New Cereal Value Chain: From Seed to Sewage[1]

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The concept of integrating technological and industry development along the cereal value chain has been captured in alliterative catchphrases such as "farm to fork" or "paddock to plate" that emphasize the close connection between the production and end-use of cereals. These opportunities for value addition can also be extended through modification of grain genetics upstream of the farm to deliver improved health-promoting attributes to consumers.

This article will discuss some of the scientific and industry opportunities made available by powerful recent developments in both cereal genetics and human nutrition science. It will also discuss ways in which delivering on the potential of specific opportunities will likely require different approaches to management of and value sharing in the cereal supply and utilization chain. In searching for a new alliterative catchphrase, the phrase "seed to sewage" has been coined to capture the advanced genetics built into the seed and to emphasize the fact that the value proposition for cereals does not end with consumption of a tasty, appealing cereal-based food but continues as that food interacts with the physiology of the consumer, delivering additional benefits to both the individual and society through improved public health.

A range of opportunities exists in the cereal value chain for the creation of differentiated products, from differentiation of processing quality through genetics to identity preservation, milling and processing innovation, food formulation and design, packaging, and marketing (Fig. 1). There is ongoing active exploitation of each of these innovation windows, either singly or in combination, in different cereal production and consumption regions around the world. Rather than replacing these established innovation windows, the linkage of cereal genetics to the human health-promoting attributes of grains provides another mechanism for value addition, and industry innovations are likely to involve combinations of these windows. For example, novel processing approaches may be required to fully exploit the potential of cereals with altered compositions and functionalities. Some strengths and weaknesses of technical innovation mechanisms are described in Table I.

In the past, cereal grains were considered almost exclusively as a source of calories and essential nutrients such as amino acids, minerals, and vitamins. However, over the past two decades a more sophisticated understanding of the role of whole grains, dietary fiber, and starch in the human diet has been developed. The case for consumption of whole grains is supported strongly by epidemiological studies showing that consumption of whole-grain foods can reduce the relative risks for a range of conditions, including cardiovascular disease, type 2 diabetes, and colorectal cancer (11,17). Innovations in production of whole-grain foods with consumer appeal encompass milling, processing, and food formulation and are rarely based on specific differentiation of the raw material outside grain commodity grades. Clearly, there are opportunities to add to the impact of whole grains on diet through further genetic tailoring of fiber and other constituents in grains.

The rapid expansion of information on the nutritional benefits of cereals beyond the supply of calories and essential nutrients has been critical to guiding research aimed at developing cereals with enhanced potential to reduce the risk of diet- and lifestyle-related diseases and emerging conditions such as gluten intolerance. The following sections illustrate examples of efforts aimed at delivering significant nutritional innovations through manipulation of cereal genetics. Examples are largely drawn from the CSIRO Food Futures Flagship program in Australia. However, there are a number of other active global efforts with similar objectives underway.

Nutritional Benefits

Dietary Fiber. No area of cereal nutrition better illustrates the change in our understanding of the role of cereal constituents in the diet than the mechanisms of action and potential health benefits of fiber. Originally considered an inert "roughage" with a primary role in constipation relief and regularity, our understanding of dietary fiber has evolved to include the role of dietary fiber in modulating glycemic response, enhancing metabolic and cardiovascular health, promoting bowel health, improving mineral bioavailability, reducing the risk of colorectal cancer, and (potentially) improving immune function and reducing the risk of inflammatory conditions. The health benefits of increasing dietary fiber consumption are supported by a strong body of epidemiological evidence and increasing numbers of human nutrition studies. This is an area where the pace of research discoveries is moving rapidly, and there is substantial room for the evidence base to be extended and deepened to a level where regulatory approval of specific health claims can be contemplated. In this process, some promising leads may not yet have achieved the evidence base required. An essential aspect of moving the field forward is to appreciate that each of the individual classes of dietary fiber contributes in different degrees to modulation of human physiological processes depending on their physical functionality, site of digestion, and interaction with gut microflora.

