

(<https://biobricks.org/bpa/>). It would be a small step to implement similar policies for synthetic biology standards, such as SBOL. Such an approach has recently been proposed by one of us for bioinformatics standards<sup>9</sup>, and numerous readily available tools exist to assist with policy development<sup>2</sup>. Best outcomes for synthetic biology will result from simultaneous consideration of technical standards and IP issues.

Accordingly, although we commend the authors on their development of SBOL and other techniques for achieving interoperability of synthetic biology elements, we hope that they will also devote some attention to the IP issues noted above to avoid some of the pitfalls that have affected and increased costs associated with standardization in other industries.

#### ACKNOWLEDGMENTS

A.K.R. gratefully acknowledges support from the National Human Genome Research Institute under Center of Excellence Grant P50 G003391002.

#### COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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Michal Galdzicki, Linda J Kahl, Drew Endy & Herbert M Sauro reply:

We thank Contreras *et al.*<sup>1</sup> for drawing attention to the important couplings between technical standards and property rights in synthetic biology. In creating a first-ever standard for information exchange in synthetic biology<sup>2</sup>, we are committed to ensuring that the synthetic biology open language (SBOL) remain free to use for all.

Members of the SBOL development group, J. Christopher Anderson, Evan Appleton, Douglas Densmore, Drew Endy, Michael Fero, Michal Galdzicki, John H. Gennari, Raik Grünberg, Linh Huynh, Jeffrey David Johnson, Linda J. Kahl, Goksel Misirli, Chris Myers, Ernst Oberortner, Matthew Pocock, Jacqueline Quinn, Cesar A. Rodriguez, Nicholas Roehner, Herbert Sauro, Evren Sirin, Guy-Bart Stan, Neil Swainston, Mandy Wilson, individually and collectively, do not hold or plan to assert property rights claims against users of SBOL. Although we can never guarantee that third parties will not assert claims against SBOL users, our intention is to develop, release and, if needed, revise SBOL so that it remains free to use.

We therefore chose to work in an open and transparent manner using the BioBricks Foundation Request For Comments (BBF RFC) process (<http://biobricks.org/programs/technical-standards-framework/>), which allows us to document the development of the SBOL standard by means of a time-stamped world-readable digital archive. For example, BBF RFC #84 (ref. 3) and BBF RFC #87 (ref. 4) were issued on October 3, 2011, and October 11, 2012, respectively. We used these BBF RFCs to formally disclose the development of SBOL at specific points in time, name all process participants and establish various aspects of prior art.

We agree with Contreras *et al.*<sup>1</sup> that the time is right for the SBOL development group and others in the synthetic biology community to consider more formal policies requiring disclosure and licensing of

property rights covering technical standards. Inevitably, there will be trade-offs in the time and resources needed for developing technical standards versus the time and resources needed to identify and evaluate property rights that may be essential for practicing those standards. As such, it will be important to establish policies for meaningful disclosure that are not overly burdensome and will not unduly hinder the standards development process.

We, together with the BioBricks Foundation and others in the synthetic biology community, would welcome additional work by legal professionals to analyze, establish and share opinions regarding the ‘freedom to operate’ for SBOL v1.1 and other standards from a property rights perspective. These opinions could, for example, be made available to the public by posting on the BioBricks Foundation’s website. By engaging in a careful and active process of public documentation and disclosure of SBOLs development, and by working with legal experts that could assist in identifying potential third-party rights (thereby enabling workarounds if needed), we hope to realize our goal of keeping the SBOL standard free to use for all.

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## Status and market potential of transgenic biofortified crops

