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Background

- Germline mutations in BRCA1/2 (gBRCAm) are associated with pancreatic ductal adenocarcinoma (PDAC) in up to 10% of cases¹
- Recently, gBRCAm have also been identified in patients with biliary tract cancers (BTC)²
- The POLO trial has demonstrated the benefit of Olaparib maintenance therapy in patients with Metastatic PDAC and a gBRCAm
- In light of this therapeutic actionability, the latest NCCN guidelines now recommend universal germline testing in PDAC
- However, the prevalence of BTC has not been quantified in gBRCAm families, and PDAC prevalence has not been assessed in Irish gBRCAm families
- We aimed to
 - To determine the prevalence of PDAC and BTC in Irish gBRCAm families
 - To compare the age and gender distribution of likely carriers to that of the unselected Irish population with PDAC

Methods

- A review of all families referred to a national genetics clinic from 09/11/1997-01/06/2018 was performed following ethics committee approval
- Demographics including such as age, sex and mutational status were collected by chart review.
- Death certificates were used to confirm the diagnosis of deceased family members
- The BOADICEA algorithm⁴ estimated the likelihood that an untested member with PDAC was a gBRCAm carrier based on age, personal and family history
- A one tailed T test was used to compare the mean age of diagnosis to data from the National Cancer Registry Ireland (NCRI) from the same time period

Results

- 3252 pedigrees were reviewed; 1193 were tested for BRCA1/2 based on Manchester Score ≥ 15 (Figure 1)
- Of the 3252 pedigrees, 296 (9%) probands had a first, second, or third degree relative (family history (FH)) with PDAC, and 44 (14%) with BTC
- Of 128 BRCA2 positive families, 27 (21%) had a FH of PDAC, and among 116 BRCA1 families, 11(9%) had a FH of PDAC (male : female ratio (m:f) = 1:0.9)

