Genomska selekcija rjave pasme goveda v Sloveniji

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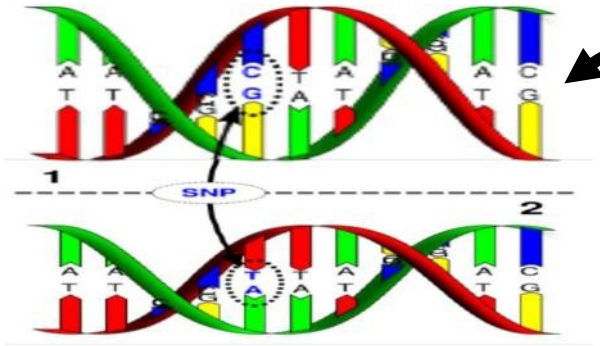
Rodica, 2. april 2012

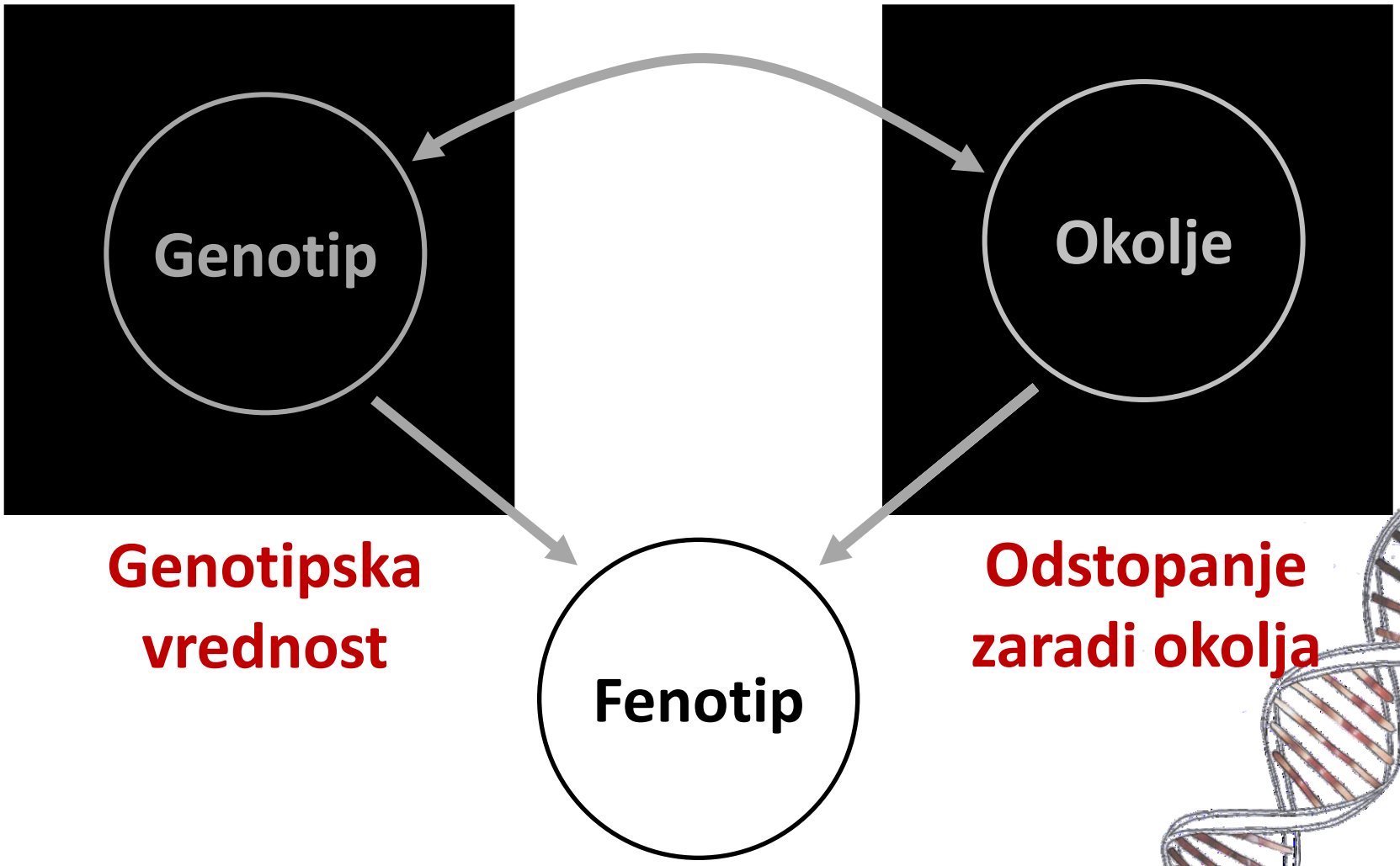
Teme

- Izvajanje selekcije pri govedu
- Konvencionalni obračun plemenskih vrednosti
  - Nacionalni nivo
  - Mednarodni nivo - MACE
- Genomski obračun plemenskih vrednosti
  - Nacionalni nivo
  - Mednarodni nivo
    - GMACE
    - InterGenomics

Fenotip = Genotip + Okolje



V praksi poznamo le …

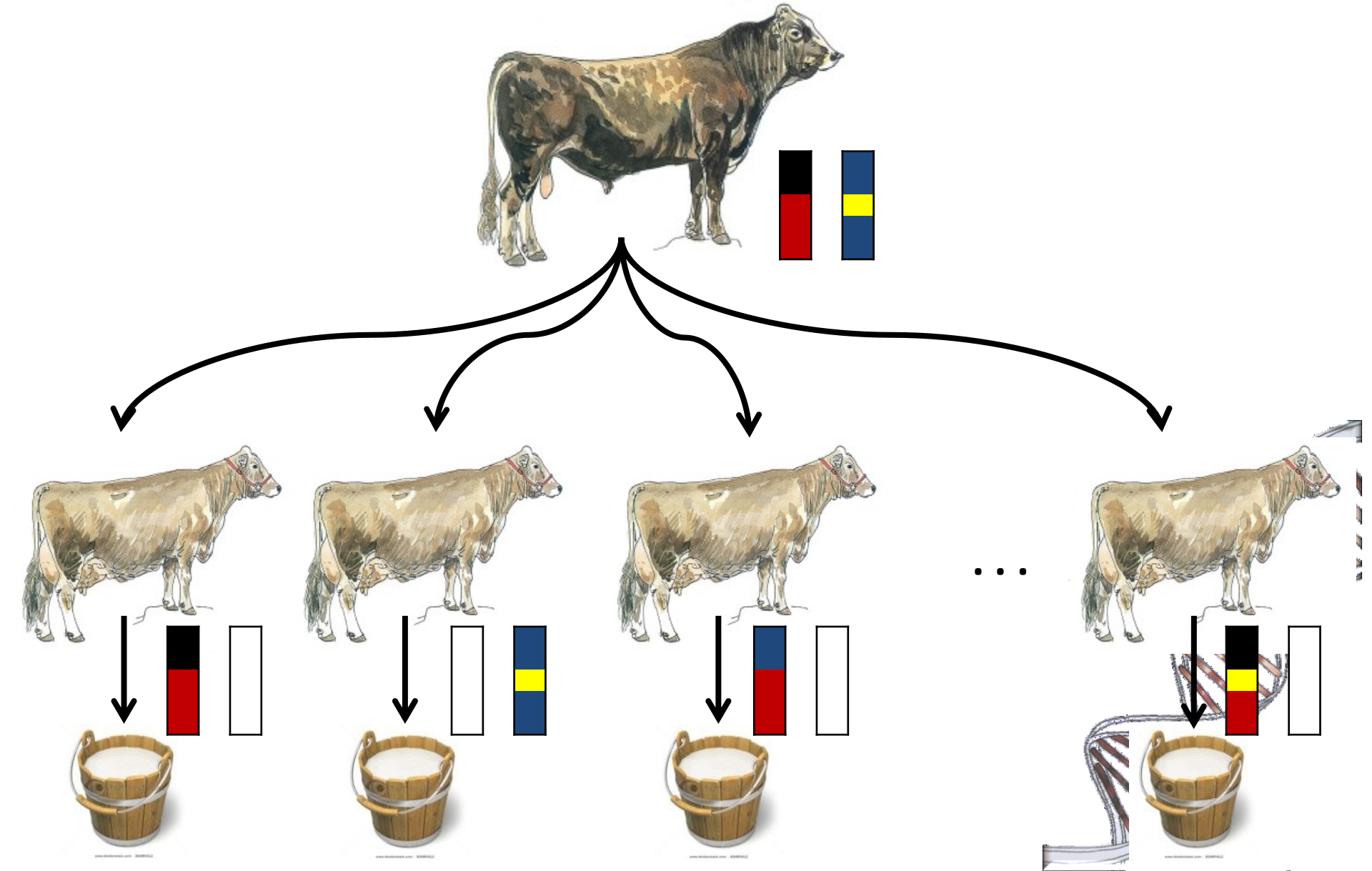


Plemenska vrednost (PV)

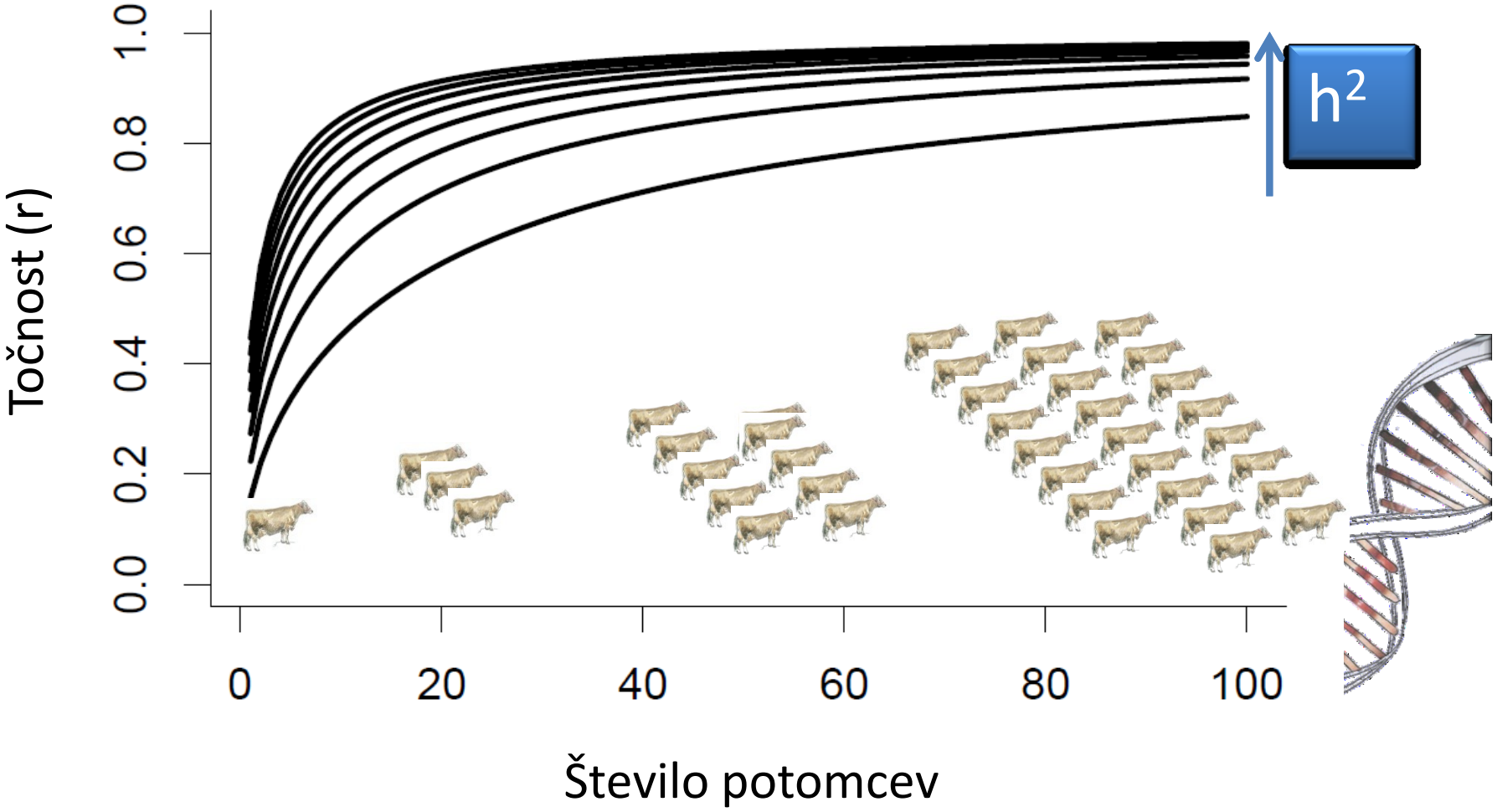
Skupni učinek genov, ki se prenaša na potomce

Ocenjujemo na podlagi podobnosti med sorodniki

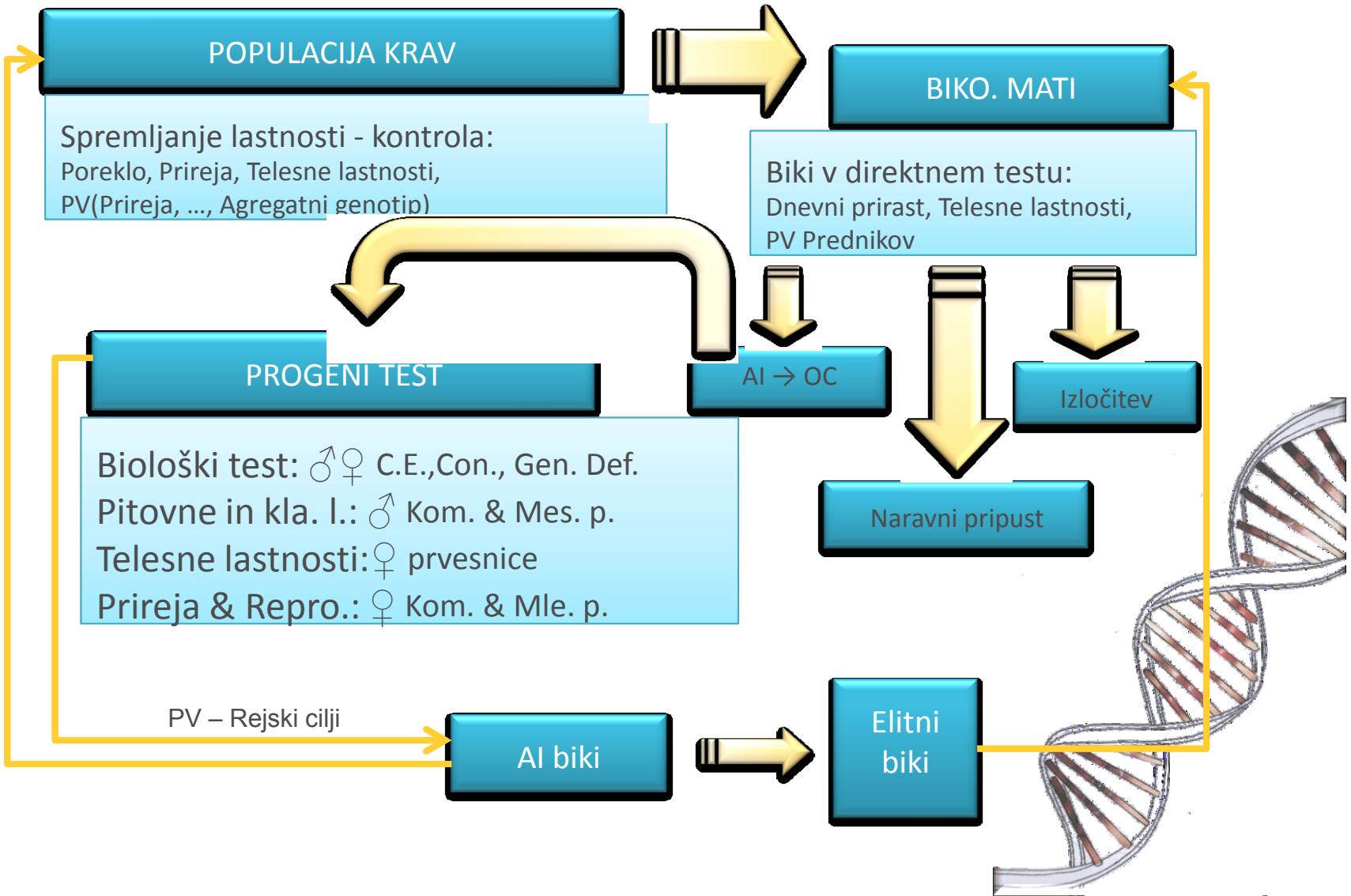
Preizkus na potomcih



Točnost



Poenostavljena shema SP



Tok informacij

Napovedovanje PV

INTERBULL

SLO - Lastnosti mlečnosti

SLO

Svet

Podatkovno skladišče

WEB

SIR, KIS, ...

