Verification and Validation Assessment in Genetic Counseling and Testing

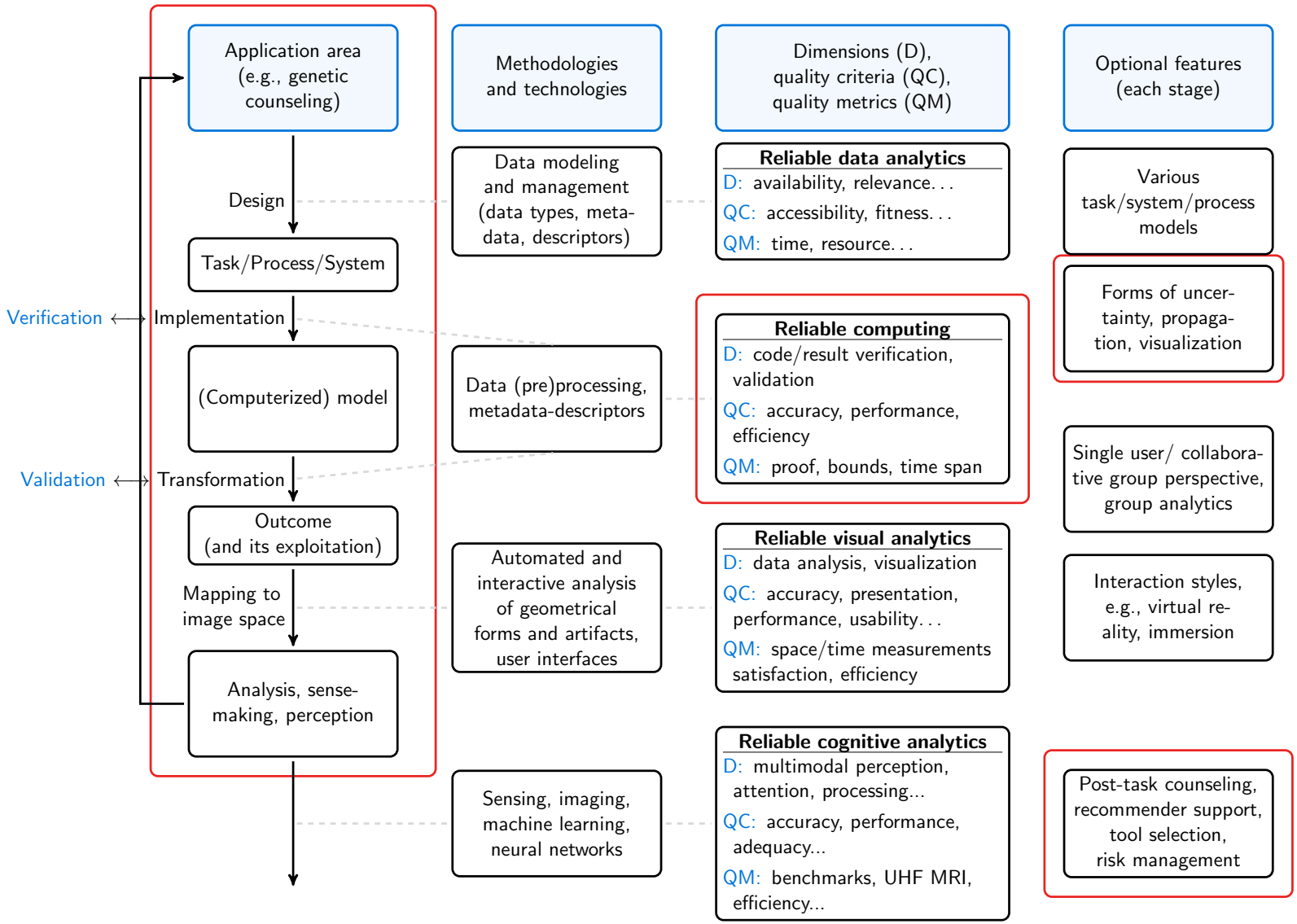
Ekaterina Auer and Wolfram Luther

University of Applied Sciences Wismar

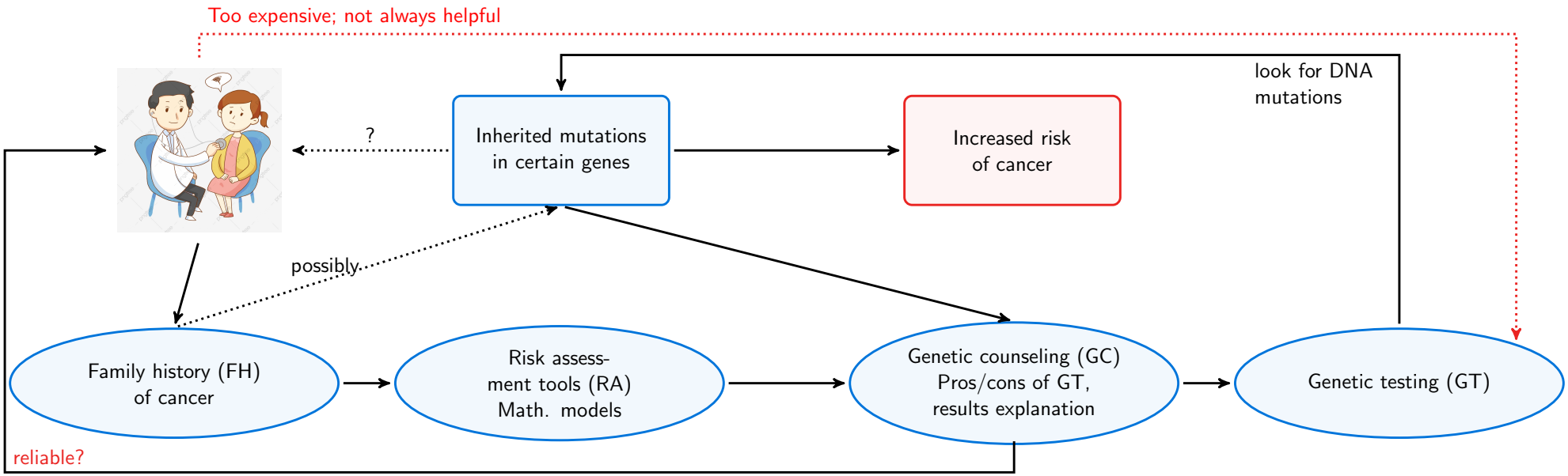
University of Duisburg-Essen

CODASSCA 2020, September 14–17, 2020

Reliable V&V Assessment



Genetic Counseling and Testing



Breast cancer (BC) risk: Important mutations are in the *BRCA1/2* genes

BRCA1 and *BRCA2* are the so-called tumor supressor genes

Gene change: More likely in a person with FH of BC (+ ovarian, etc.)

