

Physician uncertainty aversion impacts medical decision making for older patients with acute myeloid leukemia: results of a national survey

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SUPPLEMENTARY ONLINE CONTENT

Section I: web survey questionnaire.

The questionnaire send to physicians was in French. For the purpose of publication, it has been translated in English.

DUEL Study: Dealing with Uncertainty in Elderly Leukemia patients

You are invited to participate to a web survey which analyzes mechanisms of medical decision under uncertainty

This is a non-commercial, unpaid study, with scientific purposes.

Data analyzes will be entirely anonymized

Mean survey duration:10-15 minutes

There are 27 questions in this survey

1.What is your sex *

Please choose only one of the following:

- Male
- Female

2.What is your age?

Please write your answer here: --

3.What is your medical speciality?

Please choose all that apply:

- Hematology
- Oncology and Hematology
- Medical Oncology
- Oncogeriatry
- Internal Medicine
- General Medicine
- Other:

4. What is (or are) your main field(s) of interest?

Please choose all that apply:

- Acute Leukemia
- Myelodysplastic syndroms
- Myeloproliferative Neoplasms
- Lymphoma / Chronic Lymphocytic Leukemia
- Myeloma
- Bone Marrow Transplantation
- General Hematology
- Other:

5. In what kind of hospital facility do you mainly practice?

- Academic/Research Program
- Comprehensive Community Cancer Program
- Community Cancer Program
- Private Hospital
- Other:

6 In which hospital do you practice? (optional question)

Please write your answer here: ---

7. What is your current position?

- Head of department, professor or assistant professor
- Attending physician
- Hospitalist
- Fellow
- Resident/Intern
- Other

In the next 2 questions we are asking you to make a choice between 2 options

There is no wrong answer. You just have to decide as if you were really facing this choice task

8. Choice 1: Which option do you prefer?

Please choose only one of the following:

- Option A gives you 100% of chance to win 2000\$
- Option B gives you 80% of chance to win 3000\$ and 20% of chance to win 0\$

9.Choice 2: Which option do you prefer?

Please choose only one of the following:

- Option C which gives you 25% of chance to win 2000\$ and 75% of chance to win 0\$
- Option D which gives you 20% of chance to win 3000\$ and 80% of chance to win 0\$

Eight clinical cases of AML patients are presented in the hematology decision board of your department.

You are not alone to decide but we are asking you to state which treatment option would you recommend for each of this patients among:

1. Intensive chemotherapy
2. Low-intensity therapy (hypomethylating agent or low-dose cytarabine)
3. Best supportive care

Please note that:

- These patients have announced they would accept medical treatment decision
- You do not have any clinical trial to offer them.
- You have unlimited possibilities of hospitalization as inpatient or outpatient

10. Vignette#1:

A 72-year-old woman, with no comorbidity. Normal cardiac function. She has an history of untreated low-risk MDS since 2013 (IPSS 0.5). Worsening of cytopenias in 2016.

Complete Blood Count (CBC): WBC 1G/L incl. neutrophils count 0.3G/L and 5% peripheral blood (PB) blasts, Hgb 100g/L, Platelet count 120G/L.

Bone marrow aspiration: FAB1 AML with BM blast count 40 %, and adverse karyotype (monosomy 7).

Which therapeutic option would you recommend?

- 1. Intensive chemotherapy
- 2. Low-intensity therapy (hypomethylating agent or low-dose cytarabine)
- 3. Best supportive care

11. Vignette#2:

A 75-year-old man, with an history of coronary artery disease with anterior interventricular artery stenting in 2010. He as controlled ischemic cardiopathy with medication (LVEF 52%), ECOG 2, recent weight loss 4kg.

CBC: WBC count 75 G/L, PB blast count 40%, Hgb 100 g/L, platelet count 50G/L.

Bone marrow aspiration: FAB2 AML (BM blast 60%) with normal karyotype

Which therapeutic option would you recommend?