Four classes of polymers contribute the majority of the dietary fiber components found in cereal grains: arabinoxylans, β-glucans, fructo-oligosaccharides, and resistant starch. Current total dietary fiber intakes are low in populations at high risk of diet-related illnesses, so increasing total dietary fiber consumption is a significant objective in its own right. However, there are three additional dimensions that need to be considered. First, the majority of the

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Table I. Strengths and weaknesses of technical innovation mechanisms

Mechanism	Innovation	Potential Advantages	Potential Disadvantages
Genetic differentiation	Increased fiber content Increased resistant starch content	Traditional Clean label possible Diversification/value addition opportunities Can be combined with whole-grain claim Avoids cost and complexity of regulatory processes Consumer acceptance Highly scalable—from thousands to millions of tonnes Genetic modification Step change innovation possible through diverse genetics Yield penalty can be eliminated/minimized by tissue-specific modifications Value addition can be enhanced by stacking traits Dominant genetic traits Production highly scalable	Traditional Possible yield penalty Identity preservation required Innovation opportunities limited to modification of existing genetics Magnitude of differentiation may be incremental rather than step change Recessive traits increase genetic complexity Genetic modification Identity preservation required Regulatory approval required Product labeling may be required Consumer acceptance issues in many countries
Milling and fractionation technologies	Optimized milling streams Aleurone-enriched fractions	Tolerant of diverse raw material sources Can increase bioavailability of constituents Clean label No regulatory implications	May exclude whole-grain claim Requires infrastructure and expertise Innovation opportunities restricted by composition/properties of cereal substrate
Post-fractionation modifications	Heat-treated flours Enzyme digestion Chemically modified starches	May tolerate a wide variety of raw material sources Broad range of altered functionalities possible Modification process can be attenuated to deliver targeted functionality	May require product labeling Regulatory approval may be required Modification process requires infrastructure and expertise Production scalability limits may apply—available infrastructure and investment capacity may limit production volumes