Other criteria: Closeness, number, age of the affected family member(s)

There is a high degree of uncertainty in the process!

Our Observations

→ Many studies/meta-studies evaluate GT, GC, RA:

Karst, K. et al.: *Validation of the Manchester scoring system for predicting BRCA1/2 mutations in 9,390 families suspected of having hereditary breast and ovarian cancer*, 2014

Himes, D.: *Breast cancer risk assessment: Evaluation of screening tools for genetics referral*, 2019

Nelson, H. D. et al.: *Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women – Updated Evidence Report and Systematic Review for the US Preventive Services Task Force*, 2019

→ Evaluation of studies' results is focused on aleatory uncertainty

→ Epistemic uncertainty is considered indirectly through comparisons with other studies/meta-studies

→ Different studies use different criteria for test persons, ages or degrees of kinship that often cannot be mapped to each other

→ Current studies have bigger proband groups (100 $\longrightarrow$ 10000)

→ It is necessary to work with sets while comparing approaches

Our Contribution

A first step in the direction of a consistent and reliable V&V framework for RA and GC stages

In the focus:

- Merging risk factors across RA tools (e.g., FHAT and Frank tables)
- Introducing a new method combining the decision tree logic of RST with FHAT/MSS using intervals analysis to compute interval bounds for risk scores (rs), with mutation probabilities (mp) where possible

Important: Not to overestimate the risk (impairs patients in their decisions)

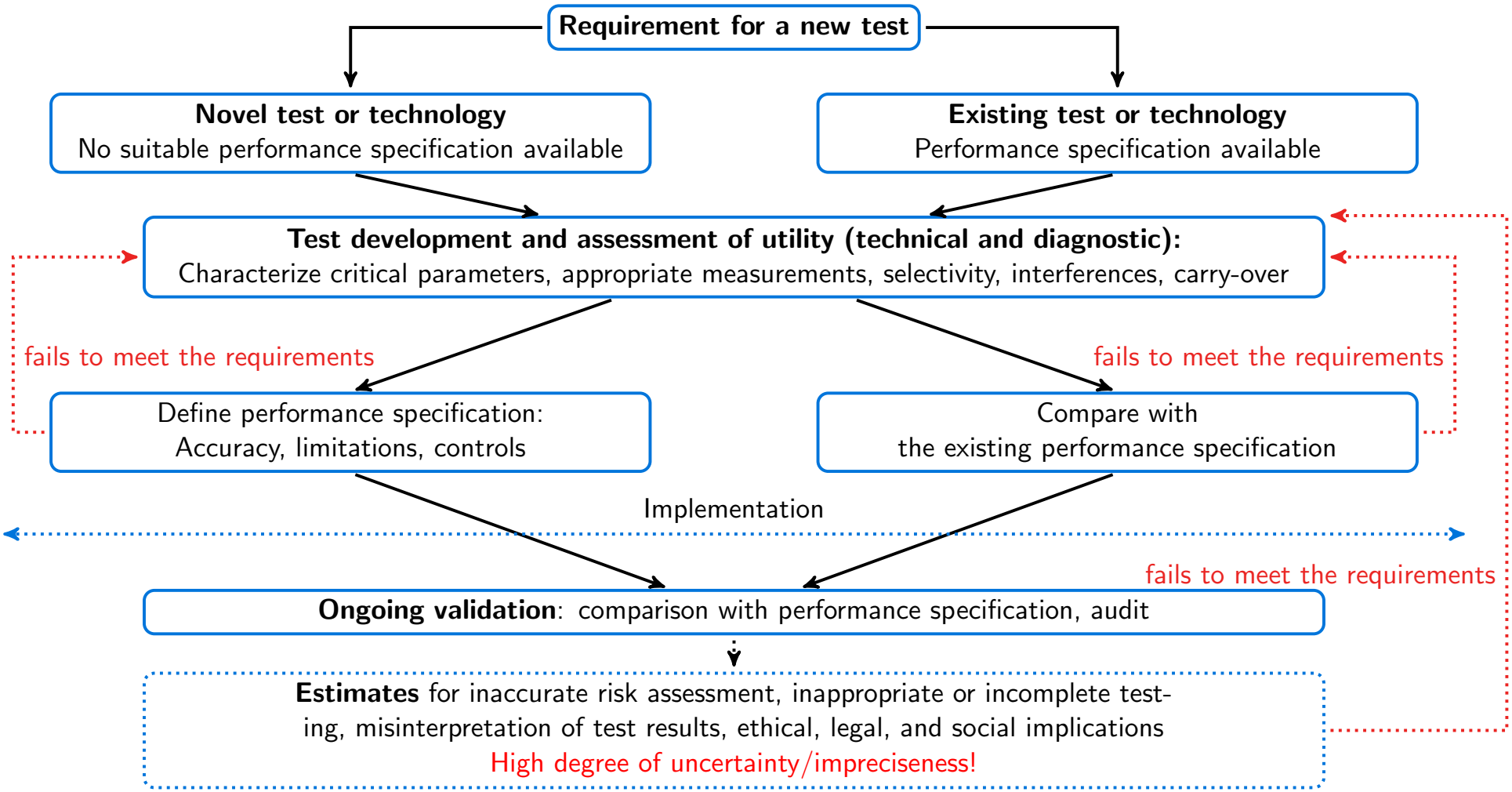
FHAT – the Ontario FH assessment tool, see Gilpin, C. A. et al: *A preliminary validation...*, 2000

MSS – the Manchester scoring system, see Evans, D. G. R. et al.: *A new scoring-system...*, 2004

RST – the referral screening tool, see Bellcross, C. A. et al.: *Evaluation of ...*, 2009

Frank tables – Frank, T. S. et al.: *Clinical Characteristics of Individuals With Germline...*, 2002

V&V of Genetic Testing



Mattocks, C. J. et al.: *A standardized framework for the validation and verification of clinical molecular genetic tests*, EJ of HG (2010)

Any Schemes for GC Comparable to V&V of GT?

To begin with...

