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Genomic Testing in Oncology

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Two Contexts:

- Cancer Genetics Clinic – all germline
- Michigan Oncology Sequencing Project – tumor/germline dyads

The Breadth of Cancer Genetic Testing in Clinical Practice

Conditions	Genes	Labs	Comprehensive Tests
21	31	15	**3796**

2820 New Patients
2002 – 2011

Why Use a Large Scale Approach?

- Cost – individually testing genes now available on panels >$25,000
- Time for results – as compared to step-wise testing approach
- Additional clinically useful information could be gained (e.g. families with more than one mutation, mosaicism)
- Occasional “diagnostic odyssey” patients, even in Cancer Genetics!

Benefits of NGS/Panels in Cancer

- Expanding knowledge about phenotypic spectrum
- Potential to gain new information to better understand clinical utility of lower penetrance or less studied genes
- Generating data of research and/or academic interest without added cost

Limitations of NGS/Panels in Cancer

- Identifying mutations where clinical utility is still unclear complicates risk assessment and clinical recommendations
- What exactly is the phenotype and who gets an “official diagnosis”?
- Generating data of research and/or academic interest on an individually small scale…need better ways to share for this to be useful

Genomics in Oncology Care

- Tumor genome testing for understanding tumor biology, identifying targets for therapy

- “Genonemic? Genomic? No, I have no idea what it all means. No idea, really. Research maybe? It’s about the genome?”

Pellegrini et al; European Journal of Cancer Care 2012 (21):242-250

Semantic Confusion in Somatic Testing

- 20/37 had some knowledge/understanding of genomic testing
- Among these, 10/20 thought it referred to or included constitutional/germline analysis
- “Although nobody told me this specifically, I thought the specimen might be used to find out whether or not there was risk of transmission to my children…”

Conclusion: “More attention should be paid to information issues in this field”

Pellegrini et al; European Journal of Cancer Care 2012 (21):242-250

MI-ONCOSEQ

- Eligibility – Phase I clinical trials (advanced refractory disease or rare cancer with no standard therapy)
- Whole exome and whole genome sequencing of tumor and germline DNA
- 4 week turn around (=standard wash out period)

Roychowdhury, SciTransIMed 2011

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AIP	C16orf57	DKC1	FANCF	HOXD4	MC1R	NOP10	PTEN	SDHC	THPO
AKT1	CASP8	ELANE	FANCG (XRCC9)	HRAS	MEN1	NRAS	PTPN11	SDHD	TINF2
ALK	CBL	EPHB2	FANCI (KIAA1794)	IGF1	MET	NSD1	PTPRJ	SH2D1A	TLR2
APC	CCND1	ERCC2 (XPD)	FANCL (PHF9/POG)	IGF2	MITF	ODC1	RAD50	SHOC2	TLR4
ATM	CDC73	ERCC3 (XPB)	FANCM (Hef)	JAK2	MLH1	PALB2 / FANCN	RAD51	SLC26A4	TMC8
ATR	CDH1	ERCC4 (XPF)	FAS	KIF1B	MLH3	PARK2	RAD51C	SMAD7	TMEM127
AURKA	CDK4	ERCC5 (XPG)	FASLG	KIT	MPL	PHB	RAD51D	SMARCB1	TP53
AXIN2	CDKN1B	EVER1	FH	KIT	MRE11A	PHOX2B	RAD54L	SOS1	TSC1
BAP1	CDKN1C	EVER2	FLCN	KRAS	MSH2	PLA2G2A	RAF1	SPRED1	TSC2
BARD1	CDKN2A	EXT1	G6PC3	LAMA3	MSH6	PMS1	RB1	STK11	VHL
BLM	CEBPA	EXT2	GALNT12	LAMB3	MSR1	PMS2	RECQL4	TERC	WAS
BMPR1A	CHEK2	FANCA	GATA2	LAMC2	MUTYH	POU6F2	RET	TERT	WRN
BRAF	COL17A1	FANCB	GFI1	MADH4	NBN	PPARG	RNASEL	TGFB1	WT1
BRCA1	COL7A1	FANCC	GPC3	MAP2K1	NF1	PRKAR1A	RUNX1	TGFBR1	XPA
BRCA2	CYP21A2	FANCD2	HAX1	MAP2K2	NF2	PRSS1	SBDS	TGFBR1	XPC
BRIP1 / FANCJ	DDB2 (XPE)	FANCE	HOXB13	MAX	NHP2	PTCH	SDHB	TGFBR2	PTCH2