#### To the Editor:

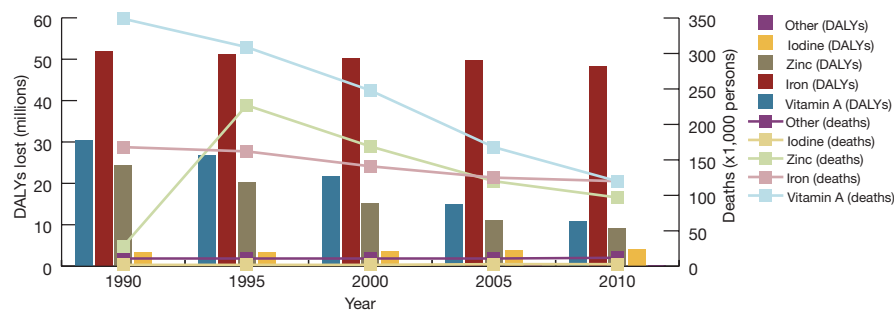
This month marks the 15th anniversary of the publication of pro-vitamin A-enriched ‘Golden Rice’<sup>1</sup>. As the crop still awaits regulatory approval, its developers have little reason to celebrate. Golden Rice is not alone in facing a political and regulatory blockade. Several other biofortified transgenic crops also await authorization, in contrast to numerous staple crops with elevated micronutrient content developed through conventional breeding techniques that are available for consumption around the world.

Currently, genetically modified (GM) crops approved for cultivation are all

products with improved agronomic traits—so-called first-generation traits that mainly benefit farmers in the developed and developing world<sup>2,3</sup>, rather than consumers. Despite the global growth in transgenic acreage of first-generation crops, there is now a world-wide ‘regulatory slowdown’<sup>4,5</sup> in approvals of GM crops, and agbiotech remains politically controversial in Europe<sup>6</sup> and elsewhere<sup>7,8</sup>.

The case of Golden Rice illustrates how second-generation GM crops face commercialization barriers similar to those the preceding generation of crops faced<sup>9</sup>, with their benefits often ineffectively

Corrected after print 14 January 2015.



**Figure 1** The global burden of micronutrient malnutrition. The number of DALYs and deaths attributable to deficiencies of key vitamins and minerals as risk factors. Source: Compilation based on IHME Global Burden of Disease database<sup>31</sup> (available at <http://www.healthdata.org/search-gbd-data>).

communicated to the public<sup>10</sup>. Nevertheless, in the past two decades, agbiotech research has steadily extended its focus toward food crops with enhanced quality traits that carry tangible benefits for consumers.

Golden Rice exemplifies the way in which transgenic technology can expand the range of micronutrient strategies available to malnourished populations, especially in poor rural regions, where industrial infrastructure and educational efforts are often lacking and/or can be difficult to implement. Indeed, despite numerous efforts to tackle vitamin and mineral deficiencies through supplementation, industrial fortification or dietary diversification, deficiencies remain widespread among two billion people (Fig. 1). This is especially the case in developing regions, where monotonous diets, mainly or solely consisting of staple crops, provide the daily caloric intake of the population<sup>11</sup>. Here, biofortified crops can play an important alternative, agriculture-based strategy to alleviate the burden of micronutrient malnutrition<sup>12</sup>.

To build a case for these biofortification efforts, researchers have gradually started to anticipate the risk of market failure by joining forces with colleagues who—putting aside regulatory constraints—assess *ex-ante* the market potential of their new product developments. The following correspondence summarizes the current state of product development in the field of transgenic biofortification as well as applied consumer research at the microlevel (i.e., consumer studies on acceptance and willingness to pay) and macrolevel (i.e., health impact assessments, cost-effectiveness and/or cost-benefit analyses) (See **Supplementary Glossary**). Out of the 60 studies selected from the peer-reviewed literature, 35 reported key findings on the development of single- or multi-biofortified

crops, with 19 and 6 studies conducting a micro- or macro-level analysis, respectively (Fig. 2 and **Supplementary Dataset**).

Biofortification can be achieved by conventional breeding or by plant biotech. Conventional breeding is possible only between closely related (sexually compatible) individuals (and thus relies on natural variation of the target compound within parental lines) and is also time-consuming. Although marker-assisted breeding (MAB) and quantitative trait loci (QTL) mapping can accelerate conventional breeding, the minimum number of breeding generations for clonally propagated crops (e.g., potato, sweet potato, banana and cassava) is estimated to be 7 generations, for self-fertilizing crops (e.g., rice, wheat and sorghum), 9 generations and for cross-fertilizing crops (e.g., corn), 17 generations<sup>13</sup>.