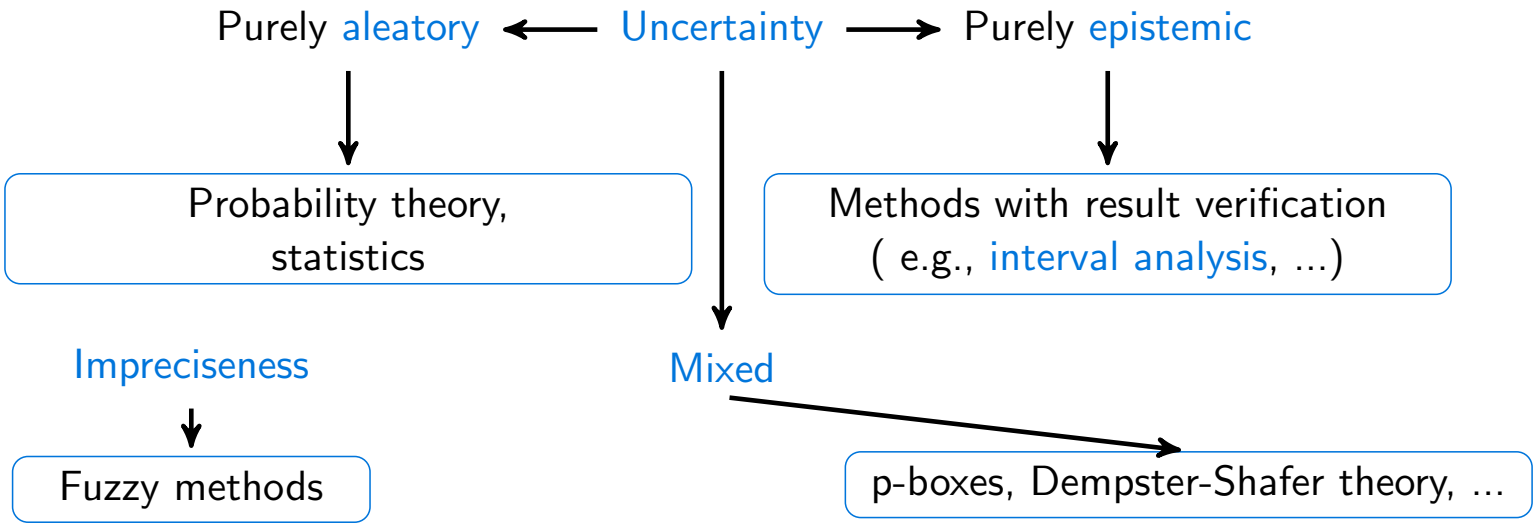
Step 1: Define unified, consistent risk factors (criteria) across risk assessment tools and studies/meta-studies $\longrightarrow$ Mergers

Step 2: Work with sets for representing epistemic uncertainty if these criteria do not map to each other in full $\longrightarrow$ Methods with result verification

Step 3: Propagate this uncertainty through the models $\longrightarrow$ ERST

ERST combines these three steps and merges FHAT/MSS/RST with mutation probabilities from Frank tables

Step 2: Uncertainty Handling, Types of Methods



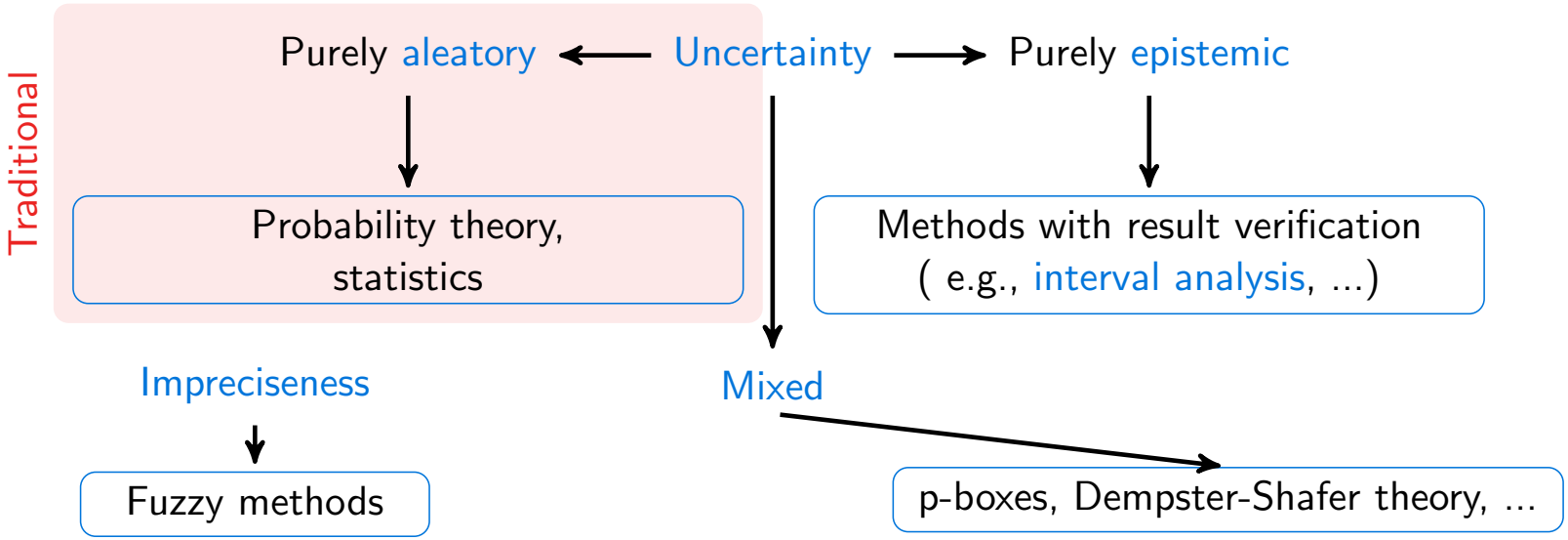
Types of methods

Rigor-preserving (≈ with result verification): the result is guaranteed to enclose the uncertainty completely, if inputs enclose it completely

Best possible (≈ inner enclosure): the result cannot get any tighter without more information

Statistical confidence: guarantee of the type "in x percent of the trials, the result is sure to enclose the uncertainty completely"

