EURACAN

ERN on adult cancers
(solid tumours)
(ERN EURACAN)

Studies
on rare populations

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

UNIVERSITÀ
DEGLI STUDI
DI MILANO

Paolo G. Casali
paolo.casali@istitutotumori.mi.it

0. Rare cancers...

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ELSEVIER
EJC

Rare cancers are not so rare: The rare cancer burden in Europe

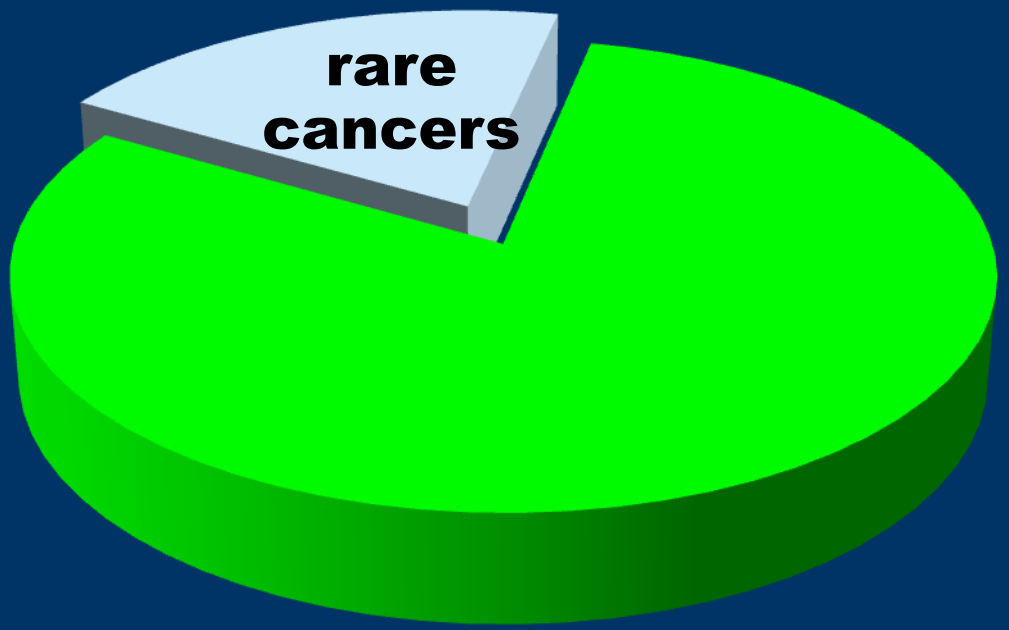
Gemma Gatta [a,], Jan Maarten van der Zwan [b], Paolo G. Casali [c], Sabine Siesling [b], Angelo Paolo Dei Tos [d], Ian Kunkler [e], Renée Otter [b], Lisa Licitra [f], Sandra Mallone [g], Andrea Tavilla [g], Annalisa Trama [a], Riccardo Capocaccia [g], The RARECARE working group*

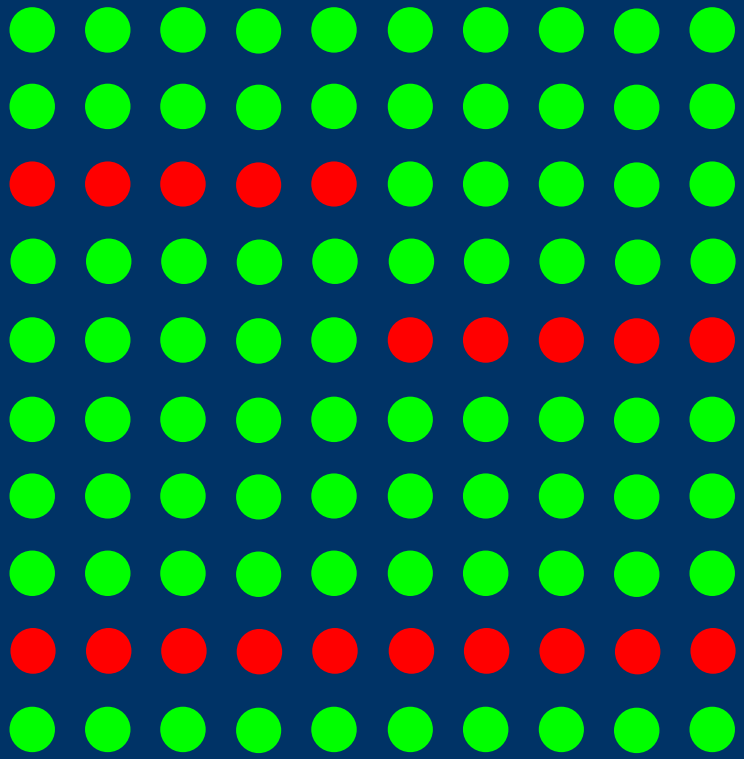
Eur J Cancer 2011;47:2493

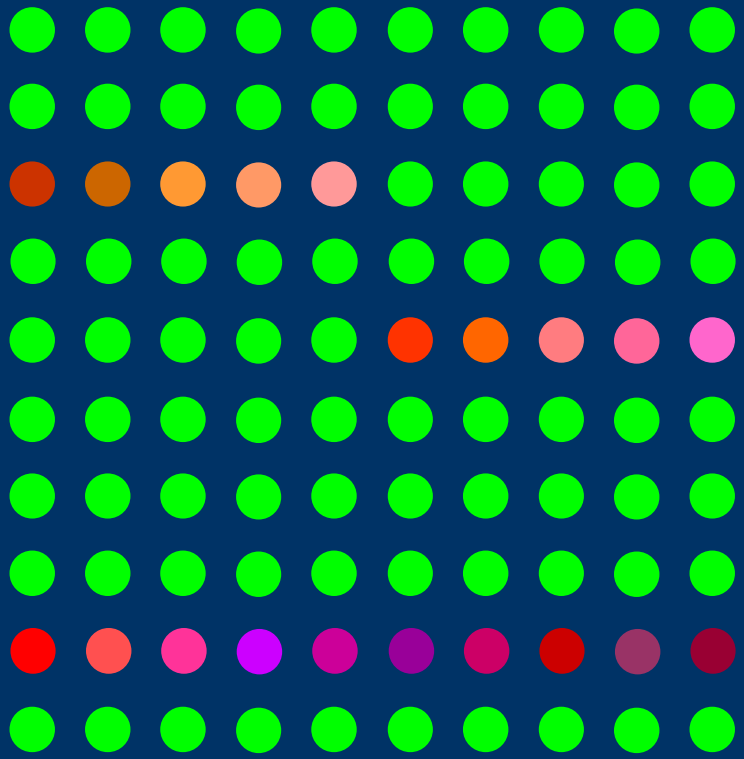
Table 3 – Data quality indicators and other characteristics of malignant cancers diagnosed in European cancer registries 1995-2002 and included in the analyses.

Country	Registry	Number of malignant cancers	Data quality indicators					
			Death certificate only (%)	Autopsy (%)	Microscopic verification (%)	Cases 1995–1998 censored before 5 years (%)	Morphology code NOS* (%)	Topography code NOS* (%)
Austria	Austria	304,495	8.9	0.0	85.2	5.9	10.1	0.6
Belgium	Flanders	144,715	0.0	0.2	89.8	0.0	7.3	0.5
France	Bas Rhin	13,113	0.0	0.0	95.8	3.3	3.9	0.2
	Calvados	5895	0.0	0.0	98.1	6.1	2.5	0.3
	Calvados digestive	2801	0.0	0.0	87.0	4.4	10.5	0.3
	Côte d'Or digestive	4376	0.0	0.0	82.8	0.5	17.5	0.2
	Côte d'Or haematol.	1884	0.0	0.0	100.0	7.2	0.0	0.5
	Doubs	5762	0.0	0.0	95.8	2.1	3.2	0.3
	Haut Rhin	9073	0.0	0.0	96.4	5.8	2.9	0.1
	Hérault	10,505	0.0	0.0	0.0	6.4	1.5	0.1
	Isère	12,526	0.0	0.0	94.1	4.6	4.1	0.1
	Loire Atlantique	3766	0.0	0.0	100.0	6.8	0.0	0.0
	Manche	6367	0.0	0.0	96.5	2.7	3.4	0.3
	Marne and Ardennes	168	0.0	0.0	100.0	3.6	0.0	0.0
	Somme	6481	0.0	0.0	94.2	6.6	5.5	0.8
	Tarn	4935	0.0	0.0	93.8	2.0	5.9	1.3
Germany	Saarland	54,132	3.9	0.0	91.8	5.8	8.0	0.5
Iceland	Iceland	8854	0.1	1.4	96.6	0.0	3.5	0.0
Ireland	Ireland	156,529	2.0	0.3	86.7	0.0	11.0	0.7
Italy	Alto Adige	18,676	0.7	0.0	89.5	0.0	9.2	0.5
	Biella	11,770	1.3	0.4	87.0	0.0	12.5	0.3
	Ferrara	23,760	1.1	0.0	88.1	0.4	9.7	0.6
	Firenze	66,087	0.9	0.1	80.4	0.4	17.7	0.8
	Friuli VG	78,882	0.6	1.9	91.0	0.3	9.8	2.1
	Genova	44,207	1.8	0.0	81.4	0.0	16.6	0.9
	Macerata	10,396	1.3	0.0	87.4	0.2	13.1	0.6
	Modena	34,947	0.5	0.0	88.6	0.4	11.8	0.5
	Napoli	8165	3.9	0.0	73.0	1.9	17.6	1.4
	Palermo	581	2.2	0.0	92.6	0.0	7.2	0.0
	Parma	23,856	1.0	0.0	86.0	0.3	13.1	0.7
	Ragusa	10,687	1.9	0.8	80.9	0.1	26.6	0.6
	Reggio Emilia	22,152	0.2	0.0	88.1	0.0	13.8	0.5
	Romagna	60,667	2.4	0.0	87.9	0.1	12.3	0.5
	Salerno	26,917	2.5	0.0	77.5	4.0	23.7	1.1
	Sassari	18,084	2.9	0.2	84.4	0.0	16.4	0.7
	Trento	17,788	2.0	0.0	85.0	0.3	27.8	3.8
	Umbria	45,221	0.7	0.0	84.0	0.1	12.6	0.6
	Varese	24,718	1.1	0.0	89.0	11.5	10.8	0.4
	Veneto	84,528	1.5	0.2	87.5	0.8	13.7	1.7

