Įrodymais pagrįsta, personalizuota ir į pacientą orientuota medicina

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2014.09.16

Įrodymais pagrįsta medicina

- **Sąžiningas, tikslus ir protingas** esamų šiuolaikinių įrodymų naudojimas, ligonių gydyme pritaikant individualias gydymo ar sveikatos priežiūros priemones.

- Dave Sackett 1994

Hill'o kriterijai

- XX amžiaus ketvirtajame dešimtmetyje žymus anglų statistikas ir vienas šiuolaikinės epidemiologijos pradininkų *A.B. Hill* suformavo 8 kriterijus, kurie apibūdina statistinį ryšį.

- Pirmasis iš šių kriterijų yra pastovumas (consistency). Teigiama, kad ryšys yra pastovus, jeigu tie patys duomenys gaunami taikant skirtingus tyrimo metodus skirtingomis aplinkybėmis.

Epidemiologiniai tyrimai

- Tai moksliniai tyrimai, kuriais siekiama nustatyti statistinius arba priežastinius ryšius tarp su sveikata susijusių numanomų rizikos veiksnių ir baigčių.

- Pagrindinės dvi epidemiologinių tyrimų grupės: stebėjimo ir eksperimentiniai tyrimai.

Kohortinis tyrimas

- Kohortinis tyrimas (angl. cohort study arba follow-up study) – tai analitinis epidemiologinis stebėjimo tyrimas, kurį atliekant stebima sveikų žmonių grupė, sudaryta iš rizikos veiksnio veikiamų bei neveikiamų individų. Tiriamųjų grupė vadinama kohorta.

Atvejo ir kontrolės tyrimas

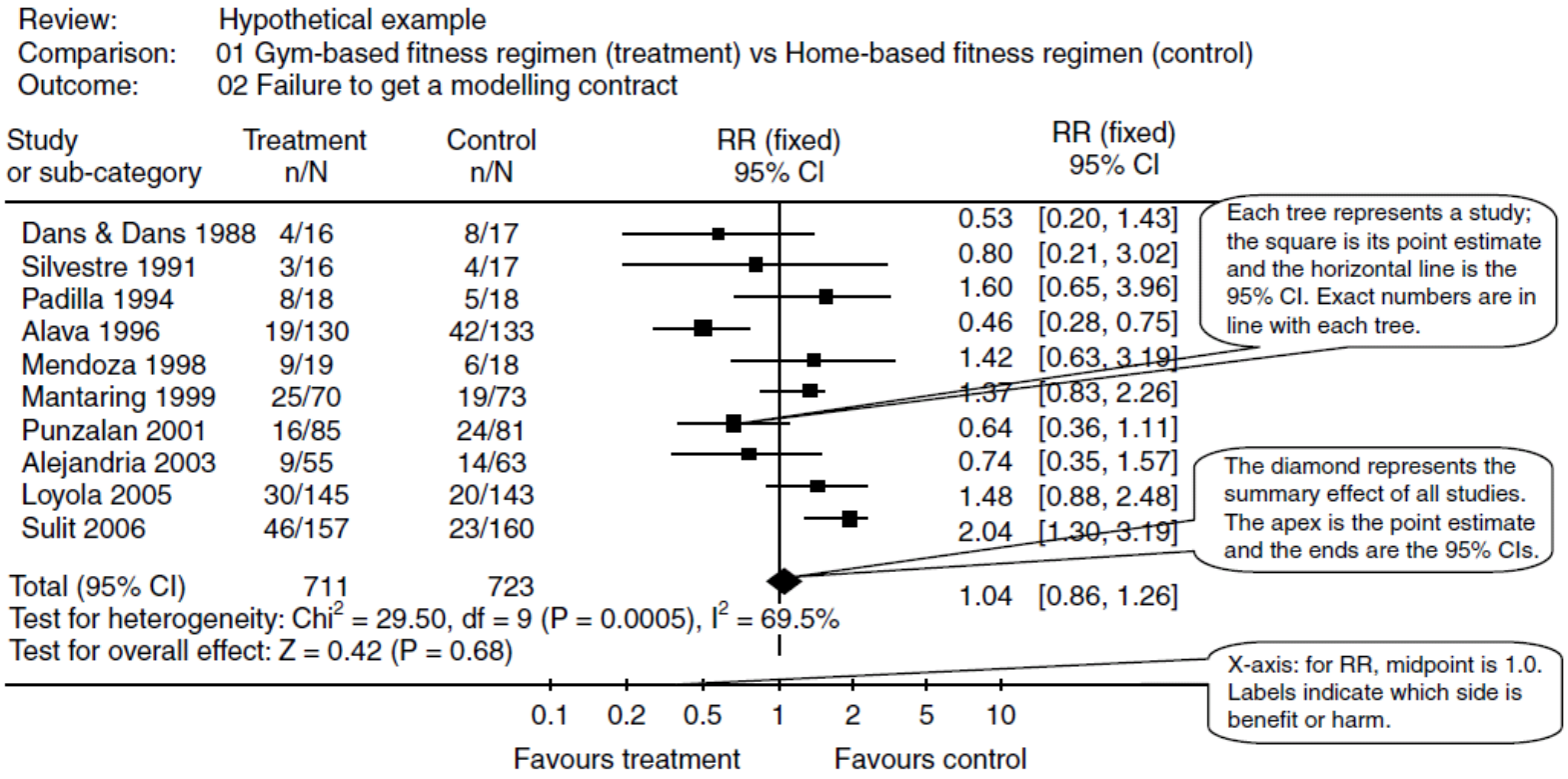
- Atvejo ir kontrolės tyrimas (angl. case-control study) – tai analitinis tyrimas, kurio tikslas – nustatyti galimas ligų priežastis, lyginant tam tikra liga sergančius (atvejai) ir nesergančius žmones (kontrolė).

