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The ownership question of plant gene and genome intellectual properties

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The restructuring of the crop agriculture industry over the past two decades has enabled patent holders to exclude, prevent and deter others from using certain research tools and delay or block further follow-on inventions.

The raging legal debates on the patent eligibility of genetic sequences extend from Europe, where in 2010 the European Court of Justice in *Monsanto Technology LLC v. Cefetra BV* held that protection for a patent claiming a DNA sequence is limited by a “functionality” requirement as disclosed in the patent document¹, to the United States, where from 2012 to 2013, the US Supreme Court in *Association for Molecular Pathology v. Myriad Genetics, Inc.*² and *Mayo Collaborative Services v. Prometheus Labs, Inc.*³ upheld a shift in the broad scope of patentability of genetic sequences. In fact, owing to additional social and moral concerns over human or plant gene patents, governments of countries such as Brazil and China have also tried, either through court decisions and/or enacted policies, to shape their own standards within the international legal framework and their ability to restrict the patentability of subject matter—be it in medicine or industrial agriculture^{4,5}.

For example, Brazil allows the patenting of methods to transform plants and expression vectors containing heterologous sequences, but it does not allow the patenting of biological sequences isolated from plants or any parts of plants and plant varieties⁶. China allows the patenting of isolated sequences, modified sequences and transformed plant cells, but carves out exclusions to make all or part of plants and plant varieties unpatentable⁷.

Thus, considering how divergent and complex the spectrum of interests in gene

patenting is becoming and how limited is our understanding of the practices across various economies, we have designed and developed a dynamic platform, the patent sequence (PatSeq) toolkit, to render biological patents and their disclosed genetic sequences more publicly accessible and their contextual navigation more evidence based⁸.

We recently reported⁹ on the mapping of patent-disclosed sequences onto three crop genomes (maize, rice and soybean), the analysis of overlapped sequences among plant and human genomes, and on the recently adopted changes to the scope of patentability introduced by the United State Patent and Trade Office (USPTO). Here, we hand edit each of the three plant genome patent sequence maps to identify sequences referenced in the claims of granted patents and analyze their corresponding patent ownership within the context of other plant intellectual property (IP) rights. We conclude by discussing the impact of the current perceptions of ownership on the industry and the public interests.

Referenced sequences that may be related to plant inventions

The task of determining which of the mapped sequences were referenced in plant-related inventions was challenging, as we could not rely on the original sequence source to identify relevant patent sequences. In addition, and unfortunately, the majority of the referenced sequences in granted claims had non-plant origins or were unknown, unspecified or artificial. We initially used US classification codes to screen the corresponding patents and eliminate non-plant patents, then hand edited the data and analyzed broadly the claims to assemble inventions that can be related to plants or cover basic research topics that may be applied to plants. We then com-

bined the findings from all three genomes to check sequence or patent overlap and redundancy.

Results show that only 24% (2,367 out of 9,838), 15% (1,190 out of 7,836) and 24% (2,595 out of 10,634) of the earlier accounted for as maize, rice and soybean referenced sequences, respectively, were actually used in plant-related inventions. These correspond to 846 maize-related patents, 493 rice-related patents and 638 soybean-related patents—or 1,633 granted patents in total, as we found some overlapping patents across the three data sets. The level of overlap among referenced sequences was 9% and redundancy was more than 30%, and only 10% of sequences comprised more than 50 base pairs.

According to the US classification codes, in the hand-edited collection, 65% of inventions were related to the processes of introducing or rearranging a nucleic acid molecule into a plant cell or part, either as such or to develop a transgenic plant or plant part; 48% were related to a plant *per se* (including a higher plant), seedling or plant seed or part; 45% were related to the use of vectors for the introduction of exogenous nucleic acid molecules in host cells; and 33% were related to the transformed plant cell or cell line or to plant proteins used as compounds.

