

Genetic Improvement of Economic Traits in Dairy Cattle

Case Study 6

Research goal	To develop methods for marker assisted selection for quantitative trait loci (QTL) for heritable traits, such as fat and protein concentrations, in dairy cattle populations.
Beneficiaries	Farmers, Breeders (commercial or cooperative), Artificial insemination organizations, Consumers
Activities conducted in order to achieve the objectives	<p>Developed marker assisted “grand-daughter” design to reduce number of genotype testing and improve power for linkage mapping of QTL.</p> <p>First use of DNA microsatellites for identification, of low heritability QTL (previously used only to map major genes)</p> <p>Identified the causative mutation in a gene affecting milk protein and fat.</p> <p>Devised a perspective on the future of genomic selection.</p> <p>Conducted one of the largest marker variant surveys for the Holstein breed of cattle.</p> <p>Demonstrated that highly accurate paternity validation or identification based on comparison of progeny and parent genotypes is required for genomic evaluation, which should also increase rates of genetic improvement.</p>
Funding	6 BARD awards \$1.67 million.
Publications	3 books and 108 peer-reviewed journal publications. 82 in the top impact factor quartile. 10 of these publications were cited more than 100 times each.
Students involved	At least 8 Ph.D. students and 10 post-doctorate researchers. Currently 5 of the Ph.D. students have academic positions, 3 in Israel and 2 in the US, 1 works in the financial sector and 1 in the agrotechnology industry.
Stakeholders' collaboration	Israel Dairy Board, U.S. Council of Dairy Cattle Breeding, establishment of two major multi-national consortia (1 encompassing N. America, 1 encompassing Europe)
Environmental impact	none
Social impact	none
Commercial engagement	Precursor to genomic selection applications that involve numerous industrial players.
Patents	1 patent
Practical agricultural applications	<p>Selection method for improvement of economic traits <i>via</i> genotyping designs in cattle.</p> <p>Genomic selection in cattle paves the way for marker assisted selection in additional livestock species.</p>

Economic Impact	<p>Net present value of the BARD's investment is \$1,135 million, thereof \$248million already attained.</p> <p>The Internal rate of return is 25%.</p> <p>Benefit cost ratio is 264, thereof 59 already attained.</p>
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1 Objective: To Improve Economically Important Traits in Dairy Cattle

Israel and the US are the world leaders in dairy cattle breeding. Holsteins are the main dairy breed in both countries. The research aimed to map quantitative trait loci (QTL) that affect traits of economic importance in dairy cattle; such as milk, fat, and protein production, by means of genetic markers. The aim was to introduce the genetic information into cattle breeding selection schemes.

2 Research Activities

Between 1985 and 2018 six BARD awards were granted to J. I. Weller, M. Ron, and E. Seroussi (ARO), D. Gianola and H. A. Lewin (U. of Illinois), G. R. Wiggans and P. M. VanRaden (USDA Beltsville Research Center) and I. Misztal (U of Georgia). See Appendix A for full details of these awards.

The research developed methods for marker assisted selection for specific quantitative trait loci (QTL) for heritable traits, such as fat and protein concentrations, in dairy cattle populations.

In the early BARD studies, the researchers introduced and demonstrated the statistical power of a novel "granddaughter" design to identify QTL-marker linkages for genes with relatively small quantitative effects. The new design was advantageous compared to the traditional "daughter" design as it required a smaller number of marker assays (male grandsires and their sons are genotyped for the genetic markers, while the quantitative trait records of the granddaughters are used for statistical analysis). The 1990 publication, presenting this design, introduced the concept of identifying QTL through marker linkages by using a large existing cattle population and also proposed implementation by routinely collecting samples from all young progeny-tested sires in the US¹. The design was successfully applied to the Israeli Holstein cattle population by genotyping the males using DNA microsatellites as markers and by determining estimated breeding values for the Israeli population for five documented (or derived) production traits². This was the first report of detection of QTL effects in dairy cattle with DNA microsatellites, previously used

¹ Weller et al., 1990, *J. Dairy Sci.* **73**: 2525-2537.

