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MEDCAN

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Proactive genetic testing in a primary care setting reveals unexpected results

Medcan Genetics Team
Presented by: Jason Abrams, Associate Medical Director

Medcan Genetics

- Established in 2005
- First clinic in North America to incorporate comprehensive genetic screening into primary care/preventative medicine
- Aims to be preventative, integrative, and innovative
- Currently employs 3 full-time and 2 casual board-certified genetic counsellors and a consulting Medical Geneticist
- All genetics appointments include a pre- and post-test consultation with a genetic counsellor

Proactive Genetic Screening

- Invitae's genetic health screen panel
- 139 genes (including 57 hereditary cancer genes, 75 hereditary cardiac genes) derived from ACMG59
- Designed for **healthy** populations
- Only pathogenic/likely pathogenic variants reported
- Physician-ordered only
- First Medcan sample received by Invitae on September 18th, 2017

Results

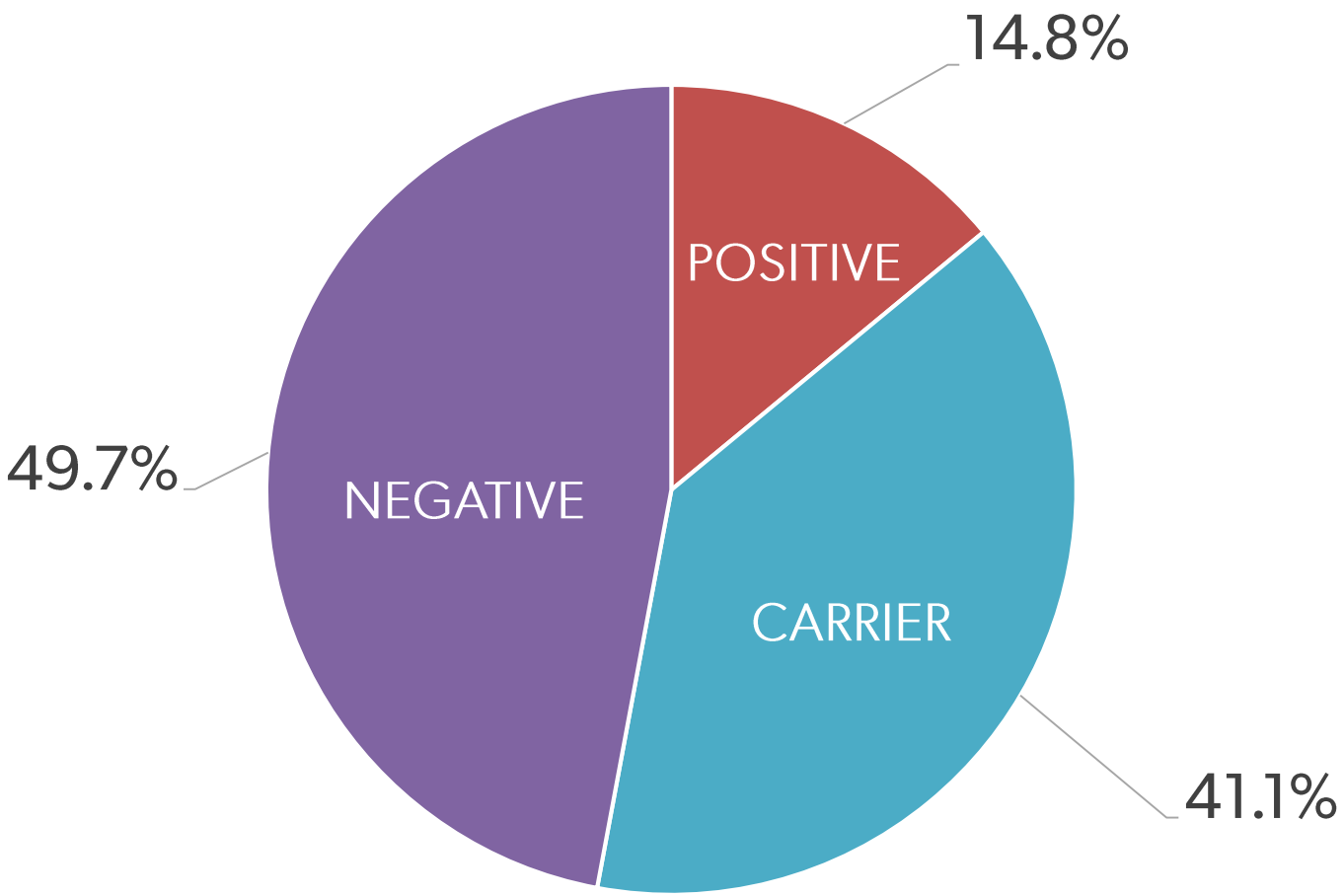
Results (n=1000)