Claim analysis, on the other hand, revealed clearer patterns of sequence use. Although sequence use was broadly similar in plant- and human-related inventions—on the basis of the categories identified in our human genome study⁸—in plant-related inventions, such use was more intertwined within a single patent document. For example, in US patent 8,692,076 (available at https://www.lens.org/lens/patent/US_8692076_B2), the sequence identified as SEQ ID No: 1 was mentioned in claim 1 as part of a larger sequence and so would have been categorized as a “Subpart” in

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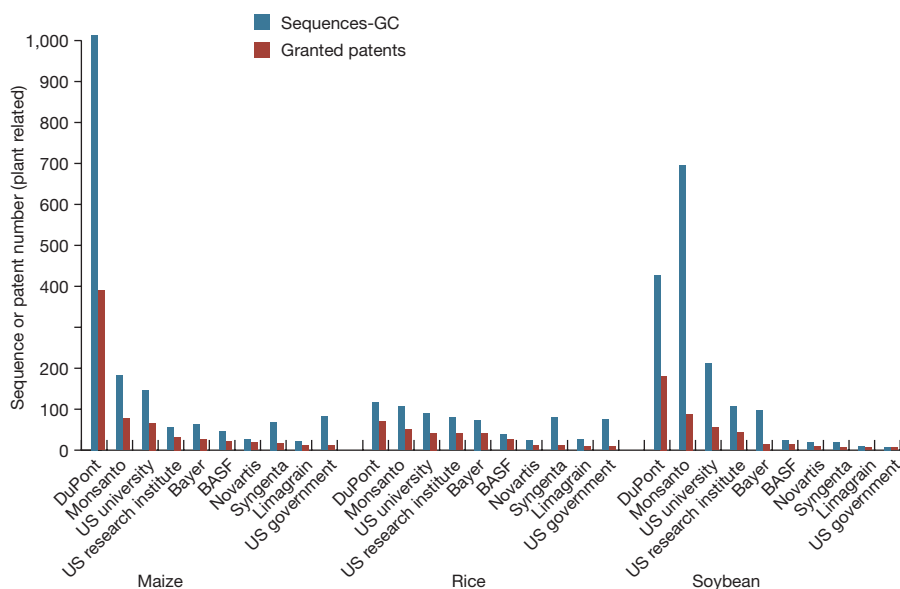


Figure 1 Holdings of granted patents and their referenced sequences in the claims (GC) of the hand-edited plant-related collection, based on the edited applicant and owner data. Only the top 10 applicants are shown.

our human genome study. The same sequence is mentioned as the target of a detection assay in claim 3 and so would have been categorized as a “Target” with respect to that claim. SEQ ID No: 1 then appears in claims 4, 7 and 12 as part of a genetically modified soybean plant or seed and so would have been categorized as “Alter phenotype” with respect to those claims. In other words, the same sequence would have been categorized three different ways for this patent, and this does not include claims that encompass the sequence without explicitly mentioning it, such as for example claim 8. Therefore, unlike in humans, granted claims covering plant-related genes or gene fragments comprised

the use of sequence as ‘isolated’ or in a vector; the use of the vector; and the use of genetically modified host cells, host plant(s), seeds, progenies and methods to produce, detect and use such sequences. Method claims, be they to regulate plant gene expression, target genome changes or improve or manage crop yield by genetic engineering methods, were very common, as were claims covering basic core research technologies. To enable further technology landscaping of the data, we provide the unedited raw sequences in PatSeq Explorer (<https://www.lens.org/lens/bio/patseqexplorer>) and are happy to collaborate on the further analyses of the hand-edited collection of plant related inventions.

Ownership of plant-related gene patents

To disambiguate applicant and owner names in the hand-edited collection, we consulted the publicly available assignment data from the USPTO (ref. 10), curated and cleaned applicant data from the European Patent Office’s DOCDB database and further explored each company, including its name changes, acquisitions, mergers and joint ventures, through press releases, company websites and other publicly available data¹¹. The cumbersome and incomplete process underlines an important need for a globally harmonized data set with persistent identifiers for patent ownership, including corporate relationships that illuminate the ultimate owner of patents.