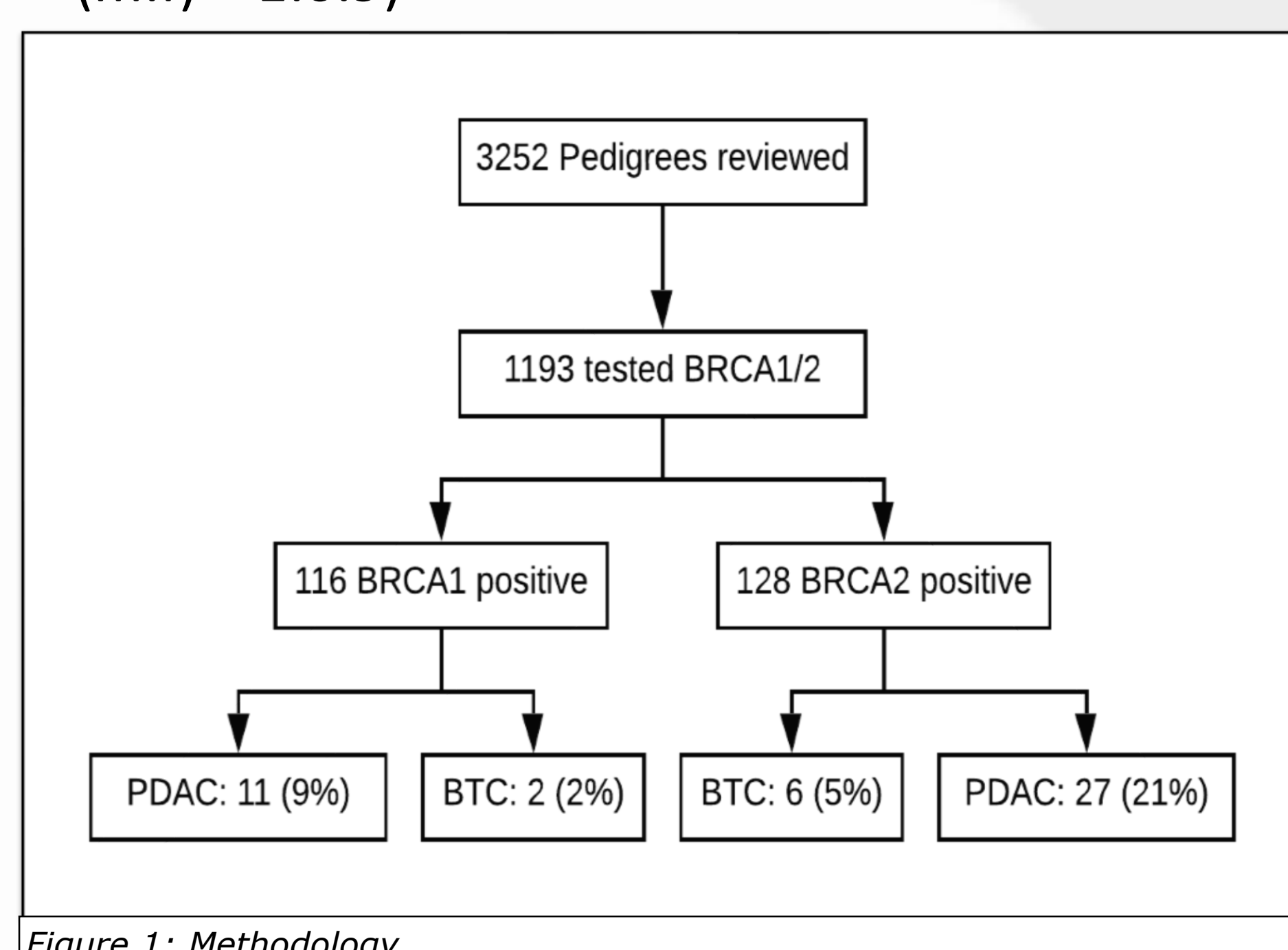


Figure 1: Methodology

- Of this 38 families, 25 untested cases of PDAC had >50% likelihood of being a mutation carrier, by BOADICEA criteria

Patient demographics	PDAC	BTC
Male	22	1
Female	16	7
Median age at diagnosis	55	65
Relationship to proband	N	N
First-degree relative	16	4
Second-degree relative	16	3
Third-degree relative	6	1
Carrier likelihood	%	%
Definite (>99%)	5	2
Very Probably (90-99%)	3	0
Probably (50-90%)	17	2
Improbable (<50%)	13	4
Germline mutation	N	N
BRCA1	11	2
BRCA2	27	6
ATM	2	-
MLH1	1	-
MSH2	1	-
PMS2	-	1
APC	1	-

Table 1: Patient demographics

- This cohort had a median age of diagnosis of 55 (33-75); and mean lower than of 8364 unselected patients with PDAC identified through NCRI (71, $p < 0.0001$)
- Eight BRCA1/2 positive probands had a FH of BTC; median age of diagnosis was 65 (33-99, m:f =1:7))
- There were heterogenous molecular aberrations in families with gBRCAm and PDAC/BTC (Table 1)

Gene	PDAC	N	BTC	N
BRCA1	Deletion exons 14-20	3	c.427G>T	1
	c.302.2delA	1	c.4065_4068delTCAA	1
	c.3718C>T	1		
	c.302.2delA	1		
	Deletion exon 3	1		
	Deletion exons 1-2	1		
	c.547+1C>G	1		
	c.2474delC	1		
	c.547+1G>T	1		
	BRCA2	c.7977-1G>C	2	c.9253dupA
c.4163_4164delinsA		2	c.5804_5807delTTAA	1
c.755_758_delACAG2		2	c.5576_5579delTTAA	1
c.6486_6489delACAA		2	c.3717delA	1
c.6275_6276delTT		1	c.1889delC	1
c.5073dupA		1		
c.2957dupA		1		
c.4276dupA		1		
c.8927delC		1		
c.956A>G		1		
c.8585dupT		1		
c.7601C>T		1		
c.2637T>G		1		
c.3717delA		1		
c.7680dupT		1		
c.4398_4402delACATT		1		
c.5684C>A, c.6092 C>A		1		
c.1456C>T		1		
c.8205-1G>C	1			
c.4866del	1			
c.8924C>G	1			