DEMOGRAPHIC INFORMATION	
Gender	**n (%)**
Male	525 (52.5)
Female	475 (47.5)
Age range (y)	**Average age (y)**
21 to 81	50.5
Self-reported ethnicity	**n (%)**
Ashkenazi Jewish	46 (4.6)
Asian (East, South, Middle East)	87 (8.7)
Black/Caribbean	7 (0.7)
[redacted]	783 (78.3)
Mixed/Other	75 (7.5)

Results (n=1000)

>1/7

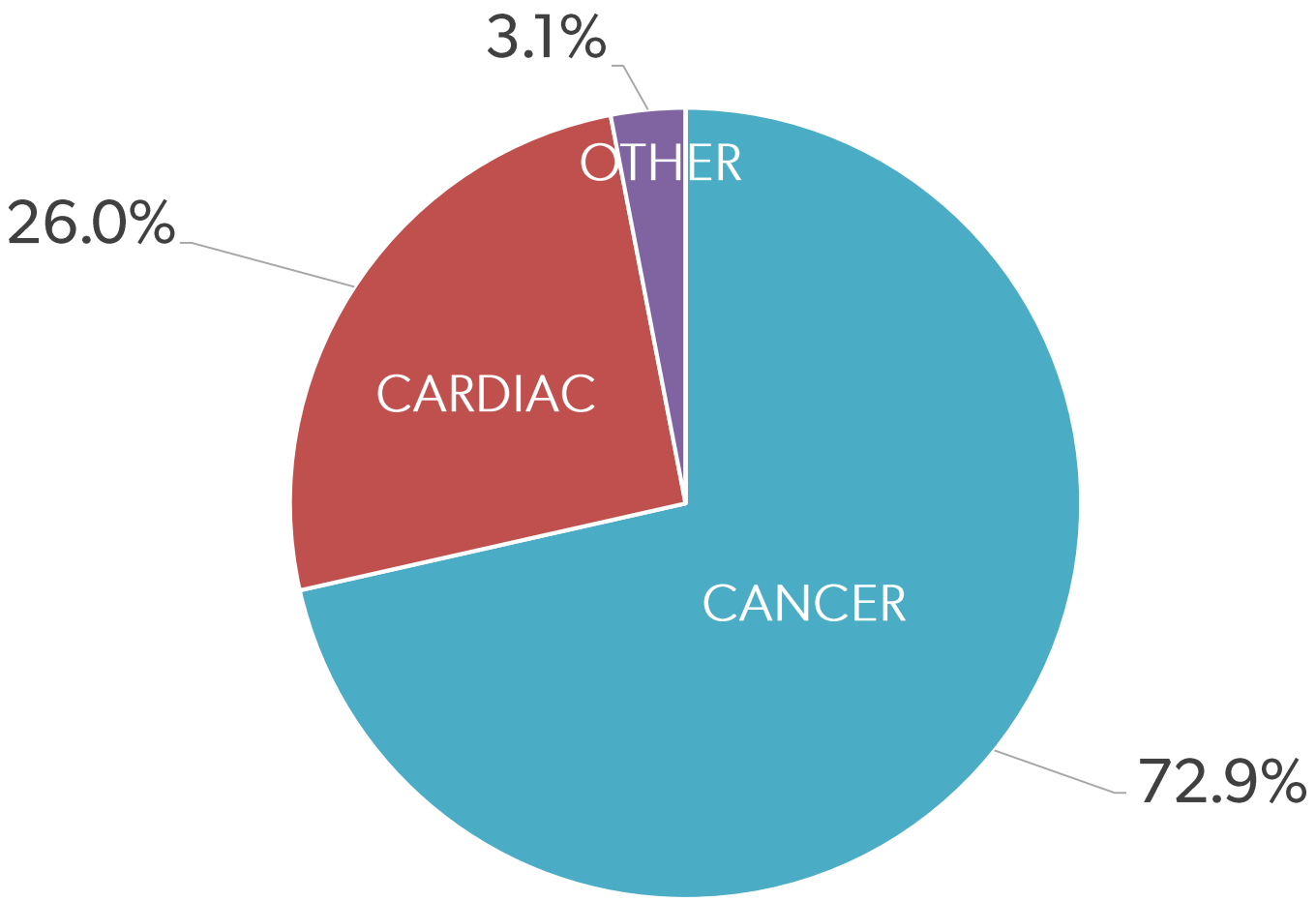
Positive Result



[redacted]

81%

resulted in a Change in Screening



Results by Clinical Area

CANCER (n = 73)	CARDIAC (n = 25)	OTHER (n = 5)
APC I1307K (7) ATM (8) BARD1 BRCA1 (4) BRCA2 (2) BRIP1 CHEK2 (17) FH HOXB13 (2) MITF (3) MSH6 (3) MUTYH (13) NBN (3) PALB2 PMS2 RAD51C (5) RET SDHA	APOB DSG2 DSP (3) KCNQ1 LDLR (3) MYBPC3 (4) MYH7 (4) MYL3 PCSK9 PKP2 (2) PROC PROS1 SCN5A SERPINC1	RYR1 (3)
Number (%) with relevant family history		
27 (37.0%)	7 (28.0%)	1 (33.3%)
Total: 35 (33.9%)		