- **Pediatric cancers**
- **Haematologic rare neoplasms**
- **Sarcomas**
- **Rare thoracic cancers**
- **Neuroendocrine tumours**
- **Head & neck cancers**
- **Central nervous system tumours**
- **Rare female genital cancers**
- **Rare urological and male genital tumours**
- **Endocrine gland tumours**
- **Digestive rare cancers**
- **Rare skin cancers & non-cutaneous melanoma**


rare
cancers





Open access Original research

ESMO Open Cancer Horizons

Check for updates

Rationale of the rare cancer list: a consensus paper from the Joint Action on Rare Cancers (JARC) of the European Union (EU)

Paolo G Casali,[1] Annalisa Trama [2]

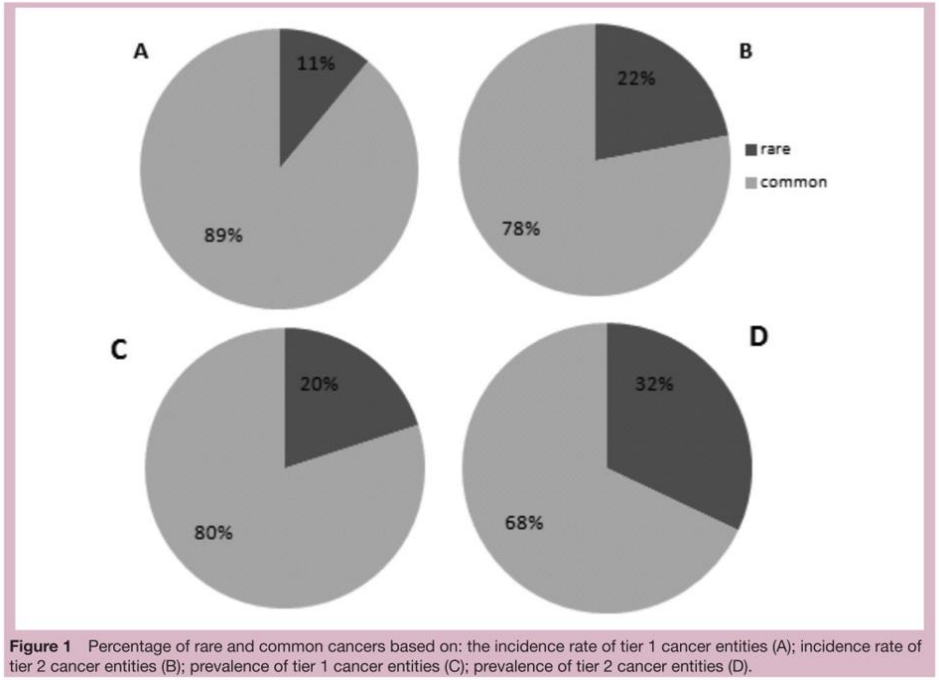


Figure 1 Percentage of rare and common cancers based on: the incidence rate of tier 1 cancer entities (A); incidence rate of tier 2 cancer entities (B); prevalence of tier 1 cancer entities (C); prevalence of tier 2 cancer entities (D).

Background The Surveillance of Rare Cancers in Europe (RARECARE) project proposed a definition and a list of rare cancers. The Joint Action on Rare Cancers (JARC), launched by the European Union and involving 18 member states and 34 partners, promoted a wide consensus effort to review the list.

Patients and methods A group of experts was set up, including scientific societies, member state representatives of JARC, representatives of the European Reference Networks dedicated to rare cancers and rare cancer patient advocates. The definition and the list of rare clinical entities, based on the incidence data provided by two European projects (RARECARE and RARECAREnet), were rediscussed through a consensus meeting of the expert panel.

Results By consensus, it was reiterated that the best criterion for a definition of rare cancers is incidence, rather than prevalence. By consensus, the experts slightly modified the composition of the tiers of rare cancers, according to the definition based on an incidence threshold <6/100 000/year, and grouped all rare cancers within 12 families of rare cancers. Even when defined conservatively this way, rare cancers are not rare collectively, since they correspond to 10%–20% of all cancer cases.

Conclusions The list of rare cancers reviewed by JARC should be viewed as a tool in the fight against rare cancers and rare diseases. It may help to appreciate that rare cancers are cancers and rare diseases at the same time, combining issues and difficulties of both. We hope that refinements to the list and a wider understanding of its implications may contribute to increase awareness of problems posed by rare cancers and to improve quality of care in a large group of patients with cancer, who may be discriminated against just because of the low frequency of their diseases.

ESMO Open. 2020;5(2):e000666

JOINT ACTION ON RARE CANCERS

RARE CANCER AGENDA 2030

Ten Recommendations from the EU Joint Action on Rare Cancers

1. Rare cancers are the rare diseases of oncology
2. Rare cancers should be monitored
3. Health systems should exploit networking
4. Medical education should exploit and serve healthcare networking
5. Research should be fostered by networking and should take into account an expected higher degree of uncertainty
6. Patient-physician shared clinical decision-making should be especially valued
7. Appropriate state-of-the-art instruments should be developed in rare cancer
8. Regulation on rare cancers should tolerate a higher degree of uncertainty
9. Policy strategies on rare cancers and sustainability of interventions should be based on networking
10. Rare cancer patients should be engaged

www.rarecancerseurope.org

RARE CANCERS EUROPE

review

Annals of Oncology 00: 1–7, 2014
doi:10.1093/annonc/mdu459

Rare Cancers Europe (RCE) methodological recommendations for clinical studies in rare cancers: a European consensus position paper

P. G. Casali[1]*, P. Bruzzi[2], J. Bogaerts[3] & J.-Y. Blay[4] on behalf of the Rare Cancers Europe (RCE) Consensus Panel

[1]*Adult Mesenchymal Tumour Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milan;* [2]*Clinical Epidemiology Unit, National Institute for Cancer Research, Genova, Italy;* [3]*European Organization for Research and Treatment of Cancer (EORTC), Brussels, Belgium;* [4]*Department of Medical Oncology, Centre Léon Bérard, Centre de Recherche en Cancérologie, Université de Lyon, Lyon, France*

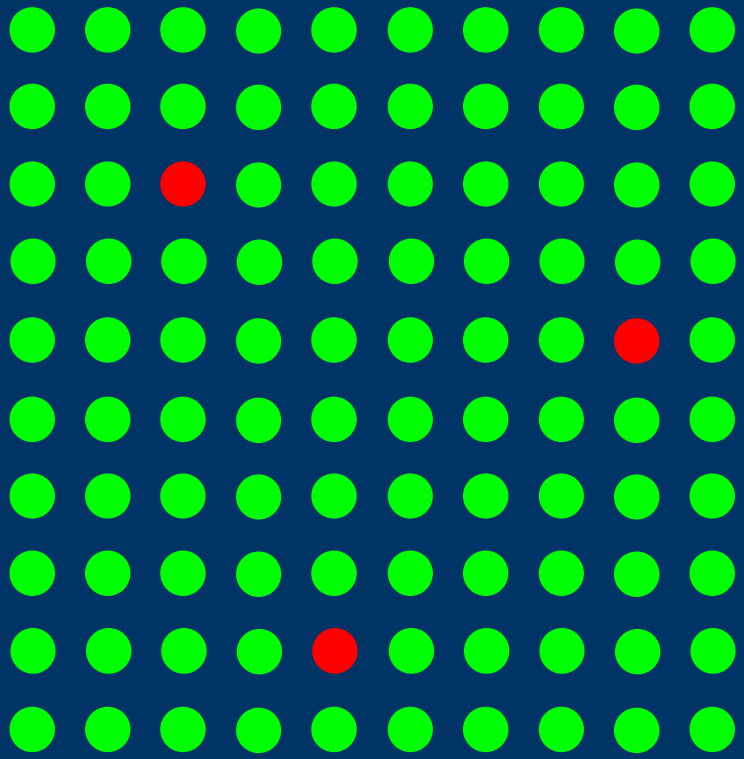
Received 29 July 2014; revised 18 September 2014; accepted 19 September 2014

While they account for one-fifth of new cancer cases, rare cancers are difficult to study. A higher than average degree of uncertainty should be accommodated for clinical as well as for population-based decision making. Rules of rational decision making in conditions of uncertainty should be rigorously followed and would need widely informative clinical trials. In principle, any piece of new evidence would need to be exploited in rare cancers. Methodologies to explicitly weigh and combine all the available evidence should be refined, and the Bayesian logic can be instrumental to this end. Likewise, Bayesian-design trials may help optimize the low number of patients liable to be enrolled in clinical studies on rare cancers, as well as adaptive trials in general, with their inherent potential of flexibility when properly applied. While clinical studies are the mainstay to test hypotheses, the potential of electronic patient records should be exploited to generate new hypotheses, to create external controls for future studies (when internal controls are unpractical), to study effectiveness of new treatments in real conditions. Framework study protocols in specific rare cancers to sequentially test sets of new agents, as from the early post-phase I development stage, should be encouraged. Also the compassionate and the off-label settings should be exploited to generate new evidence, and flexible regulatory innovations such as adaptive licensing could convey new agents early to rare cancer patients, while generating evidence. Though validation of surrogate end points is problematic in rare cancers, the use of an updated notion of tumor response may be of great value in the single patient to optimize the use of therapies, all the more the new ones. Disease-based communities, involving clinicians and patients, should be regularly consulted by regulatory bodies when setting their policies on drug approval and reimbursement in specific rare cancers.

