TOMORROW'S CATCH

Genomic technologies promise dramatic gains for aquaculture by accelerating the breeding of better strains

By **Erik Stokstad**

Two years ago, off the coast of Norway, the blue-hulled *Ro Fjell* pulled alongside Ocean Farm 1, a steel-netted pen the size of a city block. Attaching a heavy vacuum hose to the pen, the ship's crew began to pump brawny adult salmon out of the water and into a tank below deck. Later, they offloaded the fish at a shore-based processing facility owned by SalMar, a major salmon aquaculture company.

The 2018 harvest marked the debut of the world's largest offshore fish pen, 110 meters wide. SalMar's landmark facility, which dwarfs the typical pens kept in calmer, coastal waters, can hold 1.5 million fish—with 22,000 sensors monitoring their environment and behavior—that are ultimately shipped all over the world. The fish from Ocean Farm 1 were 10% larger than average, thanks to stable, favorable temperatures. And the deep water and strong currents meant they were free of parasitic sea lice.

Just a half-century ago, the trade in Atlantic salmon was a largely regional affair that relied solely on fish caught in the wild. Now, salmon farming has become a global business that generates $18 billion in annual sales. Breeding has been key to the aquaculture boom. Ocean Farm 1's silvery inhabitants grow roughly twice as fast as their wild ancestors and have been bred for disease resistance and other traits that make them well suited for farm life. Those improvements in salmon are just a start: Advances in genomics are poised to dramatically reshape aquaculture by helping improve a multitude of species and traits.

Genetic engineering has been slow to take hold in aquaculture; only one genetically modified species, a transgenic salmon, has been commercialized. But companies and research institutions are bolstering traditional breeding with genomic insights and tools such as gene chips, which speed the identification of fish and shellfish carrying desired traits. Top targets include increasing growth rates and resistance to disease and parasites. Breeders are also improving the hardiness of some species, which could help farmers adapt to a shifting climate. And many hope to enhance traits that please consumers, by breeding fish for higher quality fillets, eye-catching colors, or increased levels of nutrients. "There is a paradigm shift in taking up new technologies that can more effectively improve complex traits," says Morten Rye, director of genetics at Benchmark Genetics, an aquaculture breeding company.

PHOTO: HENDRIX GENETICS

At research pens in Chile (left) researchers develop strains of farmed Atlantic salmon (right) that grow faster and stay healthier.

Aquaculture breeders can tap a rich trove of genetic material; most fish and shellfish have seen little systematic genetic improvement for farming, compared with the selective breeding that chickens, cattle, and other domesticated animals have undergone. "There's a huge amount of genetic potential out there in aquaculture species that's yet to be realized," says geneticist Ross Houston of the Roslin Institute.

Amid the enthusiasm about aquaculture's future, however, there are concerns. It's not clear, for example, whether consumers will accept fish and shellfish that have been altered using technologies that rewrite genes or move them between species. And some observers worry genomic breeding efforts are neglecting species important to feeding people in the developing world. Still, expectations are high. "The technology is amazing, it's advancing very quickly, the costs are coming down," says Ximing Guo, a geneticist at Rutgers University, New Brunswick. "Everybody in the field is excited."

FISH FARMING may not have roots as old as agriculture, but it dates back millennia. By about 3500 years ago, Egyptians were raising gilt-head sea bream in a large lagoon. The Romans cultivated oysters. And carp have been grown and selectively bred in China for thousands of years. Few aquaculture species, however, saw systematic, scientific improvement until the 20th century.

One species that has received ample attention from breeders is Atlantic salmon, which commands relatively high prices. Farming began in the late 1960s, in Norway. Within 10 years, breeding had helped boost growth rates and harvest weight. Each new generation of fish—it takes salmon 3 to 4 years to mature—grows 10% to 15% faster than its forebears. "My colleagues in poultry can only dream of these kinds of percentages," says Robbert Blonk, director of aquaculture R&D at Hendrix Genetics, an animal breeding firm. During the 1990s, breeders also began to select for improved disease resistance, fillet quality, delayed sexual maturation (which boosts yields), and other traits.

Another success story involves tilapia, a large group of freshwater species that doesn't typically bring high prices but plays a key role in the developing world. An international research center in Malaysia, now known as WorldFish, began a breeding program in the 1980s that quickly doubled the growth rate of one commonly raised species, Nile tilapia. Breeders also improved its disease resistance, a task that continues because of the emergence of new pathogens, such as tilapia lake virus (*Science*, 6 March, p. 1064).