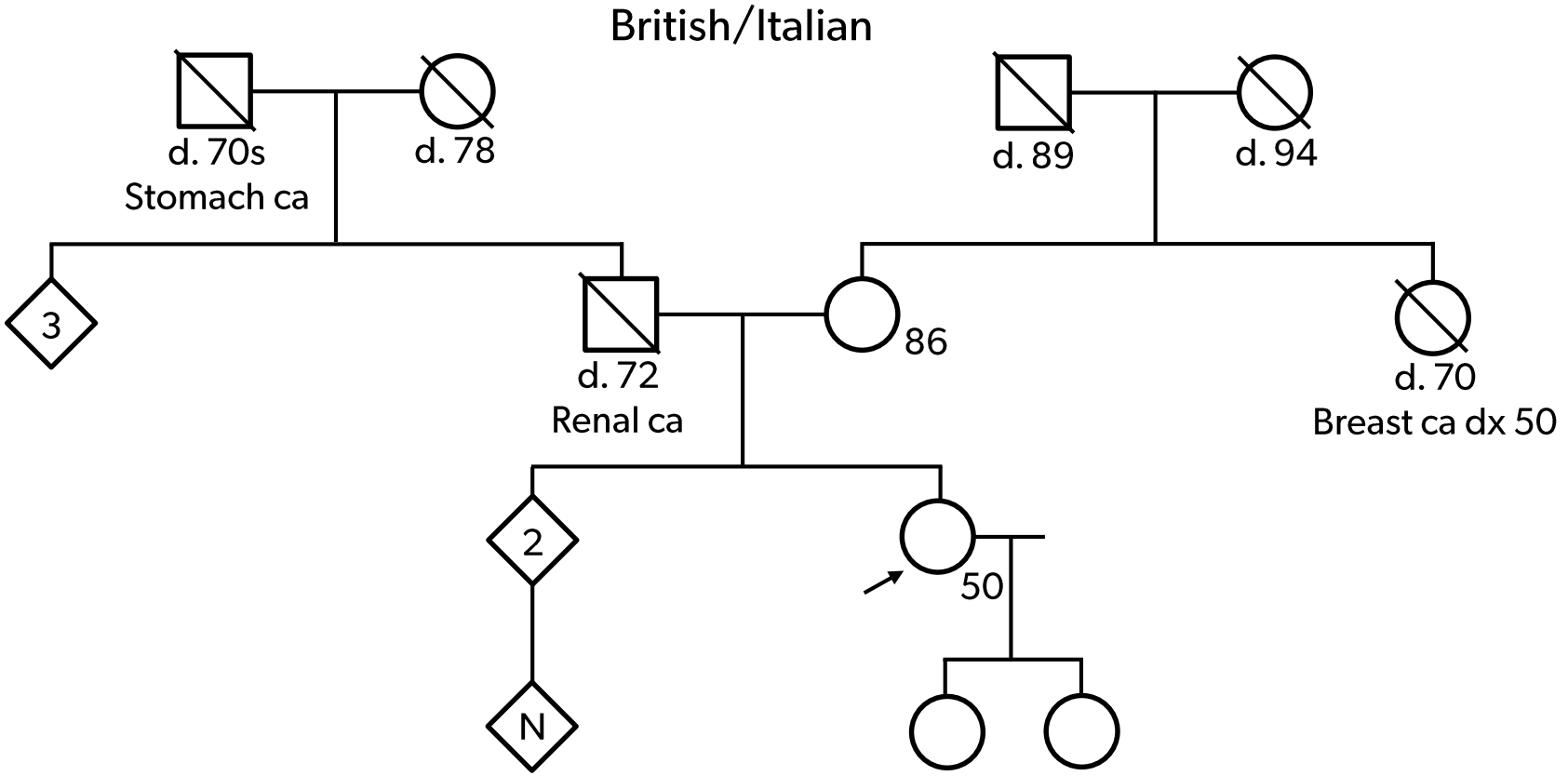
Results by Clinical Area

CANCER (n = 73)	CARDIAC (n = 25)	OTHER (n = 5)
APC I1307K (7) ATM (8) BARD1 **BRCA1 (4)** **BRCA2 (2)** BRIP1 CHEK2 (17) FH HOXB13 (2) MITF (3) **MSH6 (3)** MUTYH (13) NBN (3) PALB2 **PMS2** RAD51C (5) **RET** **SDHA**	**APOB** **DSG2** **DSP (3)** **KCNQ1** **LDLR (3)** **MYBPC3 (4)** **MYH7 (4)** **MYL3** **PCSK9** **PKP2 (2)** PROC PROS1 **SCN5A** SERPINC1	**RYR1 (3)**
Number (%) identified according to ACMG59[1]		
19 (26.0%)	22 (88.0%)	3 (100.0%)
Total: 44 (42.7%)		

[1]Kalia SS et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. *Genet Med.* 2017; 19(2):249-255.

Case Examples

Proactive Genetic Screening Case 1



Proactive Genetic Screening Case 1

Summary

A clinically significant genetic change was found in the PALB2 gene, which is associated with hereditary cancer. CARRIER RESULT: Single clinically significant genetic changes were found in the HFE and SERPINA1 genes, which is associated with being a carrier for two different hereditary conditions.