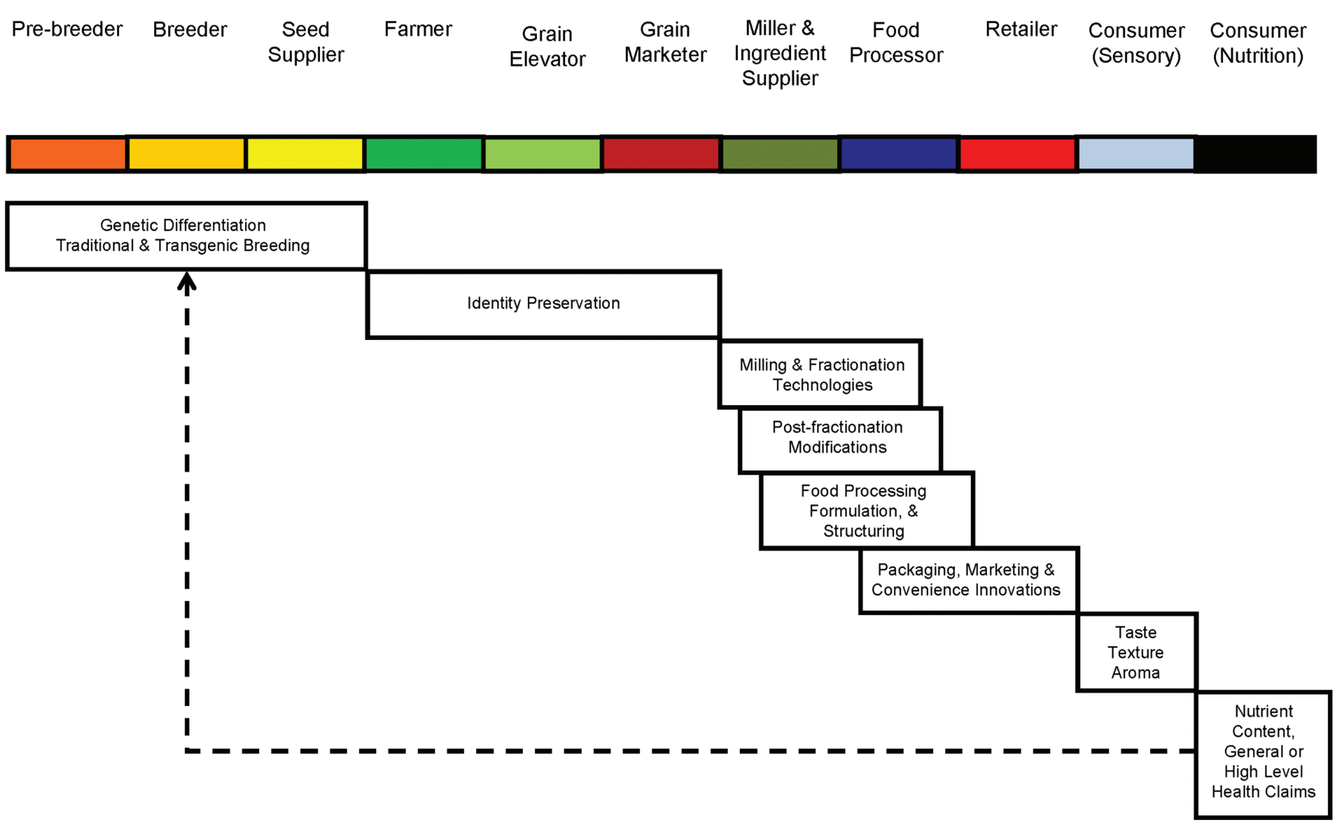

Fig. 1. Schematic representation of a "typical" cereal value chain. The dashed line shows the interaction between the nutritionist and the cereal geneticist that underpins innovation in grains that deliver health benefits for consumers.

dietary fiber contained in cereal grains is located in the bran layers, which are removed during production of simple refined flours. Increasing the dietary fiber composition of the endosperm is an attractive target because it could increase the dietary fiber composition of foods that appeal to a broad range of consumers who do not traditionally consume whole-grain products. Second, different polymers have different impacts on gastrointestinal functionality, and as will be discussed later, substantially different health impacts could be derived from increasing different dietary fiber components. Third, altering the composition of dietary fiber (through the alteration of total molecular weight, polymer fine structure, or polymer aggregation state) could influence the physiological functionality of the resultant dietary fiber. Examples of each of these strategies are provided below.

- **BARLEYmax.** The identification of high-amylose barley germplasm following sodium azide mutagenesis (18) formed the basis for the development of high-amylose barley varieties (trademarked as BARLEYmax) and the substantiation of a range of gastrointestinal and metabolic benefits in animal (1,2) and human trials (4,15). Breakfast cereals and porridge products utilizing BARLEYmax have been commercially exploited in Australia since 2009 (http://goodnesssuperfoods.com.au/).
- **β-Glucans.** Identification of the key genes, *CslF* (9) and *CslH* (12), responsible for the synthesis of mixed linkage (1,3:1,4)-β-ᴅ-glucan has resulted in the development of successful strategies for the transgenic manipulation of β-glucan content (8). Increasing the β-glucan content of wheat using transgenic wheat technology remains a primary focus of the High Fibre Grains collaboration involving the Universities of Adelaide, Melbourne, Queensland, and CSIRO in Australia.
- **Fructans.** Based on the standard approved by the Codex Alimentarius Commission, oligosaccharides with a degree of polymerization (DP) ≥3 can be classified as components of dietary fiber. Under the Codex standard, individual countries still have discretion in whether to include oligosaccharides with DP 3–10 as components of dietary fiber. Cereal fructans have been isolated from sources with elevated fructan levels (14) and, using in vitro fermentation techniques, have been demonstrated to generate short-chain oligosaccharide profiles similar to commercial inulins.

