BayesMendel v2.1-8: An R package for cancer risk prediction

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August 11, 2021

1 Introduction

The BayesMendel working group is dedicated to the development of methodologies, models, and open source software for predicting who may carry a cancer susceptibility gene. We use statistical ideas that go back to Bayes and genetic models that go back to Mendel.

This vignette will show the user how to use BRCAPRO, MMRpro, PancPRO, MelaPRO and BRCAPANCpro to:

- Calculate probabilities of being a germline mutation carrier.
- Calculate future risk of cancer.
- Incorporate supplementary information (marker testing results, germline testing results, tumor information) into the models.

2 Using the models

2.1 BRCAPRO

2.1.1 Family History

Before running your pedigree through `brcapro`, be sure it is structured as a numeric data frame with history of breast and ovarian cancers: n rows (where n is the number of family members, including the counselee) and 13 columns with column names:

Column Name	Content
ID	Member identifier
Gender	Gender (0=female, 1=male)
FatherID	Father's identifier number
MotherID	Mother's identifier number
AffectedBreast	Breast cancer status (0=no cancer, 1=breast cancer,one breast involved; 2=bilateral breast cancer, NA=unknown status)
AffectedOvary	Ovarian cancer status (0=no cancer, 1=ovarian cancer, NA=unknown status)
AgeBreast	Age of onset of breast cancer if a breast cancer case. Current age or age of death if not a breast cancer case. NA if there is no age information.
AgeOvary	Age of onset of ovarian cancer if an ovarian cancer case. Current age or age of death if not an ovarian cancer case. NA if there is no age information.
AgeBreastContralateral	Age at onset of breast cancer, second breast. Only for members with breast cancer status=2. For the rest enter a 0.
Twins	Identifies siblings who are identical twins. Each twin pair is identified by a unique number. For the rest enter a 0.
ethnic	Identifies the ethnicity of each family member. Enter "nonAJ", "AJ", "Italian", "Other" or NA (as recognized by is.na() function).
Death	Vital Status (0=Alive, 1=Dead)
AgeDeath	Family member's age at death or current age if alive.

If at least one family member is "AJ" the default is to use the prevalence associated with the "AJ" for family members with unknown ethnicity. Otherwise, the prevelance associated with "nonAJ" is used for family members with unknown ethnicity.

To begin using any BayesMendel models, load the package library:

```
> library(BayesMendel)
```

The parameters used by the model, including penetrance, allele frequency, and sensitivity/specificity of testing, are set using the function `brcaparams`. Any changes to the parameters can be made by calling this function.

```
> # Change future risk to be calculated in intervals of 2 y instead of the default of 5 y.
> # Leave all other parameters as set.
> myparams <- brcaparams(age.by=2)
> # Run BRCAPRO with family history information for example family
> out = brcapro(family=brca.fam)
```

```
[1] " Warning: age(s) older than age.max has been converted to age.max!"
[1] "Warning: Unknown ages of some unaffected and affected family members have been imputed. 
The probability of being a carrier is 0.2869353
 an BRCA1 carrier 0.133169
 an BRCA2 carrier 0.153731
The risks of developing cancers are
```

```
  By age Breast Ca Risk Ovarian Ca Risk
1     62     0.04633821      0.02369181
2     67     0.09087847      0.04762882
3     72     0.13116310      0.06961019
4     77     0.16541471      0.08831649
5     82     0.19325081      0.10299490
```

```
> slotNames(out)
```

```
[1] "family"       "posterior"    "probs"        "predictions"
[5] "counselee.id" "loglik"       "future.risk"
```

```
> out@probs
```

```
  Pr(Being a carrier) Pr(BRCA1 mutation) Pr(BRCA2 mutation)
1           0.2869353           0.133169           0.153731
  Pr(Both genes mutated)
1           3.530892e-05
```

```
> out@family
```

```
   ID Gender FatherID MotherID AffectedBreast AffectedOvary
1   1      0        3        2              0             0
2   2      0        9        8              0             1
3   3      1       11       10              0             0
4   4      0        0        1              0             0
5   5      1        3        2              0             0
6   6      0        0        0              0             0
7   7      0        3        2              1             0
8   8      0        0        0              0             1
9   9      1        0        0              0             0
10 10      0        0        0              0             0
11 11      1        0        0              0             0
12 12      0        9        8              0             0
13 13      0        9        8              0             0
14 14      0       11       10              1             0
15 15      1        5        6              0             0
16 16      1        0        7              0             0
17 17      0        0        7              0             0
18 18      0        0        7              0             0
19 19      0        0        7              0             0
20 20      0       21       12              0             0
```

21	21	1	0	0	0	0
22	22	0	9	8	2	0
23	23	0	0	22	0	0
24	24	1	5	6	0	0
25	25	1	5	6	0	0

	AgeBreast	AgeOvary	AgeBreastContralateral	Twins	ethnic	Death
1	57	57	0	0	nonAJ	0
2	70	69	0	1	nonAJ	0
3	87	87	0	0	nonAJ	0
4	32	32	0	0	nonAJ	0
5	50	50	0	0	nonAJ	0
6	57	57	0	0	nonAJ	0
7	45	47	0	0	nonAJ	0
8	65	65	0	0	nonAJ	0
9	94	94	0	0	nonAJ	0
10	75	75	0	0	nonAJ	0
11	94	94	0	0	nonAJ	0
12	85	85	0	0	nonAJ	0
13	79	79	0	0	nonAJ	0
14	1	70	0	0	nonAJ	0
15	23	23	0	0	nonAJ	0
16	12	12	0	0	nonAJ	0
17	22	22	0	0	nonAJ	0
18	19	19	0	0	nonAJ	0
19	16	16	0	0	nonAJ	0
20	54	54	0	0	nonAJ	0
21	77	77	0	0	nonAJ	0
22	40	70	45	1	nonAJ	0
23	40	40	0	0	nonAJ	0
24	17	17	0	2	nonAJ	0
25	17	17	0	2	nonAJ	0

	AgeDeath	Relation	Mastectomy	AgeMastectomy	Oophorectomy
1	57	1	0	1	0
2	70	4	0	1	0
3	87	4	0	1	0
4	32	3	0	1	0
5	50	2	0	1	0
6	NA	15	0	1	0
7	47	2	0	1	0
8	65	7	0	1	0
9	96	7	0	1	0
10	75	5	0	1	0
11	94	5	0	1	0
12	85	8	0	1	0
13	79	8	0	1	0

```
14       NA        6          0             1            0
15       23       13          0             1            0
16       12       13          0             1            0
17       22       13          0             1            0
18       19       13          0             1            0
19       16       13          0             1            0
20       54        0          0             1            0
21       77        0          0             1            0
22       70        8          0             1            0
23       40        0          0             1            0
24       17       13          0             1            0
25       17       13          0             1            0
   AgeOophorectomy BRCA1 BRCA2 ER PR CK14 CK5.6 HER2 AgeCur
1                1     0     0  0  0    0     0    0     57
2                1     0     0  0  0    0     0    0     70
3                1     0     0  0  0    0     0    0     87
4                1     0     0  0  0    0     0    0     32
5                1     0     0  0  0    0     0    0     50
6                1     0     0  0  0    0     0    0     NA
7                1     0     0  0  0    0     0    0     47
8                1     0     0  0  0    0     0    0     65
9                1     0     0  0  0    0     0    0     94
10               1     0     0  0  0    0     0    0     75
11               1     0     0  0  0    0     0    0     94
12               1     0     0  0  0    0     0    0     85
13               1     0     0  0  0    0     0    0     79
14               1     0     0  0  0    0     0    0     NA
15               1     0     0  0  0    0     0    0     23
16               1     0     0  0  0    0     0    0     12
17               1     0     0  0  0    0     0    0     22
18               1     0     0  0  0    0     0    0     19
19               1     0     0  0  0    0     0    0     16
20               1     0     0  0  0    0     0    0     54
21               1     0     0  0  0    0     0    0     77
22               1     0     0  0  0    0     0    0     70
23               1     0     0  0  0    0     0    0     40
24               1     0     0  0  0    0     0    0     17
25               1     0     0  0  0    0     0    0     17
   AgeBreastLower AgeBreastUpper AgeOvaryLower AgeOvaryUpper
1               1             57             1            57
2               1             70             1            70
3               1             87             1            87
4               1             32             1            32
5               1             50             1            50
6               1             94             1            94
```

```
7                1                47                1                47
8                1                65                1                65
9                1                94                1                94
10               1                75                1                75
11               1                94                1                94
12               1                85                1                85
13               1                79                1                79
14               1                94                1                94
15               1                23                1                23
16               1                12                1                12
17               1                22                1                22
18               1                19                1                19
19               1                16                1                16
20               1                54                1                54
21               1                77                1                77
22               1                70                1                70
23               1                40                1                40
24               1                17                1                17
25               1                17                1                17
   AgeBreastContralateralLower AgeBreastContralateralUpper  uua2
1                            1                           57 FALSE
2                            1                           70 FALSE
3                            1                           87 FALSE
4                            1                           32 FALSE
5                            1                           50 FALSE
6                            1                           94  TRUE
7                            1                           47 FALSE
8                            1                           65 FALSE
9                            1                           94 FALSE
10                           1                           75 FALSE
11                           1                           94 FALSE
12                           1                           85 FALSE
13                           1                           79 FALSE
14                           1                           94  TRUE
15                           1                           23 FALSE
16                           1                           12 FALSE
17                           1                           22 FALSE
18                           1                           19 FALSE
19                           1                           16 FALSE
20                           1                           54 FALSE
21                           1                           77 FALSE
22                           1                           70 FALSE
23                           1                           40 FALSE
24                           1                           17 FALSE
25                           1                           17 FALSE
```

```
>
```

