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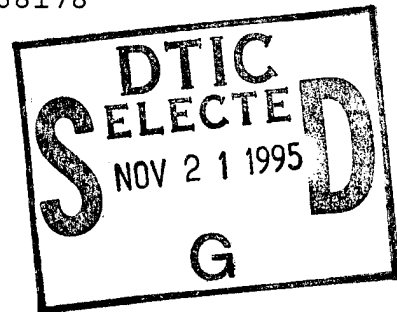
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PRINCIPAL INVESTIGATOR(S): Doctor Henry T. Lynch

CONTRACTING ORGANIZATION: Creighton University
Omaha, Nebraska 68178

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Fort Detrick, Maryland 21702-5012

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| 6. AUTHOR(S) Dr. Henry T. Lynch | |
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ABSTRACT (Maximum 200 words)
Advances in molecular genetics have made it possible to identify individuals who have a strong inherited predisposition to breast cancer ovarian cancer. Because experience in genetic counseling of members of hereditary breast cancer families is exceedingly limited, we have mounted a study focusing on the genetic counseling process, with particular attention to the psychological impact and to adherence to recommended surveillance. To date, we have provided genetic counseling to 249 individuals from eight hereditary breast/ovarian cancer families. Of the 249 participants in the baseline (pre-counseling) telephone interviews (response rate to interviews - 77%), 75% of respondents opted to receive their BRCA1 test results. Using logistic regression analysis, we identified the following positive predictors of acceptance of testing: female gender (OR=5.0; CI=1.2-20.9), higher education level (OR=9.2; CI=1.2-70.7), and high baseline distress level (OR=7.8; CI=2.0-30.8). We observed significant improvement in knowledge from baseline to one-month follow-up for both carriers and non-carriers (F (time) = 47.2; p=.0001). By one month following counseling, female mutation carriers showed an increase in breast cancer worries, while non-carriers showed a decrease (F (time by group) = 4.6; p=.02). By six months, carriers had significantly higher scores on a depression measure (F=2.1; p=.04). We continue to accrue additional families and to evaluate the short- and long-term impact of BRCA1 testing.

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FOREWORD

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INTRODUCTION:

Advances in the molecular genetics of hereditary breast cancer have provided the heretofore unprecedented opportunity for DNA-based genetic counseling. This now enables physicians, in concert with certified genetic counselors, to delicately provide family members with information pertinent to whether or not they have inherited a cancer predisposing gene, and in our case this has involved BRCA1 and, ultimately will involve BRCA2 and p53.

These unheralded opportunities followed the work of Hall, et al. Hall et al. [1] who identified linkage of breast cancer susceptibility to the D17S74 locus (probe CMM86) on chromosome 17q21. Shortly after, linkage to D17S74 was confirmed in three of five families with hereditary breast/ovarian cancer (HBOC)[2]. An international consortium studying linkage to hereditary breast/ovarian cancer reported that 45% of site-specific breast cancer families [3] and 92% of families with HBOC syndrome were linked to BRCA1 [4]. However, none of the families with male breast cancer were linked to BRCA1. There is an increased risk for cancer of the colon and prostate in BRCA1 carriers.

A second gene, BRCA2, was mapped to chromosome 13 in 1994 [5]. The majority of families with cases of male breast cancer appear to be associated with BRCA2. BRCA2 confers a high risk of breast cancer, but not, it seems, for ovarian cancer. More research is needed with respect to the full tumor spectrum in BRCA1 and 2.

Easton et al. [6] estimate the frequency of BRCA1 mutant alleles to be 0.0007, based on 44 breast cancer deaths occurring among the relatives of 1203 women with ovarian cancer (31.8 expected). It is therefore likely that the frequency of carriers of BRCA1 mutations in the population is closer to one in 500. Ford et al. [7] estimate a cumulative risk of 48% to age 70 for ovarian cancer and 85% for breast cancer. However the data best fit a model with a mix of two susceptibility genes; one with a risk for breast cancer of 71% and for ovarian cancer of 87% to age 70 and a second gene with a risk for breast cancer of 86% to age 70 and a risk for ovarian cancer of only 18%. Little linkage data are available for apparent site-specific ovarian cancer, but a few rare families have been linked to BRCA1 [8].

Based on limited data, it appears that mutations can be identified in the coding region of the BRCA1 gene in over one-half of HBOC syndrome families. It is likely that mutations in the splice junctions, introns and regulatory regions of BRCA1 are responsible for most of the other families, but a small proportion will be unlinked. With this knowledge, it is now feasible to offer predictive testing based on BRCA1 gene analysis to women from HBC or HBOC families. Because of scientific, psychological, and social concerns, predictive testing programs are currently restricted to specialized research centers.

Lerman et al have conducted extensive research on the psychological

impact of cancer risk notification and adherence to cancer screening. She and her colleagues demonstrated that cancer risk notification can produce negative psychological consequences, including anxiety, traumatic stress symptoms, and impairment in daily functioning [9,10], and that distress can impair adherence to recommended surveillance [11-13]. While most of her work has focused on breast cancer, she has collaborated on studies of colon cancer risk and screening [11,14-16]. Her more recent work focuses on psychological issues in genetic testing for cancer susceptibility [17,18], including a recent study which showed that anxiety can interfere with comprehension of genetic risk information [19].

Goals and Objectives

The goals of our study are to identify the impact of genetic counseling in HBC and HBOC families where gene linkage to BRCA1 has been identified. This study is designed to demonstrate the feasibility of genetic counseling for HBC and HBOC, and to evaluate the impact of counseling on psychological state and medical behavior. The subject of genetic counseling in HBC and HBOC has never been systematically investigated in either a research or clinical setting. The study is also designed to examine predictors of those adverse consequences that could evolve from this genetic counseling. This information may enable physicians and genetic counselors to anticipate and prevent problems in individual clients.

BODY:

Eligible members of BRCA1-linked families receive an introductory letter, followed by a baseline, structured telephone interview administered by a trained interviewer at Georgetown University under the direction of Caryn Lerman Ph.D., a clinical psychologist/geneticist at Georgetown University, Washington, D.C.. About four weeks later, these individuals have an opportunity to attend an education session at which time information about gene linkage, hereditary breast cancer and surveillance measures are again reinforced prior to individual counseling to obtain genetic test results for breast-ovarian cancer susceptibility.