Genetically improved farmed tilapia "was a revolution in terms of tilapia production," says Alexandre Hilsdorf, a fish geneticist at the University of Mogi das Cruzes in Brazil. China, a global leader in aquaculture production, has capitalized on the strain, building the world's largest tilapia hatchery. It raises billions of young fish annually.

Now, aquaculture supplies nearly half of the fish and shellfish eaten worldwide (see chart, p. 904), and production has been growing by nearly 4.5% annually over the past decade—faster than most sectors of the farmed food sector. That expansion has come with some collateral damage, including pollution from farm waste, heavy catches of wild fish to feed to penned salmon and other species, and the destruction of coastal wetlands to build shrimp ponds. Nevertheless, aquaculture is now poised for further acceleration, thanks in large part to genomics.

Breeders are most excited about a technique called genomic selection. To grasp why, it helps to understand how breeders normally improve aquaculture species. They start by crossing two parents and then, out of hundreds or thousands of their offspring, select individuals to test for desired traits. Advanced programs make hundreds of crosses in each generation and choose from the best performing families for breeding. But some tests mean the animal can't later be used for breeding; measuring fillet quality is lethal, for instance, and screening for disease resistance requires quarantining the infected individual. As a result, when researchers identify a promising animal, they must pick a sibling to use for breeding—and hope that it performs just as well.

With genomic selection, researchers can identify siblings with high-performance traits based on genetic markers. All they need is a small tissue sample—such a clipping from a fin—that can be pureed and analyzed. DNA arrays, which detect basepair changes called single nucleotide polymorphisms (SNPs), allow breeders to thoroughly evaluate many siblings for multiple traits. If the pattern of SNPs indicates that an individual carries optimal alleles, it can be selected for further breeding even if it hasn't been tested. Genomic analyses also allow breeders to minimize inbreeding.

Cattle breeders pioneered genomic selection. Salmon breeders adopted it a few years ago, followed by those working with shrimp and tilapia. As a rough average, the technique increases selection accuracy and the amount of genetic improvement by about 25%, Houston says. It and other tools are helping researchers pursue goals such as:

FASTER GROWTH

This trait improves the bottom line, allowing growers to produce more frequent and bigger hauls. Growth is highly heritable and easy to measure, so traditional breeding works well. But breeders have other tactics for boosting growth, including providing farmers with fish of a single sex. Male tilapia, for example, can grow significantly faster than females. Another strategy is to hybridize species. The dominant farmed catfish in the United States, a hybrid of a female channel catfish and a male blue catfish, grows faster and is hardier.

Inducing sterility stimulates growth, too, and has helped raise yields in shellfish, particularly oysters. In the 1990s, Guo and Standish Allen, now at the Virginia Institute of Marine Science, figured out a new way to create triploid oysters, which are infertile because they have an extra copy of each chromosome. These oysters don't devote much energy to reproduction, so they reach harvest size sooner, reducing exposure to disease. (When oysters reproduce, more than half their body consists of sperm or eggs, which no one wants to eat.)

Looking ahead, researchers are exploring gene transfer or gene editing to further enhance gains. And one U.S. company, AquaBounty, is just beginning to sell the world's first transgenic food animal, an Atlantic salmon, that it claims is 70% more productive than standard farmed salmon. But the fish is controversial and has faced consumer resistance and regulatory hurdles.

HEALTHIER FISH

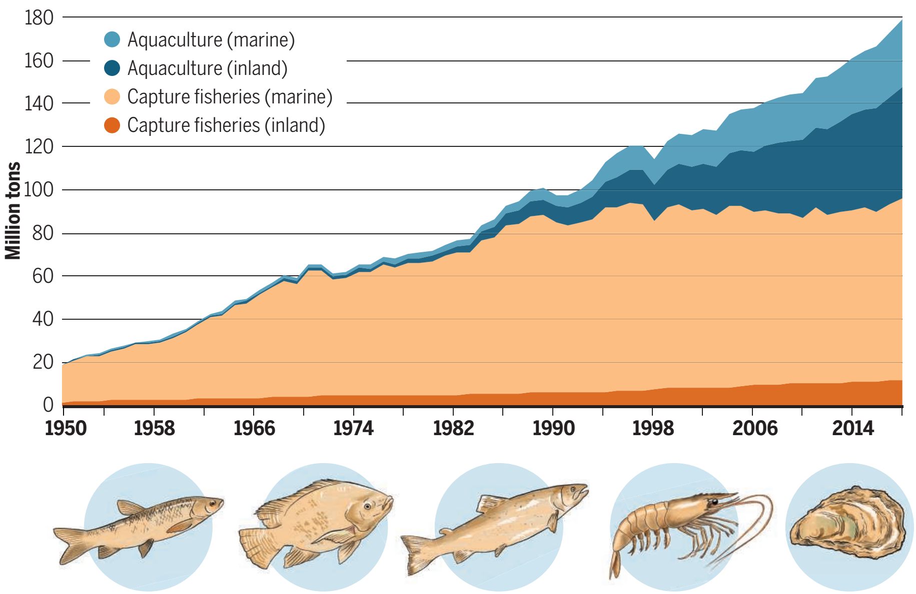
Disease is often the biggest worry and expense for aquaculture operations. In shrimp, outbreaks can slash overall yield by up to 40% annually and can wipe out entire operations. Vaccines can prevent some diseases in fish, but not invertebrates, because their adaptive immune systems are less developed. So, for all species, resistant strains are highly desirable.