Selekcionerji, rejci, ...

Model živali

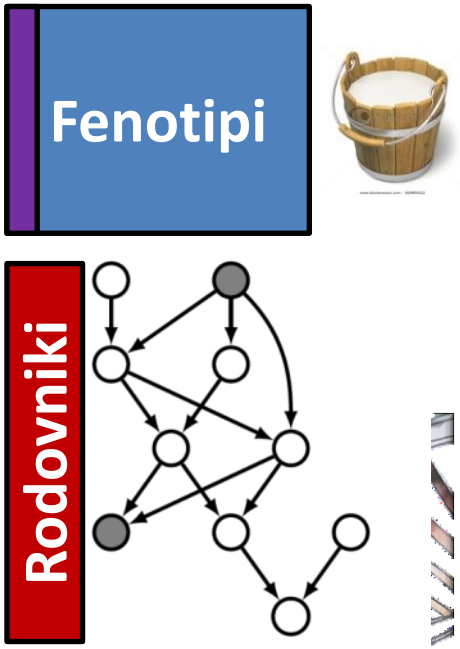
- Model

$$y = Xb + Za + e$$

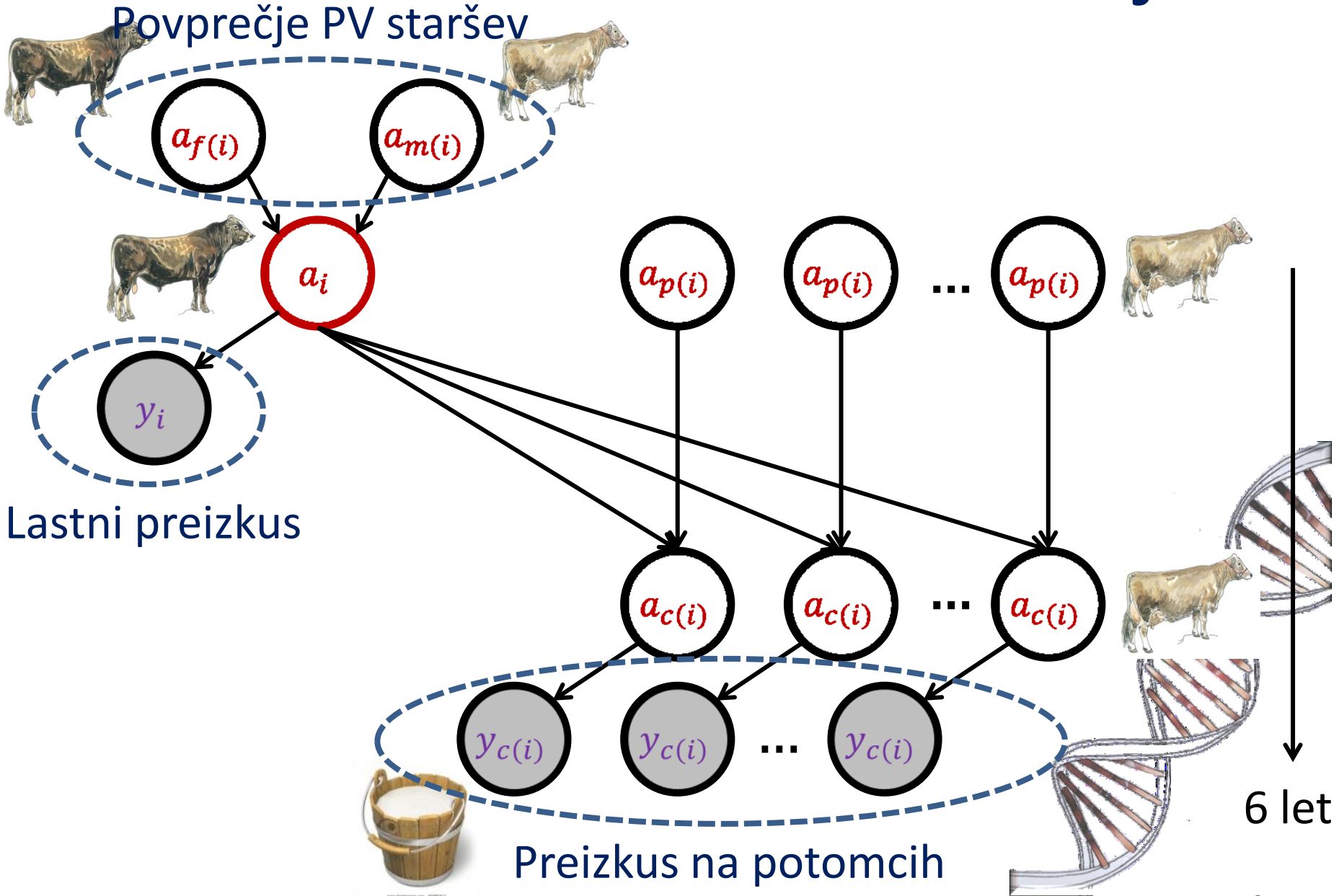
- Sistem enačb (Henderson, 1950+) - **BLUP**

$$\begin{pmatrix} X^TX & X^TZ \\ Z^TX & Z^TZ + A^{-1}\alpha \end{pmatrix} \begin{pmatrix} \hat{b} \\ \hat{a} \end{pmatrix} = \begin{pmatrix} X^Ty \\ Z^Ty \end{pmatrix}$$

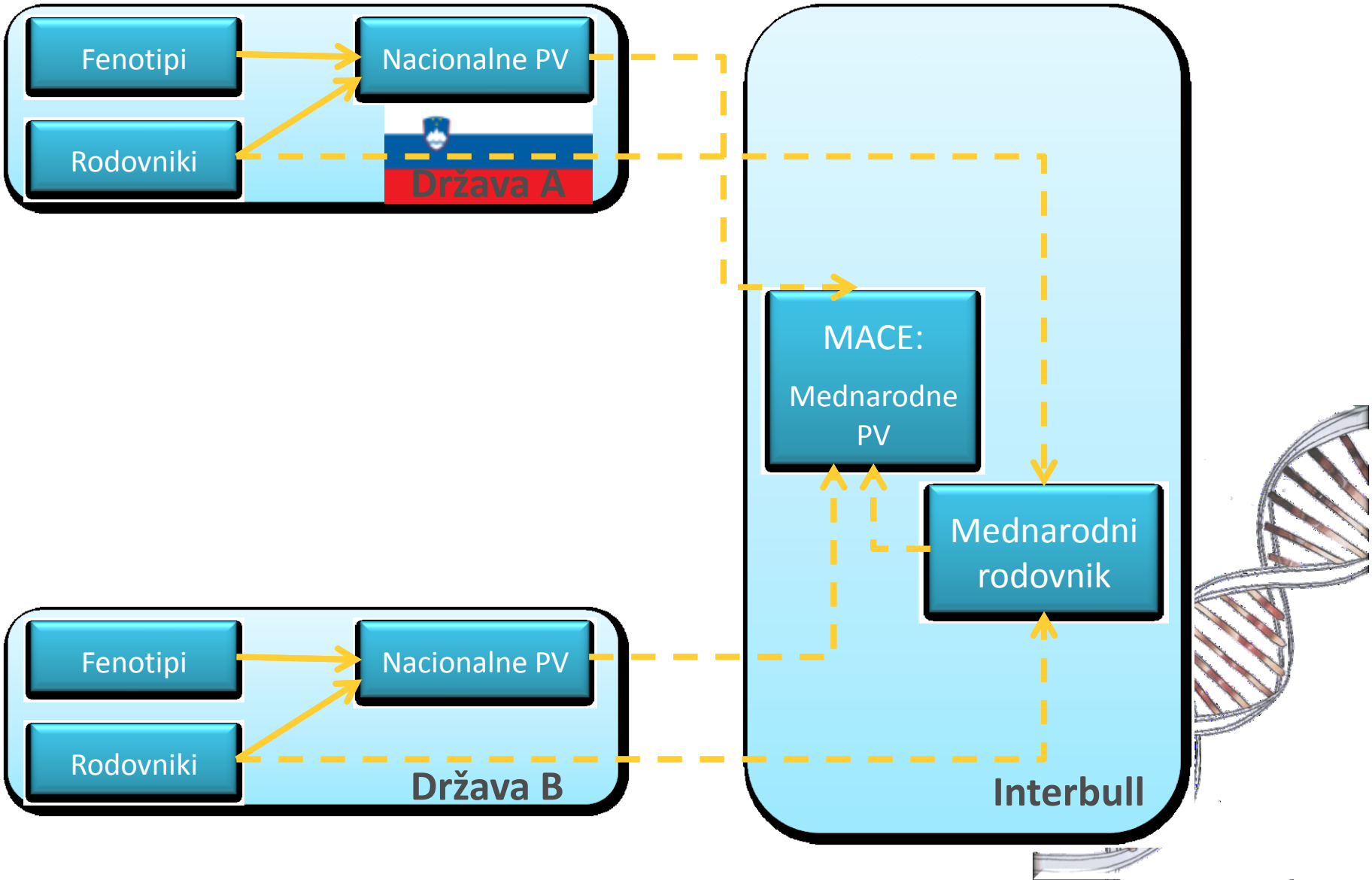
Matrika sorodstva
→ zajamemo informacije od vseh sorodnikov



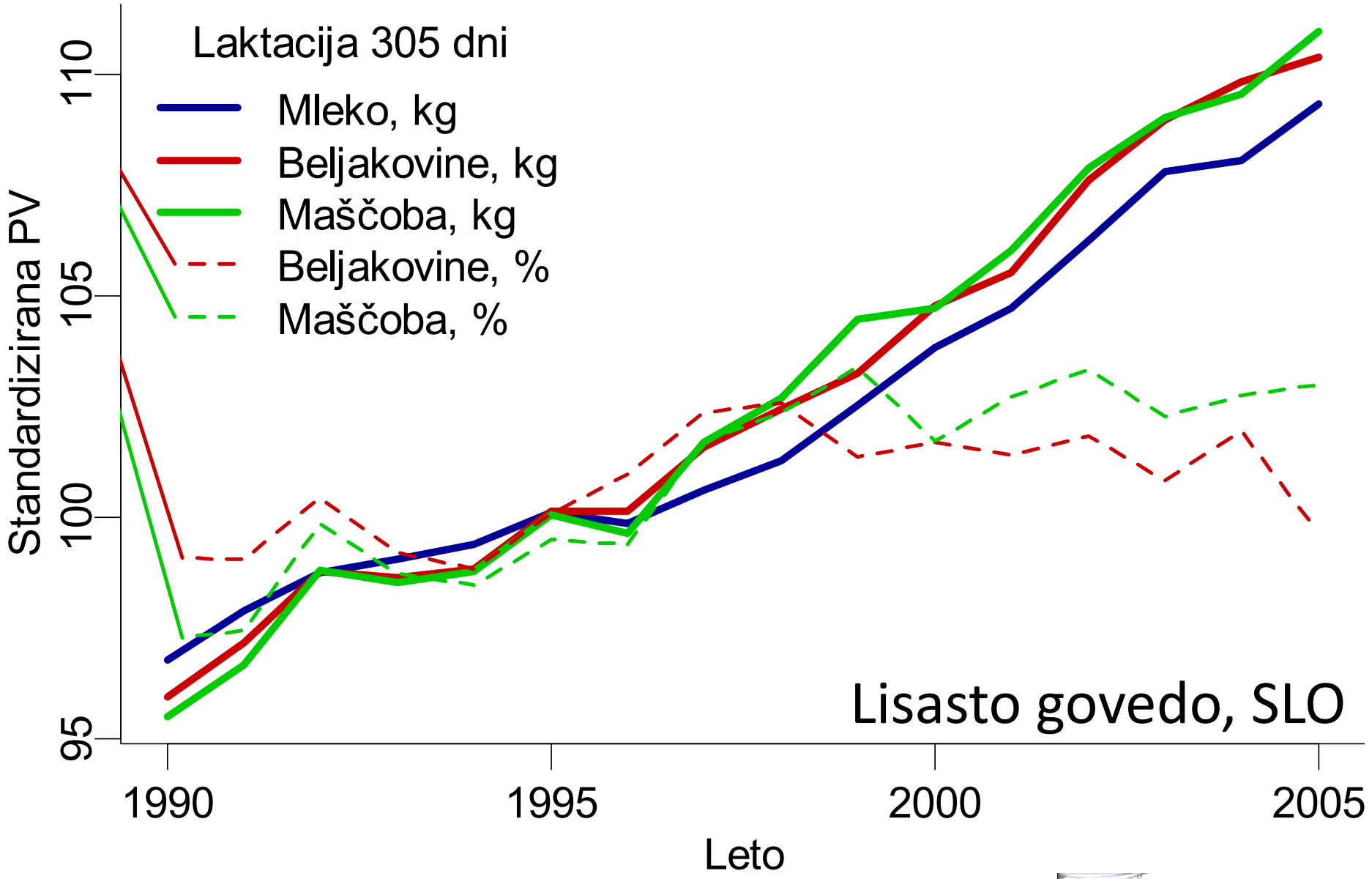
Model živali – viri informacij



InterBull - MACE



Dosedanji dosežki



Genetski napredek

$$\Delta G = (i \times r \times \sigma_a) / g$$

- **i** – intenzivnost selekcije
  - 50 % odbranih → i ~ 0,8
  - 5 % odbranih → i ~ 2,0
- **r** – točnost plemenskih vrednosti
  - povprečje staršev → r = 60 % za sklop mlečnosti
  - preizkus na potomcih → r = 95 % za sklop mlečnosti
- σ_a – standardni odklon plemenskih vrednosti
- **g** – generacijski interval

Genetski napredek - govedo

- Večja intenzivnost selekcije po moški strani

$$\Delta G = (i_{♂} \times r_{♂} + i_{♀} \times r_{♀}) / (g_{♂} + g_{♀})$$

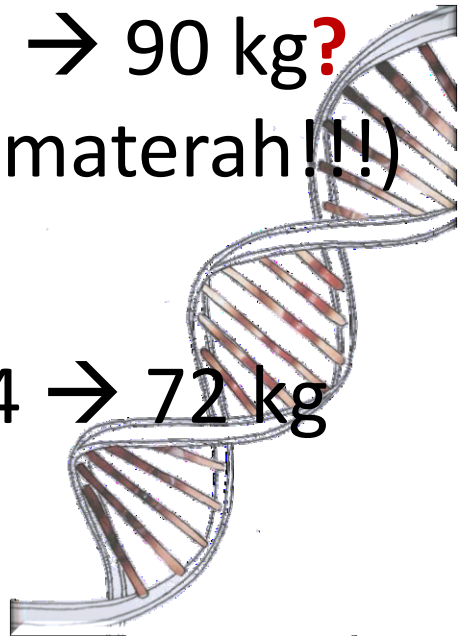
- Mladi biki – povprečje staršev

$\Delta G = (2 \times \mathbf{0,60} + \sim 0) / (\mathbf{2} + 2) = 0,30 \rightarrow 90$ kg**?**

(problem pristranosti pri bikovskih materah!!!)