At Initial Study Visit…

- Take a 4 generation pedigree (cancer focused)
- Discuss sequencing of cancer genome vs. germline, reasons for doing both
- Respond to patient questions about family history or testing process
- Discuss consent for return of results, walk through flexible default plan

Provisional Flexible-Default Informed Consent

Disease Domain	Impact/ Significance	Default	Decline Results?	Description
Cancer of Interest	Direct impact on care of current cancer	Disclose	NOT flexible	Marketed treatment available Targeted clinical trial available
	Significance for biological family	Disclose	Flexible	Increased risk of cancer for biological family
	Significance is unknown	NOT disclose	NOT flexible	Unknown mutation function or role
Conditions OTHER than cancer of interest	Potential medical impact	Disclose	Flexible	Clinically significant relative risk of disease or outcomes
	Significance for biological family	Disclose	Flexible	Significant implications for biological family decisions
	Significance is unknown	NOT disclose	NOT flexible	Mutation function or role unknown
Other	New or unanticipated issues	Determined by PMTB on case by case basis		Situations that do not readily fit into above categories PMTB may need to create new categories

Interest in Germline Findings

- Through April 31, 2013:
  - 167 adult patients consented
    - 162/167 (97%) opted to receive germline findings
  - 34 pediatric patients consented (57 through 1/31/14)
    - 30/34 (88%) opted to receive germline findings

Germline Findings – Disclosure Categories

Germline analylsis completed for 179 patients

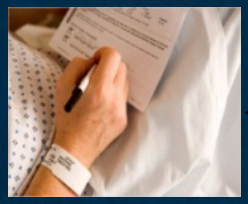
1	Previously reported pathogenic mutations in high penetrance cancer genes with known clinical utility (e.g. BRCA1/2, MLH1)	Disclose	8
2	Alleles associated with low to moderate cancer risk, clinical utility evolving or unknown (e.g. ATM, BARD1)	Case by case	7
3	Mutations associated with autosomal recessive conditions	Not disclose	11

Exceptions:
ALL germline findings relevant to current cancer (including carrier of AR condition, low to moderate penetrance alleles and possibly variants of uncertain significance)

Project 1 and 2

Project 3

Informed Consent Genetic Counseling



Aim 1

Eliciting Patient Preferences

Tumor Sequencing & Analysis

Precision Medicine Tumor Board

Aim 2

Analyzing Board Decision-Making

Disclosure: Genomic Results

Aim 3

Developing Communication Tools

Patient Responses

Aim 4

Examining Patient Responses

Mean Time to Disclosure	**Impact on Decision making**	**Frequency of Informative genes**

Genomic Sequencing in Clinical Oncology

- Informed Consent
- Privacy
- Translate, validate, and deliver results
- Making decisions regarding which results are significant
- Reporting results
- Impact of sequencing

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U Michigan CCC

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Jenae Osborne
Victoria Raymond
Carmen Williams