Pro-vitamin A-biofortified yellow corn is a prime example of a staple crop where breeding was successfully applied to increase micronutrient content to a desirable level<sup>14</sup>. In some cases, however, natural variation of the desired micronutrient is insufficient for conventional breeding. Moreover, in cereals, most of the vitamins and minerals are concentrated in the outer layers and the embryo of the kernel, which are usually removed upon milling to prolong storage, leaving only the endosperm. Thus, conventional breeding of cereals would have little or no effect on their vitamin and mineral content after milling. Enhancing micronutrient levels in staple crops by metabolic engineering greatly outpaces the results obtained by conventional breeding, MAB and QTL mapping (**Supplementary Fig. 1** and **Supplementary Table 1**). Moreover, engineering strategies can be redirected toward the accumulation of a target compound into the desired tissue, such as cereal endosperm, without

compromising micronutrient content upon milling.

Great progress has been made in increasing vitamin content in staple crops by metabolic engineering. Although enhancing vitamin bioavailability could further improve their nutritional quality, vitamin engineering strategies to date have mostly relied on the accumulation of target compounds. Often, genes originating from nonrelated organisms, such as other plant species, mammals and/or bacteria, are overexpressed in the target crop (**Supplementary Table 2**). The best known example is Golden Rice<sup>1,15</sup>, which was engineered with transgenes from daffodil and the bacterium *Pantoea* (formerly known as *Erwinia*)<sup>1</sup>. Golden Rice opened the door for the creation of other pro-vitamin A-enriched staple crops, such as corn, cassava, potato and wheat (**Supplementary Fig. 1**), whereas genes from other organisms appeared to further increase  $\beta$ -carotene content in target crops (for more details and references, see **Supplementary Table 2**).

Another well-known example is folate (vitamin B<sub>9</sub>)-enhanced rice<sup>16</sup>. Here, transgenes from *Arabidopsis* were overexpressed in rice endosperm, which resulted in a 100-fold increase in folate content<sup>16</sup>. Again, conventional breeding was not an option because of the low folate content and low natural variation of this compound in rice kernels<sup>17</sup>. Attempts to increase ascorbate (vitamin C) content in staple crops were moderately successful (**Supplementary Table 2**), mainly because the metabolism of antioxidants is tightly regulated and therefore difficult to engineer. This clearly illustrates that to successfully engineer vitamin content in target crops not only a profound understanding of the biosynthesis pathways of vitamins is required, but also knowledge of the regulation of these biosynthesis routes, as well as the turnover and accumulation of the respective vitamins.

Over the past decade, interest in improving the mineral content in staple crops has grown as well, the focus being mostly on iron and zinc. Unlike vitamins, minerals cannot be synthesized by plants, which rely entirely on their availability in the soil. The Green Revolution, which coincided with large-scale irrigation and macronutrient fertilization, compromised mineral levels and availability in crop fields. Although soil fertilization would be an obvious way to increase mineral content in staple crops, foliar fertilization is often more successful<sup>18</sup>. Iron and zinc

engineering strategies focus on enhancing both bioavailability and content. Cereals, for instance, contain antinutritional factors, such as phytic acid, which bind iron and zinc, limiting their absorption by the human intestine. Several attempts at lowering phytic acid levels both by conventional breeding and genetic engineering have been reported, mostly in cereals<sup>18</sup>. Engineering mineral content in staple crops is challenging because it involves many processes from mineral uptake by the roots, to transport throughout the plant, to accumulation in edible tissues. Metabolic engineers must correctly orchestrate these processes, which requires overexpression of multiple genes. Although numerous attempts to achieve mineral enhancement by engineering one or two processes have been reported, successful multiprocess engineering approaches are scarce.

A multi-biofortification approach is necessary to optimally tackle micronutrient deficiencies. Multivitamin white corn<sup>19</sup>, with enhanced  $\beta$ -carotene, folate and ascorbate levels, sets a good example toward this goal, as well as mineral-enriched rice, where the overexpression of a single rice gene, resulted in enhanced iron, zinc and copper content<sup>20</sup>. However, there is a growing awareness of the importance of