Table 2: BRCA mutations present in PDAC/BTC families

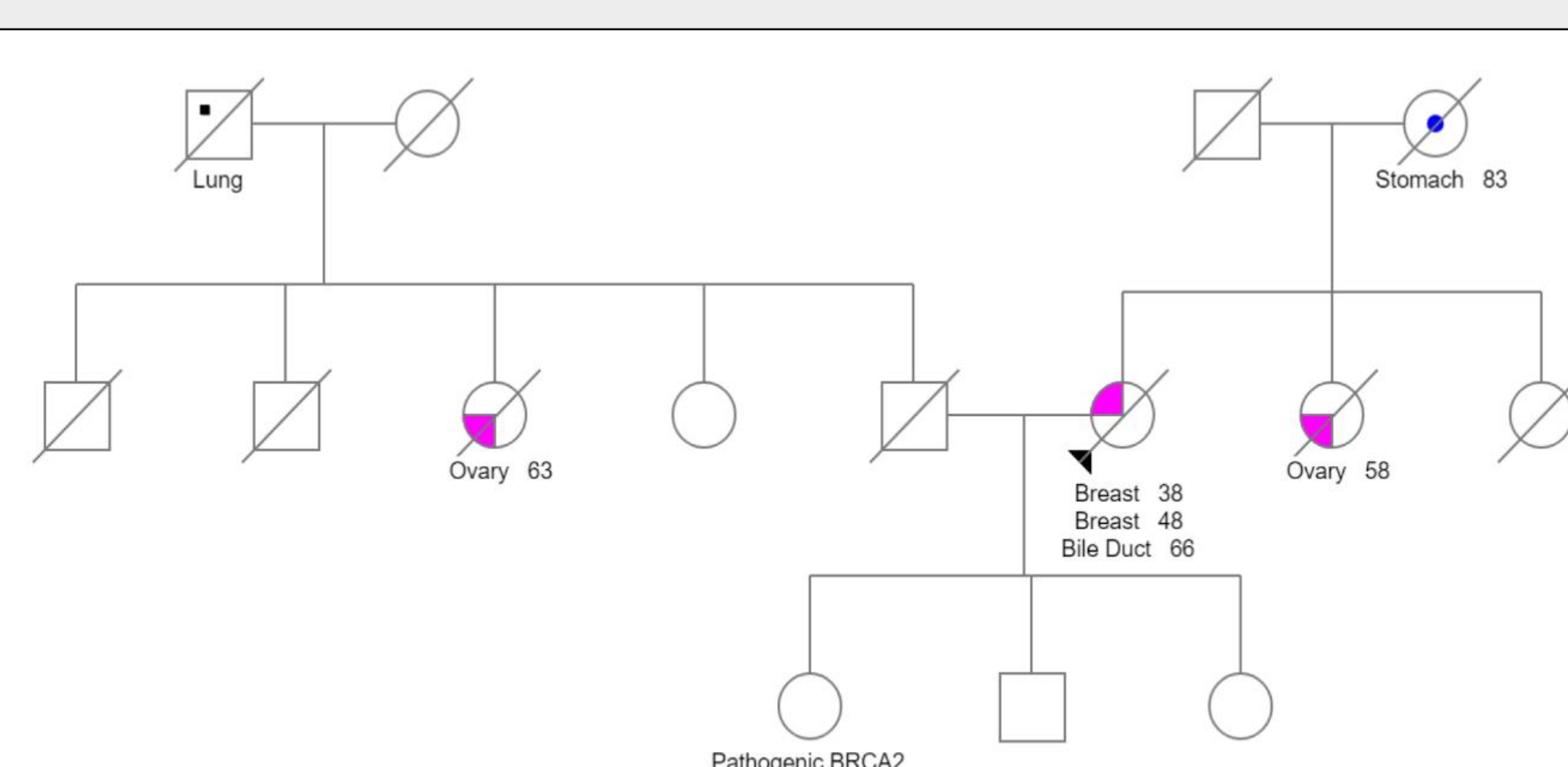


Figure 2: BRCA2 family pedigree with a strong history of BTC and other BRCA associated cancers

- Figure 3 depicts a four-generation pedigree with 3 cases of PDAC and 2 cases of breast cancer in a single lineage
- This pedigree is an example of early onset pancreatic cancer (55) in a likely carrier as well as the phenomenon of 'competing mortality' of breast and ovarian cancer in female relatives

