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The commercialization of biotechnology traits

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ABSTRACT

Over the last few decades, a vibrant base of research in model plant systems and functional plant genomics has identified the genetic basis of hundreds if not thousands of plant traits. Reports in the scientific literature often discuss the potential contribution that a trait could make if deployed in commercial agriculture. Yet, very few have actually been introduced into the farming systems of the world using biotechnology. Moving from an initial discovery, identification, and characterization of a genetic trait to the cultivation of a transgenic crop expressing that trait requires successful navigation of a series of increasingly costly and difficult research and development (R&D) challenges.

1. Introduction

Over the last few decades, a vibrant base of research in model plant systems and functional plant genomics has identified the genetic basis of hundreds if not thousands of plant traits. Reports in the scientific literature often discuss the potential contribution that a trait could make if deployed in commercial agriculture. Yet, very few have actually been introduced into the farming systems of the world using biotechnology. Moving from an initial discovery, identification, and characterization of a genetic trait to the cultivation of a transgenic crop expressing that trait requires successful navigation of a series of increasingly costly and difficult research and development (R&D) challenges.

The term 'R&D pipeline' is commonly used in industry to describe the set of new innovations that are at some point in the R&D process. A typical characterization of the phases of the R&D pipeline by industry includes: (a) discovery, (b) proof of concept, (c) early development, (d) advanced development, and (e) regulatory submission [1]. 'Discovery' includes gene or trait identification with methods such as high throughput screening or model crop testing. Potentially useful identifications can be made in university, government, and industry laboratories, but they also may arise from the fields of farmers who grow a diversity of crop varieties, such as land races cultivated near the center of origin for a given crop. To become widely utilized, however, the genetics underlying a given trait must be moved from the original organism where it is identified into breeding germplasm. This occurs in the 'proof of concept' and 'early development' phases, in which crop transformations or crosses are made. Particularly when the resulting variety is transgenic, additional work is required to evaluate the viability of the transformation event, improve expression, and test performance in greenhouse and controlled field conditions. The 'advanced development' phase includes combining or stacking the novel trait with other valued traits, field testing, agronomic evaluation, and regulatory data generation. Then, in order to comply with environmental and biosafety requirements, regulatory submissions are made. Commercial release depends upon sufficient bulking up of seed stocks in preparation for sale, and integration into the seed production and distribution system. After the R&D pipeline ends, other work for commercialization begins, including marketing and – for novel traits – sometimes considerable work with growers to help them learn how best to manage the crop with the new trait. Consider, for example, the learning and the changes in practice that were undergone by farmers adopting herbicide tolerant crops in order to take full advantage of that new characteristic.

This image of an 'R&D pipeline', associated as it is with the notion of an unimpeded linear flow, can be misleading. A more apt metaphor might be an 'R&D funnel sieve' (consider the shape of Fig. 1). R&D consists, in many regards, of progressive selection processes. According to reported industry averages [1], about 95 percent of genetic traits identified in the initial discovery phase are quickly eliminated from consideration; of those that advance

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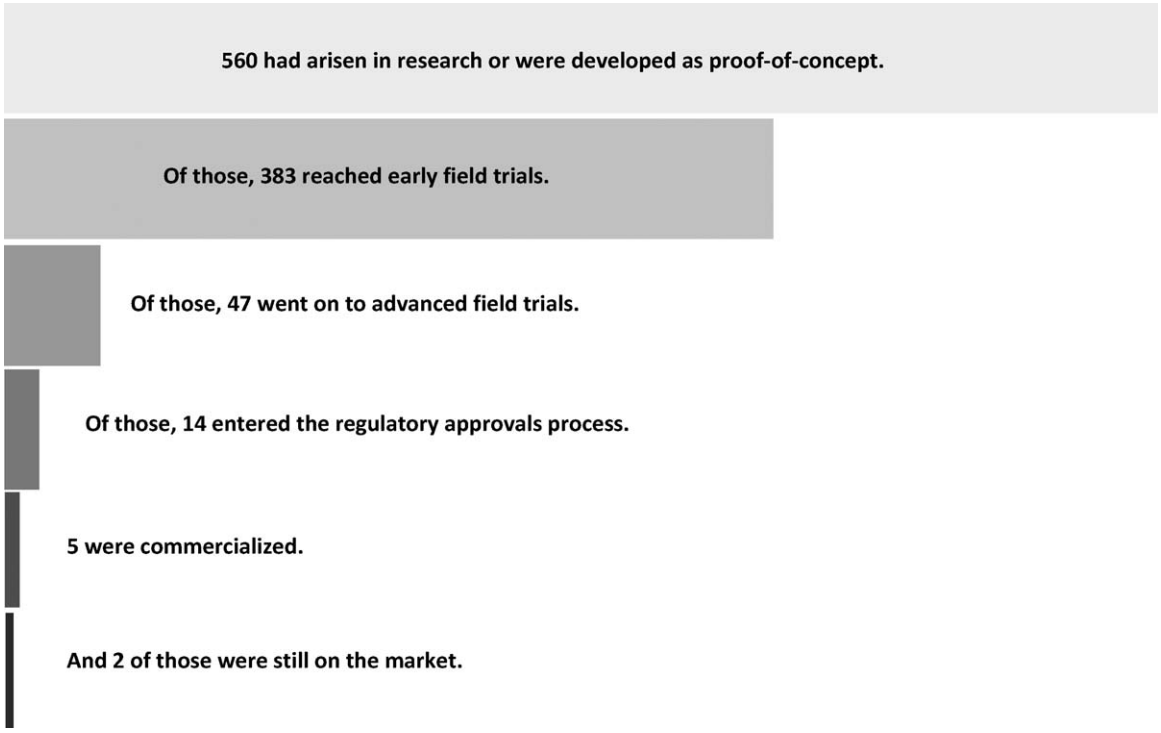

Fig. 1. The advance through R&D of the 560 nutritional and product quality crop biotech innovations observed in the survey.

to the proof-of-concept phase, about 75 percent fail to be proven. At that point, only the most promising candidates, representing just 1.25 percent of the originally discovered traits, remain in the pipeline. For this select few the odds then improve. About 50 percent of those that enter early development move on to advanced development, and about 75 percent of those in advanced development result in a regulatory submission. By that point in the process, so much scrutiny and selection has occurred that that 90 percent of those submitted get approved. The net result, however, is that the set of potential innovations that are somewhere in the process is continually being winnowed and narrowed, with fewer and fewer innovations qualifying to advance to the next stage of R&D. At the same time, the number of innovations in R&D is continually being refreshed by new ideas as they are introduced.