² Ron et al., 1994, *Anim. Genet.* **25**: 259-264.

only to map major genes. A similar analysis was later conducted on US Holstein cattle whilst increasing the numbers of animals genotyped and microsatellites,

Further research developed methodologies to predict informative frequency, analyze markers for multi-traits rather than single traits, apply larger number of microsatellites derived from full genome scans and to determine allelic frequencies in the full population, all measures to enhance the effectivity and accuracy in use of markers in selection schemes.

The research in these first 4 BARD awards (1985-2003) contributed to the understanding that a very large number of genes affect nearly all economic traits and identification of individual causal genes could not be justified due to its complexity and expected benefit. Rather, genetic improvement can be enhanced through genomic selection using genetic markers covering the whole genome.³

The advent of SNP (Single Nucleotide Polymorphisms) arrays revolutionized the ability to detect genomic regions harboring sequence variants that affect complex traits, making the genomic selection of cattle a reality. Genomic selection, in which many markers are used to track inheritance of chromosomal segments and the impact of each segment is estimated for each trait, has been successfully implemented in the major dairy producing countries around the world.

The gradual elimination of the traditional progeny test system led to a reduction in the number of sires with daughter records and fewer genetic ties between years. However, the main factor limiting the accuracy of genomic evaluations is the number of bulls with genotypes and daughter progeny test. The latter 2 BARD projects studied this limitation, especially for small populations.

3 Academic Impact

3.1 Publications

3 books and 108 peer-reviewed journal publications (including 3 invited reviews) were published based on research from the 6 BARD awards. Of these, 82 publications are in the top impact factor quartile (Q1) journals. Ten of these publications were cited more than 100 times each.

3.2 Capacity Building

At least 1 Ph.D student was involved in the research in the US. Currently, a full professor in Academia.

Seven Ph.D. students and ten post-doctorate researchers were involved in these five research projects in Israel. Currently four of the Ph.D. students have academic positions,

³ Weller et al., 2011, J. Dairy Sci. 94: 1082–1090

three in Israel and one in the US, one works in the financial sector and one works in the agrotechnology industry.

3.3 Stakeholder's Collaboration

The Israeli group works closely with the Israeli Dairy Cattle Breeders' Association on an ongoing basis. The USDA groups cooperate with the U.S. Council on Dairy Cattle Breeding.

The central role that J.I. Weller has played in research on marker-based selection of dairy cattle has led the Israeli dairy industry to be at the forefront of global cattle performance, well beyond what would be anticipated from its small size (~120,000 head). Average milk production in Israel is 12,000 kg per cow per year and is the highest in the world.

In 1997 BARD funded an 11-day international workshop/course on QTL detection and marker-assisted selection led by, amongst others, J. I Weller. The meeting was attended by 48 participants from 16 countries.

Accuracy of breeding values in the genomic selection process requires large reference populations, leading to international collaborations and the emergence of large multi-national consortia. Two major consortia are (i) the Council on Dairy Cattle Breeding (CDCB), which includes organizations from the United States, Canada, United Kingdom, Italy, Switzerland, and Japan; and (ii) Eurogenomics, which includes members from Spain, the Netherlands, France, Poland, Denmark, Sweden, and Finland. Smaller countries, such as Israel and Ireland, that are not able to meet membership requirements (submission of a quota of bulls with genotypes and genetic evaluations based on daughter records), have initiated joint genomic evaluations with larger countries. Establishment of these consortia are, in-part, a result of the research conducted in the two most recent BARD projects (IS-4394-11 R and IS-4794-15 R).

4 Commercial Engagement

Whilst female fertility of cattle is limited, male fertility, *via* artificial insemination, is virtually unlimited. Cattle breeding is based on selection of the best bulls, and in Israel, 80% of the calves born each year are progeny of only 10-15 bulls. Since bulls do not lactate, their genetic value (for milk production and other economic traits) could be determined in the past only by the progeny test system, i.e. by evaluating the production of their female offspring.