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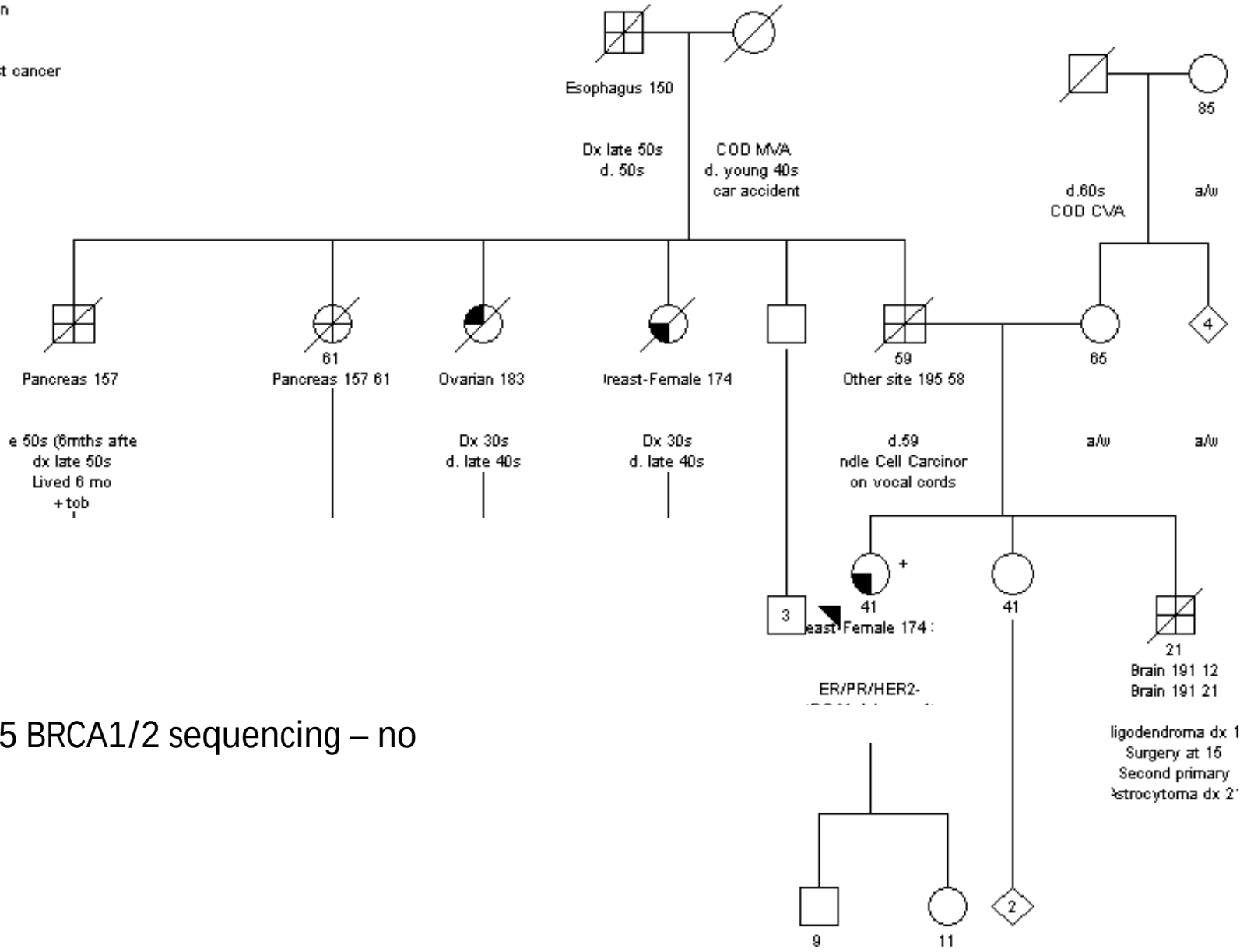