2.2 Age Imputation

By default, `brcapro` imputes the ages of family members with unknown current or affected ages, denoted either by the user with NA (new as of v2.1) or value 1 (used in previous versions). Family members who are unaffected at an unknown age have their ages imputed using the approach taken in Lyte+ (see Biswas, S. Atienza, P., Chipman, J., Hughes, K., Gutierrez Barrera, A.M., Amos, C.I., Arun, B., Parmigiani, G. (2013) "Simplifying Clinical Use of the Genetic Risk Prediction Model BRCAPRO", Breast Cancer Research and Treatment, 139: 571-579.). Family members who are affected at an unknown age have their ages imputed using a multiple imputation approach that uses SEER incidence rates of breast and ovarian cancer to sample affection ages (bounded above by the individual's current age, if known). The imputation can be turned off by using the option `imputeAges` = FALSE in the `brcapro` function. Note that the imputation of relatives must also be turned off by using option `imputeRelatives` = FALSE in `brcapro`, because by default ages are imputed for relatives who are imputed. These options apply to models `MMRpro`, `pancpro`, and `melapro`. As of v2.1-7, users can now provide provide intervals for the imputation of affection ages by providing additional columns to the pedigree data frame. For `brcapro`, users can provide columns "AgeBreastLower", "AgeBreastUpper", "AgeOvaryLower", "AgeOvaryUpper", "AgeBreastContralateralLower", and "AgeBreastContralateralUpper". Then the user can use the option `bounds` = TRUE (by default it is FALSE).

```
> # Turn off age imputation
> out <- brcapro(family=brca.fam, imputeAges=FALSE, imputeRelatives=FALSE)
> # Calculate risks with imputed ages
> out = brcapro(family=brca.fam, imputeAges=TRUE, imputeRelatives=TRUE)


[1] " Warning: age(s) older than age.max has been converted to age.max!"
[1] "Warning: Unknown ages of some unaffected and affected family members have been imputed.
The probability of being a carrier is 0.2869312
 an BRCA1 carrier 0.1331671
 an BRCA2 carrier 0.1537299
The risks of developing cancers are
  By age Breast Ca Risk Ovarian Ca Risk
1     62     0.04633764      0.02369136
2     67     0.09087743      0.04762793
3     72     0.13116170      0.06960892
4     77     0.16541306      0.08831492
5     82     0.19324896      0.10299309


> # When age imputation is done, the original
> #family (with NA inputs re-coded to
```

```
> #unaffected, age = 1) is returned by brcapro
> out@family
```

	ID	Gender	FatherID	MotherID	AffectedBreast	AffectedOvary
1	1	0	3	2	0	0
2	2	0	9	8	0	1
3	3	1	11	10	0	0
4	4	0	0	1	0	0
5	5	1	3	2	0	0
6	6	0	0	0	0	0
7	7	0	3	2	1	0
8	8	0	0	0	0	1
9	9	1	0	0	0	0
10	10	0	0	0	0	0
11	11	1	0	0	0	0
12	12	0	9	8	0	0
13	13	0	9	8	0	0
14	14	0	11	10	1	0
15	15	1	5	6	0	0
16	16	1	0	7	0	0
17	17	0	0	7	0	0
18	18	0	0	7	0	0
19	19	0	0	7	0	0
20	20	0	21	12	0	0
21	21	1	0	0	0	0
22	22	0	9	8	2	0
23	23	0	0	22	0	0
24	24	1	5	6	0	0
25	25	1	5	6	0	0

	AgeBreast	AgeOvary	AgeBreastContralateral	Twins	ethnic	Death
1	57	57	0	0	nonAJ	0
2	70	69	0	1	nonAJ	0
3	87	87	0	0	nonAJ	0
4	32	32	0	0	nonAJ	0
5	50	50	0	0	nonAJ	0
6	57	57	0	0	nonAJ	0
7	45	47	0	0	nonAJ	0
8	65	65	0	0	nonAJ	0
9	94	94	0	0	nonAJ	0
10	75	75	0	0	nonAJ	0
11	94	94	0	0	nonAJ	0
12	85	85	0	0	nonAJ	0
13	79	79	0	0	nonAJ	0
14	1	70	0	0	nonAJ	0
15	23	23	0	0	nonAJ	0

16	12	12	0	0	nonAJ	0
17	22	22	0	0	nonAJ	0
18	19	19	0	0	nonAJ	0
19	16	16	0	0	nonAJ	0
20	54	54	0	0	nonAJ	0
21	77	77	0	0	nonAJ	0
22	40	70	45	1	nonAJ	0
23	40	40	0	0	nonAJ	0
24	17	17	0	2	nonAJ	0
25	17	17	0	2	nonAJ	0

	AgeDeath	Relation	Mastectomy	AgeMastectomy	Oophorectomy
1	57	1	0	1	0
2	70	4	0	1	0
3	87	4	0	1	0
4	32	3	0	1	0
5	50	2	0	1	0
6	NA	15	0	1	0
7	47	2	0	1	0
8	65	7	0	1	0
9	96	7	0	1	0
10	75	5	0	1	0
11	94	5	0	1	0
12	85	8	0	1	0
13	79	8	0	1	0
14	NA	6	0	1	0
15	23	13	0	1	0
16	12	13	0	1	0
17	22	13	0	1	0
18	19	13	0	1	0
19	16	13	0	1	0
20	54	0	0	1	0
21	77	0	0	1	0
22	70	8	0	1	0
23	40	0	0	1	0
24	17	13	0	1	0
25	17	13	0	1	0

	AgeOophorectomy	BRCA1	BRCA2	ER	PR	CK14	CK5.6	HER2	AgeCur
1	1	0	0	0	0	0	0	0	57
2	1	0	0	0	0	0	0	0	70
3	1	0	0	0	0	0	0	0	87
4	1	0	0	0	0	0	0	0	32
5	1	0	0	0	0	0	0	0	50
6	1	0	0	0	0	0	0	0	NA
7	1	0	0	0	0	0	0	0	47
8	1	0	0	0	0	0	0	0	65

```
9                1     0     0  0  0     0     0     0     94
10               1     0     0  0  0     0     0     0     75
11               1     0     0  0  0     0     0     0     94
12               1     0     0  0  0     0     0     0     85
13               1     0     0  0  0     0     0     0     79
14               1     0     0  0  0     0     0     0     NA
15               1     0     0  0  0     0     0     0     23
16               1     0     0  0  0     0     0     0     12
17               1     0     0  0  0     0     0     0     22
18               1     0     0  0  0     0     0     0     19
19               1     0     0  0  0     0     0     0     16
20               1     0     0  0  0     0     0     0     54
21               1     0     0  0  0     0     0     0     77
22               1     0     0  0  0     0     0     0     70
23               1     0     0  0  0     0     0     0     40
24               1     0     0  0  0     0     0     0     17
25               1     0     0  0  0     0     0     0     17
   AgeBreastLower AgeBreastUpper AgeOvaryLower AgeOvaryUpper
1               1             57             1            57
2               1             70             1            70
3               1             87             1            87
4               1             32             1            32
5               1             50             1            50
6               1             94             1            94
7               1             47             1            47
8               1             65             1            65
9               1             94             1            94
10              1             75             1            75
11              1             94             1            94
12              1             85             1            85
13              1             79             1            79
14              1             94             1            94
15              1             23             1            23
16              1             12             1            12
17              1             22             1            22
18              1             19             1            19
19              1             16             1            16
20              1             54             1            54
21              1             77             1            77
22              1             70             1            70
23              1             40             1            40
24              1             17             1            17
25              1             17             1            17
   AgeBreastContralateralLower AgeBreastContralateralUpper  uua2
1                            1                          57 FALSE
```

```
2                              1                              70 FALSE
3                              1                              87 FALSE
4                              1                              32 FALSE
5                              1                              50 FALSE
6                              1                              94  TRUE
7                              1                              47 FALSE
8                              1                              65 FALSE
9                              1                              94 FALSE
10                             1                              75 FALSE
11                             1                              94 FALSE
12                             1                              85 FALSE
13                             1                              79 FALSE
14                             1                              94  TRUE
15                             1                              23 FALSE
16                             1                              12 FALSE
17                             1                              22 FALSE
18                             1                              19 FALSE
19                             1                              16 FALSE
20                             1                              54 FALSE
21                             1                              77 FALSE
22                             1                              70 FALSE
23                             1                              40 FALSE
24                             1                              17 FALSE
25                             1                              17 FALSE
```

```
> # Can also impute ages, but not relatives.
> out = brcapro(family=brca.fam, imputeAges=TRUE, imputeRelatives=FALSE)
```

```
[1] " Warning: age(s) older than age.max has been converted to age.max!"
[1] "Warning: Unknown ages of some unaffected and affected family members have been imputed. 
The probability of being a carrier is 0.2869422
 an BRCA1 carrier 0.1331724
 an BRCA2 carrier 0.1537325
The risks of developing cancers are
  By age Breast Ca Risk Ovarian Ca Risk
1     62     0.04633919      0.02369261
2     67     0.09088024      0.04763038
3     72     0.13116546      0.06961240
4     77     0.16541752      0.08831923
5     82     0.19325394      0.10299803
```

```
> # Use lower and upper bounds for imputing affection ages
> fam <- brca.fam
> fam$AgeBreastLower <- fam$AgeBreast
```

```
> fam$AgeBreastUpper <- fam$AgeBreast
> fam$AgeOvaryLower <- fam$AgeOvary
> fam$AgeOvaryUpper <- fam$AgeOvary
> fam$AgeBreastContralateralLower <- fam$AgeBreastContralateral
> fam$AgeBreastContralateralUpper <- fam$AgeBreastContralateral
> fam$AgeBreastLower[14] <- 40
> fam$AgeBreastUpper[14] <- 50
> fam$AgeOvary[2] <- NA
> fam$AgeOvaryLower[2] <- 50
> fam$AgeOvaryUpper[2] <- 60
> out = brcapro(family=fam, bounds=TRUE)
```

```
[1] " Warning: age(s) older than age.max has been converted to age.max!"
[1] "Warning: Unknown ages of some unaffected and affected family members have been imputed. 
The probability of being a carrier is 0.2805121
 an BRCA1 carrier 0.1675303
 an BRCA2 carrier 0.1129256
The risks of developing cancers are
  By age Breast Ca Risk Ovarian Ca Risk
1     62     0.04524058      0.02607270
2     67     0.08904205      0.05188428
3     72     0.12875208      0.07513883
4     77     0.16250876      0.09466697
5     82     0.18993962      0.10997848
```