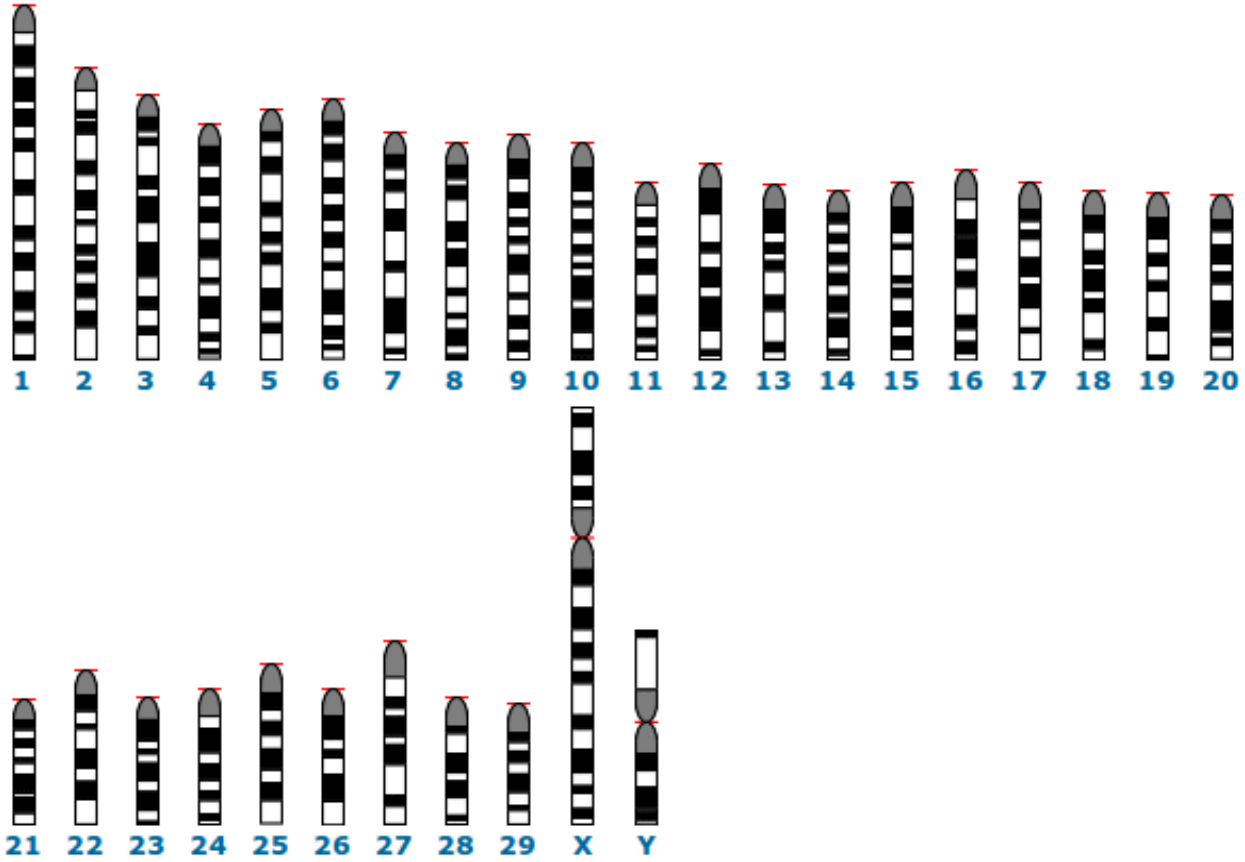
- Preizkus na potomcih

$\Delta G = (2 \times \mathbf{0,95} + \sim 0) / (\mathbf{6} + 2) = 0,24 \rightarrow 72$ kg



Genom goveda

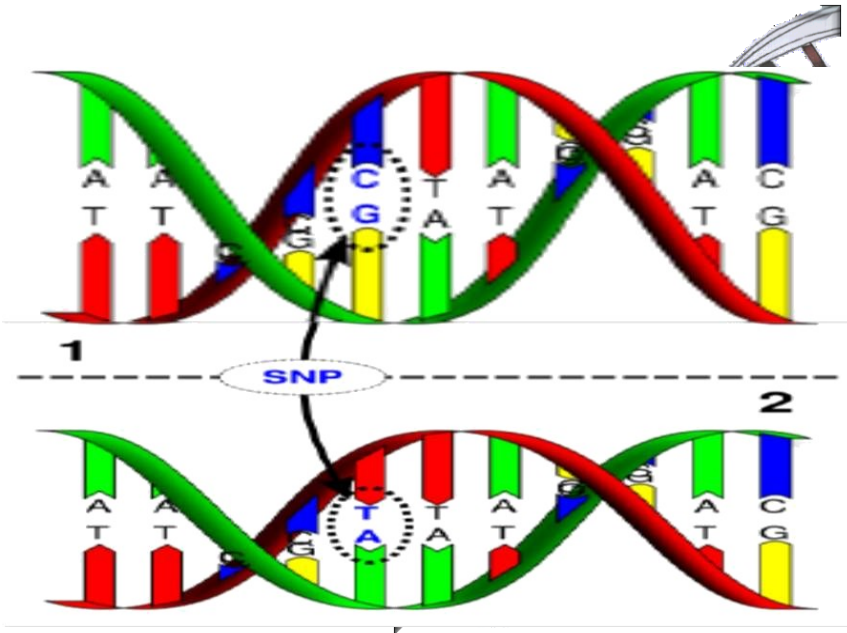
- 30 parov kromosomov (29 + 1)



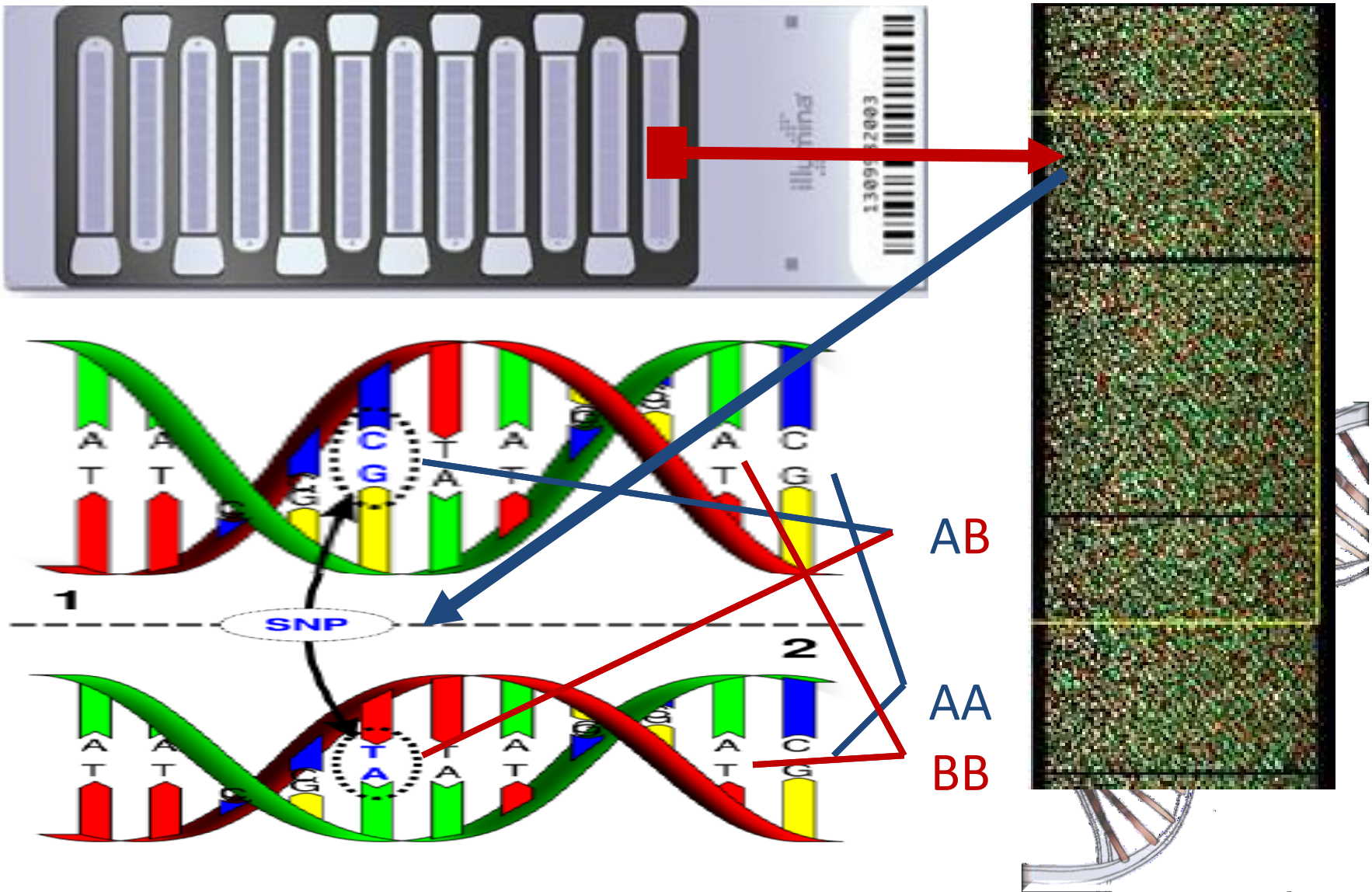
- ~ 20.000 genov (~14.000 skupnih s človekom)

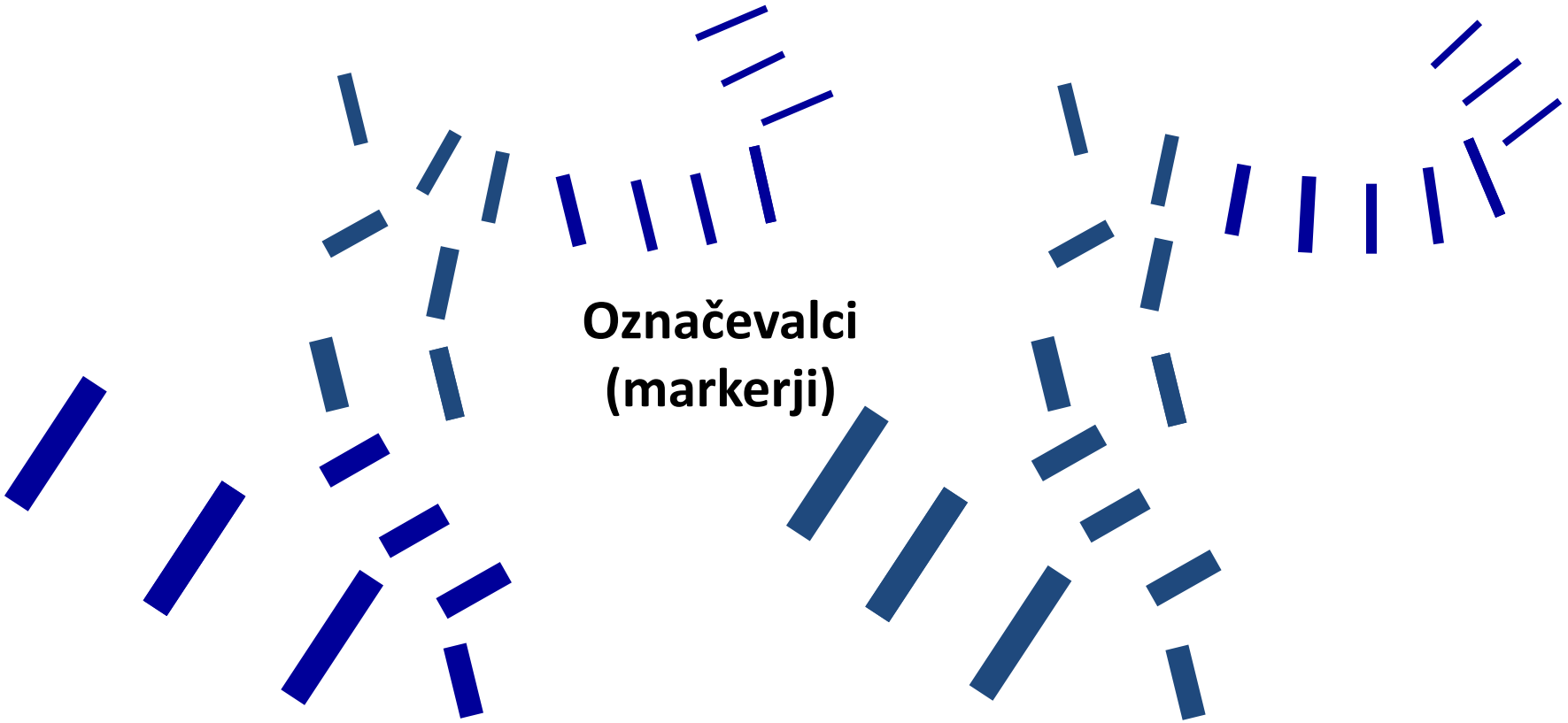
Genomski podatki

- Genom ≈ 3 milijarde baznih parov
- SNP označevalci
- SNP genotipizacija
  - 3.000 (LD) = 1:1.000.000
  - 6.000 (LD) = 1:500.000
  - 50.000 (50K) = 1:55.000
  - 800.000 (HD) = 1:4.000
- Sekvenca