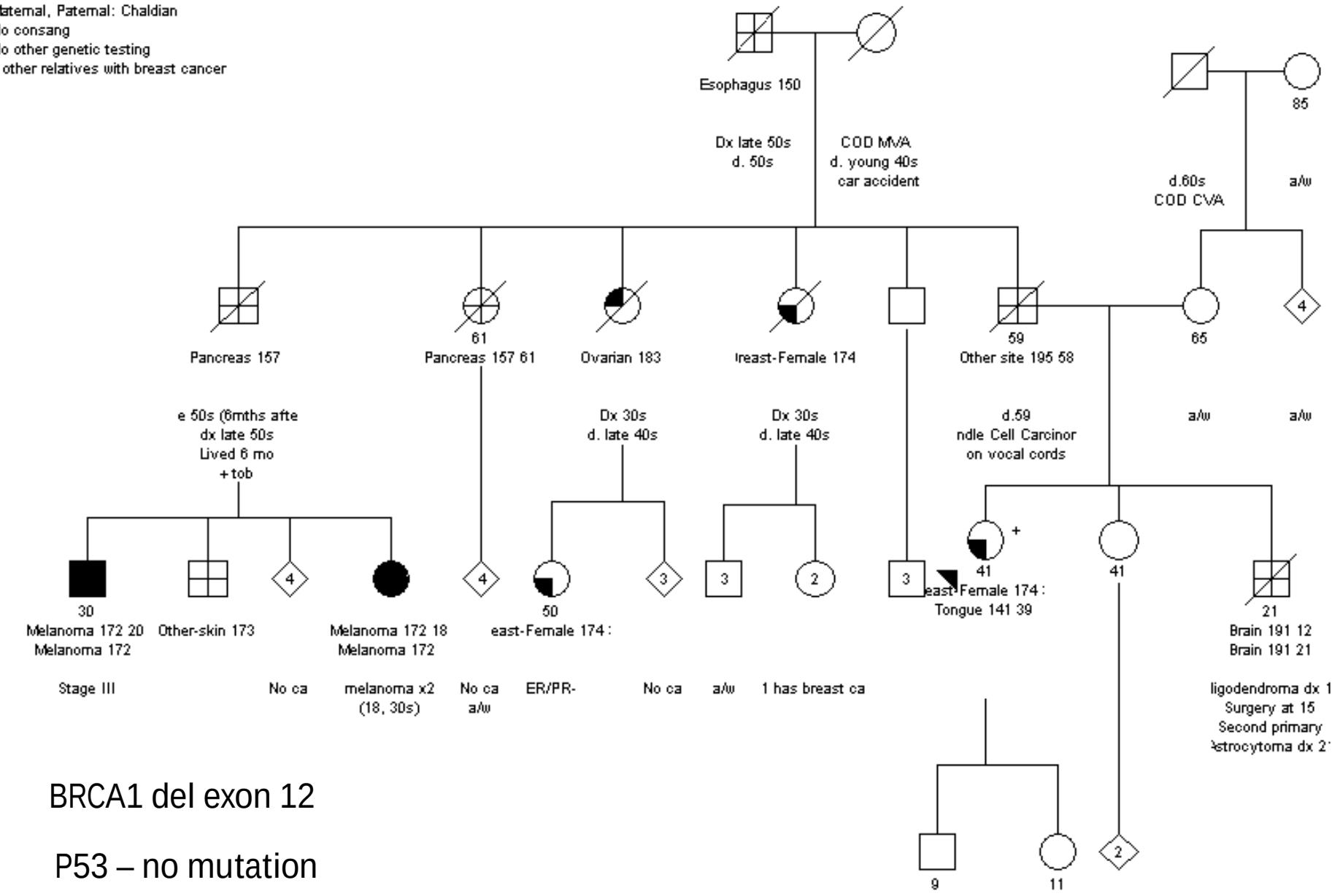
lo other genetic testing
other relatives with breast cancer