- 1. Intensive chemotherapy
- 2. Low-intensity therapy (hypomethylating agent or low-dose cytarabine)
- 3. Best supportive care

12. Vignette#3:

A 77-year-old woman, with an 8-year history of hypertension controlled with angiotensin-converting-enzyme inhibitor, a recent echocardiogram showed a LV ejection fraction of 55%

She is natural helper of her husband affected by Alzheimer's disease.

CBC: WBC 18G/L incl. 25% peripheral blast, Hgb 100g/L, platelet count 80 G/L,

Bone marrow aspiration: FAB4 AML with favorable karyotype (inv16)

Which therapeutic option would you recommend?

- 1. Intensive chemotherapy
- 2. Low-intensity therapy (hypomethylating agent or low-dose cytarabine)
- 3. Best supportive care

13. Vignette#4:

A 63-year-old-man, with a 5-year-history of asymptomatic Parkinson disease and recently diagnosed with an asymptomatic carotid artery stenosis (90%).

CBC: WBC 2G/L incl. 5% PB blast count, Hgb 80g/L, Platelet 35 G/L

Bone marrow aspiration: FAB2 AML (30% BM blast, tri-lineage dysplasia) with complex Karyotype incl. inv3, -5q, -7

Which therapeutic option would you recommend?

- 1. Intensive chemotherapy
- 2. Low-intensity therapy (hypomethylating agent or low-dose cytarabine)
- 3. Best supportive care

14.Vignette#5: Patient from the Vignette#4 but 73-year-old

A 73-year-old-man, with a 5-year-history of asymptomatic Parkinson disease and recently diagnosed with an asymptomatic carotid artery stenosis (90%).

CBC: WBC 2G/L incl. 5% PB blast, Hgb 80g/L, Platelet 35 G/L

Bone marrow aspiration: FAB2 AML (30% BM blast, tri-lineage dysplasia) with complex Karyotype incl. inv3, -5q, -7

Which therapeutic option would you recommend?

- 1. Intensive chemotherapy
- 2. Low-intensity therapy (hypomethylating agent or low-dose cytarabine)
- 3. Best supportive care

15. Vignette#6: Patient from Vignette#4 but with WBC count 40 g/L incl. PB blast count of 25%

A 63-year-old-man, with a 5-year-history of asymptomatic Parkinson disease and recently diagnosed with an asymptomatic carotid artery stenosis (90%).

CBC: WBC 40G/L incl. 25% PB blast, Hgb 80g/L, Platelet 35 G/L

Bone marrow aspiration: FAB2 AML (30% BM blast, tri-lineage dysplasia) with complex Karyotype incl. inv3, -5q, -7

Which therapeutic option would you recommend?

- 1. Intensive chemotherapy
- 2. Low-intensity therapy (hypomethylating agent or low-dose cytarabine)
- 3. Best supportive care

16. Vignette#7: patient from Vignette#4 in complete remission after intensive chemotherapy

A 63 year-old-man, with a 5-year-history of asymptomatic Parkinson disease and recently diagnosed with an asymptomatic carotid artery stenosis (90%).

CBC: WBC 2G/L incl. 5% PB blast count, Hgb 80g/L, Platelet 35 G/L

Bone marrow aspiration: FAB2 AML (30% BM blast, tri-lineage dysplasia) with complex Karyotype incl. inv3, -5q, -7

He is in CR after an induction regimen with idarubicin (8mg/m²/d, 5 days) combined with cytarabine (100mg/m², 7days). No significant complication during aplasia. He as an HLA-identical sibling donor.

Which therapeutic option would you recommend?

- 1. Allogeneic Stem Cell Transplantation with reduced-intensity conditioning
- 2. Consolidation with 2 courses of intermediate-dose cytarabine (1,5g/m²/12h, 3d)
- 3. Consolidation with 6 courses of low-dose cytarabine (50mg/m² /12h, S/C, 5d)

17.Vignette#8: patient from Vignette#4 in complete remission after 6 courses of azacitidine

A 63 year-old-man, with a 5-year-history of asymptomatic Parkinson disease and recently diagnosed with an asymptomatic carotid artery stenosis (90%).

