USE OF BIOMARKERS FOR PERSONALIZED TREATMENT OF DKD

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ARE BIOMARKERS USEFUL FOR DKD ?

PROGNOSIS

Prognostic Value of Resting Heart Rate on Cardiovascular and Renal Outcomes in Type 2 Diabetic Patients

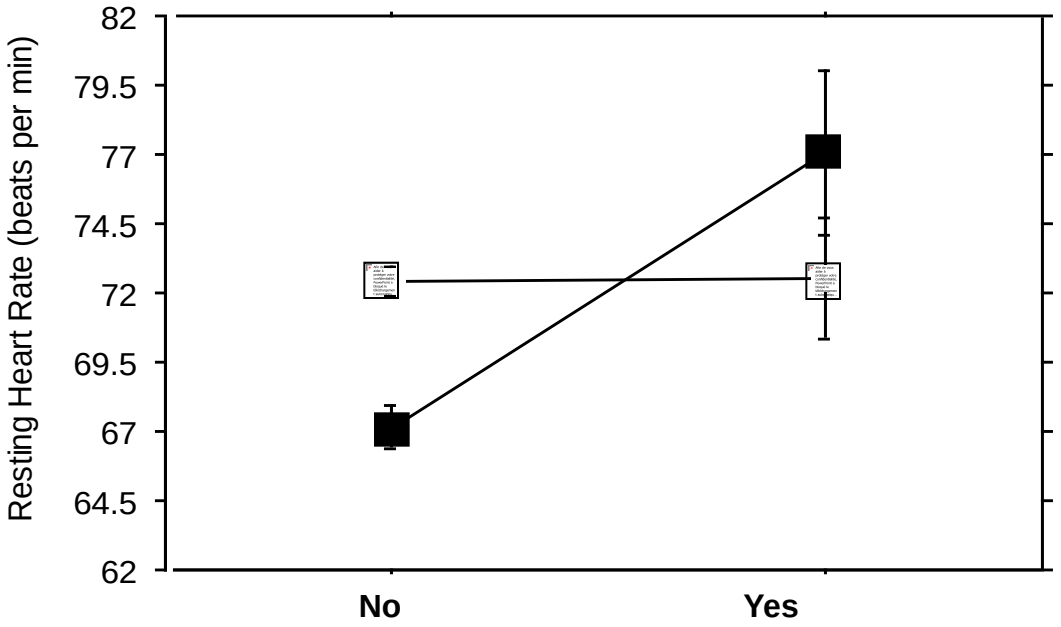
Miot A et al Diabetes Care 2012

A competing risk analysis in a prospective cohort

Table 1—*Baseline characteristics of the whole cohort of patients and in the subgroups with and without a history of CVD at baseline*