↓

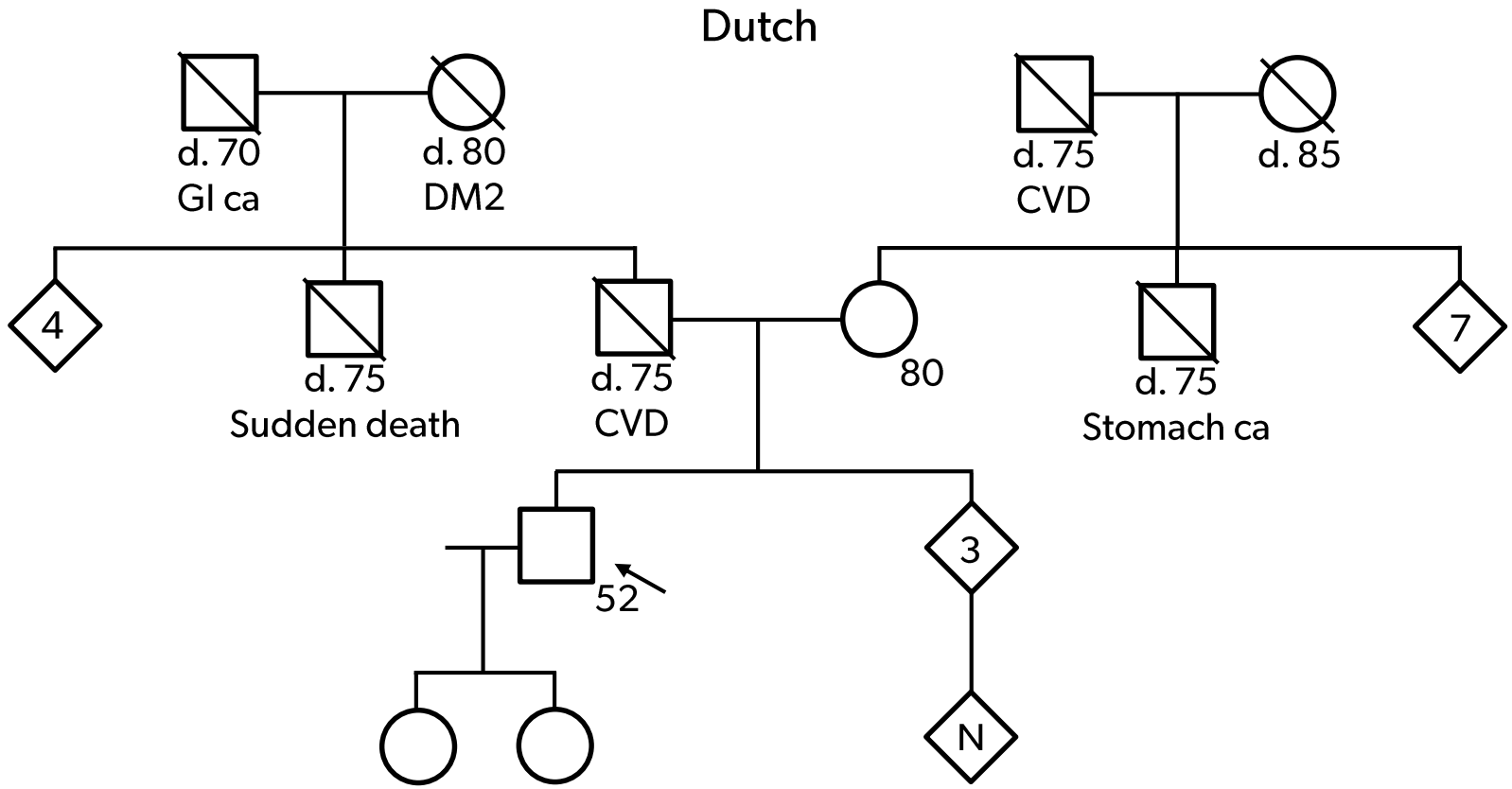
Increased risk for breast cancer (33 to 58% risk by age 70[2])
Elevated risk for pancreatic cancer
Carrier status for Fanconi anemia type N

↓

NCCN recommends annual mammography & consideration of annual breast MRI[2]

[2]Daly MB et al. Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 1.2008. NCCN Clinical Practice Guidelines in Oncology. 3 Oct 2017.

Proactive Genetic Screening Case 2



Proactive Genetic Screening Case 2

Summary
A clinically significant genetic change was found in the DSP gene, which is associated with a heart-related condition.

↓

Increased risk for arrhythmogenic or dilated cardiomyopathy
Carrier status for Carvajal syndrome

↓

Stress test included in Medcan's health assessment
Echocardiogram, 48h Holter, cardiac MRI
Regular cardiac screening with inherited cardiomyopathy specialist

Proactive Genetic Screening Case 2

Summary
A clinically significant genetic change was found in the DSP gene, which is associated with a heart-related condition.