One reason for the severe narrowing of the field is the fact that significant investment is required in the latter phases to get through regulatory approval. According to reported industry estimates, an average $50–100 million is spent on R&D to commercialize a single successful trait [1]. Of that, $35–70 million, or about 70 percent of the total, is spent in advanced development, where data is being collected for regulatory filing, and in the regulatory filing process itself.

After successfully navigating the R&D and regulatory processes and entering the market, a new kind of vetting process begins. Often initial market release is done in a controlled manner through test markets, in order to collect market data to guide the subsequent full rollout, as well as to minimize losses in the event the crop fails to perform as expected. In the marketplace, a new biotech crop variety becomes subject to the independent decisions of thousands of farmers. They ultimately are the ones who choose whether or not to adopt it for their commercial operations. These decisions by farmers depend upon a host of technical, economic, and other considerations that can only be partially anticipated during the controlled pre-market stages of R&D and regulatory analysis. The market thus exerts a very real selective pressure of its own, whereby those products that prove unfit in an economic sense do not survive, while those that prove to be well adapted to the market environment flourish.

According to a classic analysis of new drug approvals by Peltzman [2], the selective pressures of the marketplace serve important functions of protecting public interests in the safety and effectiveness of new medicines. In essence, a bad medicine that causes harm to users or fails to function properly would be quickly eliminated from the market by the overwhelming pressure of consumer decisions to avoid it. Moreover, the threats of damage to the innovator's reputation plus any incurred liabilities would quickly outweigh any profits they might expect to make from knowingly introducing a substandard medicine. These incentives, under most conditions, converge to make pharmaceutical innovators want to introduce safe, effective, reputation-enhancing innovations. In light of these market pressures and incentives, excessively strict regulatory approval requirements might not only be superfluous, but they may in fact hurt the greater public interest by depriving them of the introduction of new innovations, thereby causing losses in social welfare from the reduction in the number and variety of new medicines available on the market. According to Peltzman, excessive regulations can hurt in two ways. First, they delay the entry into the marketplace of those that do eventually pass the scrutiny of regulators, postponing the onset of the adoption process and thus delaying the gains to society ,(i.e. delaying the overcoming of disease, debilitation, and even death) that can result from using the new medicine. Second, the higher costs of overly strict regulations serve as negative signals or disincentives to innovators and thereby reduce the absolute number of new medicines that reach the market, particularly for smaller markets where smaller expected returns make it less likely for the innovator to be able to recuperate costs (so called 'orphan' drugs).

Together, the long term social losses of overly strict regulations can very well outweigh the social value of any improvements made in public safety above and beyond what the selective forces of the marketplace would have assured anyway. The argument here, to be clear, is not against having regulatory standards; rather it is about finding a socially optimal balance between *reasonable* and *excessively strict* regulatory regimes. While there can only be imperfect comparison between pharmaceuticals and crop biotechnology,

in principle this potential for overregulation certainly seems to be applicable to plant genetics. In crop biotechnology, a number have voiced concerns that the delays and costs due to unproductive regulatory stringency may be harming the greater public interest by delaying and preventing the introduction of many otherwise safe and beneficial innovations (see [3–6]). While it is impossible to know what innovations might have been commercialized under a more competitive regulatory environment, the foregone value to society of undeveloped and unadopted innovations has likely been very significant, based on reviews of social value of existing transgenic innovations (for a discussion and review see [7]).

The balance of this article seeks to analyze and explain the workings of the biotechnology R&D commercialization process as a primary way of translating fundamental knowledge of plant biology into crop improvements and enhanced utilization of seeds and plants for human benefit. Section 2 provides a brief overview of the of how better crop genetics have historically been discovered, developed, and deployed for use in farming systems, explaining how the process has evolved from an entirely public sector undertaking a century ago to a hybrid system involving both publicly funded research and private commerce today. Section 3 then outlines the key factors that influence economic decision-making in the crop genetics R&D process today, particularly within the private sector. Section 4 then illustrates empirically the workings of the crop genetics R&D and commercialization process, analyzing data from a comprehensive survey of the transgenic *product quality* or *output* traits that were in R&D between 1987 and 2004. Section 5 concludes with a discussion of the impact that regulatory costs appear to be having on commercialization trends in crop biotechnology.

2. Historical trends in commercializing genetic improvement in crops

'Innovation' is generally defined as the introduction of a new way of doing things, and it often refers to the generation of new technologies, processes, services, or products. While the process of innovation is not necessarily linear – it does not always follow the typical 'R&D pipeline' sequence of causality or operational steps – it does almost always start from an idea about a new way of doing things and eventually results in the introduction of a new product or process in the commercial marketplace.

Basic research is very important to innovation, particularly in agriculture. Indeed, innovation is one of the important byproducts of basic research. The historical tendency of basic research to generate practical innovations is, in fact, one of the central political justifications for governments' allocation of public spending on research, whether that research is conducted in government labs, universities, or private firms. Governments support and subsidize research precisely because it leads to practical innovations that can enhance the economic competitiveness of domestic farmers and industry, spur economic growth, create jobs, reduce environmental impacts, or meet consumers' needs with less costly and higher quality products. It has long been recognized by economists that to the extent that the outcomes of research have the characteristics of a 'public good' or 'public service' (as opposed to characteristics of private property), there is going to be chronic underinvestment in research by the private sector. In other words, if private investors are not able to capture sufficient returns from an investment in research, even though society at large would realize the benefits, they are not likely to make such investment it in the first place. A precondition to having private sector participation in the innovation process is for the outcomes of research to be embodied in something that you can sell. In economic terms, the investor must be able to capture or appropriate enough of the value created by the innovation to justify investment in its creation.