Atsitiktinių imčių tyrimas

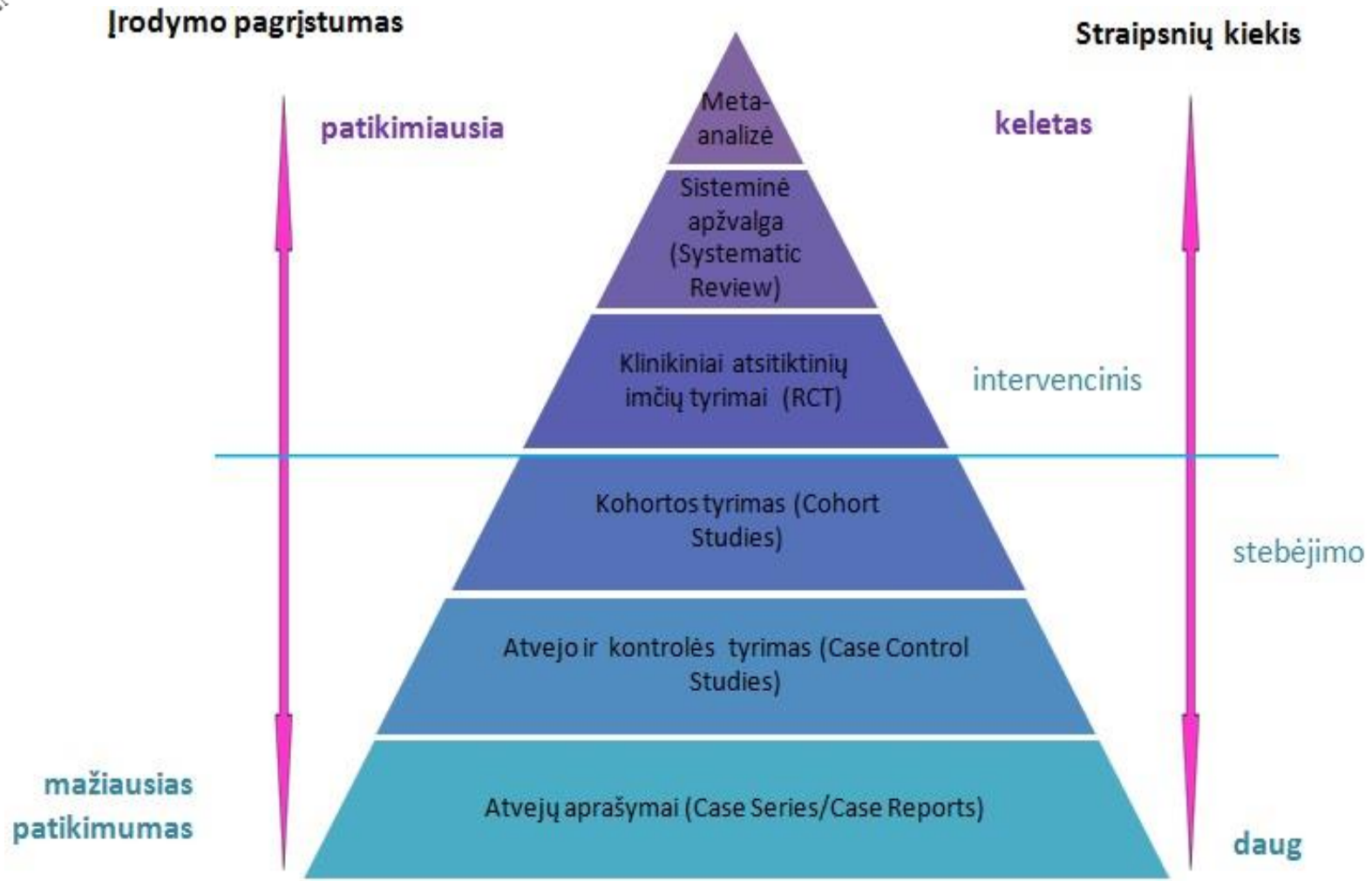
Eksperimentinis tyrimas, kai poveikio bei kontrolinės grupės sudaromos iš populiacijos atsitiktinumo principu pagrįstais metodais, o poveikis vertinamas lyginant nurodytų grupių baigčių dažnumą.

Metaanalizė

Metaanalizė yra kiekybinis metodas, leidžiantis apjungti nepriklausomų studijų (mokslinių publikacijų) rezultatus ir sintezuoti bendras santraukas ir išvadas, įvertinančias terapinį efektyvumą.”



Įrodymų hierarchija



Šaltinis: www.lmba.lt

Įrodymų apibendrinimai

- American College of Physicians PIER (http://pier.acponline.org)
- BMJ Point-of-Care
- Clinical Evidence (http://clinicalevidence.bmj.com/)
- Cochrane Database of Systematic Reviews (CDSR)
- Database of Abstracts of Reviews of Effectiveness (DARE)
- National Institute for Health and Clinical Excellence (NICE, http://www.nice.org.uk/)
- National Guideline Clearinghouse (NGC, http://www.guideline.gov/)
- Agency for Healthcare Research and Quality (AHRQ, http://www.ahrq.gov/)
- Dynamed (http://www.ebscohost.com/dynamed/)

ACTA MEDICA LITUANICA. 2010. Vol. 17. No. 1–2. P. 30–34
DOI: 10.2478/v10140-010-0004-x

How should a clinician interpret results of randomized controlled trials?

Interpretation of randomized controlled trials

- Randomizacija.
- Imties dydžio problemos.
- *Superiority* versus *equivalence* tyrimai.
- Ketinamų gydyti ar *per protocol* analizė.
- Subgrupių ir *post hoc* analizė.
- Surogatinės išeitys.
- Sustabdytos prieš laiką studijos.
- Selektyvios publikacijos.