Starch Digestibility. Both the rate and extent of starch digestion in the small intestine can influence metabolic and gastrointestinal health outcomes. Decreasing the extent of starch digestion in the small intestine leaves additional starch available to enter the large bowel; such starch is termed resistant starch. Resistant starch is accepted as a contributor to total dietary fiber, and there is increasing evidence that it has unique benefits compared with other dietary fiber fractions. These additional benefits are mediated by its physical interaction with the gut microflora and its fermentation to short-chain fatty acids (particularly butyrate) by these microorganisms. The benefits are enhanced through passage of fermentation products to the distal colon, enhancing the health of the entire organ (23). High-amylose maize starch has been studied extensively as a source of resistant starch that is derived from a mutation in the branching enzyme IIb gene (5,7). In wheat, RNAi interference has been used to down-regulate branching enzyme genes in endosperm, resulting in the generation of wheat varieties with amylose contents >70% (20). Studies with rats have confirmed that consumption of high-amylose wheat results in changes in indices of bowel health typical of the consumption of high-amylose starches—increased levels of total short-chain fatty acids (including butyrate) in the cecum and reduction in the pH of the gastrointestinal lumen (20).

Decreasing the rate of starch digestibility lowers the glycemic impact of a meal (as measured by the rise in blood glucose levels) and is associated with reduction of the risk of developing type 2 diabetes and improved management of the condition (6). Polished white rice, in particular, is characterized by a very low dietary fiber content and, generally, high starch digestibility. Although the high starch digestibility characteristics of rice are beneficial in situations where consumers are engaged in physical activities such as manual labor or crop production, high starch digestibility coupled with a sedentary lifestyle is an unfortunate combination in areas where rural populations are becoming increasingly urbanized, as is occurring in Southeast Asia and the Indian subcontinent. Low glycemic index (GI) rice varieties have been produced on an occasional basis (e.g., the variety Doongarra in Australia); however, the genetic tools to reliably generate low GI rices with acceptable sensory profiles have been lacking. Recently, Fitzgerald et al. (13) identified a strong relationship between amylose content and glycemic response in rice that will be important in future rice breeding efforts.

Modified Oils. While primarily targeted at modifying oilseeds, the science and technology now exists to modify the oil composition of cereals to increase the supply of oils with health benefits, including omega-6 fatty acids (γ-linolenic and arachidonic acids) and omega-3 fatty acids (stearidonic acid [SDA], eicosapentaenoic acid [EPA], and docosahexaenoic acid [DHA]) (19,21). Given that only a small subset of land plants can synthesize omega-3 oils as long as SDA, genetic engineering methods are required to extend the endogenous pathway through to EPA, DPA (docosapentaenoic acid), and DHA.

Micronutrients

Vitamin and mineral deficiencies are relatively rare in developed countries and can be managed relatively easily through supplementation. However, vitamin A, iron, and zinc deficiencies are more common in developing countries, where the resources to apply supplementation strategies are limited. Because these deficiencies have profound effects on these populations, nutrient delivery through staple cereals provides a robust and efficient mechanism for influencing the health of billions of people. Significant resources have been devoted to developing transgenic rice (e.g., Golden Rice) that contains vitamin A precursors and identification of cereals with increased iron and zinc contents (www.harvestplus.org/content/nutrients).

Advances in Cereal Genetics and Opportunities for Differentiation

Genetic Engineering. Over the last decade, massive expansion in our knowledge of cereal genetics has occurred through genome sequencing projects and the development of high-throughout and cost-effective molecular marker systems. In parallel, techniques for the genetic engineering of cereals and the availability of key gene sequences have increased. The following developments in traditional breeding have particular promise for developing differentiated cereals for improved food sensory and nutritional attributes.