The case for public support of agricultural research on crop genetics is, to some extent, due to the unique nature of the vehicle by which crop genetics are delivered to the user: the *seed*. Historically, because seeds could be so easily be multiplied and redistributed amongst farmers, value created by investing in improvements in seed genetics was not very easy to appropriate. Private investors had little assurance, regardless of the crop, that any genetic improvements they might introduce would not become widely copied throughout the entire market at merely the cost of reproduction and transportion by users or other vendors. Such copiers, because they spend nothing on breeding programs or genetics R&D, could undercut the prices that an innovator would need to charge to recoup the value of the initial R&D investment plus interest.

Another justification for public sector support for improvements in crop genetics is the fact that private investors inevitably calibrate their level and type of efforts based on their expected profit from the innovation; they do not take into consideration any of the other benefits that an innovation would bring to society. One major benefit that investors cannot capture, and therefore tend to disregard, is the set of benefits that accrue to consumers from a cheaper, safer, more reliable, and nutritious food supply. Another category of benefits that investors typically do not consider are the spillover effects or positive externalities that accrue to society from an innovation, whether as technological gains in unrelated markets or as improvements in environmental quality or public health.

For these reasons, historically, all crops were effectively 'orphan' crops. Initially governments had to intervene in the defunct, missing, or underperforming innovation of private seed markets through public agricultural research to provide seeds improved by scientific breeding [8]. Improved seed varieties were then transferred from public sector research institutions to private sector seed companies and farmers via 'public release', after which the business of seed companies was primarily to provide services of seed multiplication, cleaning, and distribution. Typically, levels of on-farm seed saving and sales from farmer to farmer were high.

The first reduction of public sector involvement in crop genetics began in the 1930s with changes initiated by the development of hybrid seeds. The fact that hybrids would not breed true introduced a physical mechanism of appropriability into the market for improved seeds. As hybrid corn became commonplace in the 1930s and 1940s, private sector investment in corn breeding and the improvement of hybrid corn genetics took off. At roughly the same time, in 1930, a new legal mechanism in the U.S., the 'plant patent', was introduced to enhance the appropriability of genetic improvement in asexually propagated crops. These were augmented later, in 1970, in the U.S. by the introduction of 'plant variety protections' over sexually propagated crops.

More significant changes came with the introduction of recombinant DNA, cell and tissue culture, and plant transformation technologies. Using the tools of biotechnology the cost of making genetic improvements increased, while at the same time the value of new traits that could be developed increased too. With biotechnology, the cost of research became but a small fraction of the total cost of commercialization, given the much greater needs for translation, testing, scaling up, marketing, and facilitating adoption by consumers.

While public research has and continues to make significant research contributions, the public sector is not able to justify the dedication of resources currently required to move a trait through the regulatory phase. At the same time, the primary factor that has made the large investments by the private sector economically feasible has been the adaptation of patent law so that patents can be used to protect inventions in crop genetics. In the U.S., the modifications in patent law and administrative practice came in stages between 1980 and 2001. With patents, the results of research can

be much more extensively appropriated. With the outcomes of research now much more resembling private goods, the private sector is more likely to invest. Yet, the main advantage of patents is not that they induce investment in research itself, but rather that they induce investment in development necessary for commercialization.

The role of patents in inducing follow-on investment in development is reflected in the newer process of technology transfer between public sector agricultural research and the private sector to have emerged since 1980. Today, patents are often taken out by universities and government laboratories when they make potentially useful inventions in crop genetics. About 24 percent of US patents granted in the field of agricultural biotechnology belong to public sector institutions, while about 40 percent are granted to the five leading corporations active in commercializing crop traits Monsanto, DuPont, Dow, Syngenta, and Bayer and 33 percent to other companies in the private sector [9]. The purpose of patenting by public sector institutions is not to generate financial support for their research programs: university running royalties are seldom more than 2 or 3 percent of their total institutional research expenditures [10], which still largely come from governments through grants or research subsidies. The purpose of public sector patenting is, rather, to induce private investment on the order of magnitude necessary to develop and bring the public sector innovations to market. Given the costs of development and attaining regulatory approval, if such genetic innovations were simply published and put into the public domain, it is highly unlikely they would ever make a practical contribution to society by becoming deployed in commercial agriculture.

3. Considerations that enter into crop biotech R&D investment decisions today

Throughout the commercialization process, decisions are routinely made about whether to proceed with, modify, or terminate a particular innovation in R&D. Those making such decisions – both in the private sector and in the public sector – are engaged in an exercise of calculating the expected net benefits (expected benefits minus expected costs) of taking the next step in moving the innovation towards market. In such a calculation, net benefits equal the expected net present value (NPV) of the entire future stream of profits (revenues minus costs) that the innovator will realize from selling or licensing the innovation. The magnitude of future profits depends upon the extent of consumer demand for the new product, accounting for the size and scope of the potential market and the degree of penetration into that market over time, as well as the effects of the innovation on costs of production. Expected returns may vary significantly based upon the type of trait. For input traits such as insect resistance, the relevant market consists of the population of farmers that grow a given crop, and this can be more readily captured. For output traits, however, such as high lysine content, there may be additional steps to reach the relevant market, such as livestock feed operations. As a result any increased revenues may have to be shared with farmers and feed suppliers, to induce them to adopt and produce the new product, leaving less for the innovating seed company to capture and thus reducing their return on investment. Costs of production can include both fixed upfront costs necessary for adopting the technology (such as acquisition of new equipment) and changes in the variable costs of production, which can be either higher or lower than they were using previously available technology or crop varieties. The expected costs of bringing an innovation to market consist of the R&D, intellectual property, regulatory, and market launch costs.