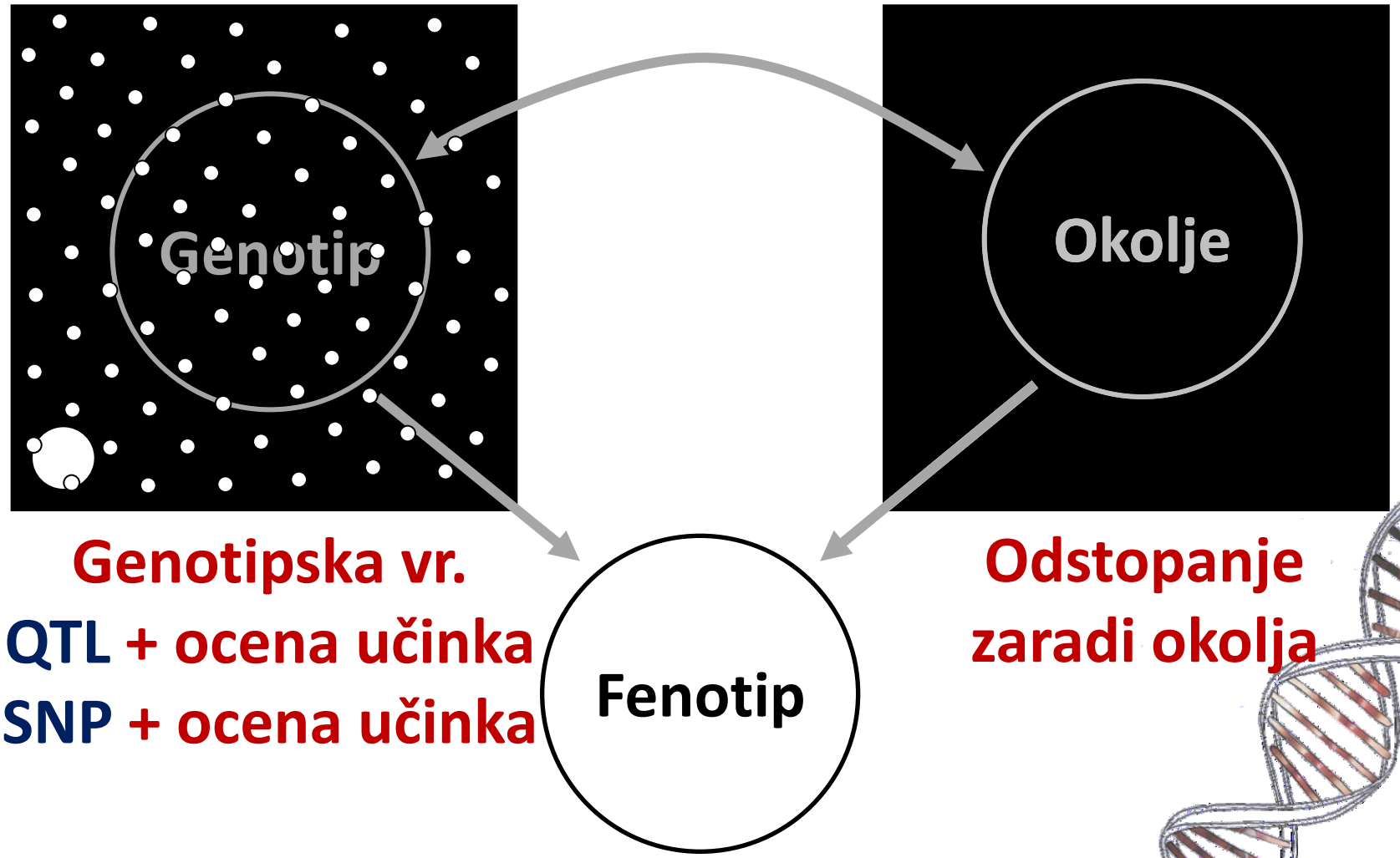


SNP čipi




Označevalci
(markerji)

V praksi poznamo le …



Genotipska vr.

QTL + ocena učinka

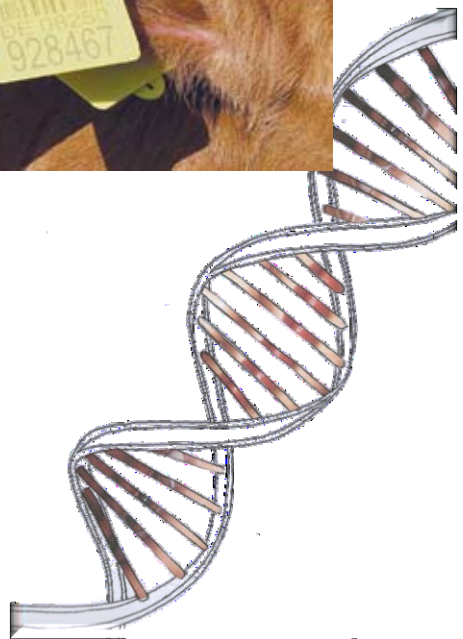
SNP + ocena učinka

Odstopanje zaradi okolja

Fenotipska vrednost

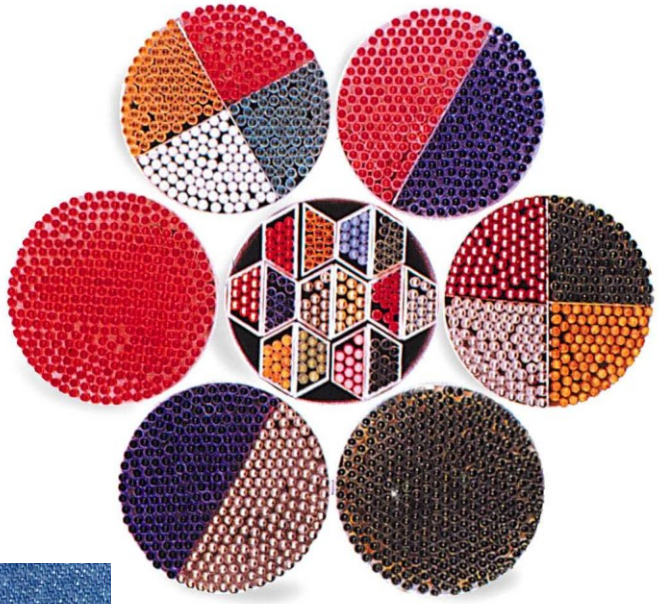
Odvzem tkiva – nosna sluznica

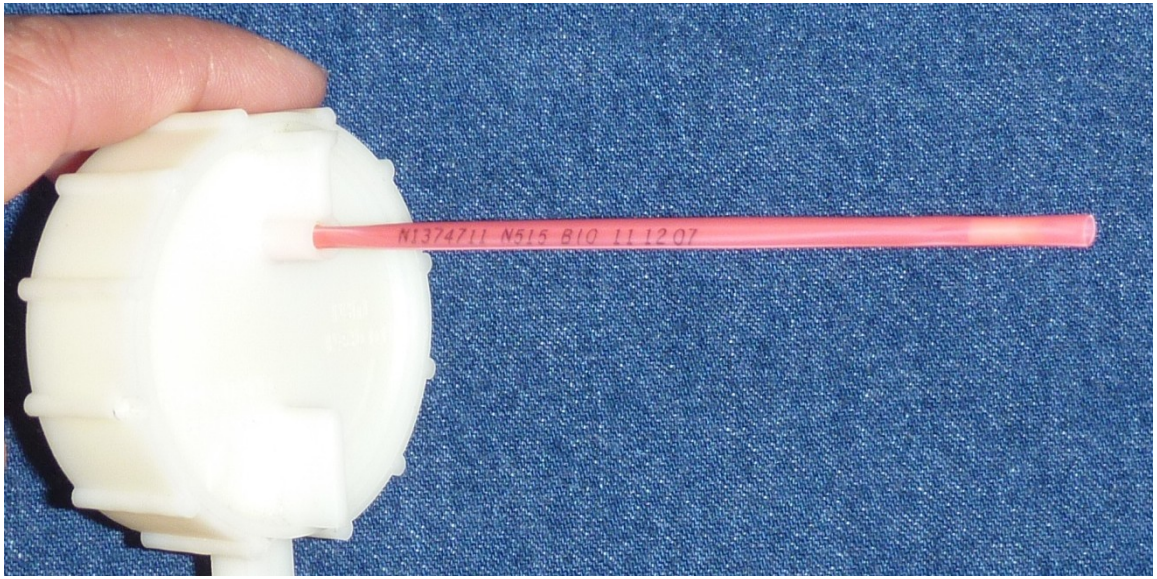
Odvzem tkiva - številčenje

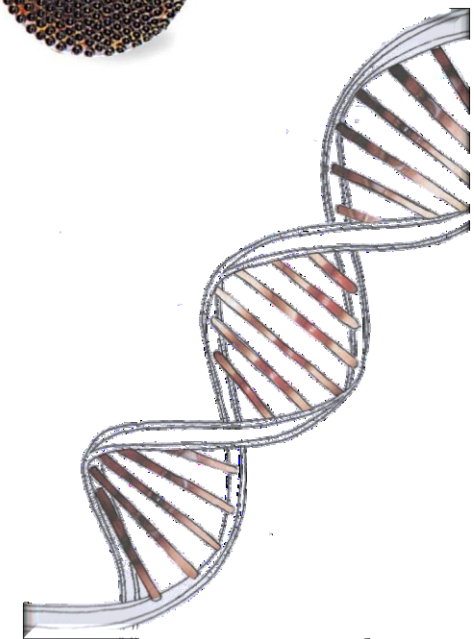


Odvzem tkiva – dlaka

Odvzem tkiva – AI biki

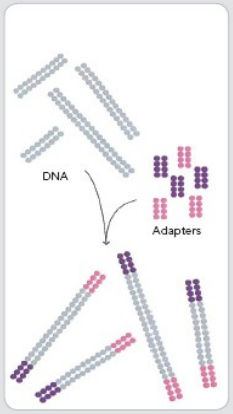






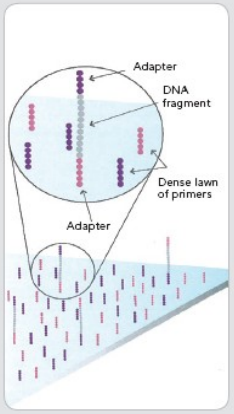
Genotipizacija

1. PREPARE GENOMIC DNA SAMPLE



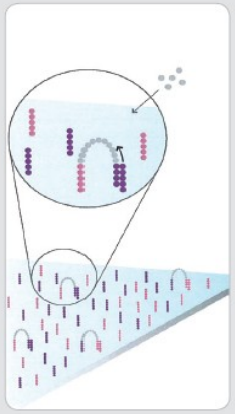
Randomly fragment genomic DNA and ligate adapters to both ends of the fragments.

2. ATTACH DNA TO SURFACE



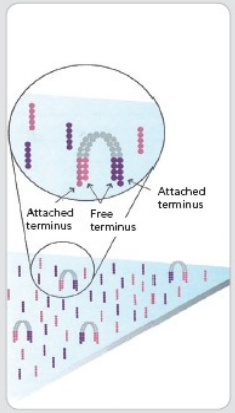
Bind single-stranded fragments randomly to the inside surface of the flow cell channels.

3. BRIDGE AMPLIFICATION



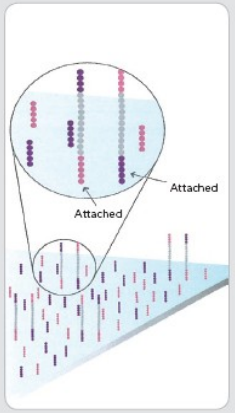
Add unlabeled nucleotides and enzyme to initiate solid-phase bridge amplification.

4. FRAGMENTS BECOME DOUBLE-STRANDED



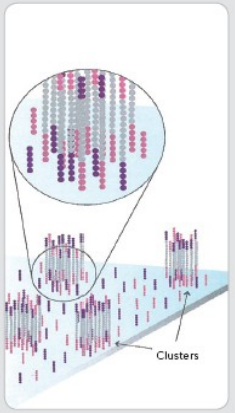
The enzyme incorporates nucleotides to build double-stranded bridges on the solid-phase substrate.

5. DENATURE THE DOUBLE-STRANDED MOLECULES



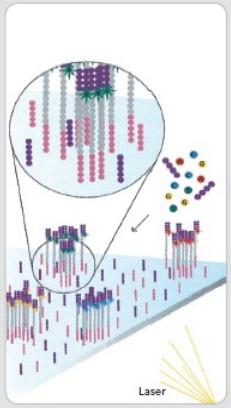
Denaturation leaves single-stranded templates anchored to the substrate.

6. COMPLETE AMPLIFICATION



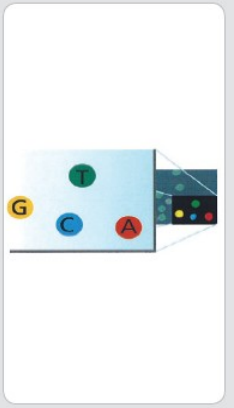
Several million dense clusters of double-stranded DNA are generated in each channel of the flow cell.

7. DETERMINE FIRST BASE



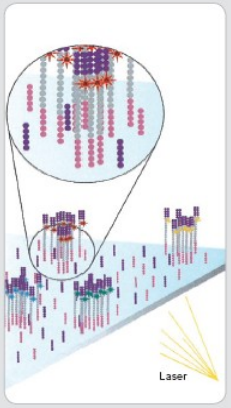
The first sequencing cycle begins by adding four labeled reversible terminators, primers, and DNA polymerase.

8. IMAGE FIRST BASE



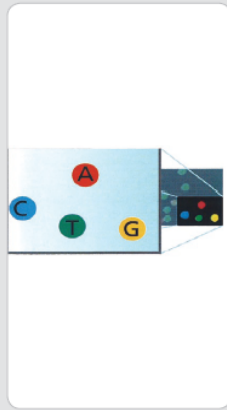
After laser excitation, the emitted fluorescence from each cluster is captured and the first base is identified.

9. DETERMINE SECOND BASE



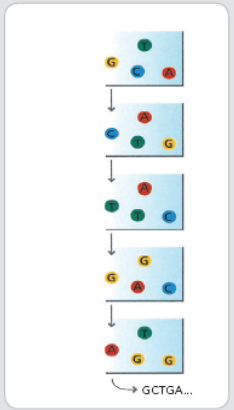
The next cycle repeats the incorporation of four labeled reversible terminators, primers, and DNA polymerase.

10. IMAGE SECOND CHEMISTRY CYCLE



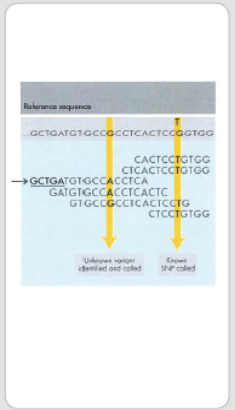
After laser excitation, the image is captured as before, and the identity of the second base is recorded.

11. SEQUENCING OVER MULTIPLE CHEMISTRY CYCLES



The sequencing cycles are repeated to determine the sequence of bases in a fragment, one base at a time.