The biggest lacuna in this analysis—the ‘elephant in the room’ of all patent analyses—is the absence in the public record of who owns the rights to a patent. Licensing information is rarely made public but would completely change the understanding of the state of competition and trust formation and the effectiveness of policy instruments, investment tools and public science and technology expenditure priorities. In principle, virtually all analyses of patent control are confounded and could be misleading or completely incorrect in the absence of comprehensive licensing information. If this is not made statutorily available, global innovation policy—in gene patenting and in all contentious and important domains of innovations—will be based on surmise and on the easy data, not the right data.

Nonetheless, with the data that can readily be gleaned publicly, our analysis of mapped and referenced patent sequences across the three crop genomes revealed DuPont and its affiliates as the holder of the largest collection

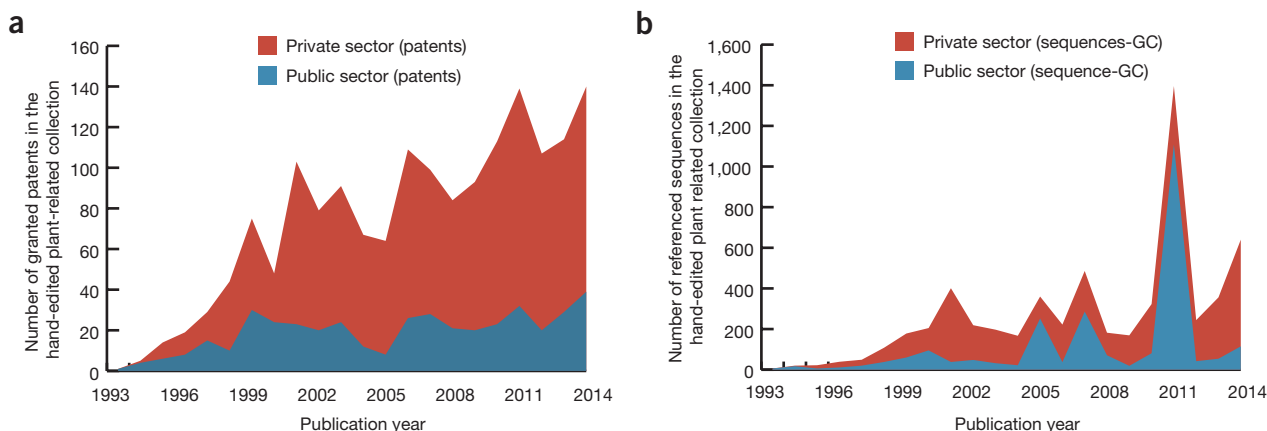


Figure 2 Contribution of public and private sectors to maize, rice and soybean gene patenting activities from 1993–2014. Number of granted patents (a) or referenced sequences in granted claims (b) in the hand-edited plant-related collection, according to the mapping of patent sequences onto maize, rice and soybean genomes combined and their reference in granted claims.