Estimating the value of an early stage technology is, however, notoriously difficult [11]. At the time that investment in a new technology must be considered, neither the future benefits nor the costs of bringing it to market can be known with anything close to certainty. Those making such decisions must rely on estimates that are fraught with randomness and guesswork. Given a simple rule of statistics, the higher the variability in these estimates the lower the expected NPV. It is precisely this variability and uncertainty that makes investment in a new technology financially risky and therefore less attractive than investment in projects with more certain outcomes, such as new manufacturing equipment or simply putting one's money in a bank deposit.

There are four primary types of uncertainty affecting R&D projects. The first is technological uncertainty, not knowing whether the innovation will meet performance parameters later on in the R&D process or in the marketplace. The second form of uncertainty is regulatory uncertainty, not knowing when, or even whether, an innovation will be approved for market release. The third type of uncertainty involves intellectual property. An innovator may not have the technical or legal resources to thoroughly examine the extent to which an innovation might infringe existing patent rights. There is also the possibility that new patents would issue in the future that might in some way limit the innovator's freedom to operate. The fourth type is market uncertainty, reflecting a range of unknowable market factors such as consumers' actual willingness to pay for a new innovation or the emergence of competing products. Different types of transgenic traits confront very different types of market uncertainty. Input traits such as pest control or disease resistance depend on the prevalence of pest or disease problems and the cost of other means of control such as chemicals. Output traits such as nutritional quality or ripening control compete in a very different market and may only impart value several steps down a complex vertical chain of markets between farmer and consumer. In general, the longer and more complex the R&D and regulatory process, the further into the future will the new innovation be introduced to market and thus the lower the NPV of the technology.

Different kinds of investors tend to have different tolerances for investment risks. Established, publicly traded corporations that must answer to shareholders or lenders who back corporate debt tend to invest in R&D projects that fall within the context of their current lines of business. Smaller entrepreneurial biotech startup companies can seek to commercialize innovations in which established corporations are not willing to invest. While startups and their investors also look at expected NPV, they are closer to being 'risk neutral' since they do not have fixed assets forcing them to specialize and thus can be quicker to move and capture new and unrelated market opportunities than could corporate R&D. Venture investors will back startups if they think they can reduce uncertainty enough to later entice others, including corporations, to invest. Universities and government laboratories have an important role relative to risk, as well. While they must generate benefits to society from their research investments, they are not beholden to the short-term expectations of shareholders or venture capital investors for returns on investment. Public sector researchers are thereby able to undertake basic and exploratory research whose payoff is, in fact, even more uncertain and distant. Public research can, most of the time, be considered successful if it generate new knowledge rather than a tangible product.

4. Empirical observations of the commercialization process: detailed results from a survey of product quality traits in R&D

A survey was conducted in 2005 to assess what transgenic nutritional and product quality traits were in R&D and which were likely be commercialized [12]. The survey found a wide range of

genetic quality improvements at some stage of R&D, including consumer-oriented characteristics like healthier fatty acid compositions of vegetable oils, the elimination of food allergens, and the enhancement of natural flavors. A number of processor-oriented and animal feed qualities were also found, such as high-starch corn for increased starch extraction efficiency, low-protein grains for better brewing, and reduced-lignin wood for easier pulping. Animal feed traits being explored included properly balanced essential amino acids, increased bioavailability of minerals like phosphorus, reduced toxins and antinutrients, and improved fiber digestibility. By definition, since there is expected to be some degree of increased valuation or 'willingness to pay' for these new characteristics by users of the agricultural output in some market downstream from the grower – whether manufacturers, livestock producers, or final consumers – they are broadly referred to as quality or output traits.

A contraction in the rate of R&D in product quality traits was revealed by the survey and reported in Graff et al. [4]. Here we provide more detailed analysis of the survey data in order to characterize trends in the R&D and commercialization process. Results reported here include the overall filtration or attrition rate, the range of traits being developed, the range of crops being developed, the global distribution of where R&D is conducted, the different roles of public and private sector R&D, and finally changes over the last two decades in the rate and probabilities with which new crop genetic discoveries move to market. While there are some variations in these R&D trends between product quality traits and production oriented traits (according to USDA APHIS data on field test release applications [12], product quality traits constituted 13% of all transgenic field trials during the time period covered by this survey), these observations can be considered representative of some of the major R&D trends for all types of transgenic crops.

The survey searched three sources of secondary data published between 1987 and 2004, and from those found 358 scientific articles, 2403 registered field trials (in 19 countries), and 36 regulatory decisions (in six countries) reporting a transgenic plant that expressed a novel trait that could affect the perceived quality of the agricultural output.[1] These records were then grouped around individual 'innovation candidates', defined as:

1. a particular type of trait ,(e.g. high lysine or modified starch composition),
2. in a particular crop species ,(e.g. maize or potato),
3. by researchers at a particular organization ,(e.g. Monsanto) or set of organizations know to be in a collaborative R&D relationship or cross-ownership ,(e.g. Amylogene and BASF).

The technique of aggregating across multiple types of data – including publications, field trials, and regulatory filings – allows individual innovation candidates to be traced through various stages of the R&D process, as far as each gets towards commercialization. It also allows for roughly uniform treatment across the full scope of the industry's R&D pipeline, given the widely varying levels of detail available from different data sources and at different stages of R&D.[2]

The survey found 560 individual nutritional or product quality innovation candidates had entered the R&D pipeline since the late 1980s when plant transformation first became routinely feasible. Of those, 383 succeeded in reaching initial field trials, 47 proceeded on to advanced field trials, 14 advanced to regulatory filings, five were commercialized, and, of these, two are still on the market (see Fig. 1). None had become a significant commercial success. The first to reach market, the FlavrSavr tomato, was in fact the first innovation of any type from agricultural biotechnology when it debuted in 1994, but it was removed from the market in 1997. The second, which reached market in 1995, was a high laurate rapeseed, also commercialized by Calgene. The third was a long shelf life tomato commercialized by Zeneca in Europe in 1995, and discontinued in 1999. The fourth was a blue-mauve colored carnation developed by Florigene and marketed in Asia-Pacific markets starting in 1996. The fifth was a reduced nicotine cigarette released in test markets in the Great Lakes states of the U.S. in 2003 by Vector Tobacco.