2.2.1 Changing the penetrance or prevalence

Generally, the user can specify the prevalence of *BRCA1* and *BRCA2* directly in the pedigree through the "ethnic" column.

The user can input their own values for prevalence by specifying ethnic = "Other" and inputting the values using the `brcaparams` function.

The user can also specify the net and crude penetrance estimates to be used by `brcapro`. The default net penetrance is the penet.brca.net object, and the default crude pentrance is penet.brca.crude. To use the penetrance estimates for the Italian population as the net penetrance, we can use `brcaparams`:

```
> myparams <- brcaparams(penetrance.net = BRCApenet.Italian.2008)
> out <- brcapro(family=brca.fam, params=myparams)
```

```
[1] " Warning: age(s) older than age.max has been converted to age.max!"
[1] "Warning: Unknown ages of some unaffected and affected family members have been imputed. 
The probability of being a carrier is 0.3202517
```

```
 an BRCA1 carrier 0.1785152
 an BRCA2 carrier 0.1416712
The risks of developing cancers are
  By age Breast Ca Risk Ovarian Ca Risk
1     62     0.04974193      0.02863679
2     67     0.09732302      0.05712815
3     72     0.14002909      0.08291403
4     77     0.17614693      0.10463543
5     82     0.20550192      0.12166739
```

2.2.2 Specifying race/ethnicity of the family

A set of race/ethnicity-specific baseline (non-carrier) penetrance values were recently added to `brcapro`. The current default assumes that the race/ethnicity of the input family is unknown, but the user can specify one of five different inputs: Asian, Black, Hispanic, NativeAmerican and White. Race/ethnicity categories and estimates were derived using the DevCan (http://srab.cancer.gov/devcan/) software provided by the National Cancer Institute (NCI). To specify a particular race, use the "race" input option in `brcapro`.

```
> out <- brcapro(family=brca.fam, race="Hispanic")
```

```
[1] " Warning: age(s) older than age.max has been converted to age.max!"
[1] "Warning: Unknown ages of some unaffected and affected family members have been imputed. 
The probability of being a carrier is 0.2900113
 an BRCA1 carrier 0.1349715
 an BRCA2 carrier 0.1549969
The risks of developing cancers are
  By age Breast Ca Risk Ovarian Ca Risk
1     62     0.04387991      0.02341315
2     67     0.08554593      0.04710024
3     72     0.12238862      0.06888901
4     77     0.15342498      0.08751894
5     82     0.17864897      0.10234033
```

2.2.3 Germline Testing Results

If the results for *BRCA1* and *BRCA2* germline testings are available, the user can input the results in data frame `germline.testing` (0=no test, 1=positive test, 2=negative test) with column names "BRCA1" and "BRCA2".

```
> # Add the testing results for BRCA1 and BRCA2
> BRCA1 <- BRCA2 <- rep(0,nrow(brca.fam))
```

```
> germline.testing <- data.frame(BRCA1,BRCA2)
> germline.testing[2,] <- c(2,0)
> out <- brcapro(family=brca.fam, germline.testing=germline.testing)

[1] " Warning: age(s) older than age.max has been converted to age.max!"
[1] "Warning: Unknown ages of some unaffected and affected family members have been imputed. 
The probability of being a carrier is 0.307824
 an BRCA1 carrier 0.000142593
 an BRCA2 carrier 0.3076402
The risks of developing cancers are
  By age Breast Ca Risk Ovarian Ca Risk
1     62     0.05013483      0.01431292
2     67     0.09715897      0.03080316
3     72     0.13936864      0.04765945
4     77     0.17529789      0.06300435
5     82     0.20450742      0.07508979
```

2.2.4 Marker Testing Results

If the results for *BRCA1* prognostic markers are available, the user can input the results in data frame `marker.testing` with column names shown below. Note that even if not all the biomarker results listed below are available, all 4 columns must contain non-missing values, which should be set to zero for biomarkers that were not tested.

Column Name	Content
ER	ER testing result. (0=no test, 1=positive test, 2=negative test)
CK14	CK14 testing result. (0=no test, 1=positive test, 2=negative test)
CK5.6	CK5/6 testing result. (0=no test, 1=positive test, 2=negative test)
PR	PR testing result. (0=no test, 1=positive test, 2=negative test)
HER2	HER2 testing result. (0=no test, 1=positive test, 2=negative test)

When the testing result for ER is negative, and the results for CK14 and CK5/6 are both also available, these 3 markers are treated as a group, and the calculations of carrier probabilities will incorporate the joint conditional probabilities of them given genetic status. If the result for either CK14 or CK5/6 is not available, the calculations of carrier probabilities will involve either the marginal conditional probability of ER given genetic status, or if HER2 testing is available, the joint conditional probability of ER and HER2 given genetic status. Note that when ER is positive, the testing results for CK14 or CK5/6 are not considered. For any family member, if the testing result for ER is available, the testing result for PR will be ignored even if it is also available. That is, PR will not be included in carrier prediction when ER is available. PR will only be used when either PR only or PR and HER2 testing are available.

```
> # Add the testing results for breast cancer markers
> marker.testing <- data.frame(matrix(rep(0,nrow(brca.fam)*5),ncol=5))
```

```
> colnames(marker.testing) <- c("ER","CK14","CK5.6","PR","HER2")
> brca.fam[1,"AffectedBreast"] <- 1
> marker.testing[1,"ER"] <- 2
> out <- brcapro(family=brca.fam, germline.testing=germline.testing, marker.testing=marker.te

[1] " Warning: age(s) older than age.max has been converted to age.max!"
[1] "Warning: Unknown ages of some unaffected and affected family members have been imputed. 
The probability of being a carrier is 0.8129797
 an BRCA1 carrier 0.0009915951
 an BRCA2 carrier 0.8113751
The risks of developing cancers are
  By age Contralateral Breast Ca Risk Ovarian Ca Risk
1     62                  0.04514924      0.03623374
2     67                  0.10869654      0.07797797
3     72                  0.18523087      0.12058843
4     77                  0.25944721      0.15932034
5     82                  0.32018518      0.18979158
```

2.2.5 Oophorectomy

If women in the pedigree have had an oophorectomy, this information can be included in the calculation by creating a data frame `oophorectomy`. Set up a data frame with two columns, one indicating if oophorectomy was done and the other with the age at oophorectomy. If no oophorectomy was done, an individual's current age should be used.

Column Name	**Content**
Oophorectomy	Oophorectomy yes/no. (0=no oophorectomy, 1=oophorectomy)
AgeOophorectomy	Age at Oophorectomy.

```
> # Add the information for oophorectomy
> Oophorectomy <- c(1,rep(0,(nrow(brca.fam)-1)))
> AgeOophorectomy <- c(30,rep(1,(nrow(brca.fam)-1)))
> oophorectomy <- data.frame(Oophorectomy,AgeOophorectomy)
> out <- brcapro(family=brca.fam, germline.testing=germline.testing, marker.testing=marker.te

[1] " Warning: age(s) older than age.max has been converted to age.max!"
[1] "Warning: Unknown ages of some unaffected and affected family members have been imputed. 
The probability of being a carrier is 0.8328211
 an BRCA1 carrier 0.001533733
 an BRCA2 carrier 0.8305426
The risks of developing cancers are
  By age Contralateral Breast Ca Risk Ovarian Ca Risk
1     62                  0.04561752     0.009709741
2     67                  0.11018288     0.020898338
```

```
3     72                  0.18811268     0.032319371
4     77                  0.26373655     0.042700655
5     82                  0.32563699     0.050867857
```

2.2.6 Mastectomy

If an individual in the pedigree has had a bilateral mastectomy, this information can be included in the calculation by creating a data frame `mastectomy`. Set up a data frame with two columns, one indicating if mastectomy was done and the other with the age at mastectomy. If no mastectomy was done, an individual's current age should be used. Only bilateral mastectomy should be included, and not mastectomy performed on only one breast.