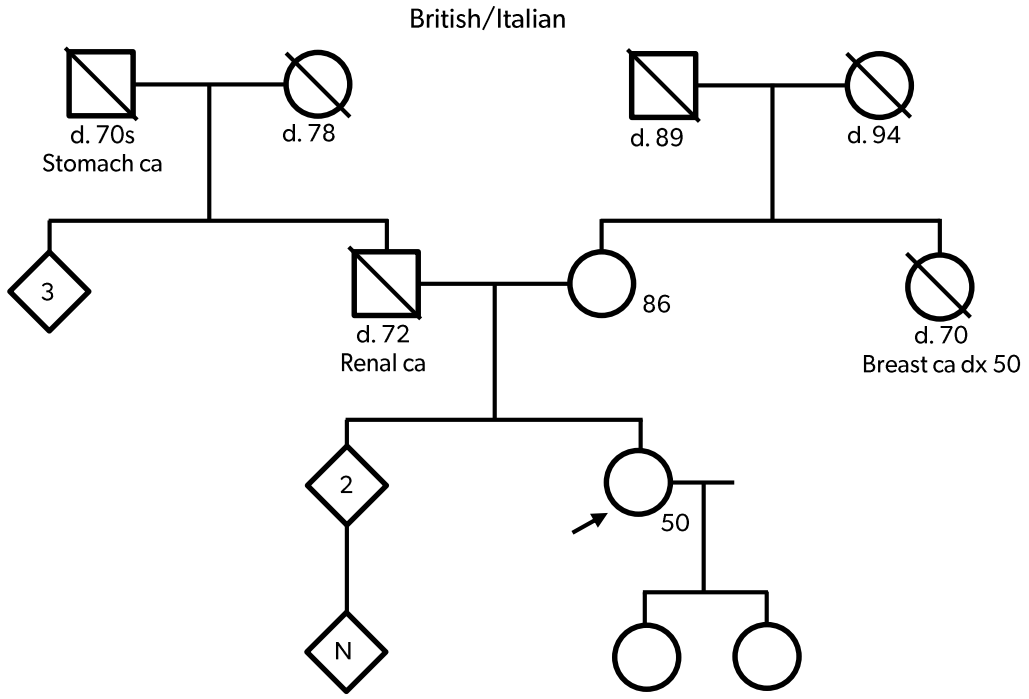
↓

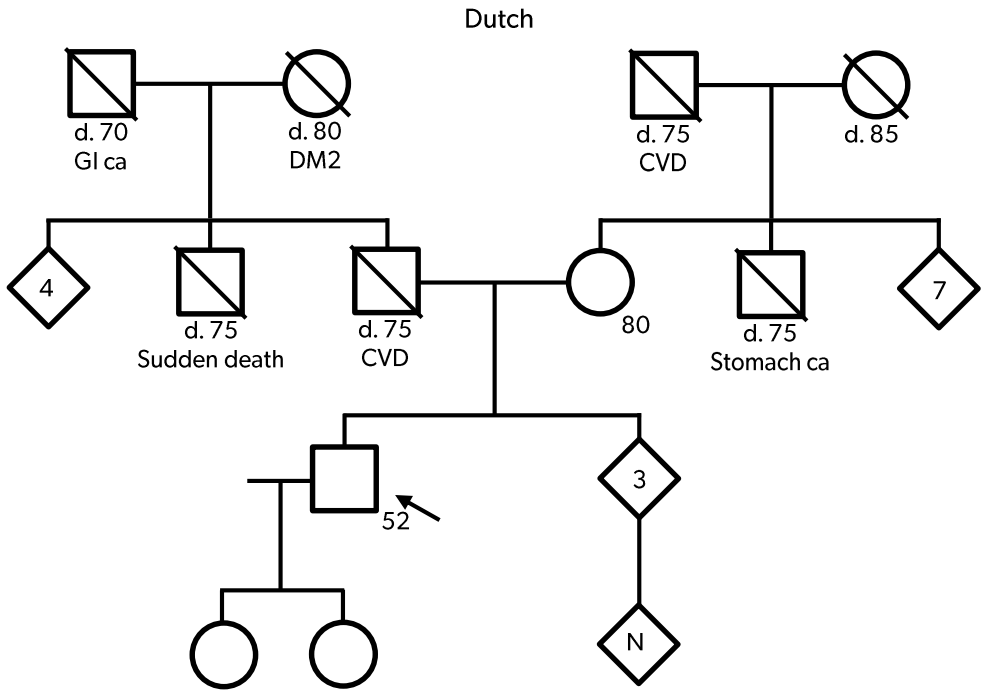
Increased risk for arrhythmogenic or dilated cardiomyopathy
Carrier status for Carvajal syndrome