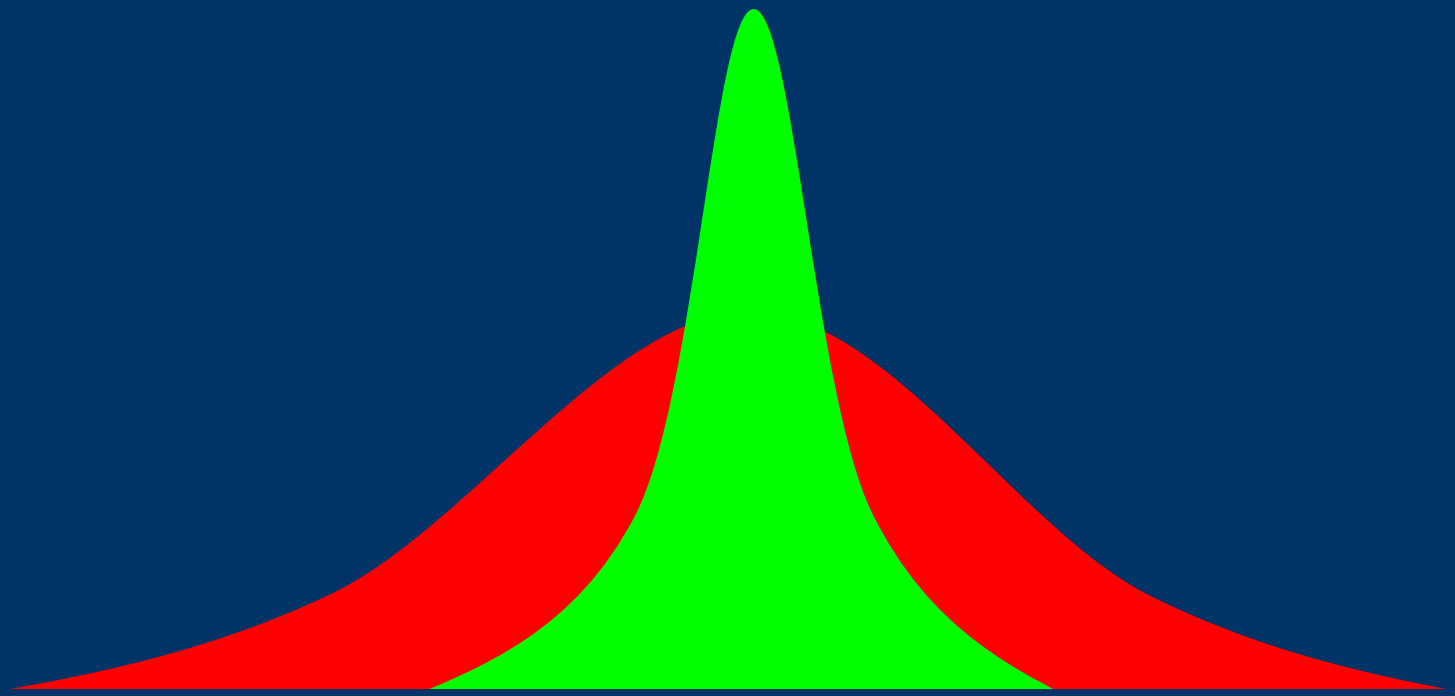
Key words: rare cancers, clinical trials, research methodology

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

London, October 3rd 2014



1. A higher degree of uncertainty should be accepted in rare cancers...



JOINT ACTION ON RARE CANCERS

RARE CANCER AGENDA 2030

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5.3 **Methodological solutions.**

5.3.1 The principle that a higher degree of uncertainty needs to be tolerated in rare cancers should be acknowledged in selecting the methodology of new clinical studies. In general, clinical studies should also be done when a lower statistical precision is likely, given available numbers, and their patient populations should be selected exclusively to maximize the chances of any new treatment to display its maximum efficacy, without widening eligibility criteria inappropriately. Even the study duration should be reasonable, given available numbers.

α β

Phase I

dose! ↓ ✓ **MTD**

Phase II → **Phase III**

activity!

✓ **OR**

✓ **OS**
✓ **QoL**

efficacy!

Phase I

dose! ↓ ✓ **MTD**

Phase II

activity! →

✓ **OR**

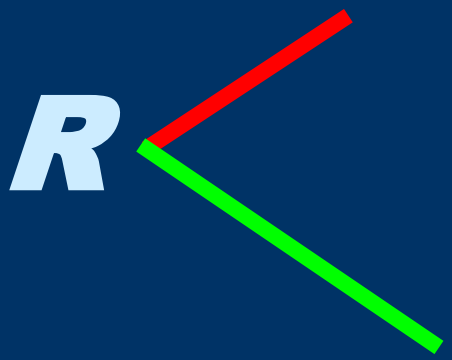
✓ **OS**
✓ **QoL**

↓ *efficacy!*

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2. We would need convincing methodologies for external controls...

systematic error!

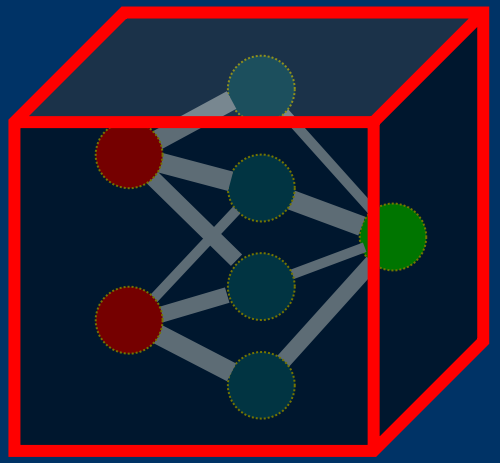


- ✓ internal control
- ✓ random allocation

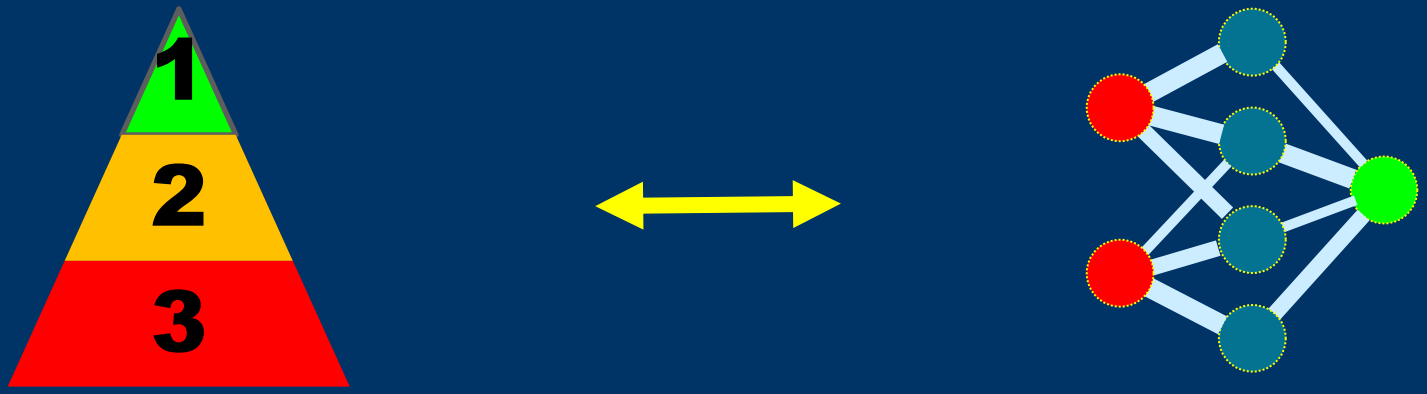
- ✓ statistical tests

random error!

systematic error!



random error!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2
3

3. The methodological implications of AI should be addressed...

Annals of Internal Medicine

IDEAS AND OPINIONS

Machine Learning and Evidence-Based Medicine

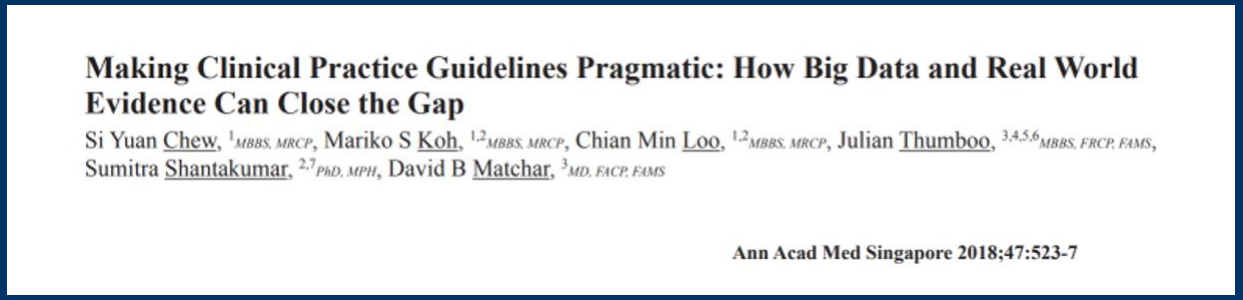
Ian A. Scott, MBBS, MHA, MEd

IDEAS AND OPINIONS

Annals of Internal Medicine

Two Ways of Knowing: Big Data and Evidence-Based Medicine

Ida Sim, MD, PhD



Making Clinical Practice Guidelines Pragmatic: How Big Data and Real World Evidence Can Close the Gap