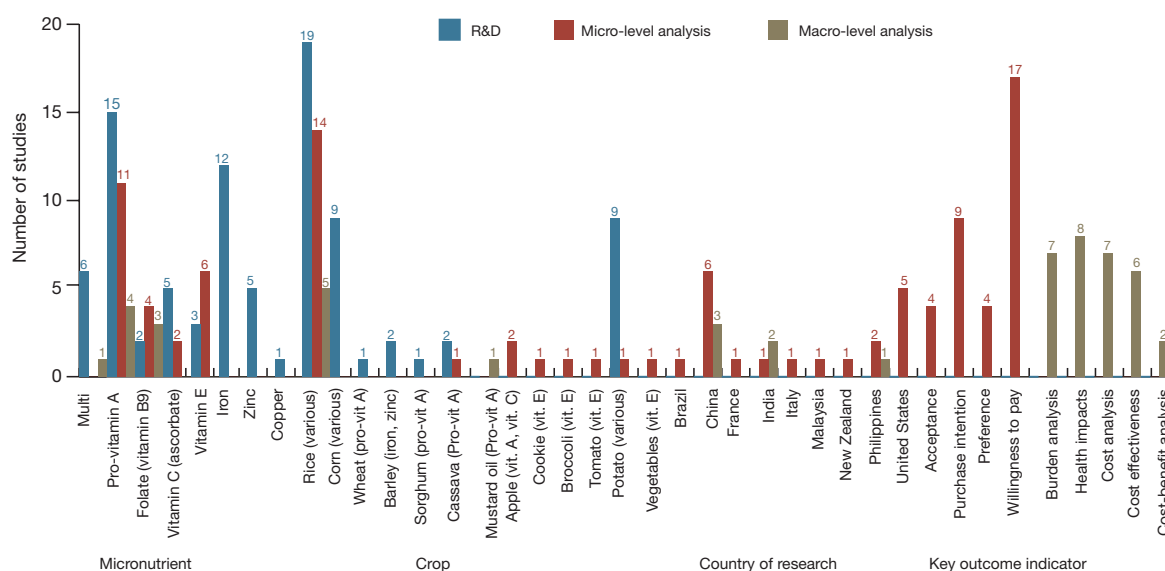
nutritional enhancement, in a broader range of essential and nonessential phytonutrients, in major crops consumed across the world.

Although an increasing number of studies report successful biofortification attempts, second-generation, staple GM crops remain unavailable to consumers, largely due to regulatory obstacles (for a discussion, see ref. 21 and **Supplementary Note** on GMO regulation. By building an evidenced-based case for the potential demand and impact of GM crops with health attributes, researchers hope to influence priority-setting and resource allocation, and thus facilitate decision-making by government authorities on whether or not to adopt them<sup>22</sup>.

As biofortification efforts have proceeded furthest in rice<sup>15,23</sup>, studies on consumer acceptance of, and willingness to pay for, transgenic biofortified crops have mainly focused on rice (14 studies); that is, rice fortified with pro-vitamin A, folate or vitamin C (9 studies, 4 studies and 1 study, respectively; **Fig. 2** and **Supplementary Table 3**). Six microlevel studies have been carried out on four products containing enhanced levels of vitamin E (in cookies and made from wheat flour, broccoli, tomato and potato), two on pro-vitamin A-enriched plants (cassava and apple) and one on a vitamin C-enhanced apple

variety. Although targeting nonstaple crops is less relevant from a health policy point of view, their results are useful for evaluating consumer reactions toward transgenic biofortification. Asia (10 studies) is by far the most-often selected research location, followed by North America (5 studies), Europe (2 studies), Oceania or South America (1 study). Despite the lack of African studies, the geographical spread of consumer research is important, given the global need to tackle micronutrient malnutrition.

