

Susceptibility Prediction in Familial Colon Cancer

Giovanni Parmigiani

gp@jhu.edu

Cancer Risk Prediction Models:

A Workshop on Development, Evaluation, and Application

NCI, May 2004

SUSCEPTIBILITY PREDICTION MODELS

Family history can be very informative
about the presence of a mutation

Predicting mutations is possible
and useful in two contexts:

SUSCEPTIBILITY PREDICTION MODELS

Family history can be very informative
about the presence of a mutation

Predicting mutations is possible
and useful in two contexts:

HIGH RISK CLINICS:

Counseling about testing decisions

Interpretation test outcomes *for individuals*

Predicting who will develop cancer

SUSCEPTIBILITY PREDICTION MODELS

Family history can be very informative
about the presence of a mutation

Predicting mutations is possible
and useful in two contexts:

HIGH RISK CLINICS:

Counseling about testing decisions

Interpretation test outcomes *for individuals*

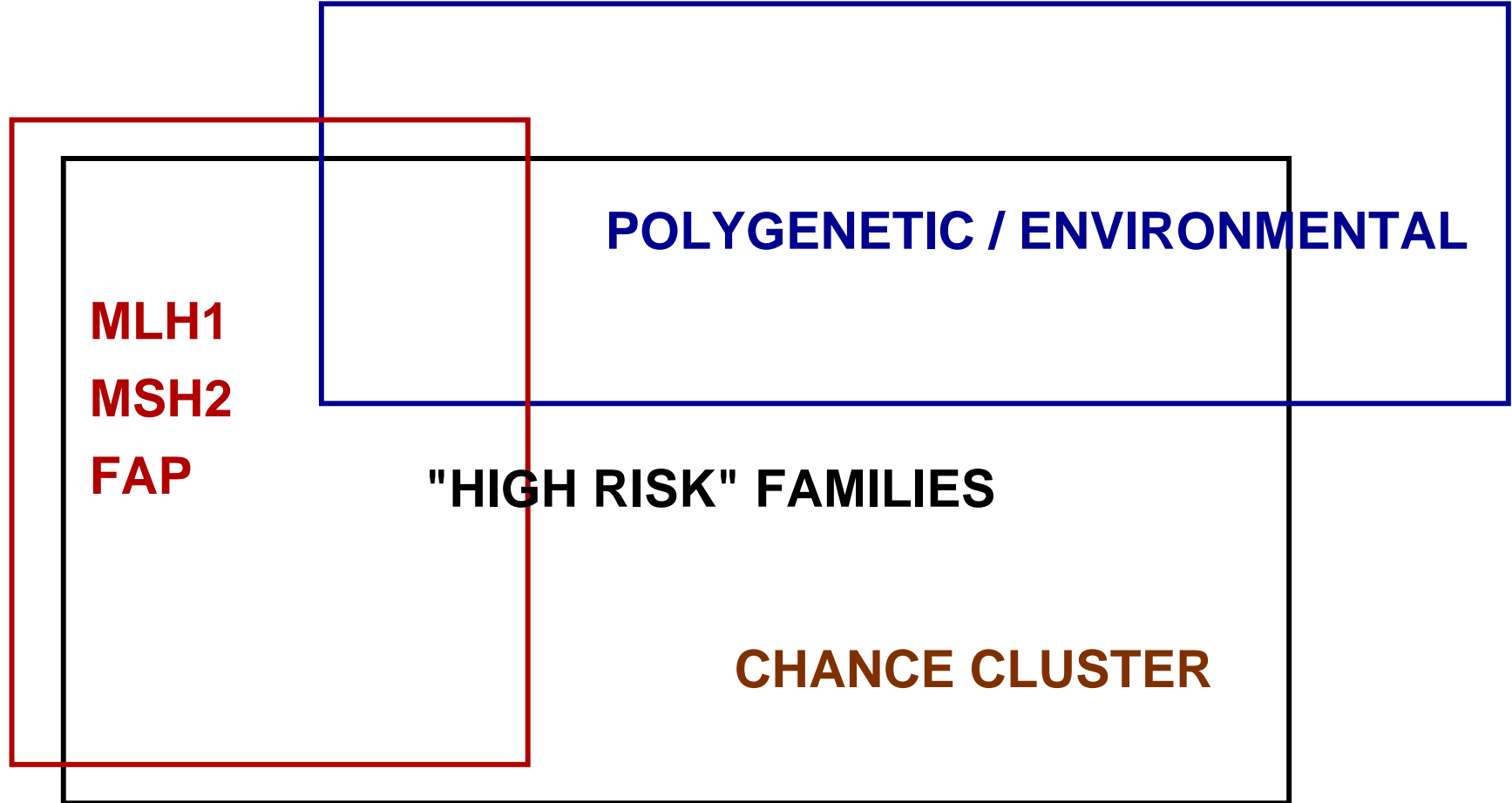
Predicting who will develop cancer

GENE CHARACTERIZATION RESEARCH:

Selecting high risk subjects

Building measures of susceptibility

OTHER FAMILIES



EMPIRICAL MODELING

$$P \left(\begin{array}{c|c} \text{Positive} & \text{Pedigree} \\ \text{Genetic} & \text{Information} \\ \text{Test} & \end{array} \right)$$

- Correlates genetic testing results to features of family history
- Relies on AI/statistics to infer the **genotype | phenotype** relationship and the **mode of inheritance**
- Generally gives broad classes of families

MENDELIAN MODELING