Step 2: Uncertainty Handling, Types of Methods



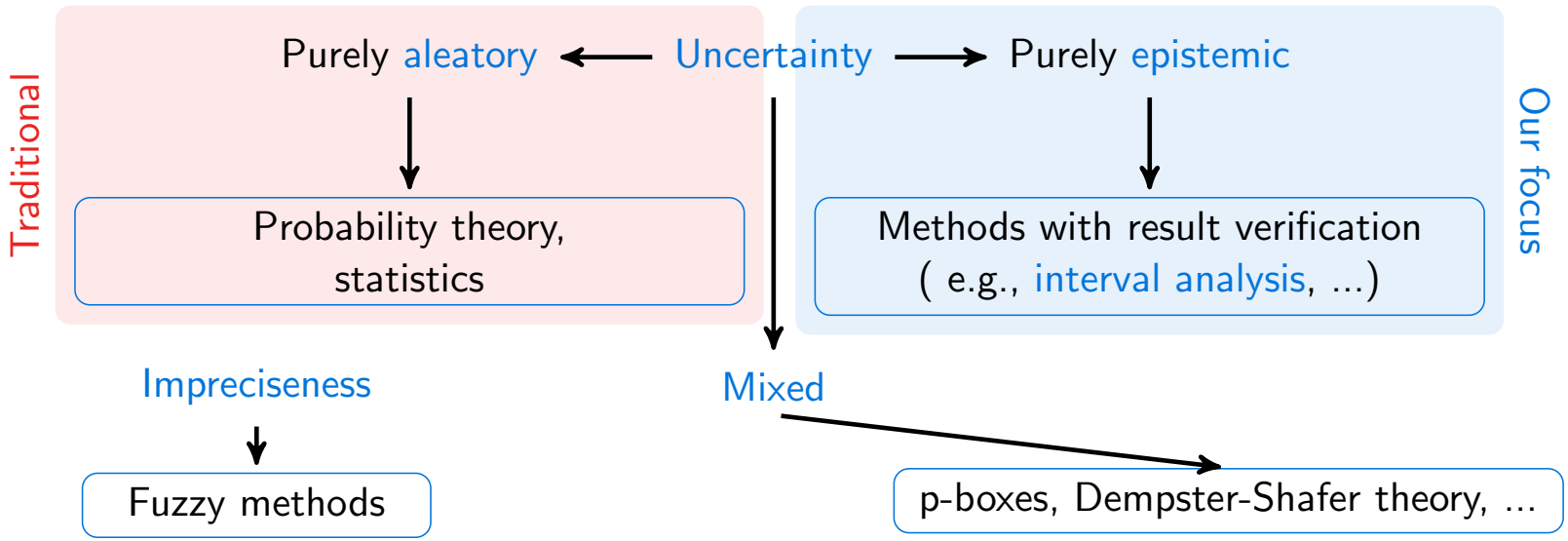
Types of methods

Rigor-preserving ($\approx$ with result verification): the result is guaranteed to enclose the uncertainty completely, if inputs enclose it completely

Best possible ($\approx$ inner enclosure): the result cannot get any tighter without more information

Statistical confidence: guarantee of the type "in x percent of the trials, the result is sure to enclose the uncertainty completely"

Step 2: Uncertainty Handling, Types of Methods



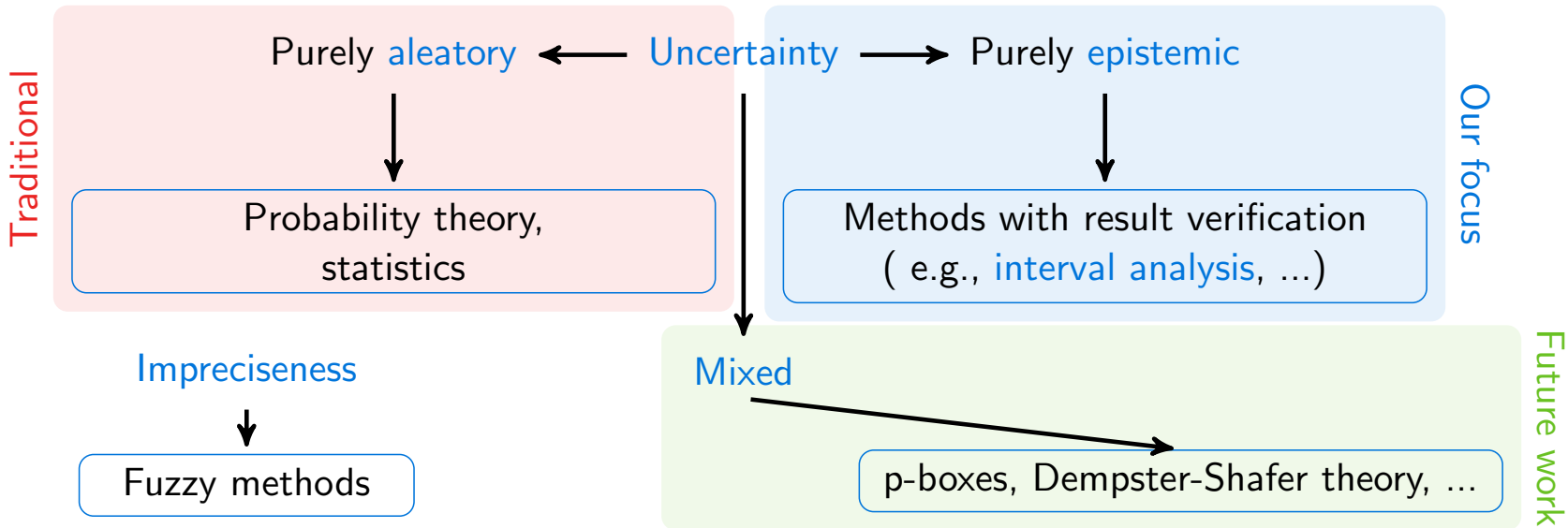
Types of methods

Rigor-preserving ($\approx$ with result verification): the result is guaranteed to enclose the uncertainty completely, if inputs enclose it completely

Best possible ($\approx$ inner enclosure): the result cannot get any tighter without more information

Statistical confidence: guarantee of the type "in x percent of the trials, the result is sure to enclose the uncertainty completely"

Step 2: Uncertainty Handling, Types of Methods



Types of methods

Rigor-preserving ($\approx$ with result verification): the result is guaranteed to enclose the uncertainty completely, if inputs enclose it completely

Best possible ($\approx$ inner enclosure): the result cannot get any tighter without more information

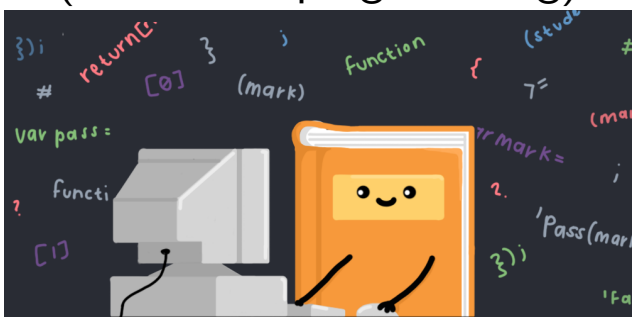
Statistical confidence: guarantee of the type "in x percent of the trials, the result is sure to enclose the uncertainty completely"

Step 2: Result Verification

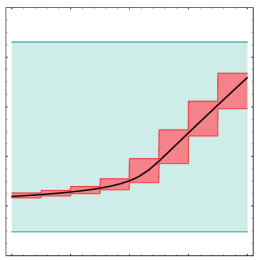
VERIFICATION — Are we building the product right?