4.1. Traits and crops of commercial interest

Traits found in the survey span ten major categories, defining the general scope of potentially feasible output traits (Table 1). The traits of each category would, by their nature, be of value to a user of the agricultural output or to someone affected economically by its use. The first five categories focus primarily on nutritional quality. The latter five cover a wider range of esthetic, processing, safety, and environmental qualities.

A wide range of crops was observed to have been given transgenic nutritional and product quality traits (Fig. 2). This diversity is partly due to the fact that many areas of interest in fundamental molecular biology research, which necessarily encompasses a wide range of plant families and species, relate to what are considered quality or output traits. The strong representation of horticultural crops since the earliest days of transgenic R&D is likely due to expectations of the relatively high economic value of quality improvements in specialty crops. By the late 1990s increased work in feed and oil quality traits caused the number of active innovation candidates in field crops to catch up with horticultural crops. Also in the mid 1990s output quality work emerged in forage and forestry species. By 2004, the innovation candidates still active in the R&D pipeline were about evenly split between horticultural and field crops, with the small remainder consisting of species used in forage and forestry systems.

4.2. The global distribution of commercialization activities

Identification of the nationality of the lead organization responsible for each of the 560 individual innovation candidates made it possible to plot the global distribution of R&D activity in product quality traits, illustrated in Fig. 3. To the extent that they were found to occur, international research collaborations are illustrated by lines connecting countries of the collaborating organizations. Nationality was identified as the country indicated by the author(s) address (if available), or alternatively as the country in which the designated R&D organization is headquartered (if address was not available).[3]

[1] The scope of the study intentionally did not include novel uses of crop agriculture for the production of regulated therapeutic compounds (plant made pharmaceuticals) and industrial non-food-grade enzymes (plant made industrial products).

[2] At the same time, there are important limitations. This treatment allows one 'product innovation candidate' (as defined here) to include more than one 'genetic transformation event' as commonly defined in the literature and by regulators. One 'innovation candidate' identified in this survey can include multiple events (and even multiple genes, if left unspecified) yet all of them conferring the same phenotypic trait in the same crop species. An extreme example of this is canola with altered oil characteristics by Calgene and subsequently Monsanto. This is identified as a single product innovation candidate, even though the data does indicate that the work involved over twenty different transgenes and at least as many events: detail in the published data was not sufficient for us to disentangle reports of the separate oil traits.

[3] For example, Syngenta registered a series of field trials in the U.S. for corn with altered seed composition, for which Switzerland is credited as the nationality of the lead organization. In another example, Umemoto [13] reports a rice with modified amylopectin starch, and the lead author, Umemoto, is identified as affiliated with Tohoku National Agricultural Experiment Station: thus Japan is credited as the nationality of the lead organization.

Table 1
The range of nutritional and product quality traits in the R&D pipeline.

Nutritional trait categories	Number of innovation candidates identified	Other product quality trait categories	Number of innovation candidates identified
Proteins and amino acids		*Esthetics and convenience*	
Protein quality and level	39	Flavor/scent	11
Lysine	19	Fruit/seed color	9
Methionine	16	Flower color	17
Tryptophan	3	Size	3
Nutrient enhancing enzymes	4	Seedlessness	3
Other nutritional proteins	10	Low maintenance landscaping	2
Protein functional qualities	10		
		Reduced non-nutrients, allergens, and toxins	
Oils and fatty acids	54	Non-nutritional, anti-nutritional, and toxins	18
		Allergens	7
Carbohydrates		Mycotoxins	2
Starches	81		
Fructans	19	*Extended shelf life*	
Sugars	18	Control of fruit ripening	64
		Control of leaf and flower wilting	11
Micronutrients and functional plant metabolites		Bruising/browning	8
Vitamins	23		
Minerals	20	*Fiber quality and biomass degradation*	
Functional secondary metabolites	23	Fiber quality for textiles	1
		Fiber quality for animal feed and forage	31
Multiple seed composition or feed quality traits	7	Fiber/wood quality for degradation	12
		Environmental quality: Bioremediation	10

The dominance of the United States is the most obvious result from this geographic analysis (Fig. 3). A total of 293 out of the 560 innovation candidates, or 52 percent of the total, were introduced by U.S. organizations. Europe is clearly the other major center of activity, generating a total of 152 out of the 560 innovations, or 27 percent of the total. Of the European innovations, the majority are from five countries – the UK, Germany, the Netherlands, France, and Switzerland – with the remainder coming from across a broad fringe of 10 other European countries. The rest of the observed innovations were found in other OECD countries – with Japan, Australia, and Canada having more than 20 innovations each – and "innovative" developing countries – particularly India, China, Malaysia, and South Africa.

The global network of R&D collaborations in product quality traits (Fig. 3) exhibits a four tiered structure. The two primary nodes in the global network, representing the most significant set of collaborative R&D relationships, are the U.S. and Europe. Within Europe, there is a significant amount of collaboration amongst European organizations across European national borders. Secondary nodes in the network are found in other OECD countries, with Japan, Australia, Canada, and Israel each maintaining collaborative links with both U.S. and European organizations. Several developing countries constitute tertiary nodes, collaborating with researchers in one of the primary or secondary nodes: India with the U.S., South Africa with Europe, and Egypt, China, Indonesia, and the Philippines with Japan. Fourth and finally, there is a set of coun-