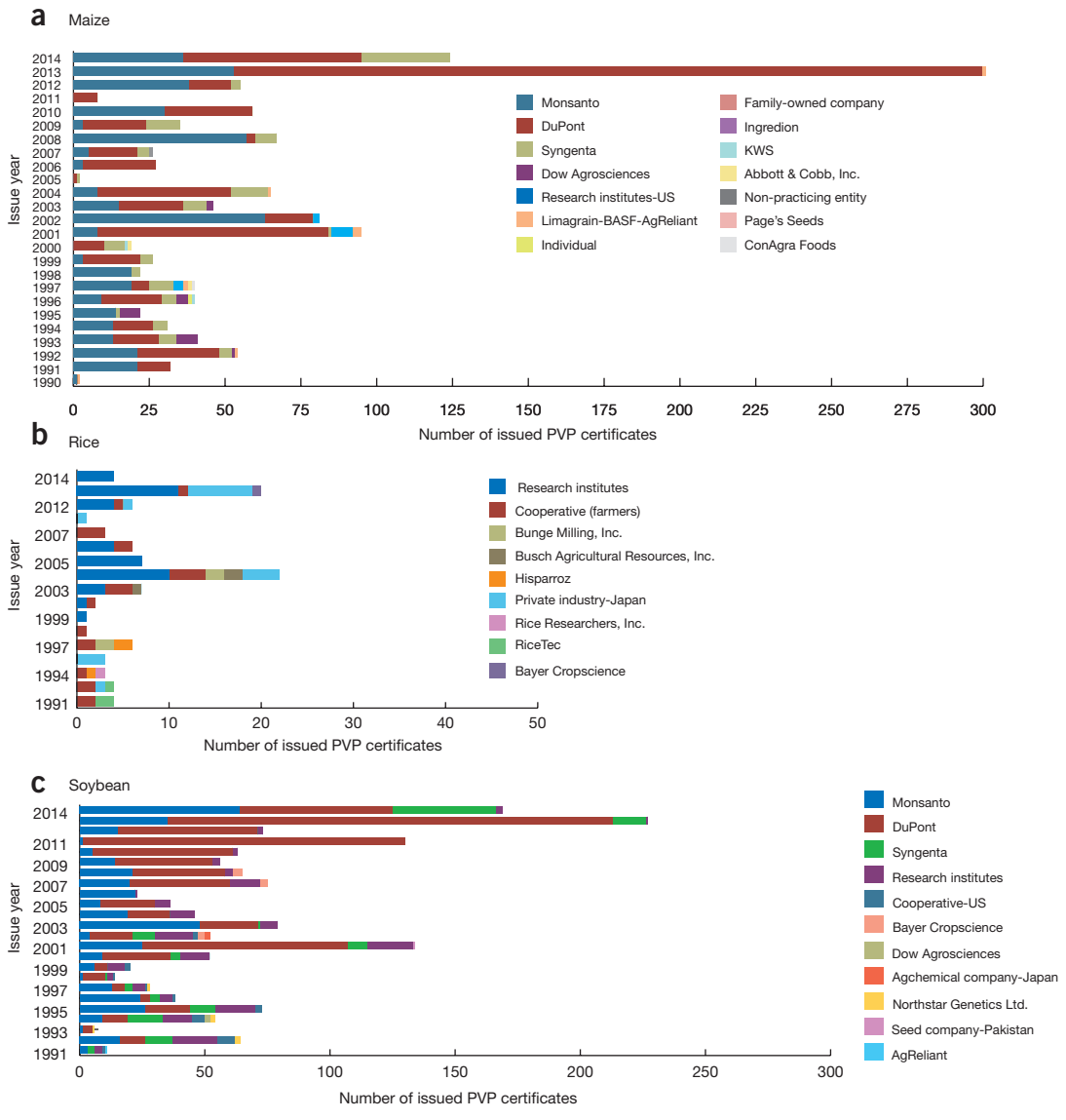


Figure 3 PVP certificates issued for three major crop varieties, 1990–2014. Number of certificates issued for maize (a), rice (b) and soybean (c) varieties in the United States, based on USDA data¹⁸.

of gene patents. It holds more gene patents than Monsanto or the rest of the US industry—including small and medium biotech companies and governmental research institutes and universities—put together (Fig. 1).

We cannot ascertain that these results represent actual practices, as we have not accounted for the cross-licensing agreements that take place between various IP owners. The results also suggest that the public sector, which includes universities, government and research institutes, is active in plant-related gene patenting. So, to draw a larger perspective on its contribution, we grouped our data on the basis of the affiliation of the applicant or owner—either to the public or the private sector—and plotted it against publication year (1993–2014). Similar grouping was also