FORMAL V
(→ model checking)

CODE V
(→ literate programming)



RESULT V
(→ interval arithmetic)

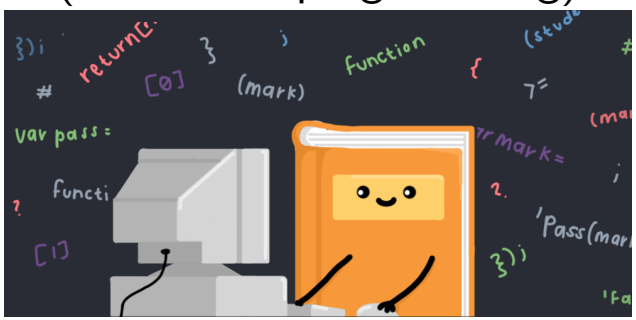


Step 2: Result Verification

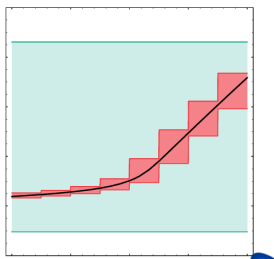
VERIFICATION — Are we building the product right?

FORMAL V
(→ model checking)

CODE V
(→ literate programming)



RESULT V
(→ interval arithmetic)



Principle: Prove mathematically the correctness of the computer result (fixed point theorems + set-based arithmetics)

Advantages: Account for rounding or conversion errors; propagate epistemic uncertainty

Disadvantages: Possibly too pessimistic ($\rightsquigarrow$ overestimation)

Approaches: Interval, affine, Taylor model, ... based methods

Risk Assessment Types and Factors

Types of risk assessment

→ The chances of developing breast cancer over a given timespan, including the lifetime

→ The chances of a mutation in a high-risk gene (e.g., *BRCA1/2*)

Risk factors

→ FH of breast cancer in relatives

- Age at onset of breast cancer
- Bilateral disease
- Degree of relationship (first or greater)
- Multiple cases in the family (part. on one side)
- Other related early-onset tumours (e.g., ovarian)
- Number of unaffected individuals

→ Hormonal, reproductive, others (e.g., obesity, diet, exercise...)

Evans, D.G.R., Howell, A.: *Breast cancer risk-assessment models*, 2007

Frank Tables, Claus Tables

Frank tables/model

Table 3. Modeled Probabilities of Women With Breast Cancer Under 50 Years of Age Carrying a Mutation in *BRCA1* or *BRCA2*

Any Relative With BrCA < 50 Years?	Any Relative With OvCa?	Proband: Bilateral BrCa or OvCa?	Proband: BrCa < 40?	Modeled Probability of Mutation in *BRCA1* (%)	Modeled Probability of Mutation in *BRCA2* (%)	Modeled Probability of Mutation in *BRCA1* or *BRCA2* (%)
•				10.1	14.5	25
•			•	28.2	11.6	40
•		•		41.5	9.5	51
•		•	•	71.1	4.7	76
	•			22.9	12.5	35
	•		•	22.9	12.5	35
	•	•		65.0	5.7	71
	•	•	•	65.0	5.7	71
•	•			22.9	12.5	35
•	•		•	50.9	7.9	59
•	•	•		65.0	5.7	71
•	•	•	•	86.7	2.2	89

Claus tables/model

Table 2. Predicted Cumulative Probability of Breast Cancer for a Women Who has One First-Degree Relative Affected With Breast Cancer, By Age of Onset of the Affected Relative

Age of woman (yr)	First-degree relative with age of onset (yr)					
	20–29	*30–39*	*40–49*	*50–59*	*60–69*	*70–79*
29	.007	.005	.003	.002	.002	.001
39	.025	.017	.012	.008	.006	.005
49	.062	.044	.032	.023	.018	.015
59	.116	.086	.064	.049	.040	.035
69	.171	.130	.101	.082	.070	.062
79	.211	.165	.132	.110	.096	.088

Predictions for mutations in *BRCA1/2* correlated with

- age of diagnosis
- personal and family history
- ethnicity: (non)-Ashkenazi

based on empirical studies and logistic regression analysis (big proband groups)

Predictions for cumulative BC probability

- age-specific risks
- women with one or more relatives with BC at various ages at onset

(empirical studies + Bayesian model, smaller proband groups)

Frank is more pessimistic, both do not include nonhereditary factors

Ontario Family History Assessment Tool (FHAT)

Risk factor		Points	Set
BC and OC	Mother Sibling 2nd/3rd dr	10 7 5	[5,10]
BC relatives	Parent Sibling 2nd/3rd dr Male	4 3 2 +2	[2,6]
BC characteristics	Onset age 20-29 Onset age 30-39 Onset age 40-49 Pre(peri)menopausal	6 4 2 (2)	[2,6]
	Bilateral/multifocal	+3	[3,3]
OC realtives	Mother Sibling 2nd/3rd dr	7 4 3	[3,7]
OC onset age	<40 40-60 >60	6 4 2	[2,6]
Prostate C	Onset age <50	1	[1,1]
Colon C	Onset age <50	1	[1,1]

Goal: Develop criteria for who should be referred for GC and GT (risk factors)

Approach: Select those who are at appr. twice the population risk of developing BC or OC (0.11/0.016)

Basis: Opinions of experts

Validation: Claus tables, BRCAPRO

Referral: Score ≥ 10 corresponds to doubling of lifetime BC risk (22%)

Manchester Scoring System (MSS)

Risk factor	Onset age	*BRCA* 1	*BRCA* 2	Set
Female BC	<30	6	5	[3,6]
	30-39	4		
	40-49	3		
	50-59	2		
	≥60	1		
Male BC	<60	5*	8*	
	≥60	5*		
OC	<60	8	5	[5,8]
	≥60	5		
Pancr. C	Any age	0	1	
Prost. C	<60	0	2	
	≥60	0	1	

Goal: Predict *BRCA1/2* mutation probability in families suspected of having hereditary breast and ovarian cancer

Referral: Score of 10 in either column or a combined score of 15 correspond to a 10% chance of identifying a *BRCA1* or *BRCA2* mutation

Referral Screening Tool (RST)

Table 3. Referral Screening Tool[a,b]

History of Breast or Ovarian Cancer in the Family? If Yes, Complete Checklist		
Risk Factor	Breast Cancer at Age ≤50 y	Ovarian Cancer at any Age
Yourself		
Mother		
Sister		
Daughter		
Mother's side		
Grandmother		
Aunt		
Father's side		
Grandmother		
Aunt		
≥2 cases of breast cancer after age 50 y on same side of family		
Male breast cancer at any age in any relative		
Jewish ancestry		

Goal: Rapid identification of individuals at potential hereditary risk for breast/ovarian cancer