In the genomic era, the progeny test system is being replaced by genomic selection breeding programs. The US and Israeli BARD researchers play a major role in these advances, are influential in the global dairy industry and are critical to the development of the industry in the US and especially in Israel. The knowledge accumulated during the years of the BARD awards provides the foundation for a highly adopted practical

application of the commercial industry. Since genomic evaluations became official, genotypes that are usable for genetic evaluations have been generated for over 1 million animals. Each year an additional 10,000 high density genotypes are conducted in the US⁴.

The USDA group led by P.M VanRaden and G.R. Wiggans was deeply involved in designing the first cattle array and many subsequent chips. They developed methods to validate the arrays and to choose additional targeted SNPs, but those studies were not directly connected to BARD.

4.1 Patents

Bovine ABCG2 gene missense mutations and uses thereof, Eyal Seroussi, Harris A. Lewin, Mark R. Band, Miri Cohen-Zinder, James K. Drackley, Denis M. Larkin, Juan J. Loor, Micha Ron, Moshe Shani, Joel Ira Weller, US 7803919 B2, Granted: 28-09-2010 to Agricultural Research Organization Volcanic Center & University of Illinois,

The patent was licensed to Monsanto and the IP has been incorporated into an array of genetic tests.

5 Practical Agricultural Applications

The progeny test scheme has the disadvantage that the bulls are approximately 5 years old by the time that progeny test records from the first crop of daughters is available. Using genomic evaluation, the sire of bull generation interval⁵ fell from ~7 years to less than 2.5 years. A genomic estimated breeding value (GEBV) can be assigned to a calf shortly after birth, enabling an immediate genetic response to changes in breeding goals.

The proven benefits and ever decreasing costs of genotyping have led to rapid implementation of genomic evaluations. Today, young-bull acquisition and marketing is based on genomic evaluations.

The research showed that highly accurate paternity validation or identification based on comparison of progeny and parent genotypes is a virtually no cost byproduct of genotyping that is required for genomic evaluation, which should also increase rates of genetic improvement⁶.

⁴ https://queries.uscdcb.com/Genotype/cur_density.html

⁵ The generation interval is the average age of the parents at birth of their offspring. The generation interval facilitates the calculation of the genetic response per year instead of per generation.

⁶ Weller et al., 2010, J. Anim. Genet. 41(5): 551-3

6 Economic Impact

6.1 Investment Cost

BARD contributed \$1.67 million in research funds between 1985 to 2018. Additional funds to the core BARD research support came from USDA. The EU and the Israeli Dairy Board contributed around \$0.83 million.

6.2 Benefits:

The Improvement in Milk Production Efficiency

Genomic selection has led to an increase in the rate of genetic improvement of over 30 major traits⁷ included in the dairy cattle selection indices. We estimate the aggregated benefit of genomic evaluation implementation by relating to the increase in milk yield (accompanied by increases in protein and fat levels). The selection indices are dynamic values that change according to the breeding targets and the weight given to each trait. We relate to the increase in the rate of increasing milk yield as an overall rate of improvement for all traits and use it as a proxy to estimate the benefits.

Prior to the introduction of genomic selection, the genetic annual gain for milk production was 50 kg per lactation per cow. This means that every year the average milk production per cow increased 50 kg compared to the previous year. Since 2009 and the onset of genomic selection the annual milk gain has increased twofold to 109 kg/head annually^{Error!}
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The average US raw-milk price at the farm-gate between 2010 and 2018 was \$0.32/kg. The US herd in 2018 consisted of 9.39 million heads producing an average 10,427 kg milk/head.⁸ When the yield increases per cow, only the marginal cost increases, as it is mainly the feed cost which is 50% of the revenue.⁹ We also assume an increase of \$0.04/kg for labor and other variables. This translates to an increase in profit of \$0.12/kg per head. In 2010 the added yield attributed to genomic selection was 59 kg/head = \$7.1/head added profit. Since the gain is accumulative as the years proceed, the added profit per head grows. As an example, in 2011 the attributed added milk yield was 118 kg/head (59+59=118), thus the added profit was \$14.2/head. In 2018 we calculate added profit per head of \$64, which is \$508 million for the total US herd. We assume that for the years 2019 – 2028 the improvement will slow down to half the rate. The annual milk production, improved yields and added profit between 201-2028 are detailed in Appendix B.