Column Name	**Content**
Mastectomy	Mastectomy yes/no. (0=no mastectomy, 1=mastectomy)
AgeMastectomy	Age at Mastectomy.

```
> # Add the information for mastectomy
> Mastectomy <- c(1,rep(0,(nrow(brca.fam)-1)))
> AgeMastectomy <- c(57,rep(1,(nrow(brca.fam)-1)))
> mastectomy <- data.frame(Mastectomy,AgeMastectomy)
> out <- brcapro(family=brca.fam, mastectomy=mastectomy)
```

```
[1] " Warning: age(s) older than age.max has been converted to age.max!"
[1] "Warning: Unknown ages of some unaffected and affected family members have been imputed. 
The probability of being a carrier is 0.8101098
 an BRCA1 carrier 0.3548522
 an BRCA2 carrier 0.4550434
The risks of developing cancers are
  By age Contralateral Breast Ca Risk Ovarian Ca Risk
1     62                  0.04780295      0.06341081
2     67                  0.10688149      0.12754977
3     72                  0.17118867      0.18644464
4     77                  0.23101200      0.23653455
5     82                  0.27927401      0.27580621
```

2.3 MMRpro

2.3.1 Family History

Before running your pedigree through `MMRpro`, be sure it is structured as a numeric data frame with history of colon and endometrial cancers: n rows (where n is the number of family members, including the counselee) and 8 columns with required column names described below.

The family history includes the information on the counselee and his/her relatives. For each member, we need information on whether he or she has been diagnosed with colorectal cancer and either the age at diagnosis or, if cancer free, the current age or the age at death. We do the same for endometrial cancer, if the member is female.

The family cancer history must be entered in data frame form, with one row for each family member and columns containing the following information:

Column	**Content**
ID	Member identifier
Gender	Gender (0=female, 1=male)
FatherID	Father's identifier number
MotherID	Mother's identifier number
AffectedColon	Colorectal cancer status (0=no cancer,1=colon/rectum cancer,NA=no information)
AffectedEndometrium	Endometrial cancer status (0=no cancer, 1=ovarian cancer, NA=no information)
AgeColon	Age of onset of colorectal cancer if a colorectal cancer case. Current age or age of death if not a colorectal cancer case. NA if there is no age information.
AgeEndometrium	Age of onset of endometrial cancer if an endometrial cancer case. Current age or age of death if not an endometrial cancer case. NA if there is no age information.
Twins	Identifies siblings who are identical twins. Each twin pair is identified by a unique number. For the rest enter a 0.

If it is known that a family member is affected, but age of diagnosis is unknown, either enter an estimate or evaluate the program at different plausible ages.

The parameters used by the model, including penetrance, allele frequency, and sensitivity/specificity of testing, are set using the function `MMRparams`. Any changes to the parameters can be made by calling this function.

```
> # Change future risk to be calculated up to age 95 instead of the default 85.
> # Leave all other parameters as set.
> myparams <- MMRparams(age.to=95)
> # Run MMRpro with family history information for example family
> out = MMRpro(family=MMR.fam, params=myparams)
```

```
[1] "Warning: individuals have an unknown age of diagnosis.  The calculation would be improve
The probability of being a carrier is 0.01904266
 an MLH1 carrier 0.008184038
 an MSH2 carrier 0.009534781
 an MSH6 carrier 0.001330323
The risks of developing cancers are
  By age Colorectal Ca Risk Endometrial Ca Risk
1     60        0.004016592         0.005523277
```

```
2     65        0.008640795         0.010706530
3     70        0.014118479         0.014671650
4     75        0.020210281         0.017895306
5     80        0.026910326         0.020414861
6     85        0.033441145         0.022071694
7     90        0.038568851         0.022886836
8     95                 NA                  NA


>
```

2.3.2 Germline Testing

Information about germline testing results is included in the `germline.testing` object. If the results of germline testing are available, the user can input them into a data frame with n rows and 4 columns with column names "MLH1", "MSH2", and "MSH6" which stores the mutation testing results for *MLH1*, *MSH2*, and *MSH6* (0=no test, 1=positive test, 2=negative test).

```
> ## The counselee's father tested negative for MLH1 and MSH2.
> ## No testing for MSH6 was done.
> MLH1 <- MSH2 <- MSH6 <- rep(0, nrow(MMR.fam))
> germline.testing = data.frame(MLH1, MSH2, MSH6)
> germline.testing[3,] <- c(2,2,0)
> out <- MMRpro(family=MMR.fam, germline.testing = germline.testing)


[1] "Warning: individuals have an unknown age of diagnosis.  The calculation would be improve
The probability of being a carrier is 0.001556468
 an MLH1 carrier 2.154079e-05
 an MSH2 carrier 2.014245e-05
 an MSH6 carrier 0.001514848
The risks of developing cancers are
  By age Colorectal Ca Risk Endometrial Ca Risk
1     60        0.002893740         0.002650113
2     65        0.006417918         0.006084631
3     70        0.010870094         0.009673106
4     75        0.016050585         0.012896007
5     80        0.022011470         0.015437592
6     85        0.028025535         0.017108443


>
```

2.3.3 Marker Testing

Information about the colorectal tumor is included in the `marker.testing` object. This object is a data frame with n rows and 2 columns with information about MSI testing and location of the colorectal tumor. For more information on determining MSI, please refer to Boland (1998). If immunohistochemistry (IHC) was performed, enter 1 if any protein expression was shown to be abnormal or 2 if all were normal.

Column Name	**Content**
MSI	Microsatellite instability result enter 1 if high instability is present 2 if low instability or stability is present, or 0 if no MSI test has been performed.
location	Location of the colorectal tumor: enter 1 if found in the proximal colon 2 if found in the distal colon, or 0 if the location of the tumor is unknown.

```
> ## Now let's say the counselee's sister has a colorectal tumor
>
> MMR.fam[7, "AffectedColon"] <- 1
> ## The counselee's sister's tumor was found to be MSI high.
> ## Add in this MSI result.
>
> MSI <- location <- rep(0, nrow(MMR.fam))
> marker.testing <- data.frame(MSI, location)
> marker.testing[7, "MSI"] <- 1
> out <- MMRpro(family = MMR.fam, marker.testing = marker.testing)


[1] "Warning: individuals have an unknown age of diagnosis.  The calculation would be improve
The probability of being a carrier is 0.3370197
 an MLH1 carrier 0.1482241
 an MSH2 carrier 0.1821491
 an MSH6 carrier 0.00683245
The risks of developing cancers are
  By age Colorectal Ca Risk Endometrial Ca Risk
1     60         0.02402179          0.05691384
2     65         0.04826763          0.09380106
3     70         0.07206843          0.10527552
4     75         0.09447800          0.10916059
5     80         0.11443344          0.11171766
6     85         0.13023883          0.11338429


>
```

2.4 PancPRO

2.4.1 Family History

Before running your pedigree through `pancpro`, be sure it is structured as a numeric data frame with history of pancreas cancer: n rows (where n is the number of family members, including the counselee) and 6 columns with required column names described below.

The family history includes the information on the counselee and his/her relatives. For each member, we need information on whether he or she has been diagnosed with pancreatic cancer and either the age at diagnosis or, if cancer free, the current age or the age at death.

The family cancer history must be entered in data frame form, with one row for each family member and columns containing the following information:

Column	**Content**
ID	Member identifier
Gender	Gender (0=female, 1=male)
FatherID	Father's identifier number
MotherID	Mother's identifier number
AffectedPancreas	Pancreatic cancer status (0=no cancer, 1=pancreatic cancer, NA=no information)
AgePancreas	Age of onset of pancreatic cancer if a pancreas cancer case. Current age or age of death if not a pancreas cancer case. NA if there is no age information.
Twins	Identifies siblings who are identical twins. Each twin pair is identified by a unique number. For the rest enter a 0.

If it is known that a family member is affected, but age of diagnosis is unknown, either enter an estimate or evaluate the program at different plausible ages.

