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Wild Introgressions: The Tomato Genome's Impact on Plant Patenting and Trademark Branding Prospects

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Diana Kennedy, an intrepid chronicler of Mexican cuisine, describes *cuatomates* as "very small cherry tomatoes with an intense flavor and enormous amount of tiny seeds." A potently flavored, tiny green *tomatillo* variety "grows wild in [Mexican] cornfields."[1]

Wild, obscure tomatoes—ones you've never seen nor tasted—represent the tomato's intellectual property asset future, in the form of valuable plant patents, closely held trade secrets and memorable trademarks. Their genomic structures tell a fascinating, if indirect story of conquest and domestication.

Successful plant breeding demands genetic variability. While the tomatoes we know appear to come in all kinds of fancy heirloom shapes and colors, their decoded genomes speak of genetic bottlenecks, of roadblocks to tomato plant improvements.

Of course, the best bred tomato falls flat without economic demand. The halting reception this novel fruit *qua* vegetable received during the Age of Exploration ironically mimics the marketing fate GMO tomatoes face today. Remember Calgene's *FlavrSavr* tomato—the epic commercial dud of the 1990s?

This post examines the prospects for inventing and branding new tomato cultivars in light of a depleted, domesticated genome.

Tomato Domestication Syndrome

The domesticated tomato's precursor "still grows wild in coastal deserts and Andean foothills of Ecuador and northern Peru. Inauspicious and easily overlooked, *S. pimpinellifolium* fruits are the size of large garden peas."[2] How did such tiny wild tomatoes (just 1 cm in diameter) balloon into the beefsteak tomatoes we relish in a Caprese salad?

Domestication of plants triggers a range of traits that distinguish them from their wild ancestors.[3] Generally speaking, domesticated plants differ in three basic ways:

- More compact growth habits.
- Reduction and loss of seed dispersal and dormancy.
- Gigantism and increased morphological diversity in the consumed portion of the plant.

Collectively, these traits are known the "domestication syndrome."[4] Studies reveal that the "traits that distinguish crop plants from their wild relatives are often controlled by a relatively small number of [genetic] loci with effects of unequal magnitude."[5]

Classic Arc of Novel Food Acceptance

During the (often horrifying) Age of Conquest, Spanish explorers observed the Amerindians would easily forego meat and "most content themselves with some tortillas spread with a chili sauce to which they usually add the fruit of a certain species of solanum called *tomamo.*"[6]

Although Spanish conquistadores brought this strange fruit back to Europe in the early 1500s, they shunned it. They feared consuming New World foods would turn them into emasculated, "phlegmatic, beardless Amerindians."[7] They much preferred a steady Iberian diet of meat, wine, olive oil and bread.

European herbalists soon classified tomatoes in the *Solanaceae* or "nightshade" family of fruits and vegetables that include eggplants, potatoes and chili peppers. At first, tomatoes were considered a decorative fruit—not to be eaten. The tomato's physical likeness with its poisonous "bittersweet nightshade" relative, *Solanum dulcamara*,[8] cautioned against ingestion. One British herbalist described tomato plants to be "of ranke and stinking savour."[9]

The first tomato described by an Italian botanist in 1544 is a yellow-fruited variety he called *mala aurea,* or "golden apples."[10] The name stuck in Italy. The first documented tomato recipe, *spaghetti con salsa di pomodoro*, appears in a 1692 cookbook published in Naples. Translated, *pomodoro* means "apple of gold." The symbolic imagery suggests a medieval conundrum: eating tomatoes could lead to tragic death and metaphorical expulsion from an Edenic garden.

The "Doctrine of Signatures" offered the wary European consumer with a countervailing, positive tomato association. This ancient notion contends that a plant's medicinal qualities can be ascertained by external appearance. Hence, a walnut becomes the "brain" food it resembles. A sliced-opened beefsteak tomato looks vaguely like the four chambers of the heart.

