‘Implementation’ of pharmacogenetic testing for antidepressants and antipsychotic medication at the Centre for Addiction and Mental Health in Toronto

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CPIC Clinical Pharmacogenetics Implementation Consortium

CPIC
Conference Call
03.03.2016

Pharmacogenetics

camh Centre for Addiction and Mental Health / Centre de toxicomanie et de santé mentale

www.pharmacogenetics.ca

Campbell Family Mental Health Research Institute

Familial occurrence of tardive dyskinesia

Müller DJ, Schulze TG, Knapp M, Held T, Krauss H, Weber T, Ahle G, Maroldt A, Alfter D, Maier W, Nöthen MM, Rietschel M. Familial occurrence of tardive dyskinesia.
Acta Psychiatr Scand 2001: 104: 375–379. © Munksgaard 2001.

Objective: Familial occurrence of tardive dyskinesia (TD) and schizophrenia has been hypothesized to confer risk to the development of TD. We investigated these hypotheses in a large patient sample applying standardized methods for phenotype characterization.
Method: Two hundred and twenty-two patients with a diagnosis of schizophrenia or schizoaffective disorder were assessed for TD and for family history of schizophrenia or schizoaffective disorder. Thirty-nine patients had 40 affected first-degree family members, one patient having two first-degree relatives. Of these, 17 pairs and one triplet were personally examined.
Results: 1) There was a tendency for TD in the affected relatives to be associated with the TD status of the index-patient; this finding was unrelated to age and doses of neuroleptic medication. 2) No association between a family history of schizophrenia or schizoaffective disorder and TD was found.
Conclusion: A family history of TD might represent a risk factor for TD, whereas a family history of schizophrenia does not.

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Key words: dyskinesias; risk factors; genetics

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Focus: Antidepressants & Antipsychotics

Pharmacopsychiatry, 2002

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Moclobemide Response in Depressed Patients: Association Study with a Functional Polymorphism in the Monoamine Oxidase A Promoter

Centre for Addiction and Mental Health (CAMH)

College St. Site

Queen St. Site

Why had CYP testing not become common practice…?

- Limited data!
- Limited knowledge of physician and patients
- Reimbursement not solved
- “Outlier” effect
- Ethical challenges (Nine months of conversation prior to approval by local REB)

Start of the ***Pharmacogenetics Research Clinic*** at CAMH (2008)

- Concept: Investigate patients with poor response or high level of side effects at lower medication dose
- Physicians would refer patients
- Genotyping of CYP2D6 & CYP2C19 in-house
- Returning interpretation to physicians
- Sollicit feedback from physicians using a questionnaire (PIP-FQ)

PGx Research Clinic: Flowchart

Patient referral – Screening for inclusion/exclusion

(eg capacity, medical history, ethnicity)

↓

RA contacts patient (for informed consent) and study entry:

SCID, PANSS, CGI, BAS, AIMS, UKU (modified), body weight and BMI

+ Blood draw for genotyping

↓

Six weeks follow-up:

PANSS, CGI, BAS, AIMS, UKU (modified), body weight and BMI

+ Blood draw for plasma levels + PIP-FQ (Physicians)

↓

Three month follow-up:

PANSS, CGI, BAS, AIMS, UKU (modified), body weight and BMI

Study exit

RESULTS

Method: Genomic DNA was extracted from whole blood using a high-salt method. DNA specimens were analyzed using the Applied Biosystems TaqMan SNP genotyping and gene copy number detection assays.

Laboratory Cytochrome P450 2C19 alleles tested: *2, *3, *17.
Laboratory Cytochrome P450 2D6 alleles tested: *3, *4, *5, *10, *17, *41; gene copy number.

Interpretations:

	Genotype	Interpretation
CYP2C19	***1/*1**	**Extensive Metabolizer**
CYP2D6	***4/*4**	**Poor Metabolizer**

Ultra rapid metabolizers (UM) have increased metabolism of substrate drugs of this enzyme and probably require higher drug dosages to achieve an average therapeutic response.
Extensive metabolizers (EM) have normal metabolic capacity and can be prescribed standard dosages of the substrate drugs.
Intermediate metabolizers (IM) may probably require modestly lower than standard drug dosages to achieve an average therapeutic response.
Poor metabolizers (PM) have decreased drug removal and are more likely to have adverse side effects.

For a list of drugs metabolized by CYP2C19 and CYP2D6, please turn page and/or visit www.pharmacogenetics.ca/Research.

Limitations:

- The accuracy of this test is >99% for the alleles tested, which are common to individuals of European-Caucasian descent.
- Enzyme activity may also be modulated by unknown or untested variants of the CYP2D6 and CYP2C19 genes.
- Drug metabolism may be affected by additional enzymes and other factors such as co-medication, physical conditions, diet, smoking and others.
- The performance of the TaqMan technology for CYP2D6 and CYP2C19 was validated by the Pharmacogenetics Group of CAMH. It has not been approved by the FDA or Health Canada.
- It is assumed that the DNA is representative of the individual.

Phase I 2009:
Start of genotyping
CYP2D6 & CYP2C19

Phase II 2012:
Start of the IMAPCT study
www.im-pact.ca

Adding:
CYP1A2
CYP3A4
CY2C9

camh IMPACT
Individualized Medicine:Pharmacogenetic Assessment & Clinical Treatment

Tanenbaum Centre for Pharmacogenetics, Neurogenetics Section
Centre for Addiction and Mental Health
250 College Street, Toronto, ON, M5T 1R8
Fax: 416-979-4666

Patient Name:
Medical Record Number:
Requesting Physician:
Sample Collected:

Lab ID:
Date of Birth:

Liver enzyme Cytochrome P450 gene testing for drug metabolizing capacity

RESULTS

Method: Genomic DNA was extracted from human tissue. DNA specimens were analyzed using TaqMan SNP genotyping and gene copy number detection assays.