All genetic counseling and testing is provided by, and/or supervised by Dr. Lynch and his colleagues. Telephone interviews are conducted from Georgetown University at one-, six-, twelve-, and twenty-four months following genetic counseling to evaluate the impact of disclosure of genetic information.

Progress in our study of genetic counseling based on BRCA1 linked markers has been extremely well-targeted and productive. We have collected 319 blood specimens for DNA analysis from a total of 43 families. The DNA is used in the search for germline mutations, in collaboration with Steven Narod, M.D., of McGill University in Montreal, Canada, and Gilbert Lenoir, Ph.D., D.V.N., in Lyon, France.

To date, genetic counseling has been provided to eight HBOC families where BRCA1 germline mutations have been identified. Pedigrees of these eight families are shown in Figures 1-8 (see Appendix). The Table shows the family number, the date when the family was counseled, and the number of members who were counseled and provided with individual risk assessment in each of the eight families. The 43 well-defined HBC/HBOC families in our resource which have sufficient gene linkage and/or DNA mutation information available are eligible for counseling in the future. The most informative of these families are being set up with appointments for genetic counseling.

TABLE

| Family Number | Date Family was Counseled | Number of Members Counseled |
|----------------------|--------------------------------------|--|
| 1234 | August 20, 1994 | 21 |
| 1813 | January 29, 1995 | 9 |
| 1816 | August 19, 1995 | 16 |
| 1973 | May 27, 1995 | 12 |
| 2090 | February 18, 1995 | 10 |
| 2651 | April 22, 1995 | 29 |
| 2770 | March 18, 1995 | 32 |
| 3079 | June 10, 1995 | 9 |

Individuals counseled since August 1, 1994 and the date on which they were counseled.

Since this grant was awarded we have identified 76 new breast cancer prone families. Of these, by pedigree analysis, 29 have

been diagnosed as consistent with HBC and 16 with the HBOC syndrome. Pedigrees of these families have been sent to Steven Narod, M.D. to determine eligibility for linkage analysis.

To date, a total of 249 individuals have participated in the baseline (pre-counseling) telephone interviews (response rate to interviews -77%). In terms of their demographic backgrounds, 100% of respondents are white, 69% are female, 88% have a high school education or greater, and 71% are employed. The average age of respondents is 43 +/- 14 years.

Thus far, about 75% of respondents have opted to receive their BRCA1 test results and 25% have declined. We conducted logistic regression analysis to identify predictors of acceptance of testing. Significant positive predictors include: female gender (OR=5.0; CI=1.2-20.9), higher education level (OR=9.2; CI=1.2-70.7), and high baseline distress level (OR=7.8; CI=2.0-30.8). Other factors have significant bivariate associations with uptake of testing include having health insurance and being more knowledgeable about hereditary breast cancer.

We have also conducted preliminary analyses of the impact of BRCA1 testing on psychological outcomes. Our data show significant improvements in knowledge from baseline to one-month follow-up for both carriers and noncarriers (F (time) =47.2; $p=.0001$). By one-month following counseling, female

mutation carriers showed an increase in breast cancer worries, while noncarriers showed a decrease (F (time by group)=4.6;p=.02). There were no significant differences between carriers and noncarriers in depression at one-month follow-up. However, by six months, carriers had significantly higher scores on a depression measure ($F=2.1;p=.04$). Increases in depression in the mutation carriers was predicted by specific coping strategies involving venting of feelings, information-seeking, and planful problem-solving.

CONCLUSIONS:

These preliminary data provide support for the feasibility of our ongoing research and the potential to elucidate clinically important information. However, since only a subset of the sample have been enrolled to date, it may be premature to draw conclusions from these data. Nonetheless, the following tentative interpretations may be made: (1) individuals who present for genetic testing are more likely to be female and to be more distressed about their risk. This points to the need to address patients' psychosocial concerns during the genetic counseling visit; (2) any adverse effects of genetic counseling may not be obvious in the short term. This underscores the need for long-term follow-up of participants in genetic counseling programs; (3) in the short term, coping strategies involving acceptance may be more beneficial than those strategies aimed at changing the situation. This points to possible avenues for

designing adjunctive psychological therapies.

Manuscripts relevant to this research are in preparation. One manuscript dealing with genetic counseling with attention to the reasons why about 25% of the members of these families decline participation in this DNA-based genetic counseling will be submitted to the New England Journal of Medicine, as it contains important public health implications. A second manuscript dealing with the psychological evaluation of the genetic counseling interviews on more than 100 BRCA1 positive and negative patients is also in preparation.