$$P \left(\begin{array}{c|c} \text{Deleterious} & \text{Pedigree} \\ \text{Mutation at} & \text{Information} \\ \text{Susceptibility Gene} & \end{array} \right)$$

- Derives carrier probabilities from genetic parameters
- Relies on statistics to infer the **phenotype** | **genotype** relationship
- Relies on Mendel's laws for the mode of inheritance.

RELATIONSHIP BETWEEN SCALES OF EMPIRICAL AND MENDELIAN PREDICTIONS

$$P \left(\begin{array}{c} \text{Positive} \\ \text{Genetic} \\ \text{Test} \end{array} \middle| \begin{array}{c} \text{Pedigree} \\ \text{Information} \end{array} \right) = \beta \times P \left(\begin{array}{c} \text{Deleterious} \\ \text{Mutation at} \\ \text{Susceptibility Gene} \end{array} \middle| \begin{array}{c} \text{Pedigree} \\ \text{Information} \end{array} \right)$$

β : Test Sensitivity; Specificity assumed complete

EMPIRICAL

MENDELIAN

LOGIC BEHIND MENDELIAN RISK PREDICTION: notation

γ	Genotype vector.
γ^*	(the 0 vector) indicates the wildtype.
θ	Penetrance-related parameters
π	Prevalence-related parameters
H	History of relevant phenotypes for an individual
$r = 1, \dots, R$	Index of relative of a counselee within a family (counselee indexed by 0)
F	A family history, vector $F = (H_0, H_1, \dots, H_R)$
T	Genetic test result

Carrier Probability: $p(\gamma_0 | H_0, H_1, \dots, H_R, \pi, \theta)$

LOGIC BEHIND MENDELIAN RISK PREDICTION: general approach

Updating:

$$p(\gamma_0 | H_0, \dots, H_R, \pi, \theta) = \frac{p(\gamma_0 | \pi) p(H_0, H_1, \dots, H_R | \gamma_0, \theta, \pi)}{\sum_{\text{all } \gamma_0 \text{'s}} p(\gamma_0 | \pi) p(H_0, \dots, H_R | \gamma_0, \theta, \pi)}.$$