The parameters used by the model, including penetrance, allele frequency, and sensitivity/specificity of testing, are set using the function `pancparams`. Any changes to the parameters can be made by calling this function.

```
> # Change the output for future risk to be calculated
> # in age intervals of 1 year up to
> # age 65 instead of the default 5 years.
> # Leave all other parameters as set.
> myparams <- pancparams(age.by=1, age.to=65)
> # Run PancPRO with family history information for example family
> pancpro(family=panc.fam, params=myparams)
```

```
[1] "Warning: individuals have an unknown age of diagnosis.  The calculation would be improve
The probability of being a carrier is 0.4168366
The risks of developing cancers are
```

```
  By age Pancreatic Ca Risk
1     58        0.003001832
2     59        0.006246162
3     60        0.009733784
4     61        0.013461607
5     62        0.017422679
6     63        0.021607807
7     64        0.025998944
8     65        0.030572112
An object of class "BayesMendel"
Slot "family":
   ID Relation Gender FatherID MotherID AffectedPancreas
1   1        1      0        3        2                0
2   2        4      0        9        8                0
3   3        4      1       11       10                0
4   4        3      0        0        1                0
5   5        2      1        3        2                0
6   6       15      0        0        0                0
7   7        2      0        3        2                1
8   8        7      0        0        0                0
9   9        7      1        0        0                0
10 10        5      0        0        0                0
11 11        5      1        0        0                0
12 12        8      0        9        8                0
13 13        8      0        9        8                0
14 14        6      0       11       10                1
15 15       13      1        5        6                0
16 16       13      1        0        7                0
17 17       13      0        0        7                0
18 18       13      0        0        7                0
19 19       13      0        0        7                0
   AgePancreas Twins Death AgeDeath ethnic AgeCur
1           57     1     0       57   Panc     57
2           70     0     0       70   Panc     70
3           87     0     0       87   Panc     87
4           32     0     0       32   Panc     32
5           50     0     0       50   Panc     50
6           57     0     0       NA   Panc     NA
7           45     1     0       45   Panc     NA
8           65     0     0       65   Panc     65
9           94     0     0       96   Panc     94
10          75     0     0       75   Panc     75
11          94     0     0       94   Panc     94
12          85     0     0       85   Panc     85
13          79     0     0       79   Panc     79
```

```
14           1     0     0       NA   Panc     NA
15          23     0     0       23   Panc     23
16          12     0     0       12   Panc     12
17          22     0     0       22   Panc     22
18          19     0     0       19   Panc     19
19          16     0     0       16   Panc     16
   AgePancreasLower AgePancreasUpper
1                 1                57
2                 1                70
3                 1                87
4                 1                32
5                 1                50
6                 1                94
7                 1                94
8                 1                65
9                 1                94
10                1                75
11                1                94
12                1                85
13                1                79
14                1                94
15                1                23
16                1                12
17                1                22
18                1                19
19                1                16

Slot "posterior":
         PANC0    PANC1        PANC2
[1,] 0.5831634 0.416267 0.0005695756

Slot "probs":
 Pr(Being a carrier)
           0.4168366

Slot "predictions":
  By age Pancreatic Ca Risk
1     58        0.003001832
2     59        0.006246162
3     60        0.009733784
4     61        0.013461607
5     62        0.017422679
6     63        0.021607807
7     64        0.025998944
8     65        0.030572112
```

```
Slot "counselee.id":
[1] 1

Slot "loglik":
NULL

Slot "future.risk":
            hFX0        hFX1
1  0.0000000000 0.000000000
2  0.0000000000 0.000000000
3  0.0000000000 0.000000000
4  0.0000000000 0.000000000
5  0.0000000000 0.000000000
6  0.0000000000 0.000000000
7  0.0000000000 0.000000000
8  0.0000000000 0.000000000
9  0.0000000000 0.000000000
10 0.0000000000 0.000000000
11 0.0000000000 0.000000000
12 0.0000000000 0.000000000
13 0.0000000000 0.000000000
14 0.0000000000 0.000000000
15 0.0000000000 0.000000000
16 0.0000000000 0.000000000
17 0.0000000000 0.000000000
18 0.0000000000 0.000000000
19 0.0000000000 0.000000000
20 0.0000000000 0.000000000
21 0.0000000000 0.000000000
22 0.0000000000 0.000000000
23 0.0000000000 0.000000000
24 0.0000000000 0.000000000
25 0.0000000000 0.000000000
26 0.0000000000 0.000000000
27 0.0000000000 0.000000000
28 0.0000000000 0.000000000
29 0.0000000000 0.000000000
30 0.0000000000 0.000000000
31 0.0000000000 0.000000000
32 0.0000000000 0.000000000
33 0.0000000000 0.000000000
34 0.0000000000 0.000000000
35 0.0000000000 0.000000000
36 0.0000000000 0.000000000
```

```
37 0.0000000000 0.000000000
38 0.0000000000 0.000000000
39 0.0000000000 0.000000000
40 0.0000000000 0.000000000
41 0.0000000000 0.000000000
42 0.0000000000 0.000000000
43 0.0000000000 0.000000000
44 0.0000000000 0.000000000
45 0.0000000000 0.000000000
46 0.0000000000 0.000000000
47 0.0000000000 0.000000000
48 0.0000000000 0.000000000
49 0.0000000000 0.000000000
50 0.0000000000 0.000000000
51 0.0000000000 0.000000000
52 0.0000000000 0.000000000
53 0.0000000000 0.000000000
54 0.0000000000 0.000000000
55 0.0000000000 0.000000000
56 0.0000000000 0.000000000
57 0.0000000000 0.000000000
58 0.0001467817 0.006996109
59 0.0003072760 0.014554791
60 0.0004811673 0.022678395
61 0.0006681923 0.031359872
62 0.0008692960 0.040581221
63 0.0010912961 0.050310849
64 0.0013350476 0.060504270
65 0.0016002603 0.071104360

>
```

2.4.2 Germline and Marker Testing

Because the PANC gene is a hypothetical gene, there are no germline or marker testing results to add to the calculation.

2.5 MelaPRO

2.5.1 Family History

Before running your pedigree through `melapro`, be sure it is structured as a numeric data frame with history of melanomas: n rows (where n is the number of family members, including

the counselee) and 6 columns with required column names described below.

The family history includes the information on the counselee and his/her relatives. For each member, we need information on whether he or she has been diagnosed with melanoma and either the age at diagnosis or, if cancer free, the current age or the age at death.

The family cancer history must be entered in data frame form, with one row for each family member and columns containing the following information:

Column	**Content**
ID	Member identifier
Gender	Gender (0=female, 1=male)
FatherID	Father's identifier number
MotherID	Mother's identifier number
AffectedSkin	Number of diagnosed melanomas
	0=no cancer,1=single melanoma, 2=multiple melanomas, NA=no information
AgeSkin	Age of onset of melanomas if a cancer case.
	Current age or age of death if not a cancer case.
	NA if there is no age information.
Twins	Identifies siblings who are identical twins.
	Each twin pair is identified by a unique number. For the rest enter a 0.

If it is known that a family member is affected, but age of diagnosis is unknown, either enter an estimate or evaluate the program at different plausible ages.