Interpretation:

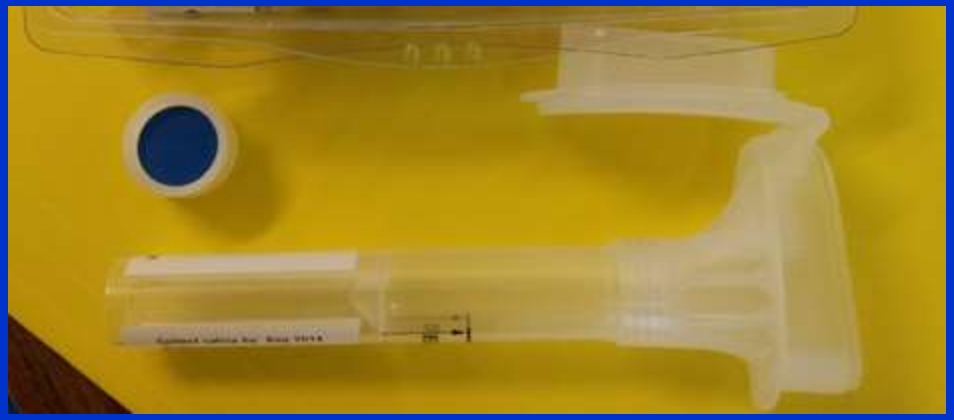
Gene	Antidepressants	Antipsychotics	Other
CYP1A2	Cymbalta (duloxetine)	Zyprexa (olanzapine) Clozaril (clozapine)	N/A
CYP3A4	N/A	Seroquel (quetiapine)	N/A
CYP2C19	Celexa (citalopram) Cipralex (escitalopram) Zoloft (sertraline) Elavil (amitriptyline)	N/A	N/A
CYP2C9	Prozac (fluoxetine)	N/A	N/A
CYP2D6	Effexor (venlafaxine) Paxil (paroxetine) Prozac (fluoxetine) Luvox (fluvoxamine) Elavil (amitriptyline) Anafranil (clomipramine) Norpramin (desipramine) PamelorÂ (nortriptyline) Tofranil (imipramine) Remeron (mirtazapine)	Haldol (haloperidol) Risperdal (risperidone) Abilify (aripiprazole) Clopixol (zuclopenthixol)	Codeine Strattera (atomoxetine)

www.im-pact.ca

Instead of blood draw: Non-invasive Sample Collection

CAMH Recruiter explains test & answers questions:

- Patient signs consent form
- Ask patient to spit into the collection tube
- Ask patient to close the lid of the funnel and return tube to package.



Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Physicians' opinions following pharmacogenetic testing for psychotropic medication

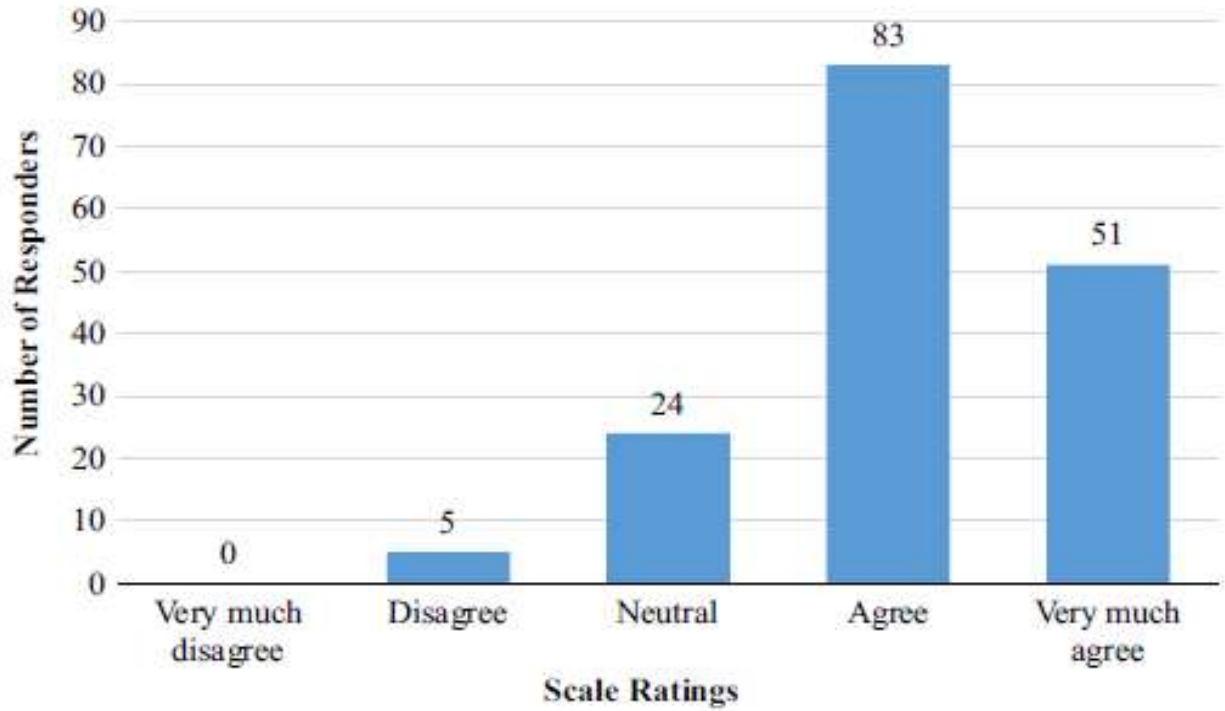
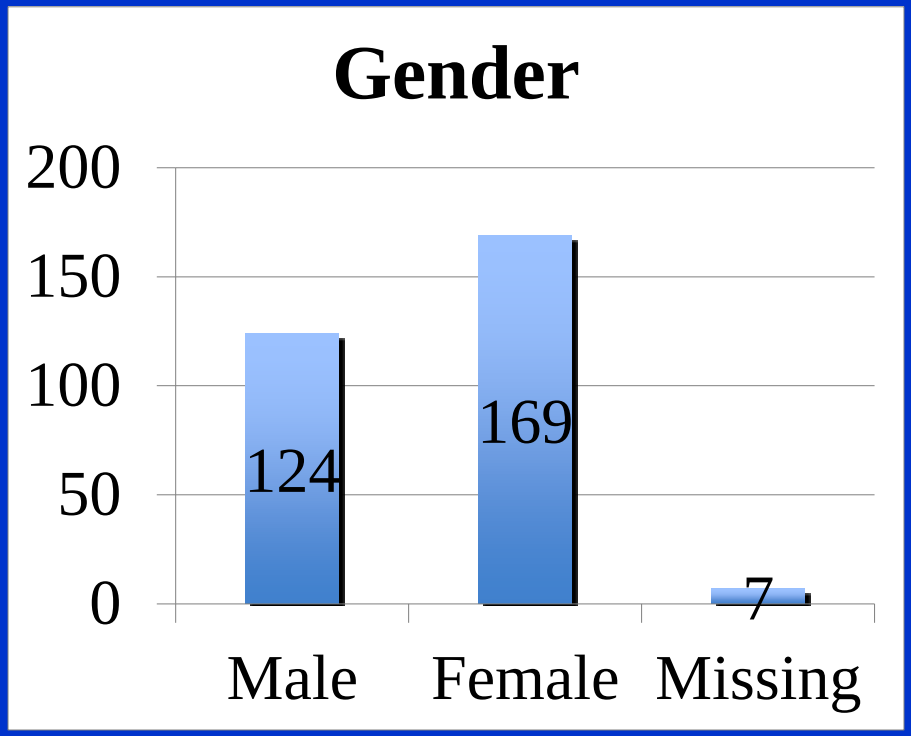
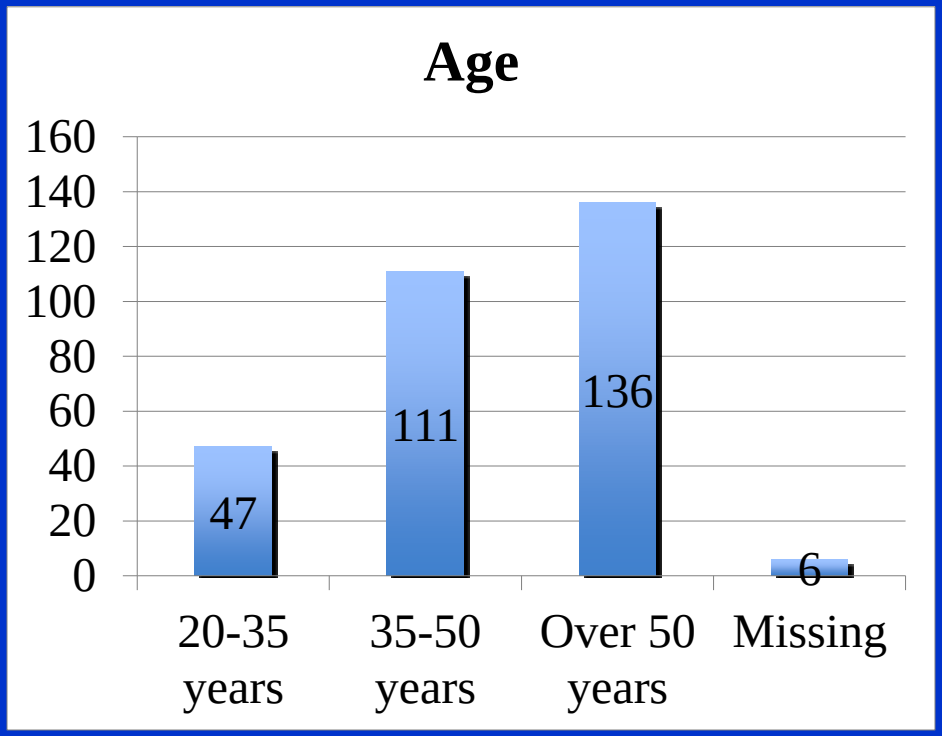