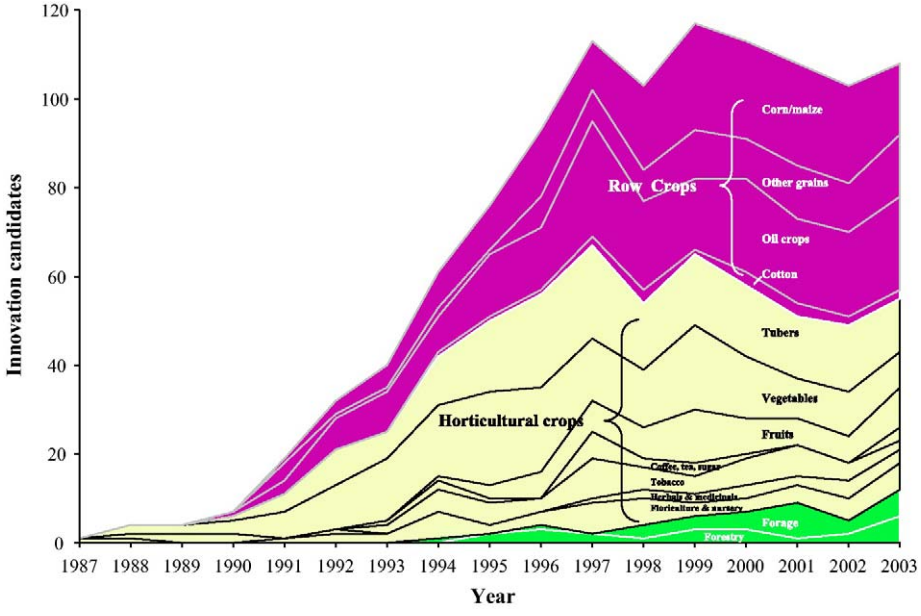

Fig. 2. Number of transgenic product quality innovation candidates active in R&D, by crop and by year.

Fig. 3. Where transgenic product quality innovations have originated, including international links for collaborations by research teams located in more than one country.

tries peripheral to the network of collaborations that do not exhibit any collaborations in the survey data.

4.3. The different roles of public and private sector organizations in the commercialization process

With such data, it was also possible to assess the type of R&D organization responsible for the surveyed innovations. What was observed is a kind of division of labor, with public sector innovators dominant in early stages of the innovation process and private sector organization more prevalent in taking innovations through regulatory filings and on to market. Of the total 560 innovations identified, 276 (or 49 percent of the total) were solely the product of a public sector R&D organization, 232 (or 41 percent) were solely the product of private sector R&D, and 44 (or 8 percent) were the result of public-private collaboration. The timeline of development for each innovation can be used to examine whether, as expected, there is systematic division of labor between the public and private sectors at different phases in the R&D pipeline. Moreover, for each of the 560 innovation candidates, it is possible to track the year that innovation reached each identifiable stage of the R&D process (as far as it progressed through the commercialization process), including (1) initial publication, (2) initial field trials, (3) mid-stage field trials, (4) late-stage field trials, and (5) regulatory filings. Trends could then be plotted showing the type of organization responsible for an innovation reaching each stage of R&D in a given year (Fig. 4).

Fig. 4 shows that, of innovation candidates reaching the stage of research publication, overall two thirds (66 percent) are by public sector organizations and an additional 17 percent are by public-private collaborations. Just 17 percent of published innovations are from private sector authors. However, at the point when field trials are initiated, roles shift significantly, with just over one third (39 percent) by public sector organizations and over half (57 percent) by firms in the private sector. The role of the public sector further decreases and the involvement by the private sector increases as innovations gets closer to commercialization. Overall, the public sector's share drops to just 25 percent of innovations in mid-stage field trials and 12 percent of innovations in late stage field trials, while the private sector's share grows to 69 percent in mid-stage field trials and 82 percent in late stage field trials. At the stage of regulatory filings the public sector is not involved, except for an occasional collaborative role: the private sector accounts for 87 percent of regulatory filings with the remaining 13 percent by public-private collaborations. The relative importance of public-private collaboration appears to be greatest at the beginning and at the end of the R&D process but not as much so in between: public-private collaborations account for 17 percent of innovations at the publication stage and 13 percent at regulatory filing, but less than 5 percent at any stage of field trials.

Both the division of innovative labor and the dynamics of the filtering process appear to change fundamentally around 1998, at which point the structural shift occurred in the rate of innovation [4] dividing product quality commercialization into an earlier phase of expansion and a more recent phase of contraction. During the earleir phase of expansion, the public sector contributed about two thirds of initial research publications, only about one quarter of initial field trials, and very little beyond that. At the same time, private sector activity grew steadily at all stages of R&D—with stable and expected rates of filtration and lag between stages. During the contraction phase, after 1998, public sector activity continued