⁷ Wiggans et al., 2017, *Annu. Rev. Anim. Biosci.* 5: 309–27

⁸ <https://downloads.usda.library.cornell.edu/usda-esmis/files/h989r321c/kk91fs56p/g445cm064/mkpr0219.pdf>
<https://downloads.usda.library.cornell.edu/usda-esmis/files/4b29b598d/6h440w199/kp78gk29p/htrl-09-13-2018.pdf>
<http://www.cdfa.ca.gov/dairy/uploader/docs/2018%201101%20Class%204a.%204b.pdf>
https://www.cdfa.ca.gov/dairy/prices_main.html

⁹ <https://www.ers.usda.gov/data-products/milk-cost-of-production-estimates/milk-cost-of-production-estimates/#Milk%20Cost-of-Production%20Estimates-2016%20Base>

High density genotyping is an additional annual cost. Each year 10,000 high density genotypes are conducted in the US at an estimated cost of \$0.5 million annually.

Milk production among major exporters (US, EU, New Zealand, Argentina, Australia), in 2018 is estimated at 300 million ton, of which the US produces one third.¹⁰ We assume that these sophisticated dairy industries adopted genomic selection during the last decade. As an example, Israel adopted it in 2015. We assume that the rest-of-the-world impact starts in delay in 2015, and we assume that the rest-of-the-world includes twice the number of cows of the US. See details in Appendix B.

The income of the retail and wholesale sector is estimated at 41% of the end-consumer price. Therefore, we added 41% to the benefit calculations.

We anticipate additional economic benefit in new fields which are not included in the economic calculation:

- Implementation of genomic evaluation has led to inclusion of more traits in the selection indices, and reduction of the emphasis on protein and fat production. More emphasis is expected on health and reproduction traits, direct selection on production efficiency, and selection for environmentally friendly production, including reduced waste production and gas emission¹¹.
- Before genomic selection, the paternity misidentification rate in advanced breeding populations was estimated to be in the range of 5% to 12%. Highly accurate paternity validation or identification based on comparison of progeny and parent genotypes is a virtually no-cost byproduct of genotyping that is required for genomic evaluation
- Costs for lower density chips are reaching the point at which routine genotyping of all female calves can be economically justified for management decisions at the farm level.
- Genomic selection in cattle paves the way for marker assisted selection in additional livestock species.

7 Economic Results

The estimated benefit in section 6.2 is derived from the disruptive changes to the dairy cattle industry following the development of SNP chips and the genomic evaluation methodology, an innovation external to the BARD awards. Many players have had a role in its development and implementation. To name but a few in the US: the USDA, the

¹⁰ <https://apps.fas.usda.gov/psdonline/circulars/dairy.pdf>

¹¹ Schöpke and Swalve, 2016; de Haas et al., 2017

Council on Dairy Cattle Breeding (CDCB), the National Association of Animal Breeders, Industry (e.g. ABS Global, Genex, Semex alliances, Taurus-Service).

To attribute a fraction of the genomic evaluation methodology to BARD we examine the foundation role of the BARD research outcomes towards advances that led to the disruptive technique. We base the attribution on the degree to which the genomic selection technique was expedited due to the BARD research outcomes. Also, we note the important role of this group of researchers in the implementation of the genomic selection in the US and in Israel.