LOGIC BEHIND MENDELIAN RISK PREDICTION: general approach

Updating:

$$p(\gamma_0 | H_0, \dots, H_R, \pi, \theta) = \frac{p(\gamma_0 | \pi) p(H_0, H_1, \dots, H_R | \gamma_0, \theta, \pi)}{\sum_{\text{all } \gamma_0\text{'s}} p(\gamma_0 | \pi) p(H_0, \dots, H_R | \gamma_0, \theta, \pi)}.$$

Integration:

$$p(H_0, H_1, \dots, H_R | \gamma_0, \theta, \pi) = \sum_{\text{all } \gamma_1 \dots \gamma_R\text{'s}} p(H_0, \dots, H_R | \gamma_0, \dots, \gamma_R, \theta) p(\gamma_1, \dots, \gamma_R | \gamma_0, \pi).$$

LOGIC BEHIND MENDELIAN RISK PREDICTION: sources of information

$p(\gamma_0)$ Prevalence studies

$p(\gamma_1, \dots, \gamma_R | \gamma_0)$ Mendel's laws +
Prevalence Studies

$p(H_0, \dots, H_R | \gamma_0, \dots, \gamma_R)$ Penetrance studies

$p(H_0, \dots, H_R | \gamma_0, \dots, \gamma_R) = \prod_r p(H_r | \gamma_r)$
Conditional independence

to HNPCC example

CRCAPRO

GENOTYPE: MLH1 & MSH2

FAMILY HISTORY:

I-st and II-nd degree relatives of counseland

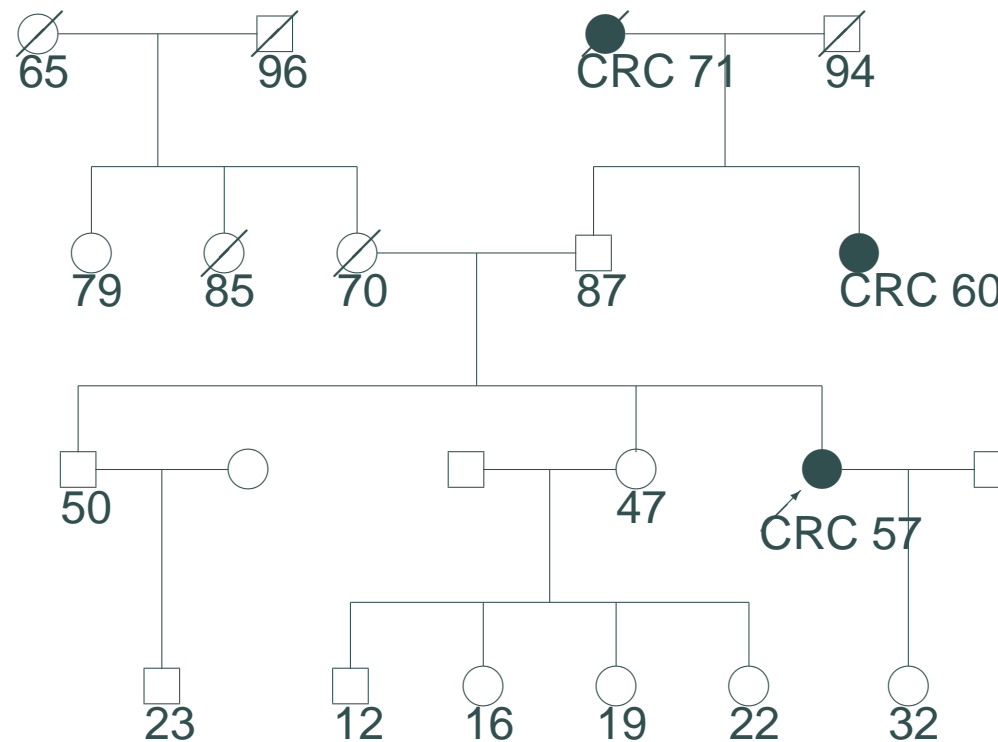
Colorectal and endometrial cancer history (m & f)

MSI testing

Age of onset, age of death or current age

PENETRANCES: Meta-analysis. Independent estimates in progress using Creighton data.