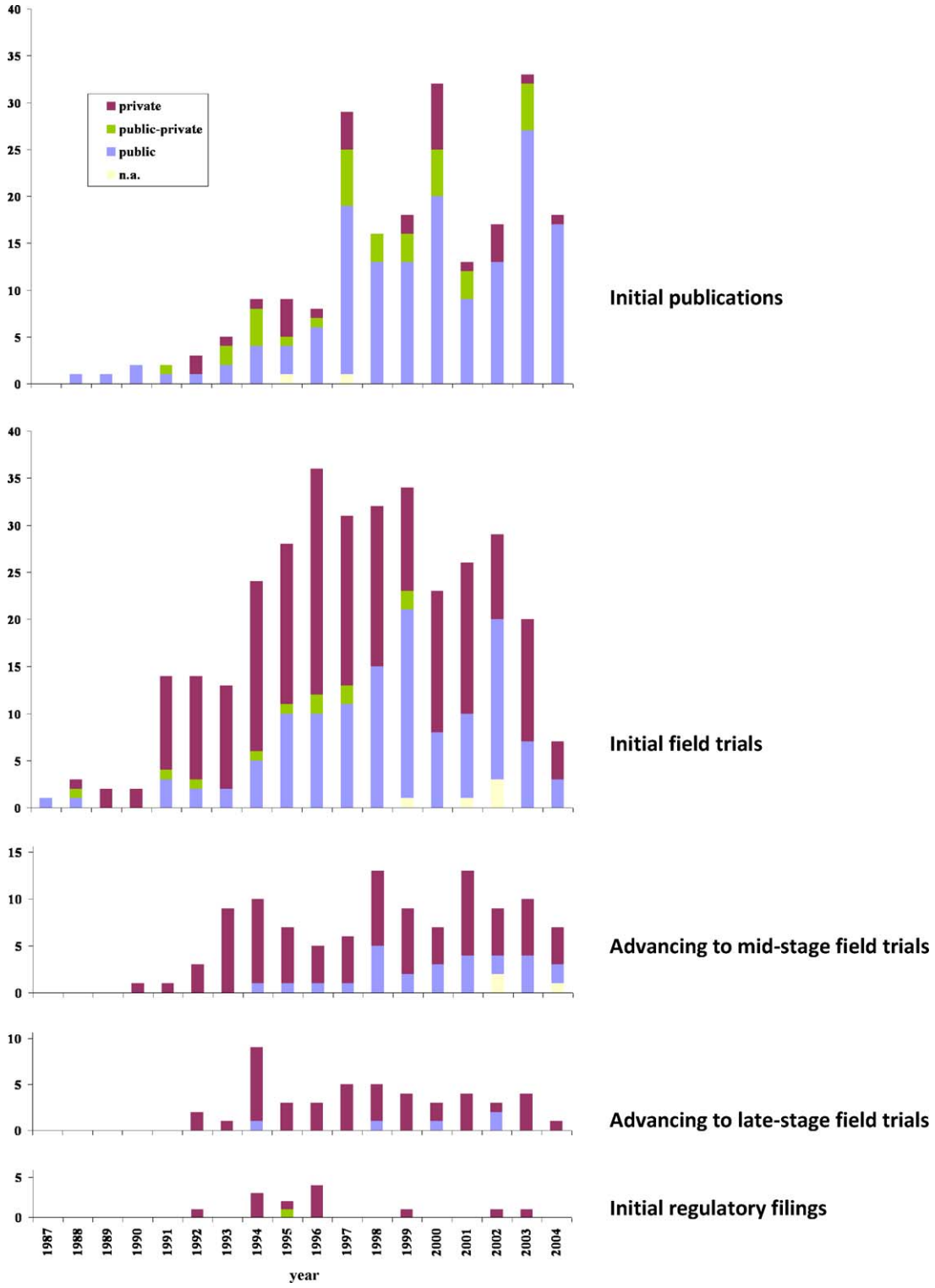

Fig. 4. Number of innovation candidates newly advanced to each stage of R&D in each year, by type of organization. (Some data series truncation is evident in publications and field trials for later years.)

to grow consistently, achieving even rates of publication and initial field trials, while also expanding forward into mid-stage field trials. However, after 1998, activity by the private sector did not continue to grow apace overall, and it clearly declined in the advanced field trials and regulatory stagess.

After 1998, the core private sector participants in the industry concentrated their R&D efforts on a set of most promising product quality candidates (primarily animal feed traits), while most other companies – including food companies and small biotech firms – reduced or abandoned their efforts in product quality traits. The public sector filled some of the vacuum left by reduced private sector activity in early and mid-stage field trials, but the public sector alone has not once carried a transgenic product quality innovation through the regulatory approvals process to release it commercially. Overall, the rate of filtration (attrition of candidates between stages) clearly increased after 1998, with significantly fewer can-

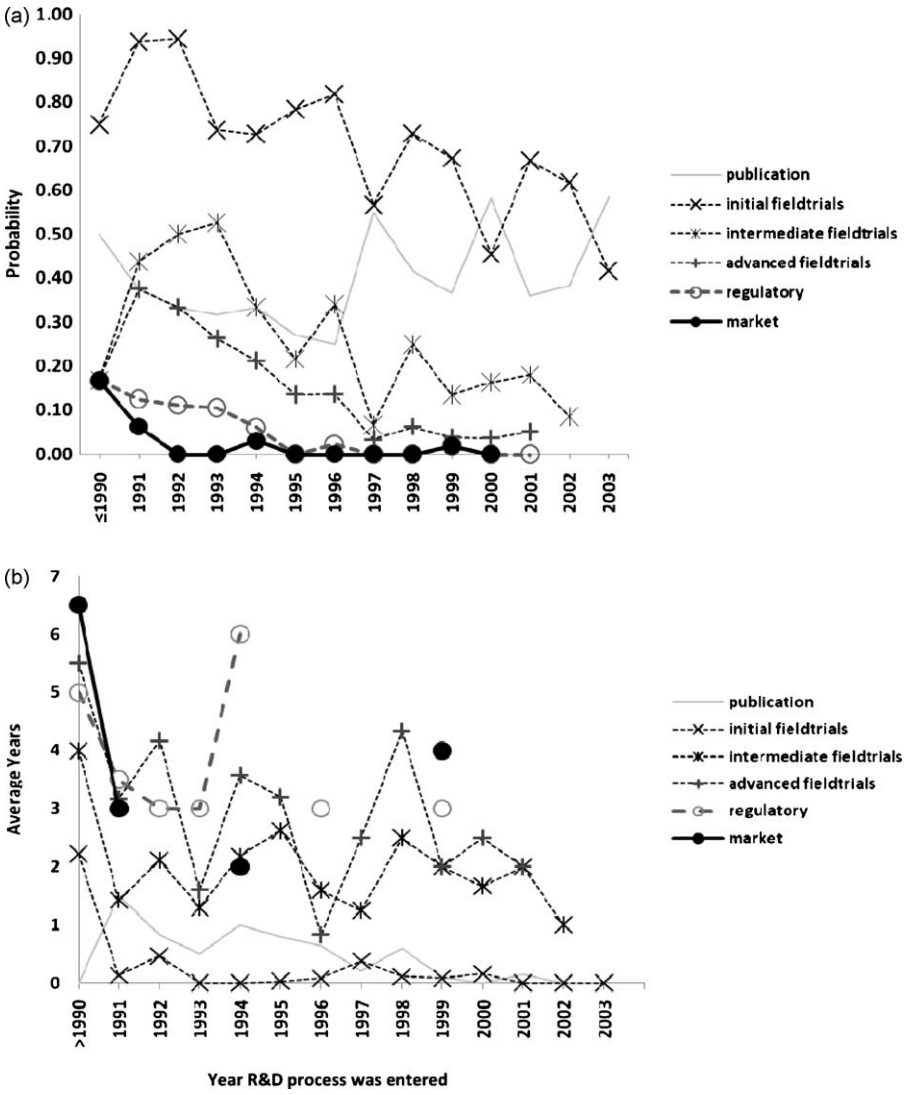

Fig. 5. For an innovation first introduced in a given year: (a) the probability that it would reach each of the stages and (b) average years to advance to each stage in the commercialization process.

