Pathogenic variants in new colorectal cancer/polyposis genes rarely identified among patients with colorectal, breast, prostate, and pancreatic cancer

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InSiGHT Meeting

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Disclosure:

Invitae Advisory Board

Introduction

- Several new genes have been associated with hereditary colorectal cancer/polyposis syndromes
  - *GALNT12*, *GREM1*, *MSH3*, *NTHL1*, *POLD1*, *POLE*, and *RPS20*.
- Many of these genes have been discovered within high risk patients or families.
- Data are lacking about the prevalence of pathogenic/likely pathogenic variants (P/LPV).

Aim

- To describe the prevalence of P/LPV within *GALNT12*, *GREM1*, *MSH3*, *NTHL1*, *POLD1*, *POLE*, and *RPS20*.

Methods

- Data were queried from a commercial genetic testing company for patients with colorectal (CRC), breast (BC), prostate (PC), or pancreatic (PAC) cancer tested for these genes.
- The number of P/LPV were counted.
- Data also collected were ICD10 codes, personal/family history and P/LPV in other genes.

Results

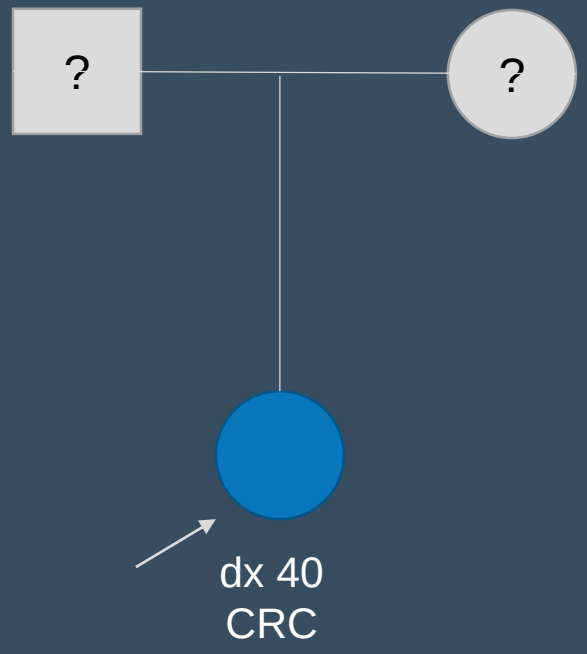
	CRC n/# testing	BC n/# testing	PC n/# testing	PAC n/# testing
GALNT12	0/2,323	0/3,931	0/341	0/480
***MSH3* biallelic**	0/3,086	0/19,655	0/1,713	0/1,046
RPS20	0/641	0/647	0/87	0/109