PREVALENCES: Meta-analysis.



	Pedigree	Mendelian	Wijnen
1	As in Figure above	0.028	.0019
2	No information about father	0.277	.0019
3	Father with CRC@60, pat. aunt unaff.	0.357	.0019
4	Sister with EC@50	0.597	.0099
5	Living maternal aunt with EC@50	0.057	.0099

SOFTWARE

BayesMendel:

R environment for Mendelian risk prediction, including:

- BRCAPRO
- CRCAPRO
- Sets of genetic parameters that are specific to ethnic groups
- Functionality to build Mendelian Models for other syndromes

CaGene:

- Inclusion of CRCAPRO (via BayesMendel) completed
- Legal details pending

[web search for BayesMendel](#)

```
> library(BayesMendel)
```

```
> data(testfam)
```

```
> testfam
```

```
[1,] 1 1 0 3 2 0 0 57 57 0 0 0
```

```
[2,] 2 4 0 9 8 0 1 70 69 0 0 0
```

```
.....
```

```
> data(HNPCCpenet)
```

```
> crcapro(testfam,penetrance=HNPCCpenet)
```

```
          [,1]          [,2]          [,3]
```

```
[1,] 2.498343e-18 2.923043e-13 1.895220e-08
```

```
[2,] 1.813742e-13 2.073328e-08 1.100074e-03
```

```
[3,] 6.683116e-09 6.653272e-04 9.982346e-01
```


VALIDATION

Data: 60 families tested for MSH1 and MLH2 at JHU.