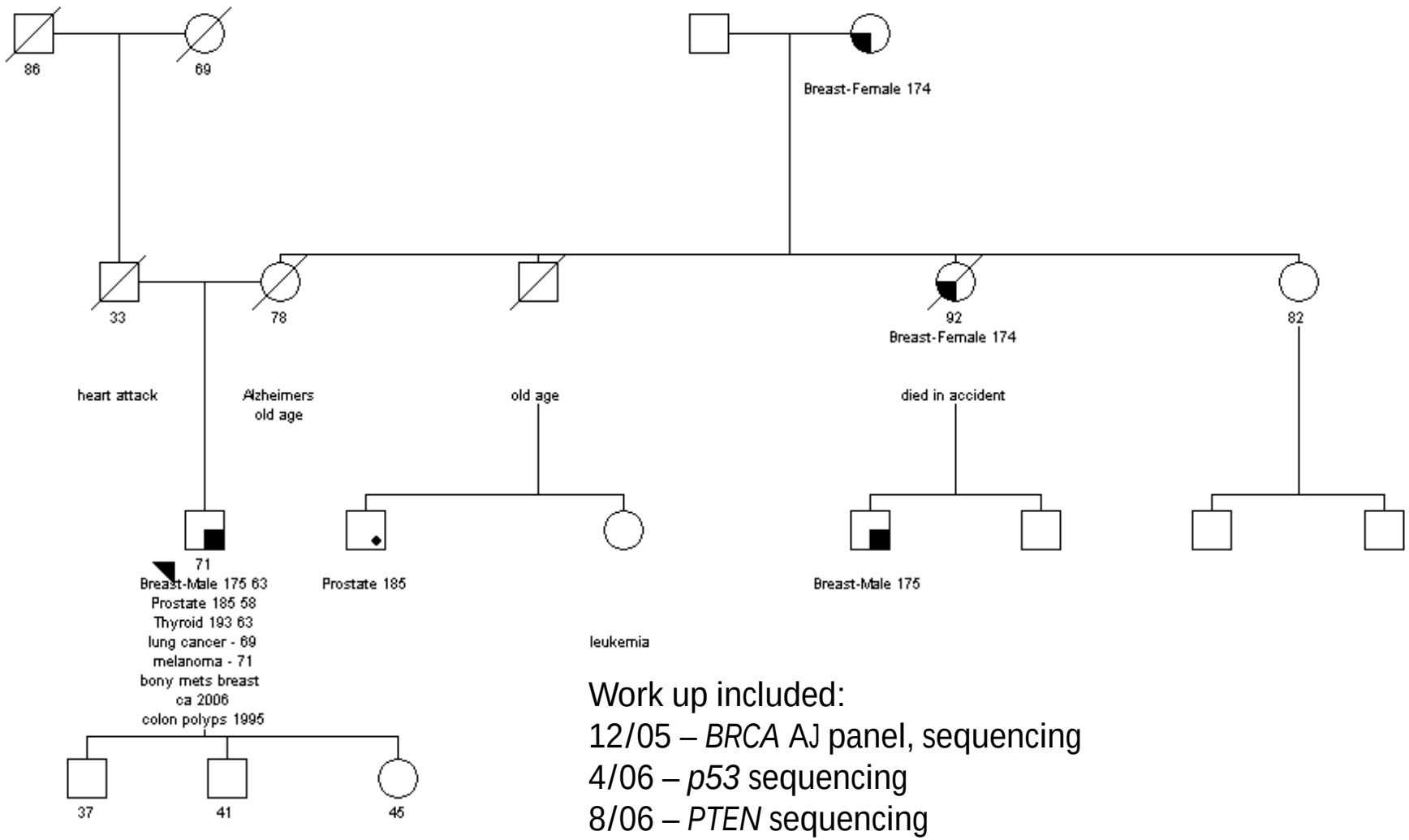
Early 2005 BRCA1/2 sequencing – no mutation