Virginijus Šapoka[1],

Vytautas Kasiulevičius[1],

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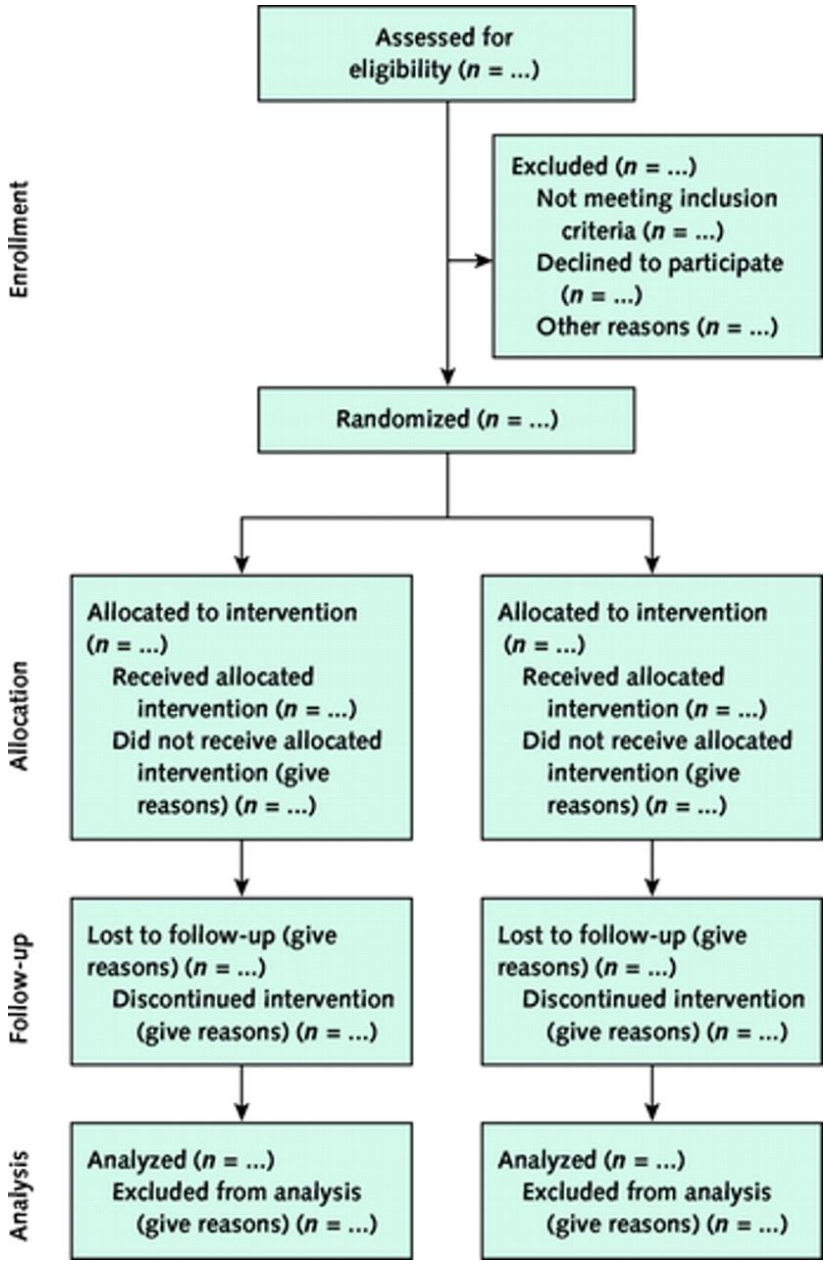
Hill’o pamokos

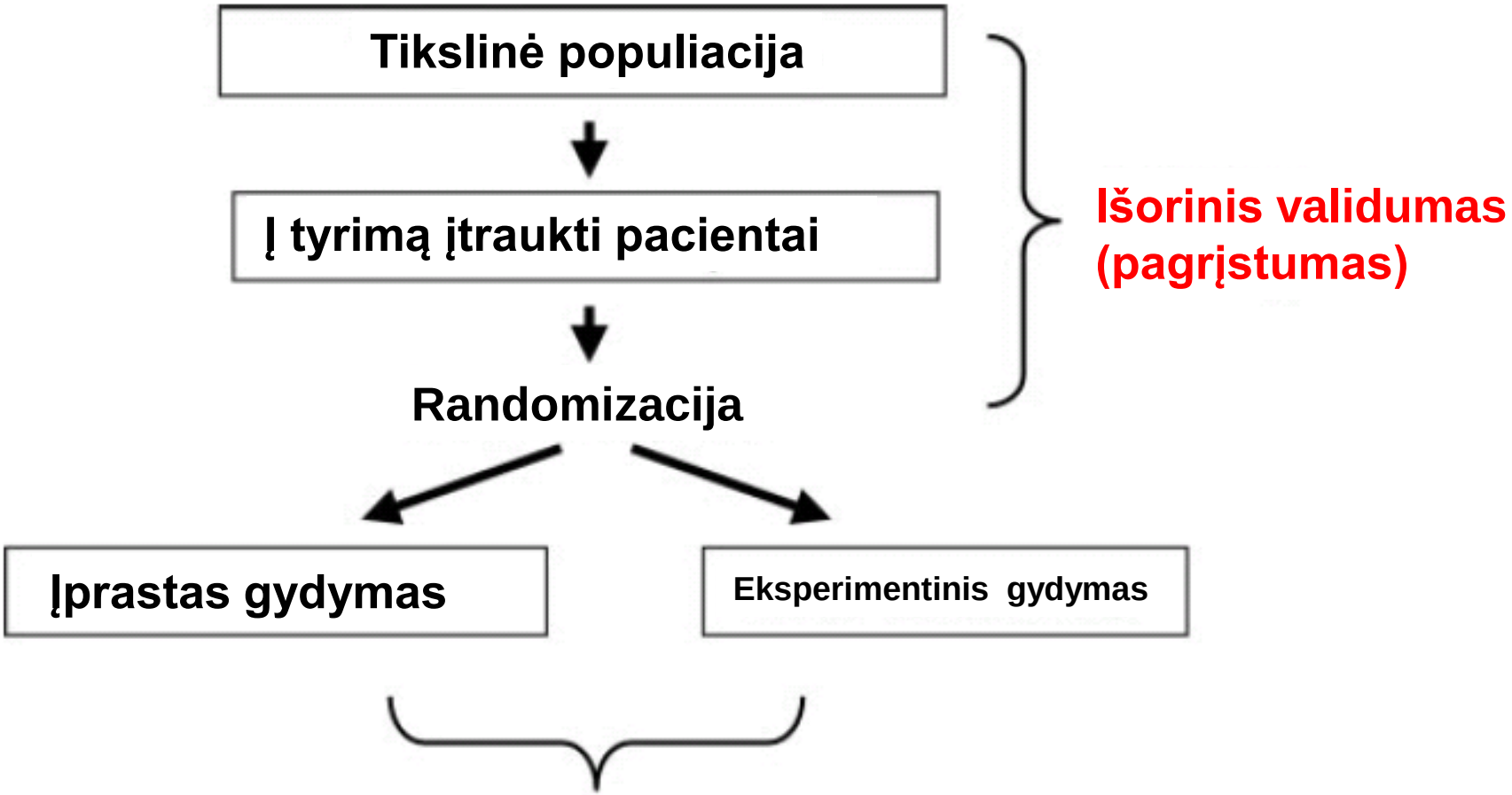
- „Geriausiu atveju tyrimas parodo, ką gali pasiekti medicina, kai vykdomas kruopštus stebėjimas, esant tam tikroms griežtoms sąlygoms. Šie rezultatai nebūtinai bus pasiekti, kai gydymas bus pritaikytas kasdienėje klinikinėje praktikoje“ (Austin Bradford Hill, 1984).