The concept of using an existing livestock population and analyzing its genetics to statistically link between QTL and observed traits (as a novel “alternative” to introgression of genes as is done for plant life) and the proposition to routinely collect genetic samples from all young progeny-tested sires was first raised in publications associated with award US-805-85. The “granddaughter” study conducted *via* award IS-1939-92CR was the first proof of concept of this proposed methodology. The BARD research demonstrated that most dairy cattle traits are controlled by small genetic effects distributed across all chromosomes and that more markers and more bulls are needed to enable genetic improvement. The research findings convinced the researchers to collect DNA from all bulls in the USA and Canada in order to get larger families.

The US and Israeli PI’s assess that the collection of DNA from all bulls in the US and Canada hastened genomic implementation by a year. The experience with marker assisted selection and the methodologies developed to improve accuracy in determination of breeding values advanced the development of statistical methods applied to genomics, The PI’s assess that this component hastened genomic implementation by an additional half a year.

We summarize that the advances made in the earlier BARD studies on marker assisted selection of multiple QTL for improvements in traits with moderate to low heritability paved the way for implementation of the genomic evaluation with the advent of the SNP technology, and expedited its implementation by 1.5 years.

Based on this assumption, the value of the benefits was attained 1.5 years earlier as a result of BARDs contribution. This is equal to \$950 million of net present value, which is 3.7% share in the total benefit.

- Net present value of BARD’s investment is \$1,135 million, thereof \$248 million already attained.
- The Internal rate of return is 25%
- Benefit cost ratio is 264, thereof 59 already attained.

The US and Israel economy benefit is calculated according to the production in these two countries and the period of adoption.

Benefits that were not attributed to the project in this calculation:

- The researcher’s groups in the US and in Israel are an essential part of the dairy industry. Their contribution to its economy is large, but not included in the calculation, even though BARD had a role in establishing these groups.

Table 1: Main Economic Results, 2018 Million Dollar-Terms

	The Project	BARD	BARD Attained	Thereof to the US	Thereof to Israel	Other Countries
BARD's Share in the Cost	100%					
Share in the Benefit		3.7%				
Cost	4	4	4	2.2	2.2	
Benefit	30,799	1,140	253			
Net Present Value	30,794	1,135	248	534	2	599
Internal Rate of Return	40%	25%	22%	26%	5%	
Benefit Cost Ratio	7,143	264	59	248	1	

7.1 Sensitivity Analysis

The low and high alternative assumptions used in the sensitivity analysis were brought together to estimate results under pessimistic and optimistic scenarios. Table 2 displays the net present value sensitivity results, between the low result: \$304 million, to the high result: \$2.8 billion.

Table 2: NPV - Sensitivity Analysis, 2018 Million Dollar-Terms

			<u>BARD's Share in the Benefit</u>		
			Low	Central	High
			2%	3.7%	6%
Change in Benefit	Low	50%	304	565	920
	Central	100%	612	1,135	1,844
	High	150%	920	1,705	2,768