Distilled, novel food acceptance—like that of the tomato—tends to occur in the following stages:

Novel Food Acceptance Patterns	*Tomatoes Enter Mainstream Americ*
New foods are at first warily shunned and scorned as impure or unhealthy; this natural reaction may be explained by moral foundations psychology and our innate, Darwinian need for assurances of food safety and sanctity.	Budding entrepreneurs stage publi demonstrations to defuse concern poisonous.
Promoters offer free samples, celebrity testimonials, extravagant health claims and favorite recipes.	Hucksters promote medicinal toma century statesmen endorse tomato consumption; immigrant tomato re ingrained in American food culture

Market forces and subsistence needs encourage novel food production and consumption.	New 19th century canning technol tomatoes into a Civil War staple foo among returning veterans; tomato disparate climates.
Time passes and no one gets demonstrably ill.	Economic adulteration, however, c defraud consumers who cannot as quality of canned foods.
A nostalgic feedback loop ensues. Past consumption experiences are romanticized and pleasing images portray the novel foodstuff. (As the mouth is the portal to the self, consumers seek emotional bonding with the foods they ingest.)	A resurgent Doctrine of Signatures[tomato consumption as "heart hea a "reduced risk of heart disease is a benefits in which tomatoes truly ex

Phenotype = Genotype + Environment

To understand the tomato's intellectual property prospects, some basic plant breeding terminology is helpful.

A *phenotype* is the composite of observable characteristics or traits in a plant. In the basic plant breeding equation, a plant's phenotype is the result of the organism's expression of its genetic code—its genotype—in conjunction with the influence of environmental factors.

Historical evidence shows that Mesoamerican farmers domesticated the earliest forms of tomatoes that, in turn, had originated somewhere in the Andean region of South America. They exercised a form of plant breeding summed up as "crossing the best with best and hoping for the best."[13] The tremendous increase in the tomato size arose from this trial and error technique.[14]

In this process, yet another form of tomato emerged. *Landrace* varieties are cultivated plants that have adapted to specific, local environmental conditions, perhaps hundreds or even thousands of years ago.

An Evolving Tomato Genome

While plant patenting laws operate at the observational, phenotype level—requiring new, distinct and stable varieties of plants for patentability purposes—trait inheritance evolves genomically:

Genomes evolve by duplication of genes, chromosomes or whole genomes, by various rearrangements, insertions of organellar, bacterial or viral DNA that are part of horizontal gene transfer (HGT), (micro)satellite expansions, transposable element insertions and other processes.

A major part of the nuclear genome of most plants is represented by repetitive DNA elements; these elements contribute to the higher evolutionary dynamics of genomes, while genes represent slowly evolving (conservative) genetic units.

Perhaps, the most distinctive feature of angiosperm [flowering plants] is the large amount of genome duplication, i.e., polyploidization [containing more than two homologous sets of chromosomes].

Higher repetitive DNA turnover, repeated polyploidizations and subsequent gene losses lead to a much more rapid structural changes of plant genomes when compared to vertebrates, where gene order conservation is evident event after hundreds of millions of years of divergence.[15]

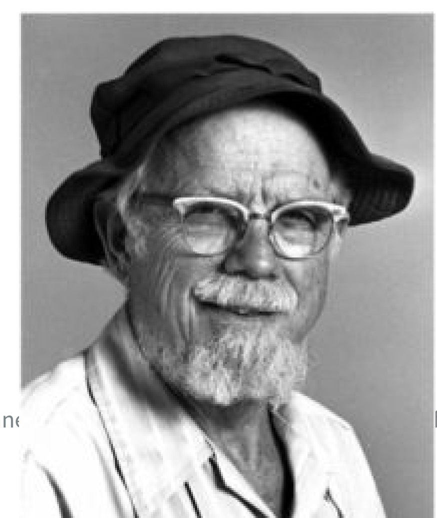
The sheer geographic distance between the original "wild" tomatoes in South America and their domesticated counterparts in Mexico (and later in Europe and North America) means that tomato genomes diverged a long time ago.

Compared with the rich reservoir in wild species, the cultivated tomato is genetically poor. It is estimated that the genomes of tomato cultivars contain [less than] 5% of the genetic variation of their wild relatives.