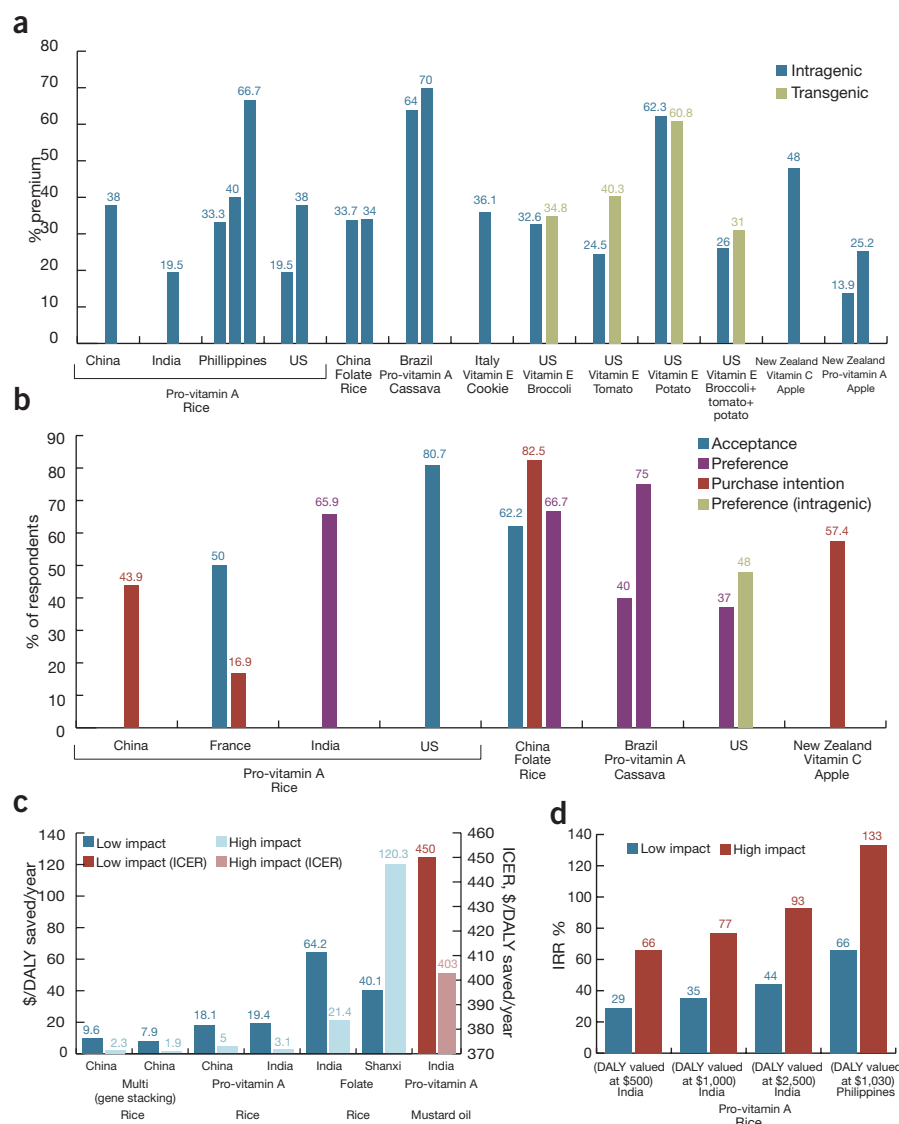
Whereas consumers often demand a discount when it comes to first-generation GM foods<sup>24</sup>, the premiums they are prepared to pay for transgenic biofortified crops are relatively high, from 20% to 70%, regardless of the targeted crop, micronutrient and country (**Fig. 3a**). In regions with high prevalence of micronutrient deficiencies, such as China and Brazil, which are considered priority target markets, willingness-to-pay levels are as high as, and often exceed, those in developed regions. Together with the optimistic purchase intentions, preference rates and acceptance levels, these findings lend support for transgenic biofortification as an alternative micronutrient strategy, especially in developing regions (**Fig. 3b**).



**Figure 2** Number of studies on the development and market potential of transgenic biofortified products organized by micronutrient, crop and country categories, and key outcome indicator. Note: under the micronutrient category, multi-biofortification included several different types of crops, whether for research studies or for macrolevel analysis (no microlevel analysis was identified in our literature survey). R&D studies included one study on pro-vitamin A- + folate- + vitamin C-enriched corn, three studies on iron- + zinc-enriched rice, one study on iron- + zinc-enriched barley, one on iron + zinc + copper rice. The one macrolevel analysis of multi-biofortification was for a pro-vitamin A + folate + conventional traits zinc + iron rice. Under the crop category, 'various' refers to rice (fortified with multiple micronutrients folate + pro-vitamin A + zinc + iron; excl. 3 R&D studies on multi-biofortification or one of pro-vitamin A, folate, vitamin C, vitamin E, iron, zinc or copper), corn (fortified with pro-vitamin A, folate, vitamin C, vitamin E or iron) and potato (fortified with pro-vitamin A, vitamin C or vitamin E). The targeted multi-biofortified crop contains transgenic (pro-vitamin A or folate) and conventional traits (zinc or iron). The 'cookie' is made from transgenic wheat (vitamin E). Several studies examine different micronutrients, crops and/or outcome indicators. For detailed information, see **Supplementary Tables 2, 3** and **5**.