Si Yuan Chew, [1] MBBS, MRCP, Mariko S Koh, [1,2] MBBS, MRCP, Chian Min Loo, [1,2] MBBS, MRCP, Julian Thumboo, [3,4,5,6] MBBS, FRCP, FAMS, Sumitra Shantakumar, [2,7] PhD, MPH, David B Matchar, [3] MD, FACP, FAMS

Ann Acad Med Singapore 2018;47:523-7

Phase I

dose! ↓ ✓ **MTD**

Phase II

activity! →

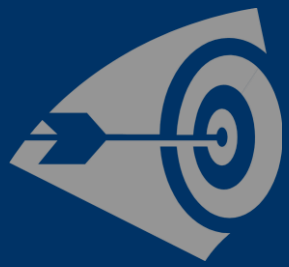
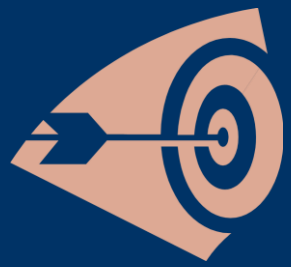
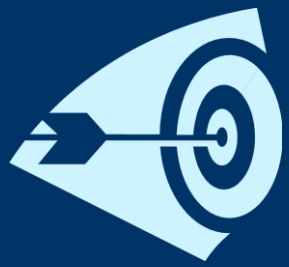
✓ **OR**

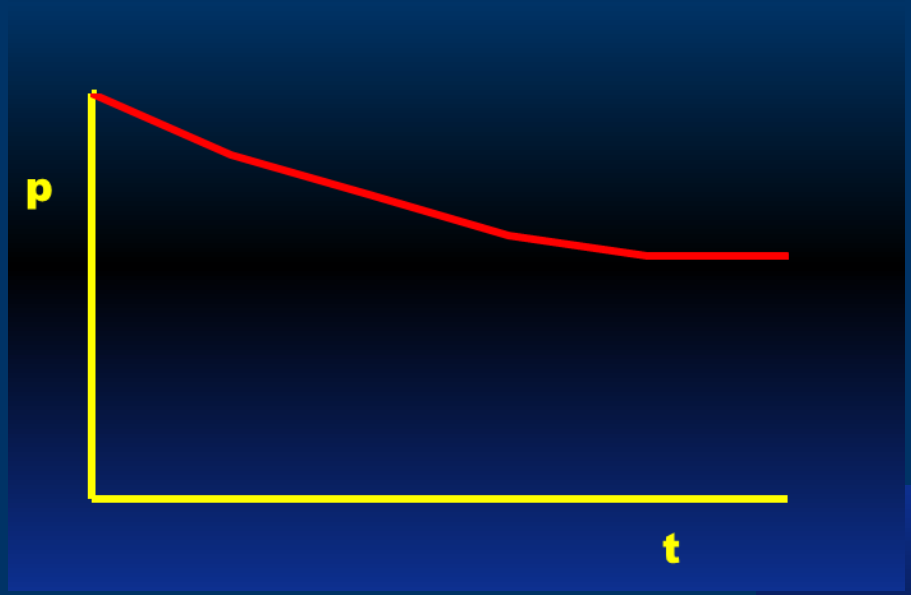
✓ **OS**
✓ **QoL**

↓ *efficacy!*

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

4. Surrogate end-points would be welcome...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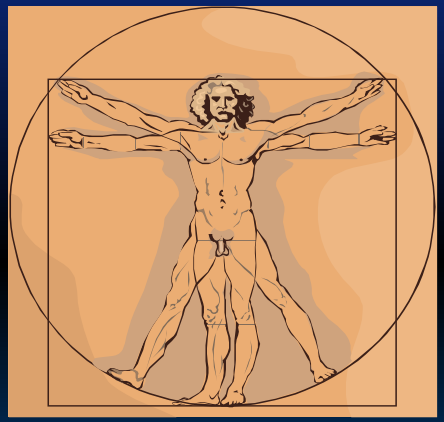