Tomato domestication experienced a severe genetic bottleneck as the crop was carried from the Andes to Central America and from there to Europe. The initial domestication process was, in part, reached by selecting preferred genotypes in the existing germplasm.[16]

Reinventing the 21st Century Tomato

During the 20th century, Charles Rick would become the tomato's most important scientist and plant breeder. Described as a cross between a Charles Darwin and an Indiana Jones, Rick traveled through the Andean region of South America collecting wild relatives of the



domesticated tomatoes. "As early as 1953, Rick showed that crosses between wild species and their cultivated relatives could reveal novel genetic variations of potential use in agriculture."[17]

Rick's astonishingly valuable collection of tomato germplasm is now maintained at the C.M. Rick Genetic Resource Center of the University of California, at Davis:

The Rick Center acts like a lending library, nurturing and preserving its 3,600-specimen collection but also making it readily available to scholars and plant breeders worldwide who want to "check out" seeds for their own experiments. Today, those seeds are kept in a vault that resembles a restaurant's walk-in refrigerator.

But the Rick collection is not really about taste. Domestic tomatoes had virtually no innate resistance to common tomato diseases and pests until breeders [like Rick] began crossing them with wild species in the 1940s. . . . . Wild tomatoes, on the other hand, are more robust. "We know of at least forty-four pathogens for which resistance has been found in wild species."

The possibilities of using wild traits to improve cultivated tomatoes seem almost limitless. Some wild species grow at chilly altitudes thirty-five hundred meters up the in the Andes, tolerating low temperatures that would cause other tomatoes to shrivel and die. Others thrive in humid rainforests. A few can eke out an existence in the desert.[18]

Crosses between wild and cultivated species of tomatoes can generate an array of novel genetic variation in their offspring. Breeding "from wild species via interspecific crosses followed by many backcrosses to cultivated tomatoes can lead to the transfer of favorable attributes" in the resulting tomato variety.[19] This is known as "wild introgression" plant breeding.

Genome Editing and Plant Breeding Bandwagons

In one way or another, all plant breeding techniques hearken back to *Experiments in Plant Breeding,* Gregor Mendel's 1866 groundbreaking article (ignored at first and rediscovered 34 years later).

By the latter 20th century, plant breeders applied increasingly sophisticated biotechnology tools to "improve" the tomato. Goals included breeding for "yield in the 1970s, for shelf life in the 1980s, for taste in the 1990s, and for nutritional quality currently."[20]

The first transgenic tomato, Calgene's *Flavr Savr* tomato, relied on recombinant DNA techniques to extend the shelf life of tomatoes by inhibiting an enzyme involved in fruit softening. The *Flavr Savr* tomato had some initial market success in the mid-1990s, then flopped. Its developers chose a tomato intended for the food processing market as the target cultivar, rather than a tomato grown for fresh food markets. Apparently, the resulting GMO tomato had very little flavor worth saving. It found its best use in the tomato processing market, but consumers rebelled against the GMO provenance.[21]

In contrast to recombinant DNA technology—in which foreign genes are inserted into a target host—a new wave of plant breeding relies on genomic editing tools, such as the CRISPR/Cas9 system. In broad terms:

Genome editing focuses on the G component of P = G +E [*i.e.,* that phenotype value (P) is the sum of genetic (G) and environmental effects (E)], and it represents an infinitely more precise form of mutation breeding. Genome editing allows changes in targeted DNA sequences, with the edits involving the deletion, substitution, or addition of one or more bases.

[G]enome editing requires prior information on gene identity and function and leads only to targeted mutations. In practice, however, the plant regeneration process after genome editing may lead to unwanted somaclonal variation in the target cultivar. Genome editing may be particularly valuable in plant species for which backcrossing (to introgress favorable alleles) is impractical due to a long generation interval or infeasible to a heterozygous recurrent parent.

[G]enome editing will be most useful in the same situations where linkage mapping of QTL [quantitative trait loci] is most useful: for traits that have major QTL or major genes. For such traits, such as disease resistance or flowering date, changes in the known underlying genes can be directly made via genome editing. These changes will involve loss-of-function mutations or gain-of-function mutations equivalent to naturally occurring mutations with known effects, or novel mutations that need to be characterized via phenotypic screening.

The many genes affecting a trait such as yield in elite germplasm remain largely unknown even after whole genomes have been sequenced.[22]

While this description of genome editing may read somewhat like Greek, the most important finding is that "most quantitative [plant] traits are controlled by a large number of small effect genes 'locked away in low-recombinant regions,' presenting challenges in (even) sequenced and highly genotyped association mapping panels."[23]

In other words, even though genomic editing is the latest and greatest biotech bandwagon, its technical shortcomings will also confound the plant breeding industry.