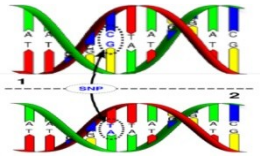
12. ALIGN DATA

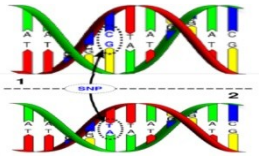


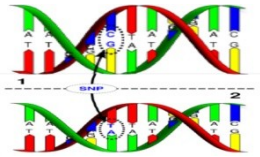
The data are aligned and compared to a reference, and sequencing differences are identified.

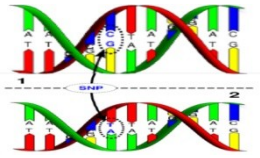
SELEKCIJA NA OSNOVI GENOMSKIH PODATKOV - REZULTATOV

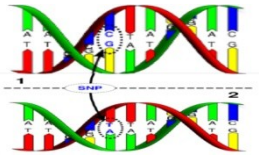
Genomska selekcija

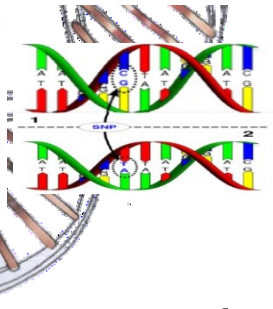
PV 

PV 

PV 

PV 

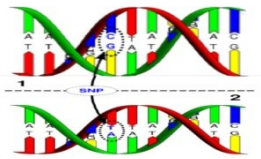
PV 

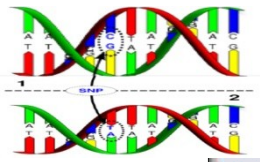


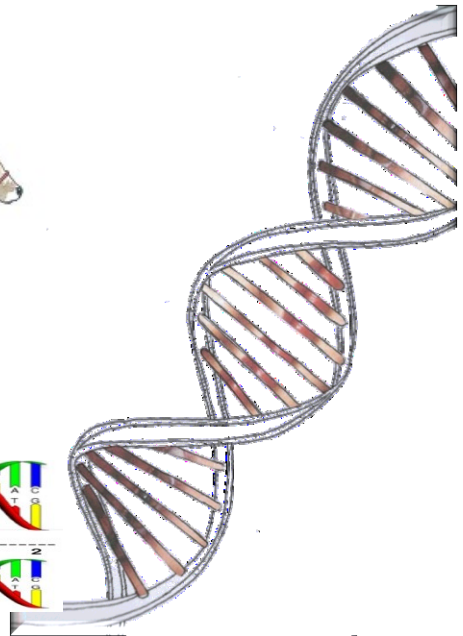
Genomska selekcija

- Ideja:
  1. ocenimo učinke SNP na **referenčni populaciji** (poznan fenotip ali PV in genotip) → **SNP enačba**

  2. **SNP enačbo** lahko uporabimo tudi na osebkih brez fenotipa, npr. novorojenih teletih







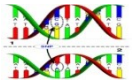
Model označevalcev

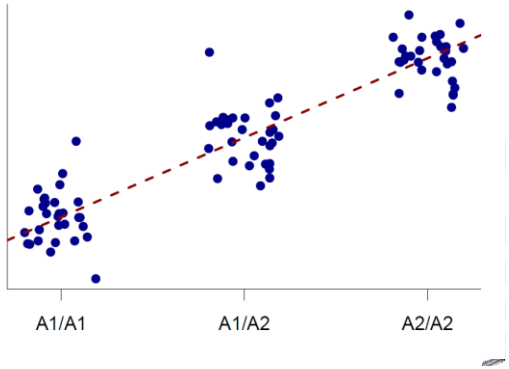
- Model

$$y = Xb + Zm + e$$

Fenotipi

SNP genotipi





- Sistem enačb – **BLUP, GBLUP**

$$\begin{pmatrix} X^TX & X^TZ \\ Z^TX & Z^TZ + I\alpha \end{pmatrix} \begin{pmatrix} \hat{b} \\ \hat{m} \end{pmatrix} = \begin{pmatrix} X^Ty \\ Z^Ty \end{pmatrix}$$

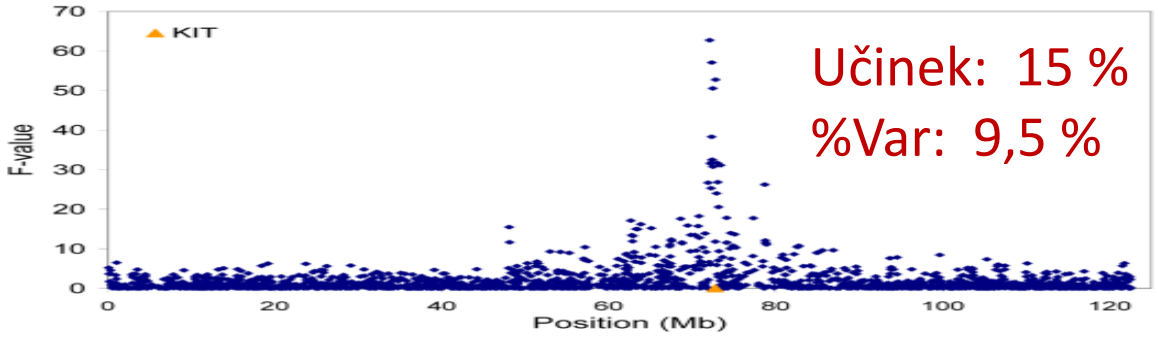
Model označevalcev (DGV)

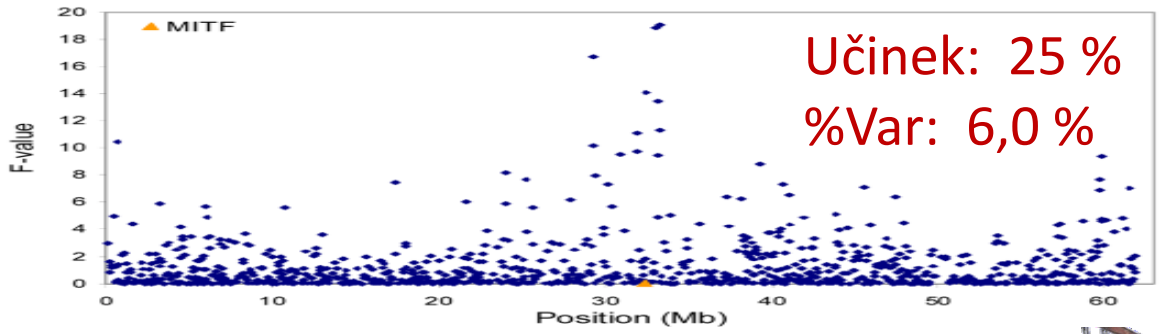
- „Direct genomic value (DGV)“

$$\hat{a} = Z\hat{m} = z_1\hat{m}_1 + z_2\hat{m}_2 + \cdots + z_k\hat{m}_k$$

„SNP enačba“

Ocene SNP učinkov

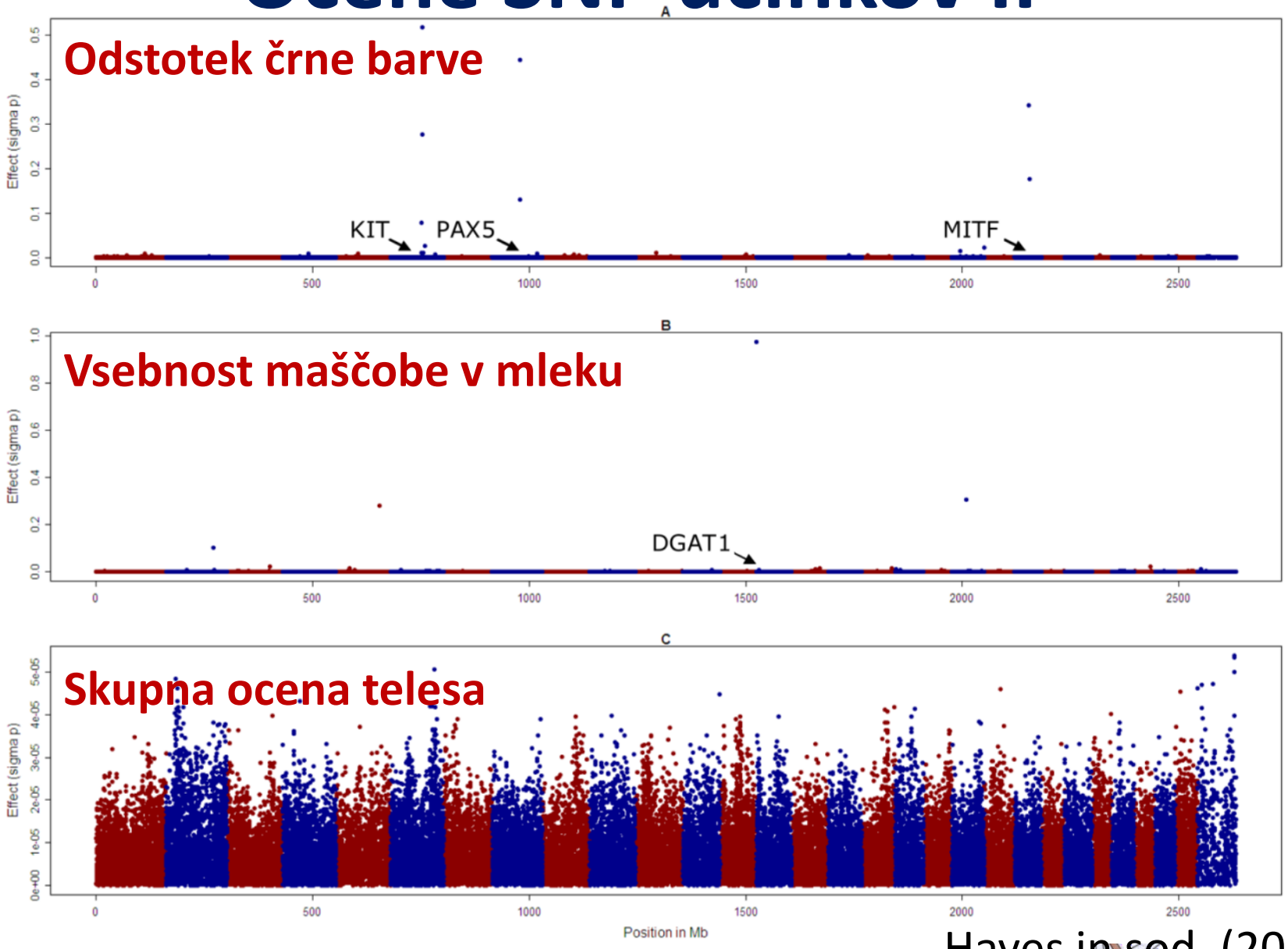




SNP praviloma niso v genih,
so pa mogoče blizu genov!!!
→ potrebno obdržati kontrolo prireje!!!

Hayes in sod. (2010)

Ocene SNP učinkov II



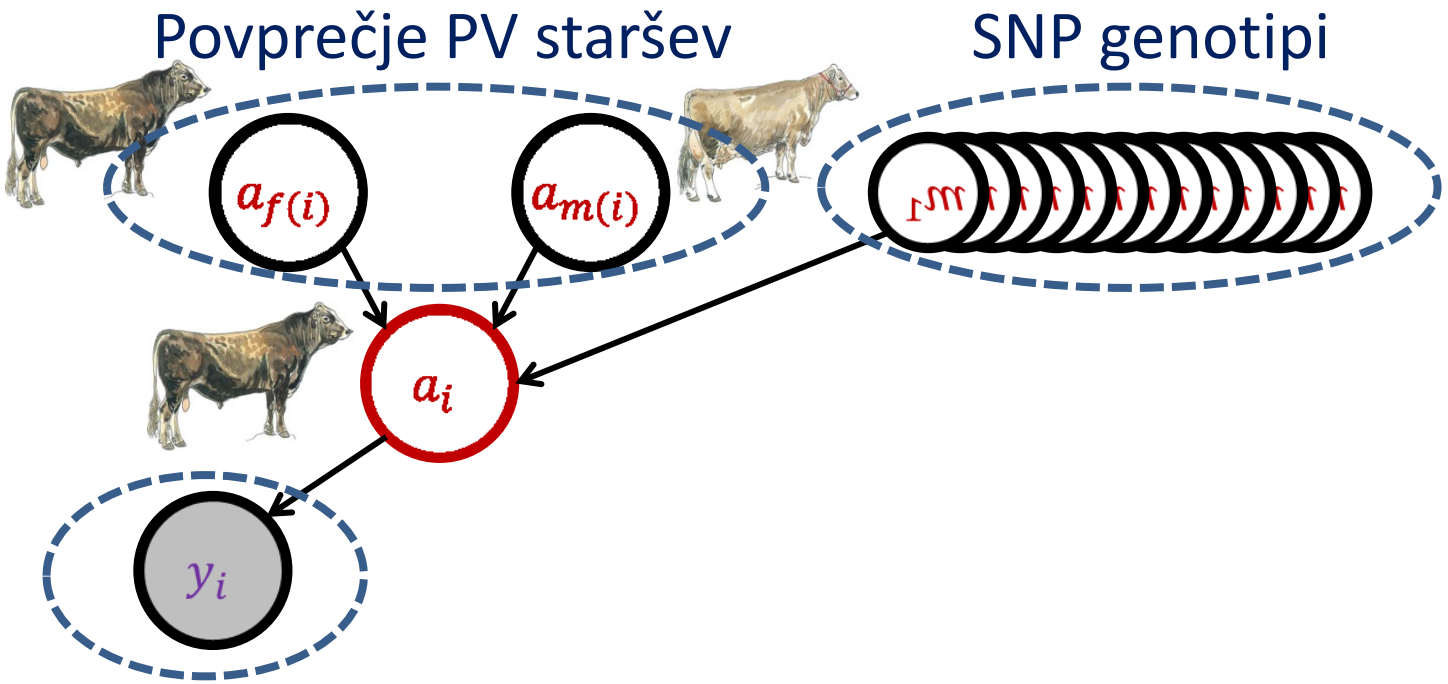
Hayes in sod. (2010)

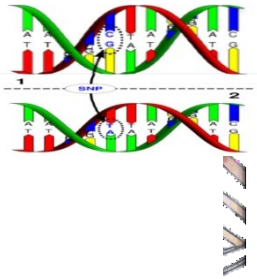
GEBV?