BRCA1 del exon 12

P53 – no mutation

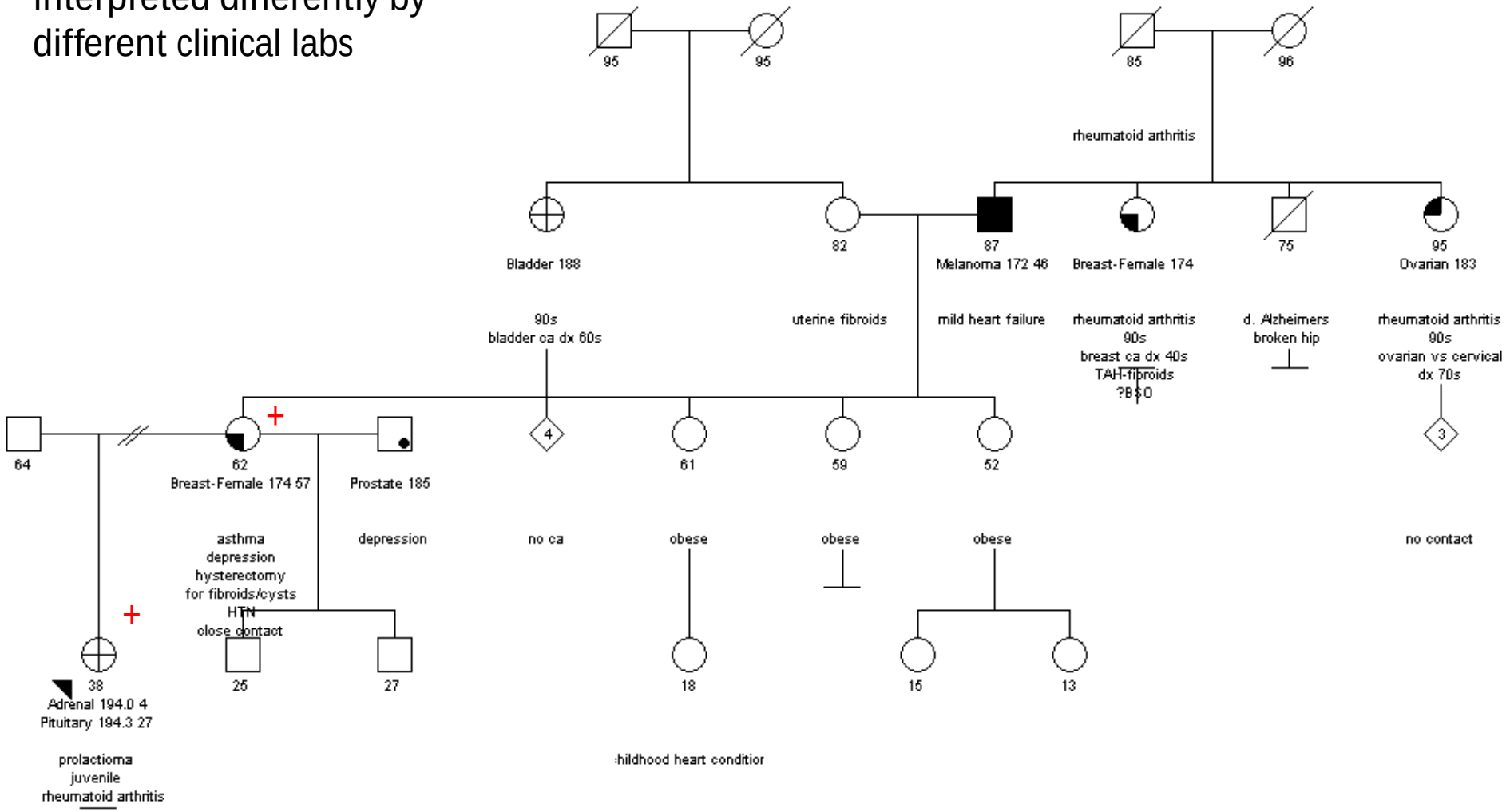
CDKN2A Q50X (c.148C>T)