"Wild" Tomatoes are Not Patentable

U.S. plant patenting laws, 35 U.S.C. §§ 161-164, protect new and distinct varieties of "asexually reproduced" plants other than those "found in an uncultivated state." More generally, U.S. utility patents, among other things, cover new and useful "compositions of matter, or any new and useful improvement thereof." 35 U.S.C. § 101. In addition, the Plant Variety Protection Act offers patent-like protections for new, distinct, uniform and stable sexually reproduced plant varieties. 7 U.S.C. §§ 2321-2582.

Plant explorers will find no solace in U.S. plant patent laws—since plants discovered in the wild are not patentable. A recent Federal Circuit decision discussing plant patenting, *In re Beineke* (2012), stands for the proposition that:

[T]wo things [are] necessary for an applicant to obtain plant patent protection: (1) the plant must have been created in its inception by human activity, i.e., it must be the result of plant breeding or other agricultural or horticultural efforts; and (2) the plant must have been created by the "inventor," i.e., the person seeking the patent must have contributed to the creation of the plant in addition to having appreciated its uniqueness and asexually reproduced it.[24]

Although plants found in the wild are not patentable, their progeny may be. These plant patenting activities appear relatively immune from a line of attack generated by the recent *Myriad/Mayo* Supreme Court cases—*i.e.,* that naturally occurring DNA segments constitute unpatentable products of nature. [25] The Plant Patent Act of 1930 altered former law rejecting plant inventions as unpatentable "laws of nature." The same can be said for the Plant Variety Protection Act.

Standard utility patent applications, however, may present separate patenting difficulties. If the utility patent claims seek to cover naturally occurring genomic sequences, new plant variety patents may be subject to *Mayo/Myriad*-based rejections.

In this regard, an analysis of patent claims in human biomedicine vs. crop-based agriculture reveals a substantive overlap in claimed genome sequences. "Such practice could, in principle, raise infringement concerns—for example, if an agribusiness and a medical diagnostic company use the same DNA primers for polymerase chain reaction-based genetic testing."[26]

If the *Mayo/Myriad* case holdings operate as a brake on plant patent activities at the genomic level, one can anticipate that agribusinesses and other plant patent inventors will guard their plant-based innovations under a reinvigorated trade secrets law, now federalized per the "Defend Trade Secrets Act of 2016.[27]

Genome Edited Plants Evade Regulatory Scrutiny

Genetically engineered (GE) plants are presumptively subject to a convoluted array of federal regulatory oversight by the Food and Drug Administration, the Environmental Protection Agency, and the United States Department of Agriculture. Generally speaking, the FDA established a voluntary structure for GE plant producers to consult with the FDA before marketing these products.

Much of this regulatory structure—developed in the mid-1980s—is premised on theoretical "plant pests" and recombinant DNA techniques involving foreign gene insertion.

The USDA regulatory process for GE crops is triggered by the use of "plant pests" in any portion of the modification process or the derived potential of the GE crop to behave as plant pests. In practice, the routine use of pest-derived genetic components triggers a *de facto* process-based regulatory regime by the USDA's inspection service, APHIS [Animal and Plant Health Inspection Service].[28]

This regulatory framework focuses on transgenic biotechnology tools—now a fading, late 20th century bandwagon. Genome editing tools tend not to trigger this GE food regulatory regime. When requested to opine on genome editing tools, APHIS determined that genome editing technologies create two potential classes of products:

(i) those in which endogenous genetic material is removed (targeted deletions); and (ii) those in which precise sequence changes are introduced by using specific template oligonucleotides (targeted substitutions and insertions).

APHIS [states] that products resulting from targeted deletions would, in most cases, not be regulated because no new genetic material is integrated into the recipient genome, and the engineered nucleases did not originate from plant pests. The second class of products (targeted substitutions and insertions) would need to be reviewed on a case-to-case basis to assess the inserted trait and determine regulatory status.[29]

Based on this dichotomy, genome editing appears to sidestep US regulatory oversight. While this may be a policy loophole, there may be little impetus to expand bureaucratic review of genome edited plant food products when a sufficiently large body of scientific literature on GE traits already shows that "DNA modification *per se* is not inherently unsafe or a threat to the environment."[30]

Guacamole Con Tomate Verde

You need not be a wild plant explorer to experience unusual tomato flavors. Green tomatillos are more widely available in American grocery store shelves nowadays. Their paper husks and sticky skin may be off-putting, but these are small bothers in a quest for sublime taste.