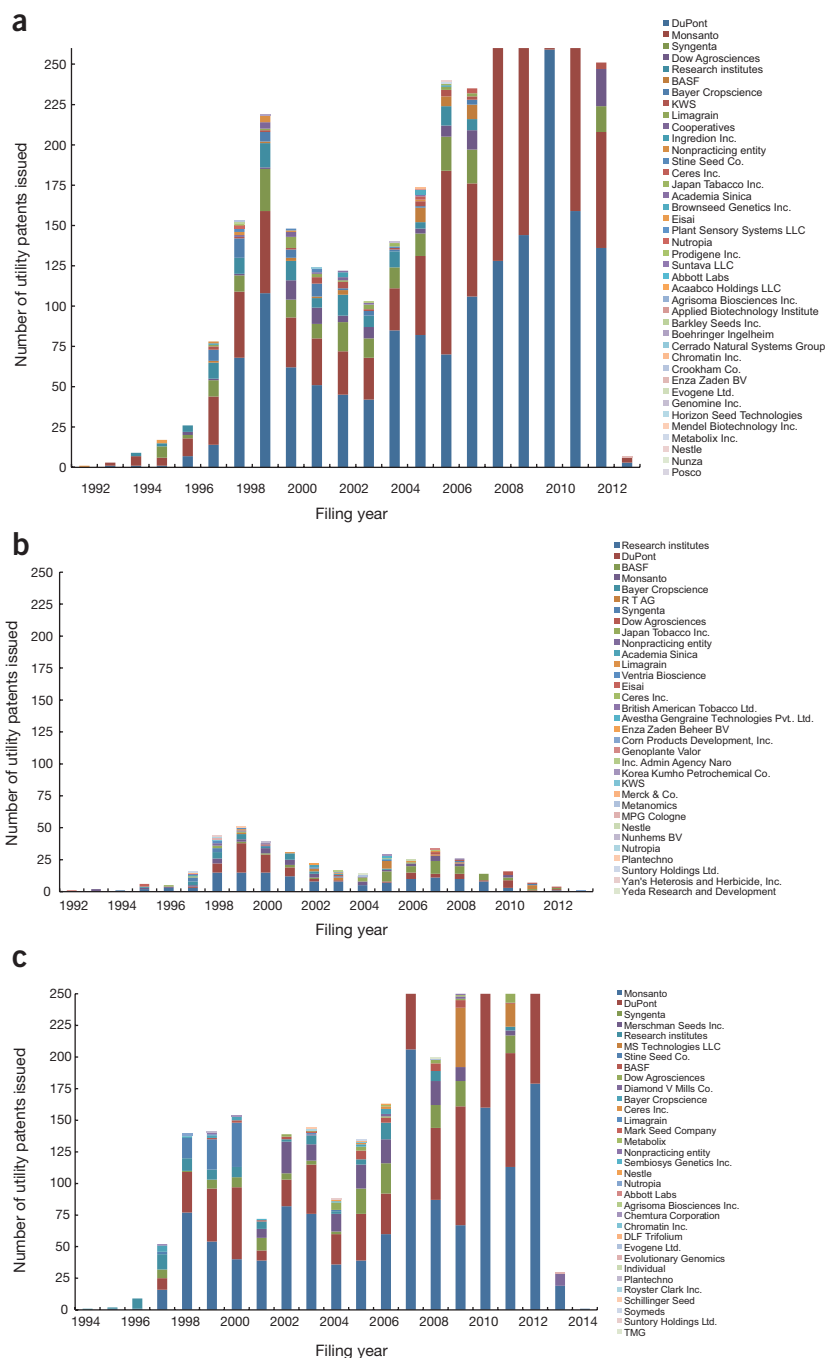
performed using the referenced sequence data.

We found that the public sector's activity in plant gene patenting has been significant throughout the past 22 years. At the early stage of biotechnology and biological research on these genomes, the public sector's contribution was 40–50% by 2000. Since then it has varied, between 12.5% (in 2005) and 27.9% (in 2014), with an average of 25% annual contribution, on the basis of the patent holdings in the hand-edited collection (Fig. 2a). These findings are similar to what was reported in 2003 (ref. 12). However, as our results cover only three major agricultural crops and extend from the 1990s to 2014, they suggest a gradually widening gap in the ownership of plant gene patents

between the private and public sectors. Again, this conclusion is subject to the caveats that assignments of public IP to private hands—or indeed exclusive licensing—are not typically a matter of public record.

Upon using the referenced sequence holdings as a proxy to public sector's contribution to the inventions, we found that in the early stages of biotechnology and biological research, the public sector was less active than the private sector in capturing or referencing sequences in patent claims until 2005, when it started to reference a large number of sequences in patent claims (Fig. 2b), implying the emergence of a convergent business model between the sectors in the past decade.