**Figure 3** Market potential of biofortified crops. (a) Willingness to pay (percentage premium).

(b) Percentage of respondents with acceptance of, purchase intention for and preference for, transgenic and intragenic biofortified crops, per target crop, micronutrient and country. Premium and preference levels are compared with a conventional, non-GM crop. Multiple blue or purple bars for one country refer to premium differences within (Brazil) or among studies (China and Philippines), except for willingness-to-pay premiums for pro-vitamin A apples in New Zealand, which were compared with apples treated with vacuum-infiltration of apples with vitamin A and irradiation (UV-treatment boosts the production of vitamin A in the latest stage of apple development), respectively. Preference levels exclude the group of indifferent respondents. Purchase intentions refer to the share of respondents that is prepared to pay a premium. All values are based on a sample of adults, except for the studies in the Philippines (students) and one study in China (34.0% and 62.2% women of childbearing age). Values based on partial data sets are not presented. (c) Cost effectiveness and (d) cost-benefits of transgenic biofortified crops. Impact scenarios differ in terms of efficacy (e.g., improved micronutrient content, post-harvest losses and, in the case of pro-vitamin A, bioavailability) and estimated market coverage (i.e., consumption levels), by which low-impact scenarios are rather pessimistic compared with the more optimistic high-impact scenarios. Shanxi Province is a high-risk region of folate deficiency in China. \$/DALY refers to the monetary cost to save one DALY. The internal rate of return (IRR) is a common measure to evaluate the economic feasibility of an intervention by calculating the annual percentage yield for each dollar invested. The IRRs on biofortification attach a monetary value to one DALY saved (i.e., \$500, \$1,000 or \$2,500 in India or the national per capita income in the Philippines, \$1,030). Only interventions with an IRR that exceeds the cost of capital (i.e., the minimum required return of the investments or 10–12% for health-related projects<sup>32</sup>) are worth implementing. Incremental cost-effectiveness ratio (ICER) figures (right y axis) represent the additional cost to save a DALY when choosing biofortification over supplementation. Data from **Supplementary Dataset**.



With respect to biofortified rice in India and China, for example, all market-share figures obtain a level above 60%, except for a study in urban China, where 43.9% of respondents still intend to purchase Golden Rice.

When also taking the share of indifferent consumers into account (**Supplementary Table 4**), transgenic biofortified crops appear to be commercially viable.

To date, all macrolevel analyses have studied rice, enriched with pro-vitamin A (two studies), folate (two studies) or a combination of micronutrients (i.e., pro-vitamin A, folate, zinc and iron), with the exception of one on pro-vitamin A-biofortified mustard oil (**Fig. 3c**). Studies on folate- and multibiofortified rice were conducted for China and, in the case of the former in Shanxi, Shanxi Province, where

there is high risk for folate deficiency, whereas India and the Philippines were selected for evaluating the potential introduction of Golden Rice and/or mustard oil, respectively.

All studies build upon the disability-adjusted life year (DALY) framework to measure the burden of micronutrient deficiencies (in DALYs lost per year) on the one hand, and to determine the potential health benefits of transgenic biofortified crops (in DALYs gained per year) on the other. DALY is a health measure that describes both mortality and morbidity associated with a health condition (e.g., vitamin deficiency) as a single index: years of life lost plus years lived with disability. To evaluate whether the resources that accrue from the implementation justify the

health impacts, six cost-effectiveness and two cost-benefit analyses were undertaken (**Supplementary Table 5**).

When comparing the potential health benefits of introducing transgenic biofortified crops, substantial differences exist between the targeted products, micronutrients and countries (for disease burden and health impact figures, see **Supplementary Table 6**). Golden Rice, for example, has the potential to lower the burden of vitamin A deficiency in China, India and the Philippines by 17–60%, 9–59% and 6–32%, respectively. In China, both folate deficiency and micronutrient malnutrition can be reduced by, respectively, 20–82% and 11–46% when folate-biofortified or multi-biofortified (pro-vitamin A, folate, iron and zinc-enriched)



rice is placed on the market. And when it comes to saving lives, Golden Rice and mustard oil both would have a substantial impact, which is largely attributable to the strong association between vitamin A deficiency and child mortality.