Būtina įvertinti tyrimo protokolą



Schulz K F et al. Ann Intern Med 2010;152:726-732

Išorinis ir vidinis pagrįstumas



Todėl būtina...

- ...perskaityti, kokie pacientai ir kaip buvo įtraukti ar neįtraukti į studiją.

Pacientai, kurie buvo įtraukti į studiją

Pacientai, kurie negalėjo dalyvauti tyrime

METHODS

STUDY DESIGN AND PATIENTS

The Alpha Omega Trial was a multicenter, double-blind, placebo-controlled trial with a 2-by-2 factorial design, which has been described in detail previously.[16] In brief, we recruited 4837 patients in collaboration with cardiologists at 32 hospitals in the Netherlands. Men and women, 60 to 80 years of age, who had had a clinically diagnosed myocardial infarction up to 10 years before randomization were eligible for participation. Major exclusion criteria were daily consumption of less than 10 g of margarine, use of n–3 fatty-acid supplements, unintended weight loss of more than 5 kg in the previous year, and a diagnosis of cancer with an estimated life expectancy of less than 1 year.

Nemažiau svarbu įvertinti bazines pacientų charakteristikas tyrimo pradžioje

Table 1. Baseline Characteristics of the Patients, According to Study Group.*

Variable	EPA–DHA and ALA (N=1212)	EPA–DHA (N=1192)	ALA (N=1197)	Placebo (N=1236)
Age — yr	69.1±5.5	69.1±5.6	69.0±5.6	68.9±5.6
Male sex — no. (%)	946 (78.1)	931 (78.1)	933 (77.9)	973 (78.7)
Time since myocardial infarction — yr	4.2±3.1	4.3±3.2	4.4±3.3	4.3±3.3
Self-reported history of stroke — no. (%)	92 (7.6)	83 (7.0)	89 (7.4)	81 (6.6)
Diabetes mellitus — no. (%)				
Patients with diabetes	245 (20.2)	262 (22.0)	258 (21.6)	249 (20.1)
Patients taking antidiabetic drugs	180 (14.9)	184 (15.4)	192 (16.0)	184 (14.9)
Use of cardiovascular medication — no. (%)				
Antithrombotic agents	1166 (96.2)	1170 (98.2)	1172 (97.9)	1210 (97.9)
Blood-pressure–lowering drugs	1088 (89.8)	1090 (91.4)	1058 (88.4)	1104 (89.3)
Lipid-lowering drugs	1058 (87.3)	1017 (85.3)	1034 (86.4)	1052 (85.1)
Antiarrhythmic drugs	34 (2.8)	37 (3.1)	31 (2.6)	42 (3.4)
Systolic blood pressure — mm Hg	140.9±22.1	142.3±21.6	141.4±21.2	141.9±21.6
Plasma glucose — mmol/liter†	6.2±2.2	6.2±2.0	6.2±2.0	6.3±2.1

Ar tinkamai parinkta vaisto dozė?

CURRENT DRUG THERAPY

CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will prescribe beta-blockers as antihypertensive therapy only when there are compelling indications for them or as add-on treatment

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Beta-blockers for hypertension: Are they going out of style?

Messerli et al[23] performed a meta-analysis published in 1998 that suggested that beta-blockers may not be as effective as diuretics in preventing cardiovascular events when used as first-line antihypertensive therapy in elderly patients. In 10 randomized controlled trials in 16,164 patients who were treated with either a diuretic or a beta-blocker (atenolol), blood pressure was normalized in two-thirds of diuretic-treated patients but only one-third of patients treated with atenolol as monotherapy.

Further, in most of the trials atenolol was used in a once-daily dosage, whereas ideally it needs to be taken more frequently, based on its pharmacokinetic and pharmacodynamic properties (a half-life of 6–9 hours).[3] Neutel et al[28] confirmed that atenolol, when taken once daily, leaves the patient unprotected in the last 6 hours of a 24-hour period, as demonstrated by 24-hour ambulatory blood pressure monitoring. It is possible that this short duration of action of atenolol may have contributed to the results observed in clinical trials that used atenolol to treat hypertension.

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

Erick H. Turner, M.D., Annette M. Matthews, M.D., Eftihia Linardatos, B.S., Robert A. Tell, L.C.S.W., and Robert Rosenthal, Ph.D.

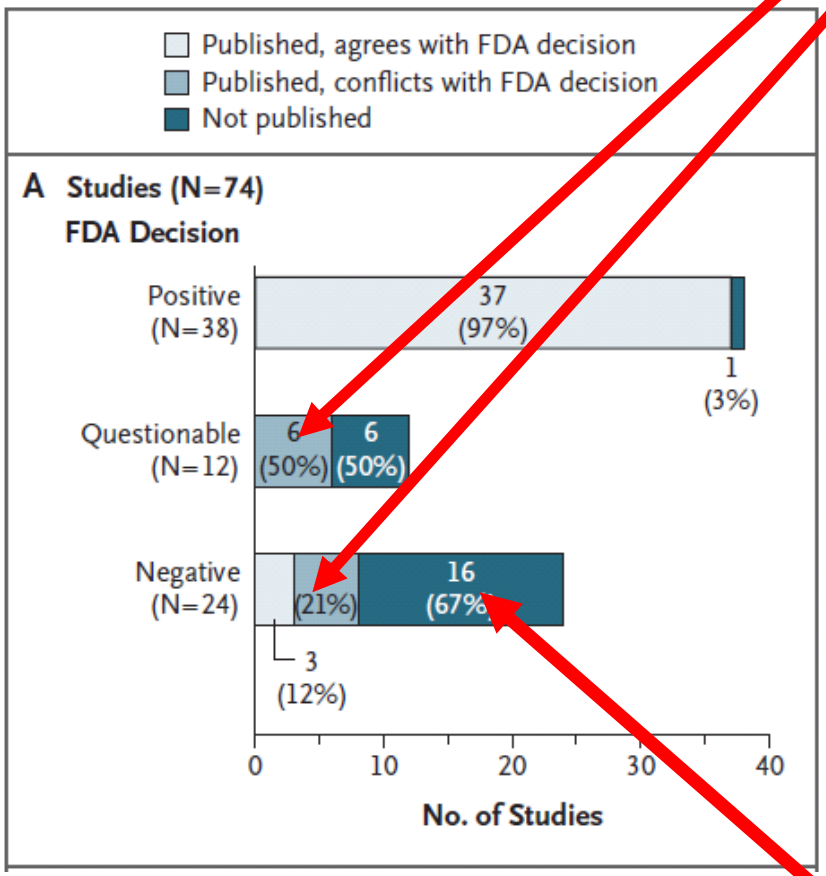
Table 1. Overall Publication Status of FDA-Registered Antidepressant Studies.