To mix up your standard guacamole recipe, try Diana Kennedy's recipe for *guacamole con tomate verde*.[31] After you've ground white onions, serrano chilies, cilantro and broiled tomatillos (preferably with a mortar and pestle), you mash—never machine blend!—avocadoes into this mixture. *Voilà*, your taste buds will be transported to the state of Mexico bordering on Morelos, where this recipe originated perhaps eons ago.

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* The opening photograph of tomatoes included in the Earth & Table version of this article is licensed under the GNU Free Documentation License, Version 1.2. For photographer information, *see* https://commons.wikimedia.org/wiki/User:Berrucomons.

[1] D. Kennedy, *The Essential Cuisines of Mexico* (2000), at 490-91.

[2] B. Estabrook. *Tomatoland: How Modern Industrial Agriculture Destroyed Our Most Alluring Fruit* (2011), at 3.

[3] Y. Bau and P. Lindhout, "Domestication and Breeding of Tomatoes: What Have We Gained and What Can We Gain in the Future," 100 *Annals of Botany* 1085, 1086 (August 2008).

[4] *Id.*

[5] *Id.*

[6] R. Earle, *The Body of the Conquistador: Food, Race and the Colonial Experience in Spanish America, 1492-1700* (2012), at 42.

[7] *Id.* at 52

[8] Photograph in the *Earth & Table* blog post version by Guido Gerding, https://commons.wikimedia.org/w/index.php?curid=1037325.

[9] A.F. Smith, *The Tomato in America: Early History, Culture, and Cookery* (1994), at 17.

[10] C. Wright, *A Mediterranean Feast: The Story of the Birth of the Celebrated Cuisines of the Mediterranean, from the Merchants of Venice to the Barbary Corsairs* (1999), at 32.

[11] *See, e.g.,* http://herbs.lovetoknow.com/doctrine-signatures.

[12] *See* http://www.whfoods.com/genpage.php?tname=foodspice&dbid=44 (World's Healthiest Food website page devoted to tomatoes).

[13] G. Acquaah, *Principles of Plant Genetics and Breeding* (2d ed. 2012), at 7.

[14] *See* n. 2, at 4.

[15] P. Smykal, et al., "From Mendel's discovery on pea to today's plant genetics and breeding," 129 *Theoretical and Applied Genetics*, 2267, 2271-72 (2016) (citations omitted and text formatting altered for readability).

[16] *See* n. 3, at 1086.

[17] S. Tanksley and G. Khush, "Charles Madera Rick 1915-2002," *Biographical Memoirs,* Vol. 84 (2003), at 10, available online at https://www.nap.edu/read/10992/chapter/17.

[18] *Id.* at 13-16.

[19] *See* n. 13, at 56.

[20] *See* n. 3, at 1088.

[21] *See* n. 13, at 256.

[22] R. Bernardo, "Bandwagons I, too have known," 129 *Theoretical and Applied Genetics* 2323 (2016), at 2329-30 (text formatting altered for readability). The reference to "elite germplasm" in the quoted material refers to germplasm that is adapted (selectively bred) and optimized to new surroundings (i.e., environment).

[23] See n. 15, at 2270.

[24] *In re Beineke*, 690 F.3d 1344, 1348 (Fed. Cir. 2012).

[25] *See Mayo Collaborative Services v. Prometheus Labs., Inc.*, 566 U.S. 66 (2012); *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. ___ (2013).

[26] O. Jefferson, et al. "Gene patent practice across plant and human genomes," 33 *Nature Biotechnology* 1033, 1035, 1037 (October 2015).

[27] *See* 18 U.S.C. § 1836(b)(1)("An owner of a trade secret that is misappropriated may bring a civil action under this subsection if the trade secret is related to a product or service used in, or intended for use in, interstate or foreign commerce.").

[28] A. Camacho, et al., "Genetically engineered crops that fly under the US regulatory radar," 32 *Nature Biotechnology* No. 11 (November 2014), at 1088.

[29] *Id.* at 1089.

[30] *Id.* at 1091.

[31] *See* n. 1, at 351 (Diana Kennedy's recipe for *Guacamole con Tomate Verde*).