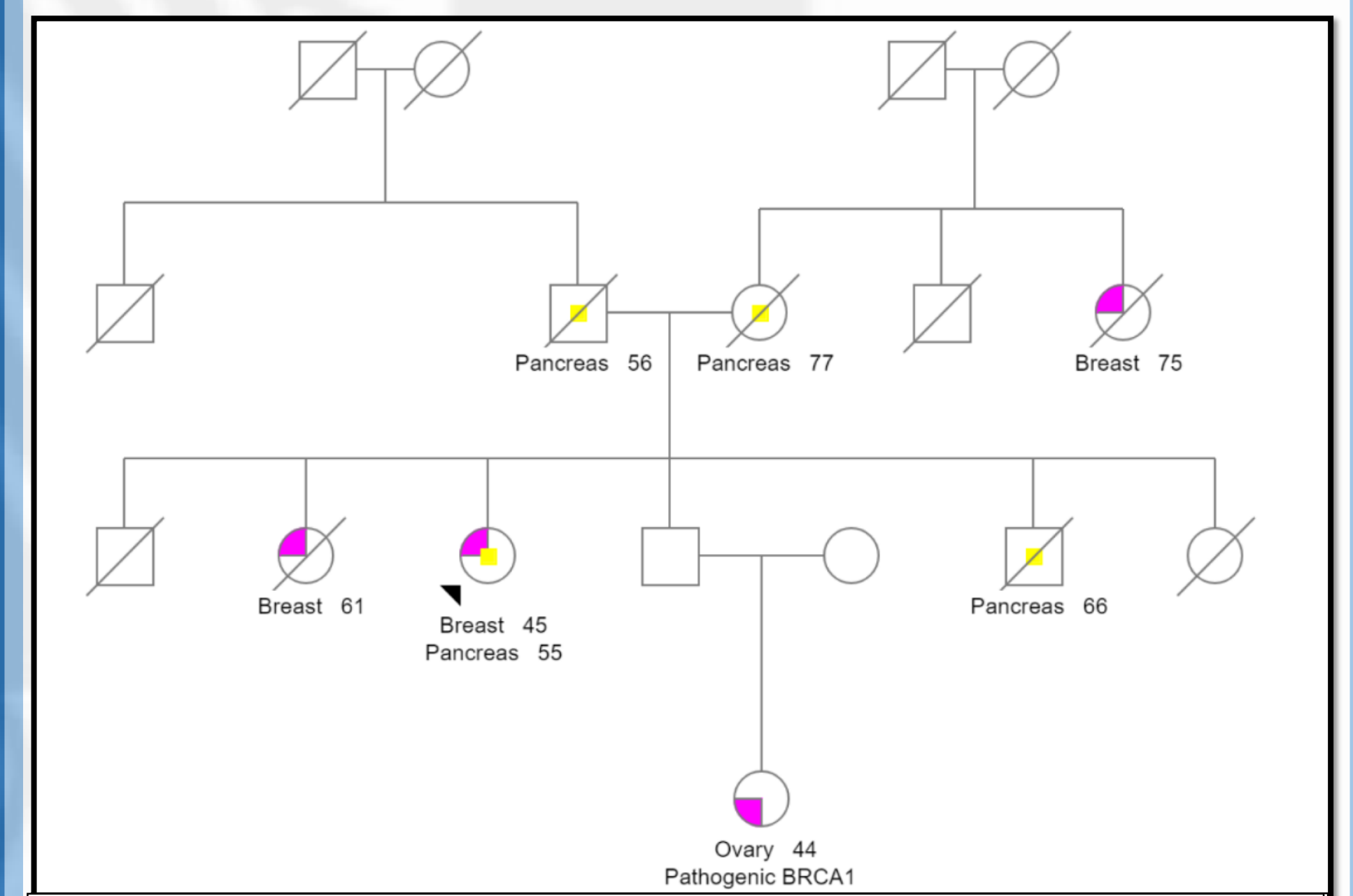


Figure 3: BRCA2 family pedigree with a strong history of BTC and other BRCA associated cancers

- Other mutations in PDAC/BTC families included ATM, Lynch syndrome and FAP (Figure 4)