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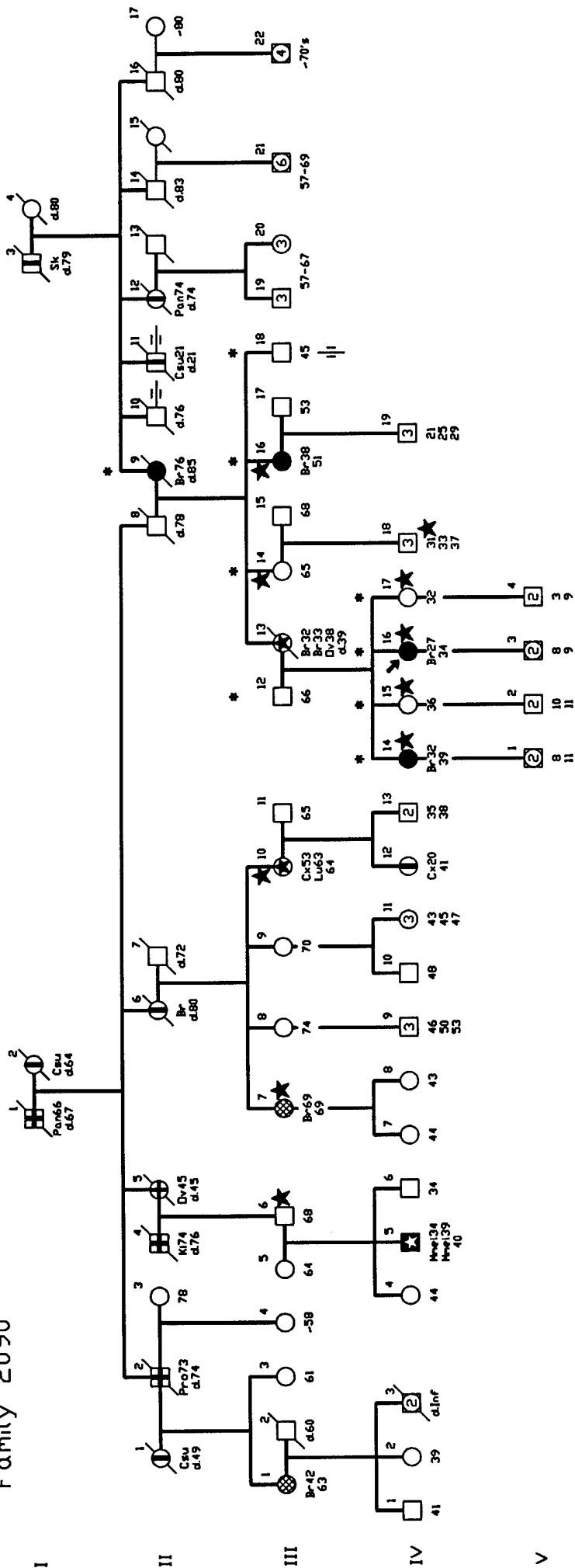
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APPENDIX

Pedigrees of eight HBOC families where BRCA1 mutations have been identified.

Family 2090

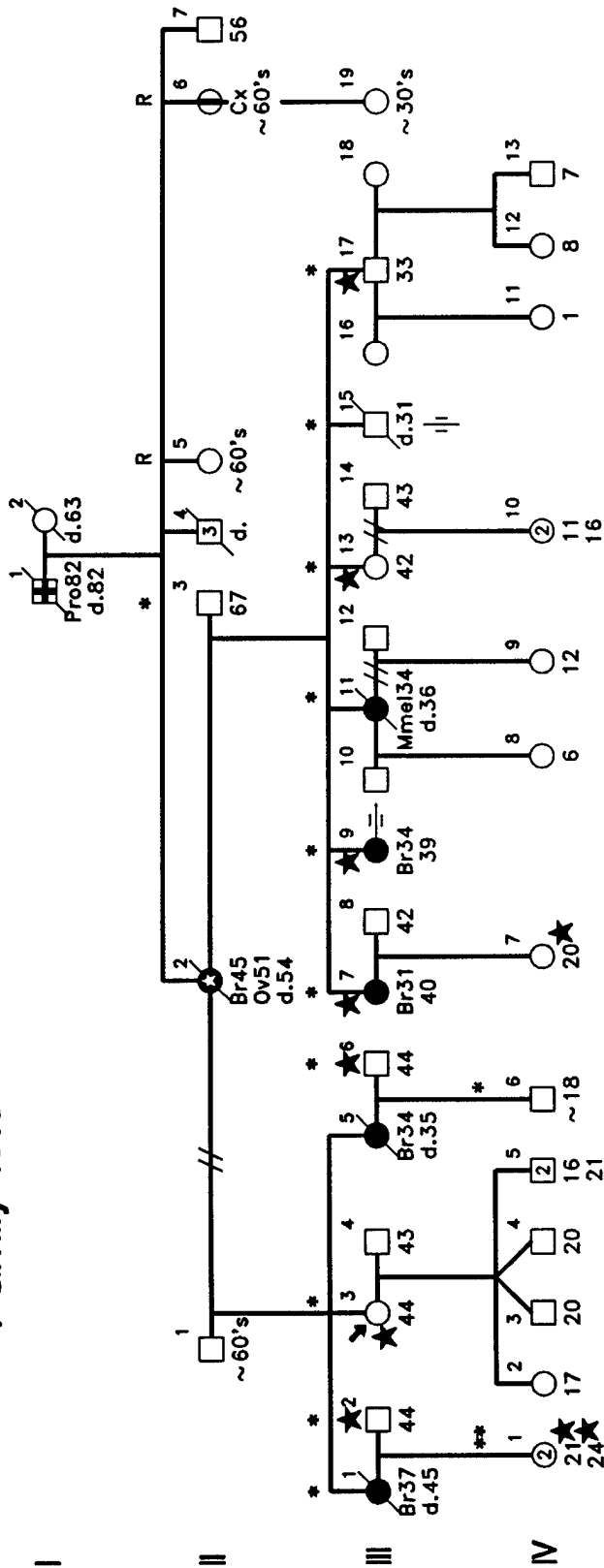


LEGEND

- | | | | |
|------|--------|---|-------------------------|
| Male | Female | Individual number | Cancer Sites |
| 1 | 2 | Unaffected | Br Breast |
| 28 | 33 | Current age | Csu Cancer Site Unknown |
| 33 | 33 | Cancer by Pathology, age at diagnosis | Cx Cervix |
| 43 | 47 | Current age | Ki Kidney |
| 45 | 47 | Cancer by Family History, age at death | Mmel Malignant Melanoma |
| 50 | 53 | In-Situ Carcinoma by Pathology Report | Dv Ovarian |
| 53 | 53 | Multiple Primary Cancers Unverified | Pan Pancreas |
| 46 | 46 | Multiple Primary Cancers by Medical Records or Death Certificates | Pro Prostate |
| 48 | 48 | Multiple Primary Cancers by Pathology | Sk Skin |
| 49 | 49 | Cancer by Death Certificate or Medical Records | * Blood Sampled |
| 51 | 51 | Number of Unaffected Progeny (Both Sexes) | ★ Counselled in 1995 |
| 52 | 52 | Proband | |

01/13/1995
2090-2
Henry T. Lynch, M.D.
Hereditary Cancer Institute
Creighton Un. School of Medicine
3300 16th Street
Omaha, NE 68178 U.S.A.
402-280-2942