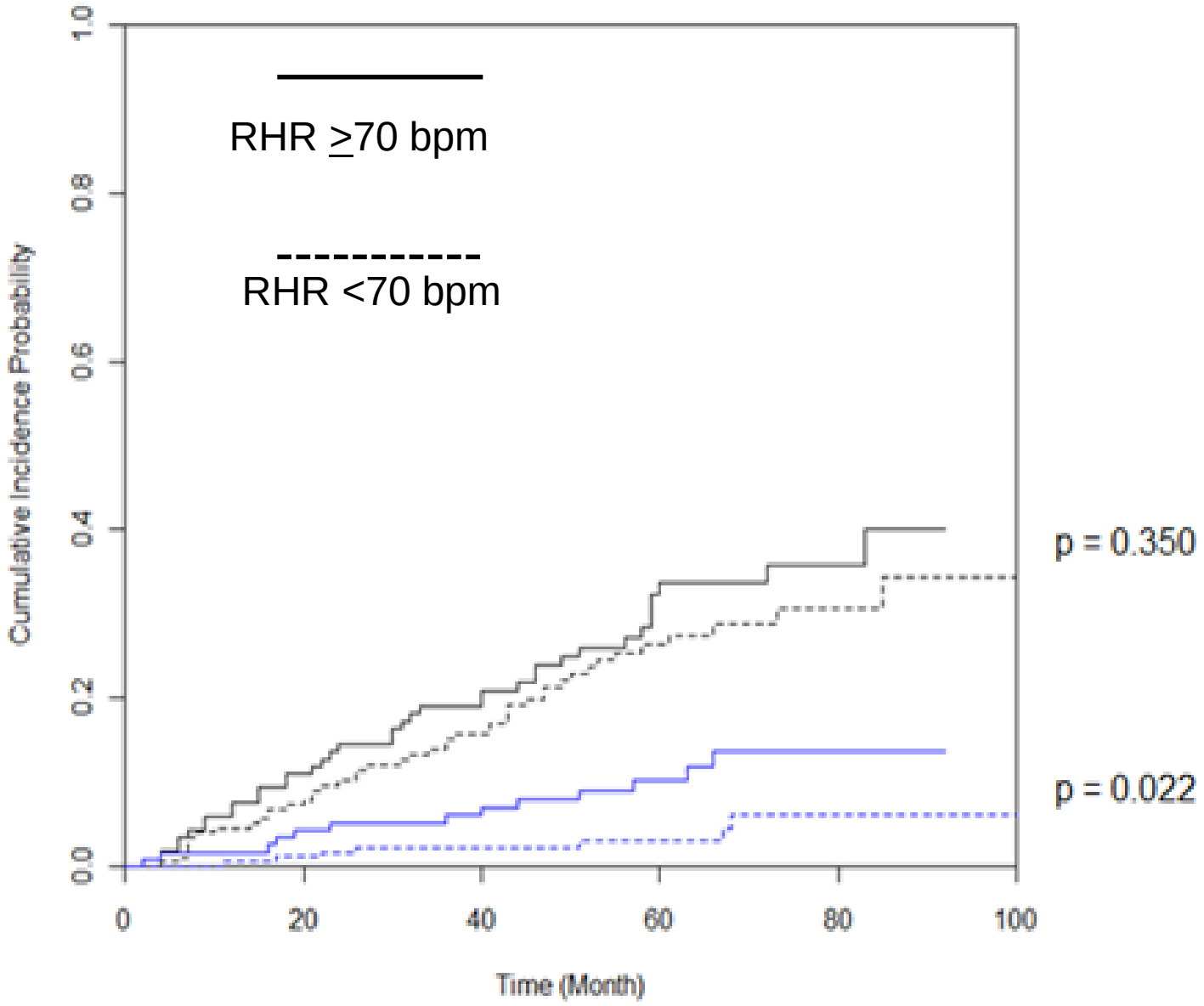
Variables	All	CVD BL$^+$	CVD BL$^-$
n (%)	1,088	336 (31)	752 (69)
Sex, men/women, *n* (%)	629 (58)/459 (42)	230 (68)/106 (32)	399 (53)/353 (47)
Age (years)	65.14 ± 10.61	68.96 ± 9.18	63.44 ± 10.76
BMI (kg/m^2)	30.93 ± 6.03	29.81 ± 5.32	31.43 ± 6.26
Active smoker: *n* (%)	116 (11)	33 (10)	83 (11)
Diabetes duration (years)	14.93 ± 10.07	18.00 ± 10.57	13.56 ± 9.54
HbA_{1c} (%)	7.87 ± 1.53	7.76 ± 1.32	7.91 ± 1.62
Creatinine level (μmol/L)	101.61 ± 74.24	120.23 ± 94.08	93.31 ± 61.72
Estimated glomerular filtration rate (mL/min) per 1.73 m^2	75.53 ± 27.71	66.55 ± 26.24	79.54 ± 27.42
History of renal disease, *n* (%)	367 (34)	150 (45)	217 (29)
Blood pressure (mmHg)			
Systolic	133.64 ± 17.71	134.72 ± 19.13	133.16 ± 17.02
Diastolic	72.90 ± 10.88	71.01 ± 10.90	73.74 ± 10.78
Total cholesterol (mmol/L)	4.94 ± 1.16	4.74 ± 1.22	5.03 ± 1.12
RHR (bpm)	70.98 ± 13.58	67.74 ± 13.78	72.42 ± 13.25
β-Blocker use, *n* (%)	349 (32)	167 (50)	182 (24)