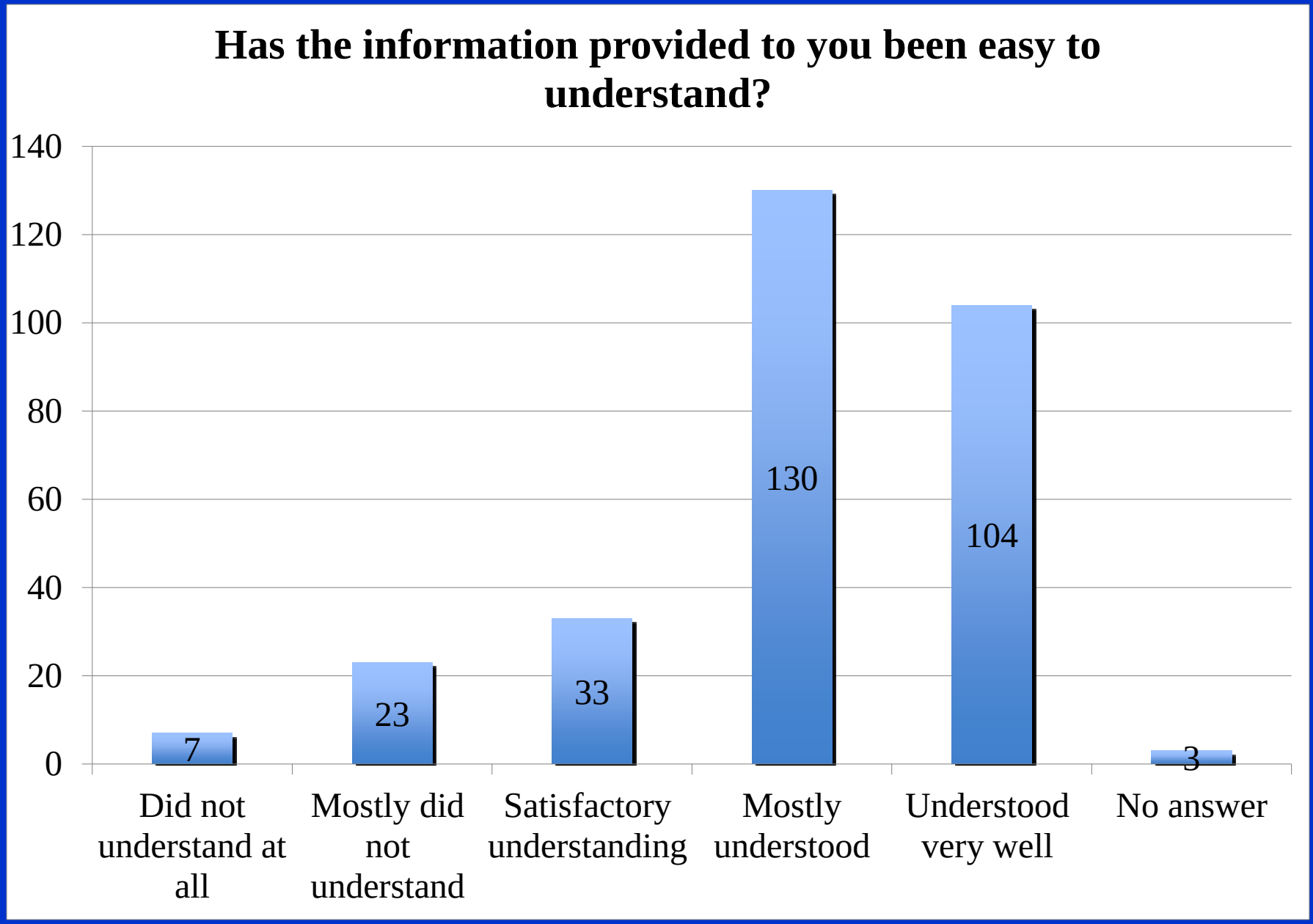
Fig. 1. Results of the question "Do you believe that genetic testing will become common standard in psychiatric drug treatment?".