Based on: BRCAPRO, Myriad II, BOADICEA, FHAT

Number of probands: 2464

Referral: If two checks in the table (high risk)

Owens, D.K., *Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer*, 2019

Merging: From Probabilities To FHAT Score

Diagnosis – The proband (Pr) has the role of a child in FH (risk factors from Frank tables)	Mutation p. (%) *BRCA1*	*BRCA2*	FHAT score (f)
Any relative with BC $<$ 50y	10.1	14.5	[4,10]
Any relative with OC	22.9	12.5	[5,13]
(BC<50y)&(Pr with BC (PrBC) $<$ 40y)	28.2	11.6	[11,19]
(BC<50y)&(OC)&(PrBC<40y)	50.9	7.9	[16,32]
(BC<50y)&(OC)&(Pr Bilateral BC or OC)	65.0	5.7	[15,35]
(BC<50y)&(OC)&(PrBilBC or OC)&(PrBC<40y)	86.7	2.2	[22,44]

Example: Any relative with BC $<$ 50y

FHAT (only female)

Risk factor	Interval
BC and OC	[5,10]
BC relatives	[2,4]
BC<50y char.	[2,6]
OC relatives	[3,7]
OC onset age	[2,6]

[2,4]+[2,6]=[4,10]

Frank tables (only female)

Table 3. Modeled Probabilities of Women With Breast Cancer Under 50 Years of Age Carrying a Mutation in *BRCA1* or *BRCA2*

Any Relative With BrCA < 50 Years?	Any Relative With OvCa?	Proband: Bilateral BrCa or OvCa?	Proband: BrCa < 40?	Modeled Probability of Mutation in *BRCA1* (%)	Modeled Probability of Mutation in *BRCA2* (%)	Modeled Probability of Mutation in *BRCA1* or *BRCA2* (%)
•				10.1	14.5	25
•			•	28.2	11.6	40
•		•		41.5	9.5	51
•		•	•	71.1	4.7	76
	•			22.9	12.5	35
	•		•	22.9	12.5	35
	•	•		65.0	5.7	71
	•	•	•	65.0	5.7	71
•	•			22.9	12.5	35
•	•		•	50.9	7.9	59
•	•	•		65.0	5.7	71
•	•	•	•	86.7	2.2	89

'OR' is exclusive

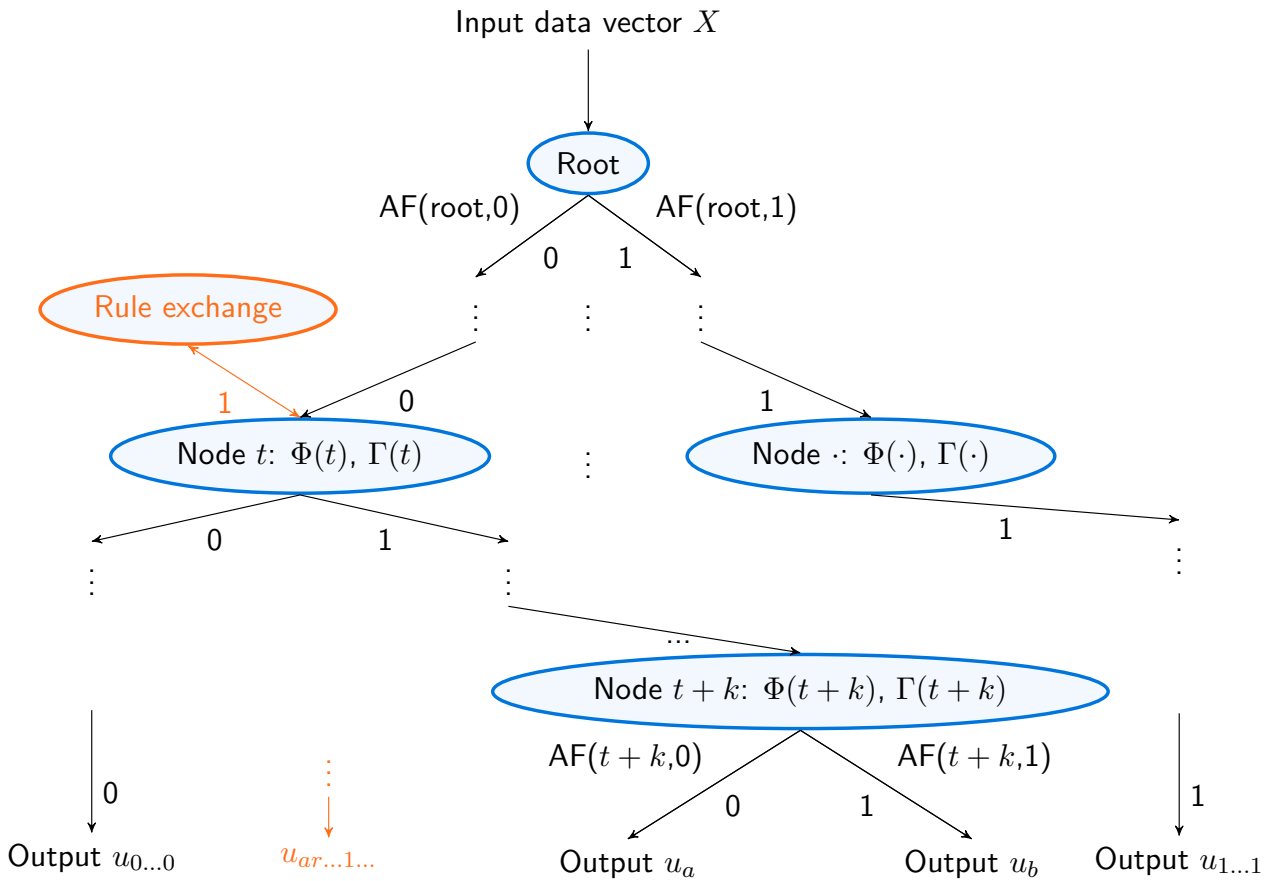
Risk factor!