Interaction between RHR and CVD with regard to renal outcome



($p_{interaction}$ =0.03)

Renal outcome in patients w/ CVD at baseline



- RHR is an independent predictor CV outcomes
- RHR is also a predictor of hard renal outcomes in T2DM patients with a Hx of CVD
- RHR is an interesting bio-marker
  - Easy and unexpensive to determine
  - Established for CV outcomes
  - Promising for renal outcomes
  - Convergent data published (ADVANCE)
  - Therapeutic target (ivabradine) but intervention studies required

Circulating TNF Receptors 1 and 2 Predict ESRD in Type 2 Diabetes

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JASN 2012

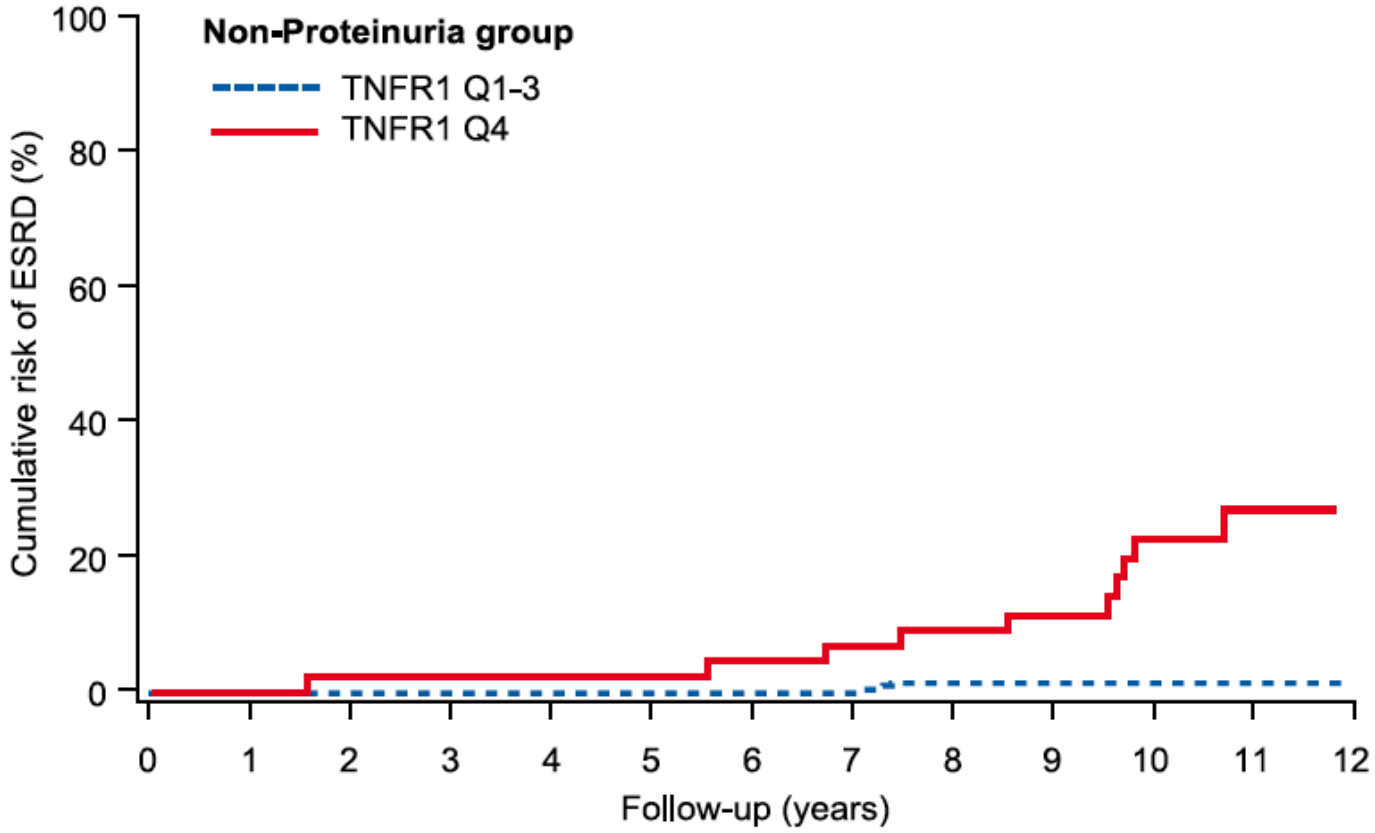


Table 4. Multivariate Cox proportional hazard models of the risk of ESRD in patients with T2D with clinical predictors and the plasma concentration of a TNF marker stratified according to the presence of proteinuria

	Nonproteinuria		Proteinuria	
	HR[a] (95% CI)	*P* Value	HR[a] (95% CI)	*P* Value
Clinical predictor[b]				
HbA1c	1.56 (0.86, 2.82)	0.14	1.24 (0.96, 1.61)	0.10