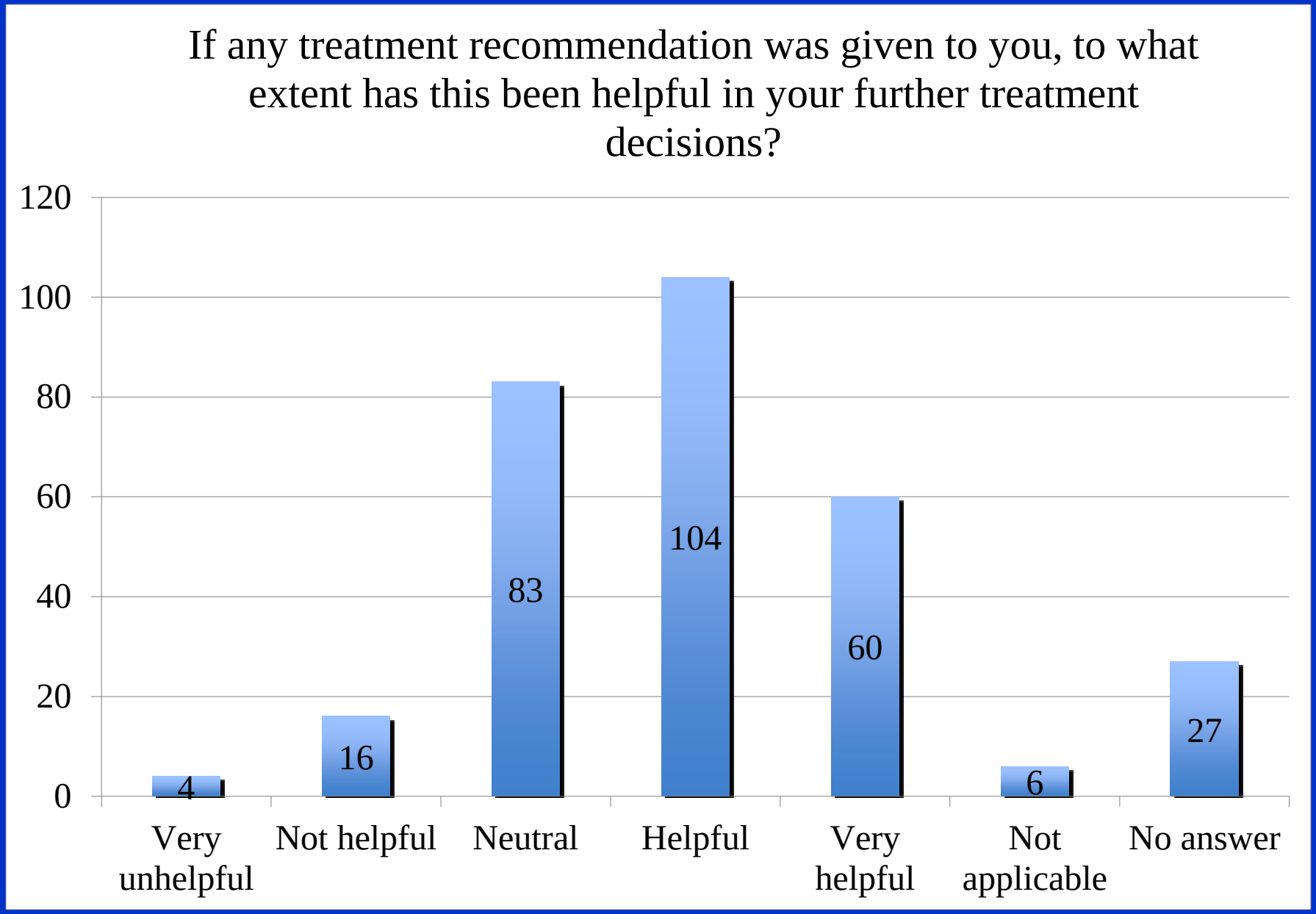
Walden et al., 2015

Survey of 300 physicians in the Toronto area

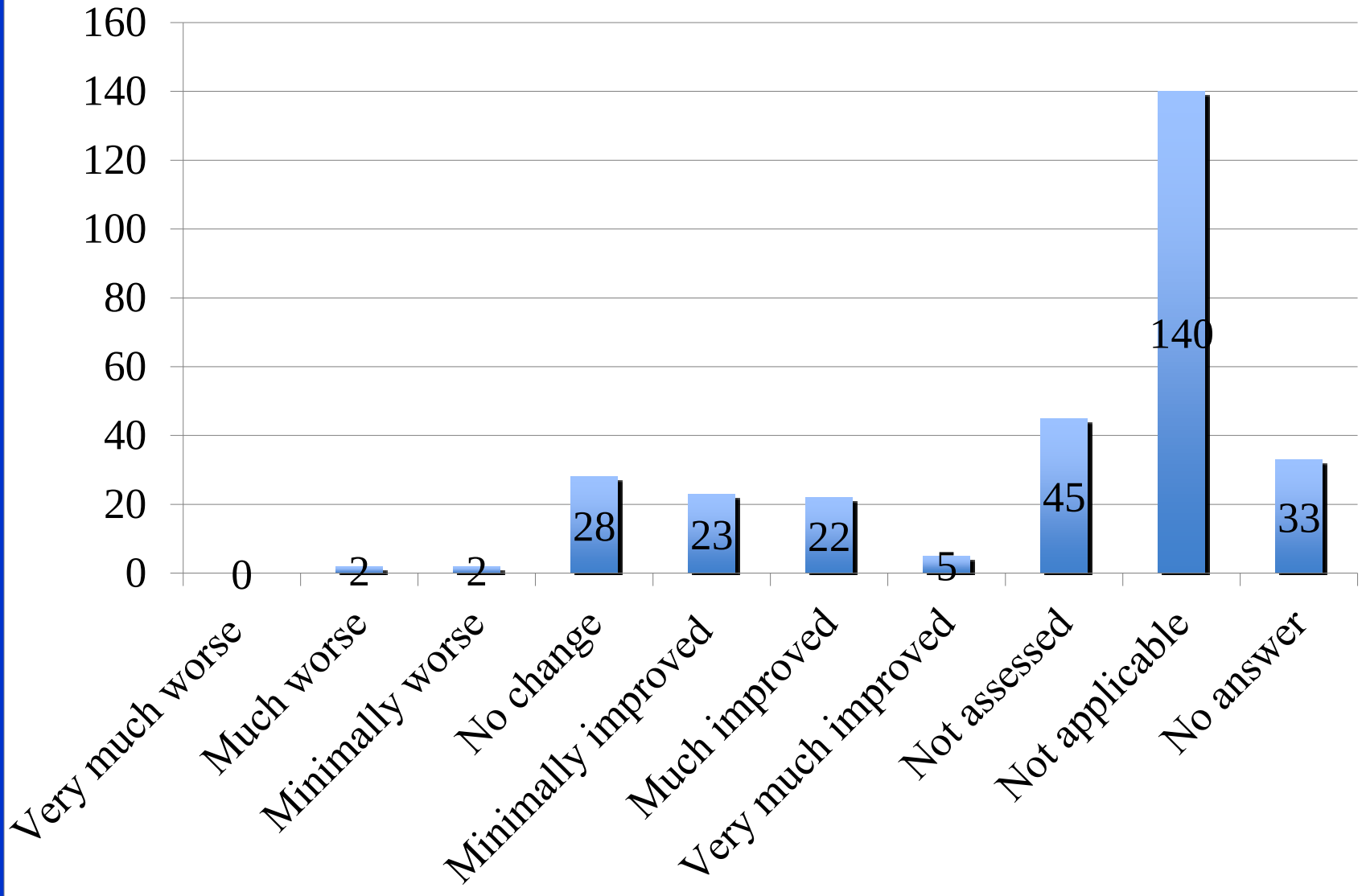


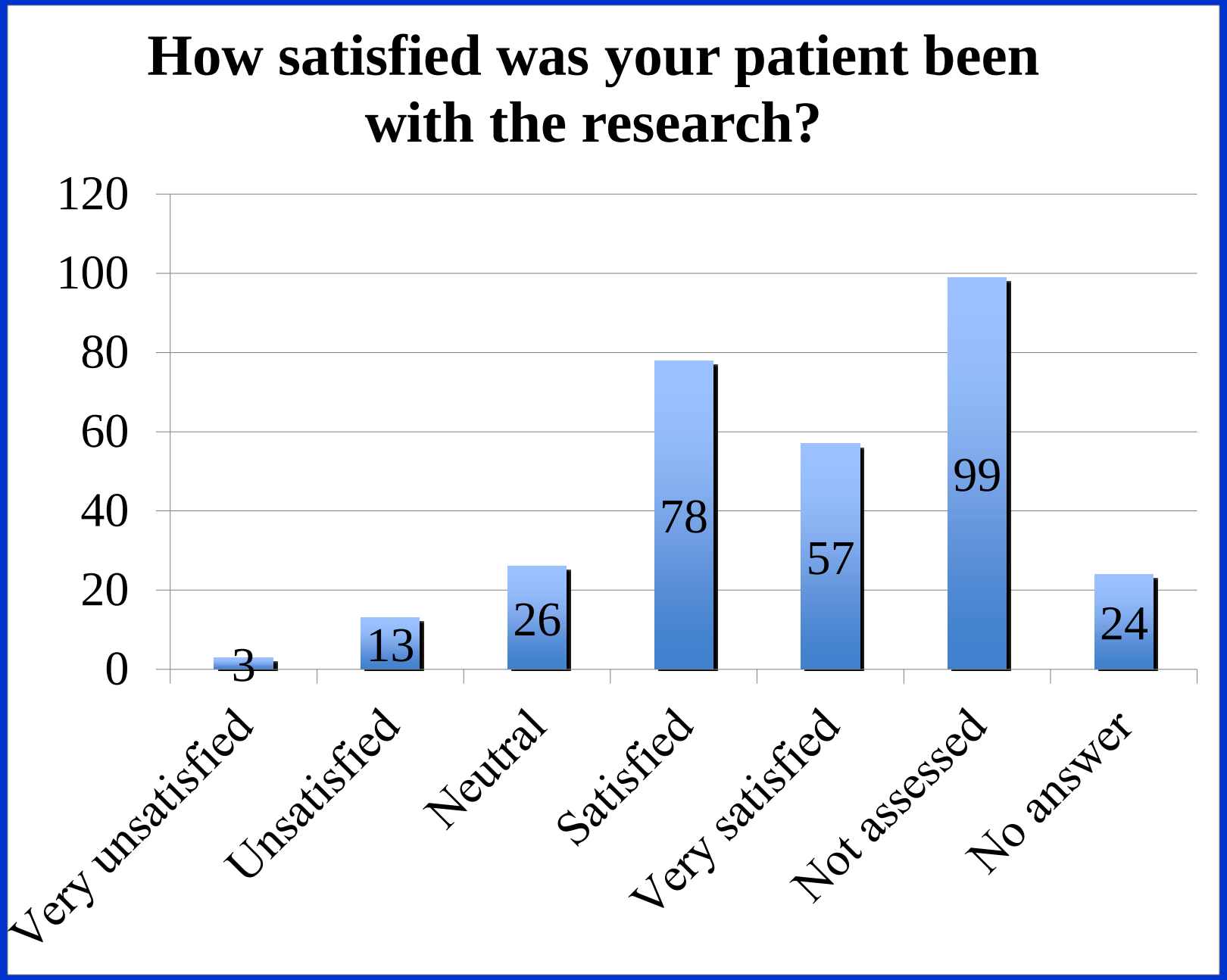



Has the information provided to you been easy to understand?
140
120
100
80
60
40
20
0
7
23
33
130
104
3
Did not understand at all
Mostly did not understand
Satisfactory understanding
Mostly understood
Understood very well
No answer


If any treatment recommendation was given to you, to what extent has this been helpful in your further treatment decisions?
120
100
80
60
40
20
0
4
16
83
104
60
6
27
Very unhelpful
Not helpful
Neutral
Helpful
Very helpful
Not applicable
No answer

How much change occurred in your patient's side effects?