CBC: WBC 2G/L incl. 5% PB blast count, Hgb 80g/L, Platelet 35 G/L

Bone marrow aspiration: FAB2 AML (30% BM blast, tri-lineage dysplasia) with complex Karyotype incl. inv3, -5q, -7

He is in CR after 6 cycles of azacitidine. He has an HLA-identical sibling donor.

Which therapeutic option would you recommend?

- 1. Allogeneic Stem Cell Transplantation with reduced-intensity conditioning
- 2. Azacitidine until disease progression
- 3. Consolidation with 2 courses of intermediate-dose cytarabine (1,5g/m²/12h, 3d)

In the next four questions, we are asking you a self-evaluation of your willingness to take risks on a 0-10 scale where:

- 0 means «not at all willing to take risks»

- 10 means «fully prepared to take risks»

18. Are you generally a person who is fully prepared to take risks or do you try to avoid taking risks?

0 1 2 3 4 5 6 7 8 9 10

In your daily life

19. For the management of your personal finances, how would you rate your willingness to take risks, from 0 to 10?

0 1 2 3 4 5 6 7 8 9 10

Your personal finances

20. Regarding your medical behaviour involving the health of your patients, how would you rate your willingness to take risks, from 0 to 10?

0 1 2 3 4 5 6 7 8 9 10

Your patient's health

21. Regarding your medical behaviour involving your own health, how would you rate your willingness to take risks, from 0 to 10?

0 1 2 3 4 5 6 7 8 9 10

Your own health

22. In which year did you start residency? *

Please write your answer here:

23. Approximately how many older AML patients do you personally manage per year?

Please write your answer here: __

24. Do you consider yourself as an expert in the field of acute myeloid leukemia?

Please choose only one of the following:

- Yes
- No

25. In general, do medical decisions for AML patients of your center follow specific guidelines?

Please choose only one of the following:

- Yes
- No

In the next two questions, there are two options: Option A is a gain of X dollars for sure and option B is lottery that gives 500 dollars or nothing depending on the drawing of a ball in an urn.

In each question, you must provide the amount of money X above which you prefer to keep the sure gain and below which you prefer the lottery.

In other words, we are asking you to determine the amount of money X that makes you indifferent between getting it for sure or playing the lottery (with a superior but uncertain gain)

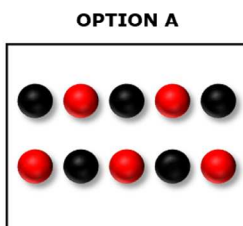
For example, if you choose X=250 this means that you prefer to have 260 dollars for sure rather than to play the lottery and you prefer to play the lottery rather than to have 240 dollars for sure.

26.

Please consider these two options:

Option A

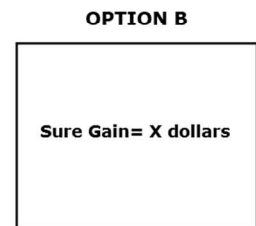
A draw is made from an urn containing 10 balls with 5 red and 5 black balls.
If the drawn ball is red you win **500 dollars** but if the ball is black you win **nothing**



• → 500 dollars
• → 0 dollar

Option B

There is **no drawing**
You win X dollars **for sure.**



Please move the slider on **the amount X** below which you choose option A and above which you choose option B



Remark:

It is unlikely that you will choose X=500 dollars because it would mean that you would rather play the lottery (and potentially win nothing) instead of getting 499 dollars for sure.

Similarly, it is unlikely that you will choose X=0 dollar because it would mean that you rather accept 1 dollar for sure instead of playing the lottery (and potentially win 500 dollars).

27.

Please consider these two options:

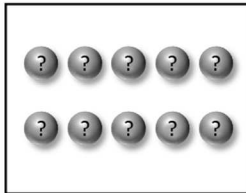
Option A

A draw is made from an urn containing 10 red and black balls but **in unknown proportion**. (For example, there could be 7 red and 3 black balls or, alternatively 3 red and 7 black balls).
If the drawn ball is red you win **500 dollars** but if it is black you win **nothing**

Option B

There is **no drawing**
You win X dollars **for sure**.