Family 1813

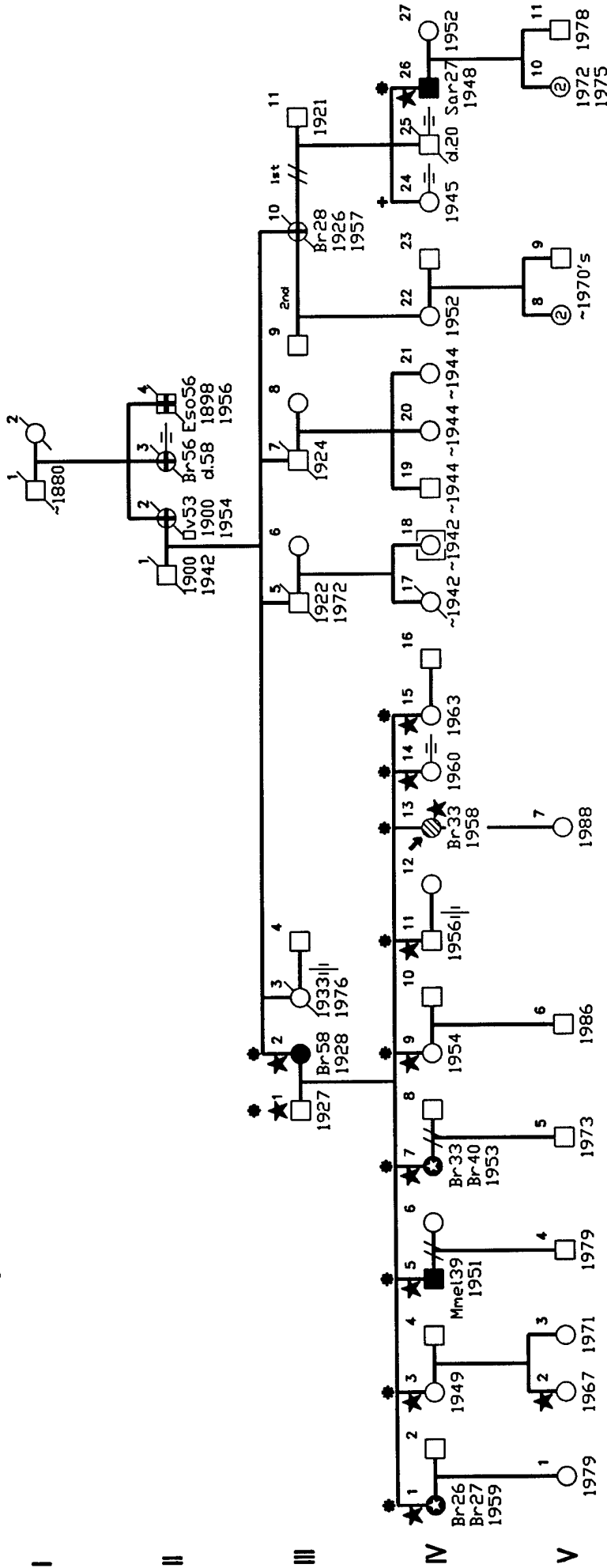


LEGEND

- Male 1
- Female 2
- Unaffected 28
- Current age 33
- Cancer by Pathology, age at diagnosis Br45 47
- Current age 47
- Cancer by Family History, age at death d.86
- Multiple Primary Cancers Unverified d.54
- Multiple Primary Cancers by Medical Records or Death Certificates
- Multiple Primary Cancers by Pathology
- Cancer by Death Certificate or Medical Records
- Number of Unaffected Progeny (Both Sexes) 4
- Proband
- Twins
- Identical Twins
- Cancer Sites: Br (Breast), Cx (Cervix), Ov (Ovarian), Pro (Prostate)
- * Blood Sampled
- R Refusing
- ★ Counselor in 1995

01/19/1995
1813-2
Henry T. Lynch, M.D.
Hereditary Cancer Institute
Creighton Un. School of Medicine
California @ 24th Street
Omaha, NE 68178 U.S.A.
402-280-2942

