Institution: University of Edinburgh/Scotland's Rural College		
Unit of Assessment: 6		
Title of case study: J: Genomics-enabled breeding for disease resistance prevents mortality and improves welfare in aquaculture		
Period when the underpinning research was undertaken: 2004 – 2019		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Ross Houston	Chair of Aquaculture Genetics	2004 – present
Steve Bishop	Chair of Animal Disease Genetics	2007 – 2015
Period when the claimed impact occurred: 2007 – 2020		
Is this case study continued from a case study submitted in 2014? This case study describes a combination of impact continued from REF2014/6/1e and emerging impact arising from further work on the application of genetic technologies to aquaculture.		

1. Summary of the impact

Underpinning Research: As reported in REF2014/6/1e, we discovered genetic markers to predict resistance to Infectious Pancreatic Necrosis (IPN), a viral disease of farmed salmon, and developed methods to implement marker-assisted selection practically to breed IPN-resistant stock. Since then, we have also developed genomic tools to breed salmon stocks resistant to sea lice and oyster stocks resistant to oyster herpes virus.

Significance and Reach of Impact: Marker-assisted selection for resistance to IPN has nearly eradicated this disease from farmed salmon stocks, averting the death of 8,000,000-18,000,000 salmon across Norway, Chile, and Scotland, thus increasing salmon production by between 36,800 and 79,600 tonnes and adding between GBP108,000,000 and GBP234,000,000 to the global salmon farming industry between 2013 and 2020.

The success of breeding for IPN resistance has helped spark widespread uptake of genomic technologies to tackle other diseases of salmon and other aquaculture species. The primary target is sea lice, and our genomic tools for selecting for sea lice resistance are currently being applied in commercial salmon breeding programmes, with major potential to produce lice-resistant stocks in the future. In addition, our genomic tools for oysters are being widely applied to tackle oyster herpes virus, with 8,000 units bought by industry in the first year.

2. Underpinning research

The Challenge: Infectious diseases are a major problem in aquaculture

Farmed fish and shellfish will overtake wild fish as the main source of seafood. Since outbreaks of disease spread more easily in farmed systems, infectious diseases represent a major problem for the global aquaculture industry. For example, one of the primary threats to farmed salmon over the past few decades has been the viral disease IPN, which has typical mortality levels of approximately 25%, with severe outbreaks killing as many as 80-90% of fish on farm in the major salmon producing countries (Norway, Chile and the UK).

We have pioneered genetics and genomics methods to understand the genetic basis of resistance to key diseases of aquaculture and to develop tools to breed more resistant stock.

Reported in REF2014: Tackling IPN in farmed salmon

Through an extensive Biotechnology and Biological Sciences Research Council-funded programme, ongoing since 2004, our research was the first to discover a major quantitative trait locus (QTL) in the salmon genome which explains almost all the genetic variation in resistance to the IPN virus. Using this information, we developed the key theory and tools to prevent IPN [3.1].

We worked together with industry collaborators Landcatch Natural Selection, now Hendrix Genetics, to optimise methods to incorporate this QTL into selective breeding programmes using genetic markers to select the most resistant fish for breeding. We then improved the technology by comparing the differences in DNA sequence between resistant and susceptible salmon using high-throughput sequencing, and discovered single nucleotide polymorphism (SNP) markers in the genome that showed association with resistance to the IPN virus at the population level [3.2]. Incorporation of these improved SNP markers into selective breeding programmes further improved the accuracy and simplicity of genetic tests that enable the identification of IPN-resistant fish at an early stage from a DNA sample [3.2]. A licence agreement was signed in 2011 to ensure that Hendrix Genetics can apply the tests commercially, including selling to other breeders and producers, for which our unit receives an annual royalty.

New since REF2014: Applying genetic technologies to other diseases of aquaculture
The flagship example of using genetic markers to prevent IPN mortalities has given rise to several projects targeting the use of genomic tools to breed for resistance to other infectious diseases in aquaculture, underpinned by a strategic partnership between our unit and Hendrix Genetics. This partnership won major grant funding to develop and apply new genomic tools to help tackle sea lice, a major continuous problem for salmon aquaculture worldwide. Sea lice are parasites that attach to the skin of salmonid fish and feed on tissue, mucus and blood, causing a significant adverse impact on salmonid health and welfare, and additional environmental concerns due to transfer to wild stocks. The global costs of sea lice prevention and treatments are estimated at GBP800,000,000 per annum, and furthermore, the chemicals used for treatments are stressful to the salmon and can spill over to affect wildlife adjacent to sea farms, particularly crustaceans such as various crab and shrimp species.