Goal: Compare CRCAPRO to Wijnen

OVERALL PERFORMANCE by RMSE

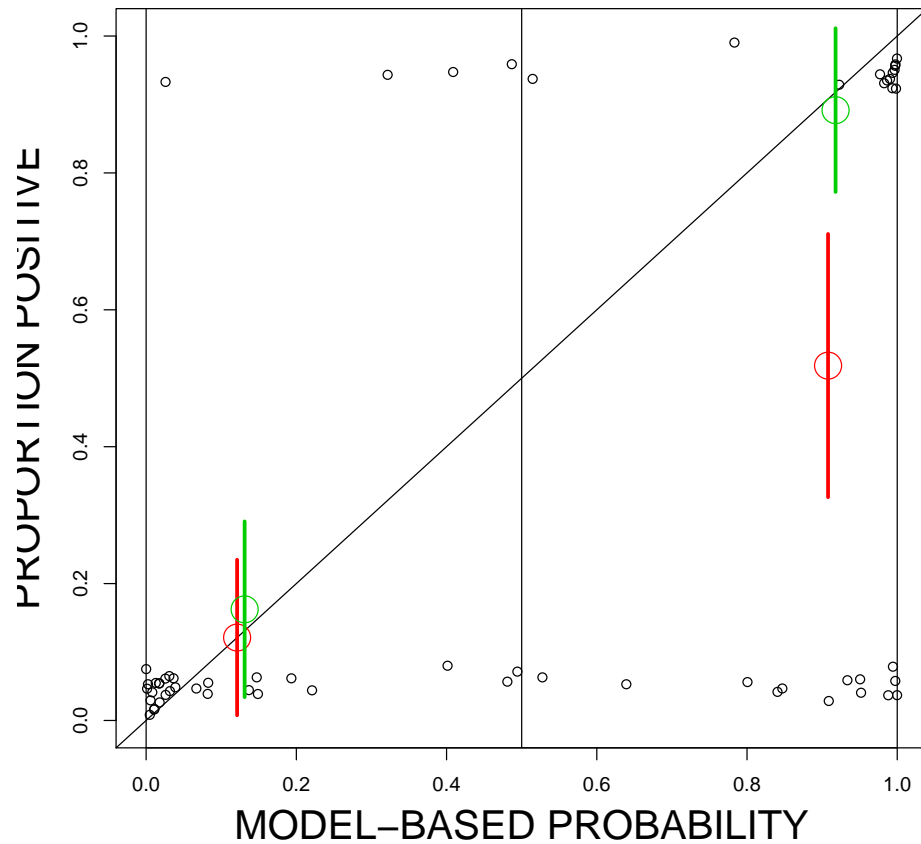
CRCAPRO	0.30
Wijnen	0.44

LOGISTIC PREDICTION of POSITIVE TEST RESULT

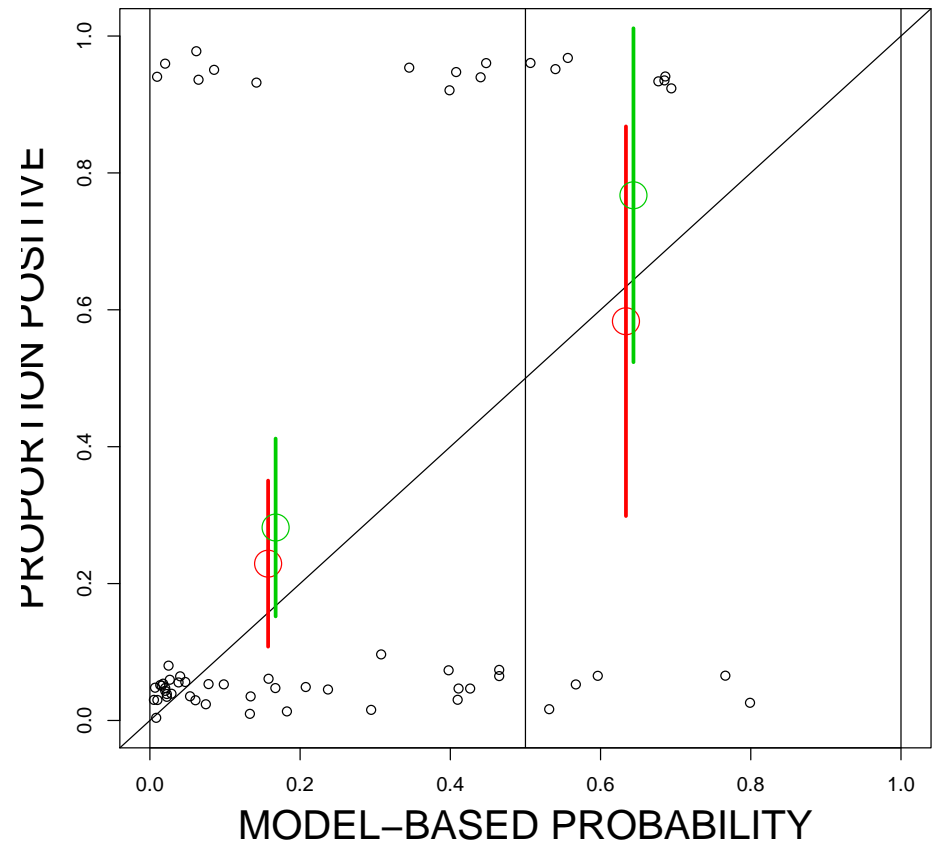
	Estimate	Std. Error	z value	Pr(> z)	
(Intercept)	-2.7342	0.7224	-3.785	0.000154	***
CRCAPRO	2.9138	1.0087	2.889	0.003867	**
Wijnen	0.6476	1.5523	0.417	0.676549	