Family 1973

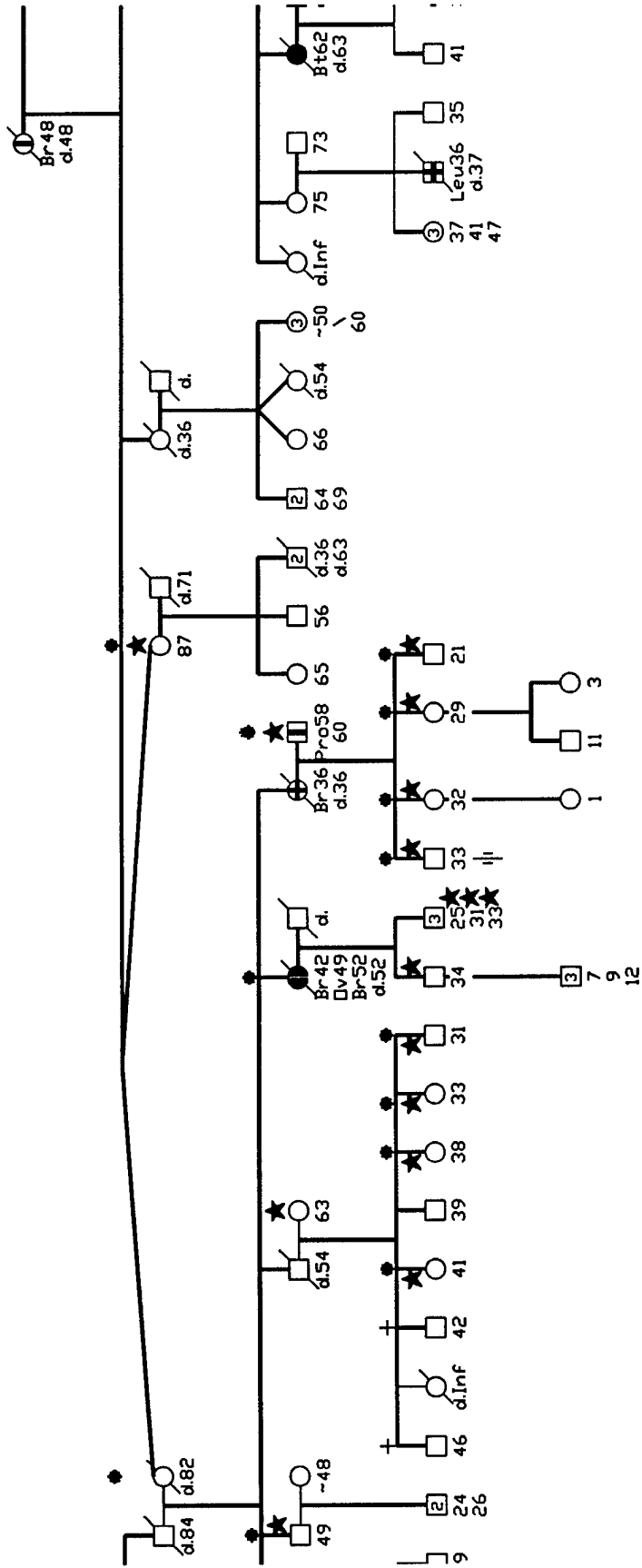


LEGEND

- | | | | |
|-------------|---------------|--|-------------------------|
| Male | Female | Individual number | Cancer Sites |
| 1 | 2 | Unaffected | Br Breast |
| 28 | 33 | Current age | Eso Esophagus |
| Lu53 55 | Br-45 47 | Cancer by Pathology, Current age | Mmel Malignant Melanoma |
| Lu53 55 | Br-45 47 | In-Situ Carcinoma by Pathology Report | Ov Ovary |
| d.54 | d.56 | Cancer by Family History, age at death | Sar Sarcoma |
| ★ | ⊕ | Multiple Primary Cancers by Pathology | ★ Blood Sampled |
| ⊕ | ⊕ | Cancer by Death Certificate or Medical Records | + Blood Kit sent |
| ⊕ | ⊕ | Number of Unaffected Progeny (Both Sexes) | ★ Counselored in 1995 |
| ⊕ | ⊕ | Proband | |

03/29/1995
1973GR-2
Henry T. Lynch, M.D.
Hereditary Cancer Institute
Crawford Un. School of Medicine
Chapel Hill, NC 27599
402-286-2942

Family 2651



LEGEND

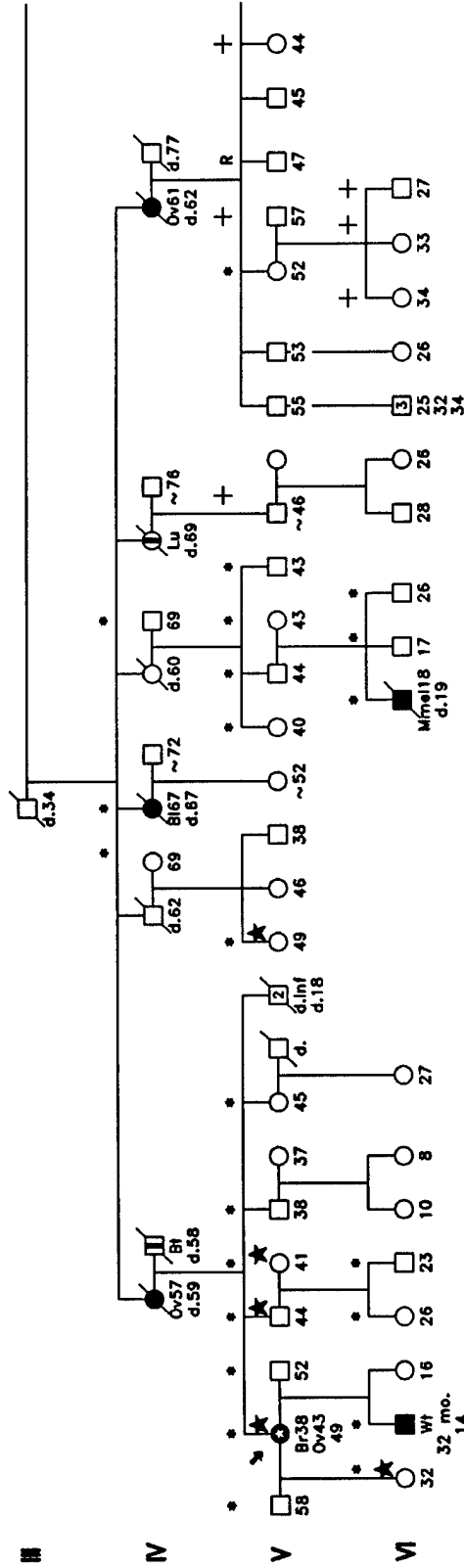
- Male 1
- Female 2
- Unaffected 28
- Current age 33
- Cancer by Pathology, age at diagnosis 45, 47
- Current age 48
- Cancer by Family History, age at death 54
- Multiple Primary Cancers by Medical Records or Death Certificates 48
- Multiple Primary Cancers by Pathology 48
- Cancer by Death Certificate or Medical Records 48
- Adopted 48
- Number of Unaffected Progeny (Both Sexes) 48
- Proband 48
- Twins 48
- Identical Twins 48