To improve disease resistance, researchers need a rigorous way to test animals. Thanks to a collaboration with fish pathologists at the U.S. Department of Agriculture (USDA), Benchmark Genetics was able to screen tilapia for susceptibility to two major bacterial diseases by delivering a precise dose of the pathogen and then measuring the response. They identified genetic markers correlated with infection and used genomic selection to help develop a more resistant strain. USDA scientists have also worked with Hendrix Genetics to increase the survival of trout exposed to a different bacterial pathogen from 30% to 80% in just three generations.

Perhaps the most celebrated success has been in salmon. After researchers discovered a genetic marker for resistance to infectious pancreatic necrosis, companies quickly bred strains that can survive this deadly disease. Oyster breeders, meanwhile, have had success in developing strains resistant to a strain of herpes that devastated the industry in France, Australia, and New Zealand.

A rising tide

Aquaculture is rivaling catches from wild fisheries and is projected to increase. Much of the growth comes from freshwater fish in Asia, such as grass carp, yet most research has focused on Atlantic salmon and other high-value species. Genomic technology is now spreading to shrimp and tilapia.



	Grass carp	Nile tilapia	Atlantic salmon	Whiteleg shrimp	Pacific cupped oyster
Value ($ billions)	12.6	7.6	16.7	26.7	1.2
Harvest (thousand tons, annually)	5704	4525	2436	4966	644
***First research on breeding**	2010	1989	1971	1995	1984

*First scientific report of breeding for a specific trait

PARASITE-RESISTANT SALMON

A big problem for Atlantic salmon growers is the sea louse. The tiny parasite clings to the salmon's skin, inflicting wounds that damage or kill fish and make their flesh worthless. Between fish losses and the expense of controlling the parasites, lice cost growers more than $500 million a year in Norway alone. Lice are attracted to fish pens and can jump to wild salmon that pass by.

For years farmers have relied on pesticides to fight lice, but the parasite has become resistant to many chemicals. Other techniques, such as pumping salmon into heated water, which causes the lice to drop off, can stress the fish.

Researchers have found that some Atlantic salmon are better than others at resisting lice, and breeders have been trying to improve this trait. So far, they've had modest success. Better understanding why several species of Pacific salmon are immune to certain lice could lead to progress. Scientists are exploring whether sea lice are attracted to certain chemicals released by Atlantic salmon; if so, it's possible these could be modified with gene editing.

STERILE STOCK

No sex on the farm. That's a goal with many aquaculture species, because reproduction diverts energy from growth. Moreover, fertile fish that escape from aquaculture operations can cause problems for wild relatives. When wild fish breed with their domesticated cousins, for instance, the offspring are often less successful at reproducing.

Salmon can be sterilized by making them triploid, typically by pressurizing newly fertilized embryos in a steel tank when the chromosomes are replicating. But this can have side effects, such as greater susceptibility to disease. Anna Wargelius, a molecular physiologist at Norway's Institute of Marine Research, and colleagues have instead

CREDITS: (GRAPHIC) N. DESAI/SCIENCE; (DATA, TOP TO BOTTOM) FOOD AND AGRICULTURE ORGANIZATION OF HE UNITED NATIONS; HOUSTON ET AL., NATURE REVIEWS GENETICS 21, 389 (2020)

The fecundity of most aquatic species, like this trout (left), helps breeding efforts. Salmon eggs, 0.7 millimeters wide, are robust and easy for molecular biologists to work with.