The parameters used by the model, including penetrance, allele frequency, and sensitivity/specificity of testing, are set using the function `melaparams`. Any changes to the parameters can be made by calling this function.

```
> # Change likelihood ratio for single melanomas
> # among noncarriers from default 0.702 to 0.80
> myparams <- melaparams(spm.lr.noncarrier=0.80)
> # Run PancPRO with family history information for example family
> melapro(family=mela.fam, params=myparams)

[1] "Warning: individuals have an unknown age of diagnosis.  The calculation would be improve
The probability of being a carrier is 0.1204639
The risk of developing cancer is
   By age Melanoma Risk
1      35    0.01116896
2      40    0.02295988
3      45    0.03501317
4      50    0.04710430
5      55    0.05901270
6      60    0.07047355
7      65    0.08147133
8      70    0.09176121
```

```
9      75    0.10088929
10     80    0.10850911
11     85    0.11429754
An object of class "BayesMendel"
Slot "family":
   ID Gender FatherID MotherID AffectedSkin AgeSkin Twins Death
1   1      0        2        3            0    30.0     0     0
2   2      1       20       21            1    40.0     0     0
3   3      0       11       12            0    36.0     0     0
4   4      0        2        3            1    29.0     0     0
5   5      0        2        3            0    50.0     0     0
6   6      1        0        1            0    24.0     0     0
7   7      0        0        1            0    23.0     0     0
8   8      1        0        1            0    20.0     0     0
9   9      0        0        5            0    26.0     0     0
10 10      0        0        5            0    22.0     0     0
11 11      1        0        0            0    63.0     0     0
12 12      0        0        0            0    92.0     0     0
13 13      1       11       12            0    64.0     0     0
14 14      1       11       12            0    74.0     0     0
15 15      0       14        0            1     1.0     0     0
16 16      0       14        0            0    30.0     0     0
17 17      1       14        0            0    30.0     1     0
18 18      1       14        0            0    30.0     1     0
19 19      1       14        0            0    30.0     0     0
20 20      1        0        0            0    94.0     0     0
21 21      0        0        0            0    94.0     0     0
22 22      0       20       21            0    68.5     0     0
23 23      0       20       21            1     1.0     0     0
24 24      0       20       21            1     1.0     0     0
25 25      1       20       21            0    16.0     0     0
26 26      0        0       24            0    30.0     0     0
27 27      1        0       24            0    30.0     0     0
28 28      1        0       23            0    30.0     0     0
   AgeDeath ethnic Relation P16 AgeCur AgeSkinLower AgeSkinUpper
1        30    HBI        1   0     30            1           30
2        40    HBI        4   0     NA            1           94
3        36    HBI        4   0     36            1           36
4        29    HBI        2   0     NA            1           94
5        50    HBI        2   0     50            1           50
6        24    HBI        3   0     24            1           24
7        23    HBI        3   0     23            1           23
8        20    HBI        3   0     20            1           20
9        26    HBI       13   0     26            1           26
10       22    HBI       13   0     22            1           22
```

```
11       63    HBI        7   0     63            1           63
12       92    HBI        7   0     92            1           92
13       64    HBI        8   0     64            1           64
14       74    HBI        8   0     74            1           74
15       NA    HBI        0   0     NA            1           94
16       NA    HBI        0   0     NA            1           94
17       NA    HBI        0   0     NA            1           94
18       NA    HBI        0   0     NA            1           94
19       NA    HBI        0   0     NA            1           94
20       99    HBI        5   0     94            1           94
21      100    HBI        5   0     94            1           94
22       NA    HBI        6   0     NA            1           94
23       NA    HBI        6   0     NA            1           94
24       NA    HBI        6   0     NA            1           94
25       16    HBI        6   0     16            1           16
26       NA    HBI        0   0     NA            1           94
27       NA    HBI        0   0     NA            1           94
28       NA    HBI        0   0     NA            1           94

Slot "posterior":
          P160      P161         P162
[1,] 0.8795361 0.1204616 2.293133e-06

Slot "probs":
 Pr(Being a carrier)
           0.1204639

Slot "predictions":
   By age Melanoma Risk
1      35    0.01116896
2      40    0.02295988
3      45    0.03501317
4      50    0.04710430
5      55    0.05901270
6      60    0.07047355
7      65    0.08147133
8      70    0.09176121
9      75    0.10088929
10     80    0.10850911
11     85    0.11429754

Slot "counselee.id":
[1] 1

Slot "loglik":
```

```
NULL

Slot "future.risk":
            hFX0       hFX1
1  0.0000000000 0.00000000
2  0.0000000000 0.00000000
3  0.0000000000 0.00000000
4  0.0000000000 0.00000000
5  0.0000000000 0.00000000
6  0.0000000000 0.00000000
7  0.0000000000 0.00000000
8  0.0000000000 0.00000000
9  0.0000000000 0.00000000
10 0.0000000000 0.00000000
11 0.0000000000 0.00000000
12 0.0000000000 0.00000000
13 0.0000000000 0.00000000
14 0.0000000000 0.00000000
15 0.0000000000 0.00000000
16 0.0000000000 0.00000000
17 0.0000000000 0.00000000
18 0.0000000000 0.00000000
19 0.0000000000 0.00000000
20 0.0000000000 0.00000000
21 0.0000000000 0.00000000
22 0.0000000000 0.00000000
23 0.0000000000 0.00000000
24 0.0000000000 0.00000000
25 0.0000000000 0.00000000
26 0.0000000000 0.00000000
27 0.0000000000 0.00000000
28 0.0000000000 0.00000000
29 0.0000000000 0.00000000
30 0.0000000000 0.00000000
31 0.0001666687 0.01668756
32 0.0003465995 0.03365895
33 0.0005348096 0.05087558
34 0.0007304603 0.06830090
35 0.0009335321 0.08590033
36 0.0011440044 0.10364104
37 0.0013622627 0.12149190
38 0.0015907353 0.13942299
39 0.0018297821 0.15740585
40 0.0020793720 0.17541350
41 0.0023394615 0.19342038
```

```
42 0.0026107151 0.21140212
43 0.0028973655 0.22933472
44 0.0032000438 0.24719531
45 0.0035186513 0.26496227
46 0.0038530725 0.28261523
47 0.0042040053 0.30013479
48 0.0045761129 0.31750149
49 0.0049700017 0.33469687
50 0.0053854584 0.35170363
51 0.0058222547 0.36850563
52 0.0062793688 0.38508771
53 0.0067518608 0.40143493
54 0.0072386931 0.41753332
55 0.0077395899 0.43337006
56 0.0082542535 0.44893343
57 0.0087838650 0.46421261
58 0.0093368899 0.47919677
59 0.0099142944 0.49387600
60 0.0105155306 0.50824151
61 0.0111400438 0.52228559
62 0.0117873526 0.53600111
63 0.0124575000 0.54937938
64 0.0131497805 0.56241250
65 0.0138633045 0.57509382
66 0.0145971564 0.58741788
67 0.0153486300 0.59937953
68 0.0161063139 0.61096990
69 0.0168673629 0.62218096
70 0.0176306408 0.63300638
71 0.0183950116 0.64344154
72 0.0191588188 0.65348229
73 0.0199178428 0.66311993
74 0.0206700202 0.67234715
75 0.0214137840 0.68115915
76 0.0221476307 0.68955356
77 0.0228693099 0.69752853
78 0.0235726352 0.70507457
79 0.0242548677 0.71218469
80 0.0249141455 0.71885613
81 0.0255488666 0.72509006
82 0.0261580732 0.73088893
83 0.0267425968 0.73624571
84 0.0273001065 0.74115824
85 0.0278281805 0.74563124
```

```
>
```

2.5.2 Germline and Marker Testing

Information about germline testing results is included in the `germline.testing` object. If the results of germline testing are available, the user can input them into a data frame with n rows and 2 columns with column name "P16" which stores the mutation testing results for *P16* (0=no test, 1=positive test, 2=negative test).

```
> # The counselee's sister was tested for
> # germline mutations in P16, and one was found.
> # Proband was also tested, but no mutation was found.
> P16 <- rep(0, nrow(mela.fam))
> germline.testing = data.frame(P16)
> germline.testing[4,] <- 1
> germline.testing[1,] <- 2
> out <- melapro(family=mela.fam, germline.testing = germline.testing)
```

```
[1] "Warning: individuals have an unknown age of diagnosis.  The calculation would be improve
The probability of being a carrier is 0
The risk of developing cancer is
   By age Melanoma Risk
1      35  0.0009335321
2      40  0.0020793720
3      45  0.0035186513
4      50  0.0053854584
5      55  0.0077395899
6      60  0.0105155306
7      65  0.0138633045
8      70  0.0176306408
9      75  0.0214137840
10     80  0.0249141455
11     85  0.0278281805
```

```
>
```

2.6 BRCAPANCpro

2.6.1 Family History

Before running your pedigree through `brcapancpro`, be sure it is structured as a numeric data frame with history of breast, ovarian, and pancreatic cancers: n rows (where n is the number

of family members, including the counselee) and 13 columns with column names:

Column Name	**Content**
ID	Member identifier
Gender	Gender (0=female, 1=male)
FatherID	Father's identifier number
MotherID	Mother's identifier number
AffectedBreast	Breast cancer status (0=no cancer, 1=breast cancer,one breast involved; 2=bilateral breast cancer, NA=unknown status)
AffectedOvary	Ovarian cancer status (0=no cancer, 1=ovarian cancer, NA=unknown status)
AffectedPancreas	Pancreatic cancer status (0=no cancer, 1=pancreatic cancer, NA=unknown status)
AgeBreast	Age of onset of breast cancer if a breast cancer case. Current age or age of death if not a breast cancer case. NA if there is no age information.
AgeOvary	Age of onset of ovarian cancer if an ovarian cancer case. Current age or age of death if not an ovarian cancer case. NA if there is no age information.
AgePancreas	Age of onset of pancreatic cancer if a pancreatic cancer case. Current age or age of death if not a pancreatic cancer case. NA if there is no age information.
AgeBreastContralateral	Age at onset of breast cancer, second breast. Only for members with breast cancer status=2. For the rest enter a 0.
Twins	Identifies siblings who are identical twins. Each twin pair is identified by a unique number. For the rest enter a 0.
ethnic	Identifies the ethnicity of each family member. Enter "nonAJ", "AJ", "Italian", "Other" or NA (as recognized by is.na() function).
Death	Vital Status (0=Alive, 1=Dead)
AgeDeath	Family member's age at death or current age if alive.