didates advancing to the final stages of R&D, despite an ever-larger pool of early stage candidates from which to draw.

4.4. Changes in the probability and the rate of progress in the commercialization process

Other more direct measures of the probability and speed with which crop traits progress through the stages of R&D and enter the market, and how these have changed over time, are also possible. It is important to caution that so few traits have reached market that statistical evidence is not significant for progress through all stages of R&D to eventual commercial release. These cases must, in a sense, remain anecdotal. But measures of progress through the earlier stages of R&D, perhaps even earleir measures for reaching regulatory stage, are sufficiently robust. Analysis of the survey data by annual cohort suggests that the probability of new traits advancing through R&D has gone down over the years since 1990 (Fig. 5a), but for those that do progress, the speed at which they do so has increased over the years (Fig. 5b).

Fig. 5a considers the conditional probabilities, given the year in which an innovation candidate was first introduced, of it eventually being published, entering initial, intermediate, or advanced field trials, receiving regulatory approval, and entering the market. Because so few traits were identified and introduced before 1990 these are all lumped together into a single cohort. In most years the probability that a newly introduced innovation would eventually reach market was in fact zero, which follows from the fact that out of the entire set of 580 innovations, only five actually reached market. Thus, in most years, all of the new ideas introduced into the R&D pipeline during that year never ended up making it to market. Of the five that did succeed, two were introduced prior to 1990, one was introduced in 1991, one in 1994, and one in 1999. The probabilities of reaching other earlier stages of R&D exhibit a similar trend. Innovations introduced in the 1980s and early 1990s were more likely to reach regulatory filings than those that came later. Probabilities of reaching any of the field trial stages declined steadily over the years. Indeed, the only measure to increase over time is the probability of being published.

Fig. 5b analyzes the timeframe of commercialization for these product quality traits. Speed to market has remained constant or, if anything, has become quicker since 1990. The two innovations introduced before 1990 that eventually reached market took an average 6.5 years to go from initial discovery to market entry. The one innovation that entered the pipeline in 1991 took three years to reach market, and the one from 1994 took only two years. The last successful innovation, which entered R&D in 1999, took four

years to reach market. Beyond these isolated instances of successful market entry, we can also assess average times for reaching earlier stages in the R&D process—including publication, initial, intermediate, and advanced field trial milestones. Time to each stage appear to have remained consistent or to have gotten shorter over the years (Fig. 5b).

Yet, generalizations are difficult to make about average time to reach regulatory filing and market entry, given that so few have reached either since the mid 1990s. It may be the case that these final stages of the commercialization process are taking significantly longer in the last decade. In other words, eventual successes were simply not observed in the survey. It is also interesting to note that prior to 1998 publications were less likely than initial field trials (Fig. 5a) and publications came, on average, later than initial field trials (Fig. 5b), but after 1998 any difference in the probability of publication and initiating field trials disappeared, as did the publication lag.

5. Summary and conclusions

Two general sets of causes need to be considered in seeking explanations for the contraction after 1998 in rates of crop genetic innovations advancing through later stage R&D and toward the market. The first set of considerations consists of technical factors, with the apparent progress of earlier years likely having been slowed by encountering complexities in engineering more advanced traits. Such challenges as consistent expression or yield stability have not been uncommon when working with output quality traits.

The second and more influential set of causes, however, include economic and political factors, which can certainly affect investors' calculation of projected costs and benefits. Reasons for higher projected costs of late stage R&D and commercialization primarily include the growing complexity and cost of navigating access to essential intellectual property and of achieving regulatory compliance in multiple countries. Reasons for the decline in projected demand include competition from reasonably close non-transgenic product substitutes, consumer uncertainties over food uses of biotechnology, political and media-focused activism against genetically modified crops, and key decisions made by major institutional buyers and retailers such as McDonalds to avoid biotechnology. But the greatest impact has been from increased costs of regulatory compliance and actual or effective regulatory bans of the technology in some markets, such as the *de facto* moratorium that began in Europe in 1998. Such regulatory constraints also have indirect effects on other countries whose agricultural sectors are reliant upon trade with the countries that ban or restrict import of transgenic products.

The most significant effect of transgenic crop innovations over the next decade are likely to be found in the cumulative incremental reductions – over time and through sustained innovation – in the resource requirements and environmental impacts of agricultural and natural resource systems achieved through efficiency gains, while at the same time making more nutritious and safer agricultural products more affordable and thus more broadly available to resource-constrained consumers.

Thus, the observed downturn in rates of crop genetic innovations reaching later stages of R&D and commercialization may be a serious unintended side effect of increasing intellectual property and regulatory costs. Much of the existing intellectual property and regulatory environment has been shaped by intense competition and governance challenges created by the main commercial applications of crop biotechnology to date, namely pest control traits. As a result, other unrelated applications are, perhaps inadvertently, being required to shoulder the efforts and costs required for introducing a new pesticide product to market, even when they pose little or no corresponding risk profile to public health or environmental safety. As a result of this inefficiency, foregone gains in social welfare from a decreased rate of innovation in other areas of application, like product quality traits, may in the long run be a collateral social cost imposed by competition and concerns over commercialization of first-generation pest control biotechnologies.

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