- Rodovniki - dodatna informacija za mlade živali

$$GEBV = f(DGV, PA)$$

„Genomically enhanced breeding value“





„Lastni preizkus“

Model živali

- Model

$$y = Xb + Za + e$$

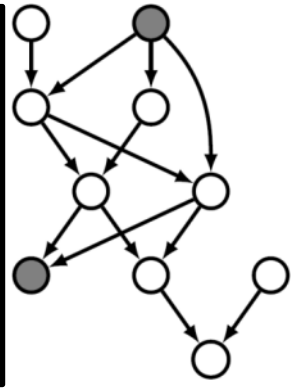
- Sistem enačb (Legarra in sod., 2009) – **BLUP**

$$\begin{pmatrix} X^TX & X^TZ \\ Z^TX & Z^TZ + H^{-1}\alpha \end{pmatrix} \begin{pmatrix} \hat{b} \\ \hat{a} \end{pmatrix} = \begin{pmatrix} X^Ty \\ Z^Ty \end{pmatrix}$$

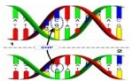
$$H^{-1} = A^{-1} + \begin{pmatrix} 0 & 0 \\ 0 & G^{-1} - A_{g,g}^{-1} \end{pmatrix}$$

Fenotipi

Rodovniki



SNP genotipi



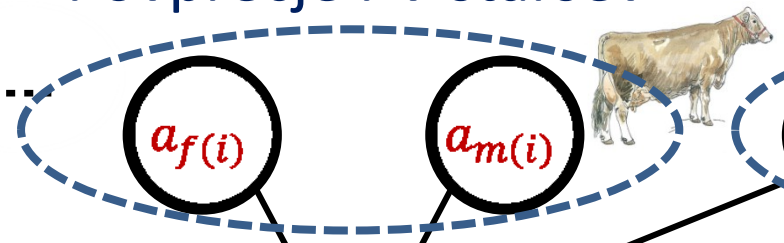
Klasična matrika sorodstva

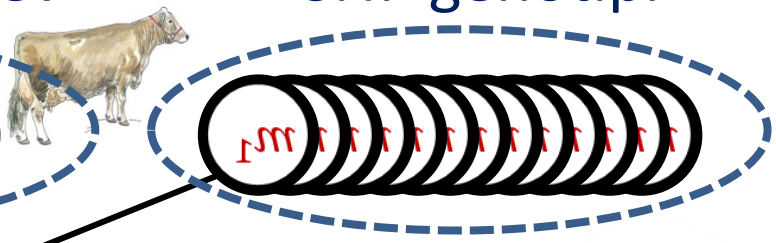
Genomska matrika sorodstva

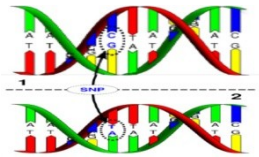
Model živali – viri informacij

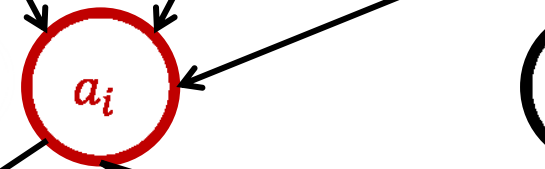
Povprečje PV staršev

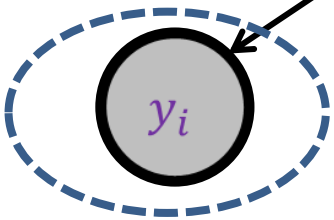
SNP genotipi



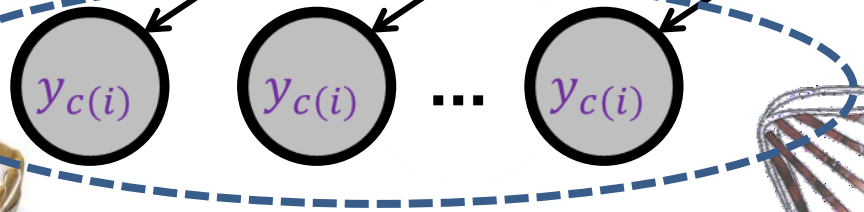






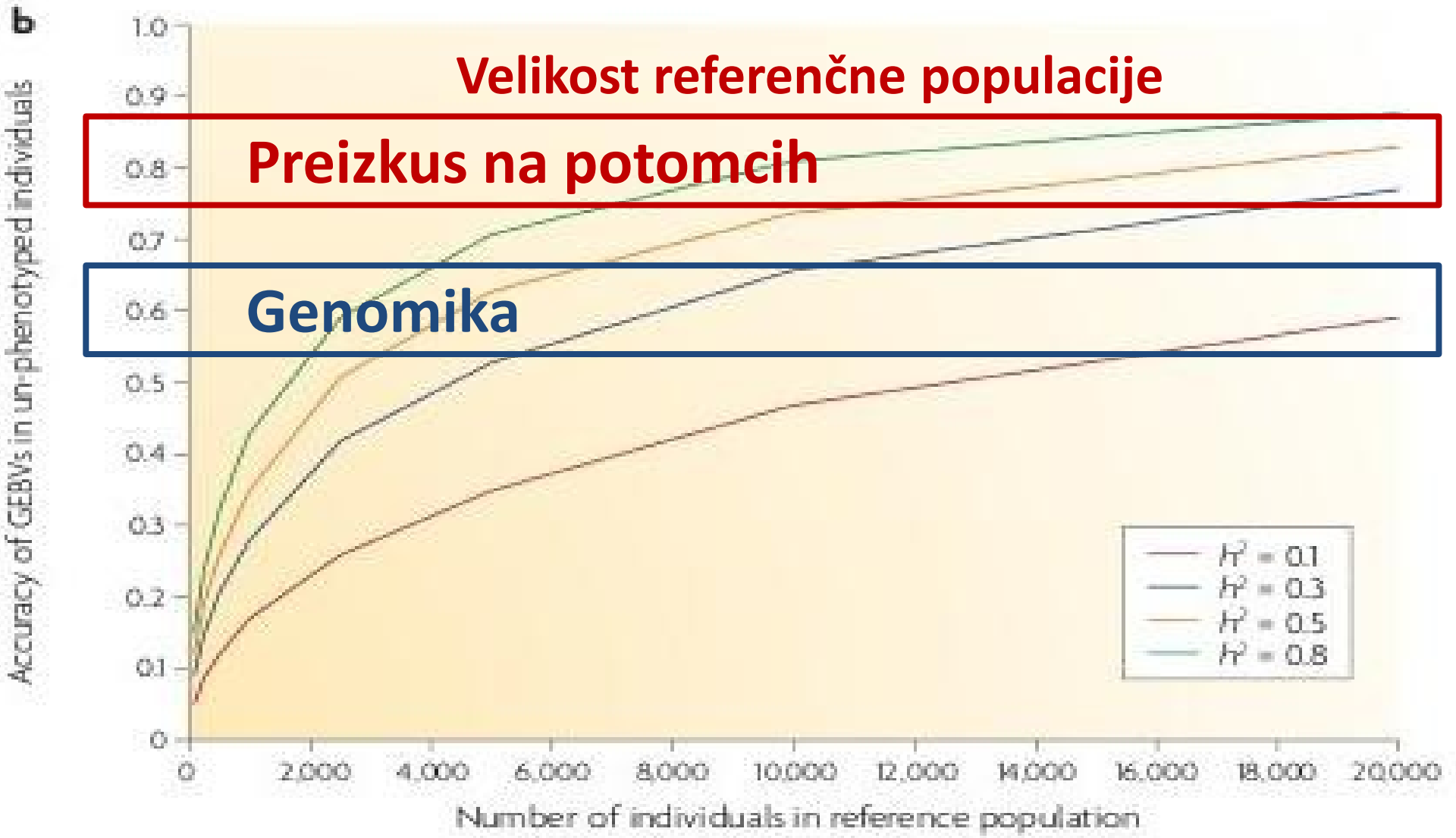


Lastni preizkus



Preizkus na potomcih

Potrebni pogoj



Goddard in sod. (2009)

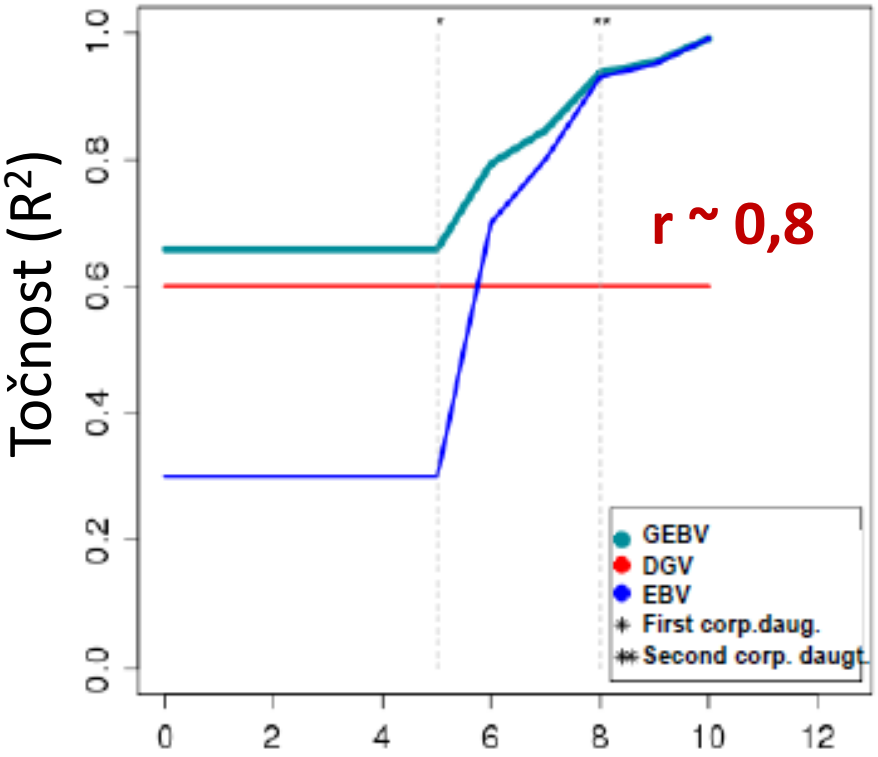
Genetski napredek

$$\Delta G = (i \times r \times \sigma_a) / g$$

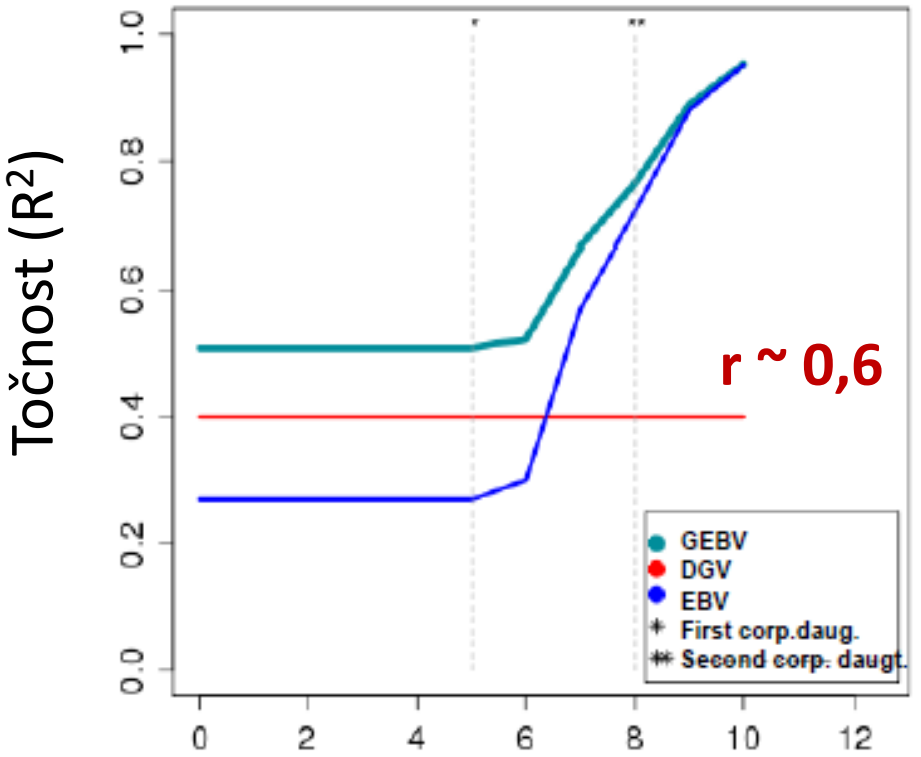
- **i** – intenzivnost selekcije
  - 50 % odbranih → i ~ 0,8
  - 5 % odbranih → i ~ 2,0
- **r** – točnost plemenskih vrednosti
  - povprečje staršev → r = 60 % za sklop mlečnosti
  - preizkus na potomcih → r = 90 % za sklop mlečnosti
- σ_a – standardni odklon plemenskih vrednosti
- **g** – generacijski interval

Točnost (R^2) skozi čas - biki

Mlečnost



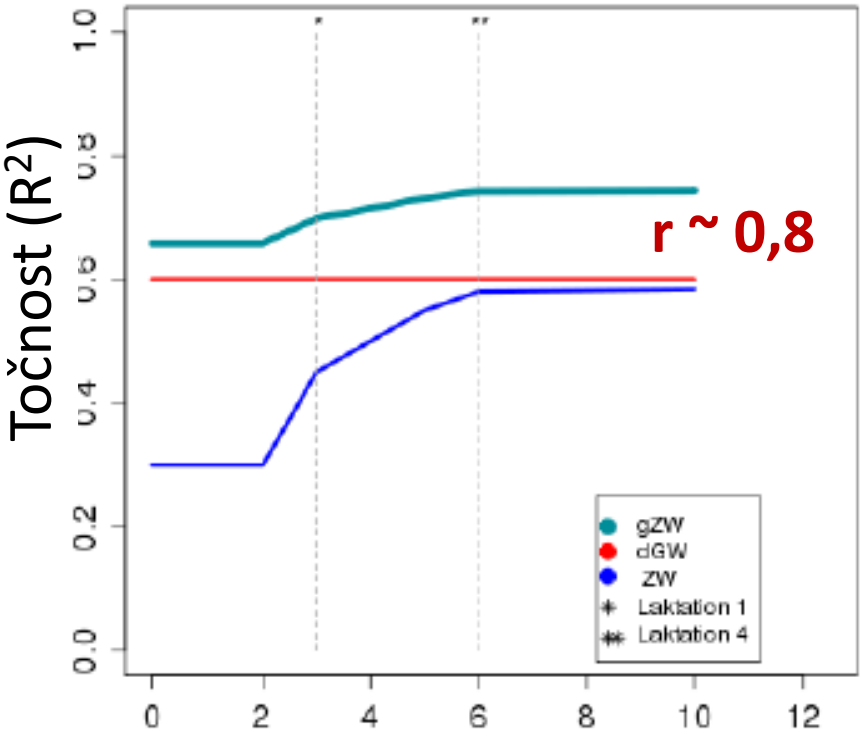
Dolgoživost



Reents (2010)