AER	2.23 (1.11, 4.48)	0.02	2.52 (1.14, 5.56)	0.02
eGFR	1.10 (0.72, 1.67)	0.67	1.37 (1.11, 1.69)	0.004
Individual marker[c]				
free TNFα	2.22 (1.20, 4.12)	0.01	1.21 (0.81, 1.81)	0.34
total TNFα	2.53 (1.25, 5.13)	0.01	2.61 (1.42, 4.81)	0.002
TNFR1	7.11 (2.13, 23.69)	0.0004	7.05 (2.23, 22.30)	0.0018
TNFR2	3.82 (1.59, 9.20)	0.0008	5.88 (2.10, 16.43)	0.0013

[a]Effect measures are expressed as the HR for a one-quartile increase in the distribution of each covariate except for eGFR, for which it is a one-quartile decrease. Quartile definitions are based on the full cohort.
[b]Clinical predictors examined together with TNFR1.
[c]Individual TNF markers examined together with all three clinical predictors.

The improvement of prediction with TNFR1 relative to AER was highly significant ($p<0.001$) and that to eGFR had a P value of $p=0.02$.

BIOMARKERS ARE USEFUL FOR DKD ?

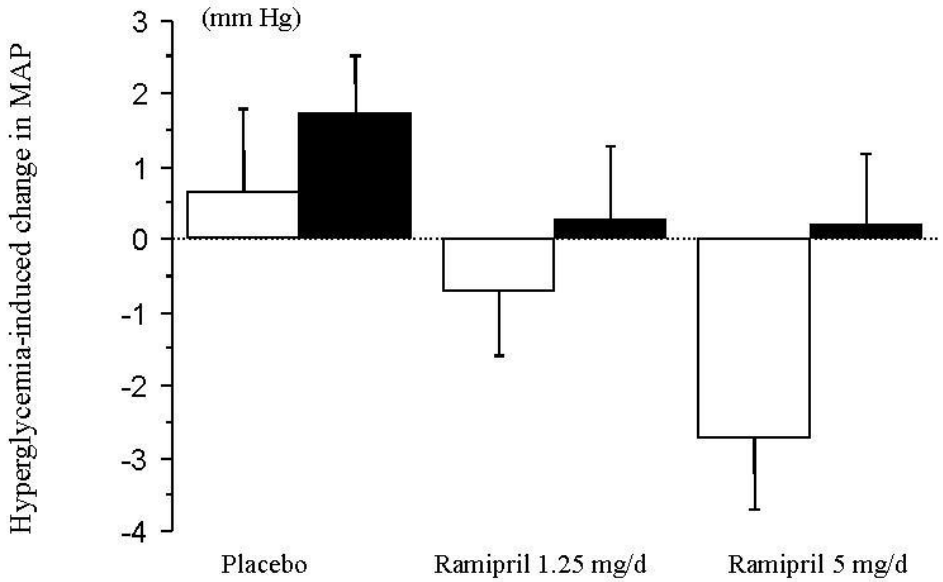
TREATMENT

PHARMACOGENOMICS

- Old concept used in tuberculosis (INH Tx)
- Widely used for cancer (ER and breast cancer)
- Modern examples available (SCLO1B1 and statin-induced myopathy)