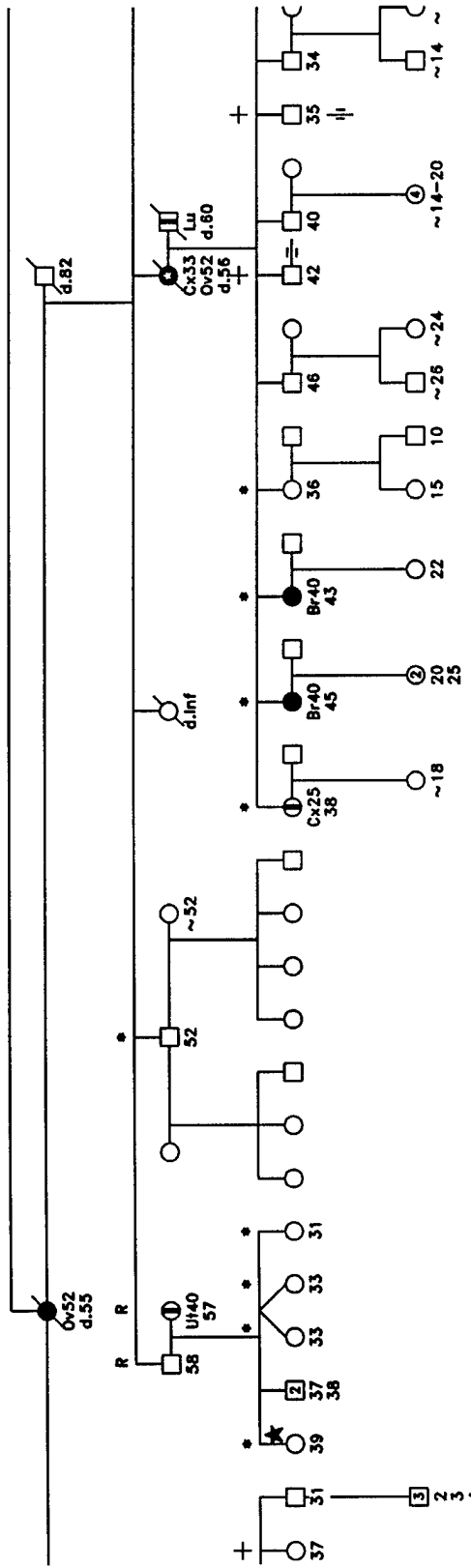
- ### Cancer Sites
- Br Breast
 - Bt Brain Tumor
 - Co Colon
 - Csu Cancer Site Unknown
 - En Endometrium
 - Gb Gallbladder
 - Ki Kidney
 - Leu Leukemia
 - Lu Lung
 - Lyn Lymphoma
 - Dv Ovary
 - Pan Pancreas
 - Psu Primary Site Unknown
 - St Stomach

- ★ Counseled in 1995
- Blood Sampled
- + Blood Kit sent

04/20/1995
2651-6

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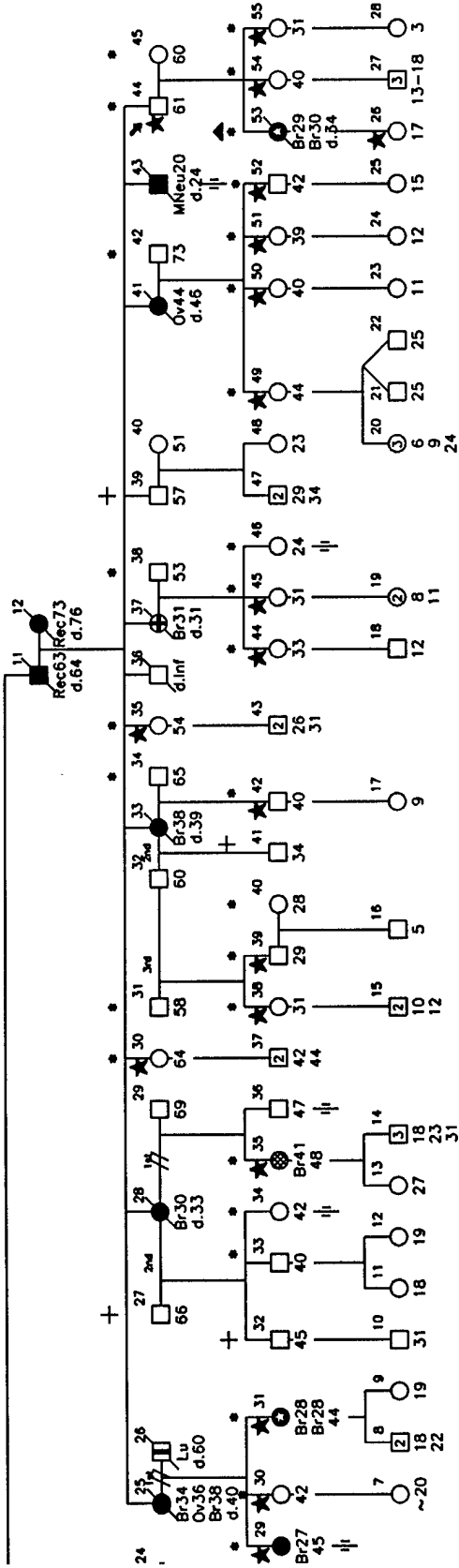
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- Female: 1 (circle), 2 (circle with dot), 3 (circle with diagonal lines), 4 (circle with horizontal lines)
- Individual number
- Unaffected
- Current age
- Cancer by Pathology, age at diagnosis
- Current age
- In-Situ Carcinoma by Pathology Report
- Cancer by Family History, age at death
- Multiple Primary Cancers Unverified
- Multiple Primary Cancers by Medical Records or Death Certificates
- Multiple Primary Cancers by Pathology
- Cancer by Death Certificate or Medical Records
- Number of Unaffected Progeny (Both Sexes)
- Proband

- Cancer Sites
- Br Breast
 - Bl Brain Tumor
 - Cx Cervix
 - Fe Female
 - LgBo Large Bowel
 - Lu Lung
 - Mmel Malignant Melanoma
 - Mou Mouth
 - Ov Ovarian
 - Pan Pancreas
 - Pro Prostate
 - St Stomach
- + Blood Kit sent
 - * Blood Sampled
 - R Refusing
 - ★ Counseled in 1995

08/18/1994
Henry T. Lynch, M.D.
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Cancer Center, Baltimore, MD 21201 U.S.A.
410-280-2942