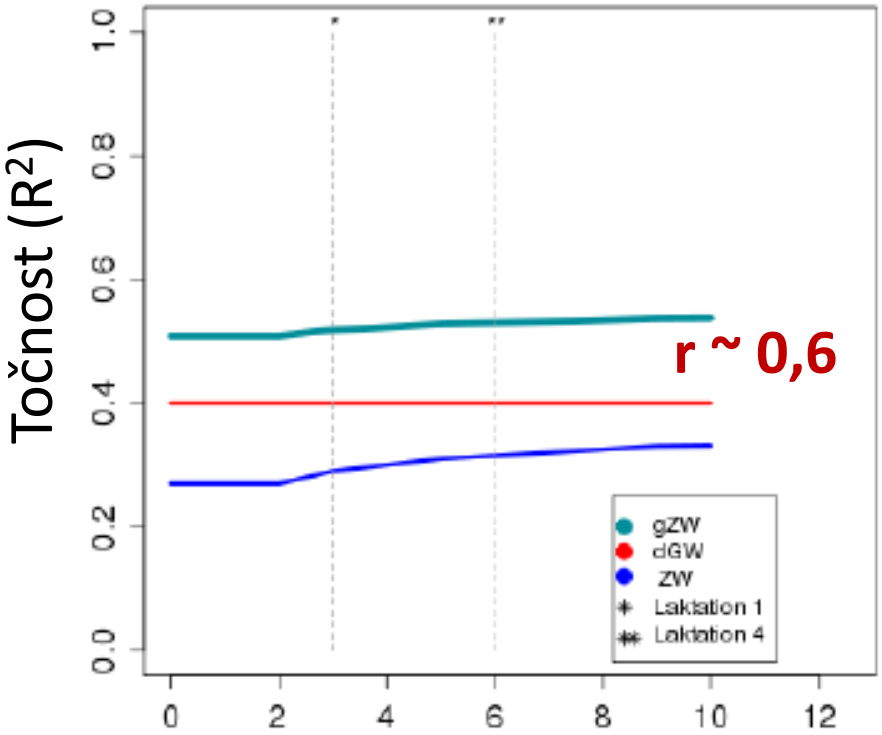
Točnost (R^2) skozi čas - krave

Mlečnost



Starost (leta)

Dolgoživost



Starost (leta)

Reents (2010)

Genetski napredek - govedo

- **Večji genetski napredek**
  - Mladi biki – povprečje staršev

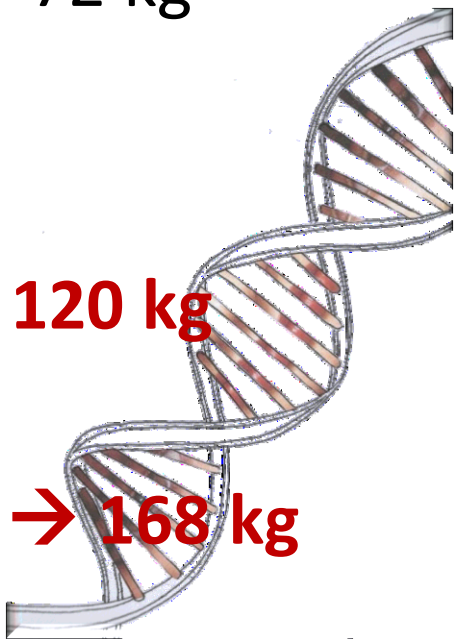
    $\Delta G = (2 \times \mathbf{0,60} + \sim 0) / (\mathbf{2} + 2) = 0,30 \rightarrow 90$ kg**?**
  - Preizkus na potomcih

    $\Delta G = (2 \times \mathbf{0,95} + \sim 0) / (\mathbf{6} + 2) = 0,24 \rightarrow 72$ kg

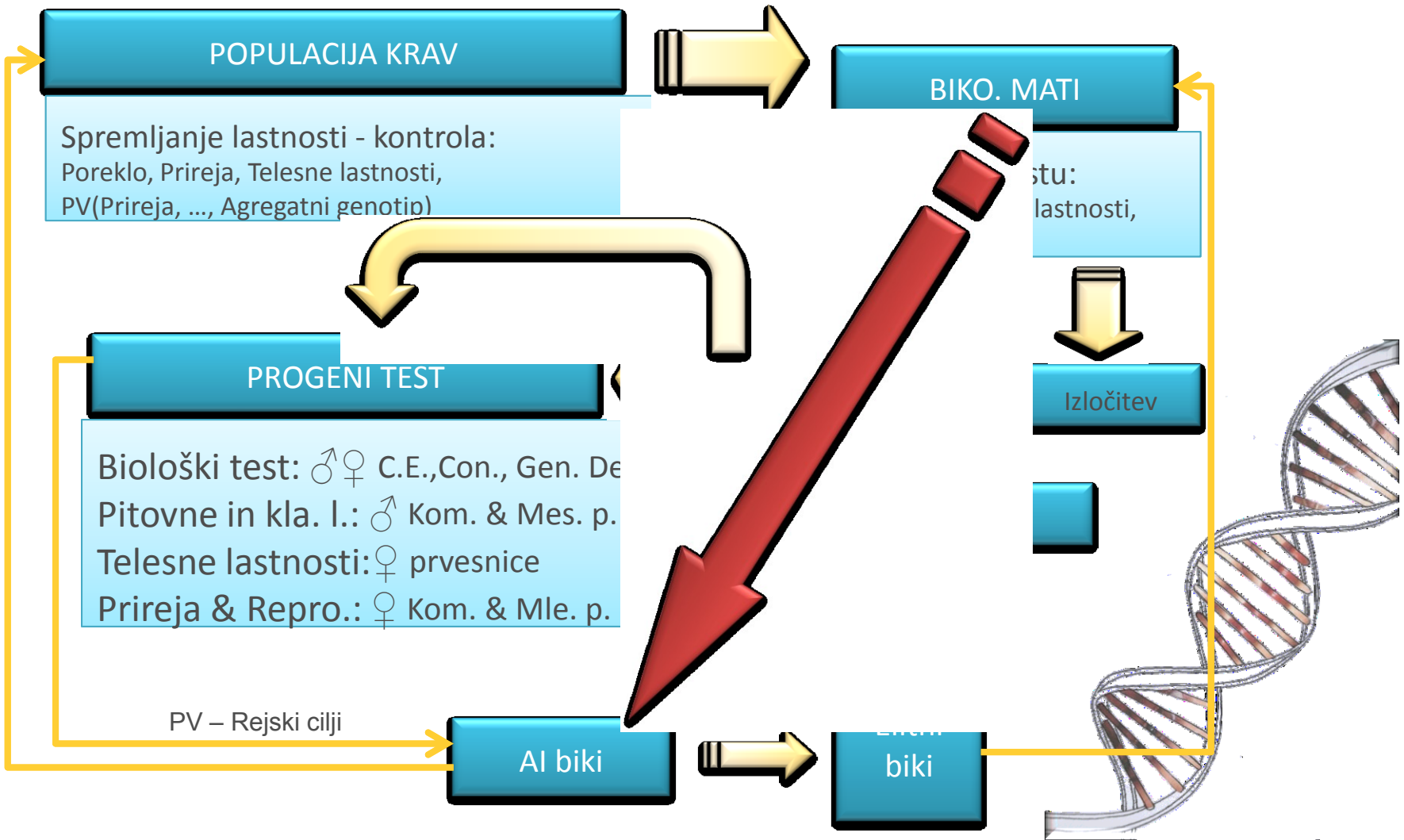
  - GS mladi biki

    $\Delta G = (2 \times \mathbf{0,80} + \sim 0) / (2 + 2) = \mathbf{0,40 \rightarrow 120}$ **kg**
  - GS mladi biki + "bikovske" matere

    $\Delta G = (2 \times \mathbf{0,80} + \mathbf{0,8} \times \mathbf{0,80}) / (\mathbf{2} + 2) = \mathbf{0,56 \rightarrow 168}$ **kg**



Poenostavljena shema SP



Sprememba rejskih programov
(primer iz Francije, 2009)

- **Preizkus na potomcih**
  - 800 telet
  - 400 lastni preizkus
  - 130 mladih bikov
  - 15 elitnih bikov
- **Genomska selekcija**
  - 2400 telet
  - 400 lastni preizkus
  - 80 mladih bikov

→ Genetski napredek: ~1x več

→ Inbriding: ~1/3 manjši porast

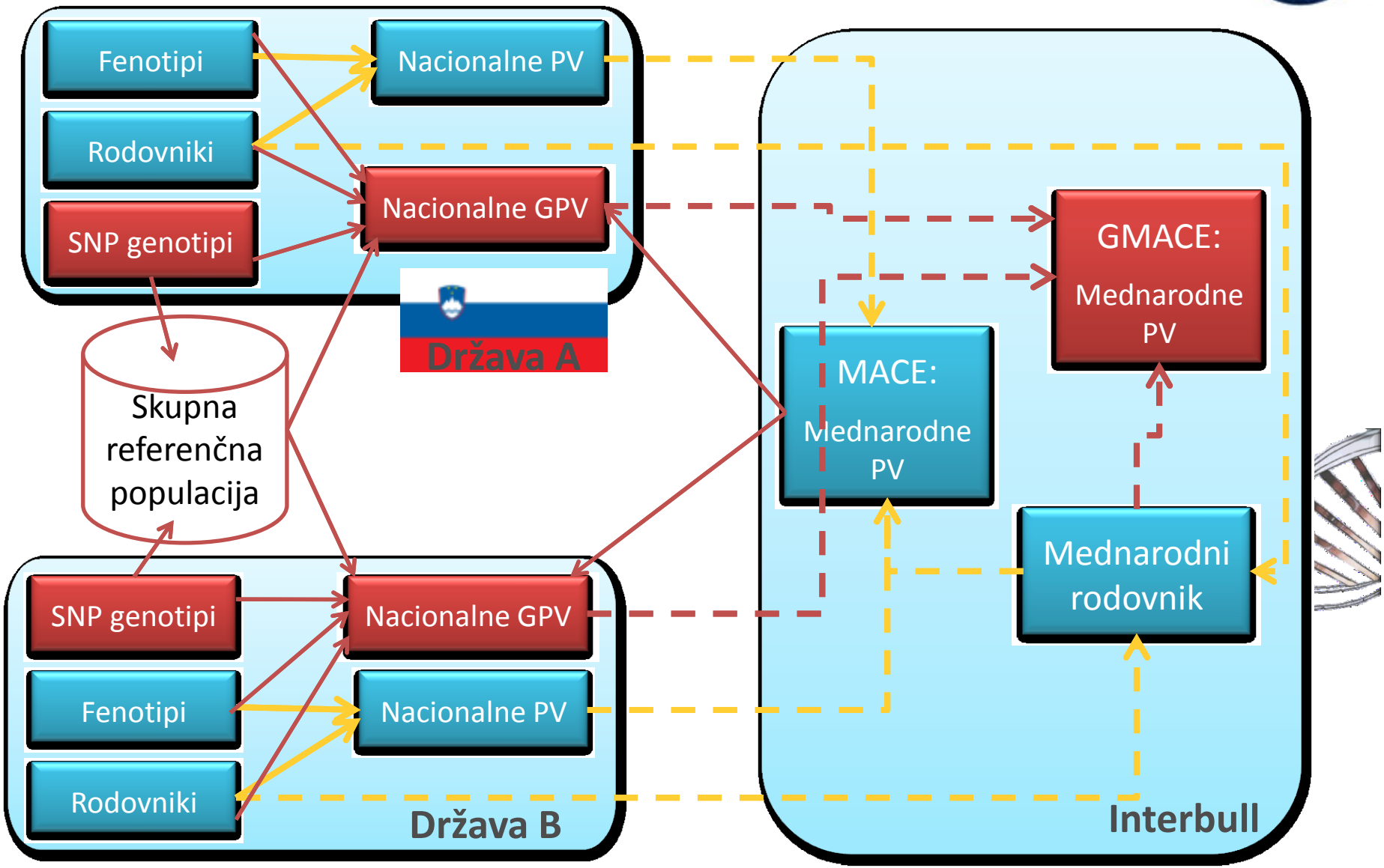
Slovenija – nacionalni nivo

- Rjava pasma 191 bikov 
- Model živali (fenotipi + rodovniki + SNP genotipi)
- Točnosti (količina beljakovin)

	Vsi biki	Mladi biki
Fenotipi + rodovniki	0.96 (0.53 – 1.00)	**0.66** (0.62 – 0.68)
… + SNP genotipi	0.96 (0.51 – 1.00)	**0.68** (0.64 – 0.70)

Premajhno število za lasten genomski program!!!

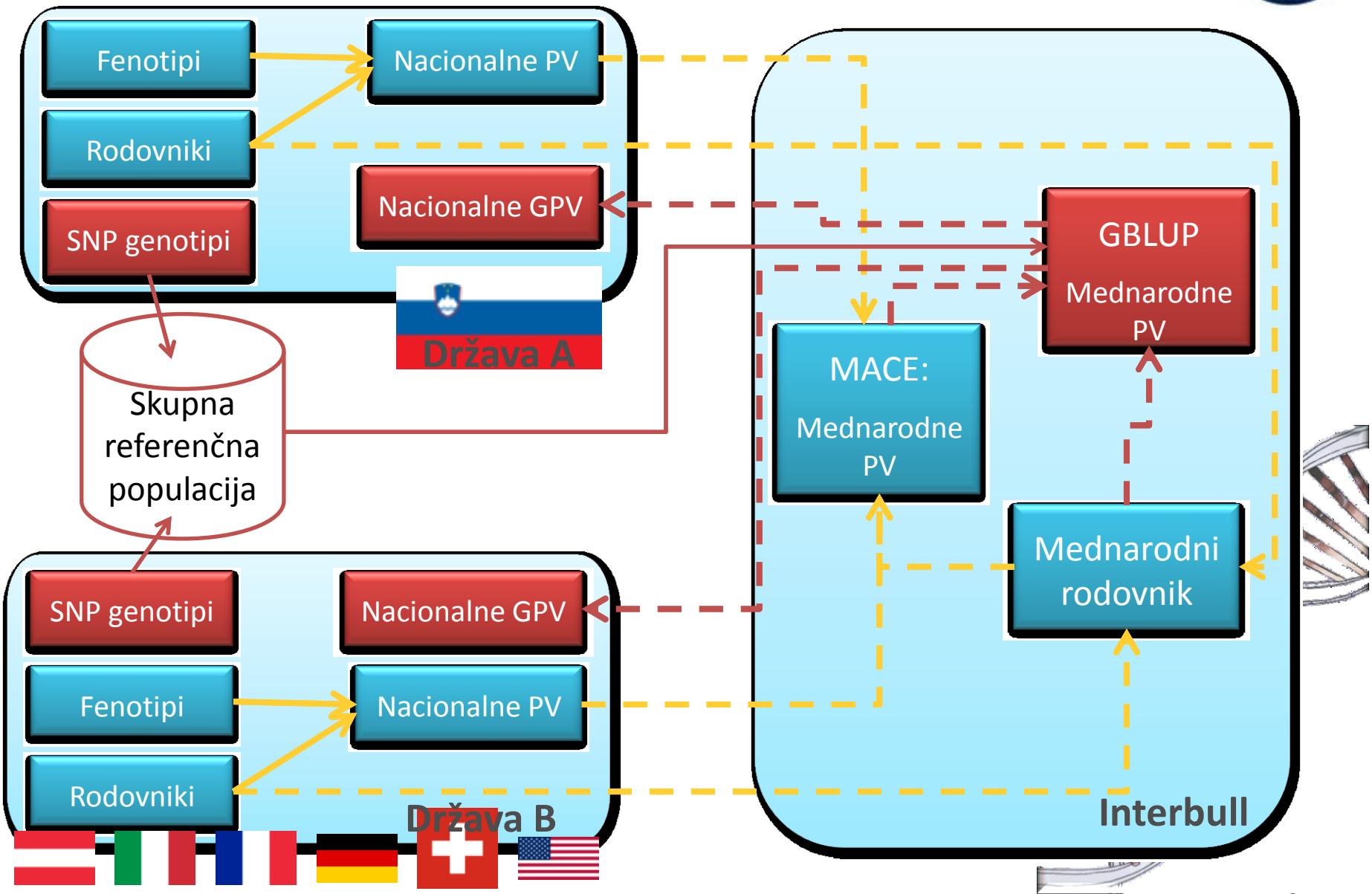
InterBull - GMACE



Konzorciji za Slovenijo

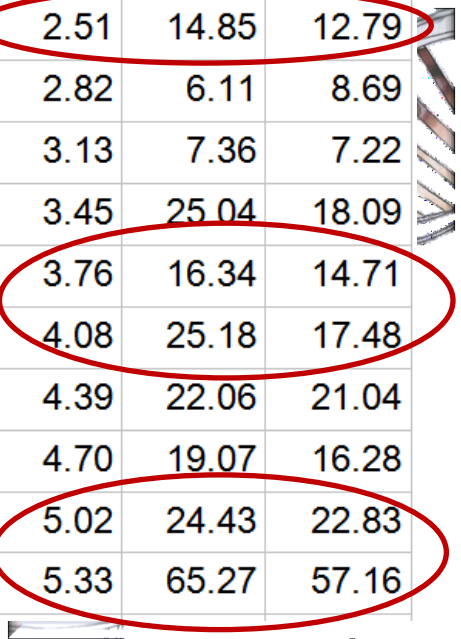
- Rjava pasma 191 bikov
- Črno bela pasma 192 bikov - ??? konzorcij
- Lisasta pasma ???