OPTION A

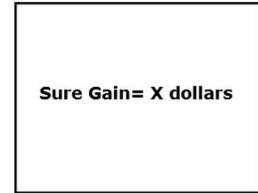


● → 500 dollars
● → 0 dollar

Please move the slider on **the amount X** below which you choose option A and above which you choose option B



OPTION B



Remark:

It is unlikely that you will choose $X=500$ dollars because it would mean that you would rather play the lottery (and potentially win nothing) instead of getting 499 dollars for sure.

Similarly, it is unlikely that you will choose $X=0$ dollar because it would mean that you rather accept 1 dollar for sure instead of playing the lottery (and potentially win 500 dollars).

Thank you for your precious participation

Section II: Description of the risk and uncertainty attitudes measurement tools

Risk attitude: individual attitudes toward risk were obtained through certainty equivalent elicitation of a lottery. Using a scrollbar (Figure 1A), respondents were asked to provide the amount of money that makes them indifferent between gaining it for sure or playing the lottery giving them 500 euros with half a chance and nothing otherwise. The expected gain of this lottery is 250 euros, so when the elicited certainty equivalent is inferior (equal/superior) to 250 euros, the respondent is considered as risk averse (neutral/seeking).

Uncertainty attitude: individual attitudes towards uncertainty were obtained through certainty equivalent elicitation of a lottery where the probability of gain is unknown. Using the same scrollbar (Figure 1B), respondents were asked to provide the amount of money that makes them indifferent between gaining it for sure or playing the lottery giving them 500 euros with an unknown probability and nothing with an unknown probability.

EU versus non-EU: The expected utility theory is an axiomatic model of decision under uncertainty and is often considered as a normative model of rationality. Allais²⁴ and Kahneman and Tversky²⁵ proposed a set of two binary choices that allow to test the independence axiom of the expected utility theory under risk and therefore the adequacy of an individual to the model. These tasks are summarized in Figure 1C.

Hereafter, we show why choice patterns AD and BC reveal violation of EU (*irrational*) and why AC and BD are consistent with EU (*rational*): Under EU, a lottery $(x,p;0)$ which gives x with probability p and 0 with probability $1-p$ is evaluated as the expected value of the utilities obtained with each possible gain, i.e. $pU(x)+(1-p)U(0)$. Therefore in the first decision task, choosing A over B reveals that the expected utility of option A is higher than the expected utility of option B, i.e. $U(2000) > 0.8 * U(3000)$ where U is the utility function of the respondent and $U(0)=0$. Similarly choosing D over C in the second decision task reveals that $0.25 * U(2000) < 0.2 * U(3000)$ and therefore that $U(2000) < 0.8 * U(3000)$ which contradicts the first inequality. Consequently, choice pattern AD indicates a violation of EU. Same line of reasoning applies for the choice pattern BC.

Willingness to take risk (Figure 1D): respondents were asked to self-evaluate their propensity to take risk using a 11-point Likert scale ranging from «not at all willing to take risks» to «fully prepared to take risks» in 4 different domains including their daily life, their personal finances, their patient's health and their own health.

Section III: K-means clustering description

The table below shows the results of the k-means clustering with a constraint of k=3 in order to identify groups of clinicians rather homogeneous regarding their therapeutic choices across the clinical scenarios. As we described in the method section, we computed an overall score by summing the modalities of each scenario resulting in a score between 6 and 18, which aimed at translating the global individual choice in the study. The higher the score, the higher the propensity to choose best supportive care. Conversely, the lower the score, the higher the propensity to choose intensive chemotherapy.