Here also, we limited our analysis to plant-related gene patents, but to provide a broader



varieties can be protected by a specific plant patent under the Plant Patent Act of 1930 for asexually reproducible plants; by a plant variety protection (PVP) certificate under the Plant Variety Protection Act of 1970 for sexually reproducible plants or tuber-propagated plant varieties; or, since 1985, by utility patents¹⁶.

Because several types of protection can be granted at the same time—for example, either a plant patent or a PVP certificate with a utility patent—and exclusive rights extend for 20 years, any IP right holder on any of the crops can in principle benefit not only by enforcing their IP rights but also by holding off competition in the market and potentially delaying innovation on certain technologies, especially when the granted rights are under utility patents¹⁷. Utility patents have a broader scope, including protection on the plant itself, its diverse uses, its progenies and the method used to produce it, and they have an impact on follow-on innovations.

To examine utility patent holdings and PVP certificates issued on maize, rice and soybean, we requested and received records on plant variety certificates issued on each of the three crops from the United States Department of Agriculture¹⁸ and created utility patent collections in the Lens, using US classification codes for maize (800/320.1), rice (800/320.2) and soybean (800/312). In addition, for each data set we hand-edited and disambiguated the names of applicants or owners and plotted patent and certificate holdings on the basis of the date issued (for certificates) or the filing year (for utility patents). We found that between 31 August 1990 and 19 September 2014, a total of 1,963; 111; and 1,991 PVP certificates were issued on maize, rice and soybean varieties, respectively, and 3,566; 409; and 2,967 utility patents were granted on each crop, respectively.

Plotting PVP and patent holdings over the past 25 years confirms that DuPont and Monsanto, including their published subsidiaries and acquisitions, have held a dominant position over maize and soybean genome IP over time, followed by Syngenta and BASF (Figs. 3 and 4). The data also show that the major IP holders were involved in IP acquisitions as early as 1990 and that although the number of holdings was increasing, a gap was forming between these entities and other applicants and owners (Figs. 3a,c and 4a,c) in that industry, confirming a gradual consolidation of IP in a few key players. By 2008–2010, small or individual owners appear to have been almost nonexistent.

In rice, trends were slightly different. With fewer holdings in both PVP and utility patents

Figure 4 Utility patents issued from 1990 to 2014. Utility patents issued on maize (a), rice (b) and soybean (c) plants, based on searches for US classification codes 800/320.1 (maize), 800/320.2 (rice) and 800/312 (soybean).

view of current maize, rice and soybean IP practices, we extended the analysis to include those on utility patents that target genomes rather than genes and other IP data such as that on plant variety protection certificates. Currently, various legal regimes are available to protect plants¹³, the industry is heavily concentrated¹⁴ and old gene technologies are evolving into genome-based modifica-

tion technologies¹⁵, particularly in the United States, where applicants can double protect a plant genome.

Genome IP practices in the United States

Uniquely in the United States, plants and their products can be protected by patents and by other IP mechanisms at the same time. Plant

than for maize or soybean, rice showed a more diverse set of applicants. It seems that from 2003 onward, research institutes and farmer cooperatives have been more engaged in acquiring PVP certificates than have DuPont or Monsanto, for example (Fig. 3b). However, DuPont has remained active in acquiring utility patents on rice since 1996, as far as the public records show (Fig. 4b).

Complementing these results with those obtained from ownership analysis of the hand-edited plant-related collection re-asserts the dominant role of DuPont and its affiliates in plant-related IP portfolio globally, followed by the US industry, which includes small biotech companies, governmental research institutes and universities, and then by Monsanto and its affiliates.

These results may or may not represent actual practices; as discussed above, patent owners are not legally required to disclose reassignment or licensing data to the patent office. The public can see only the information that a patent owner chooses to provide. For example, a large biotech could license all or part of its patent portfolio to another large biotech, which could in turn sublicense it to a smaller company. A young entrepreneur interested in that collection of patents could spend huge sums on lawyer's fees for investigating the true ownership of each patent or developing a freedom-to-operate analysis before even beginning to make a product for market.