Family 2770



Family 1816

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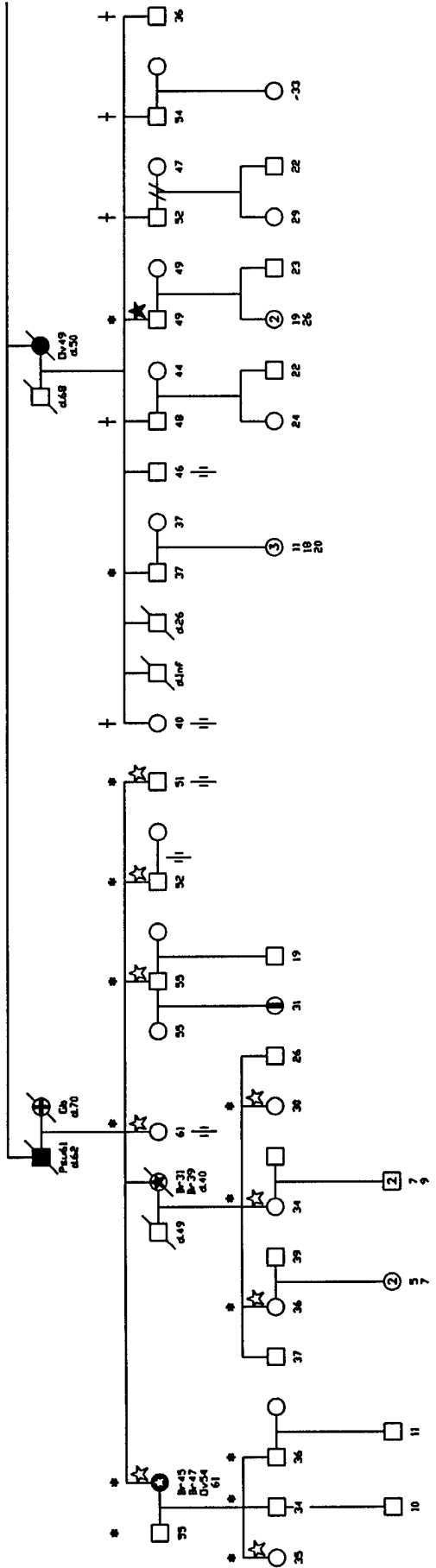
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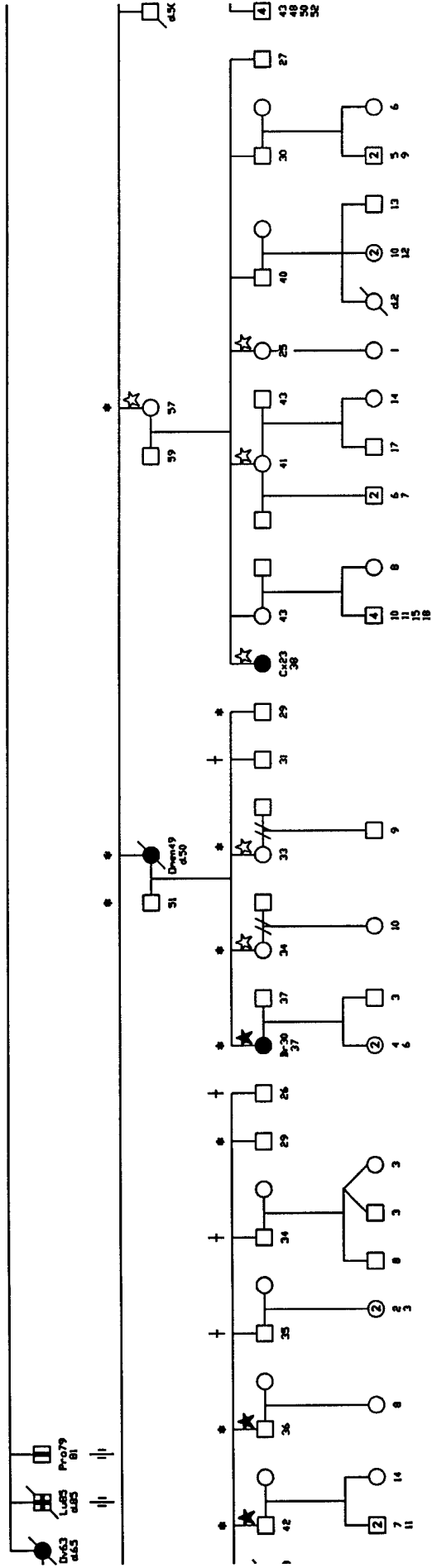
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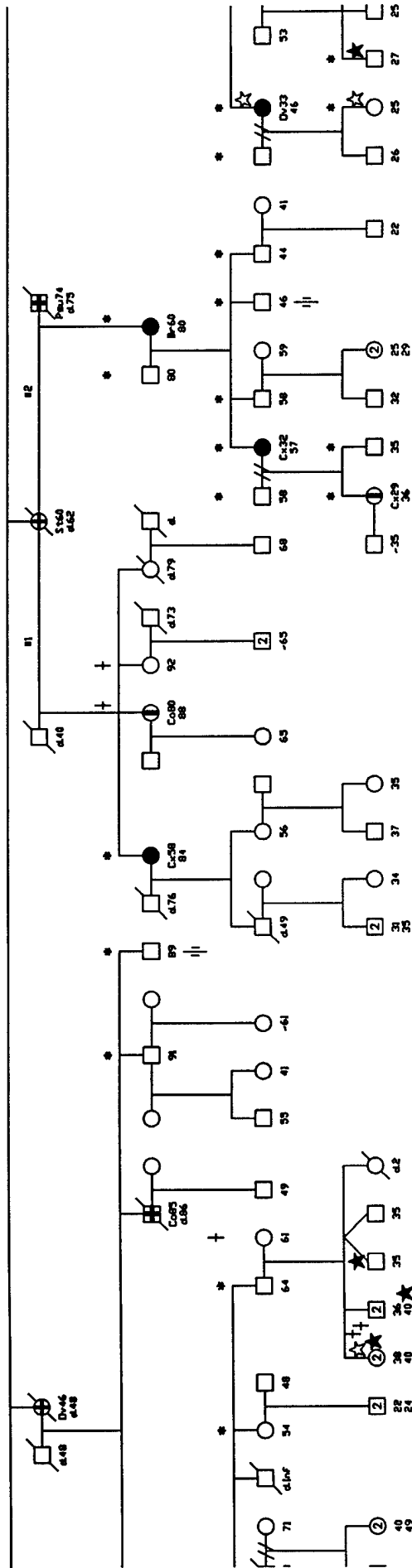
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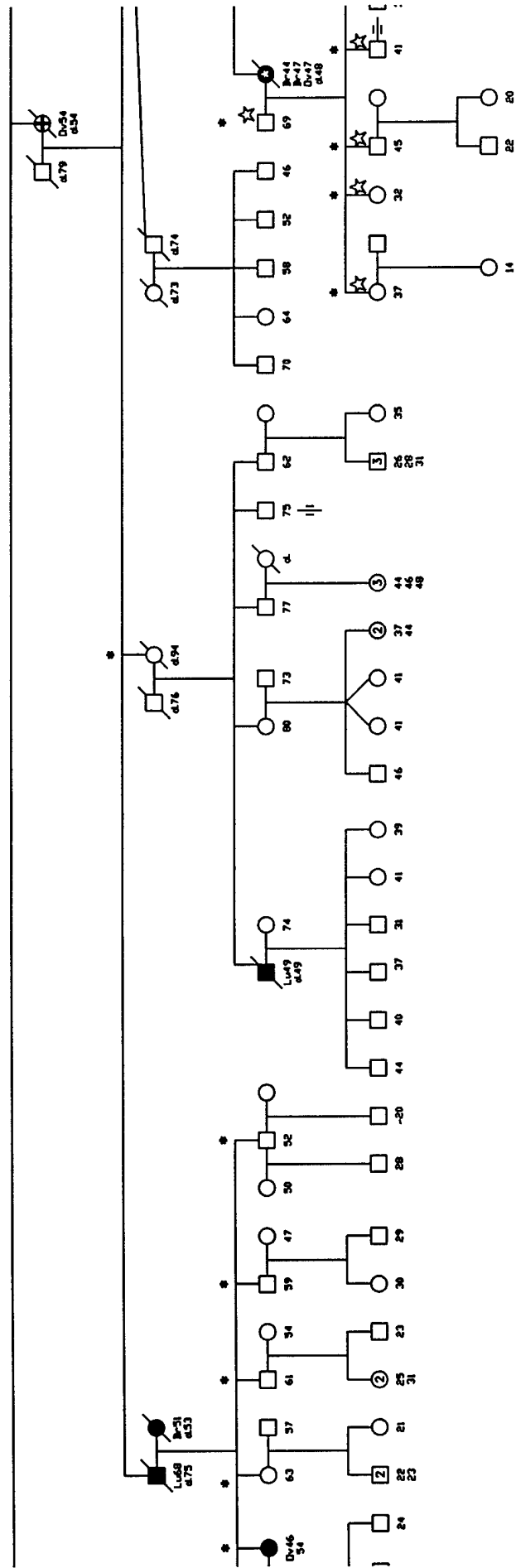