CALIBRATION

CRCAPRO



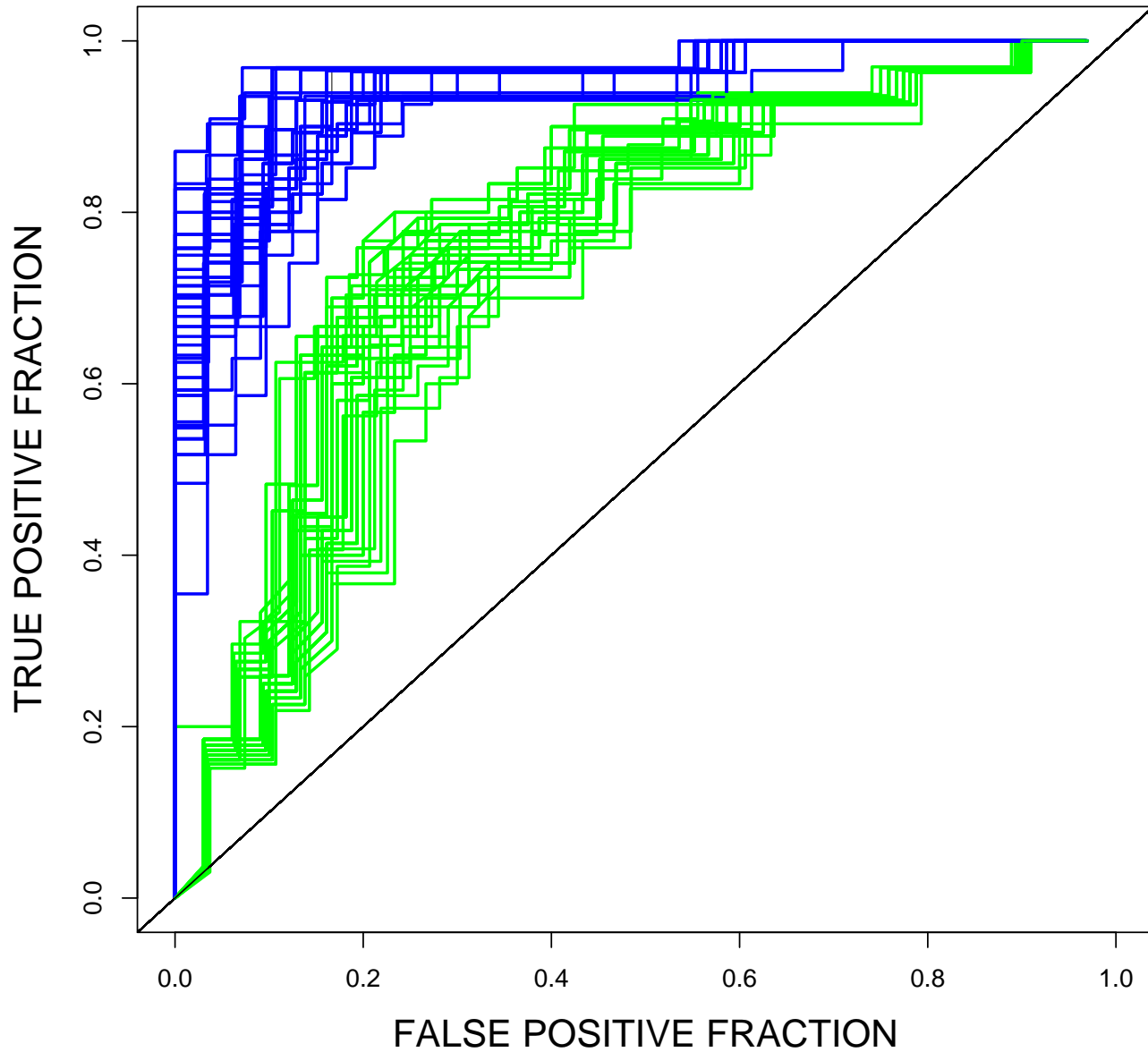
Wijnen



RED: prior to adjustment for mutation screening sensitivity

GREEN: after adjustment for mutation screening sensitivity

DISCRIMINATION: ROC curves



CRCAPRO

Wijnen

Credits



Lab: Karl Broman, Sining Chen, Ed Iversen, Wenyi Wang

Clinical collaborators: Ken Kinzler, Francis Giardiello, David Euhus

SPORE collaborations: Chris Amos, Steve Gruber, Sapna Syngal, Patrice Watson