Global trends of gene and genome IP practices

Plant gene practices in Europe may vary slightly, as Europe's IP laws are different. Under Articles 1–11 of Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions, IP rights on plants are permissible only when the invention covers plants in general and regardless of the kind of plant variety, so plant varieties as such are not a patentable subject matter¹⁹. Diverse national policies have been adopted worldwide to regulate IP rights on plants and plant varieties (Supplementary Table 1), especially in jurisdictions where plants are part of the country's culture and basic food; for example, in Asia specific provisions were incorporated into national IP laws to render rice a nonpatentable subject matter²⁰.

Moreover, under Article 27.3 of the international Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), each member government has the authority to provide its own *sui generis* IP systems to protect plants or plant varieties as an alternative to utility patents and carve exclusions²¹. Plant variety protection, which is based on the International

Union for the Protection of New Varieties of Plants (UPOV) guidelines, is a valid alternative used by many governments. Under UPOV, members may, and in some cases have introduced exclusions such as “[i] exclusion of plants from patent protection; [ii] exclusion of plant varieties from patent protection; [iii] exclusions of both plants and plant varieties from patent protection; [iv] allowing the patentability of plants, and [v] excluding or allowing the patentability of essential biological process for the production of plants.”²⁰ Further discussions on such flexibilities can be found in the document prepared by the Secretariat of the World Intellectual Property Organization (WIPO) and published at the 13th session of the Committee on Development and Intellectual Property (CDIP).

Conclusions

The restructuring of the crop agriculture industry in the 1980s and 1990s and the strategic use of patent rights enabled some large-scale patent holders to exclude or deter others from using critical research tools and materials^{14,22}. This legal and expected use—delaying or otherwise limiting competitive products or follow-on inventions—allowed a few corporations to influence or control much of global agricultural innovation, a situation that many find disquieting, and which may lie at the heart of the ongoing resistance to new agricultural technologies.

Efforts to improve the system to increase fairness, relevance, diversity of participation and trust must be based on sufficient transparency to ensure evidence-based and inclusive policy and practice.

For instance, plant-related gene patents were fewer and harder to identify through patent sequence analyses than human-related gene patents, because many of the referenced sequences in granted patents either did not originate from a plant species or had artificial or unspecified ‘declared species’ information associated with them. Further examination of this issue revealed inconsistencies in the provision of valid species information among the various data sources. To remedy such a situation, parsers can capture other metadata related to sequence origin; we intend to incorporate this in new releases. Patent offices should do likewise and enforce their requirement for such disclosure.

Our ownership analyses of gene patents show that the public sector has been an active contributor to the research, development and commercialization of these three crops throughout the past two decades. However it is unclear what this limited ownership data means. Has ownership been transferred outright and unrecorded? Even if the data were open and comprehensive,

it would not be enough. The power of a patent lies in the rights to exclude, or not be excluded, and these rights can be transferred separately from ownership in the form of a license.

A critical policy imperative should mandate public disclosure and recordation of licensing status of patents derived from such public research, or conducted by public institutions under contract. Only then can we sensibly assess the degree of compliance with public goals, or capture by private interests, and take evidence-based steps to improve the desired outcomes.

As public investment in crop agriculture continues to stagnate²³, the public innovation space risks capture by private interests, and moving away from modest market and margins, or innovations with many but diffuse beneficiaries, such as those promoting environmental benefit, focusing rather on financially valuable inventions with high-value capture potential. This outcome would be of questionable desirability for goals of diversification and resilience and could affect many economies, environments and communities.

Only through dramatic improvements in transparency—of patent meaning, of patent ownership, of license status and of placement of patent rights in the context of innovation knowledge—can the full potential of science and technology in agricultural innovation be reached, with the broadest canvas of ideas, participants and public support.

Note: Any Supplementary Information and Source Data files are available in the online version of the paper (doi:10.1038/nbt.3393).

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COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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