8 Appendix A: BARD Awards

Table 3: List of 6 BARD awards granted between 1985-2015

Project No	Full Title				
	Investigators	Institutes	Budget	Duration	Start Year
US-805 - 85	Development of Methods for Genetic Analysis of Discrete Traits of Economic Importance in US and Israeli Dairy Cattle Population				
	Gianola, D. Weller, J.I. R.L. Fernando C.R. Henderson	U Illinois ARO, Min. Ag. Iowa St. U U Illinois	\$200,000	3 years	1985
IS-1939-92CR	Detection and Mapping of Genes Affecting Traits of Economic Importance in Dairy Cattle with the Aid of Molecular Genetic Markers				
	Weller, J.I. M. Ron Lewin, H.A. G.R. Wiggans	ARO, Min. Ag. ARO, Min. Ag. U Illinois USDA, ARS	\$ 250,000	3 years	1992
IS-2383-95C	A Systematic Genome Search for Genes Affecting Economic Traits Dairy Cattle with the Aid of Genetic Markers				
	Weller, J.I. M. Ron Lewin, H.A. G.R. Wiggans P.M. VanRaden	ARO, Min. Ag. ARO, Min. Ag. U Illinois USDA, ARS USDA, ARS	\$ 330,000	3 years	1995
IS-3103-00CR	Determination of Allele Frequencies for Quantitative Trait Loci in Commercial Animal Populations				
	Weller, J.I. M. Ron Lewin, H.A.	ARO, Min. Ag. ARO, Min. Ag. U Illinois	\$ 300,000	3 years	2000
IS-4394-11 R	Optimization of methodology for genomic selection of moderate and large dairy cattle populations				
	Weller, J.I. M. Ron Misztal, I.	ARO, Min. Ag. ARO, Min. Ag. U Georgia	\$ 290,000	3 years	2011
IS-4794-15 R	Determination of actual polymorphisms responsible for economic trait variation in dairy cattle				
	Weller, J.I. M. Ron E. Seroussi	ARO, Min. Ag. ARO, Min. Ag. ARO, Min. Ag.	\$ 300,000	3 years	2015

	Bickhart, D.M.	USDA, ARS			
	G.R. Wiggans	USDA, ARS			
	G. Liu	USDA, ARS			

9 Appendix B: Milk Production, Yield Improvement and Added Profit

		A	B	C	D=A*C	E	F=E*A	G=(D+F)*1.41
Year	US Milk Cows (000')	Thereof 85% Estimated US Holstein Breed Milk Cows (000')	Added kg milk attributed to genomic selection (59 kg/head/year gain)	Added Profit \$/head (\$0.12/kg)	Added US Profit attributed to genomic selection, million \$	Other Countries Added Profit \$/head (\$0.12/kg)	Other Countries Added Profit, million \$	Total Added Profit attributed to genomic selection, + 41% Contribution to End-Consumer Price Reduction million \$
2010	9,086	7,723	59	7.1	55			77
2011	9,155	7,782	118	14.2	110			155
2012	9,235	7,850	177	21.2	167			235
2013	9,221	7,838	236	28.3	222			313
2014	9,207	7,826	295	35.4	277			391
2015	9,306	7,910	354	42.5	336	7.1	112	632
2016	9,310	7,914	413	49.6	392	14.2	224	869
2017	9,346	7,944	472	56.6	450	21.2	337	1,110
2018 Est.	9,385	7,977	531	63.7	508	28.3	452	1,354
2019 Proj.	9,385	7,977	561	67.3	537	35.4	565	1,553
2020	9,385	7,977	590	70.8	565	42.5	678	1,752
2021	9,385	7,977	620	74.3	593	49.6	791	1,951
2022	9,385	7,977	649	77.9	621	56.6	904	2,150
2023	9,385	7,977	679	81.4	650	63.7	1,017	2,349
2024	9,385	7,977	708	85.0	678	67.3	1,073	2,469
2025	9,385	7,977	738	88.5	706	70.8	1,130	2,588
2026	9,385	7,977	767	92.0	734	74.3	1,186	2,708
2027	9,385	7,977	797	95.6	762	77.9	1,243	2,827
2028	9,385	7,977	826	99.1	791	81.4	1,299	2,947

10 Appendix C : Information providers: Personal communication

- Joel Weller – PI for BARD awards, Department of Ruminant Science, ARO, Min. of Agr.

- George Wiggans – Investigator for BARD awards, Research Geneticist, USDA, ARS. Currently consultant for Council on Cattle Dairy Breeding
- Micha Ron - Co-Investigator for BARD awards, Department of Ruminant Science, ARO, Min. of Agr.
- Ignacy Misztal – Co-PI for BARD award, Animal Breeding and Genetics Group, U. Georgia
- Paul Van Raden - Co-Investigator for BARD award, Animal Genomics and Improvement Laboratory, USDA, ARS
- Liron Tamir - Chief economist of the Israeli Dairy Board