FROM GENETICS TO THERAPEUTICS

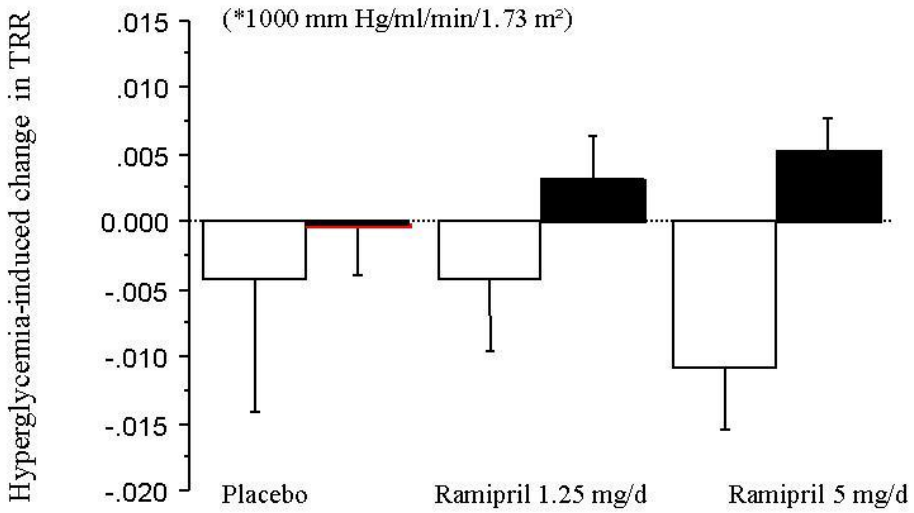
Figure 1E:



Weekers et al, Diabetes 2005

FROM GENETICS TO THERAPEUTICS

Figure 1F:



Weekers et al, Diabetes 2005

ACE Gene Polymorphism and Losartan Treatment in Type 2 Diabetic Patients With Nephropathy

Hans-Henrik Parving,* Dick de Zeeuw,† Mark E. Cooper,‡ Giuseppe Remuzzi,§ Nancy Liu,‖ Jared Lunceford,‖ Shahnaz Shahinfar,‖ Peggy H. Wong,‖ Paulette A. Lyle,‖ Peter Rossing,¶ and Barry M. Brenner**

J Am Soc Nephrol 19: 771–779, 2008.