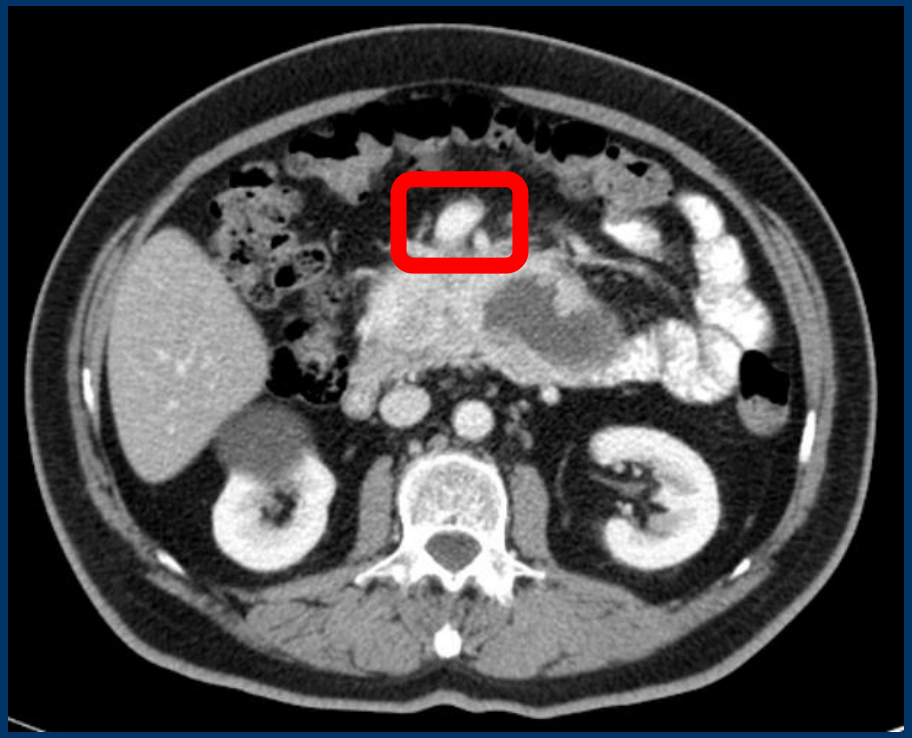

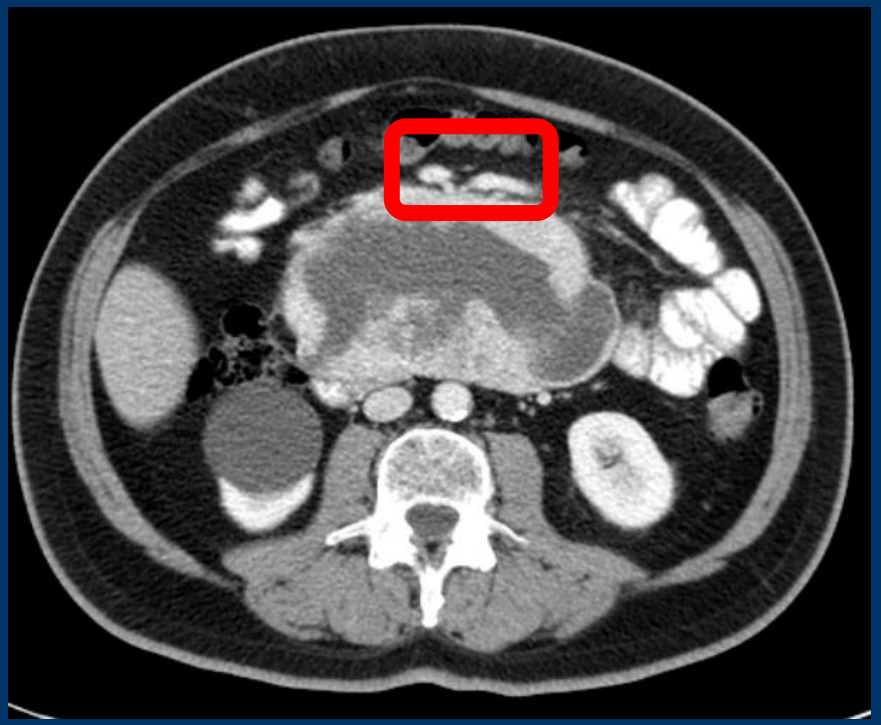

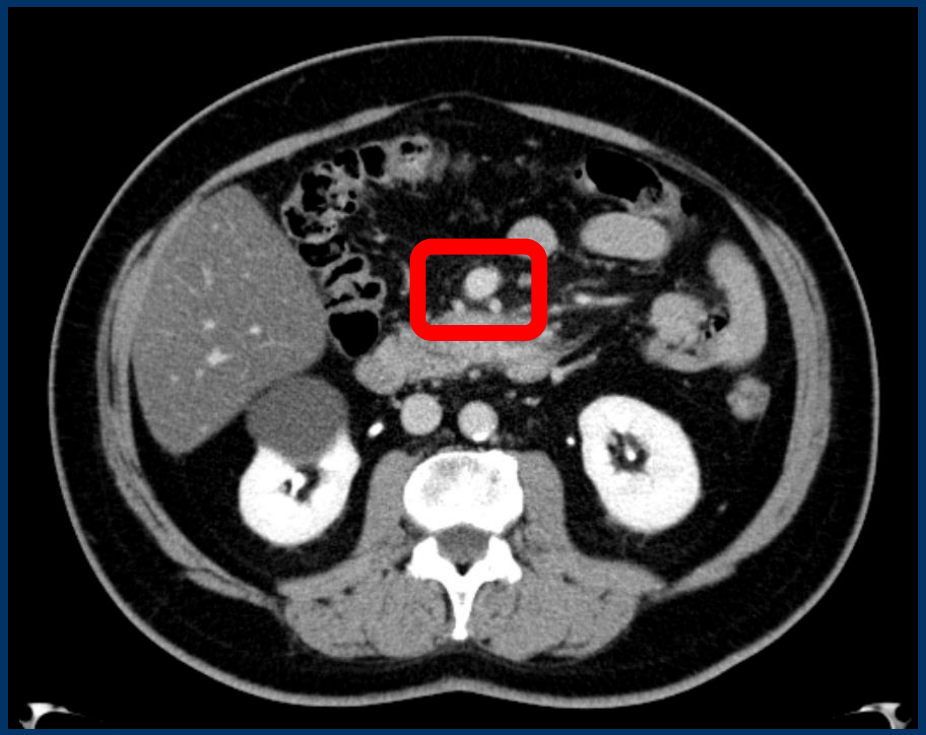

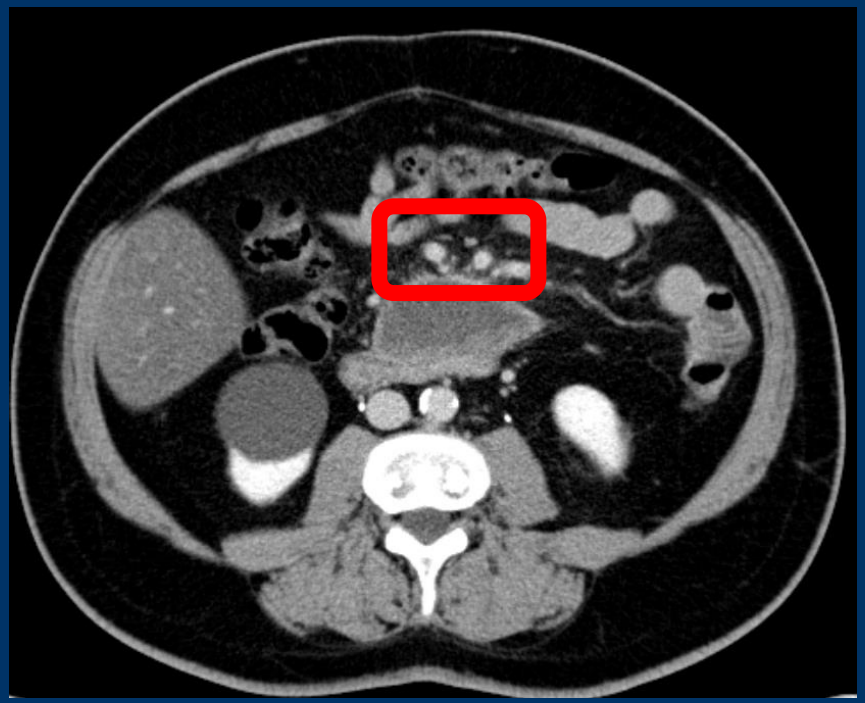

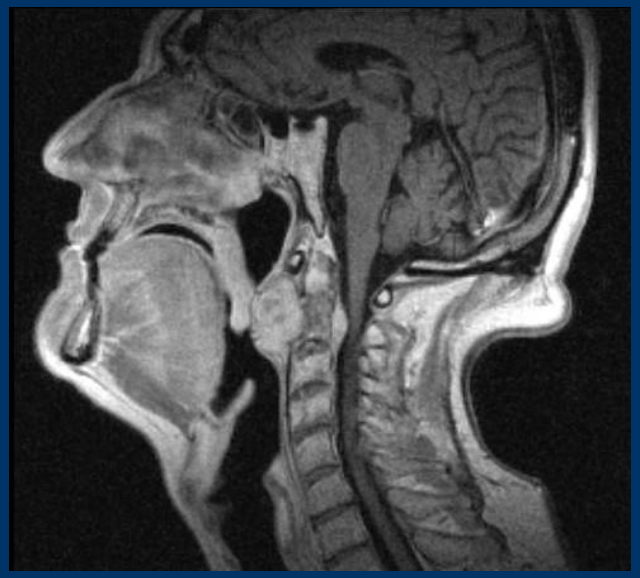

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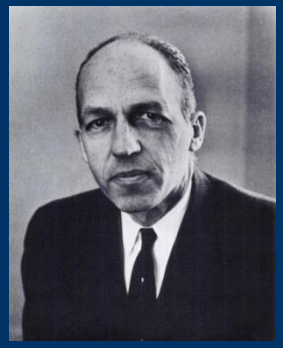
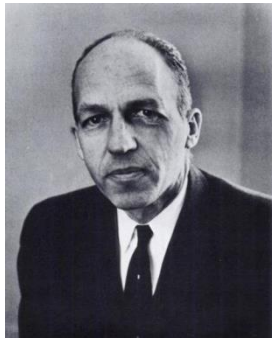


D.A. Karnofsky (1914-1969)

THE USE OF THE NITROGEN MUSTARDS IN THE PALLIATIVE TREATMENT OF CARCINOMA

With Particular Reference to Bronchogenic Carcinoma

DAVID A. KARNOFSKY, M.D.,* WALTER H. ABELMANN, M.D., LLOYD F. CRAVER, M.D., and JOSEPH H. BURCHENAL, M.D.†



PERFORMANCE STATUS

Definition	%	*Criteria*
Able to carry on normal activity and to work. No special care is needed.	100	Normal; no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work. Able to live at home, care for most personal needs. A varying amount of assistance is needed.	70	Cares for self. Unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospitalization is indicated although death not imminent.
	20	Very sick; hospitalization necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead.

CARCINOMA OF THE LUNG

Per Cent of Patients Showing Objective and Subjective Improvement and Change in Performance Status Following the Combination of HN_2 and Roentgen-Ray Therapy

		% Improvement						*Performance status % Change*						
		Subjective			*Objective*									
Group	*No. cases*	*G*	*F*	*O*	*++*	*+*	*0*	*—10*	*0*	*10*	*20*	*30*	*40*	*50*
Anaplastic	6	50	33	17	67	16	17	0	33	16	17	16	0	17
Epidermoid	6	0	67	33	0	50	50	0	67	17	16	0	0	0
Total group	14	43	36	21	28	36	36	0	36	14	29	14	0	7

Cancer 1948;1:634

SPECIAL ARTICLE

New Guidelines to Evaluate the Response to Treatment in Solid Tumors

Patrick Therasse, Susan G. Arbuck, Elizabeth A. Eisenhauer, Jantien Wanders, Richard S. Kaplan, Larry Rubinstein, Jaap Verweij, Martine Van Glabbeke, Allan T. van Oosterom, Michaele C. Christian, Steve G. Gwyther

In some institutions, the technology now exists to determine changes in tumor volume or changes in tumor metabolism that may herald shrinkage. However, these techniques are not yet widely available, and many have not been validated. Furthermore, it was recognized that the utility of response criteria to date had not been related to precision of measurement. The definition of a partial response, in particular, is an arbitrary convention—there is no inherent meaning for an individual patient of a 50% decrease in overall tumor load. It was not thought that increased precision of measurement of tumor volume was an important goal for its own sake. Rather, standardization and simplification of methodology were desirable.

J Natl Cancer Inst 2000;92:205

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J Natl Cancer Inst 2000;92:205

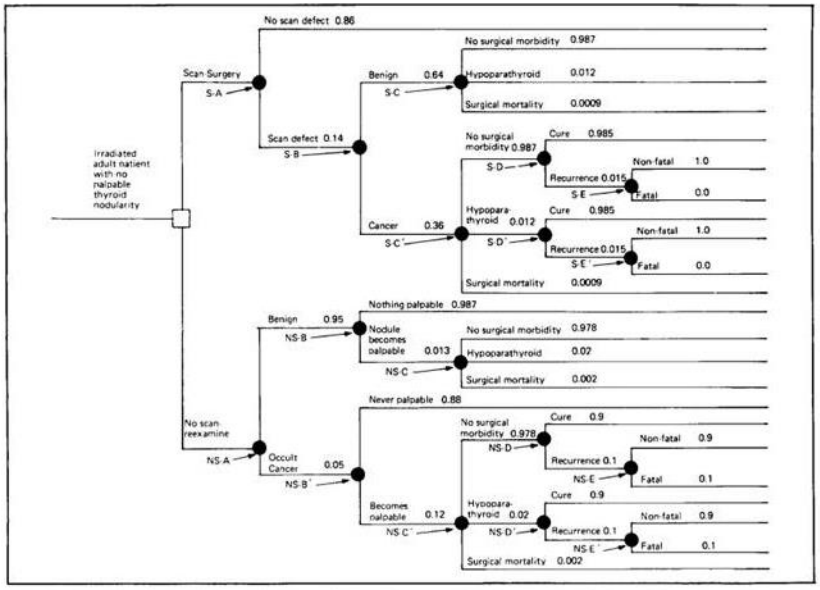
5. Clinical decision-making can handle extra-uncertainty…

MEDICAL PROGRESS

DECISION ANALYSIS

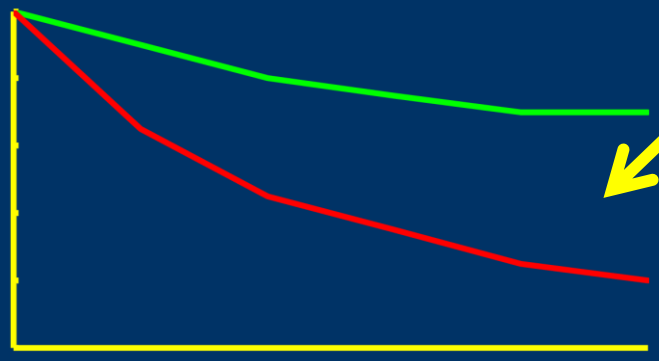
STEPHEN G. PAUKER, M.D., AND JEROME P. KASSIRER, M.D.

$$* \quad P_{dis|find} = \frac{P_{dis} \times P_{find|dis}}{\sum_{i=1}^{n} P_{dis\ i} \times P_{find|dis\ i}},$$



N Engl J Med 1987;316:250

the «frequentist» logic...