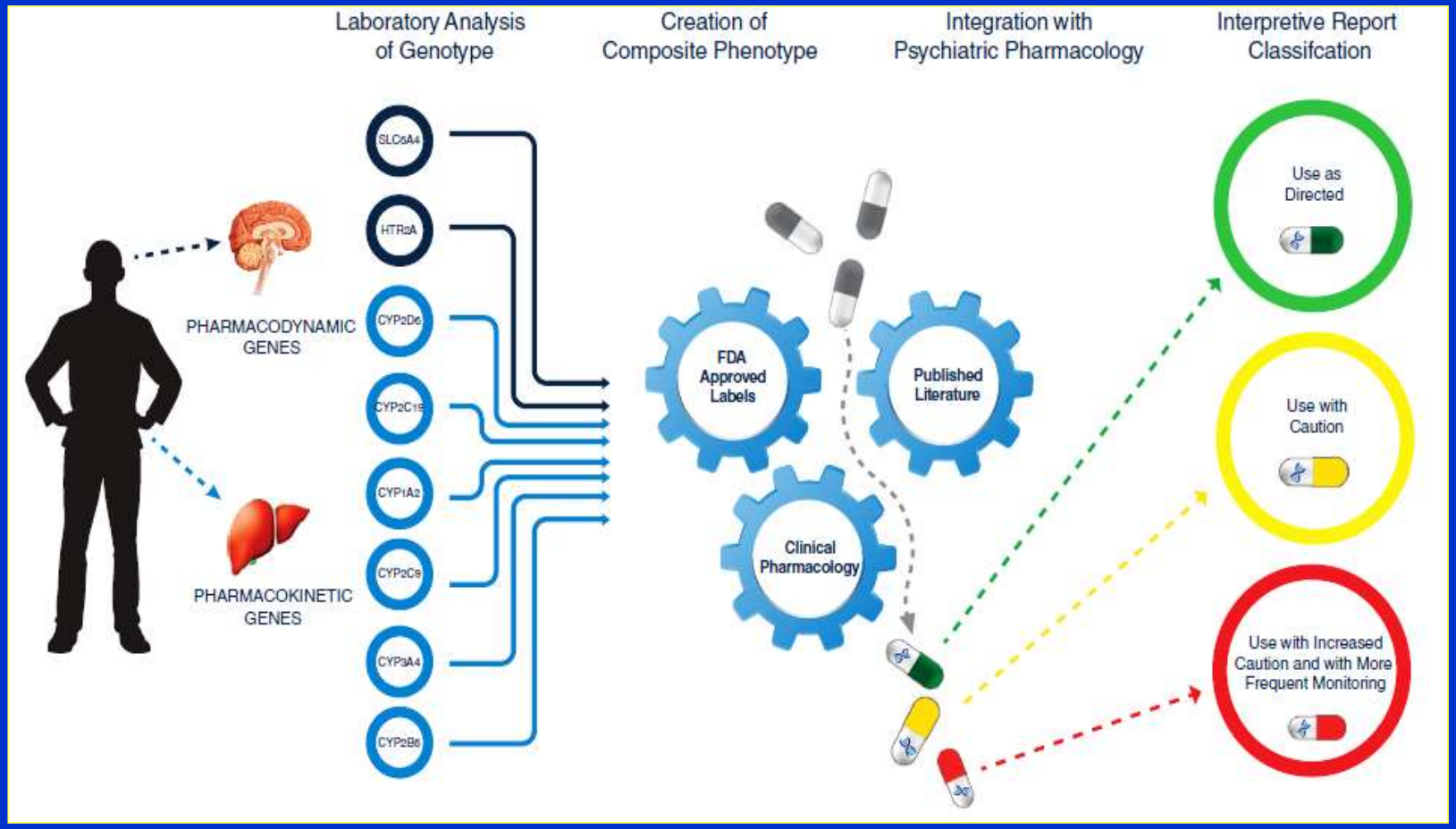

How satisfied was your patient been with the research?
120
100
80
60
40
20
0
3
13
26
78
57
99
24
Very unsatisfied
Unsatisfied
Neutral
Satisfied
Very satisfied
Not assessed
No answer

Results of multiple genes = new problems

- More difficult to explain & understand
- Not user friendly
- How to best consider gene-gene interactions?

- Start of Phase III

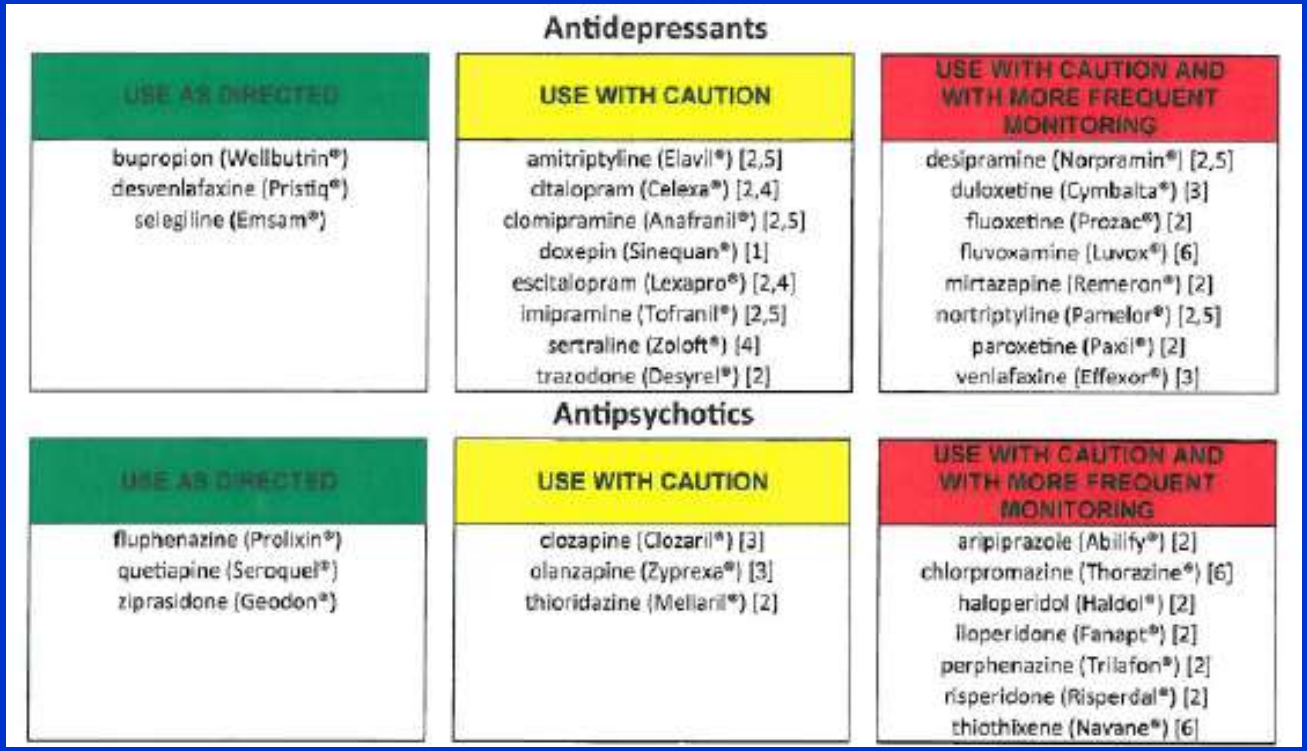
Combinatorial Pharmacogenomic Decision Support Model