InterBull - InterGenomics



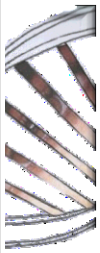
InterGenomics - rezultati

Bik				Beljakovine - BV			Beljakovine - pr.rang		
ID	Ime	Roj.	Gen.	MACE	DGV	GEBV	MACE	DGV	GEBV
BSWDEUM000910075535	VINOS	1987		13	12	14	0.31	2.95	1.73
BSWUSAM000000191184	PRONTO-ET	1995		12	12	13	0.63	2.84	3.22
BSWDEUM000808024689	HUSSLI	1994		12	13	14	0.94	0.89	1.02
BSWITAMBZ0000582001	MOIADO	1998		12	13	14	1.25	1.79	1.13
BSWITAM024000415939	OSOPPO	2005		12	12	13	1.57	2.51	2.92
BSWSVNM000052577185	TONIS	2003	D	11	9	11	1.88	11.50	8.01
BSWDEUM000933943664	HUSIR	2001		11	11	12	2.19	5.01	5.62
BSWSVNM000042391555	VASKO	2001	D	10	9	10	2.51	14.85	12.79
BSWUSAM000000191552	MASCOT-ET	1995		10	11	11	2.82	6.11	8.69
BSWDEUM000913932380	VINEB	1993		10	10	11	3.13	7.36	7.22
BSWDEUM000912481701	NOPAU	1996		10	7	9	3.45	25.04	18.09
BSWSVNM000012801181	AMAS	2003	D	10	8	9	3.76	16.34	14.71
BSWSVNM000042432573	OSMY	2003	D	10	7	9	4.08	25.18	17.48
BSWITAMTN0000138198	BRUGET	1992		9	7	8	4.39	22.06	21.04
BSWDEUM000910136233	STREBAL	1988		9	8	9	4.70	19.07	16.28
BSWSVNM000072913970	GOLD	2004	D	8	7	8	5.02	24.43	22.83
BSWSVNM000063020582	VAJET	2005	D	8	3	4	5.33	65.27	57.16



InterGenomics - rezultati

Bik				Beljakovine - BV			Beljakovine - pr.rang		
ID	Ime	Roj.	Gen.	MACE	DGV	GEBV	MACE	DGV	GEBV
BSWSVNM000001011800	GROF	1991	D	-9	-9	-10	99.37	97.45	97.22
BSWSVNM000043235434	HOPS	2006	D	-10	-3	-4	99.69	88.80	90.94
BSWSVNM000001885954	BENO	1999	D	-11	-11	-12	100.00	98.94	98.58
BSWSVNM000023164765	CODAK	2007	D		6	6		36.68	42.92
BSWSVNM000023413571	MODIAN	2007	D		7	8		24.56	23.45
BSWSVNM000033062026	VOJAGER	2005	D		-3	-3		89.02	87.12
BSWSVNM000033415503	EREKT	2007	D		3	3		63.67	61.81
BSWSVNM000063115200	VERIS	2006	D		-3	-2		88.22	86.77
BSWSVNM000073115072	BINEST	2007	D		6	6		37.82	41.26
BSWSVNM000073115728	BREGO	2007	D		2	2		67.97	67.98
BSWSVNM000073265074	GUSTI	2007	D		-6	-5		94.47	91.46
BSWSVNM000073314367	EMATOR	2007	D		3	4		59.43	53.20
BSWSVNM000083265994	BECY	2006	D		4	4		54.67	55.30
BSWSVNM000083380389	COS	2007	D		5	6		39.65	41.66
BSWSVNM000083415508	METEOR	2007	D		4	5		52.50	49.93



Korelacije

Beljak.	N	Pov.	SD	Min	Max
PV	319	1.8	4.39	-11.2	13.1
DGV	254	2.3	3.95	-11.3	13.4
GEBV	254	2.7	4.19	-12.0	14.2

	DGV	GEBV
PV	0.966 242	0.983 242
DGV		0.993 254

Točnost - validacija

Celotni set podatkov (preizkus na potomcih)

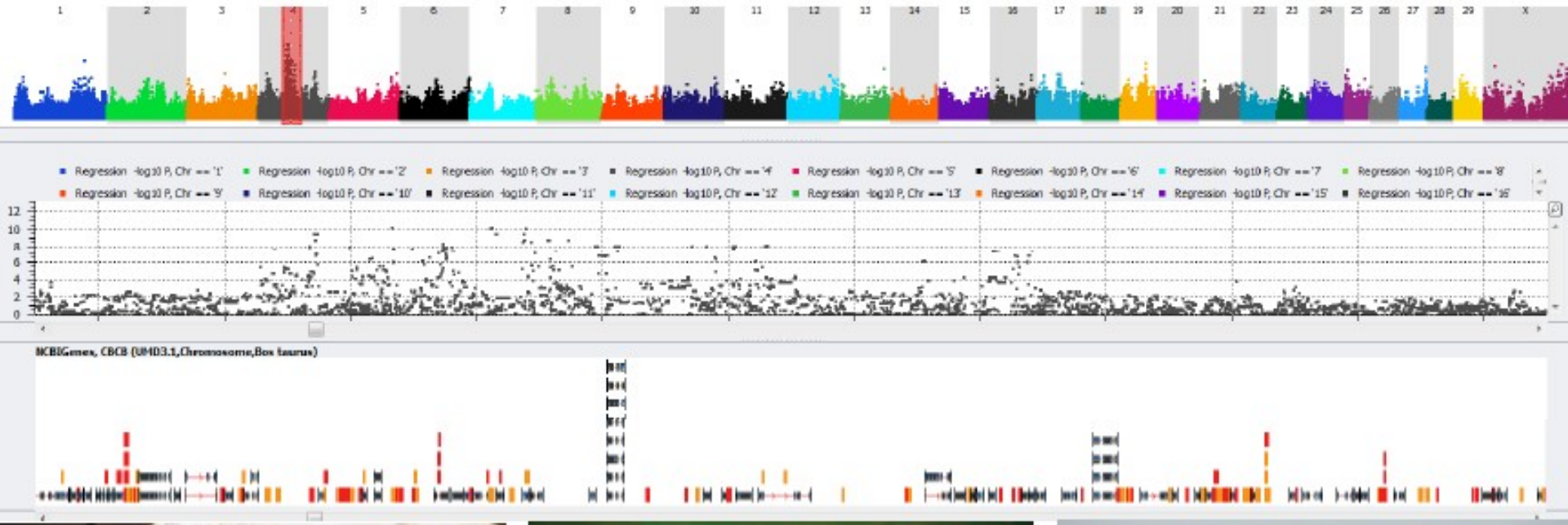
Kalibracija

Validacija

- Količina mlečnih beljakovin
  - povprečje staršev (klasično): 0,56
  - genomika (novo): 0,79

→ **Potrditev teoretičnih pričakovanj**

Tudi pri drugih vrstah!!!

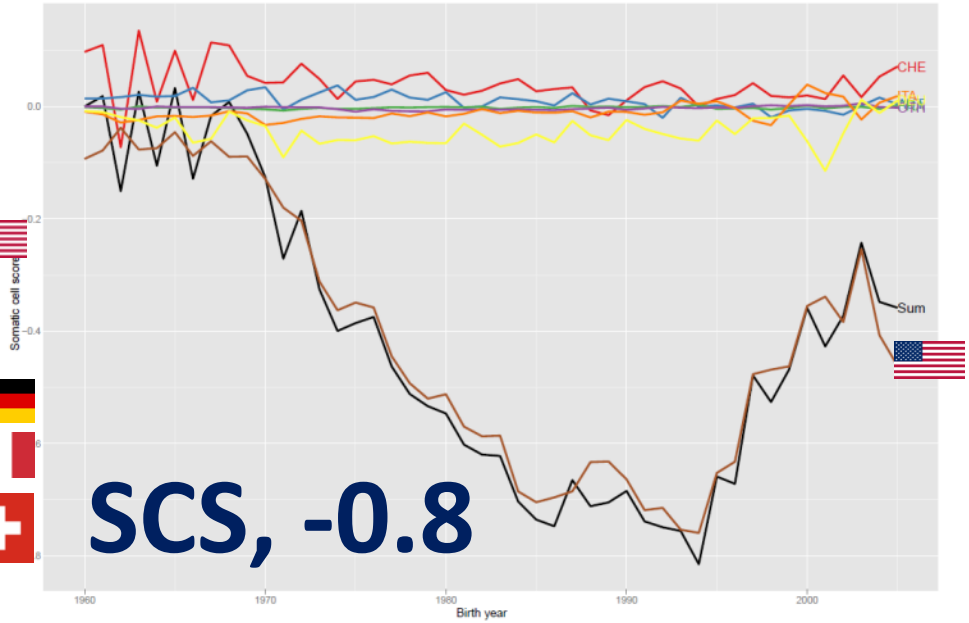


McClure (2011)

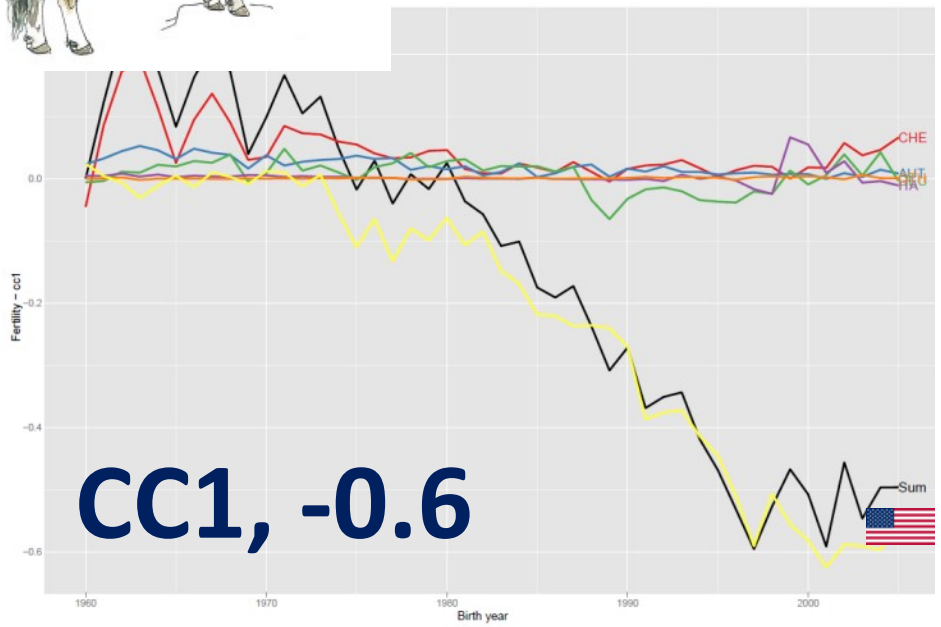
Pomen nacionalne selekcije v globalizaciji?

PRO, +3

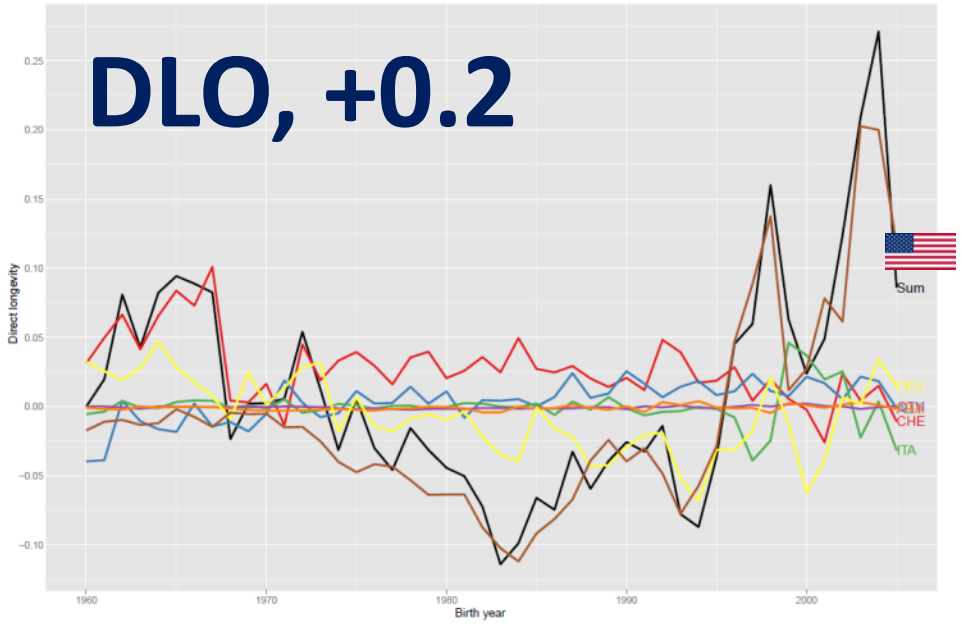
SCS, -0.8



CC1, -0.6



DLO, +0.2



Pomen nacionalne selekcije v globalizaciji?

- Evropa v preveliki meri uvaža genetiko iz ZDA
  - izboljšana prireja
  - poslabšana plodnost

- Izzivi za Slovenijo
  - Implementirati genomske selekcije v praksi
  - Vzpodbuditi promet s tujino
  - Ohraniti slovensko rjavo pasmo