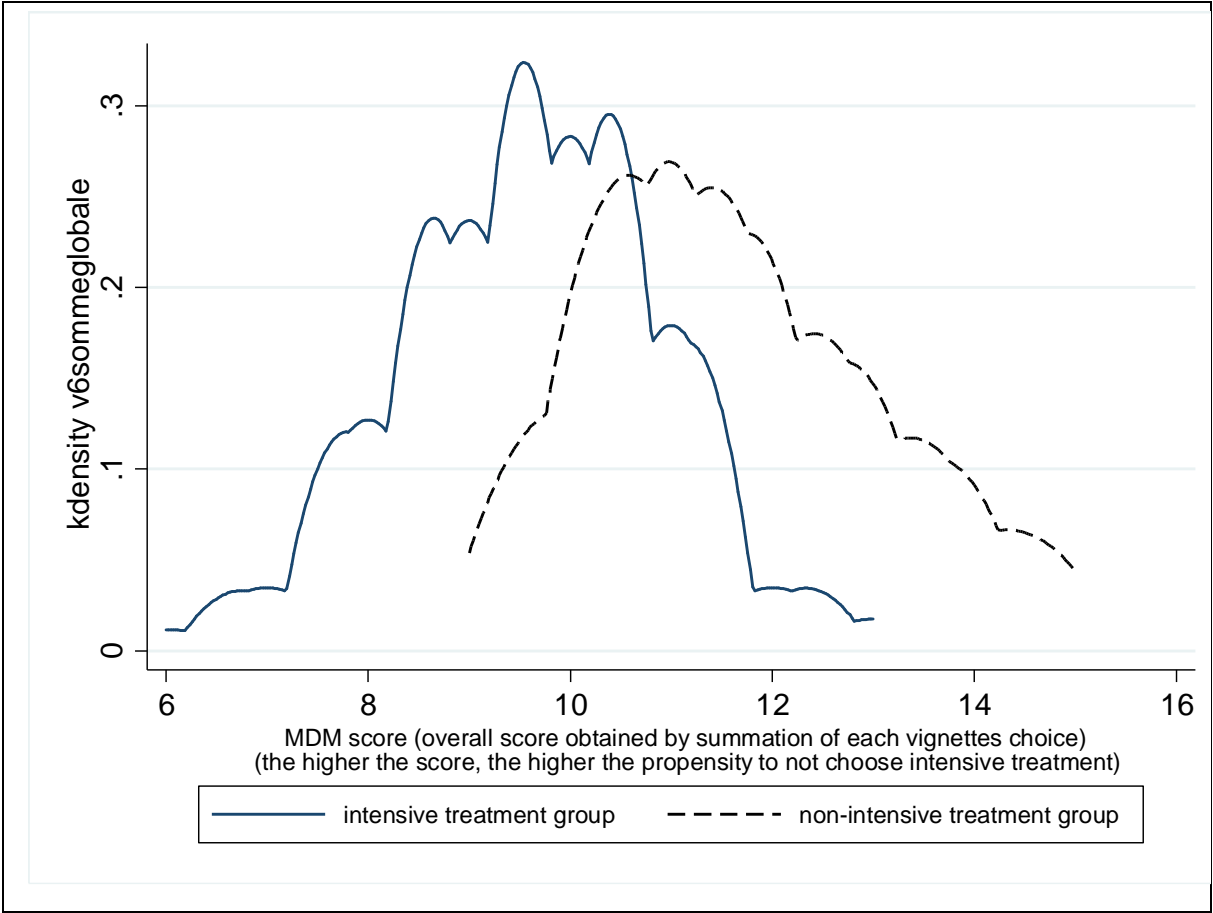
Thus, we obtained two groups with an overall score means of 9.63 [9.43; 9.84] and 11.67 [11.33; 12.01] we identified respectively as a group with clinician more inclined to choose intensive chemotherapy “IC group” and a group with clinician more inclined to not choose intensive chemotherapy “non-IC group”.