Patient Genotypes and Phenotypes

CYP2D6	Ultrarapid Metabolizer	*2A/*2A
CYP2C19	Intermediate Metabolizer	*1/*2
CYP2C9	Extensive Metabolizer	*1/*1
CYP1A2	Ultrarapid Metabolizer	-163C>A - A/A
SLC6A4	High Activity	L/L
HTR2A	Reduced Activity	G/G

Phase III



AssureX GeneSight Test (2015)

Speaker has no financial relationship to AssureX

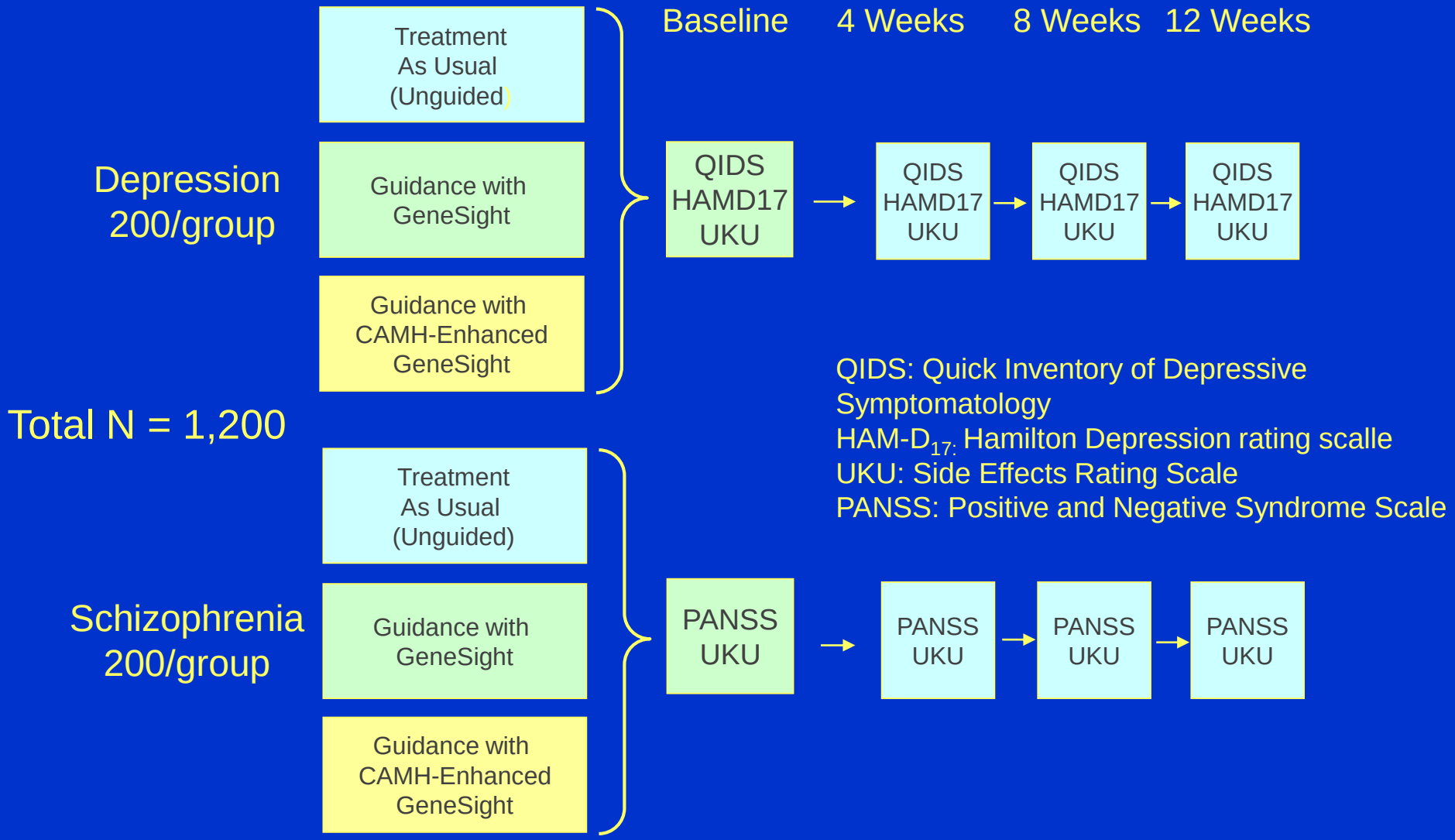
All nice and good,…

…but:

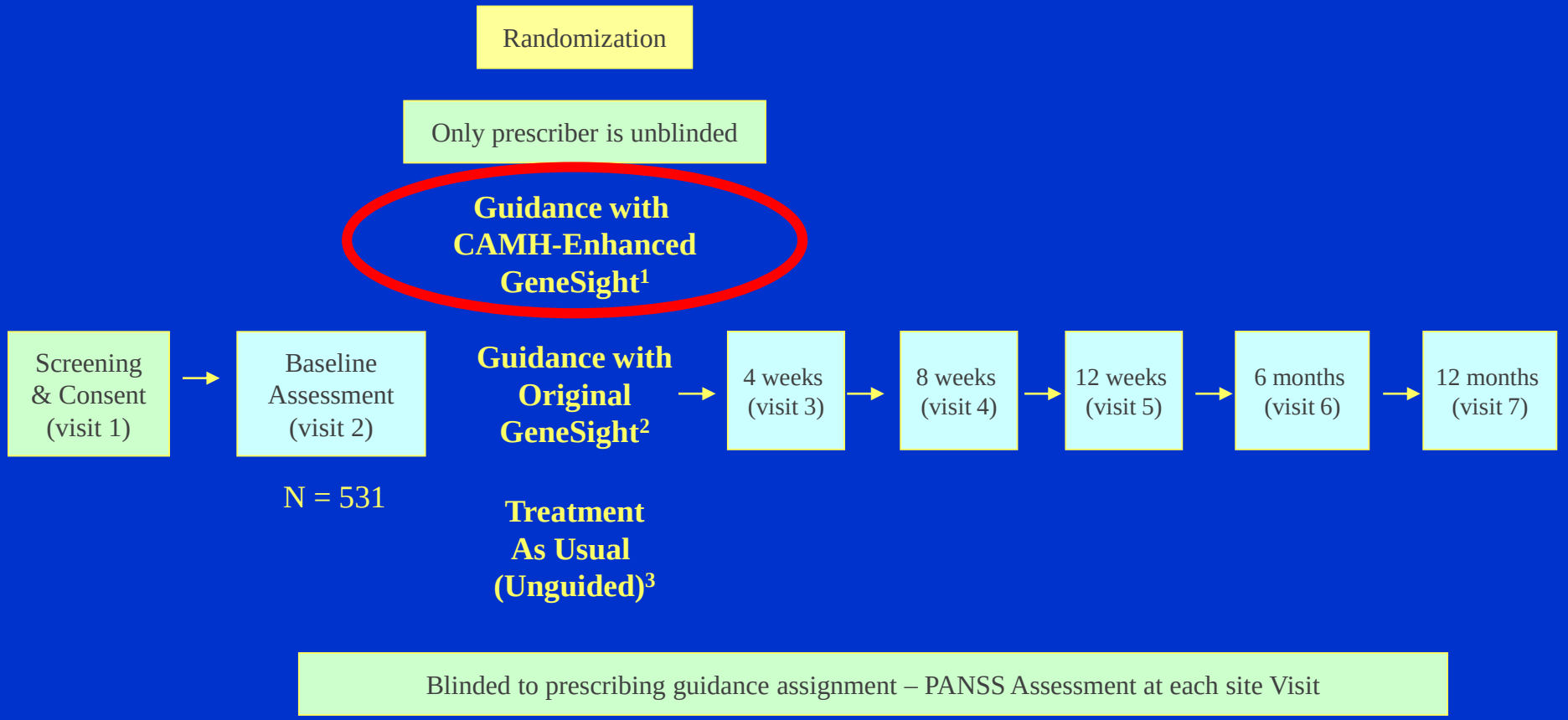
randomized controlled blinded studies are required to validate clinical utility and estimate economic benefits

= Applying for large funding source (start of phase IV) = ‘GAPP’ Study at CAMH

Phase IV: GAPP Clinical Trial Design



Schizophrenia Clinical Trial



[1] Guidance with CAMH-Enhanced GeneSight: improved GeneSight test by incorporation of new markers developed at CAMH.

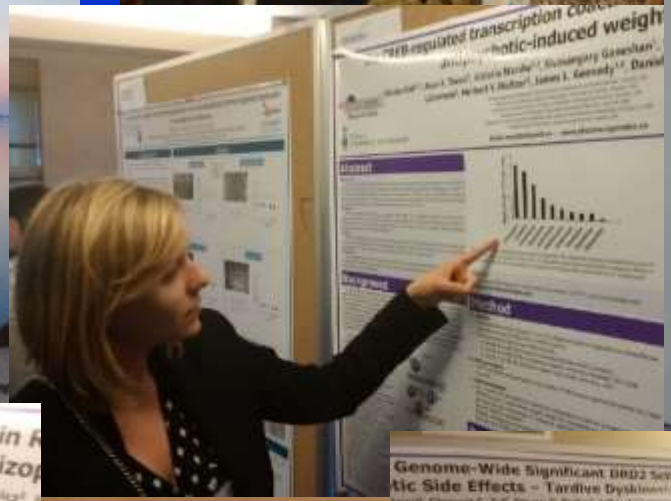
[2] Guidance with Original GeneSight: current test with six genes (*CYP2D6, CYP2C19, CYP1A2, CYP2C9, CYP3A4, CYP2B6; SLC6A4*, and *HTR2A*) and information to guide the physician for selection and dosing of the 33 most commonly prescribed Health Canada approved antidepressant and antipsychotic medications.

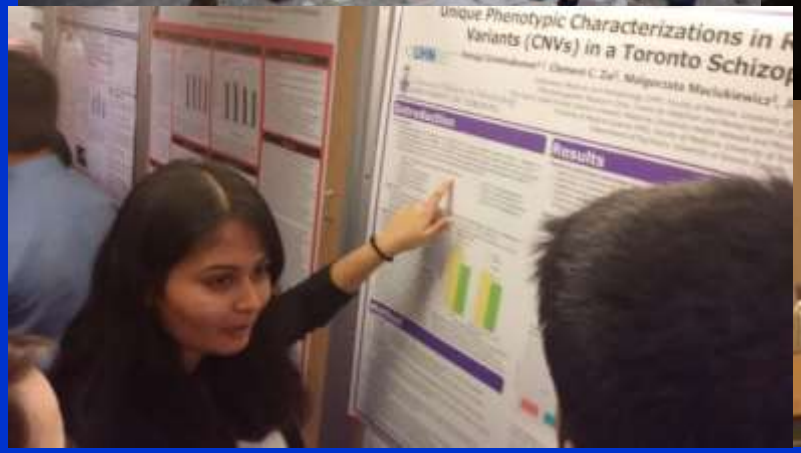
[3] Treatment As Usual (Unguided): standard medication treatment provided by the physician without guidance from GeneSight or CAMH-Enhanced GeneSight.

So much left undone!
Next steps:

- Continue recruiting patients for IMPACT and GAPP studies
- Conduct further research to enhance exiting algorithms
- Incorporate genetic results in EMR (currently already part of medical records)
- Negotiate reimbursment with provincial/national ministry of health

PGx Team Toronto





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Thank you for your attention.