Our collaboration with Hendrix Genetics led to the development of the first high-density SNP array – a method for detecting SNPs – for Atlantic salmon. This tool enabled the development and implementation of genomic selection for improved resistance to sea lice [3.3; 3.4]. We then went on to demonstrate that genomic selection to improve resistance to sea lice can be performed very cost-effectively through a combination of high-density SNP platforms with low-density platforms using genotype imputation [3.5]. This improvement in cost-efficiency facilitated commercial adoption of the technology.

In addition, we have pioneered the application of genomics technologies to other aquaculture species. Notably, we were the first to develop a medium-density SNP array for Pacific and European oysters, and to apply this to select for resistance to oyster herpes virus, a major problem experienced in oyster aquaculture worldwide [3.6].

3. References to the research

[3.1] Houston RD, Haley CS, Hamilton A, Guy DR, Tinch AE, Taggart JB, McAndrew BJ, Bishop SC (2008). Major QTL Affect Resistance to Infectious Pancreatic Necrosis in Atlantic Salmon (Salmo salar). Genetics 178: 1109-1115. doi: 10.1534/genetics.107.082974

[3.2] Houston RD, Davey JW, Bishop SC, Lowe NR, Mota-Velasco JC, Hamilton A, Guy DR, Tinch, AE, Thomson ML, Blaxter ML, Gharbi K, Bron JE, Taggart JB (2012) Characterisation of QTL linked and genome-wide restriction site-associated DNA (RAD) markers in farmed Atlantic salmon. BMC Genomics 13, 244. 13:244. doi: 10.1186/1471-2164-13-244

[3.3] Houston, RD, Taggart, JB, Cézard, T, Bekaert, M, Lowe, NR, Downing, A, Talbot, R, Bishop SC, Archibald AL, Bron JE, Penman DJ, Davassi A, Brew F, Tinch AE, Gharbi K & Hamilton A (2014) 'Development and validation of a high density SNP genotyping array for Atlantic salmon (Salmo salar)' *BMC Genomics*, vol. 15(1) 90. doi: 10.1186/1471-2164-15-90

[3.4] Tsai H, Hamilton A, Tinch AE, Guy DR, Bron JE, Taggart JB, Gharbi K, Stear M, Matika, O, Pong-wong R, Bishop S & Houston RD (2016) 'Genomic prediction of host resistance to sea lice in farmed Atlantic salmon populations' *Genetics Selection Evolution*, 48(1), 47. doi: 10.1186/s12711-016-0226-9

[3.5] Tsai H-Y, Matika O, Hoj-Edwards S, Antolin R, Hamilton A, Guy DR, Tinch AE, Gharbi K, Stear MJ, Taggart JB, Bron JE, Hickey JM & Houston RD (2017) 'Genotype Imputation to Improve the Cost-Efficiency of Genomic Selection in Farmed Atlantic Salmon' *G3*, 7(4) pp. 1377-1383. doi: 10.1534/g3.117.040717

[3.6] Gutierrez AP, Turner F, Gharbi K, Talbot R, Lowe NR, Peñaloza C, McCullough M, Prodöhl PA, Bean TP & Houston RD (2017) 'Development of a Medium Density Combined-Species SNP Array for Pacific and European Oysters (Crassostrea gigas and Ostrea edulis)', *G3*, 7(7) pp. 2209-2218. doi: 10.1534/g3.117.041780

4. Details of the impact

Continued from REF2014: Impact on salmon mortality from IPN

The adoption of MAS to combat IPN was reported in REF2014, but at the time, no real-world data were available to demonstrate reductions in salmon mortality from IPN. Data is now available from Mowi, the world's largest producer of Atlantic salmon, to illustrate the marked impact of marker-assisted selection (MAS) on salmon mortality from IPN: since the implementation of MAS in 2009, salmon deaths from IPN in Norway have fallen from approximately 16,000,000 per year to near zero in 2014 and remaining at that level in 2019 (**Figure 1**) [5.1].

By 2015, IPN had been eradicated to the point where it is no longer a notifiable disease by the Veterinary Institute of Norway, meaning that official statistics of IPN losses are no longer recorded; however, losses have remained close to zero, according to communication from the heads of Mowi and Benchmark salmon breeding programmes (**Figure 1**; [5.2a, b]).