PHOTOS: HENDRIX GENETICS

altered the genes of Atlantic salmon to make them sterile, using the genome editor CRISPR to knock out a gene called *deadend*. In 2016, they showed that these fish, though healthy, lack germ cells and don't sexually mature. Now, they're working on developing fertile broodstock that produce these sterile offspring for hatcheries. Embryos with the knocked-out genes should develop into fertile adults if injected with messenger RNA, according to a paper the group published last month in *Scientific Reports*. When these fish mature later in December, they will try to breed them. "It looks very promising," Wargelius says.

Another approach would not involve genetic modifications. Fish reproductive physiologists Yonathan Zohar and Ten-Tsao Wong of the University of Maryland, Baltimore County, are using small molecule drugs to disrupt early reproductive development so that fish mature without sperm or eggs.

BONE-FREE FILLETS

Cooks and diners hate bones. Nearly half of the top species in aquaculture are species of carp or their relatives, which are notorious for the small bones that pack their flesh. These bones can't be easily removed during processing, so "you can't just get a nice, clean fillet," says Benjamin Reading, a reproductive physiologist at North Carolina State University.

Researchers are studying the biology of these fillet bones to see whether they might one day be removed through breeding or genetic engineering. A few years ago, Hilsdorf heard that a Brazilian hatchery had discovered mutant brood stock of a giant Amazonian fish, the widely farmed tambaqui, that lacked these fillet bones. After trying and failing to breed a boneless strain, he's studying tissue samples from the mutants for clues to their genetics.

Geneticist Ze-Xia Gao of Huazhong Agricultural University is focusing on blunt snout bream, a carp that is farmed in China. Guided by five genetic markers, she and colleagues are breeding the bream to have few fillet bones. It could take 8 to 10 years to achieve, she says. They have also had some success with gene editing—they've identified and knocked out two genes that control the presence of fillet bones—and they plan to try the approach in other carp species. "I think it will be feasible," Gao says.

NEW ITEMS FOR THE MENU

Aquaculture projects worldwide are hustling to domesticate new species—a kind of gold rush rare in terrestrial farming. In New Zealand, researchers are domesticating native species because they are already adapted to local conditions. The New Zealand Institute for Plant and Food Research began to breed the Australasian snapper in 2004. Early work concentrated on simply getting the fish to survive and reproduce in a tank. One decade later, researchers started to breed for improved growth, and they've since increased juvenile growth rates by 20% to 40%.

Genomic techniques have proved critical. Snapper are mass spawners, so it was hard for breeders to identify the parents of promising offspring, which is crucial for optimizing selection and avoiding inbreeding. DNA screening solved that problem, because the markers reveal ancestry. The institute is also breeding another local fish, the silver trevally, aiming for a strain that will reproduce in captivity without hormone implants. "It's a long-term effort to breed a wild species to make it suitable for aquaculture," says Maren Wellenreuther, an evolutionary geneticist at the New Zealand institute and the University of Auckland.

THESE BREEDING EFFORTS require money. Despite the growth of aquaculture, the field's research funding lags the amounts invested in livestock, although some governments are boosting investments.

Looking globally, geneticist Dennis Hedgecock of Pacific Hybreed, a small U.S. company that is developing hybrid oysters, sees a "huge disparity" between breeding investment in developed countries—which produce a fraction of total harvests but have the biggest research budgets—and the rest of the world. Simply applying classical breeding techniques could rapidly improve production, especially in the developing world, he says. Yet the hundreds of species now farmed could overwhelm breeding programs, especially those aimed at enhancing disease resistance, Hedgecock adds. "The growth and the production is outstripping the scientific capability of dealing with the diseases," he says, adding that a focus on fewer species would be beneficial.

For genomics to help, experts say costs must continue to come down. One promising development in SNP arrays, they note, is a technique called imputation, in which cheaper arrays that search for fewer genetic changes are combined with a handful of higher cost chips that probe the genome in more detail. Such developments suggest genomic technology is "at a pivot point where you're going to see it used broadly in aquaculture," says John Buchanan, president of the Center for Aquaculture Technologies, a contract research organization.

Many companies are already planning for larger harvests. SalMar will decide next year whether it will order a companion to Ocean Farm 1. It has already drawn up plans for a successor that can operate in the open ocean and would be more than twice the size, big enough to hold 3 million to 5 million salmon at a time. ■

Science

Tomorrow's catch

Erik Stokstad

Science **370** (6519), 902-905.
DOI: 10.1126/science.370.6519.902

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005. The title *Science* is a registered trademark of AAAS.