Modeled mutation probabilities:
BRCA1 10.1
BRCA2 14.5

Merging: FHAT and MSS

Risk factor		**FHAT**	**MSS** *BRCA1 / BRCA2*
BC and OC	Mother/Sibling/2nd-3rd dr	10 / 7 / 5	see age
BC relatives	Parent/Sibling/2nd-3rd dr	4 / 3 / 2	see age
	Male	+2	[5,8]
BC onset age	20-29	6	6 / 5
	30-39	4	4 / 4
	40-49	2	3 / 3
	50-59		2 / 2
	$\geq$60		1 / 1
	Bilateral/multifocal	+3	
OC realtives	Mother/Sibling/2nd-3rd dr	7 / 4 / 3	see age
OC onset age	<40	6	8 / 5
	40-60	4	
	$\geq$60	2	0 / 1
Prostate C	Onset age <50	1	2 / 2
	Onset age <60	1	
	Onset age $\geq$60		1 / 1
Panrc.C	Any age		1 / 1
Colon C	Onset age <50	1	

Merging: Multi-Criteria Binary Decision Trees and RA



$\Phi(t)$ Interval features

$\Gamma(t)$ Decision rule

$\mathrm{AF}(t,\cdot)$ Risk function, e.g., (scores rs, mutation probabilities mp)

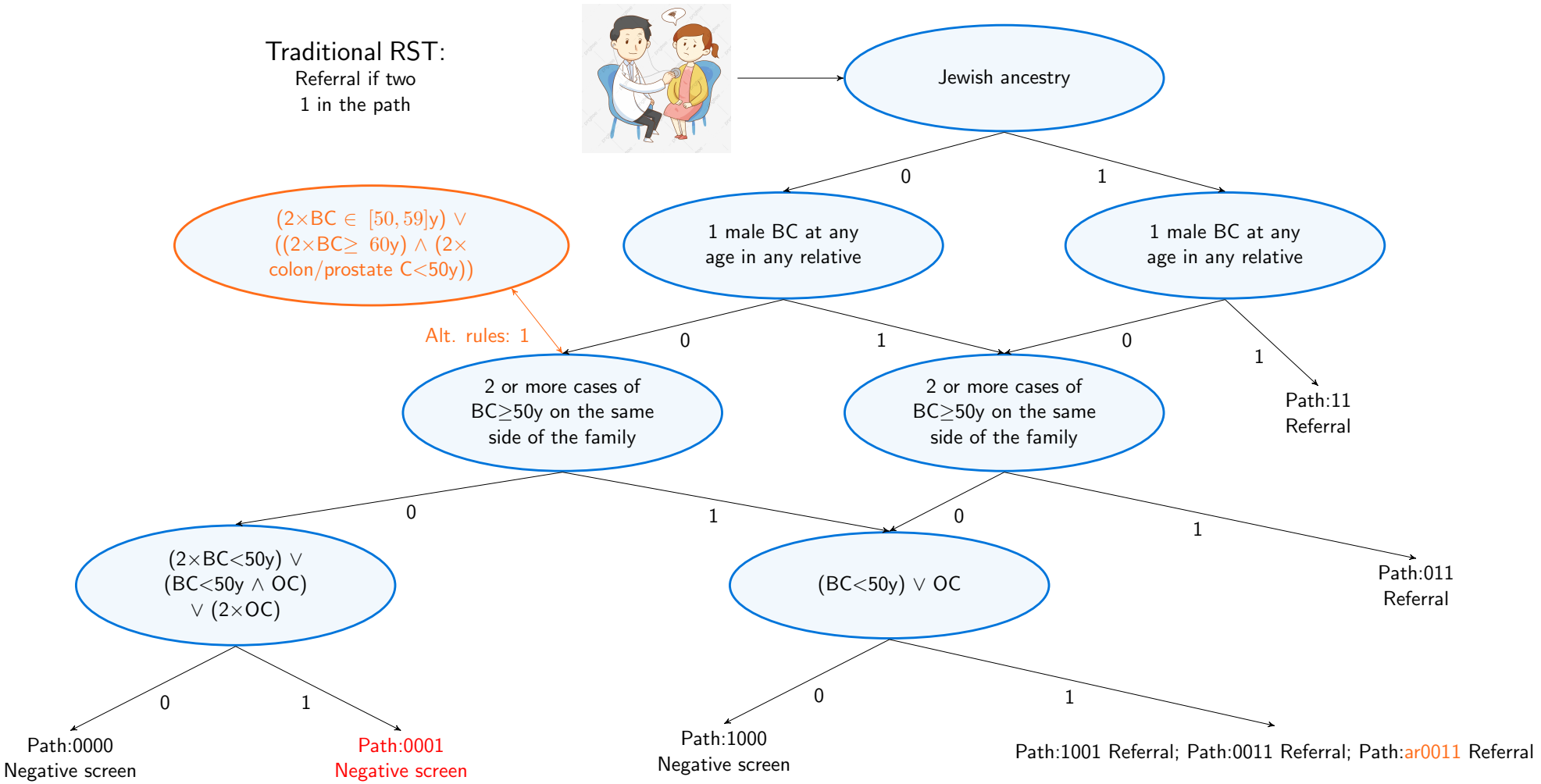
Exchange: Alternative rules

$u_a, u_b, \ldots$: In format (interval rs, mp%)

Index: Binary decision path (decimal, left to right)

Zhang, Q., Varshney, P. K.: *Towards the fusion of distributed binary decision tree classifiers,* 1999

Example: Merging RST Decision Rules with Binary Trees



Combine with FHAT, MSS, Frank tables (bigger groups, more info, ...)

ERST: RST Tree with FHAT, MSS and Frank Tables

Extended RST
FHAT,MSS:
Referral if rs≥10, rs≥15
mp≥10%

Jewish ancestry

0 1

$(2\times BC \in [50,59]y) \vee ((2\times BC \geq 60y) \wedge (2\times$ colon/prostate C<50y))
$(2\cdot[2,4]) \cup (2\cdot[2,4]+2\cdot[1,1])$

1 male BC at any age in any relative
[4,6] + [2,6]

1 male BC at any age in any relative
[4,6] + [2,6]

[4,10]/[4,6] [6,12]/[5,8] [6,12]/[5,8]

Alt. rules: 1

0 1 0 1

2 or more cases of BC≥50y on the same side of the family
2·[2,4]

2 or more cases of BC≥50y on the same side of the family
2·[2,4]

Path:11
u_3 = ([6,12]/[5,8], 39%)

[4,8]/[2,4] [4,8]/[2,4]

0 1 0 1

(2×BC<50y) ∨ (BC<50y ∧ OC) ∨ (2×OC)
[8,20] ∪ [9,23] ∪ [10,26]

(BC<50y) ∨ OC
[4,10] ∪ [5,13]

Path:011
$u_6 = ([10,20]/[7,12], ?\%)$

[4,13]/[3,8]

[8,26]/[6,16]

0 1 0 1

Path:0000
u_0 =(negative screen, 5.4%)

Path:0001
u_8 =([8,26]/[6,16], 16%)

Path:1000
u_1 =(negative screen, 4.8%)
Path:0100
u_2 =([6,12]/[5,8], 21%)

Path:1001
u_9 =([4,13]/[3,8], 14.5%)
Path:0011
u_{12} =([8,21]/[5,12],?%)
Path:ar0011
$u_{ar12} = ([8,23]/[7,14], ?\%)$