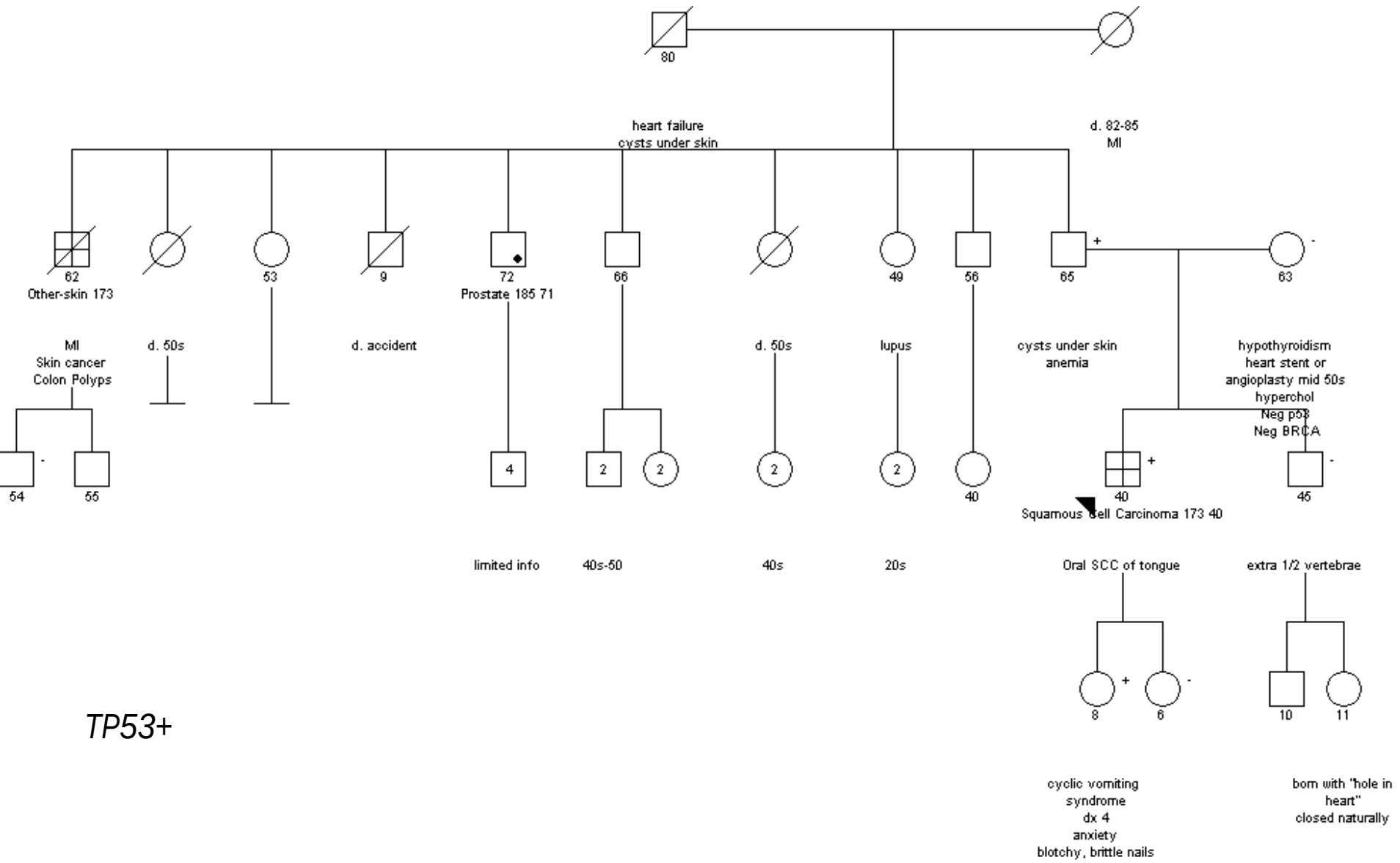


Work up included:

12/05 – *BRCA* AJ panel, sequencing
4/06 – *p53* sequencing
8/06 – *PTEN* sequencing
1/07 – *PTEN* DGGE (research)
10/07 – *BRCA* MLPA (research)
4/09 – *p53* dosage, *CHEK2* sequencing
6/10 – *PALB2* sequencing

TP53 p.R267Q
Interpreted differently by different clinical labs




80
heart failure
cysts under skin
d. 82-85
MI
62
Other-skin 173
53
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72
Prostate 185 71
66
49
56
65
+
63
-
MI
Skin cancer
Colon Polyps
d. 50s
d. accident
d. 50s
lupus
cysts under skin
anemia
hypothyroidism
heart stent or
angioplasty mid 50s
hyperchol
Neg p53
Neg BRCA
-
54
55
4
2
2
2
2
40
+
40
Squamous Cell Carcinoma 173 40
-
45
limited info
40s-50
40s
20s
Oral SCC of tongue
extra 1/2 vertebrae
+
-
8
6
10
11
cyclic vomiting
syndrome
dx 4
anxiety
blotchy, brittle nails
born with "hole in
heart"
closed naturally

TP53+