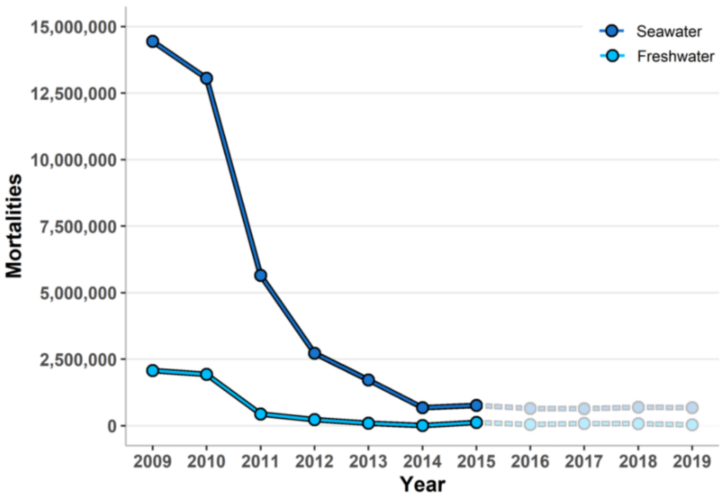

Figure 1. The reduction in farmed Atlantic salmon IPN-related mortality in Mowi's salmon farms in Norway due to the implementation of MAS. Source: Norris (2017) *Marine Genomics* [5.1], and since 2015 communication from the Lead Geneticist at Mowi [5.2a] and the Head of Fish Health and Director of Genetics at Benchmark [5.2b].

Continued from REF2014: Economic impact

Following our collaboration, in 2008 Hendrix Genetics became the first company in the world to implement MAS for IPN resistance into the production of all eggs and smolt (young salmon) for sale. Hendrix sells IPN-resistant eggs and smolt directly to commercial salmon farmers, covering 10% of the global market for Atlantic salmon in 2020. In addition to this 10% market share from direct sales, since 2011 Hendrix has licenced the intellectual property required to generate IPN-resistant eggs and smolts to several other salmon breeding and production companies throughout Norway, Chile and Scotland (the 3 largest salmon-producing countries in the world). The number of these Hendrix customers has increased since 2011, such that by 2020 they held a combined market share of approximately 20% [5.3]. Thus, IPN-resistant stocks of salmon directly derived from our research account for approximately 30% of the global salmon market.

An independent economic analysis [5.3] showed that between August 2013 and July 2020, the application of our research to reduce IPN outbreaks has averted the death of 8,000,000-18,000,000 salmon smolts in Norway, Chile and Scotland, and thus increased production of salmon by between 36,800 and 79,600 tonnes across the 3 countries. The total value of this increased production, after accounting for feeding costs, has been between GBP108,000,000 and GBP234,000,000 to the global salmon farming industry. **Figure 2** below illustrates the cumulative additional outputs of salmon and associated cumulative financial gains that IPN resistance has conferred to the industry.

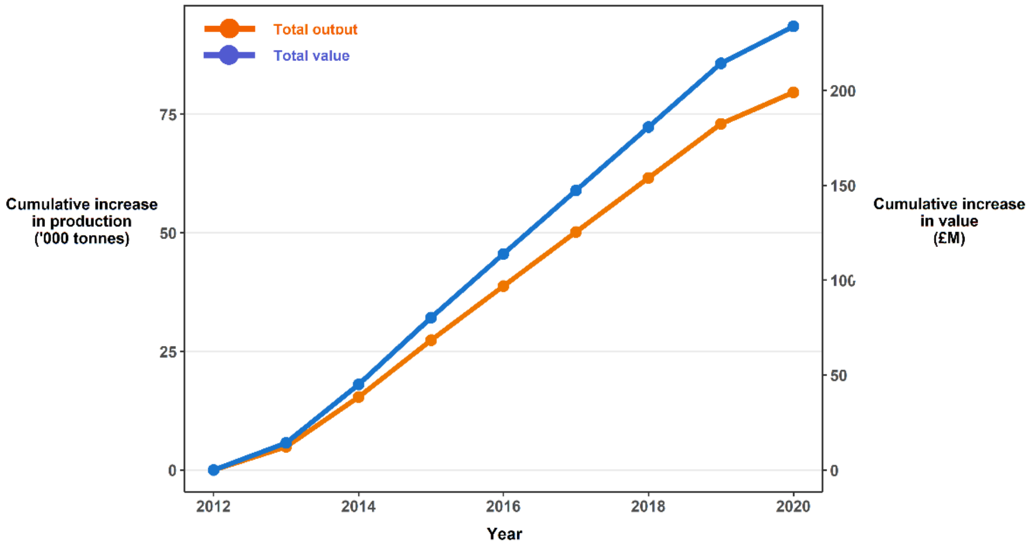

Figure 2. Cumulative gain, at upper limit of estimated range, in annual production as tonnes of gutted weight, of Atlantic Salmon and its value in Chile, Norway and Scotland from 2013 to 2020, due to IPN resistance [5.3].

New since REF2014: Impact on aquaculture industry in wider adoption of genomic tools for disease prevention

The success of our approach based on a QTL for IPN in tackling a major infectious disease problem for salmon breeding sparked substantial interest and investment from industry into the use of genetics technologies as a means of disease prevention in aquaculture more widely.