ERST: Details on Decision Path 0001

FHAT

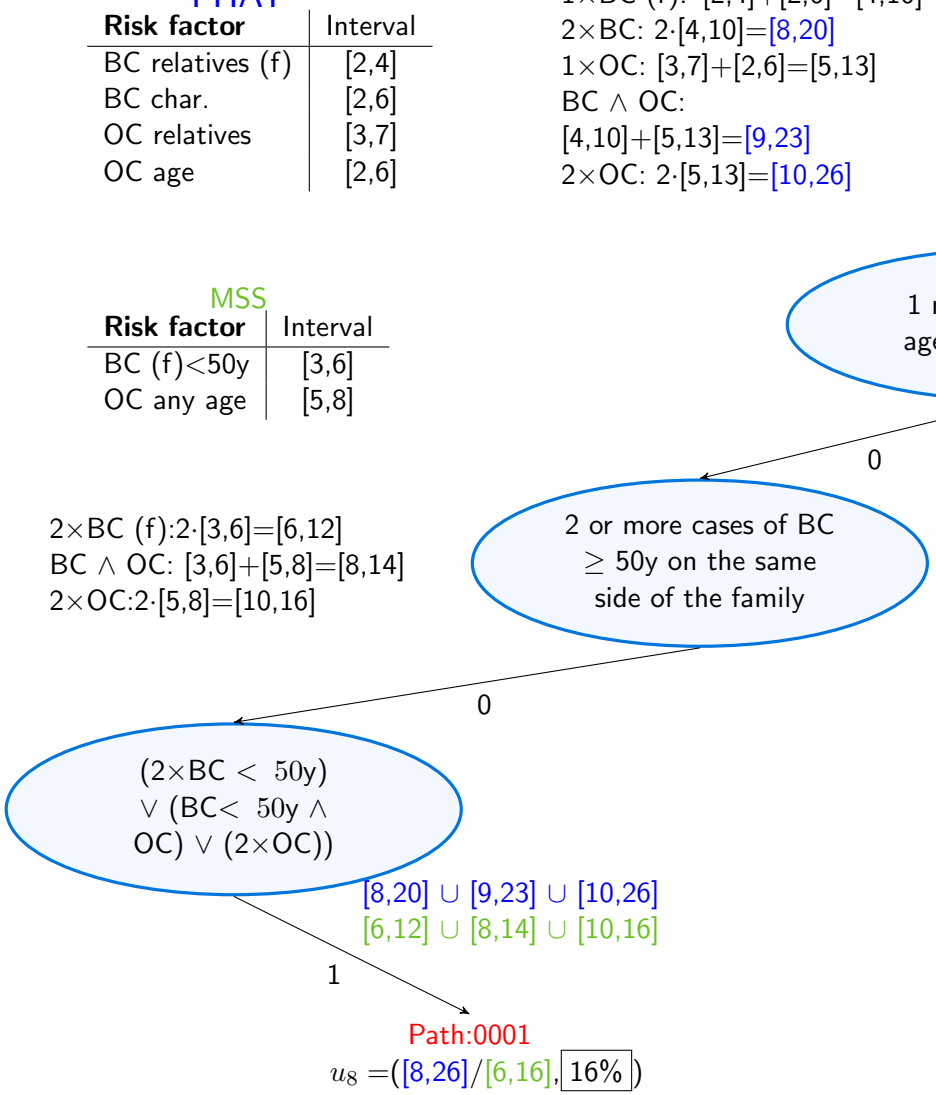
Risk factor	Interval
BC relatives (f)	[2,4]
BC char.	[2,6]
OC relatives	[3,7]
OC age	[2,6]

1×BC (f): [2,4]+[2,6]=[4,10]
2×BC: 2·[4,10]=[8,20]
1×OC: [3,7]+[2,6]=[5,13]
BC ∧ OC:
[4,10]+[5,13]=[9,23]
2×OC: 2·[5,13]=[10,26]

MSS

Risk factor	Interval
BC (f)<50y	[3,6]
OC any age	[5,8]

2×BC (f):2·[3,6]=[6,12]
BC ∧ OC: [3,6]+[5,8]=[8,14]
2×OC:2·[5,8]=[10,16]



Mutation probability (Frank, lower bound)

2×BC<50y (f): 46/419;89/484;5/25
BC< 50y ∧ OC: 58/354;12/118;19/87;34/194;14/41;1/9
2×OC: 10/117;1/18;23/83;1/6
Total: 313/1955, 16% or [5.6,34.1]

Table 1. Prevalence of Mutations in *BRCA1* and *BRCA2* Correlated With Personal and Family History of Cancer in 4,716 Non-Ashkenazi Individuals

	Family History											
	No Breast Cancer < 50 Years of Age or Ovarian Cancer in Anyone		Breast Cancer < 50 Years of Age in One Relative; No Ovarian Cancer in Anyone		Breast Cancer < 50 Years of Age in > One Relative; No Ovarian Cancer in Anyone		Ovarian Cancer at Any Age in One Relative; No Breast Cancer < 50 Years of Age in Anyone		Ovarian Cancer in > One Relative; No Breast Cancer < 50 Years of Age in Anyone		Breast Cancer < 50 Years of Age and Ovarian Cancer at Any Age	
Proband	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
No breast cancer or ovarian cancer at any age	9/229	3.9	19/434	4.4	46/419	11	6/153	3.9	10/117	8.5	58/354	16.4
Breast cancer ≥ 50 years of age	4/172	2.3	22/197	11.2	12/118	10.2	3/69	4.3	1/18	5.6	19/87	21.8
Breast cancer < 50 years of age	55/579	9.5	89/484	18.4	117/322	36.3	34/194	17.5	7/42	16.7	126/267	47.2
Ovarian cancer at any age, no breast cancer	5/77	6.5	14/41	34.1	11/26	42.3	23/83	27.7	12/28	42.9	38/71	53.5
Breast cancer ≥ 50 years of age and ovarian cancer at any age	5/27	18.5	1/9	11	4/11	36.4	1/6	17	1/3	33	3/6	50
Breast cancer < 50 years of age and ovarian cancer at	5/25	20	7/14	50	4/5	80	5/9	56	2/2	100	13/18	72.2

Conclusions

Requirements for genetic risk evaluation should address:

- → Standardized evaluation and V&V of processes and their models including unified risk factors and fusion of conclusions
- → Standardized data with a focus on the test participants' numbers and age; also origin (geographical, national, ethnic ⇝ differences in health care)
- → Representation and propagation of (bounded) uncertainty in the data using suitable data types and algorithms ⇝ the presented method ERST
- → Merging recommendations of the experts into proposals for risk management is feasible only after that!
- → Consideration of the consequences of risk assessment and post-test counseling