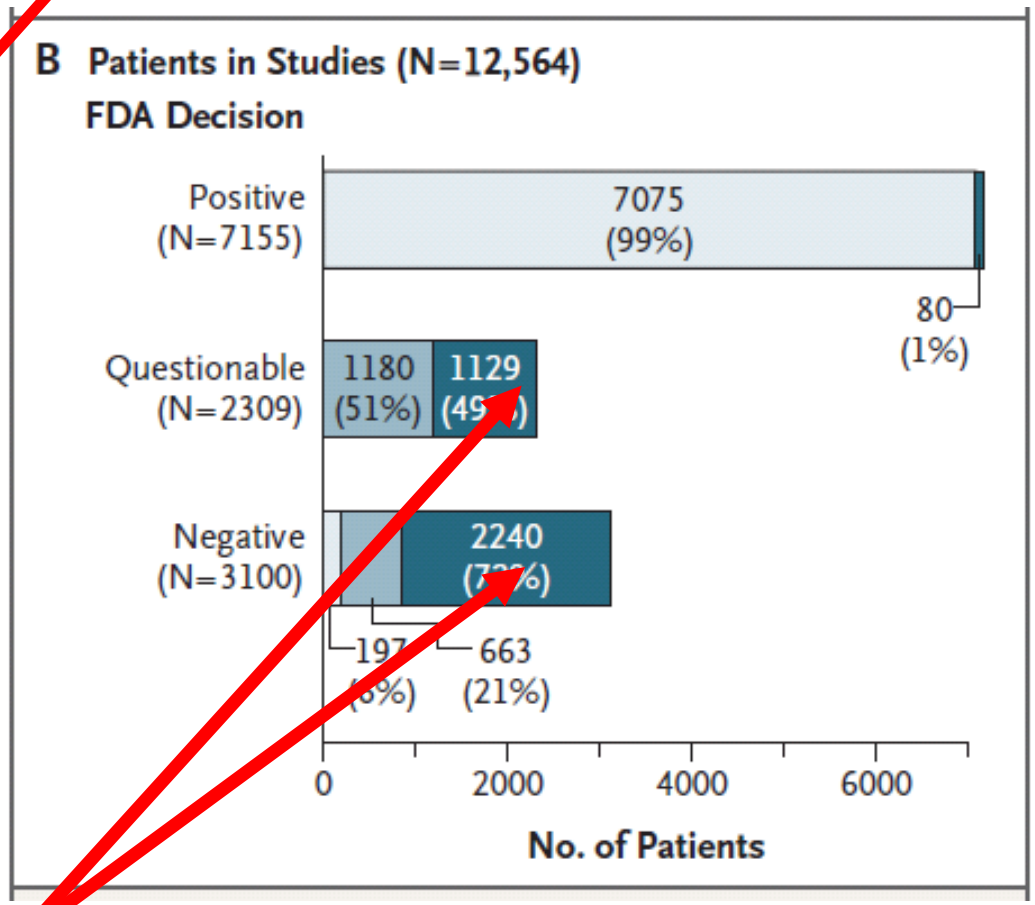
Publication Status	No. of Studies (%)	No. of Patients in Studies (%)
Published results agree with FDA decision	40 (54)	7,272 (58)
Published results conflict with FDA decision (published as positive)	11 (15)	1,843 (15)
Results not published	23 (31)	3,449 (27)
Total	74 (100)	12,564 (100)

Daugybė nepalankių farmacinėms kompanijoms studijų rezultatų niekada neskelbiama medicininiuose žurnaluose.

N Engl J Med. 2008 Jan 17;358(3):252-60

Daugybė ,,pozityvių" studijų rezultatų nepripažįsta FDA, nors jie skelbiami medicininiuose žurnaluose.





Daugybė nepalankių farmacinėms kompanijoms studijų rezultatų niekada neskelbiama medicininiuose žurnaluose.

N Engl J Med. 2008 Jan 17;358(3):252-60

Nepublikuojama daugybė didelių klinikinių tyrimų ir ne tik farmacijos kompanijų remiamų. Deja, to nedaro ir mokslo institucijos.

UNPUBLISHED NEUROLOGY TRIALS WITH NEGATIVE FINDINGS

The following eight major neurology trials (with more than 500 subjects) were found by Christopher W. Jones, MD, an attending physician in the department of emergency medicine at Cooper Medical School of Rowan University in New Jersey, to remain unpublished nearly five years after completion. Information on the trials was accessed from Clinicaltrials.gov on December 12, 2013.

- NCT00322036: Global Efficacy Study of MPC-7869 to Treat Patients With Alzheimer's. Sponsor: Myrexis, Inc. Study terminated; Myriad has discontinued the development of Flurizan.
- NCT00217763: European Study of 3APS in Mild to Moderate Alzheimer's Disease Patients. Sponsor: Bellus Health, Inc. Estimated study completion date: December 2007.
- NCT00083421: Effects of ONO-2506PO in Patients With Alzheimer's Disease. Sponsor: Ono Pharma USA Inc. Study completed: July 2007.
- NCT00087724: A Randomized Study to Evaluate FK962 in Subjects With Mild to Moderate Alzheimer's Disease. Sponsor: Astellas Pharma Inc. Study completed: September 2006.
- NCT00231946: ALADDIN Study - Phase III: Antigonadotropin-Leuprolide in Alzheimer's Disease Drug INvestigation (VP-AD-301). Sponsor: Voyager Pharmaceutical Corporation. No study completion date given, but record last updated September 2007.
- NCT00046761: A Study to Evaluate the Effects of ONO-2506 Intravenous Infusion in Patients With Acute Ischemic Stroke. Sponsor: Ono Pharma USA Inc. Study completed: May 2005.
- NCT00229177: Study of ONO-2506 in Patients With Acute Ischemic Stroke. Sponsor: Ono Pharmaceutical Co. Ltd. Study completed: September 2006.
- NCT00283738: MIST II PFO-Migraine Trial With BioSTAR® Bioabsorbable Septal Repair Implant. Sponsor: NMT Medical. Study completed: March 2008.