***P* <0.05**

the probability
we had to find this difference
if there were no difference
(null effect)...

the «Bayesian» logic...

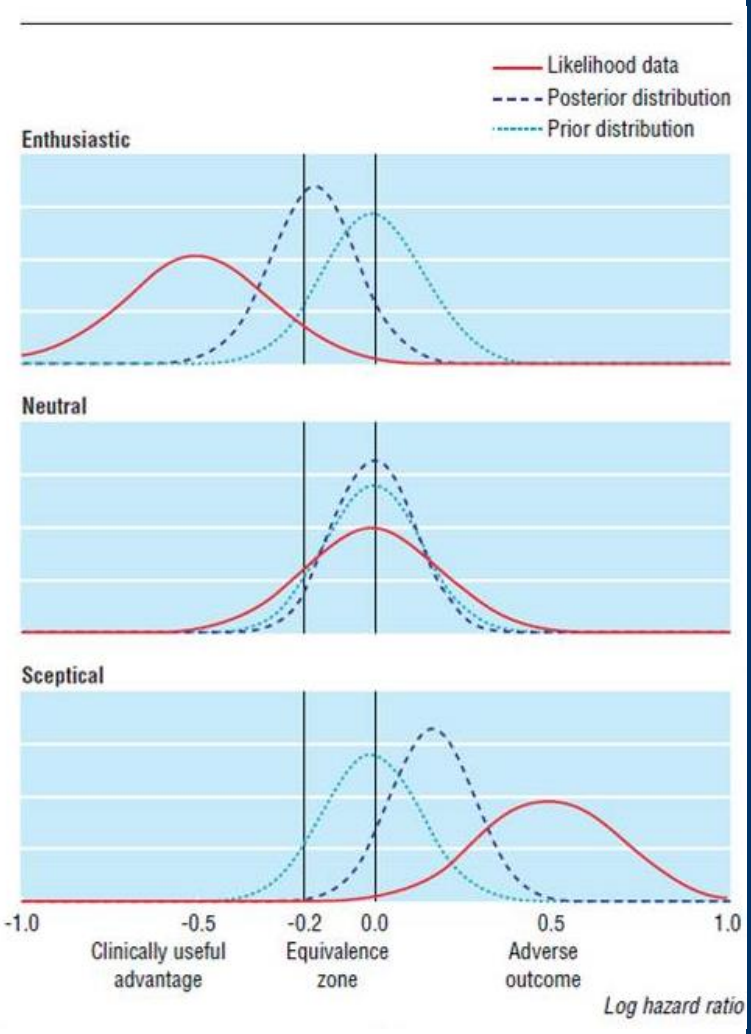
the probability
that the treatment is effective...

Education and debate

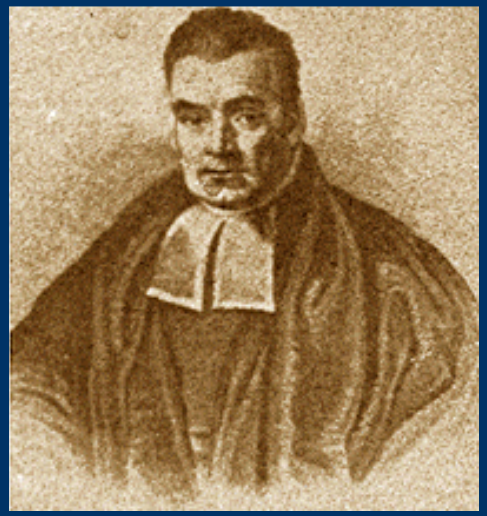
Strategy for randomised clinical trials in rare cancers

Say-Beng Tan, Keith B G Dear, Paolo Bruzzi, David Machin

Proving that a new treatment is more effective than current treatment can be difficult for rare conditions. Data from small randomised trials could, however, be made more robust by taking other related research into account



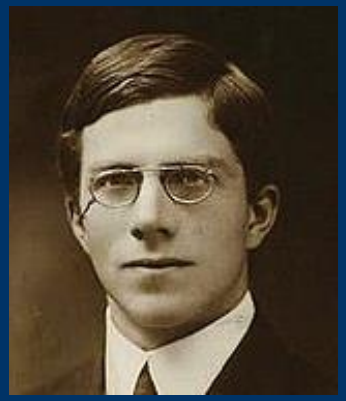
BMJ 2003;327:47

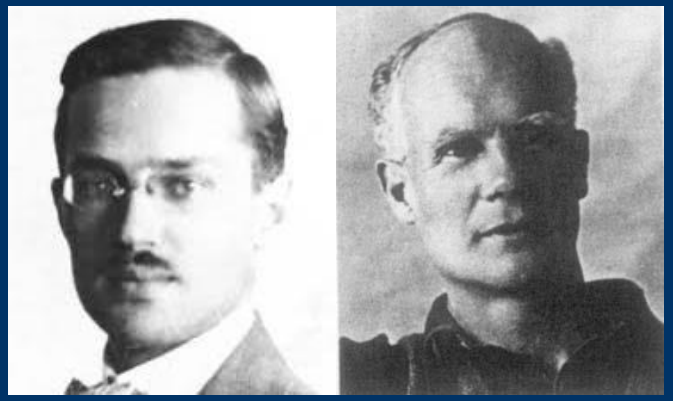


$$P[A|B] = P[A] \times \frac{P[B|A]}{P[B]}$$

Mr. Bayes & Mr. Price. Phil Trans 1763;53:370

$$P[A|B] = P[A] \times \frac{P[B|A]}{P[B]}$$





Sir R.A. Fisher

J. Neyman **E. Pearson**

6. We should refrain from compromises on external validity in rare cancers...

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

EDITORIAL

'Rare cancers': not all together in clinical studies!

In recent decades, the oncology community has become aware of 'rare cancers'. They are the 'rare diseases' of oncology; in Europe, a definition was proposed, a list was released and issues were highlighted. Some recommendations were put forward: health care should exploit clinical networking; research methodology should tackle low numbers, while a higher degree of uncertainty should be tolerated; shared clinical decision making should be resorted to in order to manage such uncertainty.[1-6] All these could eventually diminish the discriminations which rare cancer patients can suffer from because of the rarity of their condition. More recently, some researchers and study sponsors began envisaging clinical studies encompassing all, or several, rare cancers together, namely rare adult solid cancers.[7] For example, clinical studies were designed in 'rare cancers' in order to test the efficacy of a new drug, or treatment, or to address a set of specific research items. In general, this should be praised. Sometimes, however, this may be worrisome, when it goes against the essential reasons underlying rare cancer advocacy by artificially pooling together highly heterogeneous conditions.

In brief, studies were published,[8,9] and others are ongoing (ClinicalTrials.gov Identifier: NCT04166006; NCT03074513; NCT02721732) of a single drug, or a combination of drugs, in all, or some, rare cancers. Some studies have been launched testing the efficacy of radiation treatments in rare cancers as well as addressing quality of life, survivorship problems, the risk of second neoplasms or investigating the efficacy of genomics or radiomics in rare cancers[10-15] (NCT04498767). Clearly, the good in all these is that rare cancers have become a subject of interest for clinical studies. A classical argument has always been that rare diseases are neglected, starting from drugs, which may become 'orphan', due to the lack of interesting markets for their 'parents', i.e. pharma companies. So, it should only be good news that clinical studies are undertaken on rare cancers. What is the problem, then?

The problem lies in how data are analyzed, interpreted and reported. For example, an anticancer agent may be tested in 'rare cancers'. Often this means a number of different rare adult solid cancers, such as sarcomas, neuroendocrine tumors, rare head and neck cancers, etc. Then, a trial may be conceived as a series of parallel phase II studies, being merged for convenience, since a single study protocol is more easily manageable.[16-21] This means that the study sample size is properly planned for each category of rare cancers, and results are published separately. All this is more than desirable but what should be avoided in principle is providing results on all patients together (even if splitting them thereafter), or planning the study sample size on the whole study population. The reason is that a trial showing a benefit in some of the tumor entities included might be taken as evidence of efficacy in all of them. A regulatory approval, say, might be sought in all 'rare cancers'. Or, vice versa, a negative trial might be interpreted as evidence against efficacy in all 'rare cancers', even if responses have been seen in a few patients with a specific tumor entity and any enrichment has been prevented. In particular, early stopping rules might be set for the whole study, aside from the possibility that subgroups might benefit. In other words, a positive result might end up in overtreating a proportion of patients, a negative result in missing strong signs of efficacy in small subgroups. These subgroups would correspond to well-defined cancer entities, rare though they may be, such as sarcomas, mesothelioma or neuroendocrine tumors. This might apply to any treatment modality, an omic investigation, a quality-of-life questionnaire or an excess risk of late effects.

It is worth recalling that the RARECARE list of rare cancers was developed by a number of European experts having in mind the problems that rarity may imply for a health care organization and the methodology of clinical research. Thus, the common denominator of these tumors was simply to be below an incidence threshold. No common denominator other than frequency was envisaged, let alone any biological or clinical factor. Nothing keeps rare cancers under the same label but their frequency. So defined, they encompass >20% of new cancer cases, including diverse cancer groups as all pediatric cancers; many, if not all, hematological neoplasms; and 10 diverse groups of rare adult solid cancers, i.e. rare head and neck rare cancers, rare digestive cancers, rare male genital and urological cancers, central nervous system tumors, sarcomas, endocrine organ tumors, neuroendocrine tumors, rare thoracic cancers, rare female genital cancers, rare skin cancers and uveal melanoma. In the end, what is the main risk run by rare cancer patients in clinical research? In essence, the risk is that either they are not represented in clinical studies, because they are too few to give rise to adequate sample sizes, or they sink within large sample sizes artificially created by merging different tumor groups.