↓

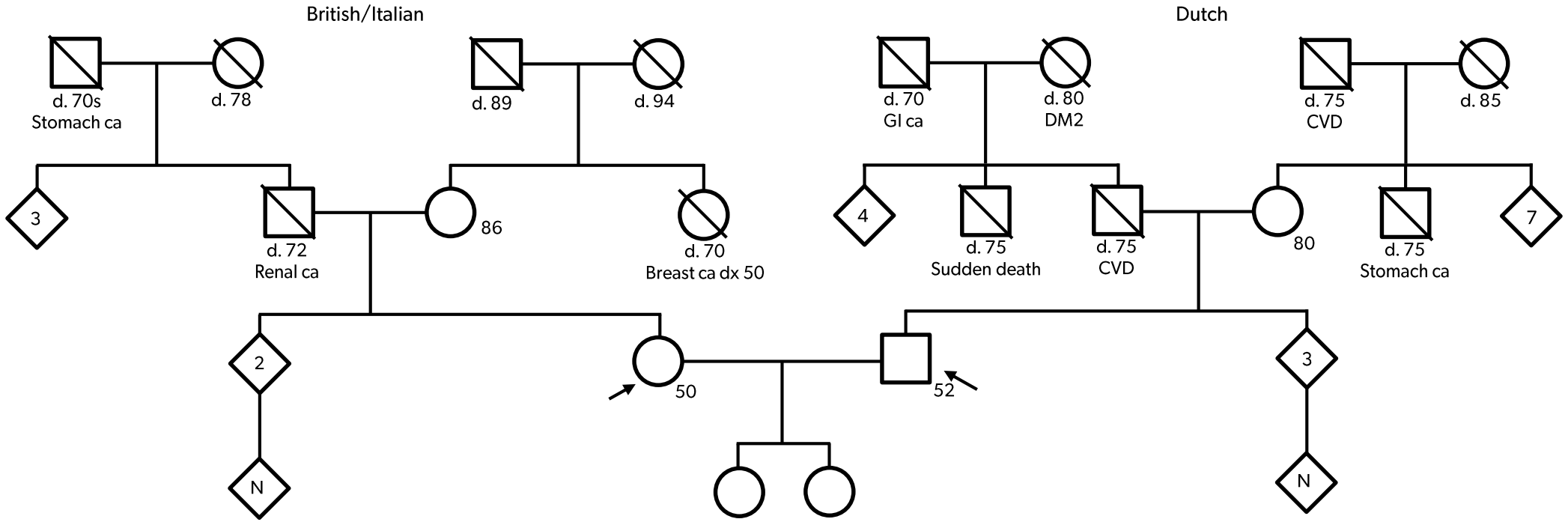
Stress test -- **frequent PVCs**
Echocardiogram -- **severely dilated right atrium**, 48h Holter, cardiac MRI
Regular cardiac screening with inherited cardiomyopathy specialist

