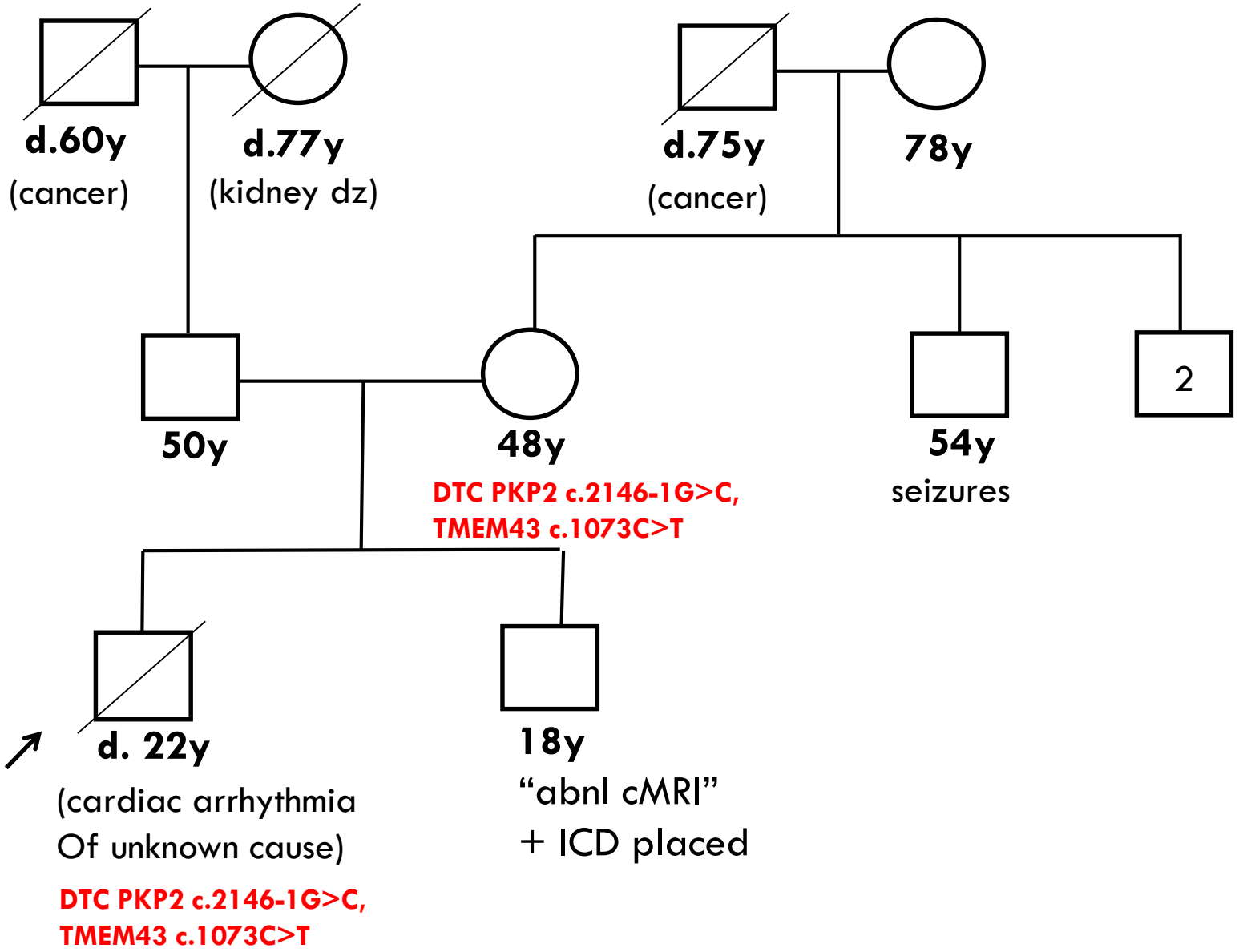
- Healthy 22-year-old male self-referred to an HCM clinic after his raw data from DTC testing; processing thru TPI tools revealed a SNP
  - *MYBPC3* p.Asp770Asn
  - Significant anxiety about result: took medical leave from PhD program "to focus on [my] HCM and risk of sudden death", was avid cyclist 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…

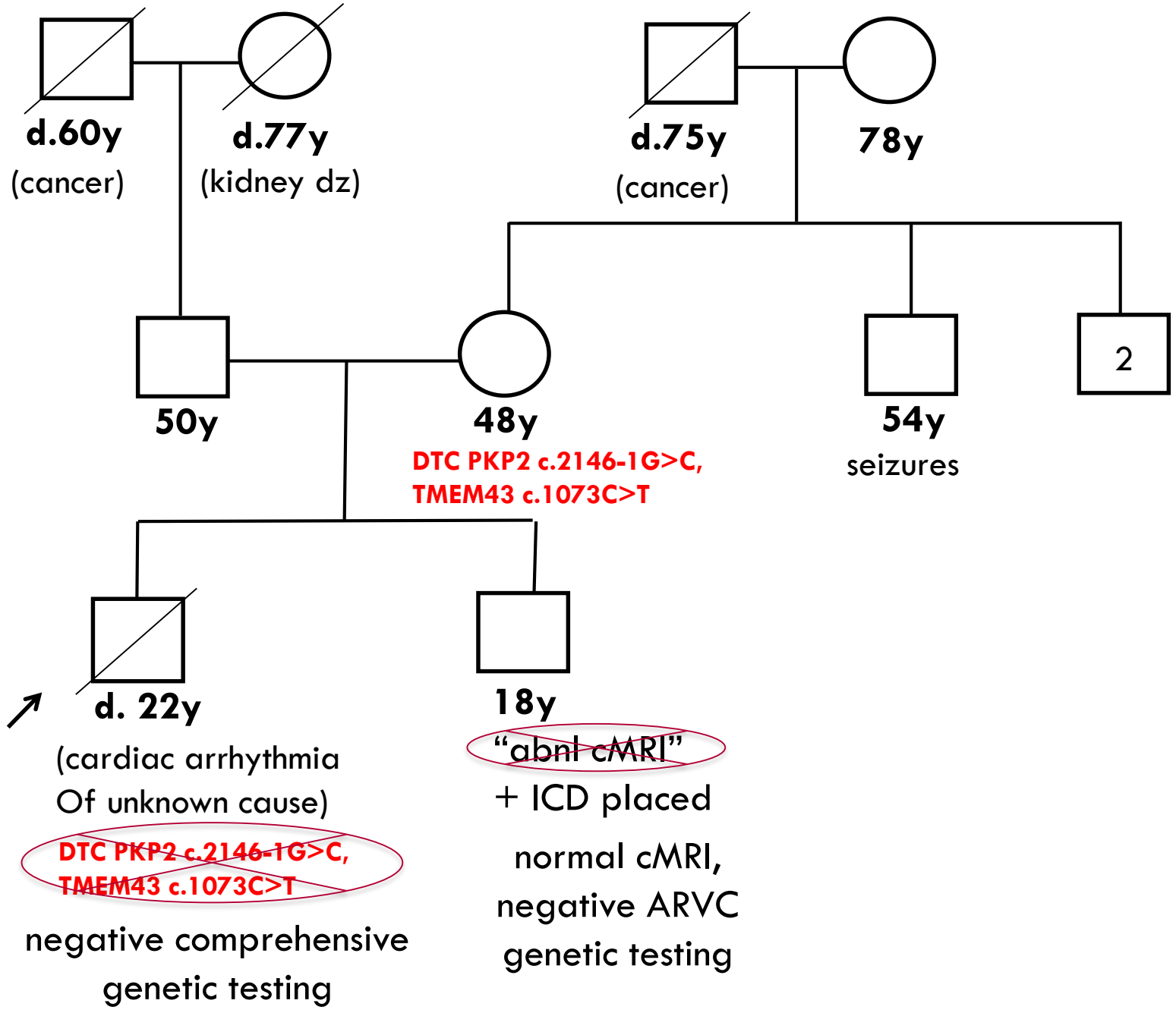
- 22-year-old male died suddenly, “cardiac arrhythmia of unknown cause”
- DTC genetic testing completed
- “If you click the tools to see Raw Data, I found the below information that was the same for me and my deceased son.”
  - *TMEM43* rs63750743-look at Clinical Significance-Pathogenic Allele-ARVC
  - *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.60y
(cancer)
d.77y
(kidney dz)
d.75y
(cancer)
78y
50y
48y
DTC PKP2 c.2146-1G>C,
TMEM43 c.1073C>T
54y
seizures
2
d. 22y
(cardiac arrhythmia
Of unknown cause)
DTC PKP2 c.2146-1G>C,
TMEM43 c.1073C>T
18y
"abnl cMRI"
+ ICD placed

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
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48y
DTC PKP2 c.2146-1G>C,
TMEM43 c.1073C>T
54y
seizures
2
d. 22y
(cardiac arrhythmia
Of unknown cause)
DTC PKP2 c.2146-1G>C,
TMEM43 c.1073C>T
negative comprehensive
genetic testing
18y
"abnl cMRI"
+ ICD placed
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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