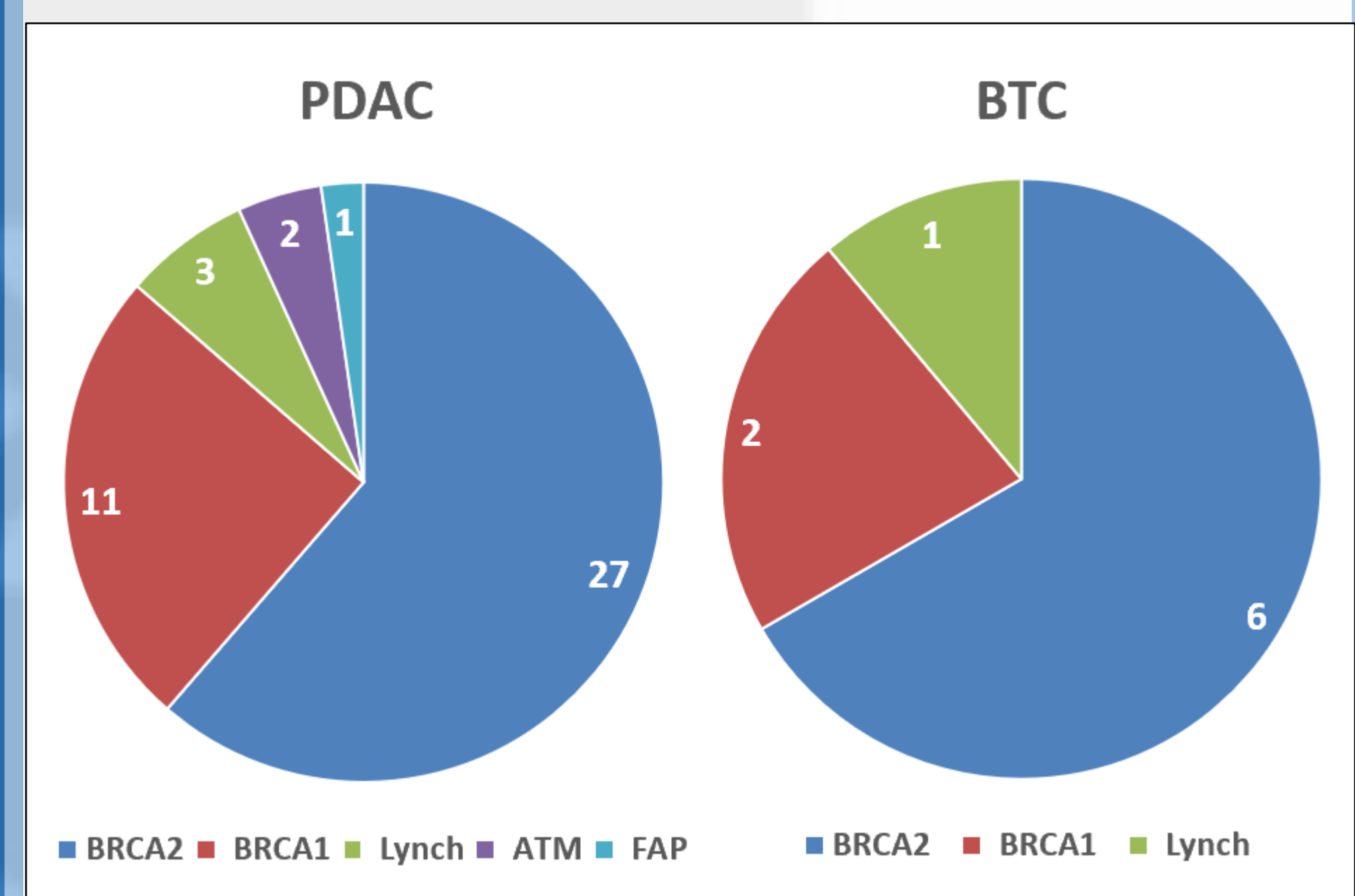


Figure 4: BRCA2 family pedigree with a strong history of BTC and other BRCA associated cancers

Conclusion

- PDAC and BTC are prevalent in Irish families with a gBRCAm but rarely undergo germline genetic testing
- Likely BRCA carriers with PDAC or BTC have early onset malignancy
- This supports current guidelines advising universal germline testing in PDAC patients

References

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