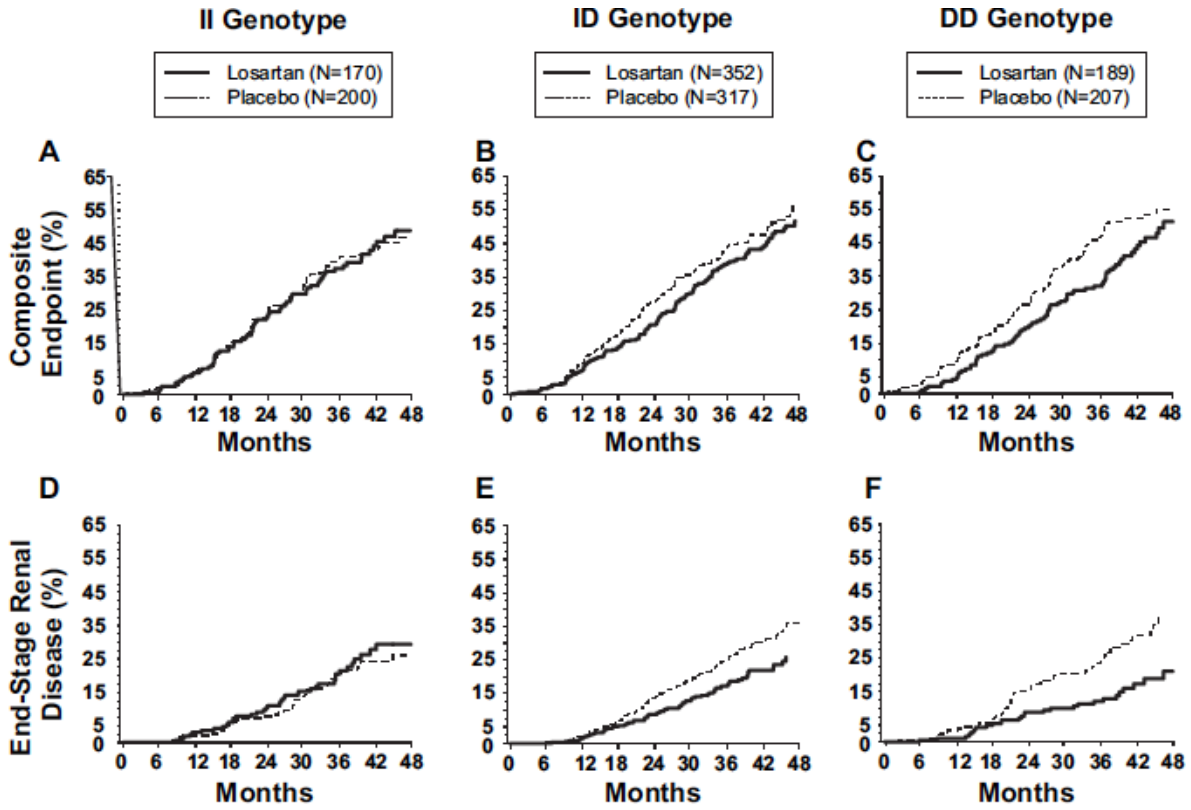


Figure 2. Kaplan-Meier curves of the percentage of patients with the primary composite endpoint in the II (A), ID (B), and DD (C) genotype groups and one of its individual components, end-stage renal disease, in the II (D), ID (E), and DD (F) genotype groups. The mean follow-up time was 3.4 yr (42 mo). The *P* values for treatment × genotype interaction analyses are shown in Table 4.

GWAS and drug safety

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 21, 2008 VOL. 359 NO. 8

SLCO1B1 Variants and Statin-Induced Myopathy — A Genomewide Study

The SEARCH Collaborative Group*

Baseline Characteristic	No. of Participants	Definite or Incipient Myopathy at Any Time (N = 98)	
		No.	Relative Risk (95% CI)
Age			
<65 yr	3019	31	1.0
≥65 yr	3012	67	2.2 (1.4–3.4)
Sex			
Male	5005	72	1.0
Female	1026	26	1.8 (1.1–2.8)
Estimated glomerular filtration rate			
≥60 ml/min/1.73 m^2	5209	71	1.0
<60 ml/min/1.73 m^2	822	27	2.5 (1.6–3.9)
Creatinine			
<85 μmol/liter (1.0 mg/dl)	2731	29	1.0
≥85 μmol/liter (1.0 mg/dl)	3300	69	2.0 (1.3–3.1)
Use of amiodarone			
No	5893	86	1.0
Yes	138	12	6.4 (3.4–12.1)
Use of calcium antagonists			
No	4459	61	1.0
Yes	1572	37	1.7 (1.2–2.6)
Diabetes mellitus			
No	5398	82	1.0
Yes	633	16	1.7 (1.0–2.9)