The parameters used by the model, including penetrance, allele frequency, and sensitivity/specificity of testing, are set using the function `brcapancparams`. Any changes to the parameters can be made by calling this function.

```
> # Change future risk to be calculated in intervals of 2 y instead of the default of 5 y.
> # Leave all other parameters as set.
> myparams <- brcapancparams(age.by=2)
> # Run BRCAPRO with family history information for example family
> data(brcapanc.fam)
> out = brcapancpro(family=brcapanc.fam)
```

```
[1] " Warning: age(s) older than age.max has been converted to age.max! Warning: age(s) older
The probability of being a carrier is 0.5172612
 BRCA1 carrier is 0.1827323
 BRCA2 carrier is 0.214929
 PANC carrier 0.03227949
The risks of developing cancers are
  By age Breast Ca Risk Ovarian Ca Risk Pancreas Ca Risk
1     62     0.06907509      0.04100611      0.006524576
```

```
2     67     0.12817206      0.08770403      0.015927756
3     72     0.17788158      0.13683371      0.028097043
4     77     0.22573537      0.18555318      0.042415932
5     82     0.27130488      0.23122898      0.058200550
```

```
> slotNames(out)
```

```
[1] "family"       "posterior"    "probs"        "predictions"
[5] "counselee.id" "loglik"       "future.risk"
```

```
> out@probs
```

```
  Pr(Being a carrier) Pr(BRCA1 mutation) Pr(BRCA2 mutation)
1           0.5172612          0.1827323           0.214929
  Pr(PANC mutation) Pr(BRCA1 and PANC mutation)
1        0.03227949                   0.01189045
  Pr(BRCA1 and BRCA2 mutation) Pr(BRCA2 and PANC mutation)
1                   0.05739731                   0.01415459
  Pr(All three genes mutated)
1                 0.003878078
```

```
> out@family
```

```
   ID Gender FatherID MotherID AffectedBreast AffectedOvary
1   1      0        3        2              0             0
2   2      0        9        8              0             1
3   3      1       11       10              0             0
4   4      0        0        1              0             0
5   5      1        3        2              0             0
6   6      0        0        0              0             0
7   7      0        3        2              1             0
8   8      0        0        0              0             1
9   9      1        0        0              0             0
10 10      0        0        0              0             0
11 11      1        0        0              0             0
12 12      0        9        8              0             0
13 13      0        9        8              0             0
14 14      0       11       10              1             0
15 15      1        5        6              0             0
16 16      1        0        7              0             0
17 17      0        0        7              0             0
18 18      0        0        7              0             0
```

```
19 19       0         0         7                0             0
20 20       0        21        12                0             0
21 21       1         0         0                0             0
22 22       0         9         8                2             0
23 23       0         0        22                0             0
24 24       1         5         6                0             0
25 25       1         5         6                0             0
   AgeBreast AgeOvary AgeBreastContralateral Twins ethnic Death
1         57       57                      0     0  nonAJ     0
2         70       69                      0     1  nonAJ     0
3         87       87                      0     0  nonAJ     0
4         32       32                      0     0  nonAJ     0
5         50       50                      0     0  nonAJ     0
6         57       57                      0     0  nonAJ     0
7         45       47                      0     0  nonAJ     0
8         65       65                      0     0  nonAJ     0
9         94       94                      0     0  nonAJ     0
10        75       75                      0     0  nonAJ     0
11        94       94                      0     0  nonAJ     0
12        85       85                      0     0  nonAJ     0
13        79       79                      0     0  nonAJ     0
14         1       70                      0     0  nonAJ     0
15        23       23                      0     0  nonAJ     0
16        12       12                      0     0  nonAJ     0
17        22       22                      0     0  nonAJ     0
18        19       19                      0     0  nonAJ     0
19        16       16                      0     0  nonAJ     0
20        54       54                      0     0  nonAJ     0
21        77       77                      0     0  nonAJ     0
22        40       70                     45     1  nonAJ     0
23        40       40                      0     0  nonAJ     0
24        17       17                      0     2  nonAJ     0
25        17       17                      0     2  nonAJ     0
   AgeDeath AffectedPancreas AgePancreas Relation Mastectomy
1        57                0          57        1          0
2        70                0          70        4          0
3        87                1          60        4          0
4        32                0          32        3          0
5        50                0          50        2          0
6        NA                0          57       15          0
7        47                0          47        2          0
8        65                0          65        7          0
9        96                0          94        7          0
10       75                0          75        5          0
11       94                0          94        5          0
```

12	85	0	85	8	0
13	79	0	79	8	0
14	NA	0	70	6	0
15	23	0	23	13	0
16	12	0	12	13	0
17	22	0	22	13	0
18	19	0	19	13	0
19	16	0	16	13	0
20	54	0	54	0	0
21	77	0	77	0	0
22	70	0	70	8	0
23	40	0	40	0	0
24	17	0	17	13	0
25	17	0	17	13	0

	AgeMastectomy	Oophorectomy	AgeOophorectomy	BRCA1	BRCA2	ER	PR
1	1	0	1	0	0	0	0
2	1	0	1	0	0	0	0
3	1	0	1	0	0	0	0
4	1	0	1	0	0	0	0
5	1	0	1	0	0	0	0
6	1	0	1	0	0	0	0
7	1	0	1	0	0	0	0
8	1	0	1	0	0	0	0
9	1	0	1	0	0	0	0
10	1	0	1	0	0	0	0
11	1	0	1	0	0	0	0
12	1	0	1	0	0	0	0
13	1	0	1	0	0	0	0
14	1	0	1	0	0	0	0
15	1	0	1	0	0	0	0
16	1	0	1	0	0	0	0
17	1	0	1	0	0	0	0
18	1	0	1	0	0	0	0
19	1	0	1	0	0	0	0
20	1	0	1	0	0	0	0
21	1	0	1	0	0	0	0
22	1	0	1	0	0	0	0
23	1	0	1	0	0	0	0
24	1	0	1	0	0	0	0
25	1	0	1	0	0	0	0

	CK14	CK5.6	HER2	AgeCur	AgeBreastLower	AgeBreastUpper
1	0	0	0	57	1	57
2	0	0	0	70	1	70
3	0	0	0	87	1	87
4	0	0	0	32	1	32

5	0	0	0	50	1	50
6	0	0	0	NA	1	94
7	0	0	0	47	1	47
8	0	0	0	65	1	65
9	0	0	0	94	1	94
10	0	0	0	75	1	75
11	0	0	0	94	1	94
12	0	0	0	85	1	85
13	0	0	0	79	1	79
14	0	0	0	NA	1	94
15	0	0	0	23	1	23
16	0	0	0	12	1	12
17	0	0	0	22	1	22
18	0	0	0	19	1	19
19	0	0	0	16	1	16
20	0	0	0	54	1	54
21	0	0	0	77	1	77
22	0	0	0	70	1	70
23	0	0	0	40	1	40
24	0	0	0	17	1	17
25	0	0	0	17	1	17

	AgeOvaryLower	AgeOvaryUpper	AgeBreastContralateralLower
1	1	57	1
2	1	70	1
3	1	87	1
4	1	32	1
5	1	50	1
6	1	94	1
7	1	47	1
8	1	65	1
9	1	94	1
10	1	75	1
11	1	94	1
12	1	85	1
13	1	79	1
14	1	94	1
15	1	23	1
16	1	12	1
17	1	22	1
18	1	19	1
19	1	16	1
20	1	54	1
21	1	77	1
22	1	70	1
23	1	40	1

```
24             1            17                          1
25             1            17                          1
   AgeBreastContralateralUpper AgePancreasLower AgePancreasUpper
1                           57                1               57
2                           70                1               70
3                           87                1               87
4                           32                1               32
5                           50                1               50
6                           94                1               94
7                           47                1               47
8                           65                1               65
9                           94                1               94
10                          75                1               75
11                          94                1               94
12                          85                1               85
13                          79                1               79
14                          94                1               94
15                          23                1               23
16                          12                1               12
17                          22                1               22
18                          19                1               19
19                          16                1               16
20                          54                1               54
21                          77                1               77
22                          70                1               70
23                          40                1               40
24                          17                1               17
25                          17                1               17
    uua2  uua3
1  FALSE FALSE
2  FALSE FALSE
3  FALSE FALSE
4  FALSE FALSE
5  FALSE FALSE
6   TRUE  TRUE
7  FALSE FALSE
8  FALSE FALSE
9  FALSE FALSE
10 FALSE FALSE
11 FALSE FALSE
12 FALSE FALSE
13 FALSE FALSE
14  TRUE  TRUE
15 FALSE FALSE
16 FALSE FALSE
```

```
17 FALSE FALSE
18 FALSE FALSE
19 FALSE FALSE
20 FALSE FALSE
21 FALSE FALSE
22 FALSE FALSE
23 FALSE FALSE
24 FALSE FALSE
25 FALSE FALSE

>
```

Note that `brcapancpro` does not include the option for net/crude future risk. All the optional inputs for `brcapro` and `pancpro` such as germline testing results, marker testing results, race, ethnicity, mastectomies, and oophorectomies can be used for `brcapancpro`.

2.7 brcaproPlusBCRAT

`brcaproPlusBCRAT` is a model that combines `brcapro` and BCRAT (Gail, Mitchell H., et al. "Projecting individualized probabilities of developing breast cancer for white females who are being examined annually." JNCI: Journal of the National Cancer Institute 81.24 (1989): 1879-1886.). BCRAT is available through the BCRA R package on CRAN. `bcraproPlusBCRAT` uses BCRAT relative risks to modify the `brcapro` penetrances. Users can also run brcaproPlusBCRAT using `brcapro`, with the option `plusBCRAT = TRUE`.

Users can directly provide the relative risks through the option `rr.bcrat`, which is a vector of length 2 denoting the proband's BCRAT relative risk before 50 and the proband's BCRAT relative risk after 50. Alternatively, the user can provide input data for the BCRAT model using the option `bcrat.vars`, which can then be used as an input for the `relative.risk` function in the BCRA package.

2.8 LFSpro

LFSpro is a Mendelian model that estimates the probability of carrying a TP53 mutation, which is the main cause of Li-Fraumeni Syndrome (Peng, Gang, et al. "Estimating TP53 mutation carrier probability in families with Li-Fraumeni syndrome using LFSPRO." Cancer Epidemiology and Prevention Biomarkers 26.6 (2017): 837-844.). For more details about running the package, see https://bioinformatics.mdanderson.org/public-software/lfspro/.