Proactive Genetic Screening Cases 1 & 2





Proactive Genetic Screening Cases 1 & 2



Discussion

Next Steps

- Redefining "rare": updated prevalence and long-term penetrance data
  - Unexplained hypertrophic cardiomyopathy:
    1 in 500 (0.2%) in literature[4], 9 in 1000 (0.9%) in our cohort
  - BRCA1/2 (excluding Ashkenazim):
    1 in 400 (0.25%) in literature[3], 5 in 954 (0.53%) in our cohort
- Potential changes to eligibility criteria for funded genetic testing
  - 7 of 101 positives (6.9%) would have qualified based on personal/family history
- September 12th, 2018: addition of 8 genes to the panel (ATP7B, AXIN2, FLNC, GDF2, MSH3, NF1, NTHL1, OTC)

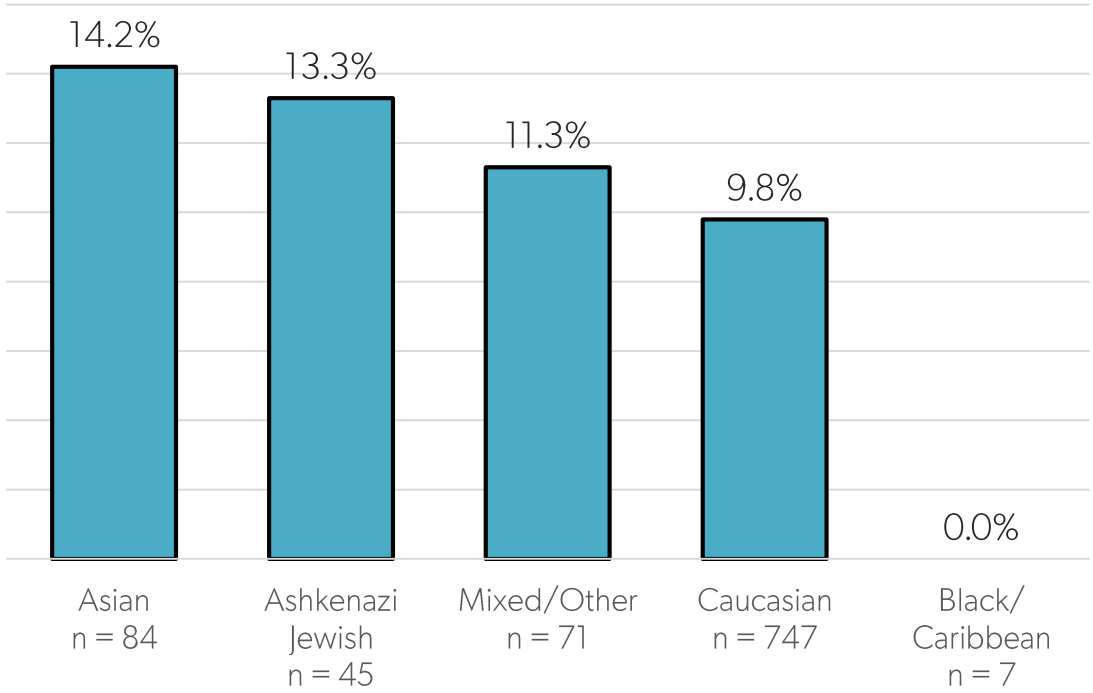
[3]Petrucelli N et al. *BRCA1*- and *BRCA2*-Associated Hereditary Breast and Ovarian Cancer. GeneReviews®. 15 Dec 2016. https://www.ncbi.nlm.nih.gov/books/NBK1247/
[4]Cirino AL et al. Hypertrophic Cardiomyopathy Overview. GeneReviews®. 16 Jan 2014. https://www.ncbi.nlm.nih.gov/books/NBK1768/

Challenges

- Available risk estimates from studies on high-risk families
- "Screening apathy"
  - Two women identified with pathogenic MSH6 variants:
    i. One diagnosed with colonic adenocarcinoma soon after, keen to follow all management recommendations
    ii. One disappointed in increased colonoscopy frequency
- Integration into the public health care system, cascade testing, and downstream costs
- Variant reclassification
  - Four likely pathogenic variants reclassified as VUS (negative): ATM, COL3A1, FH , MYH7

Limitations

- Positive rates by ethnicity:



- Unrepresentative cohort
- Other medically actionable genes

Acknowledgements

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Thank you! Questions?

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