- **TILLING (Targeting Induced Local Lesions in Genomes).** The development of techniques for the generation and/or identification of sequence variations in plant genomes has dramatically increased the power of strategies for the identification of sequence variations in cereal genes. TILLING techniques (22) provide a powerful mechanism for identifying allelic series of mutations in key target genes. In wheat, the hexaploid nature of the genome allows high mutagenic loads to be tolerated, allowing the efficient recovery of mutants. An alternative route for identifying genetic diversity relies on the use of deep sequencing technologies to efficiently screen large numbers of genes in diverse germplasm to identify naturally occurring gene variants with the potential to be introgressed into elite germplasm. Both technologies illustrate the power of modern molecular breeding techniques to identify and harness specific mutations to generate useful and differentiated phenotypic diversity.
- **"Smart Breeding."** While genetic resources such as genome sequences and molecular markers are highly developed for cereals such as maize and rice, such resources are far less advanced for wheat, barley, and rye. High-density polymorphic marker sets and genetic populations are now available that encompass both diversity and extensive recombination (such as MAGIC [multiparent advanced generation intercross] populations) (10), while nested association mapping populations (16) provide the opportunity for specific quality or compositional attributes to be enhanced and reliably achieved in breeding programs. The range of phenotypes generated can be extended by accessing additional diversity from mutation populations, accessing wide genetic diversity, or in combination with transgenic breeding.

Transgenic Modification. The majority of transgenic traits commercialized to date have been "input" traits rather than traits conferring an end-use advantage. Although there is significant technical potential to develop transgenic, consumer-orientated traits, the value proposition for consumer-orientated traits developed using genetic modification technology must be sufficiently large so the developers of the technology are able to recoup their development, regulatory, identity preservation, and technology maintenance costs. For these reasons, beneficial health traits that only deliver an incremental advantage or that can be achieved through a traditional breeding route are unlikely to be developed beyond the laboratory. Furthermore, in some markets, such as the European Union, significant consumer resistance to genetically modified crops remains, limiting global market penetration. Combining input traits in "gene stacks" is a proven method of delivering value for farmers in a more cost-effective manner, and the potential exists to combine end-user and production traits in stacks that address consumer quality preferences while enhancing yield and production efficiency. In a world facing significant global food security, sustainability, and malnutrition (over- and under-nutrition) issues, there is a compelling case to be made for the continued development and application of transgenic technology in all major cereal crops because of the ability of these technologies to deliver step changes in both productivity and nutritional quality.

Regulatory and Production Integrity Issues

There is strong epidemiological evidence to support the general proposition that the consumption of grain-based foods, in particular whole-grain and high-fiber foods, provides a wide range of health benefits. However, the introduction of new cereals or cereal-derived ingredients based on their health-promoting properties may necessitate substantiation of specific health outcomes. On-pack label or other health claims are policed by various regulatory agencies (U.S. Food and Drug Administration [FDA], European Food Safety Authority [EFSA], Food Standards Australia New Zealand [FSANZ], etc.) according to the level and specificity of the particular claim being made. Claims tend to fall into one of three categories:

1) **Nutrition Content Claim.** A claim about the presence or absence of a property of the food, other than a claim about alcohol content.
2) **General Level Health Claim.** A health claim that does not directly or indirectly refer to a serious disease or a biomarker.
3) **High Level Health Claim.** A claim that directly or indirectly refers to a relationship between a food and a health outcome.

In addition to the initial step of identifying health state(s) that can be affected positively through the modification of cereal composition and functionality, nutrition science has a key role to play in the substantiation of benefits through the generation of appropriate laboratory and animal and human trial data. Clearly, the nature of the evidence for each type of health claim differs. For a nutrition content claim it is only necessary to demonstrate that the claimed composition is achieved and, with a reasonable tolerance, to account for production and analytical variability. Establishing the fact that a particular constituent reduces the risk or severity of a serious disease state requires a much higher level of support from highly robust trials such as well-conducted randomized controlled trials. Specific regulatory agencies may require that at least one trial be conducted within their jurisdiction.