Table S1: description of the groups of homogeneous patterns of decision (n=230)

	clinicians who are more inclined to propose:	
	intensive chemotherapy (group “IC”)	best supportive care (group “non-IC”)
number of clinician	160	70
overall score* (mean [95% confidence interval])	9.63 [9.43; 9.84]	11.67 [11.33; 12.01]

* The higher the score, the higher the propensity to choose best supportive care. Conversely, the lower the score, the higher the propensity to choose intensive chemotherapy.

Supplementary figure 1: Kernel Density of the Groups of Homogeneous Patterns of Decision to the 6 Clinical Vignettes (n=230)



Section IV: Response rate analysis and sample representativeness

According to the American Association of Public Opinion Research guidelines¹, the unadjusted response rate of our survey (Response rate 2) is 18.8% (Table S1). Our target population (eligible) was French physicians who treat AML patients, mainly composed of hematologist physicians. This population is known to have very low response rates to mail or internet surveys. In the 2014 Canadian National Physician Survey, response rate among hematologists was 8.9% only, while it was 16% among the entire panel of surveyed physicians².

However, given the target population and the characteristics of our mailing list, the adjusted response rate (AAPOR, response rate 4), which takes into account the estimated proportion of cases of unknown eligibility that are eligible, is 45.4%. We detailed hereafter the calculation of this adjusted response rate.

Over our 1337 internet invitation of specifically-named persons for answering the survey, about one half are hematologists³. Two third of these physicians are expected to be involved in AML (and therefore to be eligible). The other half of the sample is composed of internists and oncologists, among which 10% are expected to be eligible. This gives us an estimated eligibility rate of 38% in our sample (i.e. 508 eligible physicians total). We obtained 230 interviewed and 41 eligible non-interviewed physicians (category 1+2, table S1) and 42 non-eligible (category 4). On the remaining 1024 unknown eligibility non-interviewed physicians (Category 3), we expect 237 (508-271) eligible physicians (applying our eligibility rate of 38 % on the whole sample). This gives us an estimated e (proportion of cases of unknown eligibility that are eligible) equal to the ratio $237/1024 = 0.23$. Using this value for the calculation of response rate 4, we obtain a value of 45.4% (table S1).

One strategy to enhance the response rate would have been to narrow the mailing list to AML specialized hematologists (and thus increase the eligibility rate of the sample). However, in order to reach the largest participation of clinicians producing direct care for AML patients, we decided to enlarge the mailing list to others medical specialties such as oncology and internal medicine, being aware this would automatically reduce the number of surveyed eligible physicians and conversely the response rate.

Beside response rates, the responder's population displays characteristics of physicians who treat AML patients, confirming the effectiveness of our eligibility condition. In fact, 86 % of them were specialist in hematology, 72% were practicing in academic centers and the median number of older AML pts

¹ http://www.aapor.org/AAPOR_Main/media/publications/Standard-Definitions20169theditionfinal.pdf

² <http://nationalphysiciansurvey.ca/wp-content/uploads/2014/10/NPS-2014-Demographics-Internal-Medicine-EN.pdf>

³ <http://www.data.drees.sante.gouv.fr>

treated a year per physician was 20.7. Comparison of respondents versus non-respondents' characteristics showed no differences in term of gender and geographical area. (table S2).

Table S2: AAPOR Outcome Rate Calculator (Internet specifically named persons)

	Final Disposition Codes	
Interview (Category 1)		230
Complete (all versions)	1.0/1.10	211
Partial (all versions)	1,2000	19
Eligible, non-interview (Category 2)	2,0000	41
Refusal (phone, IPHH, mail, web)	2,1100	12
Household-level refusal (phone, IPHH, mail, web)	2,1110	0
Known-respondent refusal (phone, IPHH, mail, web)	2,1120	0
Logged on to survey, did not complete any item (web)	2,1121	4
Read receipt confirmation, refusal (web)	2,1122	0
Break off/ Implicit refusal (phone, mail, web, mail_U)	2,1200	20
Non-contact (phone, IPHH, mail, web, mail_U)	2,2000	0
Respondent unavailable during field period (web)	2,2600	5
Completed questionnaire, but not returned during field period (mail, web, mail_U)	2,2700	0
Other, non-refusals (phone, IPHH, mail, web, mail_U)	2,9000	0
Unknown eligibility, non-interview (Category 3)	3,0000	1024
Unknown if housing unit/unknown about address (phone, IPHH, mail, web, mail_U)	3,1000	0
Not attempted or worked/not mailed/No invitation sent (phone, IPHH, mail, web, mail)U)	3,1100	0
Nothing returned (mail, web, mail_U)	3,1900	1024
Housing unit, unknown if eligible respondent (phone, IPHH, mail, mail_U)	3,2000	0
No screener completed (phone, IPHH, mail, mail_U)	3,2100	0