The Director of Norway's Akvaforsk Genetics Centre, who is a global authority on aquaculture genetics with more than 20 years' experience in commercial salmon breeding, confirmed: *"The successful example of IPN triggered rapid implementation of genomic technologies across the salmon genetics sector. Today we see a clear similar trend for the uptake of genomic tools in selection programs for a number of other aquaculture species also, including shrimps, marine fish, and tilapias."* [5.4].

As an example of this wider uptake of genomic tools, the SNP array we developed to select oysters for resistance to oyster herpes virus was made commercially available in 2019. Since then, it has been widely applied across the world, with 8,064 arrays sold in countries including Australia, New Zealand, France, Spain, USA, and Mexico in the first year [5.5a]. Since severe outbreaks of oyster herpes virus can result in the loss of up to 90% of stock, and individual farms may take up to 10 years to return to economically viable levels of production following such an outbreak, improved resistance will result in significant benefits to the industry [5.5b].

New since REF2014: Impact on breeding sea lice resistant salmon stocks

As sea lice are now the single largest problem for the global salmon farming industry, and our research has developed the tools needed to breed stock with improved sea lice resistance, this has become a primary target trait for improvement using genomic selection. The world's primary salmon breeding and production companies have begun to incorporate MAS and genomic selection methods into their routine breeding programmes; since 2014, Hendrix has sold eggs and smolts only from stock selected for sea lice resistance [5.6].

Due to the 4-year interval between generations of Atlantic salmon, the impact of improved resistance to sea lice has yet to be fully realised. However, with current treatment costs for sea lice estimated at GBP800,000,000 per year, the improvements achieved by genomic selection are beginning to have a significant, cumulative economic impact through reduction in treatment costs. By 2026, the reduced treatment costs are estimated to result in savings of GBP24,000,000 per year. This figure is based on: 1) our research showing that genetic gain for resistance is 27% higher per generation with genomic selection compared with the previously-used pedigree selection and 2) an independent preliminary analysis suggesting that such improved resistance may result in 10% fewer treatments being required per year after 4 generations of selection [5.7]. Given Hendrix's 30% of the global market share, a 10% reduction in treatments would translate to savings of approximately GBP24,000,000 per year.

Furthermore, improved resistance to sea lice brings additional benefits through improved health and welfare of farmed salmon, reduced transfer of sea lice from farmed to wild fish, and reduced spill-over of chemicals from sea farms to adjacent wild habitats.

The importance of the genomic tools that our research has developed has been recognised by the Scottish Government-funded Scottish Aquaculture Innovation Centre in its 2017 vision for the sector: "*Genomic selection […] is already having a dramatic impact in several farmed animal species*." [5.8]. In addition, an article in the Scottish Herald newspaper on 10 April 2020 entitled "*'Super' salmon project could end the scourge of sea lice*" describes our work as a cost-effective way to both improve animal welfare and production and to safeguard the wild marine environment which is adversely affected by anti-louse treatments [5.9].

5. Sources to corroborate the impact

[5.1] Norris, A. Application of genomics in salmon aquaculture breeding programs by Ashie Norris: Who knows where the genomic revolution will lead us? 2017 *Marine Genomics* 36, 13-15. doi: 10.1016/j.margen.2017.11.013

[5.2] Emails from major salmon breeding companies to attest to continued absence of IPN outbreaks since 2015 a. Email from Lead Geneticist at Mowi, 12th May 2020 b. Email trail including information from Head of Fish Health at Benchmark Genetics and Director of Genetics at Benchmark, 14th May 2020, containing the quote: "*I have spoken to others lately in the matter and they have the same answer. One large company in Norway have had one outbreak due to IPN since 2014. Another one of the largest players have had 2 to 3 in the same 5 year period. This is in comparison to around 200 outbreaks in the year 2010*"

[5.3] Economic impact report from AbacusBio Ltd

[5.4] Email statement from Director of Norway's Akvaforsk Genetics Center, 20th May 2020.

[5.5] a. Email from Thermo Fisher Scientific re: sales of oyster herpes virus SNP array b. Aquaculture Alliance website article on 31st July 2017 on oyster SNP array

[5.6] Hendrix website attesting to having implemented IPN and sea lice resistance in all eggs

[5.7] Gharbi K, Matthews M, Bron J, Roberts R, Tinch A and Stear M. (2015) The control of sea lice in Atlantic salmon by selective breeding *Journal of The Royal Society Interface* doi: 10.1098/rsif.2015.0574

[5.8] Scottish Government report (2017) "Scottish Aquaculture: Vision towards 2030", p. 36

[5.9] "Super salmon project could end the scourge of sea lice" article in the *Scottish Herald*, 10th April 2020.