The cost effectiveness of enhancing several micronutrients simultaneously is by far the most promising option because it generates aggregated health benefits at a relatively low additional cost (\$1.9–9.6 per DALY saved); followed by Golden Rice and folate-biofortified rice (Fig. 3c). Even so, all transgenic, biofortified rice varieties fall well below the standard benchmark for evaluating micronutrient interventions (i.e., the upper boundary for highly cost-effective interventions of \$267.4 per DALY saved in 2013, as set by the World Bank<sup>25</sup>). This demonstrates that from a public health perspective, these interventions are a worthwhile undertaking. Moreover, the generally low (recurrent) costs are often put forward as a major advantage. Even if biofortification is expected to be more costly than supplementation, which is the case for Golden mustard oil, its potential health impact is (among) the highest. Cost-benefit analyses, though conducted only for Golden Rice in India and the Philippines (Fig. 3d), further support the sizable health benefits of transgenic biofortified crops and justify the \$15.7-million and \$21.4- to 27.9-million investments to put Golden Rice on the Indian and Philippine market, respectively (for cost figures, see **Supplementary Dataset**). Although caution is needed when interpreting these findings, owing to crop-, micronutrient- and country-dependent data assumptions and methodological choices, they all confirm the market potential of transgenic biofortification research.

Given the market potential of transgenic biofortified crops, their cost effectiveness and the positive consumer reactions, one might argue that their authorization could break the legacy of first-generation GM crops and become a catalyst for the adoption of transgenic crops in the future. According to a recent review on GM rice, for example, the global value of the second-generation varieties that are currently in the R&D pipeline amounts to about \$56 billion per year<sup>26</sup>. Golden Rice, in particular, of which delayed adoption in Asia alone results in an annual economic loss of about \$16 billion, would generate large welfare gains that outweigh those of first-generation GM rice varieties<sup>27</sup>. Nevertheless, to successfully

market such crops, an (economic) incentive should be provided to farmers. Therefore, the targeted micronutrient trait should be crossed into high-yielding varieties, as intended for Golden Rice in the Philippines<sup>28</sup>. Improving both micronutrient and yield traits will increase the likelihood of farmer adoption, as such crops deliver benefits for consumers and, both directly and indirectly, for farmers. A humanitarian license, similar to 'future' Golden Rice<sup>29</sup>, or a governmental subsidized credit for seed purchases should also be considered.

At a time of repeated delays in Golden Rice commercialization, despite the extensive campaigning to reverse this trend (e.g., see the recent launch of the Allow Golden Rice Society), research continues to produce important new transgenic biofortification traits and economists demonstrate their market potential. Notwithstanding the positive outcomes in both fields, the anti-GM organisms lobby continues to block the introduction of these products. Meanwhile, the hidden hunger of micronutrient deficiencies remains a major public health problem, calling for alternative strategies that aim to help those who need it the most. Though using staple crops for transgenic biofortification is an appropriate strategy to reach poor, malnourished populations, these crops remain a meager source of various other untargeted micronutrients.

Certainly, transgenic biofortification is not a panacea for eliminating malnutrition<sup>30</sup>, but it does offer a complementary, cost-effective intervention. In this context, we hope the data presented in this study can be used constructively not only by those developing biofortified crops, but also by those seeking a combined approach to reduce the burden of micronutrient malnutrition.

*Note: Any Supplementary Information and Source Data files are available in the online version of the paper.*

#### COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

#### ACKNOWLEDGMENTS

D.B. is indebted to FWO (Fund for Scientific Research Flanders) for a postdoctoral fellowship.

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## Corrigendum: Status and market potential of transgenic biofortified crops

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*Nat. Biotechnol.* 33, 25–29 (2015); published online 9 January 2015; corrected after print 14 January 2015

In the version of this article initially published, Figure 3a had three errors. The heights for bars '26' and '31' for US, Vitamin E, broccoli + tomato + potato were ~7 and ~25, respectively; the transgenic (green) value US, vitamin E, tomato was given as '24.5', but should be '40.3'. The errors have been corrected in the HTML and PDF versions of the article.