Results

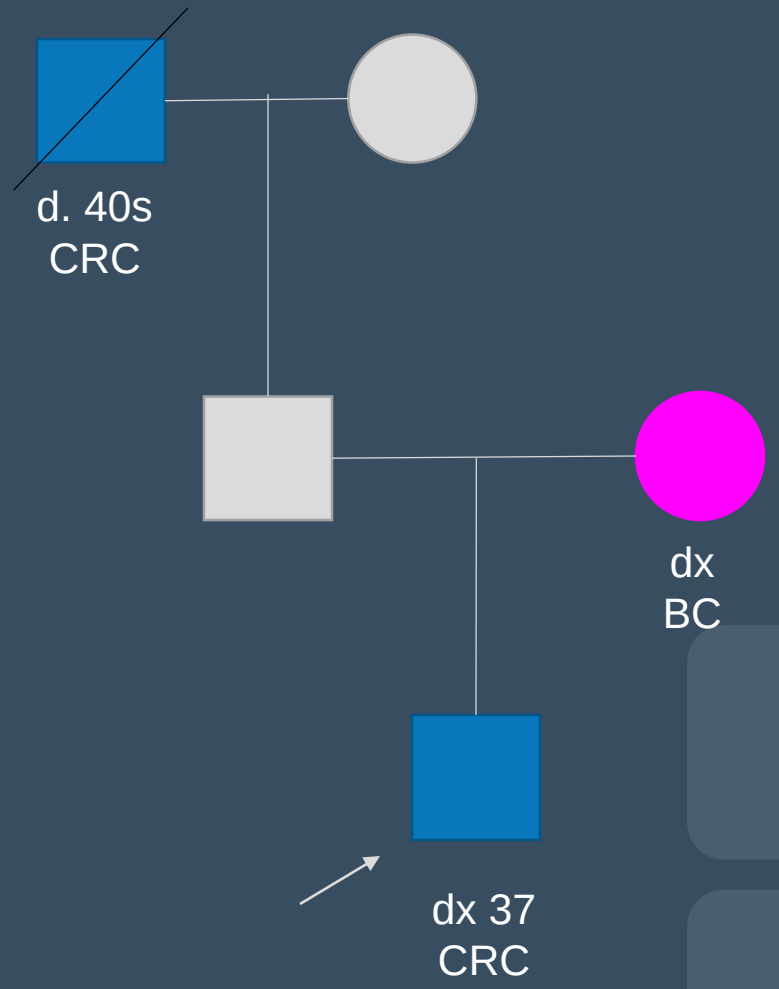
	CRC n/# testing (%)	BC n/# testing (%)	PC n/# testing (%)	PAC n/# testing (%)
GREM1	2/9,405 (0.02)	0/58,112	0/4,421	0/480
***MSH3* monoallelic**	6/3,086 (0.19)	22/19,655 (0.11)	4/1,713 (0.23)	4/1,046 (0.38)
NTHL1 **Monoallelic** **Biallelic**	 7/3,089 (0.23) 1/3,089 (0.03)	 74/19,647 (0.38) 2/19,647 (0.01)	 8/1,706 (0.47) 0/1,706	 5/1,045 (0.48) 0/1,045
POLD1	1/9,552 (0.01)	0/62,675	0/4,554	0/3,240
POLE	1/9,530 (0.01)	0/58,644	0/4,509	0/3,182