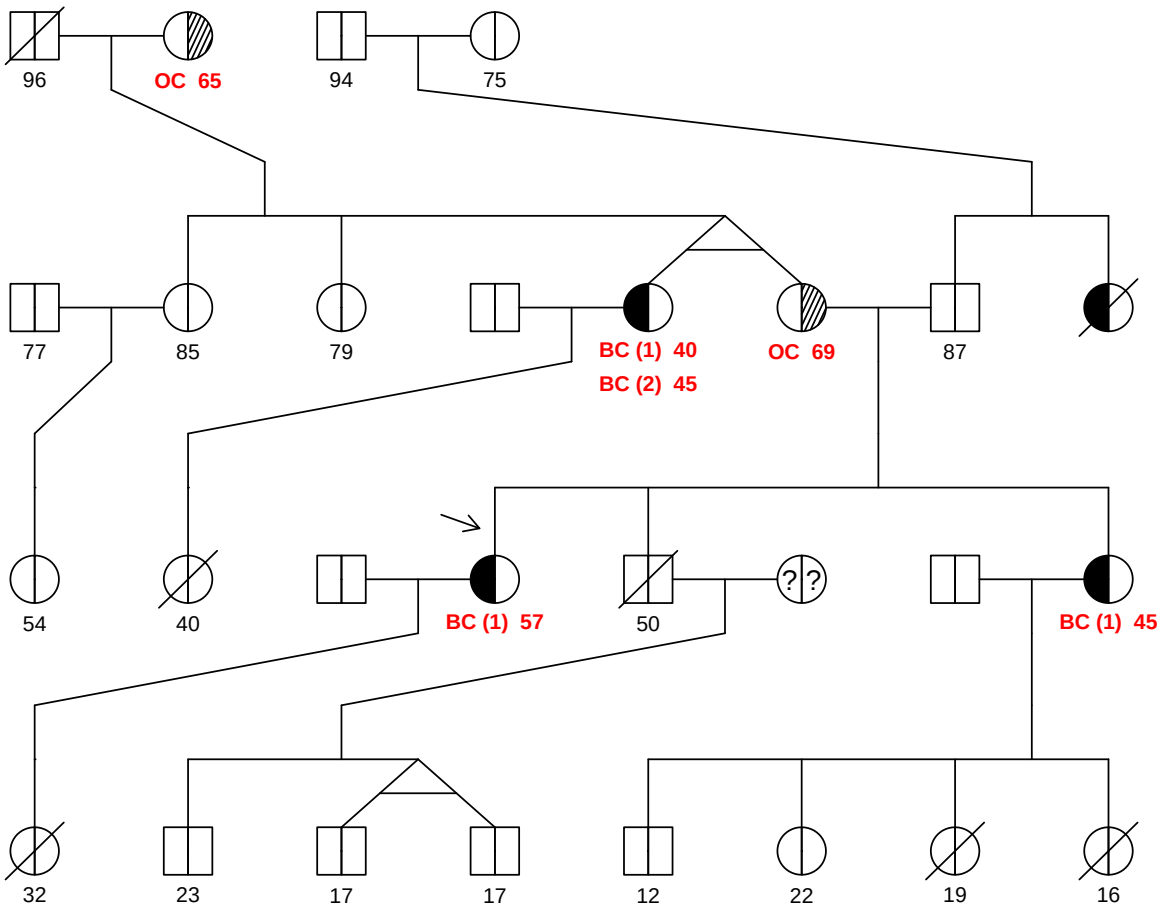
3 Other Features

3.1 Plotting a pedigree

The family history data frame can be displayed graphically in a traditional pedigree plot. There are two options for plotting your pedigree. If you want to plot your pedigree without running it through any of the models, the family history data frame `family` must be set to be part of the BayesMendel class and then plotted by simply using the generic function `plot`. If the vital status of family members is known, it can included by adding a column labeled "status" can be added to the family data frame. Enter 0 if the individual is alive, or 1 if not alive.

```
> pdf("brcafamplot.pdf")
> brca.fam$Death <- rbinom(nrow(brca.fam), 1, 0.2)
> myfamily <- new("BayesMendel", family=brca.fam, counselee.id=1)
> plot.BayesMendel(myfamily, cex=0.2)
> dev.off()


null device
          1
```



The pedigree can also be run through any of the models and plotted with the carrier probabilities displayed on the graph.

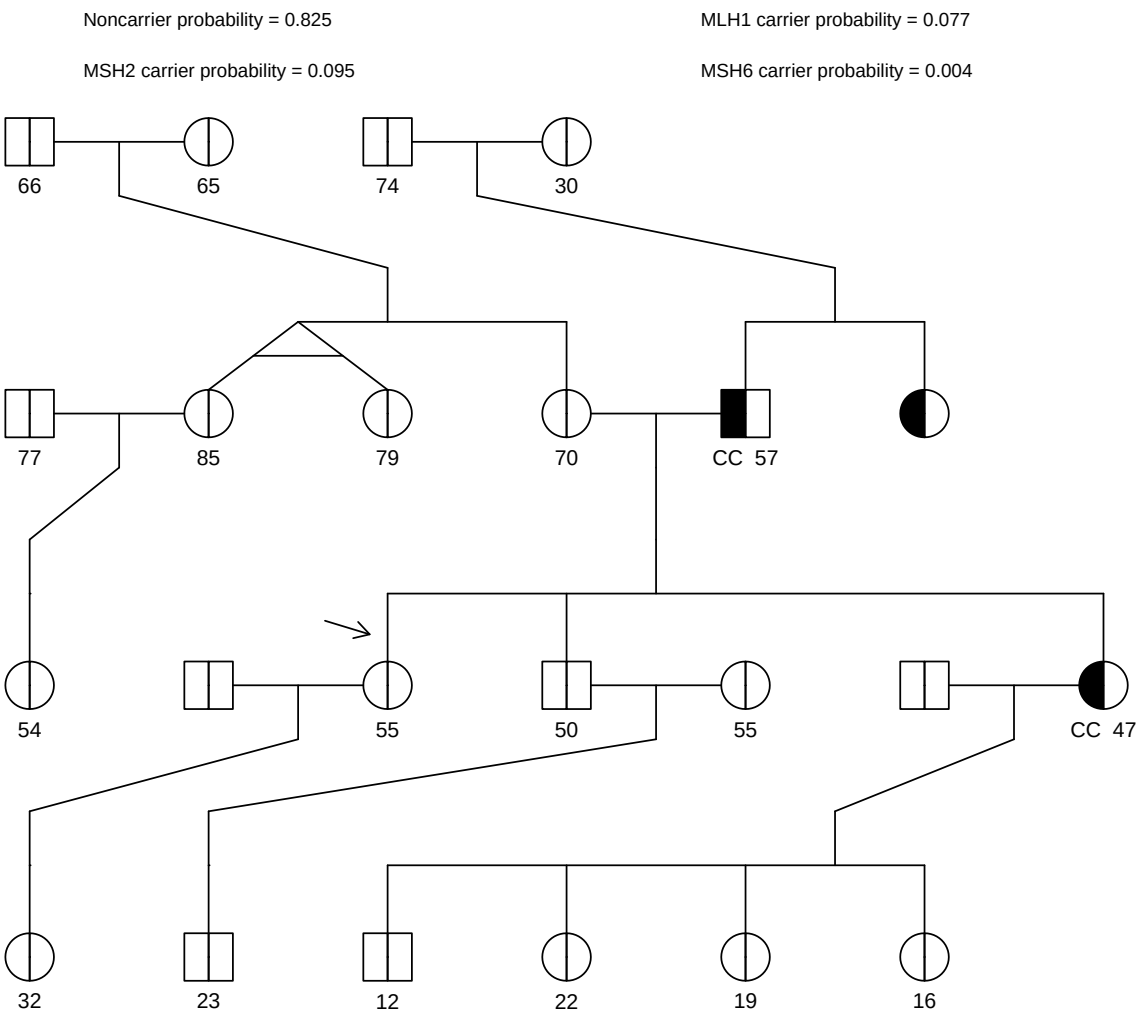
```
> pdf("mmrfamplot.pdf")
> MMR.fam$Death <- rbinom(nrow(MMR.fam), 1, 0.2)
> mmrpro.out <- MMRpro(family=MMR.fam, counselee.id=1)
```

```
[1] "Warning: individuals have an unknown age of diagnosis.  The calculation would be improve
The probability of being a carrier is 0.1751956
 an MLH1 carrier 0.07663265
 an MSH2 carrier 0.09514061
```

```
 an MSH6 carrier 0.003518854
The risks of developing cancers are
  By age Colorectal Ca Risk Endometrial Ca Risk
1     60         0.01386688          0.03081084
2     65         0.02814948          0.05156948
3     70         0.04264259          0.05918417
4     75         0.05675906          0.06269512
5     80         0.06997522          0.06520771
6     85         0.08106401          0.06685401
```

```
> plot(mmrpro.out, cex=0.2)
> dev.off()
```

```
null device
          1
```



4 Interpreting the Risk Predictions

The BayesMendel models can predict both net and crude future risk. Let T_C be the theoretical (discrete, in years) age of the specific cancer of interest of the proband. Thus, in the hypothetical scenario where the proband does not die before this age, the proband would develop the cancer of interest at this age. It is important to note that the proband may or may not actually observe this outcome. Now let T_D be the age of death from causes other than the cancer for the proband, and let $T = \min(T_C, T_D)$ be the age of the first outcome, either the cancer of interest or death from other causes. Let $J = C$ if $T = T_C$; i.e., if the proband actually

develops the cancer of interest, and let $J = D$ if $T = T_D$.

Net t-year risk predictions in these models can be interepreted as the probability of developing the disease within t years, conditional on being disease-free at the current age, assuming no death from other causes. Thus the t-year net risk, given that the proband is currently age t_0, is

$$P(T_C \leq t_0 + t | T_C > t_0).$$

Crude t-year risk is the probability of developing the disease within t years (without death from other causes), conditional on being disease-free and alive at the current age. Thus the t-year crude risk is

$$P(T \leq t_0 + t, J = C | T > t_0).$$

Here we ignore the dependency on the gender and genotype in the penetrance functions.

5 Further Information

More information about our methods and software can be found at our website https://projects.iq.harvard.edu/bayesmendel. We can also be reached by email at BayesMendel@jimmy.harvard.edu.