All the more, the risk of artificial merging applies to 'ultrarare cancers'.[22] However, technically defined, ultrarare cancers are those with an incidence >10 times lower than the threshold for rare cancers (6/100 000 per year). This means an incidence in the 0.1/100 000 per year range. For example, a clinical study on an mTOR inhibitor in all sarcomas was negative, but a specific ultrarare sarcoma histology, perivascular epithelioid cell tumors marked by a derangement in the mTOR pathway, was responsive.[23,24]

The issue of such studies in rare cancers might seem to cross the problem of agnosticism in anticancer drug development. Actually, the two things are completely different. A histologically agnostic 'basket' or 'platform' study on one or several new drugs assumes that the expression of a molecular target is able to dictate drug efficacy across histologies.[25] Under this assumption, histology disappears as a criterion to separate cancers. Of course, this may well apply also to rare cancers. Indeed, doing precision-oncology studies in rare cancers is welcome, because by definition rare cancers might be under-represented in basket or platform studies on all cancers, so that reserving some of these studies only to rare cancers enhances their chances to be investigated under histologically agnostic assumptions. Clearly, there is an open debate about agnosticism per se, but this debate has nothing to do with the need to properly study rare entities (however defined), i.e. respecting their specificities no more and no less than one would do with a common cancer, such as lung, colon, breast or prostate cancers. Likewise, 'umbrella' studies, i.e. those carried out in one cancer, should not see all rare cancers as their subject. Indeed, an umbrella study would be inappropriate by definition if carried out in a heterogeneous group of rare cancers, such as sarcomas plus head and neck cancers plus thoracic tumors, etc.

In cancer medicine, we will always face rare subgroups, and they should be respected. Any other option would mean that rare cancer patients are discriminated against because of the rarity of their condition. Rather than artificially grouping rare subsets, clinical studies should correctly select their patient populations, rare though they may be. Then, it is the methodology of research that must address the challenge of rarity.[5] For example, under a frequentist logic, low-power clinical studies can be designed; under a Bayesian logic, the whole evidence can be valued by updating a prior probability when any new data are gained, and so forth. In the end, clinicians, regulators and third payers will have to tolerate a higher degree of uncertainty in rare cancers, as compared to common cancers. Though methodologies can always be improved, no shortcuts are allowed, let alone artificially merging all or several rare adult solid cancers.

So, in our view, what should we do when planning, or reading, studies on 'rare cancers'?

i. Clinical trials should be conceived by choosing homogeneous patient populations, according to a strict biological and clinical rationale. Then, if a study, as an organizational solution, actually merged different patient populations, analysis of data should be broken down by each of them and results should be reported accordingly. No response rate, no progression-free survival and no overall survival data should be provided for all of them together. No 'rare cancer' label should be used to justify conclusions encompassing different populations.
ii. All strategies for small-population trials should be resorted to, accepting the idea that statistical uncertainty may not be shrunk in rare cancers as it can be done (more often) in common cancers. However, artificially increasing the sample size through a heterogeneous population should not be a strategy.
iii. When making a clinical decision in a rare cancer patient, physicians should look for data specifically corresponding to the patient population which their patient belongs to. Whatever the study conclusions are, the physician should dig into study results looking for the specific patient subgroup. The small size and the unplanned nature of the subgroup search may certainly leave behind a higher degree of uncertainty than ideal, but this might be a reasonable price to pay in order to make a clinically sound decision.

Again, all this is meant to prevent rare cancer patients from being discriminated against, which might well happen even when they are increasingly becoming the subject of clinical investigations, as is now happening, a couple of decades on from when their existence was first asserted.

P. G. Casali[1,2]*, L. Licitra[3,2], A. M. Frezza[4] & A. Trama[4]

[1]*Medical Oncology Unit 2, Fondazione IRCCS Istituto Nazionale Tumori, Milan;*
[2]*Oncology and Haemato-Oncology Department, University of Milan, Milan;*
[3]*Medical Oncology Unit 3, Fondazione IRCCS Istituto Nazionale Tumori, Milan;*
[4]*Evaluative Epidemiology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy*
(*E-mail: paolo.casali@istitutotumori.mi.it).
Twitter handles: @annamariafrezza, @casali_pg, @licitra_lisa

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basket

1 target / 1 drug

n tumors

platform

1 target / n drugs

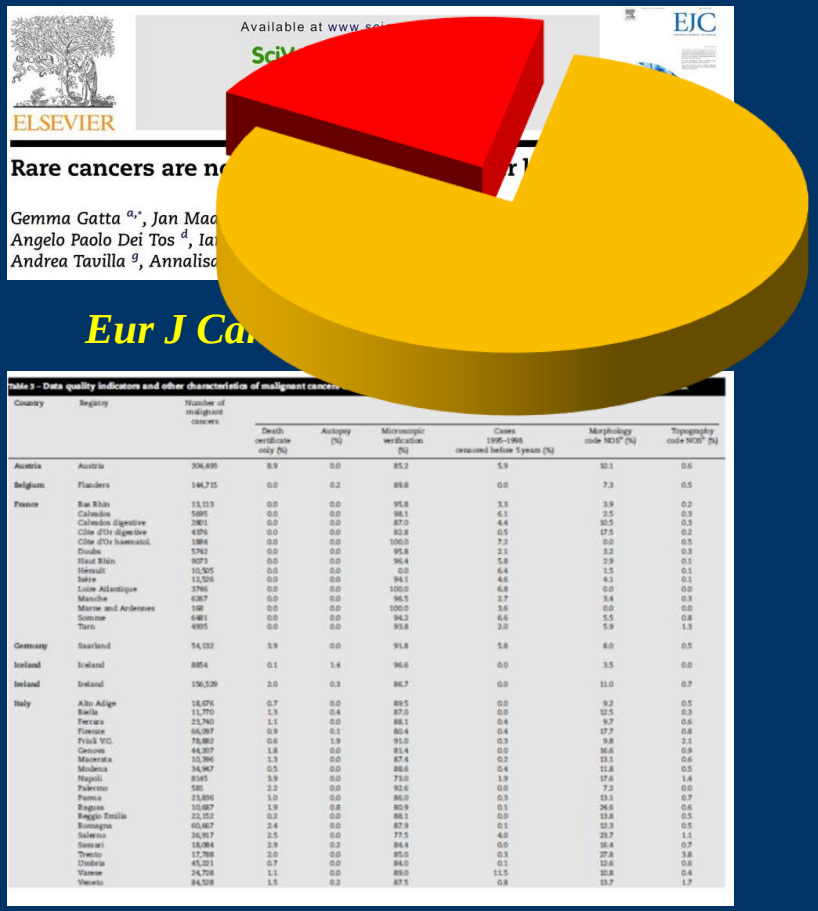
n tumors

umbrella

n targets / n drugs

1 tumor

7. Rare cancers remain rare even in times of precision oncology...



ELSEVIER

Available at www.sci

EJC

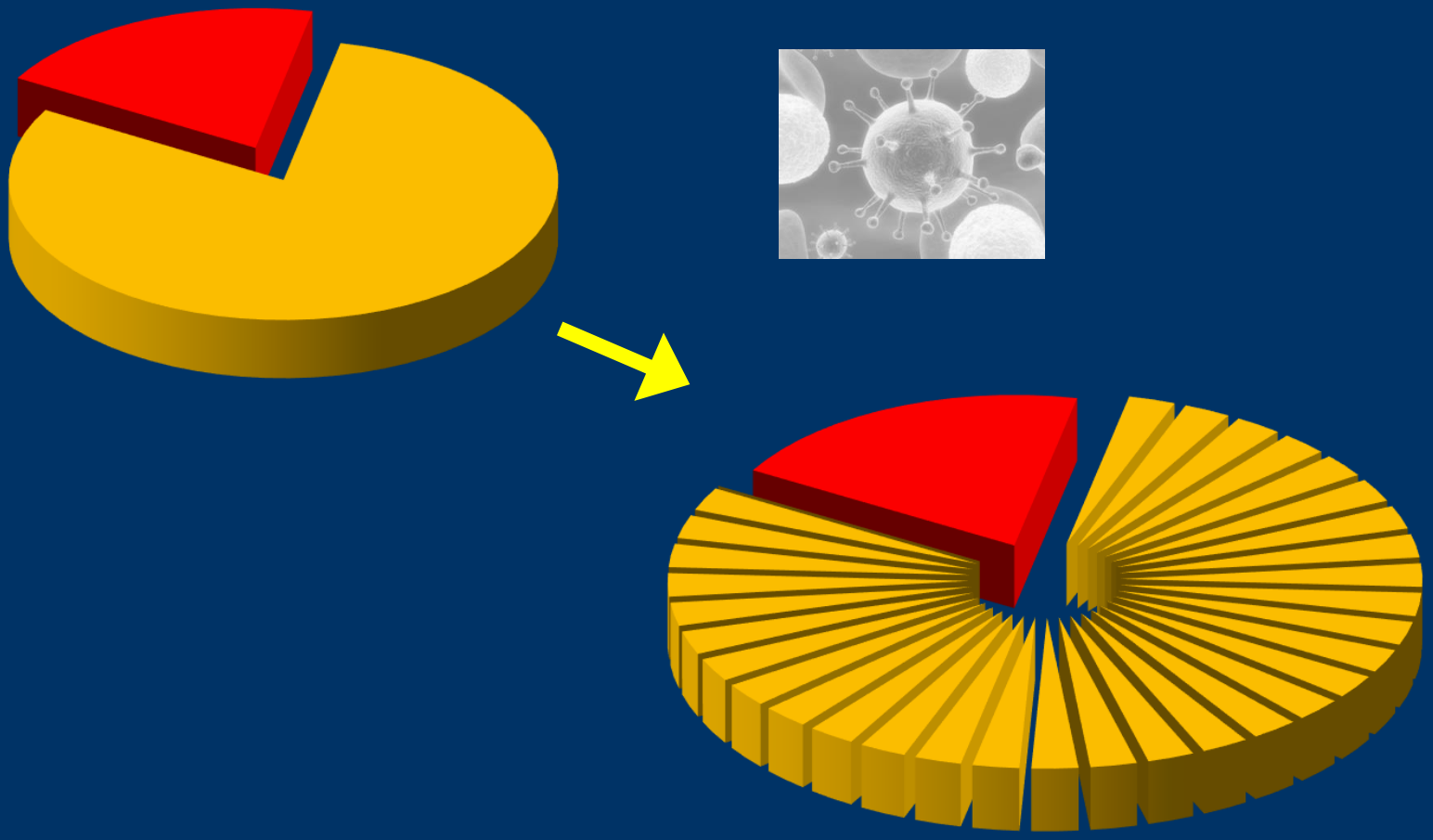
Rare cancers are n

Gemma Gatta [a,*], Jan Maa
Angelo Paolo Dei Tos [d], Ia
Andrea Tavilla [g], Annalisa