GREM1 Patients' Histories

White/Caucasian



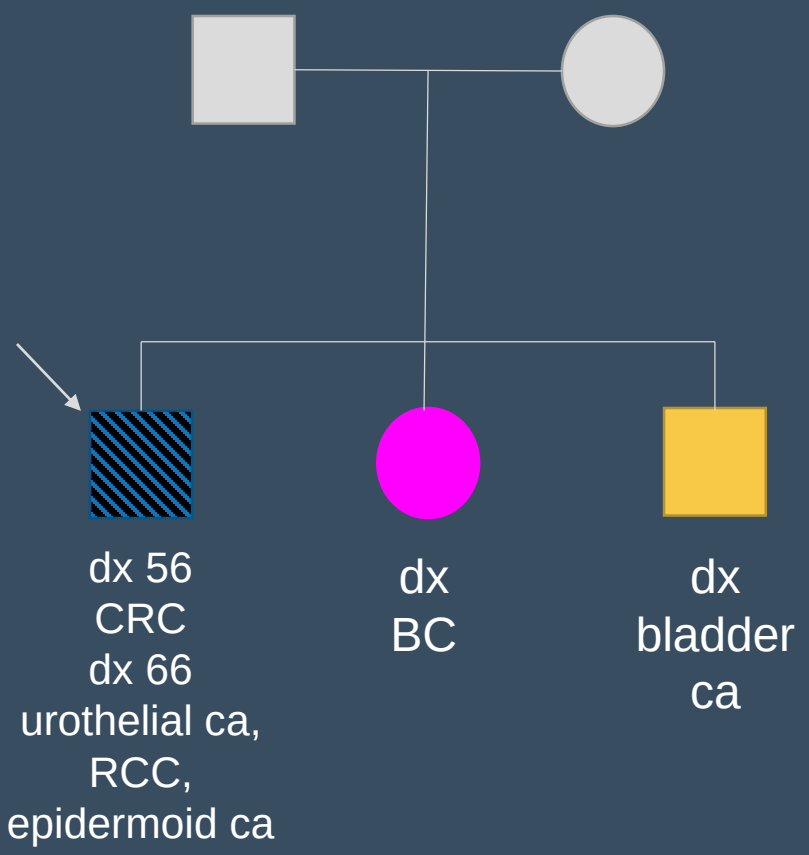
Ashkenazi Jewish



NTHL1 Patients' Histories

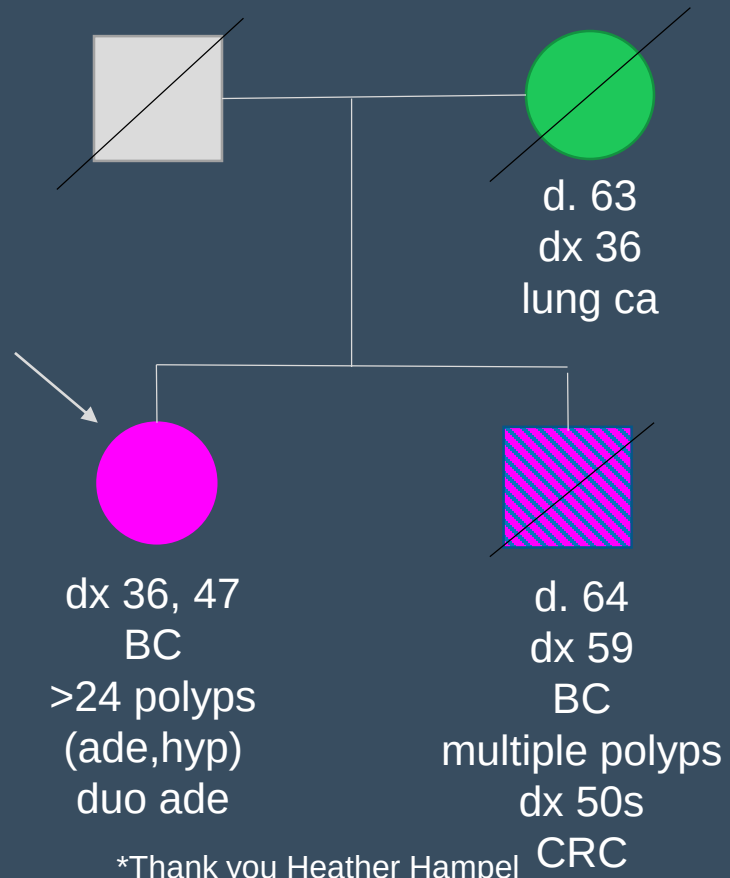
p.Gln90*/p.Gln90*

Syrian



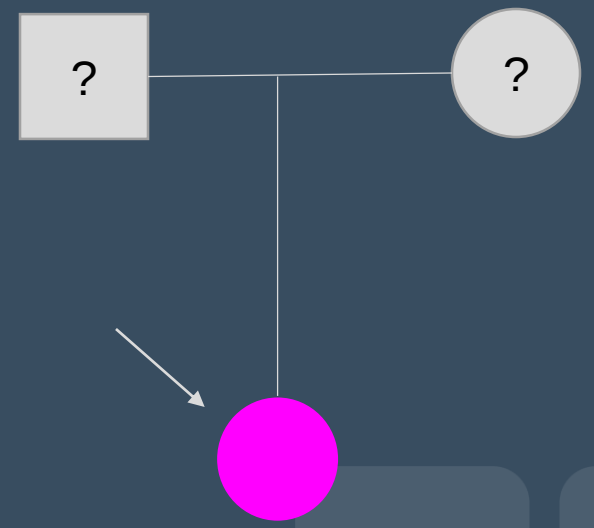
p.Gln90*/p.Ser139Glnfs*30

White/Caucasian



c.139+1G>A/c.139+1G>A
BRCA1 p.Arg1699Gln

White/Caucasian

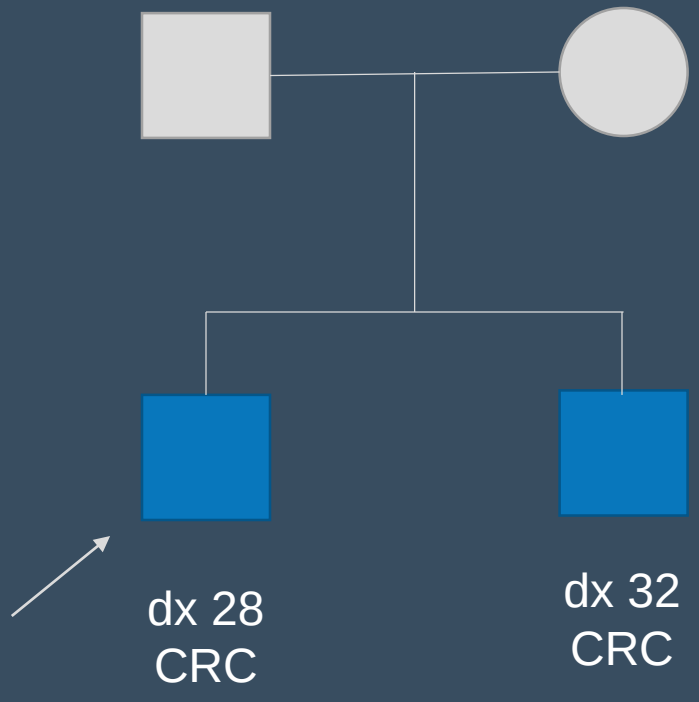


*Thank you Heather Hampel

POLE/POLD1 Patients' Histories

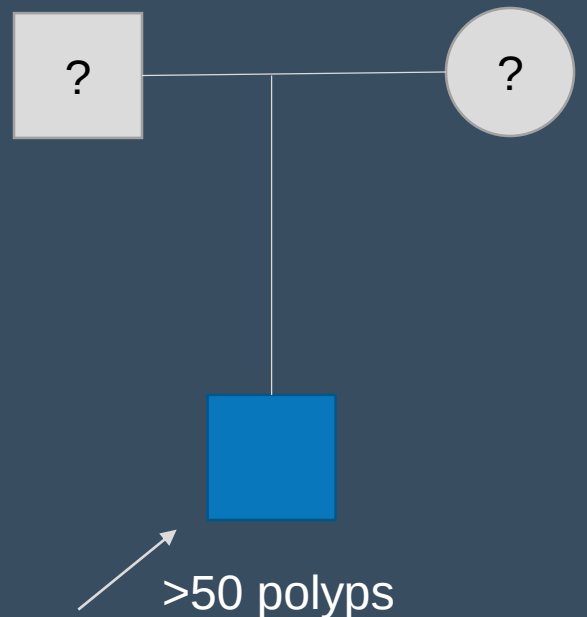
POLD1 p.Ser478Asn

Black/African American



POLE p.Leu424Val

White/Caucasian



Limitations

- Incomplete medical and family history data
- Fewer patients underwent *RPS20* and *GALNT12* testing

Conclusions

- At one commercial lab P/LPV in *GALNT12*, *GREM1*, *MSH3*, *NTHL1*, *POLD1*, *POLE*, and *RPS20* are rarely identified in CRC, BC, PC, and PAC patients.
- Patients with P/LPV had striking phenotypes.
- Despite the low detection rate, with the decreasing cost of next generation sequencing panels, we believe it remains important for these genes to be included on panels.

Cleveland Clinic

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