GWAS and drug safety

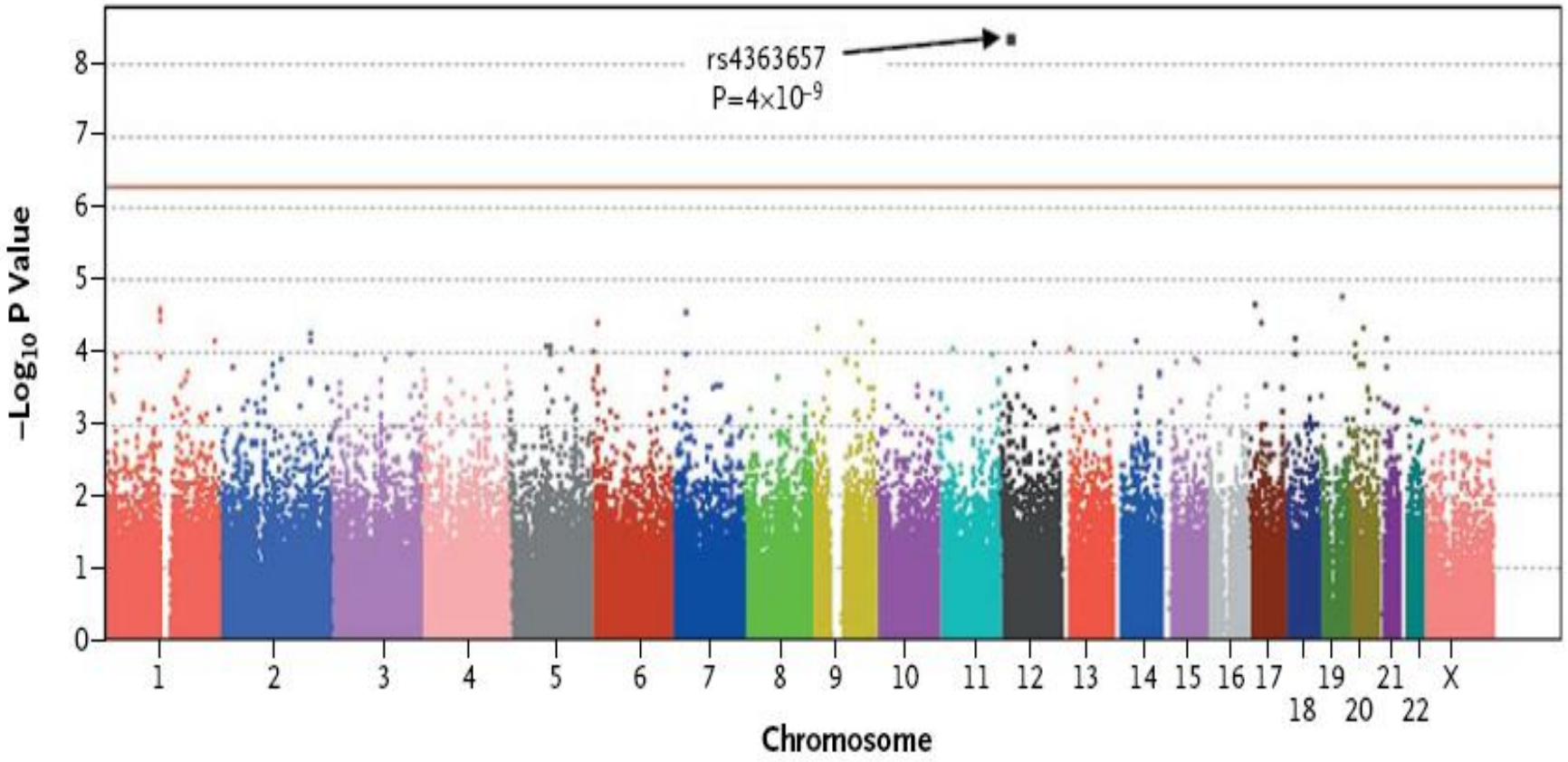


Figure 1. Results of Tests for a Trend in the Association between Myopathy and Each SNP Measured in the Genome-wide Association Study.

Personalized medicine: drug safety

Chromosome	SNP	Position	P Value for Trend (1 df)	P Value for Genotypic Test (2 df)	Risk Allele	Other Allele	Risk-Allele Frequency	
							Cases	*Controls*
Strong evidence of association								
12p12	rs4363657	21259989	4.1×10^{-9}	2.5×10^{-8}	C	T	0.46	0.13

Odds Ratio (95% CI) per Risk Allele	Odds Ratio for Hetero-zygotes	Odds Ratio for Homo-zygotes	Gene
4.3 (2.5–7.2)	4.4	17.4	*SLCO1B1*

CONCLUSION

- Biomarkers are useful for prognosis refinement
- New biomarkers can be simple - cheap / complex - expensive
- Additive value needs to be further established
- Cost effectiveness to be ensured
- Translation into treatment is harder but
  - Good examples for safety (pharmacogenomics)
  - New discoveries in cancer research