Gina Shaw. (2014) Nearly One-Third of Large Clinical Trials Go Unpublished — in Neurology, Too. Neurology Today 14:2, 24-25

Publication bias in clinical trials due to statistical significance or direction of trial results (Review)

Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K

AUTHORS' CONCLUSIONS

Implication for systematic reviews and evaluations of healthcare

Trials with positive findings are more likely to be published and published quicker than trials with negative findings. Those carrying out systematic reviews need to ensure they assess the potential problems of publication bias in their review and consider methods for addressing this issue by ensuring a comprehensive search for trials in both the published and unpublished literature. The prospective registration of all clinical trials at inception and before their results become available would enable review authors to know when relevant trials have been conducted, so that they can ask the responsible investigators for the relevant study data.

Pozityvūs rezultatai bus paskelbti greičiau negu negatyvūs.

Farmacijos industrijos finansuotų tyrimų duomenų skirtumai klinikinių tyrimų registruose ir publikacijose.

Table 3 Number of deaths, suicide-related and homicide-related events, and psychiatric serious adverse events in drug-treated participants

	Death	Suicide, completed	Suicidal ideation, attempts, injury	Homicidal ideation	New or worsened psychiatric symptoms	Total
Aripiprazole						
Trial summary (n=28)	79	1	4	0	79	163
Journal article (n=28)	27 (34.2)*	1 (100.0)	5 (125.0)	0	66 (83.5)	99 (60.7)
Unpublished trial summary† (n=21)	15	1	10	0	92	118
Olanzapine						
Trial summary (n=33)	50	9	18	0	85	162
Journal article (n=33)	19 (38.0)	1 (11.1)	4 (22.2)	0	14 (16.5)	38 (23.5)
Unpublished trial summary (n=18)	7	3	21	1	95	127
Ziprasidone						
Trial summary (n=8)	0	1	13	1	30	45
Journal article (n=8)	0 (0)	1 (100.0)	5 (38.5)	1 (100.0)	14 (46.7)	20 (44.4)
Unpublished trial summary (n=21)	18	1	23	3	141	186
Atomoxetine						
Trial summary (n=31)	0	0	7	0	6	13
Journal article (n=31)	0	0	0 (0)	0	0 (0)	0 (0)
Unpublished trial summary (n=20)	1	0	5	0	5	11
Duloxetine						
Trial summary (n=35)	11	4	40	0	27	82
Journal article (n=35)	11 (100.0)	4 (100.0)	33 (82.5)	0	21 (77.8)	69 (84.1)
Unpublished trial summary (n=13)	3	0	10	0	20	33
Sertraline						
Trial summary (n=7)	11	0	5	0	11	27
Journal article (n=7)	0 (0)	0	0 (0)	0 (0)	0 (0)	0 (0)
Unpublished trial summary (n=9)	1	0	10	1	4	16
All Drugs						
Trial summary (n=142)	151	15	87	1	238	492
Journal article (n=142)	57 (37.7)	7 (46.7)	47 (54.0)	1 (100.0)	115 (48.3)	227 (46.1)
Unpublished trial summary (n=102)	45	5	79	5	357	491

*Percent as reported in associated trial summaries.
†Unpublished trial summary refers to clinical trial summaries posted on the publicly accessible clinicalstudyresults.org website, but having no associated stand-alone journal article.

- S. Hughes, D. Cohen, R. Jaggi. (2014) Differences in reporting serious adverse events in industry sponsored clinical trial registries and journal articles on antidepressant and antipsychotic drugs: a cross-sectional study. BMJ Open 4:7

Svarbu užtikrinti galimybę pasiekti informaciją duomenų bazėse

Table 1
ICTRP primary registries.

Name of database	Identifier prefix	Country or region	Year created	# Trials (Sept. 2013)	Provides results	Link to publication	Additional identifiers	History of changes
ClinicalTrials.gov	NCT	Global	2000	152,296	Yes	Yes	Yes	Yes
EU Clinical Trials Register	EUCTR	Europe	2001	21,301	No	No	Only sponsor ID	No
Australian New Zealand Clinical Trials Registry	ACTRN	Australia/New Zealand	2005	8216	No	Yes	Yes	Yes
Current controlled trials	ISRCTN	Springer Science (Global)	1998	11,875	No	Yes	Yes	No
Clinical Trials Registry – India	CTRI	India	2007	4003	No	Yes	Yes	Yes
Chinese Clinical Trial Registry	ChiCTR	China	2005	3573	Yes	No	Yes	No
Japan Primary Registries Network	JPRN-JapicCTI	Japan	2004	1238	No	No	Yes	Yes
	JPRN-UMIN	Japan	–	11,694	No	Yes	Yes	Yes
	JMA	Japan	–	139	No	Yes		Yes
The Netherlands National Trial Register	NTR	Netherlands	–	3966	No	Yes	Yes	Yes
Clinical Research Information Service – Republic of Korea	KCT	Korea	–	841	No	Yes	Yes	Yes
Iranian Registry of Clinical Trials	IRCT	Iran	–	4825	No	No	No	No
Brazilian Clinical Trials Registry (ReBec)	RBR	Brazil	–	271	No	No	Yes	Yes
Cuban Public Registry of Clinical Trials	RPCEC	Cuba	–	487	No	Yes	Yes	No
German Clinical Trials Register	DRKS	Germany	–	2008	No	Yes	Yes	Yes
Sri Lanka Clinical Trials Registry	SLCTR	Sri Lanka	–	109	No	Yes	Yes	Yes
Pan African Clinical Trial Registry	PACTR	Pan African	–	222	No	No	Yes	Yes

ICTRP, International Clinical Trials Registry Platform.

Personalizuota medicina

- Personalizuotoje medicinoje medicinos modelis, medicininiai sprendimai, praktika ir gydymo metodai yra taikomi individualiam pacientui.