Unknown if person is a HH resident/ mail returned undelivered (phone, mail, web, mail_U)	3,3000	0
Other (phone, IPHH, web)	3,9000	0
Returned from an unsampled email address (web)	3,9100	0
Not eligible (Category 4)	4,0000	42
Out of sample - other strata than originally coded (phone, IPHH, mail, web, mail_U)	4,1000	19
Not eligible - duplicate listing (phone, IPHH, mail, web, mail_U)	4,8100	17
Other	4,9000	6
Total sample used		1337
I=Complete Interviews (1.1)		211
P=Partial Interviews (1.2)		19
R=Refusal and break off (2.1)		36
NC=Non Contact (2.2)		
O=Other (2.0, 2.3)		0
e is the estimated proportion of cases of unknown eligibility that are eligible.		0.23
UH=Unknown Household (3.1)		904
UO=Unknown other (3.2-3.9)		0
Response rates		
Response Rate 1 = $I/(I+P) + (R+NC+O) + (UH+UO)$		0.163
Response Rate 2 = $(I+P)/(I+P) + (R+NC+O) + (UH+UO)$		0.178
Response Rate 3 = $I/((I+P) + (R+NC+O) + e(UH+UO))$		0.417
Response Rate 4 = $(I+P)/((I+P) + (R+NC+O) + e(UH+UO))$		0.454
Cooperation rates		
Cooperation Rate 1 = $I/(I+P)+R+O$		0.793
Cooperation Rate 2 = $(I+P)/((I+P)+R+O)$		0.865
Cooperation Rate 3 = $I/((I+P)+R)$		0.793
Cooperation Rate 4 = $(I+P)/((I+P)+R)$		0.865
Refusal rates		
Refusal Rate 1 = $R/((I+P)+(R+NC+O) + UH + UO)$		0.028

Refusal Rate 2 = $R/((I+P)+(R+NC+O) + e(UH + UO))$		0.071
Refusal Rate 3 = $R/((I+P)+(R+NC+O))$		0.133
Contact rates		
Contact Rate 1 = $(I+P)+R+O / (I+P)+R+O+NC+ (UH + UO)$		0.205
Contact Rate 2 = $(I+P)+R+O / (I+P)+R+O+NC + e(UH+UO)$		0.525
Contact Rate 3 = $(I+P)+R+O / (I+P)+R+O+NC$		0.982

Table S3: Characteristics of French Physicians to Whom the Survey Was Mailed, Including Respondents and Nonrespondents

		Overall sample (n=1337)		Respondents (n=230)		Non respondents (n=1107)		p-value
		n	%	n	%	n	%	
gender	men	670	50.1	123	53.5	547	49.5	0.346
	women	667	49.9	107	46.5	560	50.5	
workplace	academic centers	857	64.1	166	72.2	691	62.4	0.017
	non-academic centers	480	35.9	64	27.8	416	37.6	
geographical area	north	160	12	34	14.8	126	11.4	0.340
	east	187	14	38	16.5	149	13.5	
	west	216	16.2	30	13	186	16.8	
	south-west	222	16.6	45	19.6	177	16	
	south méditerranée	166	12.4	27	11.7	139	12.6	
	rhône-alpes/Auvergne	139	10.4	24	10.4	115	10.4	
	île de France	248	18.5	32	13.9	216	19.5	