Eur J Ca

Table 3 – Data quality indicators and other characteristics of malignant cancers

Country	Registry	Number of malignant cancers	Death certificate only (%)	Autopsy (%)	Microscopic verification (%)	Cases 1995–1998 censored before 5 years (%)	Morphology code NOS* (%)	Topography code NOS* (%)
Austria	Austria	304,495	8.9	0.0	85.2	5.9	10.1	0.6
Belgium	Flanders	144,715	0.0	0.2	89.8	0.0	7.3	0.5
France	Bas Rhin	13,113	0.0	0.0	95.8	3.3	3.9	0.2
	Calvados	5895	0.0	0.0	98.1	6.1	2.5	0.3
	Calvados digestive	2801	0.0	0.0	87.0	4.4	10.5	0.3
	Côte d'Or digestive	4376	0.0	0.0	82.8	0.5	17.5	0.2
	Côte d'Or haematol.	1884	0.0	0.0	100.0	7.2	0.0	0.5
	Doubs	5762	0.0	0.0	95.8	2.1	3.2	0.3
	Haut Rhin	9073	0.0	0.0	96.4	5.8	2.9	0.1
	Hérault	10,505	0.0	0.0	0.0	6.4	1.5	0.1
	Isère	12,526	0.0	0.0	94.1	4.6	4.1	0.1
	Loire Atlantique	3766	0.0	0.0	100.0	6.8	0.0	0.0
	Manche	6367	0.0	0.0	96.5	2.7	3.4	0.3
	Marne and Ardennes	168	0.0	0.0	100.0	3.6	0.0	0.0
	Somme	6481	0.0	0.0	94.2	6.6	5.5	0.8
	Tarn	4935	0.0	0.0	93.8	2.0	5.9	1.3
Germany	Saarland	54,132	3.9	0.0	91.8	5.8	8.0	0.5
Iceland	Iceland	8854	0.1	1.4	96.6	0.0	3.5	0.0
Ireland	Ireland	156,529	2.0	0.3	86.7	0.0	11.0	0.7
Italy	Alto Adige	18,676	0.7	0.0	89.5	0.0	9.2	0.5
	Biella	11,770	1.3	0.4	87.0	0.0	12.5	0.3
	Ferrara	23,740	1.1	0.0	88.1	0.4	9.7	0.6
	Firenze	66,087	0.9	0.1	80.4	0.4	17.7	0.8
	Friuli VG.	78,882	0.6	1.9	91.0	0.3	9.8	2.1
	Genova	44,207	1.8	0.0	81.4	0.0	16.6	0.9
	Macerata	10,396	1.3	0.0	87.4	0.2	13.1	0.6
	Modena	34,947	0.5	0.0	88.6	0.4	11.8	0.5
	Napoli	8165	3.9	0.0	73.0	1.9	17.6	1.4
	Palermo	581	2.2	0.0	92.6	0.0	7.2	0.0
	Parma	23,896	1.0	0.0	86.0	0.3	13.1	0.7
	Ragusa	10,687	1.9	0.8	80.9	0.1	26.6	0.6
	Reggio Emilia	22,152	0.2	0.0	88.1	0.0	13.8	0.5
	Romagna	60,667	2.4	0.0	87.9	0.1	12.3	0.5
	Salerno	26,917	2.5	0.0	77.5	4.0	23.7	1.1
	Sassari	18,084	2.9	0.2	84.4	0.0	16.4	0.7
	Trento	17,788	2.0	0.0	85.0	0.3	27.8	3.8
	Umbria	45,221	0.7	0.0	84.0	0.1	12.6	0.6
	Varese	24,718	1.1	0.0	89.0	11.5	10.8	0.4
	Veneto	84,528	1.5	0.2	87.5	0.8	13.7	1.7



JOINT ACTION ON RARE CANCERS

RARE CANCER AGENDA 2030

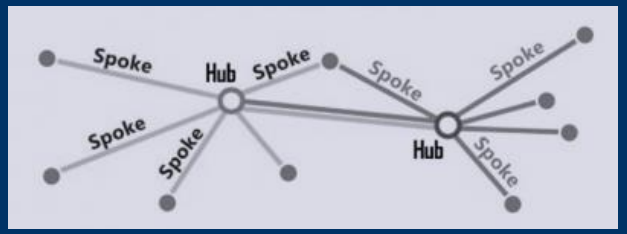
Ten Recommendations from the EU Joint Action on Rare Cancers

1. Rare cancers are the rare diseases of oncology
2. Rare cancers should be monitored
3. Health systems should exploit networking
4. Medical education should exploit and serve healthcare networking
5. Research should be fostered by networking and should take into account an expected higher degree of uncertainty
6. Patient-physician shared clinical decision-making should be especially valued
7. Appropriate state-of-the-art instruments should be developed in rare cancer
8. Regulation on rare cancers should tolerate a higher degree of uncertainty
9. Policy strategies on rare cancers and sustainability of interventions should be based on networking
10. Rare cancer patients should be engaged

3. Health systems should exploit networking…

…around multidisciplinary centres of reference, to improve quality of care in rare cancers by rationalizing patient access to available best expertise and lowering/rationalizing health migration

8. Let's exploit healthcare networking, where available, even for research…



European Commission

European Reference Networks

EpiCARE . BOND . CRANIO . ENDO . ERKNet . EYE . ERNICA . VASCERN . LUNG . RND . SKIN . EURACAN . GUARD-HEART . EuroBloodNet . eUROGEN . GENTURIS . ITHACA . MetabERN . PaedCan . RARE-LIVER . ReCONNET . EURO-NMD . TRANSPLANT-CHILD . RITA

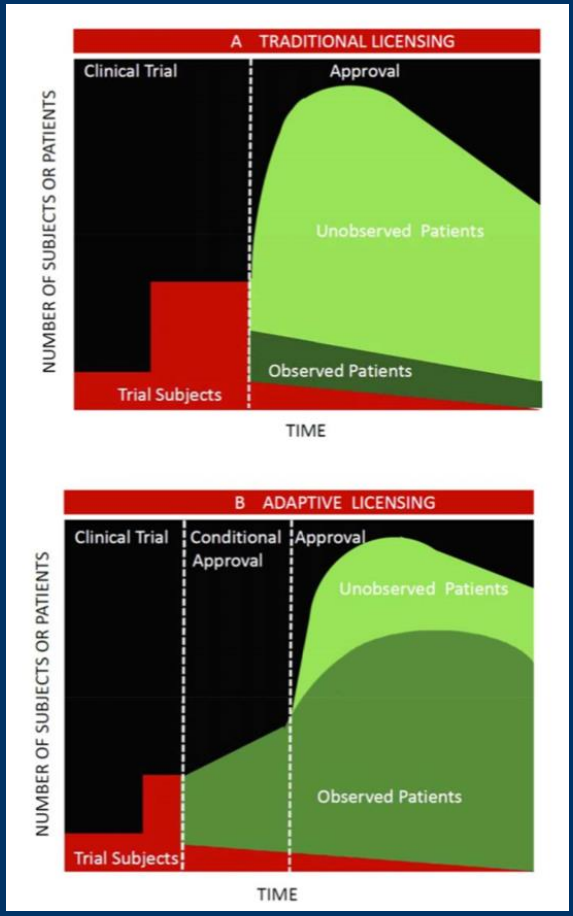
Share. Care. Cure.

EuroBloodNet

EURACAN

European Reference Network
for rare or low prevalence complex diseases
Network
Paediatric Cancer
(ERN PaedCan)

European Reference Network
for rare or low prevalence complex diseases
Network
Genetic Tumour Risk Syndromes (ERN GENTURIS)



Oye KA et al. Clin Pharmacol Ther 2016;100:626

0. Rare cancers are not so rare!
1. A higher degree of uncertainty shuld be accepted in rare cancers…
2. We would need convincing methodologies for external controls…
3. The methodological implications of AI should be addressed…
4. Surrogate end-points would be welcome…
5. Clinical decision-making can handle extra-uncertainty…
6. We should refrain from compromises on external validity in rare cancers…
7. Rare cancers remain rare even in times of precision oncology…
8. Let’s exploit healthcare networking, where available, also for research…

Pandora's box

J.W. Waterhouse - 1896

EURACAN

ERN on adult cancers
(solid tumours)
(ERN EURACAN)

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

UNIVERSITÀ
DEGLI STUDI
DI MILANO

paolo.casali@istitutotumori.mi.it

@casali_pg