- *Wikipedia*

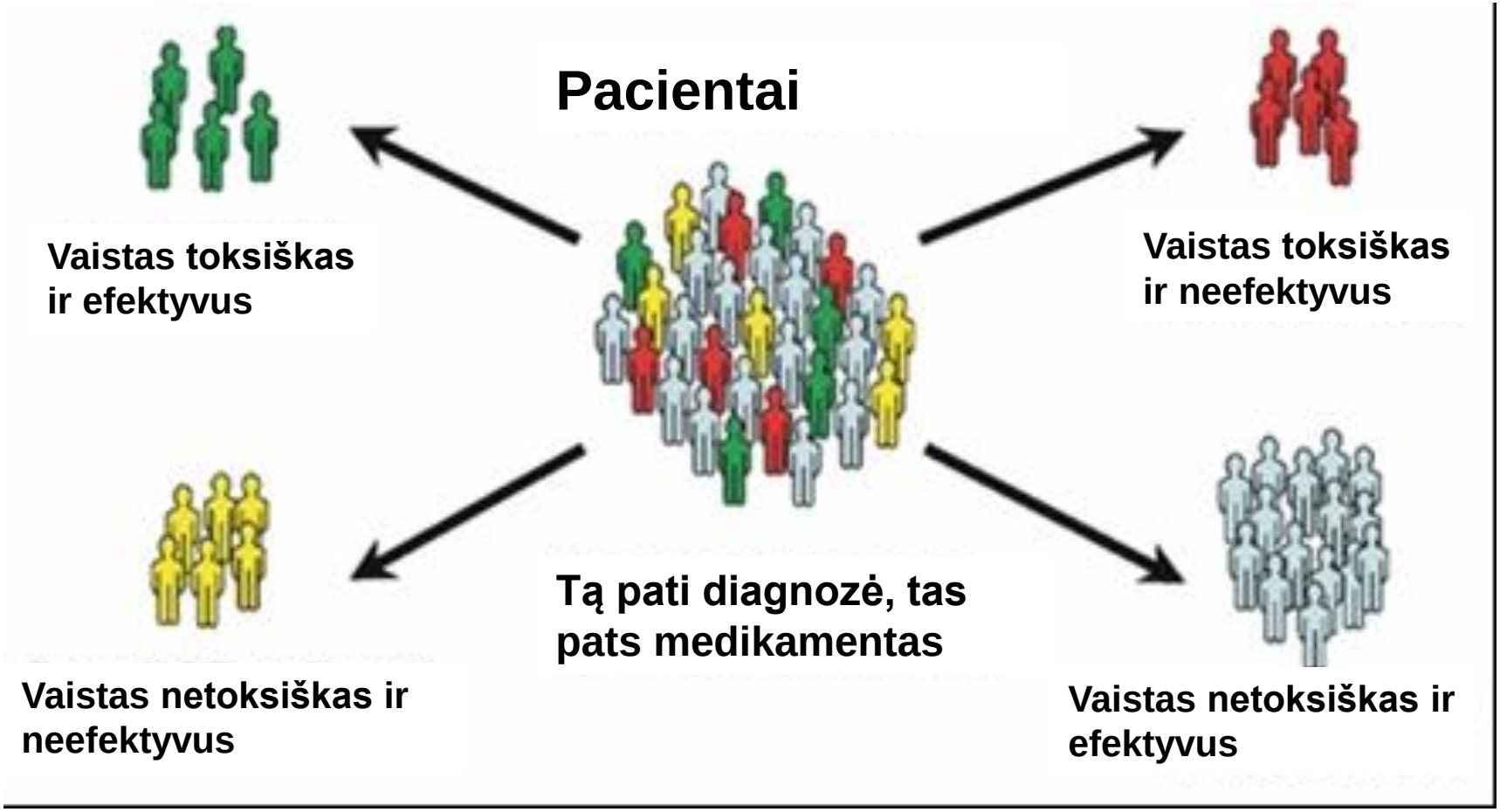
Kadangi egzistuoja genetiniškai nulemtas P450 polimorfizmas, pacientai yra:

- normaliai metabolizuojantieji vaistus (angl.: EM)
- lėtai metabolizuojantieji vaistus (angl.: PM)
- labai greitai metabolizuojantieji vaistus (angl.: URM)

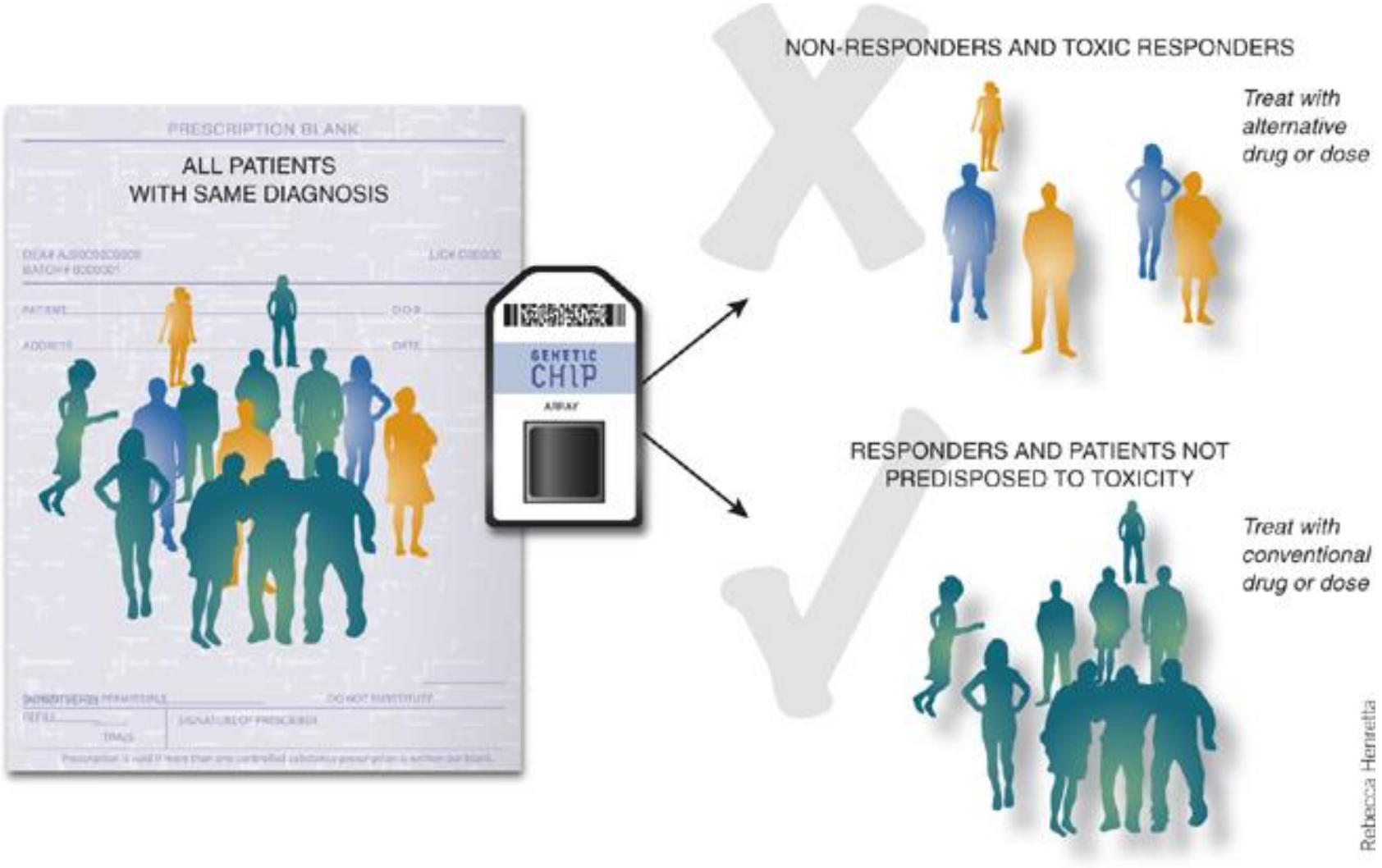
CYP polimorfizmas skirtingai paplitęs skirtingose populiacijose