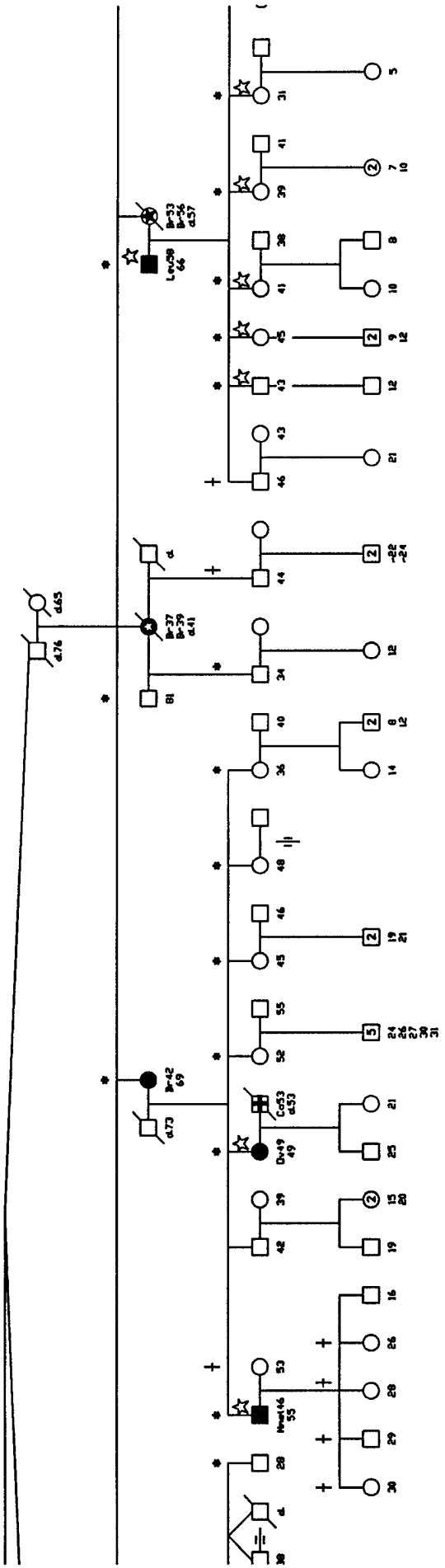
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|--------|---------------------------------------|----------------------|----------------------------------|
| Female | Individual number | Bladder | 08/10/1995 |
| 1 | Unaffected | Breast | 1816-41 |
| 2 | Current age | Colon | Henry T. Lynch, M.D. |
| 3 | Cancer by Pathology, | Cancer Site Unknown | Hereditary Cancer Institute |
| 4 | age at diagnosis | Cx | Creighton Un. School of Medicine |
| 5 | Current age | Gallbladder | California @ 24th Street |
| 6 | Cancer by Family History, | Leukemia | Omnipoint, U.S.A. |
| 7 | age at death | Lung | 402-280-2142 |
| 8 | Multiple Primary Cancers Unverified | Malignant Melanoma | |
| 9 | Multiple Primary Cancers by | Omentum | |
| 10 | Medical Records or Death Certificates | Ovarian | |
| 11 | Multiple Primary Cancers by Pathology | Primary Site Unknown | |
| 12 | Cancer by Death Certificate or | | |
| 13 | Medical Records | | |
| 14 | Number of Unaffected Progeny | | |
| 15 | (Both Sexes) | | |
| 16 | Proband | | |
| 17 | Twins | | |
| 18 | Identical Twins | | |
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