In addition to regulatory requirements, there are obligations mandated by relevant "trade practices" legislation to ensure that any claimed benefits are actually delivered to consumers. Cereal food manufacturers are very aware that the integrity of their products is critical in maintaining strong relationships with their consumers. This provides an overarching imperative for the substantiation of claimed health benefits. There is, therefore, a compelling case to be made for the need to manage the supply chain for such cereals more closely. This can be accomplished through contract or closed-loop production systems to ensure that the identity of a grain is maintained and that any specific production requirements are met, such as achievement of specific compositional targets. Having access to rapid methods for validating specific value addition components (e.g., fiber, oil, or resistant starch contents, etc.) is important throughout the value chain. While this can be reasonably straightforward for a compositional change (e.g., oil content determined by NIR), validating the content of a grain constituent that is present based on a human physiological outcome (low glycemic response or resistant starch content) rather than the presence of a specific compositional entity is more problematic. To this end, various methods have been developed to predict glycemic index and resistant starch content using automated instruments (3,13).

Global Challenges and Social Responsibility

Three high-level challenges face humanity, and they are all strongly relevant to the future of the cereals industry:

1) **Food Security.** Food security considerations are generally focused on enhancing the productivity of cereals, particularly under either short-term climatic variations or in response to longer term climate changes such as global warming. While food security is often considered to be largely concerned with maintaining the supply of calories, it is important to note that the supply of essential dietary components such as vitamins, minerals, and macronutrients is also critical to good public health and should also be considered an aspect of food security.
2) **Malnutrition.** Malnutrition can be caused by either under- or overnutrition. The great irony facing the global community is that while approximately a billion people globally suffer from malnutrition approximately the same number suffer from obesity as a result of excessive food intake and sedentary lifestyles. Cereals can play a very important preventative role in reducing the risk of lifestyle-associated diseases and also provide improved management of these conditions once they appear. The healthcare costs associated with obesity-related diseases and type 2 diabetes will be a major challenge for most affluent countries, while for countries with less developed healthcare systems meeting the needs of type 2 diabetics will more than exhaust current budgets to manage a single condition.
3) **Land Availability.** Restrictions on land availability, preservation of the environment, and reduction of greenhouse gas emissions create substantial pressure to not only improve the production and nutritional quality of cereals, but also to consume fewer resources in doing so and release minimal pollutants (e.g., CO_2 and fertilizers) into the environment in the process.

Meeting these global challenges will require the cereals industry to continue to develop the technology and expertise to simultaneously make progress in breeding cereals with enhanced yields, despite biotic and abiotic stresses, and meet consumer expectations for sensory quality and nutrition. The "smart breeding" technologies outlined earlier can provide breeders with tools to select for improved varieties using traditional plant breeding; however, the enormity of the challenge and the step changes in performance and functionality required create a powerful imperative for the community to reconsider the role that transgenic cereals can play in delivering not only increased amounts of food, but also higher quality food over the coming decades.

Conclusions

The scientific collaboration between plant geneticists and nutrition scientists has provided important opportunities to add value to cereals by increasing the value and appeal of products offered to consumers while also providing the technology required to generate the necessary compositional and functional differentiation. The genetic differentiation of the nutritional quality of grains does not conflict with traditional mechanisms for cereal value addition through milling, chemical or physical ingredient modification, and processing but instead is another tool that can be used in combination with existing value addition strategies. Although the bulk of grain crops will continue to be produced and marketed as a commodity product, the future is likely to see the further development of value-added streams, often based on closed-loop production and marketing systems, that provide participants along the value chain with the opportunity to innovate. In developing value-added production chains, consideration needs to be given to generating solutions that are compatible with, and contribute to, meeting global concerns such as food security, malnutrition (both under- and over-nutrition), and sustainability.

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