Fermentas	Chromosoma	Trūkumo dažnis (%)	
		Europiečiai	Azijiečiai
CYP1A2	15	ND	ND
CYP2B6	19	3-4	
CYP2C9	10	1-3	
CYP2C19	**10**	**3-5**	**15-20 (60)**
CYP2D6	22	5-10	1
CYP2E1	10	ND	ND
CYP3A4,5	7	ND	ND

Personalizuota medicina



Personalizuota medicina



Į pacientą orientuota medicina

- Klinikinių sprendimų priėmimas pagarbiai atsižvelgiant į paciento pasirinkimą, poreikius ir vertybes.

Institute on Medicine. "Crossing the Quality Chasm: A New Health System for the 21st Century". 26 November 2012.

Paciento autonomija

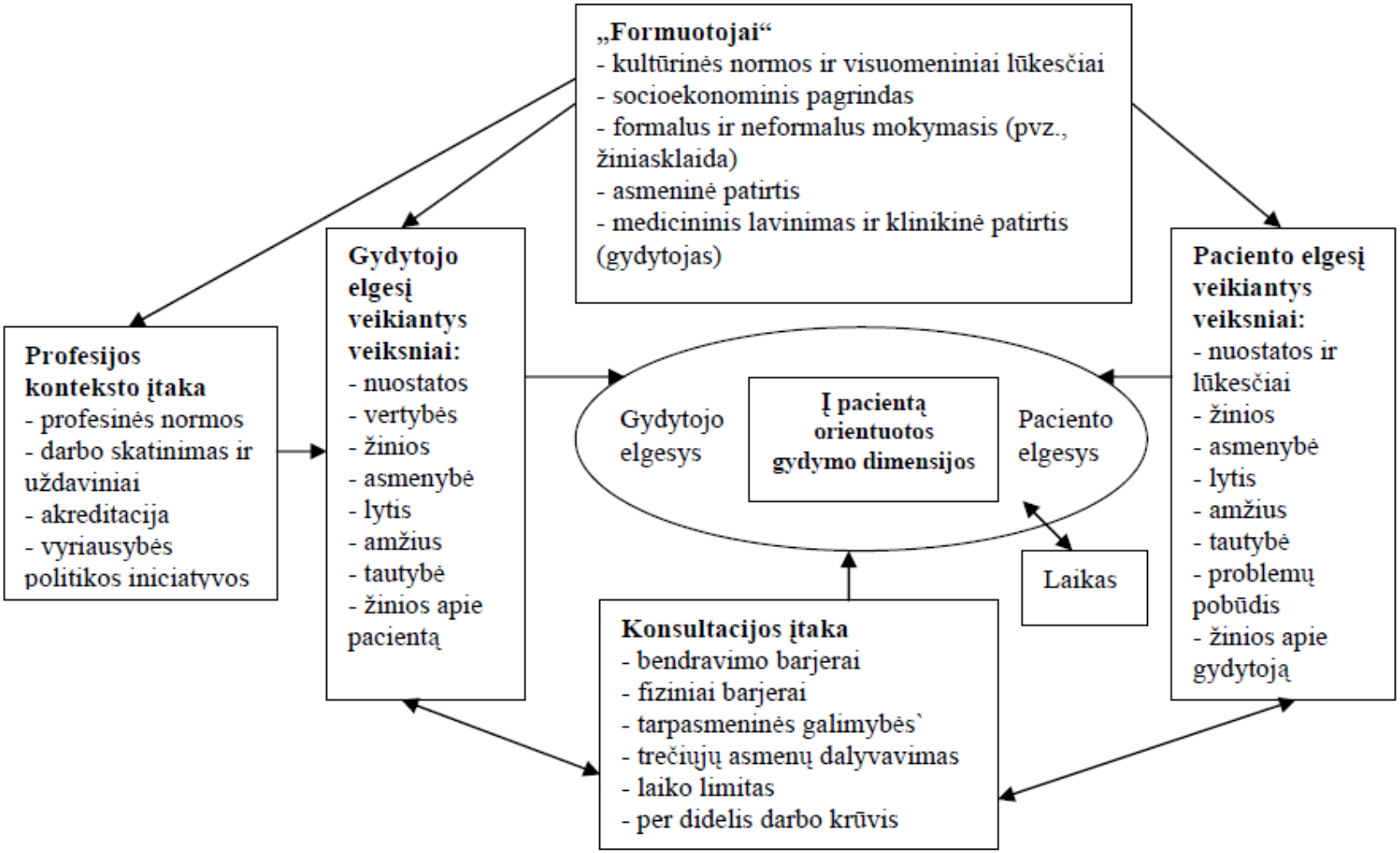
Penkios svarbiausios pacientų teises:

- - teisę į pasirinkimą,
- - teisę į informaciją,
- - teisę į asmens privatumą,
- - teisę išlaikyti paslaptį (konfidencialumas),
- - teisę būti nediskriminuojamam.

Paciento autonomija

- Pacientas nepaisydamas patiriamo skausmo, diskomforto ar kitų fiziologinių sutrikimų (išskyrus sunkius psichinius sutrikimus), **gali racionaliai mąstyti ir save patį suvokti, daryti sprendimus, vertinti ir numatyti savo veiklos tikslus bei motyvus.**

Į pacientą orientuota medicina



Rytė Giedrikaitė. Disertacija, 2008. Adaptuota pagal N. Mead ir P. Bower.

Koks mūsų tikslas?

- Įrodymais pagrįsta, personalizuota ir į pacientą orientuota medicina.

Dėkoju už dėmesį !